Prostate Cancer

A Revolutionary Wholistic Approach
Applications for Botanical and Nutritional Medicine

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Section I

Introduction to Prostate Cancer

Nearly all men in the course of their lifetimes will experience a health issue relating to the prostate and many, if they live long enough, have a good chance of it being prostate cancer. An estimated 220,900 new cases and 28,900 deaths from prostate cancer cells occurred in 2003. Although prostate cancer is the second leading cause of cancer-related deaths in US men,1 most men die with prostate cancer, rather than of the disease. However, of the men with prostate cancer who undergo definitive local therapy (surgery or radiation therapy), approximately one-third will have biochemical PSA failure within 10 years and one-third of these will develop clinical disease progression within 5 years.2-7

The treatment options for these men are generally limited to salvage radiation therapy, androgen deprivation therapy, and attempts at chemotherapy protocols after failure of the previous therapies; and then clinical trials of new agents. Salvage radiation therapy is rarely beneficial in patients with high-risk prostate cancer,8 and I am of the opinion that this treatment only furthers the progression of the cancer, and can create many complications, such as post-radiation swelling, scarring, and hemorrhaging. Androgen deprivation therapy (ADT) is effective in controlling prostate cancer for a period of time, usually anywhere from 1-8 years; however its continuous use has been associated with a myriad of acute and chronic symptoms; other diseases which can often lead to a shorter lifespan then what would have otherwise occurred from the prostate cancer. Side effects of ADT include hot flashes, impotence, loss of libido, muscle atrophy, and osteoporosis. The use of intermittent androgen deprivation therapy (IADT) has sought to lessen the impact of these symptoms and prevent some of the potential long-term side effects of chronic testosterone deprivation. In certain circumstances I am in favor of this approach as opposed to the standard ADT. It appears that IADT is as effective long-term as ADT as a palliative treatment for many patients, and has reduced side effects.9

In the wake of the failure of conventional treatment modalities, especially of hormone refractory prostate cancer, new revolutionary approaches based on phyto-therapy-based compounds is the most effective modality to improve the outcome of this disease. Exciting research in this area, the area in which I apply in my practice, has lead to effective means to prevent or delay the progression of the disease by strategies implementing the use of botanical and nutritional compounds together with diet. I have many years of successful treatment plans for men with prostate cancer at various stages.

Introduction to my Healing Philosophy

Humans are not meant to “function,”” machines function. Humans create, feel, respond, and are positioned to heal and love. Humans that “function” like machines make a diagnosis according to an illness; for example “you have high blood pressure.” Right away, a label. “You have cancer,” which sometimes translates into you are cancer. Instead we should ask, what is causing cancer? And how can we in a rational harmonious way bring balance to this person, and generate their own self-healing into occurring? People say that in so many years we will have cured cancer. Cancer is evolving and mutating faster then we are finding cures. We should stop looking at the masses with regards to cancer and start focusing on the individual.

I never look at the masses with regard to anything; I look at the individual just as you must. I can only help one person at a time. I can only love one person at a time. Just one, one, one. So you begin…I begin. The whole work is only a drop in the ocean. But if I didn’t put the drop in, the ocean would be one drop less. It isn’t about how many diplomas, or degrees you have received, or how much you made, or how many great things you have done. It is merely, I was sick and you cared for me with all of your love.

Before I touch a patient, before I listen – I PRAY. Just has you should have clean hands to touch, you need a clean heart to love. It is not how much we do – it is how much love we put into the doing. To love and to heal are not a luxury for the few! They are our simple duty, and they are what bring us joy.

I believe the practitioner of Natural Medicine should be first and foremost of a religious character.

“Religion, in truth, is not a matter of dogmas, beliefs, of rituals and superstitions; nor is it the cultivation of personal salvation, which is a self-centered activity. Religion is the total way of life, the pursuit of pure Love (God); the understanding of Truth; where ‘ALL’ that we do is exemplified as Religion.” Donald Yance

A person with cancer can often feel betrayed by their body; invaded, as if something alien and foreign has taken hold. The language of oncology endorses this adversarial view in talking of ‘the war on cancer’ and in cutting, poisoning, and burning as fast as possible, as if somehow obliterating the offending part will solve the problem. But cancer is not alien. It is, in fact, both of you and not of you. Tumors are not some external, malign parasite but are actually comprised of normal body cells whose only uniqueness is that they have lost their ability to communicate properly and to receive growth control messages from adjacent cells. Nothing a cancer cell does is unique to cancer. All of the metabolic activities of a cancer cell can also be carried out by normal healthy cells. Cancer cells simply don’t know when to stop. Thus, in designing drugs to address specific facets or aspects of cancer cell function, it is virtually impossible to avoid side effects and corollary damage because healthy cells are doing the same metabolic activities.

Many cytotoxic agents have a relatively narrow therapeutic margin, and in many patients with incurable diseases, the odds of experiencing treatment-related adverse effects are greater than the probability of obtaining a clinical benefit. If, on the other hand, the focus is redirected from attacking the cancer cells directly with toxins to up regulating and supporting the intra-cellular and extra-cellular functions that should normally operate to identify and remove rogue cells, then less adverse events can be expected because the treatment is more physiological in its functions. Targeting specific pathways to stop cancer growth can be less toxic to normal cells and thus improve tolerability. The rapidly expanding knowledge of the pathogenesis of many cancers at the molecular level is now providing new targets for agents. Indeed, anticancer drug discovery has shifted from an empiric random screening approach to a more rational, mechanistic, and target-based approach whereby specific abnormalities in cell functioning are modulated in a classical drug-receptor fashion.

**Prostate Cancer Epidemiology**

Accumulated epidemiologic evidence implicates the environment as the major contributor to the development of most prostate cancers. Epidemiological evidence also suggests that the progression and promotion of prostate cancer (CaP) can be modulated by diet. Prostate cancer incidence and mortality displays wide geographic variation, with high rates of prostate cancer incidence and mortality in the United States and Western Europe, and low prostate cancer risks more characteristic of Asia. African Americans in the United States have a very high risk of prostate cancer. The geographic variation in prostate cancer incidence and mortality can best be explained by lifestyle influences, as Asian immigrants to North America typically adopt higher prostate cancer risks.

The key aspect of lifestyle in the United States most likely responsible for high prostate cancer incidence and mortality is the diet, generally rich in animal fats and meats, and poor in fruits and vegetables. In the Health Professions Follow-up Study, a prospective cohort study involving 51,529 men, total fat intake, animal fat intake, and consumption of red meats were associated with increased risks of prostate cancer development. Red meat consumption similarly correlated with prostate cancer risk in the Physicians Health Study, and in a large cohort study in Hawaii. The cooking of red meats at high temperatures, or on charcoal grills, is known to lead to the formation of both heterocyclic aromatic amine and polycyclic aromatic hydrocarbon carcinogens. Ingestion of 2-amino-1-methyl-6-phenylimidazopyridine (PhIP), one of the heterocyclic amine carcinogens that appear in "well-done" red meats, leads to prostate cancer in rats. Excess consumption of commercial dairy products also appears to increase the risk of prostate cancer, an effect that may be more attributable to calcium intake than to dietary fat or protein.

High calcium and nonfat dairy products are also associated with an increased risk of PC. Analysis of data from the Health Professionals Follow-Up Study indicates the possible detrimental effects of high calcium intake: a 4.6-fold increased risk of metastatic prostate cancer was seen in men who consumed > 2000 mg calcium daily compared with those consuming < 500 mg/day. Of note, the increased risk with consumption of calcium from supplements was independent of that seen from dairy-based dietary intake, indicating that the association is separate and distinct from other nutritive factors found in dairy products. Similarly, data from a Swedish case-control study indicate that calcium intake > 1183 mg/day, separate from other nutritive factors in dairy products, confers a higher risk of prostate cancer compared with those consuming < 825 mg/day.
Further expanding upon these observations, data from the Physicians' Health Study showed that each additional increase of 500 mg calcium per day conferred a 16% increase in prostate cancer risk, and that each additional increase of 300 mg/day conferred a 2 pmol/L decrease in 1,25(OH)2 D3. Of note, although the majority of calcium was consumed from dairy foods, and from skim milk in particular, other factors in dairy foods, such as dairy fat and protein, were not associated with prostate cancer risk. Similarly, data from the Cancer Prevention Study II Nutrition Cohort showed that higher calcium intake, but not increased dairy intake, was associated with a small but significant increase in PC risk. In another very recent study analysis of different milk products showed some evidence for lowfat milk as a potential risk factor for prostate cancer.

**Nutrigenomics and the Risk of Prostate Cancer**

Consumption of vegetables, fruits, and antioxidant micronutrients reduces the risks of prostate cancer. High intake of tomatoes, which contain lycopene, and of cruciferous vegetables, which contain sulforaphane, and diindole methane (DIM) are protective against prostate cancer development. Lycopene is found in high concentrations in tomatoes and tomato products, but not all tomatoes have equal amounts of lycopene. Concentrations vary from 50 mg/kg in red tomatoes to 5 mg/kg in yellow tomatoes. Other reddish foods, such as watermelon, papaya, and pink grapefruit, may also contain lycopene, but at lower concentrations than in tomatoes.

Lycopene likely prevents prostate cancer development by acting as a redox coupling agent, regulating IGF signaling, and Intercellular Gap Communication. As part of a recent clinical trial, men were provided tomato sauce-based pasta dishes for 3 weeks before radical prostatectomy for prostate cancer. For these men, tomato consumption was associated with increased lycopene levels in the blood and in the prostate, with decreased oxidative genome damage in leukocytes and in prostate cells, and with a reduction in serum PSA.

Greater levels of selenium, vitamin E, and lycopene have been shown to reduce prostate cancer risk in one out of every four Caucasian males; and those who inherit a specific genetic variation that is particularly sensitive to oxidative stress. A recent study found that higher prediagnostic serum concentrations of alpha tocopherol (vitamin E), was associated with lower risk of developing prostate cancer, particularly advanced prostate cancer.

**Sulforaphane (SFN),** a compound found abundantly in broccoli sprouts, that can prevent cancer in animals by triggering induction of carcinogen-detoxification enzymes, also can act as an antioxidant and a preventative agent against prostate cancer. In a recent study, a single ingestion of 68g broccoli sprouts inhibited HDAC activity in circulating peripheral blood mononuclear cells 36h after consumption, leading to a gene-silencing effect in cancer cells. SFN has important implications for cancer prevention and therapy.

In addition to lycopene and sulforaphane, other phytonutrients, such as the micronutrients vitamin E and selenium, also may reduce prostate cancer risks. A clinical trial of supplementation with vitamin E and selenium to prevent prostate cancer (the SELECT Trial), involving a planned 32,400 men, has just been initiated. Eating a diet with omega-3 fatty acids from oily fish could stop the spread of prostate cancer, according to recent research.

**Pomegranate juice** has shown to inhibit prostate cancer and slow down the growth of existing prostate cancer. Flavonoid-rich polyphenol fractions from the pomegranate fruit exert anti-proliferative, anti-inflammatory, anti-angiogenic activities as well. Avocados have been shown to inhibit the growth of prostate cancer cells as well.

**Flax seeds** supplemented in the diet of men with prostate cancer reduced both the proliferation rate and increased apoptosis. Flaxseeds have potent antiestrogenic effects on estrogen receptor positive breast cancer, and recently were found to down-regulate cancer-induced vascular endothelial growth factor (VEGF). One study demonstrated that supplementation of 10% flaxseed in mice with established human breast tumors, reduced tumor growth and metastasis. Flaxseed also decreased extracellular levels of VEGF, which appears to be one mechanistic explanation for the decreased tumor growth and metastasis. Flax seeds have also been found to be beneficial for cardiovascular health. Studies indicate that flax lowers lipids, including cholesterol and triglycerides. They also have shown to prevent obesity, a strong risk factor for prostate and other cancers.

A recent study involved men scheduled to undergo surgery for the treatment of prostate cancer. The researchers gave them 30 grams of flaxseed every day for an average of 30 days. When the men's tumors were removed, the researchers were able to determine how quickly the cancer cells had multiplied. The men taking flaxseed, either alone or in conjunction with a low-fat diet, were compared to men following just a low-fat diet, and men in a control group, who did not alter or supplement their daily diet. Each group was made up of about 40 participants. Men in both of the flaxseed groups had the slowest rate of tumor growth.
Flax seeds are proving to be beneficial in breast and prostate cancer prevention strategies. I recommend men consume 1-3 tablespoons per day of freshly ground flaxseed, often mixed into the daily smoothie that all my patients are put on.

The consistent finding of a protective effect of various nutrients against prostate cancer development suggests that oxidative stresses might contribute to prostatic carcinogenesis. Low levels of specific nutrients include selenium, gamma tocopherol, folic acid, lycopene & other carotenoids, and isothiocyanates. Reactive oxidative species (ROS) can be generated by metabolic processes, by a number of different exposures, by diet, and by inflammation.56, 57 Also a fatty acid imbalance of omega-3 to 6 fatty acid ratio, is implicated in prostate cancer. A long-term successful program (The Yance Triphasic Approach) addresses a number of causative factors including the reduction of exposure to ROS as well as a treatment plan that improves the removal of ROS, a process, called free radical scavenging, that reduces mutagenic change and even repairs damaged DNA.

A recent published study in the August 1, 2003 issue of the journal, The Prostate, showed a remarkable effect of diet and exercise on the destruction of prostate cancer cells. The researchers added blood serum from three groups of middle-aged men to cultured human prostate cancer cells and observed the effects. The first group consisted of fourteen men who were overweight and sedentary, and had diets that were high in fat and sugar. The second group of men had been following a healthy plant-based diet, low in fat, sugar and sodium and high in fiber for fourteen years. The third group included twelve men who consumed typical American diets but had been part of the University of Nevada Las Vegas Adult Fitness Program for fourteen years.

Serum from both groups of exercisers was found to contain lower levels of insulin-like growth factor 1 (IGF-1) and higher levels of IGF binding protein 1 than that of the nonexercising group of men. Three days after administering the sera to the prostate cancer cell cultures, it was found that the serum of the third group destroyed one quarter of the prostate cancer cells, compared to the destruction of only 3 percent of the cells by serum from the first group. However, followers of the healthy plant-based diet had blood serum that killed half of the prostate cancer cells when added to the culture.58

Even research has been done to advise a diet consisting of a wide variety of plant-based foods and fish; similar to what is recommended, and well established, for the primary prevention of heart disease.59

**Soy**

Several studies have demonstrated a consistent anticancer effect of diets containing soy compared with controls in a variety of prostate cancer animal studies.60 Epidemiologic evidence also supports the role of traditional soy foods as an anti-prostate-cancer food.

In countries like Japan, where soy consumption is high, there is approximately an 80 percent lower incidence of prostate cancer than in the West. In a study that followed Japanese men who immigrated to the United States and abandoned their traditional diets, it was found that within one generation there was a four-fold to nine-fold increase of prostate cancer among them.61-64

A prospective study of 12,395 Seventh Day Adventists in California demonstrated that frequent consumption of soy-milk (at least daily) was associated with a 70% reduction in the risk of developing prostate cancer.65

In one recent pilot study, patients received escalating doses of a soy supplement from the time of study enrollment until prostatectomy. Serum levels of prostate specific antigen (PSA), testosterone, and estrogen were measured at study enrollment and prior to prostatectomy. A total of 13 patients were enrolled in this pilot study and 11 patients were assessable for response. With soy supplementation, serum testosterone levels decreased in 9 of 11 patients and estrogen levels decreased in 8 of 10 patients in a dose-dependent manner. There was a variable effect on ERalpha expression with down-regulation of receptor expression seen at the highest dose level. The soy supplement also produced a consistent decrease in serum sex hormone levels.66 Reducing the levels of circulating androgens and estrogens prior to surgery may reduce the risk of cancer recurrence in the future.

The results were even more exciting in another recent study whereby soy isoflavone intake was associated with a 50% reduction in the incidence of prostate cancer. This study recruited 43,509 Japanese men (average age 57) with a generally high soy isoflavone intake. Dietary assessment was performed using a validated 147-item food frequency questionnaire. During the five years of follow-up, 307 men were newly diagnosed with prostate cancer (74 cases were advanced), and 220 cases were organ localized. While no relationship between total prostate cancer...
risk and dietary intakes of genistein, daidzein, miso soup, and soy food was observed, all four food items were associated with significant risk reduction for localised prostate cancer. The highest intake of soy isoflavones (at least 32.8 milligrams of genistein per day) had a 40 percent reduced risk compared to those with the lowest intake (less than 13.2 mg/d), the researchers found. This research confirms that isoflavones and soy food are associated with a dose-dependent decrease in the risk of localized cancer; with relative risks for men in the highest quartile of genistein, daidzein, and soy food consumption compared with the lowest of 0.52, 0.50, and 0.52, respectively.\(^\text{67}\)

A recent animal study was conducted involving Lobund-Wistar (LW) rats, which have high testosterone levels, are predisposed to develop hormone-refractory prostate cancer (HRPC) spontaneously and by methylhnitrosourea (MNU) induction, and in whom the development of HRPC progresses through 2 stages. In LW rats: moderate caloric restriction prevented development of spontaneous prostate cancer; dietary 4-hydroxy-2-nitrophenylretinamide prevented MNU-induced prostate cancer; and dietary supplementation with soy protein isolate with high isoflavones prevented spontaneous and induced tumors. In rats 12 mo of age and younger, changing from the control diet to the soy+isoflavone diet significantly prevented progression of spontaneous tumors to the refractory stage of disease. Tumors that developed spontaneously and after MNU induction showed similar developmental stages and morphology, but MNU-induced tumors had shorter latency periods before development. The accumulated data indicate that soy-based diets are effective in the prevention of prostate cancer.\(^\text{68}\)

Soy isoflavones also increase the effectiveness of radiation therapy for the treatment of prostate cancer. Soy isoflavones inhibited cell survival and potentiated radiation cell killing in PC-3 tumor cells in vitro. Increased cell killing correlated with inhibition of the antiapoptotic molecules Bcl-xL and survivin, the upregulation of the proapoptotic Bax molecule, and with PARP cleavage, suggesting activation of apoptotic pathways. In vivo, using the PC-3 orthotopic metastatic mouse model, soy isoflavones and prostate tumor irradiation led to enhanced control of primary tumor growth and metastasis, as observed with pure genistein and radiation.\(^\text{69}\)

I recommend my patients to only eat high-quality soy foods, preferable fermented such as tempeh, miso, and tamari, but permit tofu and a small intake of soy-milk. However no commercial, refined, GMO soy foods should be eaten, and soy foods should be integrated into a well-balanced diet, eaten 3-5x a week. The only supplemental soy product I recommend is a fermented soy powder, Soy Essence by Jarrow, which can be put into the morning smoothie, a staple in the Triphasic Model.

**Dietary Phytochemicals as Gene-Behavior-Mediators**

Through modification of one’s diet, and with the use of dietary adjuncts in the form of concentrated botanical/phytochemical compounds as gene-behavior mediators (GBM) and adaptogens, the expression of genes involved in the advent of cancer can be reprogrammed. The phenolic antioxidant resveratrol, found in berries and grapes, inhibits the formation of prostate tumors by acting on the regulatory genes such as p53, while activating a cascade of genes involved in cell cycle and apoptosis including p300, Araf-1, cdk inhibitor p21, p57 (KIP2), p53 induced Pig 7, Pig 8, Pig 10, cyclin D, and DNA fragmentation factor 45. The group of genes significantly altered by selenium includes cyclin D1, cdk5, cdk4, cdk2, cdc25A, and GADD 153. Vitamin D shows impact on p21(Waf1/Cip1), p27, cyclin B, and cyclin A1. Genomic expression profile with vitamin D indicated differential expression of gene targets such as c-JUN, JUNB, JUND, FREAC-1/FoxF1, ZNF-44/FOX7, plectin, filamin, and keratin-13 involved in anti proliferative differentiation pathways. Curcumin mediated the Nrf2 pathway and significantly altered p21(Waf1/Cip1) levels. Aromatase inhibitors, such as Grape seed extract and Chrysin, affected the expression of cyclin D1. The Green Tea polyphenol, EGCG, has a significant effect on TGF-beta expression, while several other earlier studies have shown its effect on cell cycle regulatory proteins.\(^\text{70,71}\) The comprehensive diet and supplement foundation program within the Triphasic Model addresses cell cycle regulatory pathways modifying genes in cancer.

Other risk factors include:

- **Virus:** A newly identified virus, tentatively called XMRV, appears to be associated with the development of prostate cancer in genetically susceptible men;\(^\text{72}\)
- **Overweight and obesity:** Overweight and obese men are more likely than their normal weight counterparts to be diagnosed with prostate cancer. Also, among overweight and obese men, increasing body mass index (BMI) is directly related to the risk of advanced disease;\(^\text{13}\) (section II – 204, 208, 209)
- **Obese men who underwent a radical prostatectomy (RP) had higher-grade tumors, a trend toward increased risk of positive surgical margins, and higher biochemical failure rates compared to normal weight men treated with RP. A BMI > or = 35 kg/m(2) was associated with a higher risk of failure than a BMI between 30 and 35 kg/m(2);\(^\text{74}\)
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- Obesity, however, may appear protective for prostate cancer in younger men. Obesity has been associated with lower serum testosterone, theoretically resulting in decreased PSA production. Obesity has also been associated with prostatic enlargement, making the detection of existent cancer more difficult; 75
- **Family history:** Men from families with a history of prostate cancer are at increased risk of developing the cancer themselves, especially men whose fathers were diagnosed before age 70; 76
- Men with only daughters have a higher risk of prostate cancer than men with at least one son, suggesting a chromosome defect; 77
- **Lack of sunlight:** Geographic distribution of prostate cancer mortality is the inverse of that of UV radiation. This effect is strongest in counties north of 40 degrees N latitude, where vitamin D synthesis is limited to non-winter months; 78, 79
- **Smoking:** Smoking increases the risk of extraprostatic prostate cancer in younger men; 80
- **Exposure to pesticides:** Working with pesticides may increase a man's risk of prostate cancer, research suggests. People routinely in contact with pesticides had a 13 percent higher chance of developing the disease than those who were not exposed to the chemicals; 81
  Epidemiological evidence did not allow identifying a specific pesticide or chemical class that would be responsible for the increased risk but the strongest evidence comes from workers exposed to phenoxy herbicides, possibly in relation with dioxin and/or furan contamination; 82
- **Smaller prostate:** In men with prostate cancer, smaller prostate size is associated with higher grade, more advanced prostate cancer, and a greater risk of biochemical progression. 83
- **PC Risks Rise With Shift Work:** Workers on rotating shifts were four times more likely to develop PC than those working regular hours, whether on day or night shifts.

A study, which examined more than 14,000 workers over eight years, also found that night shift workers were at a slightly increased risk of PC. Eighty percent of the workers studied worked daytime hours, 7 percent worked nights, and about 13 percent rotated their work schedules from night to day.

The reason for the effects relate to an HPA-melatonin dysfunction causing a reduced secretion of melatonin in those who work irregular hours and, to a lesser extent, nights. Reduced secretion of melatonin has been linked to increased production of sex hormones, which help to regulate prostate tissues. 84

**Adaptation, the 24-hour circadian clock and prostate cancer**

The ancient adaptation of a 24-hour circadian clock has profound effect on our daily biochemical, physiologic, and behavioral processes, including the monitoring of sex hormone levels. Although the disruption of the circadian cycle has been implicated in the etiology of hormone-related female breast cancer, few studies have been undertaken to determine if a link exists in the development of the most common cancer type among men whose etiology remains largely unknown: hormone-related prostate cancer. Both altered-lighted environments and genetic variations in genes responsible for maintaining circadian rhythms may result in deregulation of clock-associated biological processes, such as androgen expression, and consequently influence an individual's risk of PC. There is also a potential for the interaction of genetic variants and exposures, such as evening shift work. 85

**A target for chemoprevention**

Prostate cancer is an attractive target for chemoprevention because of its ubiquity, treatment-related morbidity, long latency between premalignant lesions and clinically evident cancer, and defined molecular pathogenesis. I could go as far as to say that most men with prostate cancer that go on my program will achieve a longer and healthy life because of prostate cancer. Keep in mind that cancer should not be viewed in the black-and-white way that conventional medicine would have us believe it is. You can live with cancer, slow down its growth, but never completely eliminate it. You can also significantly outlive a person that was treated for their cancer and supposedly told they were “cured,” only to have it return several years down the road in his/her bones, ultimately becoming the cause of death in this person. An herbal, nutritional, dietary, and lifestyle approach to cancer often helps a person live with cancer much longer then they would have without cancer. Pause and think about that for a minute.

**The Fear Factor**

Men seem to be more afraid of prostate cancer than heart disease, even though heart disease possessess a much greater threat; and even still when they may have several cardiovascular risk factors and be on drugs for cardiovascular disease. The Prostate Cancer Prevention Trial has provided the first firm evidence that this cancer can be prevented by diet and nontoxic plant-based supplementation.
It seems these days that everything people do with regards to decision-making is based more on fear than on rational thinking, intelligence, common sense, and prayer. I am not just referring the patient. Today most doctors make choices based on what the norm is and on fear. There must be a paradigm shift away from the ungodly energy of fear that is becoming the cancer of medicine. We must also see the importance in a relationship with plants that is truly healing. When plants are ingested they communicate with our genes, they are, in a sense, the humble love of our Creator speaking where love and healing can replace the fear.

Section II

Prostate Cancer Staging

A staging system helps us understand the extent of the disease, although in my Triphasic System this does not help with forming the protocol, or with understanding the characteristics needing to be addressed. The T1 is an incidental finding in prostate cancer; it is not very common now. The T1c is by far the most common. T1c occurs when you have a PSA elevation alone (you can have many false positives going on a PSA alone) -- you have a normal digital exam, and nothing else suggests cancer except elevation of PSA. That scenario now accounts for about 70% of all newly diagnosed prostate cancer patients. The T2 lesion is one you can feel, a nodule or an abnormality on the digital rectal exam. The T2 lesions are divided into stages T2A, T2B, and T2C. The T3 lesion is locally advanced, where you feel something and you have lost the contour of the prostate. Distant disease is classified as stage T4.

Currently the only available variables to predict the outcome of prostate cancer include clinical stage, serum PSA level velocity, and biopsy Gleason scores; however, it is becoming increasingly apparent that these are inadequate to accurately predict the outcome. There are many more effective test that could be run that would help us understand the apparent benign-like cancer or the potentially aggressive. A variety of other biochemical, molecular, and genomic markers of tumor progression have been identified but have not been tested in neural network models. I therefore propose to include these newer markers with routine variables in a neural network model to improve the accuracy of predicting outcomes.

It is clear to me that the staging of prostate cancer should undergo significant changes. Several new tests, markers, and imaging modalities are now available that can improve staging accuracy. These can also help the holistic practitioner with identifying those patients that need more aggressive protocols. Furthermore, there are many newer models available now that incorporate information from demographic, clinical, biochemical, imaging, systematic biopsy, and novel molecular markers into one unified predictive model. Neural network technology is also now available and seems very promising in predicting the pathological stage using the above mentioned information. This model will help immensely in patient management.

One very important point I want to make is that it is the biochemical characteristics of the cancer’s DNA (a mutation of our own DNA), plus the internal and external environment that can up-regulate the cancer, causing progression and invasion, and lead to the development of life-threatening cancer. It really doesn’t matter if you remove a local tumor or not. The great cancer physician Eli G. Jones wrote a book on cancer in 1894 called “Cancer – Its causes, symptoms, and treatments.” In it, he states “A surgeon can only cut out what is seen and felt under the knife, while millions of cancer cells grow and multiply in the blood, the nuclei of future cancer. Another fact that the surgeon forgets is that every operation is a shock to the nervous system, it lowers the nerve power, weakens the power of resistance to disease, and thus encourages the invasion of cancer.” With this discovery and understanding, and the role that inflammation plays in angiogenesis, tumor suppressor genes, and various growth factors, modern medicine is just beginning to perhaps recognize this.

“May God hasten the day when it will be considered a crime to cut out a cancer. After forty-three years’ experience with cancer I can honestly say that I have never seen a genuine case of cancer permanently cured by a surgical operation. To cut out a cancer is the worst form of malpractice, for it is only trying to remove the effect without touching the cause. From an extensive correspondence with physicians from every State in the Union I find that the rank and file of the profession are tired and disgusted with operations for cancer, for they have seen them return time and time again. They are more than anxious to find a better and saner method of treatment for cancer that offers at least some hope of a cure.”

Three reasons why I believe in implementing a systemic program, particularly prior to surgery:

1) If you have been successful at shrinking the tumor, or removing it entirely, your long-term prognosis is good; but if you remove the tumor, then start a systemic program, you have no way of knowing how you are affecting the cancer;
2) If you have shrunk the tumor, surgery becomes easier, less invasive, and often spares the need for reconstruction; the smaller the tumor the less aggressive the surgery often needs to be;

3) Because cancer is a systemic disease, treating it upfront and systemically reduces the risk of metastasis.

Recent data from several scientific experiments has concluded that surgery can potentially spread cancer. Four recent separate colon cancer studies found that the primary tumor suppressed angiogenesis in its distant metastasis, and that removal of the primary lesion caused a flare-up in vessel neoformation and thus, enhanced metabolic activity in its liver metastasis.14

Breast cancer surgery can induce angiogenesis and proliferation of distant dormant micrometastases, especially in young patients with positive nodes and more aggressive types of cancer.6-7 In Kidney cancer, which tends to be very aggressive, surgery also appears to spread the cancer, not suppress it.5 Surgery increases vascular endothelial growth factor (VEGF) and other angiogenic growth factors.10-12 Although to date there has been no research regarding prostate cancer surgery spreading the cancer, I would bet that in the more aggressive types it would, and in the slower types it most likely has little barring on outcome. I realize this is totally out of the box but it is what I truly believe. I also want to say I never tell a person to do surgery or not to do it. I simply tell them what I think and that I will support them in any way I can.

Long-term Research Studies on Treatment Outcomes

A number of studies specifically addressed the long-term effectiveness of surgery in localized prostate cancer. Inman and colleagues9 studied 25-year mortality rates after surgery in 849 men followed in the PORT II study. Results were stratified by grade and stage. Younger men (under age 65) with localized prostate cancer had 25-year prostate cancer mortality rates of approximately 19% for Gleason 6 disease, 37% for Gleason 7 disease, and 50% for Gleason 8-10 disease. Compared to a similar historical cohort of men treated with observation,14 the study authors concluded that the survival advantage of surgery appears to offer benefit in men with higher stage disease. None of these studies compare surgery or radiation therapy to my comprehensive protocol. I would love to do a research project comparing my protocols verse surgery or radiation therapy and hopefully this can happen in the very near future.

Surgery verses Radiation

Based on new comparative research, surgery is superior to radiation in localized prostate cancer in terms of prolonging overall and disease-specific survival.15

In a study from Johns Hopkins University in Baltimore, Maryland, Freedland and colleagues examined 379 men who underwent radical prostatectomy and had a biochemical recurrence from 1982 to 2000. They specifically addressed whether time to PSA recurrence after surgery portended worse survival. They found that men with a greater time to recurrence were less likely (hazard ratio, 0.76; 95% confidence interval, 0.66-0.88) to die of prostate cancer than those with a quicker time to recurrence. Specifically, 15-year actuarial survival for men who had a PSA recurrence within 3 years of surgery was 41%, as opposed to 87% for patients who recurred more than 3 years from surgery. In a multivariate analysis that controlled for other confounders, men who had a biochemical recurrence within 3 years of surgery were 2.7 times more likely to die of prostate cancer than those who recurred more than 3 years from surgery.16

Radical Radiation for Localized Prostate Cancer Results in a Late Wave of Metastases

This study investigated whether failure to maintain local control of prostate cancer following radiation therapy increases the likelihood of distant metastasis (DM). The study group included 1469 patients with clinically localized prostate cancer who were treated with radical radiation therapy between 1972 and 1999. Disease outcome was retrospectively reviewed for all patients who received more than 2 years follow-up. The actuarial 10-year local-control rate was 79%. Gleason score was 7 or greater; prostate-specific antigen (PSA) was greater than 15; and presence of T3 or T4 tumors predicted a higher incidence of local failure, designated as palpable recurrence or a positive result on biopsy.

The 10-year distant metastasis-free survival (DMFS) was 74%. Gleason score was 7 or greater, PSA was greater than 15, and the presence of T3 or T4 tumors predicted a higher incidence of distant failure. Local failure was the strongest predictor for DM in a multivariate model. The 10-year DMFS for patients with local control was 77%, compared with 61% for patient with local failure. Median time to distant failure was prolonged in patients with local

Prostate Cancer – Donald Yance
failure compared with patients with locally controlled disease (54 vs 34 months). Hazard rate analysis of the time to DM revealed that patients whose disease is locally controlled have a lower rate of DM which remains constant over time. Patients who ultimately develop local failure have a higher initial rate of DM which increases with time.

The findings suggest that patients with locally persistent prostate cancer are at greater risk for DM. The higher initial risk of DM is associated with both an increased likelihood of subclinical micrometastases before treatment, and with post-treatment tumor embolization. The prolonged time to appearance of DM in patients with local failure, and the increasing risk of DM over time, is most associated with a late wave of metastases from a locally persistent tumor.

Surgery versus Watchful Waiting

Prostate cancer usually has relatively slow growth. Some prostate tumors (15-20%), however, can have very rapid growth. Prostate cancer often metastasizes to lymph nodes and to the bones, but in later stages it can also go to the liver, lung, and even the brain. A radical prostatectomy for early prostate cancer offers no overall survival benefit over watchful waiting; and we know it doesn’t improve quality of life, according to the results of two studies reported in the Sept. 12, 2002 issue of the New England Journal of Medicine. In another more recent study, radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression; but the absolute reduction in the risk of death after 10 years was small and not significant.

Casodex versus Standard Care

Casodex, 50 mg daily, is used in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue, as an anti-androgen therapy for the treatment of Stage D2, metastatic carcinoma of the prostate. In evaluating the efficacy and tolerability of bicalutamide, (Casodex) 150 mg following standard care (radiotherapy, radical prostatectomy, or watchful waiting) in patients with early, non-metastatic prostate cancer, there was no significant difference in overall survival; despite a reduction in the risk of progression by 34% versus standard care alone.

Mechanisms of Hormone Resistance

I want to start by reviewing some of the mechanisms of hormone resistance, which will hopefully help us understand the basis for the relative chemo-resistance seen with advanced prostate cancer, and also how targets are identified for biologic agents.

Most hormone resistant PC is also chemo-resistant, although standard therapy usually is a combination of mitoxantrone and prednisone, which is a palliative regimen. It's been shown in 2 Phase III trials not to prolong survival, but it does slightly improve quality of life. In terms of future cytotoxics, Taxotere (docetaxel) has shown to be the most effective. Chemotherapy does have a place in the treatment of advanced PC but it should be used in combination with botanical and nutritional agents, and possibly targeting drugs based on the tumor pathology report. I think the future is going to be based on the development of new biologic agents that target the molecular basis of resistance and progression.

Progression to androgen independence is a complex and multi-factorial process that occurs in highly heterogeneous tumors. It results from combinations of clonal selection, adaptation, and a number of factors that lead to ligand-independent activation of the androgen receptor. In the past, clonal expansion and adaptive responses were felt to be a black and white world. I think these 2 processes are not mutually exclusive. Genetic instability over time leads to an increase in tumor burden, an increase in heterogeneity, and the ability of subpopulations of cancer cells to respond differentially when confronted by changes in their environment. What's important, though, is that this is a dynamic process. It's not a static process, and it's one in which cancer cells change in response to changes in their environment. Because of this, protocols often need to adapt and change somewhat based on each evaluation. Targeted therapy is based on improved understanding of the biologic mechanisms involved in cancer progression, as well as the internal condition of the patient in response to the cancer. Not only is this going to result in improved activity and specificity from targeted treatment plan, but also from a patient or disease point of view. This is how we can greatly extend the life of those patients with refractory, aggressive, metastatic, prostate cancer.

Testing for Prostate Cancer

The Ups-and-Downs of the PSA
It has been nearly a quarter of a century since the introduction of prostate-specific antigen (PSA) serology as been the standard for screening and monitoring biomarkers for prostate cancer. To reduce the number of unnecessary biopsies resulting from elevated levels of PSA, the sensitivity and specificity of the PSA screening tool must be increased. Proposed methods to increase sensitivity and specificity include reinterpretation of PSA levels as they change over time, paying close attention to individual differences (PSA velocity), and use of more specific markers, such as PSA level divided by prostate volume (PSA density) free PSA levels, and age-specific PSA ranges.25

The validity of PSA as a marker for prostate cancer screening and early detection has been the focus of widespread investigations ever since its development. The death knoll of PSA screening appeared imminent several years ago when a Dr. Thomas Stamey proclaimed that the "PSA was dead as a screening test."26-28 A recent study shows that while PSA measurement remains an important monitoring tool, it performs poorly in distinguishing those who will develop lethal prostate cancer from those at low or no risk of disease progression. "In this study, both baseline PSA and rate of change in PSA during the first 2 years of follow-up carried prognostic information. However, despite extensive exploration of different statistical models, the researchers could not substantiate any PSA curve characteristic as a good classifier of who would develop lethal disease and who would not."113 I do see benefit in checking PSA values more in relation to the indiviual, and as a marker that can be grafted over a long period of time to gauge significant changes; for example the PSA velocity.

The rate at which PSA levels reach a threshold value (PSA velocity) may provide useful information for identifying men who need further evaluation, and/or closer surveillance for the presence of life-threatening prostate cancer. Beginning in 1991, PSA measurements and digital rectal exam were performed every 2-3 years. Their study included 980 men - 856 with no diagnosis of prostate cancer, 104 who had prostate cancer that was not lethal, and 20 who died of prostate cancer. According to the authors, most subjects had initial PSA levels < 4 ng/mL. Results showed that 10 to 15 years before the diagnosis of prostate cancer, PSA levels of men who died of the disease were rising at an exponential rate.29

Results of a recent study conducted through Memorial Sloan-Kettering Cancer Center in New York found that a single total PSA (tPSA) test, done between the ages of 44 and 50, can reliably predict PC up to 20 years afterward. The research team analyzed the long-term predictive power of tPSA, free PSA (fPSA), and human kallikrein 2 (hK2) levels measured between the ages of 44 and 50 years in 21,277 men enrolled in the Malmo (Sweden) Preventive Project between 1974 and 1986. The analysis focused on 462 participants who later developed prostate cancer and 1222 matched controls who did not. The risk of prostate cancer at an older age ranged from 1.0% to 7.5% if the mid-life tPSA was 0.5 ng/mL or lower. Men with a tPSA of 0.51 to 1.0 ng/ml had a 2.5-fold increase in prostate cancer risk compared with men with tPSA levels of 0.5 ng/ml and lower. Men with tPSA levels of 2.0 to 3.0, which are often considered within the normal range, had more than 19-fold increase in PC risk compared with men with tPSA levels of 0.5 ng/ml and lower. Free PSA and hK2 levels at baseline were also significant predictors of PC. If this data is correct it suggests that early biochemical changes (ie, slightly increased release of PSA and hK2 into blood) indicate a predisposition to PC that may be detectable long before it manifests.30

I believe the PSA should be checked, monitored, and charted over time; together with other effective screening tests, such as the free/total PSA, the PAP (prostatic phosphatase), and the new urine test, called a Prototype Aptima PCA3 molecular urine test.31

**PCA3 Gene Urine Test**

Expression of the *PCA3* gene is upregulated in prostate cancer and can be detected in urinary sediment after DRE. A group of investigators from California evaluated the PCA3 test in 147 men with either treated cancer (post prostatectomy), benign prostatic hypertrophy, untreated prostate cancer, or normal prostate; the last 3 were based on transurethral ultrasonography (TRUS) biopsies. There was near-complete separation of the groups on the basis of only PCA3 results. With biopsy as the reference method, the sensitivity was 62% and the specificity 82%. These promising results indicate that PCA3 may be used in conjunction with PSA serology for prostate cancer detection.32-34

**New Blood Test for PC Showing Promise**

Testing for a blood protein called early prostate cancer antigen (EPCA)-2 may overcome some of the limitations of current practices. Several groups have been working to identify new biomarkers for prostate cancer, and the EPCA-2 test is showing great potential as a new serum-based test. EPCA-2 is the second prostate-cancer marker, identified by the same researchers, that has outperformed PSA; EPCA-1 being the other. The efficacy of EPCA-1 as a test of
biopsy samples is currently being studied.\textsuperscript{114}

**ProstaScint**

ProstaScint is an immunoconjugate containing a monoclonal antibody (MAb) directed toward prostate-specific membrane antigen (PSMA). Expression of this antigen is higher in prostate adenocarcinoma cells than in nonmalignant tissue and higher in metastatic lesions than in primary tumors. ProstaScint is indicated for use in newly diagnosed patients, with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation (e.g. chest x-ray, bone scan, CT or MRI), who are at high risk for pelvic lymph node metastases. ProstaScint may also be used in postprostatectomy patients with rising PSA and a negative or equivocal standard metastatic evaluation, in whom there is a high clinical suspicion of occult metastatic disease. The information provided by ProstaScint should be considered in conjunction with other available diagnostic information. ProstaScint provides diagnostic information in high-risk patients that complements PSA, Gleason score, and pathological stage. An abnormal ProstaScint scan may detect metastatic prostate cancer in lymph nodes or other sites.\textsuperscript{35-37}

**Gleason Score: an expert review**

A modification of the Gleason scoring system for men with Gleason 7 disease revealed a difference in outcome after radical prostatectomy.\textsuperscript{38} The Gleason score is a critical item; it is used as a variable in virtually every prognostic and treatment algorithm. An accurate GS mandates an expert pathology opinion from a PC pathology expert. The premier person is David Bostwick. Others that might do high-level biomarker analysis using the tissue block include Oppenheimer, Dianon and UroCor. Here is information on a very good lab for reading the Gleason score.

David Bostwick, MD, Bostwick Laboratories, 2807 North Parham Road, Suite 114, Richmond, VA 23294 1-800-214-6628, www.bostwicklaboratories.com <http://www.bostwicklaboratories.com>

**Prostatic Acid Phosphatase (PAP) and Acid Phosphatase (ACP): Important Markers in PC**

I am a strong believer in running routine PSA, and grafting the results over many years; as well as running baseline prostatic acid phosphatase (PAP), and routinely checking this number as well. The PAP is a much less sensitive test, though more reliable; whereas the PSA can tend to be altered from causes other than cancer, and it also has a different scale from individual to individual.

The value of pretreatment PAP to predict pathological stage and recurrence in radical prostatectomy cases is still very relative to disease reoccurrence and outcome.\textsuperscript{39} In one study conducted between February 1, 1990 and May 3, 1996, pretreatment PAP was measured in 295 patients who underwent radical prostatectomy. From February 1, 1990 to May 17, 1992, PAP assays were analyzed individually, and the results were combined with pretreatment prostate specific antigen (PSA) values to assess the ability to predict organ confined prostate cancer, and serological recurrence after radical prostatectomy. PAP testing was not of value for predicting organ confined disease or positive margins. However, this test was useful for predicting the first serological PSA recurrence in the 3 periods (77 to 85% correct) and overall (82% correct, p < 0.001, odds ratio 6.06). The Kaplan-Meier disease-free survival rate at 4 years was 78.8% for men with PAP less than 3 ng./ml., and 38.8% for those with PAP 3 ng./ml. or greater; which was significant when pretreatment PSA was less than 10 ng./ml. (p = 0.047), 10 ng./ml. or greater (p = 0.012) and overall (p < 0.001). PAP testing added prognostic information to pretreatment PSA values and it was an independent predictor of recurrence. The widely available and inexpensive PAP assays are predictors of recurrence and overall (p < 0.001). PAP testing added prognostic information to pretreatment prostate specific antigen (PSA) >15 ng/ml (32 patients), or elevated serum PAP (25 patients). Patients received 41 Gy conformal EBRT to a limited pelvic field, followed 4 weeks later by a 103Pd boost (prescription dose 80 Gy). Biochemical failure was defined as a PSA greater than 1 ng/ml (normal <4 ng/ml). The overall actuarial freedom from biochemical failure at 4 years after treatment was 79%. In Cox-proportional hazard multivariate analysis, the strongest predictor of failure was elevated pretreatment PAP (p = 0.02), followed by Gleason score (p = 0.1), and PSA (p = 0.14). The PAP was the strongest predictor of long-term biochemical failure. It may be a more accurate indicator of micrometastatic disease than PSA, and as such, we suggest that it be reconsidered for general use.\textsuperscript{40}

In another study, one hundred twenty-four consecutive patients with Stage T2a-T3 prostatic carcinoma were treated from 1992 through 1995. Each patient had at least one of the following risk factors for extracapsular disease extension: Stage T2b or greater (100 patients), Gleason score 7-10 (40 patients), pretreatment prostate specific antigen (PSA) >15 ng/ml (32 patients), or elevated serum PAP (25 patients). Patients received 41 Gy conformal EBRT to a limited pelvic field, followed 4 weeks later by a 103Pd boost (prescription dose 80 Gy). Biochemical failure was defined as a PSA greater than 1 ng/ml (normal <4 ng/ml). The overall actuarial freedom from biochemical failure at 4 years after treatment was 79%. In Cox-proportional hazard multivariate analysis, the strongest predictor of failure was elevated pretreatment PAP (p = 0.02), followed by Gleason score (p = 0.1), and PSA (p = 0.14). The PAP was the strongest predictor of long-term biochemical failure. It may be a more accurate indicator of micrometastatic disease than PSA, and as such, we suggest that it be reconsidered for general use.\textsuperscript{41}
Although serum acid phosphatase (ACP) was once used as an effective marker for advanced prostate cancer, with the development of assays for PSA, the use of ACP has greatly diminished, but this has been a big mistake in my opinion. This study investigated the prognostic value of preoperative serum ACP in predicting prognosis for men with localized prostate cancer following radical retropubic prostatectomy (RRP). Of 2293 men treated from 1982 to 1998, 1681 men had a preoperative ACP measurement using an enzymatic assay. We analyzed the actuarial freedom from biochemical (PSA) progression following RRP according to ACP levels. We used multivariate logistic regression, and proportional hazards models to determine the independent prognostic value of ACP level with respect to pathologic stage and biochemical recurrence. ACP was not an independent predictor of organ confinement or lymph node involvement in the multivariate logistic regression models using preoperative variables. However, in the proportional hazards model, ACP was an independent predictor of tumor recurrence following RRP, and there was a statistically significant improvement in biochemical, recurrence-free survival for men with lower levels of ACP (P <0.001).42

Osteoprotgerin

Serum osteoprotgerin (OPG) is the most effective marker in detecting bone metastatic spread, as bone markers in serum of patients with prostate cancer, for early detection of bone metastases and their usefulness as predictors of PCa-caused mortality.43

A more recent summarized review stated that OPG, PAP, and/or ACP are important markers that should continue to be used in a total workup analysis for men with prostate cancer.44

Zinc-alpha2-glycoprotein Expression: a Predictor of Metastatic Prostate Cancer Following Radical Prostatectomy

A decrease in zinc-alpha2-glycoprotein (AZGP1) mRNA levels in malignant prostate epithelium was previously shown to predict biochemical recurrence, as defined by rising levels of serum PSA after radical prostatectomy. We assessed the reliability with which AZPG1 expression could predict clinical recurrence and metastatic progression. Using immunohistochemical methods, we analyzed AZPG1 expression in malignant prostate epithelium in prostatectomy specimens from 228 prostate cancer patients. Low (i.e., absent or weak) AZGP1 expression was associated with clinical recurrence (defined as confirmed localized recurrence, metastasis, or death from prostate cancer; hazard ratio [HR] = 4.8, 95% confidence interval [CI] = 2.2 to 10.7, P<.001), and with bony metastases or death from prostate cancer (HR = 8.0, 95% CI = 2.6 to 24.3, P<.001). Among the 17 patients in the cohort in whom clinical recurrence was associated with short PSADT, absent or weak AZGP1 expression was observed in 13 patients. If these preliminary findings are validated in independent cohorts, the measurement of AZGP1 levels in radical prostatectomy specimens may permit an accurate and timely assessment of risk of metastatic progression after radical prostatectomy.45

Chromogranin A

The prognostic significance of plasma chromogranin A (CgA) was assessed in a series of consecutive prostate cancer patients with hormone-refractory disease. One hundred and eight patients with newly diagnosed, hormone-refractory prostate cancer entered the study. Plasma CgA levels and other biochemical parameters, such as serum prostate specific antigen, serum alkaline phosphatase, serum lactate dehydrogenase, serum albumin, and hemoglobin concentration, were measured at baseline (i.e. when hormone refractoriness occurred) and their prognostic role was evaluated together with patient performance status, Gleason score (at diagnosis of prostate cancer), and the presence of visceral metastases. Furthermore, plasma CgA was prospectively evaluated in 50 patients undergoing chemotherapy. At baseline, 45 patients (43.3%) showed elevated CgA values. Plasma CgA negatively correlated with survival, either in univariate analysis (P=0.008), or in multivariate analysis, after adjusting for previously mentioned prognostic parameters (P<0.05). In the patient subset undergoing chemotherapy, median CgA (range) values were 13.3 (3.0–141.0) U/l at baseline, 19.1 (3.0–486.0) U/l after 3 months, 20.8 (3.0–702.0) U/l after 6 months, and 39.4 (3.0–414.0) U/l after 9 months (P<0.01). The corresponding supranormal rates were 17/50 (34%), 23/50 (46%), 26/50 (52%), and 34/50 (68%) respectively (P<0.005). Elevated plasma CgA levels are frequently observed in prostate cancer patients with hormone-refractory disease, and correlate with poor prognosis.46

In another study, CgA level was measured in plasma samples which were obtained from 40 patients with prostate cancer. Overall, CgA was elevated in 18 patients (45%), including 25% of the patients with organ confined disease, 52.9% with locally advanced disease, 71.4% of the patients with metastases, 75% of the patients with hormone refractory prostate cancer, and 23.1% of patients with hormone sensitive disease (p = 0.009). Mean CgA and PSA
levels among patients with elevated CgA was 100.2 u/L (27-717), and 301 ng/ml (4.5-1450) respectively; in comparison to 18.8 u/L (14-26) and 14.7 ng/ml (2.6-59.7) respectively, in patients with CgA within the normal range (p = 0.05). PSA at the time of CgA sampling did not differ among the two groups. In this study, high plasma CgA levels correlated with known poor prognostic factors, including advanced and metastatic disease at the time of presentation, high pretreatment PSA levels, and hormone refractoriness.\(^\text{37}\)

In a 3rd study, involving one hundred and eight patients with newly diagnosed hormone-refractory prostate cancer, CgA was prospectively evaluated in 50 patients undergoing chemotherapy. At baseline, 45 patients (43.3%) showed elevated CgA values. Plasma CgA negatively correlated with survival, and again the conclusion was that elevated plasma CgA levels are frequently observed in prostate cancer patients with hormone-refractory disease and correlate with poor prognosis.\(^\text{48}\)

If AZGP1, CgA, and other markers which I will discuss were routinely run, we would begin to know which men, regardless of what conventional treatment they do or don’t do, would be at risk for life-threatening metastatic PC. If a man was assessed, and showed a high risk of metastatic cancer, we then could be more aggressive with systemic therapies up front rather then wait until the cancer takes a stronger foothold.

**Hypermethylation, an Independent Prognostic Factor in PC Reoccurrence**

Biomarker analyses were done retrospectively on tumors from 74 prostate cancer patients, all with a Gleason score of 3 + 4 = 7 and minimum follow-up period of 7 years. Using quantitative methylation-specific PCR, we analyzed six gene promoters in primary prostate tumor tissues. Time to any progression was the primary end point, and development of metastatic disease, and/or death from prostate cancer was a secondary point. At a median follow-up time of 9 years, 37 patients (50%) had evidence of recurrence: biochemical/prostate-specific antigen relapse, metastases, or death from prostate cancer. In the final multivariate analysis for time to progression (TTP), the significant factors were age > 60 [hazard ratio (HR), 0.4; 95% confidence interval (95% CI), 0.2-0.8; P = 0.01], **hypermethylation of GSTP1** and **APC**. In another multivariate analysis, a profile of hypermethylation of APC and cyclin D2 hypermethylation was significant as well: if either one was hypermethylated, or if both were hypermethylated. Methylation status of selected genes in prostate cancer patients can help predict time to recurrence in Gleason 7 patients undergoing prostatectomy.\(^\text{49}\) Eat a diet rich in green vegetables and fruits containing folic acid, and supplementing with various methyl-donor vitamins. B-6, B-12, and folic acid assist in healthy methylation.\(^\text{50}\)

**Triple Hormonal Blockage**

In conventional medicine, after PC has returned following surgery or radiation therapy, or even as a first treatment in older men, hormone (androgen) blockage therapy is then the next route of treatment. Hormone blockage therapy for prostate cancer is a major cause of male hypogonadism. Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of treatment for metastatic prostate cancer and a routine part of management for many men with locally advanced or recurrent, nonmetastatic prostate cancer. More than 500,000 men are treated with a GnRH agonist annually in the US.\(^\text{115}\)
Androgen deprivation causes an increase in insulin resistance, a contributor to PC development and progression; and also heart disease, diabetes, stroke, and neurological disease as well. So the question is: when do the benefits outweigh the risk? I normally suggest doing whatever you can do naturally to either reverse the cancer, stop the growth, or dramatically slow the progression. If you are not 100% successful, then you may want to consider intermittent hormonal therapy (IHT) with Avodart (5 alpha reductase blocker), which lowers dihydrotestosterone (DHT). The next step would then be adding a Gonadotropin-releasing hormone (GnRH) agonist, such as Lupron. Rather than giving these drugs at the recommended doses forever, or until the PC returns, you would pulse dose them. Pulse dosing would depend on many factors, but an example would be three months on and 2-3 months off. You could stay on the Advodart and just pulse dose the Lupron. There is little research on this but I am seeing some wonderful results with a group of men using this type of IHT in conjunction with my protocol. However the majority of men I treat do not need to implement this at all.

There are many advantages to this therapy, not the least of which is sexual function. Men on standard hormone blockage therapy for more than two years run a strong risk of being hypogonadal forever. Whereas men on hormone blockage therapy for one year or less are likely to have restoration of normal testicular function in the future.

The other issue is that most men on standard hormone therapy become refractory as early as one year. What this means is that although initially successful, antiandrogen therapy eventually fails and androgen depletion independent (ADI) disease emerges. The PC has learned to proliferate even with testosterone being blocked. One of many factors that contribute to this is amplification of the androgen receptor. So to a degree, ADI prostate cancers still rely on a functional androgen receptor (AR).

Although most conventional doctors would strongly suggest using high dose casodex, at 150 mg. per day, for further suppression of testosterone, I prefer to hold off on use of this drug. This is because Casodex can, and most likely will, cause a switch from an antagonist of the androgen receptor to an agonist. p300 is required for ADI activation of the AR and is up-regulated in PC, in which its expression is associated with cell proliferation, and it predicts aggressive tumor features. Short-term and long-term androgen deprivation results in marked up-regulation of p300 expression. Increased p300 expression upon androgen starvation is crucial for prostate cancer cell proliferation, as loss of p300 expression severely reduces expression of cyclins governing G\(1\)-S and G\(2\)-M cell cycle transition, and decreases 5-bromo-2'-deoxyuridine incorporation. This is why I prefer to wait on hormone therapy entirely if possible, and when called for be as conservative as possible.

**Bone Loss in Prostate Cancer**

Osteoporosis is an important and preventable adverse effect of androgen deprivation therapy for prostate cancer, scientists in the United States report. Androgen deprivation therapy, by either bilateral orchiectomies or administration of a gonadotropin-releasing hormone agonist, decreases bone mineral density and increases fracture risk in men with PC. Most people would be surprised to known that men experience one-third of all hip fractures, and mortality rates after hip fractures are higher in men than women.

**Testing for Bone Mineral Density**

Quantitative CT bone densitometry is superior to DEXA in evaluating bone density in middle to older age patients with PC. The DEXA scan, considered to be the "gold standard" in BMD, is known to be significantly affected by arthritic changes and vascular calcifications, and falsely "normalizes" the actual BMD. In light of the significance of bone integrity in the natural history of PC, QCT bone densitometry should be the preferred method of investigation.

**Bisphosphonates for Bone Protection in PC**

Treatment-related osteoporosis can be prevented by intermittent administration of either intravenous pamidronate or zoledronic acid. Pamidronate (60 mg intravenously every 3 months) prevents bone loss during androgen deprivation therapy. Zoledronic acid (4 mg intravenously every 3 months) not only prevents bone loss but also increases bone mineral density.

A recent, randomized, double-blind, placebo-controlled, partial crossover trial was conducted. The first-year, was a preplanned analysis of a 2-group, parallel-design phase;112 men with nonmetastatic prostate cancer receiving ADT were given Alendronate, 70 mg once weekly, or placebo. All patients received calcium and vitamin D supplementation. Bone mineral density of the spine and hip and markers of bone resorption and formation were...
analyzed. At baseline, 39% of men had osteoporosis and 52% had low bone mass. In men treated with alendronate, bone mineral density increased over 1 year by 3.7% (95% CI, 2.8% to 4.6%; P < 0.001) at the spine and 1.6% (CI, 0.4% to 2.8%; P = 0.008) at the femoral neck. Men in the placebo group had losses of 1.4% (CI, -2.7% to -0.03%; P = 0.045) at the spine and 0.7% (CI, -1.5% to 0.01%; P = 0.081) at the femoral neck. At 12 months, the difference between the 2 groups was 5.1 percentage points (CI, 3.5 to 6.7 percentage points; P < 0.001) at the spine and was 2.3 percentage points (CI, 1.0 to 3.7 percentage points; P < 0.001) at the femoral neck. Bone turnover showed statistically significant decreases with active therapy compared with placebo. The groups did not differ in adverse events. Bone loss that occurred with ADT was prevented and improved with once-weekly oral alendronate.206

Supplementation with Vitamin D; anabolic botanicals, such as Epimedium, Rhaponticum c., Mumie, Royal Jelly; EPA/DHA-rich fatty acids; nutrients including B-12 and folic acid; anabolic nutrients, such as specific amino acids and boron, as well as ipriflavone, strontium, and vitamin K. Boron is specific for bone health and may also possess some prostate cancer inhibiting effects.

**TGF-ß1 Level: an important Prognostic Marker**

Preoperative plasma levels of transforming growth factor ß1 (TGF-ß1) "strongly predicts" cancer progression in patients who undergo radical prostatectomy. Preoperative identification of patients with a high probability of disease progression might help "spare men the morbidity" of ineffective radical prostatectomy or radiation therapy.25-35 To investigate, the researchers followed 120 patients who had undergone radical prostatectomy because of clinically localized prostate cancer. TGF-ß1 levels were correlated with outcomes and compared with levels in 44 cancer-free controls, 19 men with prostate cancer metastatic to regional lymph nodes, and 10 with prostate cancer metastatic to bone. The mean plasma TGF-ß1 level in those with lymph node metastases (14.2 ng/mL) or bone metastases (15.5 ng/mL) was higher than that in prostatectomy patients (5.2 ng/mL) and healthy controls (4.5 ng/mL). Preoperative TGF-ß1 levels were significantly elevated in patients with biochemical progression irrespective of the pathologic stage. This elevation, the investigators conclude, may be due to "an association with occult metastatic disease present at the time of radical prostatectomy." TGF-ß1 should be included in preoperative nomograms for prediction of progression.36

TGF-beta(1) stimulates migration/invasion of mouse transformed keratinocytes and increases urokinase (u-PA) expression/secretion. Two naturally occurring inhibitors, genistein (in isoflavones from soy) and curcumin (from turmeric), inhibit protein tyrosine kinases that could stimulate the enhancement of u-PA levels induced by TGF-beta(1). Genistein and curcumin also blocked the expression TGF-beta(1)-induced synthesis of fibronectin, an early responsive gene to the growth factor.37 **Curcumin,** has demonstrated to an elite chemopreventive agent against prostate cancer effecting global gene expression, growth factors and their receptors, including TGF-B1; blocking its activation at multiple sites.38 **Green tea extract,** 40% EGCG, has a significant effect on TGF-beta expression, as well as cell cycle regulatory proteins involved in suppression of prostate cancer.39 The comprehensive diet and supplement foundation program within the Triphasic System addresses cell cycle regulatory pathways modifying genes in cancer.

Patients can be tested for TGF-B1 and also IL-6sR by Josie Beck:
Tumor Markers Division
Scott Department of Urology
Baylor College of Medicine
One Baylor Plaza, Room N730
Houston, TX 77030
Phone 713-798-7264
Fax 713-798-1891
Attention Laboratory Director: Dolores Lamb, Ph.D and Medical Director, Kevin M. Slawin, MD

**Androgens, Androgen Receptors, and Prostate Cancer**

The observation that prostate cancer is an endocrine-dependent tumor was first made in the 1940s when Huggins and Hodges showed that castration was effective in reducing the symptoms of metastatic cancer.60 Androgens, necessary for normal prostate development and function, have been reported to increase oxidant production in prostate cancer cells.61, 62 When prostate cancer growth first begins it is primarily regulated by androgens, and therefore androgen ablation therapy, by surgery, radiation, or hormone blocking drugs, is carried out as the first line of treatment. However, prostate cancer often relapses and can become androgen independent; in some cases within a few years, while other times over many years.63 For many older men this process can be so slow that they will die with cancer rather then because of it. What is most impressive is that if men would implement my natural treatment-
plans they would not only be spared the devastation of the progression of prostate cancer, but their overall health would improve dramatically, and they would live longer and healthier because of prostate cancer.

Many men are faced with heart disease, hypertension, elevated lipids, homocysteine, etc… and it doesn’t faze them, but for whatever reason the “C” word does. We need to take a much more thorough and deep look into people and the cancer they manifest, rather then just cut or burn them. This is the approach I take and I am calling the system the “Triphasic Model.” Do you realize that hormone deprivation therapy increases the risk of many diseases such as depression, osteoporosis, diabetics, heart diseases, cachexia, etc…? Because of this, the treatment of the disease, prostate cancer, can detract from the ultimate goals. Goal #1: increase quality-of-life, and goal # 2: increase lifespan. I am getting ahead of myself so let me return to the role androgens play in prostate cancer and health.

The role of androgens in prostate cancer is a bit misunderstood. Let me explain, for one, why it is that younger men with high testosterone levels seldom get prostate cancer, but as men age the risk goes up and up while the testosterone level goes down? Two reproductive hormone changes that occur in men while they age, that contribute to an increase in prostate cancer risk with age and promote prostate cancer growth, are dihydrotestosterone (DHT) and estrogen via the conversion through aromatase. The importance of the role that testosterone and DHT play in the development of both the normal and the malignant prostate gland is critical to understanding PC development and progression.

**Dihydrotestosterone (DHT): an important marker for prostate cancer**

Testosterone, being the major circulating androgen hormone in men, is mostly bound to sex hormone-binding globulin (SHBG). The remaining free testosterone exerts the biological effects. After synthesis in the Leydig cells of the testes, free testosterone enters the prostate gland where it is converted to DHT. This reaction is catalyzed by the membrane-bound enzyme, steroid 5-alpha reductase (SRD5A), an important target of botanicals (as well as drugs) in PC treatment and prevention. Two isoenzymes have been described, SRD5A1 and SRD5A2, with SRD5A2 being the predominant enzyme in the prostate gland. The 2 main types of receptors within the prostate cell are type 1 and type 2 5 alpha-reductase. Type 2 is the predominant form, but type 1 is still present. Once formed, DHT binds to the intracytoplasmic androgen receptor, and the receptor–androgen complex is then translocated to the cell nucleus. This complex binds to DNA and leads to increased protein synthesis, and eventually cellular proliferation. So DHT promotes prostate-cell proliferation and suppresses apoptosis, blocking the programmed cell-death process. It also increases vascularization and when something grows, it needs a vascular supply, so we suspect that DHT is important.

DHT maintains the balance between cell proliferation and cell death. Furthermore, early studies suggested that the suppression of DHT might inhibit the carcinogenic transformation of prostate cells. However, the emergence of prostate cancer with a higher grade for patients treated with finasteride (Proscar), the first 5-alpha-reductase inhibitor drug introduced, may be in favor of the hypothesis that decrease of DHT is associated with more aggressive tumors, although finasteride inhibited PC overall.

Finasteride, which was introduced with much fanfare about 10 years ago, dosen’t really work quite so well; but we learned that it tends to work in men with larger glands, and it takes a while to work, about 6 to 9 months before you have noticeably improved symptoms. The other thing to remember is that PSA is decreased about 50% on 5-alpha-reductase inhibitors because they shrink the gland. It makes sense. It cuts the glands down; the glands make PSA; therefore, your PSA is going to be affected.

There is another drug more recently introduced on the market called dutasteride (Avodart). It blocks both type 1 and type two 5-alpha-reductase enzymes, with a much more rapid decrease in DHT and more rapid relief of symptoms. This is important because Avodart is an alpha-blocker that works very well and is also a better 5-alpha-reductase inhibitor.

**The Paradoxical Effects of Androgens and Prostate Cancer**

Testosterone levels decrease with age and elderly men present a partial androgen deficiency; yet prostate cancer increases with age. The evolution of androgen deficiency has been estimated to be 16.2% (40–49 years), 20% (50–59 years), 22.6% (60–69 years), and 26% (80 years and more). Testosterone deficiency is associated with multiple deregulations that can lead to such symptoms as decreased libido, loss of muscle mass, osteoporosis, decreased cognitive ability, and depression.

Clinical studies have shown that low free testosterone levels in serum is associated with aggressive prostate cancer,
such as has been observed in men with prostate cancer under prostate cancer chemoprevention by finasteride. These data suggest that an androgen pathway disruption in the prostate is responsible for cell deregulations that may be associated not only with apoptosis of differentiated prostatic cells, but also with potential cell transformation. The effect of androgen-blockage therapy for prostate cancer induced in a short time is that the cancer is suppressed. However with time, cells adapt to low levels of androgens leading to the evolution of an androgen-independent tumor, which is more aggressive and most often fatal, as I have previously stated. One hypothesis is that such mechanisms could be initiated in elderly men with an androgen deficiency, and perhaps through the use of botanical adaptogens and specific endocrine enhancers, you could prevent prostate cancer. Many herbs, such as Epimedium, Pygium, Saw palmetto, and Panax ginseng, known as “male tonic” herbs, have demonstrated an inhibitor effect on prostate cancer. An encouraging recent study performed on rats demonstrated a protective effect of DHEA for prostate cancer. The stress hormone, cortisol, which is the opposing hormone to DHEA, may play a role in the development of prostate cancer. Patients with newly diagnosed, untreated PC yielded significantly higher cortisol levels compared to those without PC.

Hormonal Control of Androgen Receptor Function Comes Through SIRT1.

Sirtuins are involved in lifespan extension of model organisms through interactions with the insulin/IGF-like pathway; and with biologic mechanisms underlying caloric restriction, the dietary manipulation of organisms ranging from yeast to mammals that extends lifespan.

The androgen receptor (AR) is a ligand-regulated modular nuclear receptor governing prostate cancer cellular proliferation, differentiation, and apoptosis in response to androgens, including dihydrotestosterone (DHT). SIRT1 antagonists induce endogenous AR expression and enhance DHT-mediated AR expression. SIRT1 binds and deacetylates the AR at a conserved lysine motif. Human Sirtuin 1(hSIRT1) repression of DHT-induced AR signaling requires the NAD-dependent catalytic function of hSIRT1 and the AR lysine residues deacetylated by SIRT1. SIRT1 inhibited coactivator-induced interactions between the AR amino and carboxyl termini. DHT-induced prostate cancer cellular contact-independent growth is also blocked by SIRT1, providing a direct functional link between the AR, which is a critical determinant of progression of human prostate cancer, and the sirtuins.

Resveratrol, the phenolic compound found in wine, has shown to suppress prostate cancer in a diversity of ways. One of the mechanisms includes the inhibition of insulin responses in a SirT1-dependent pathway. Another way is through its inhibition of insulin-signaling pathways, independently of its activation of SirT1 histone deacetylase. Resveratrol also regulates PPARalpha, a transcriptional factor that regulates gene expression by acting as an insulin sensitizer, and which has shown significant protection from cardiovascular disease in humans.

Estrogens and the Aromatase Enzyme in Prostate Cancer

The normal growth and development of the prostate requires the presence and action of androgens, which are also known risk factors in the origins of benign and malignant prostate disease. Aromatase breaks the bonds on testosterone and creates estrogen. As stated before, the incidence of prostate disease increases with age when serum androgen levels are in decline and emerging evidence suggests that estrogens may also be important in the normal prostate, as well as in the etiology of prostate disease. Testosterone is metabolized into estrogens, stimulating the growth of the fibromuscular tissue of the prostate. In a man growing older, the estrogen-androgen ratio changes in favor of the estrogens. My approach to prostate cancer is not to eliminate testosterone; this only delays the cancer (a kind of “honeymoon effect”) and often causes a more aggressive phenotype to occur that in the end has not contributed to a higher quality of life or a longer life. Normalization to a more youthful state of endocrine balance using botanical adaptogens works by lending a helping hand to the entire endocrine-hormonal system, leading to harmonious hormone balance both in the prostate itself and throughout the entire body. Testosterone is vital to a man’s health and well-being and is associated with a long and disease-free life. Low testosterone in men is linked to a great many diseases, most importantly heart disease.

Testosterone is an essential hormone for health. Maintaining healthy testosterone levels is vitally important to physical strength. It is known to increase de novo protein synthesis as well as muscle mass, and is important for the regulation of muscle-to-fat ratio. Enhancing testosterone in older people can lead to a reduction in body fat, particularly visceral body fat, which as I stated earlier is an important determining factor to health and lifespan. Enhancement of testosterone increases libido in men, and increases libido and sexual performance in hypogonadal men. Testosterone also possess an anti-depressant effect as evidenced by improved mood and a greater sense of well-being in both hypogonadal and older men.

I do not advocate testosterone replacement therapy. I recommend anabolic botanical agents that naturally build the entire neuroendocrine system in a safe, harmonious, and cooperative manner.
Both types of estrogen receptor subtypes (ERα and ERβ) are present in the prostate, demonstrating that the gland responds directly to estrogens. Recent data suggests that estrogens play a role in prostate disease, demonstrating that high doses of estrogens induce premalignant dysplasia; and in combination with high doses of androgens, malignancy. The production of estrogens from androgens is mediated by the aromatase enzyme, the aberrant expression of which plays a critical role in the disease process in other tissues, most notably the breast. The prostate expresses aromatase within the stroma of benign tissue, while in malignancy there is an induction of epithelial expression with altered promoter utilization. The presence of aromatase in the prostate and its aberrant expression in prostate cancer is significant and should be considered a target for prostate cancer treatment.\(^88\)

### Endocrine Disruptors

Endocrine disruptors are synthetic chemicals found in pesticides and some plastics that can enter the body through the food chain and interfere with hormone balance, and disturb proper endocrine health. When the level of endocrine disruptors in the body rises, so too does body mass index, and with it the risk of several cancers, fibroid tumors, endocrine-related diseases, and infertility, to name a few. The rise in breast cancer in men is thought to be a result of these hormone-imitating toxins.\(^89\)

Many of these chemicals mimic estrogen. They have been labeled xenoestrogens, and they elicit a reduction in male hormones and lead to higher levels of fat. Xenoestrogens, which have been implicated in a variety of medical problems, act in part as false messengers that disrupt the process of reproduction.

The last six decades have witnessed a massive introduction of hormonally active, synthetic chemicals into the environment leading some to postulate that the diverse outcomes documented in human and wildlife populations might be the result of extemporary exposure to xenoestrogens during development. In other words, observations of disturbances in wildlife have implicated estrogenic exposure. Continuing evidence of the feminizing effects of xenoestrogens on a range of wildlife species increases the need to assess the human health risk of these estrogen-mimicking compounds.\(^90\) In male traffic policemen, occupational exposure to urban pollutants caused alterations on 17-alfa-hydroxy-progesterone plasma levels, resulting in related diseases, including PC.\(^91\)

The estrogen-mimic bisphenol-A (BPA) is used as a model agent for endocrine disruption. BPA is used in the manufacture of polycarbonate plastics and epoxy resins from which food and beverage containers and dental materials are made. Perinatal exposure to environmentally relevant BPA doses results in morphological and functional alterations of the male and female genital tract and mammary glands that predispose the tissue to earlier onset of disease, reduced fertility, and breast and prostate cancer.\(^92\)

The anabolic effects of this herbal and nutritional program will lead to profound changes in body composition, mental clarity, vitality, mood, bone health, and one’s overall sense of well-being. Nutritional status plays a significant role as well in the production of energy in muscle and other tissue. Diet, sleep, stress-reducing techniques, exercise programs, and a reduced stress load can all contribute to maintaining healthy muscle tissue and improving mitochondrial energy production, as well as creating an endogenous environment, non-conductive for cancer growth. Those of us that promote a more natural way to optimal wellness need to look more to the plant world for enhancement of health rather then to drugs and replacement hormones.

### Elevated Prolactin promotes Prostate Cancer

There is a recent understanding of the correlation between prolactin, a hormone produced by male and female pituitary glands, and how it promotes growth of cells in the prostate. Pioneering work by Dr. Nevalainen and colleagues established that prolactin serves as a local growth factor for prostate cells, and that Stat5 is the specific signaling device for prolactin in prostate cells. In other words, Stat5 acts as an internal signaling device within the cell, receiving and sending messages of prolactin to the cell's DNA.

In one study, Nevalainen explored what happens if the activation of Stat5 in prostate cancer cells is blocked. Using human prostate cancer cell lines and viral gene delivery of an inhibitory mutant of Stat5, Nevalainen and her colleagues found that blocking the activity of this protein in prostate cancer cells will trigger extensive cell death.\(^93\)

The implications of increased prolactin secretion as an adverse effect for regulatory toxicology of drugs and chemicals, and in high-risk patients receiving therapeutic drugs with hyperprolactinaemic side effects, is becoming more and more evident. Alteration of prolactin level is a novel mechanism that requires consideration in endocrine disruption research, since both endogenous estrogens and also xenoestrogens stimulate prolactin secretion or affect
prolactin receptors. These events can contribute to hormonal dysregulation in prostate cancer.\textsuperscript{94}

The herb Mucuna (\textit{Mucuna pruriens}) increases dopamine, which in turn inhibits/reduces prolactin production. Mucuna is the richest natural source of L-dopa,\textsuperscript{95-97} and the extract I use contains 40\% L-dopa. Several studies have confirmed its ability to raise dopamine levels, which is important for growth hormone and testosterone production.\textsuperscript{98-103} The enhancement of \textit{growth hormone and testosterone} are important contributions to Mucuna’s overall anti-aging effects.\textsuperscript{104-111} Concentrations of serotonin have also been found in the pod, leaf, and fruit.\textsuperscript{112} Common sage, which can be added to herbal teas, is also helpful at reducing prolactin as well.

\textbf{Section III}

\textbf{Growth Factors Up-Regulated in Prostate Cancer}

\textbf{Basic Fibroblast Growth Factor (bFGF)}

Basic fibroblast growth factor (bFGF), a potent angiogenic factor, is thought to play an important role in the induction of microvasculature. One study evaluating bFGF expression in prostatic carcinoma, assessed by enzyme-linked immunosorbent assay (ELISA), concluded that increased bFGF is associated with a more aggressive tumor phenotype.\textsuperscript{1,2} bFGF also increased microvessel density which further correlates with higher Gleason grade.\textsuperscript{3} \textit{Curcumin} inhibits angiogenesis in vivo, in part, by down-regulating bFGF.\textsuperscript{4}

\textbf{EGFR and HER2 neu Gene Amplification and Expression in PC}

Relapse during androgen withdrawal therapy is a significant cause of morbidity and mortality from prostate cancer. Androgen receptor mutations (6-10\%) and amplifications (20-30\%) explain relapse in some patients, but in approximately 70\% of cases alternative mechanisms must be invoked and preliminary evidence points to type I receptor tyrosine kinases playing a role in mediating hormone escape. In one study, EGFR and HER2 gene amplification and expression were analyzed in a cohort of matched tumor pairs (one taken before and one after hormone relapse) from 49 prostate cancer patients. No EGFR amplification and low-level, heterogeneous HER2 amplification were observed (6.5\%). No significant correlation between EGFR/HER2 gene copy and protein expression was found. Almost one quarter of the cases (12/49, 24.5\%) showed increased HER2 or EGFR expression at hormone relapse; this was associated with a significant reduction in time from hormone relapse to death (p = 0.0003). Increased expression of HER2 or EGFR may influence progression to androgen independence in about a quarter of prostate cancer, as a rise in EGFR/HER2 expression at hormone relapse is associated with a significant reduction in time to death. The EGFR/HER2 pathway may represent one of a number of independent routes to hormone escape in prostate cancer.\textsuperscript{5}

\textbf{Epidermal Growth Factor (EGF)}

Activation and progression of prostate cancer involves the up-regulation of lipoxygenase (LOX) and cyclooxygenase (COX) pathways, and epidermal growth factor receptor (EGFR). Dietary animal fats, which increase the risk of prostate cancer, stimulate release of intestinal neurotensin (NT), a growth-promoting peptide that enhances the formation of arachidonic acid metabolites in animal blood and activates the EGF receptor (EGFR) and downstream kinases (ERK, AKT), as well as stimulation of DNA synthesis. NT and EGF enhanced \textit{[3H]-AA} release, and their effects, are diminished by 5 and 12-LOX inhibitors such as baicalein and boswellic acids, as well as COX inhibitors such as curcuminoids. Cells treated with NT and EGF showed an increase in 5-HETE levels by HPLC. 5-LOX activity is required for NT to stimulate growth via EGFR and its downstream kinases. NT may enhance 5-HETE formation, and also up-regulates cPLA2 and 5-LOX protein expression.\textsuperscript{6} This is why a diet low in animal protein, particularly meat, is important for PC inhibition.

\textbf{Her-2-neu}

Her-2-neu expression appears to increase with progression to androgen independence in prostate cancer. Therapeutic targeting of this tyrosine kinase in prostate cancer should be tested, although many natural compounds are effective mediators of Her-2-neu.\textsuperscript{7} Surprisingly, in one study high Her-2 membrane expression in hormone-sensitive tumors was associated with an increased time to biochemical relapse (P = 0.0003).\textsuperscript{8}

\textbf{Vascular Endothelial Growth Factor (VEGF)}

Prostate Cancer – Donald Yance
Vascular Endothelial Growth Factor (VEGF) is a mitogen that is specific for endothelial cells and is involved in tumor angiogenesis. VEGF is one of the important inducers of angiogenesis in prostate cancer, as well as most other cancers. VEGF increases with tumor stage and grade, while bFGF expression increases only with tumor stage. In addition, VEGF is important and clinically relevant to the induction of angiogenesis in PC. Both VEGF and c-met appear to influence tumor progression, mainly through their effect on microvessel density (MVD).9,10 A recent study demonstrated that a combination of androgen ablation and inhibition of VEGF signaling, in an androgen-sensitive human prostate cancer xenograft model (LNCaP) that develops androgen-independent growth after androgen ablation, showed that a VEGF inhibiting drug, ZD6474, sustained cancer suppression. In comparison with orchietomy, ZD6474 treatment produced greater tumor growth inhibition (P < 0.001), inducing complete cytostasis for the duration of dosing. More importantly, combination therapy (castration plus ZD6474) produced a comparable therapeutic effect to treatment with ZD6474 alone (in noncastrated mice).20

Other Important Growth Factors

In addition to VEGF, several other protein growth factors are involved in the angiogenic process. Prominent among these is basic fibroblast growth factor (bFGF), which acts synergistically with VEGF in stimulating capillary growth. Transforming growth factor-(TGF)-beta is angiogenic in vivo, but it appears to function primarily as an indirect mitogen for vascular endothelial cells, exerting its stimulatory activity by upregulating VEGF. Insulin-like growth factor I was found to induce VEGF expression in colon cancer cells, an effect that appeared to involve an increase in the transcription of the VEGF gene.11-17

Currently, specific growth factor pathways implicated in prostate cancer include, the IGF-IGFBP axis, which has been demonstrated to play a very important role. The tumor promoting functions of VEGF have been defined in tumor angiogenesis and currently remains the central focus of anti-angiogenesis therapy in prostate cancer. Another key cytokine, TGF-beta (1 and 2), has tumor-suppressing functions in a normal prostate gland, but its pleiotropic functions in prostate cancer are influenced by the hormonal state of the disease. In partnership with other deregulated growth factor signaling, the TGF-beta cascade has also been implicated in the spread of prostate cancer. Other active members of the HER family, particularly the HER-2 receptor, and EGF receptor, have also been recognized as crucial elements of aberrant signal transduction pathways which induce activation of downstream signaling, are involved in cellular proliferation, cell survival, and angiogenesis. The abnormal function of a number of growth factors in prostate cancer biology explains the heterogeneity of its histologic grade, mode of presentation, and disease prognosis.18

Insulin, Insulin resistance, and Insulin growth factors (IGFs)

There is a strong relationship between insulin resistance and prostate cancer. A recent study of nearly 16,000 men living in Oslo, Norway, shows that the presence of two or more factors comprising the metabolic syndrome increases the risk of prostate cancer. The more metabolic syndrome factors present, the higher the risk. This research showed a link between insulin-like growth factor-1 (IGF-1) and prostate cancer.19

In another previous study, participants were a population-based sample of 1,880 men from eastern Finland without history of cancer or diabetes mellitus at baseline. Metabolic syndrome (WHO criteria) was present in 357 (19%) of the subjects. During an average follow-up of 13 years, a total of 183 cancers occurred, of which 56 were due to prostate cancer. The metabolic syndrome at baseline was related to a 1.9-fold (95% confidence interval, 1.1-3.5) risk of prostate cancer after adjustment for age, alcohol consumption, physical fitness, and energy, fat, fiber, calcium, vitamin E, and alpha-linolenic acid intake. The association between metabolic syndrome and risk of prostate cancer was stronger among overweight and obese men with a body mass index > or = 27 kg/m2 (adjusted relative risk, 3.0; 95% confidence interval, 1.2-7.3) than in lighter men (relative risk, 1.8; 95% confidence interval, 0.7-4.7).20

IGF-1 Levels Stimulate PC Growth, Upregulate uPA, and Stimulate Angiogenesis

It has clearly been established that both insulin and IGF-1 act as growth factors involved in cancer that promote cell proliferation and inhibit apoptosis.21-27

Higher IGF-1 levels are associated with a fourfold greater risk of developing PC. IGF-1 is a known mitogen (stimulator of cell division and tumor growth) for PC. IGF-1 receptors are found on the PC cell as well as on osteoblasts. IGF-1 stimulates the PC cell to make uPA (urokinase-type plasminogen activator), a cell product implicated in the invasiveness and metastasis of PC. The uPA receptors are also found on the PC cell and on osteoblasts. IGF-1 adds further insult by also acting as an angiogenic growth factor.28,29
Fasting insulin, glucose, Hemoglobin A1C, Lipid panels, IGF-1, C-peptide, and Leptin levels should all be accessed to determine baselines and targets for intervention.

There are five major pathways in which elevated glucose and insulin promote prostate and other cancers:

1. Direct, whereby elevated glucose and insulin, and insulin receptor impairment causes a desensitization of the IGF binding proteins (I & II), enabling the free circulating insulin to proliferate cancer cells and inhibit apoptosis,
2. Increases uPA (urokinase-type plasminogen activator), and PAI-1 (plasminogen activator inhibitor-1)
3. Increases aromatase enzyme causing higher levels of estrogen which also promotes cancer,
4. Increased levels of inflammation (TNF-a, IL-6 etc.),
5. Increased levels of oxidative damage, particularly Advanced Glycation End products (AGEs), which are highly damaging reactive molecules created from prolonged levels of glucose reacting with proteins. It is like rust on pipe forming.
Leptin and Leptin resistance in PC

Leptin, a product of adipocytes, is involved in the regulation of body weight and results are strongly correlated to body fat content. An excess of fat mass represents a risk factor for breast cancer, particularly in postmenopausal women, and for prostate cancer as well. Leptin stimulates estrogen production through the increase of aromatase expression and activity in human luteinized granulosa cells and adipose stromal cells. It has been demonstrated that leptin is able to drive aromatase expression in breast cancer, and most likely in prostate cancer too.\(^{202}\)

Blood samples from 69 patients with prostate cancer and 137 age-matched control subjects were collected. Serum leptin level was investigated by radioimmunoassay, and body mass index was calculated. There was a strong association with significantly elevated serum leptin levels, and high body mass index in patients with prostate cancer than in control subjects.\(^{203}\) Prior studies, also reported significantly elevated serum leptin and insulin levels in patients with prostate cancer, suggesting a strong link with obesity as an increased risk factor.\(^{204}\)

Both obesity and prostate cancer are epidemic in Western society and multiple biological links exist between the two including higher estradiol, insulin, free IGF-1, and leptin levels, and lower free testosterone and adiponectin levels, all of which may promote more aggressive cancers.\(^{207}\) Adiponectin levels are lower in patients with prostate cancer and are inversely associated with grade of disease. Adipokines, such as IL-6, tend to be levelated in obesity, and exert a variety of biologic effects on prostate cancer cells, modulating cellular differentiation, apoptosis, proliferation, and angiogenesis.\(^{208}\) A recent study found that C-peptide and homeostatic model assessment of insulin resistance (HOMA-IR) were strongly inversely related to non-aggressive cancer but were non-significantly
positively related to risk of aggressive disease ($p$ (heterogeneity) = 0.007 and 0.01, respectively). Our data suggest that androgens, which are inversely associated with insulin resistance, are important in the early prostate cancer development, whereas insulin resistance related factors may be important for tumour progression. 209

Platelet-derived Growth Factor (PDGF)

Expression of platelet-derived growth factor (PDGF), and activation (by autophosphorylation) of its receptor (PDGFR), a tyrosine kinase, is associated with the growth of metastatic prostate tumor cells in the bone parenchyma. Inhibiting PDGFR phosphorylation may, especially in combination with agents (Taxane-rich extracts, or Artemisinin with whole plant extract), produce substantial therapeutic effects against prostate cancer bone metastasis. 30, 31

Inhibiting phosphorylation of PDGFR, by treatment with the PDGFR kinase inhibitor imatinib, and the chemotherapeutic agent paclitaxel, reduces the incidence and size of human prostate cancer bone lesions in nude mice. 32

Inflammation and Prostate Cancer

Chronic inflammation is an etiological event for most, if not all, human cancers, and is very evident in prostate cancer. Toll-like receptors (TLRs) are important mediators of inflammation as they recognize and respond to a broad range of insults, such as microbial pathogens, bacteria, and viruses; and interact with various adaptor proteins to activate different transcription factors, including nuclear factor-kB (NF-kB) and activator protein-1 (AP-1); and induce innate and adaptive immune response. TLRs are essential in the short term in fighting off diseases but when they are activated as part of an ongoing state within, they can promote cancer. 33

The Importance of Measuring CRP and IL-6

A blood test for C-reactive protein (CRP), which is readily available and already used to assess the risk of cardiovascular disease, could be useful in predicting prognosis for men with advanced prostate cancer. Data from a prospective clinical trial showed that patients with elevated levels of CRP had a higher risk for death, and were less likely to respond to treatment with docetaxel, than patients with normal CRP levels.

Results from a recent study show that an elevated level of CRP (greater than 8 ng/L) is a significant predictor of poor survival. Men with elevated levels of this protein had nearly a 3-fold increase in the risk for death compared to men with normal levels of CRP (8 ng/L or less). The hazard ratio was 2.96 (95% CI, 1.52 – 5.77; $P = .001$). Men with elevated CRP levels were also less likely than those with normal levels to respond to treatment with docetaxel; the odds ratio was 0.74 (95% CI, 0.6 – 0.92; $P = .007$). Each doubling of CRP increased the risk of death by 27% and reduced the probability of responding to treatment by 19%. Inflammation plays a major role in driving prostate cancer progression and in its resistance to therapy. 34

IL-6, a pleiotropic cytokine, is implicated in the neoplastic process of a variety of neoplasms, and is a mediator of prostate cancer morbidity. In normal-weight men, high levels of two markers of inflammation (IL-6 and CRP), measured nearly a decade prior to diagnosis of prostate cancer, are associated with the development of prostate cancer. High pre-diagnostic levels of IL-6 are also associated with a less favorable prostate cancer outcome in normal-weight men. These results provide further evidence that inflammation is involved in prostate cancer development and progression. High levels of CRP levels were associated with a 40% higher risk of developing prostate cancer among all men. Because IL-6 is secreted by adipose tissue, levels of this cytokine are naturally higher in overweight and obese men. It is possible that high levels of IL-6 and CRP in men of a healthy weight "may produce a cellular environment more conducive to oncogenesis and cancer progression." 35

IL-6, a cytokine with growth-promoting activity in different cell types, has been implicated in the progression of prostate cancer and associated with the metastatic phenotype. IL-6 has also been shown to mediate ligand-independent activation of the androgen receptor pathway in prostate cancer cells. 36, 37

In the present study, we investigated the expression of members of the IL-6 supergene family and related cytokines, and the potential role of IL-6 in prostate cancer growth regulation. IL-6 appears to undergo a functional transition from paracrine growth inhibitor to autocrine growth stimulator during progression of prostate cancer to the hormone-refractory phenotype. 38

Herbal Agents, Better Modulators of Inflammatory COX-2 and LOX Pathways than Drugs

Prostate Cancer – Donald Yance
Emerging on the horizon in cancer therapy is an expansion of the scope of treatment beyond cytotoxic approaches to include molecular management of cancer physiopathology. The goal in these integrative approaches, which extends beyond eradicating the affected cells, is to control the cancer phenotype. One key new approach appears to be modulation of the inflammatory cascade, as research is expanding that links cancer initiation, promotion, progression, angiogenesis, and metastasis to inflammatory events. There is an emerging relationship between neoplasia and inflammatory eicosanoids (PGE2 and related prostaglandins), with a focus on how inhibition of their synthesizing oxidases, particularly cyclooxygenase (COX), offers anticancer actions in vitro and in vivo. Although a majority of this research emphasizes the pharmacological applications of nonsteroidal, anti-inflammatory drugs and selective COX-2 inhibitors, these agents fail to address alternate pathways available for the synthesis of proinflammatory eicosanoids. Evidence is presented that suggests the inhibition of lipoxygenase (LOX) and its byproducts-LTB4, 5-HETE, and 12-HETE represents an overlooked but crucial component in complementary cancer therapies. Based on research, natural agents capable of modulating both LOX and COX may advance the efficacy of cancer therapy. Selected nutritional and botanical agents (notably, omega-3 fatty acids, boswellia, Chinese skullcap, curcumin, and quercetin) favorably influence eicosanoid production.39

**COX-2 Inhibitors**

COX-2 is one of two inducible isoforms of cyclo-oxygenase which convert arachidonic acid to prostaglandins (PGs), most specifically PG2, thereby mediating acute and chronic inflammation, pain, and cellular repair mechanisms. Inhibition of COX-2 expression blocks its pro-inflammatory effects and reduces expression of androgen receptors and androgen-inducible genes. COX-2 also plays a role in malignant transformation in the prostate.40, 41 In one recent study positivity for COX-2 was found in in 72.1% of prostatic, intraepithelial neoplasia, and in 44.7% of prostate carcinomas, with an overexpression of COX-2 in prostate cancer.42 Overexpression of COX-2 in prostate cancer is also associated with an increase in Polo-like kinase 1 (PLK1), which is linked to higher-grade tumors. PLK1 is known to be one of the key players in the regulation of mitosis of both normal and malignant transformed cells. Moreover, several studies reported an overexpression of PLK1 in human malignancies including prostate cancer.43

**Lipoxygenase (LOX) pathways and PC**

The metabolites of the lipoxygenases (LOX), hydroxyeicosatetraenoic acid (HETE) derivatives in the arachidonic acid (AA) cascade have been shown to inhibit apoptosis, or programmed cell death. Cellular AA is generally liberated from membrane phospholipids by cPLA2, and then peroxidized at specific sites by 5-LOX, 12-LOX, and 15-LOX. Inhibition of LOX has been shown to effectively induce apoptosis. The mechanism of LOX inhibitors is to promote apoptosis by decreasing the antiapoptotic gene bcl-2, and by decreasing the antiapoptotic phosphatidylinisitol-3 (PI-3) kinase-Akt signaling pathway. Furthermore, a link has been shown between the activity of the tumor-suppressor gene p53, and 15 LOX. When the p53 is mutated, the h15-LO is increased, causing tumor growth and preventing cell death. Similarly, in vascular smooth muscle cells, lipoxygenase metabolites promote vascular cell growth by stimulating cFos, cJun, and cMyc mRNA expression.44-50

**12-Lipoxygenase (LOX) up-regulated in PC**

Arachidonic acid is metabolized by 12-LOX to 12(S)-hydroxyeicosatetraenoic acid [12(S)-HETE], and this biologically active metabolite is involved in prostate cancer progression by modulating cell proliferation in multiple cancer-related pathways, inducing angiogenesis, and metastasis. Increased expression of 12-LOX in PC-3 cells caused a significant change in cell adhesiveness, spreading, motility, and invasiveness.51

Although all LOX inhibitors have shown to cause a marked inhibition of PC cells through apoptosis, the effect of a 5-LOX inhibitor was stronger than 12-LOX inhibitor at inhibiting the growth of PC, in a recent study. LOX inhibition has potent antiproliferative effects against PC cells through differentiation.52

12-LOX transfected PC-3 cells were more adhesive toward vitronectin, type I and IV collagen, but not to fibronectin or laminin, than cells transfected with control vector. Increased spreading on vitronectin, fibronectin, collagen type I and IV also was observed in 12-LOX transfected PC-3 cells when compared to control PC-3 cells. The increased spreading of 12-LOX transfected PC-3 cells was blocked by treatment with the 12-LOX inhibitors, baikalein and curcuminoids; boswellic acids are also effective inhibitors of 12-LOX. In vivo, tumor cell invasion to surrounding muscle or fat tissues was more frequent in nude mice bearing s.c. tumors from 12-LOX transfected PC-3 cells than in those from control vector transfected cells. There was also an increase in tumor metastasis to human bone by 12-
LOX transfected PC-3 cells demonstrating that 12-LOX expression enhances the metastatic potential of human prostate cancer cells. 53

Curcumin is an effective inhibitor of 12-LOX. Using a homology model of the three-dimensional structure of human 12-LOX, we did computational docking of curcuminoids to identify inhibitors superior to curcumin. Docking of the known inhibitors curcumin and NDGA to P-12-LOX was used to optimize the docking protocol for the system in study. Over 75% of the compounds of interest were successfully docked into the active site of P-12-LOX, many of them sharing similar binding modes. Curcuminoids that did not dock into the active site did not inhibit P-12-LOX. From a set of the curcuminoids that were successfully docked and selected for testing, two were found to inhibit human lipooxygenase better than curcumin. Additionally, the curcuminoids inhibiting 12-LOX were tested for their ability to reduce sprout formation of endothelial cells (in vitro model of angiogenesis). Only curcuminoids inhibiting human P-12-LOX and the known inhibitor NDGA reduced sprout formation. At IC(50), a substantial amount of 12-HETE can be produced by lipooxygenase, providing a stimulus for angiogenic sprouting of endothelial cells. Increasing the concentration of lipooxygenase inhibitors above IC(50), thereby decreasing the concentration of 12(S)-HETE produced, greatly reduced sprout formation for all inhibitors tested. 54

Gammalinolenic acid (GLA) and eicosapentaenoic acid (EPA) have independently been reported to suppress growth of prostate cancer in part by regulating the LOX pathways. 55 GLA is found in Pine seed oil, Primrose oil, Borage seed, and Black current seed oil; while EPA is from fish oil.

We can naturally shift the eicosanoid pathways away from AA production by dietary maneuvers that avoid refined carbohydrate intake and the resulting insulin stimulation. So putting our attention to dietary and pharmacologic approaches that prevent overproduction of AA or inhibit AA production is essential. If we neglect this pathway, overproduction of AA occurs. Specific metabolic products of AA such as PGE2 and 5-HETE are created through the actions of the enzymes COX-2, 5-LOX, 12-LOX, and 15-LOX. These metabolites are examples of bad eicosanoids and have been implicated in PC growth and metastasis. LOX and COX products of omega-6 fatty acid metabolism are implicated in angiogenesis. In a study of human PC where 5-LOX, and its metabolite 5-HETE, were evaluated in malignant versus benign prostate tissue within the same patient, both 5-LOX and 5-HETE were significantly overexpressed in the PC tissue. In other words, specific eicosanoids are modulators of tumor cell interactions with certain host components within the context of cancer growth, invasion, and spread. What the layperson can do to inhibit AA is to reduce insulin-stimulating carbohydrate ingestion and to use a high quality of EPA/DHA to inhibit the AA pathway. 56-58

C-reactive Protein levels should be routinely checked. The level should be <.8, and IL-6 can be monitored as well.

Hypercoagulation: D-Dimer and Fibrinogen as Important Tests

In health, haemostasis and angiogenesis are tightly regulated processes, but may become deregulated in cancer. Patients with prostate cancer, as well as many other cancers including lung and breast, have a seven-fold increased risk for blood clots in the legs or lungs (venous thrombosis). Recent evidence suggests that platelet activation may link these processes as platelets can release angiogenic factors such as VEGF. Furthermore, inflammation has also been implicated in regulating both coagulation and angiogenesis, possibly by activating platelets directly and increasing, for example, plasma fibrinogen. 59

Embolic strokes are the most common cause of stroke in patients with cancer, due partially to hypercoagulability; whereas atherosclerosis accounted for only 22% of stroke in this population. Outcome was primarily determined by the underlying malignancy and the patient's neurologic condition. 60

Patients with advanced prostate cancer are likely to be at increased risk for thrombosis. The results of a controlled study of changes in specific and sensitive markers of coagulation activation in patients with prostate cancer was conducted, and concluded that advanced prostate cancer patients have significantly increased levels of sensitive markers of coagulation activation compared with healthy age-matched controls. 61

D-Dimer levels assess both coagulation and fibrinolytic (thrombophilic) activity, and fibrin formation and removal is continuous during the development of malignancy. Plasma D-dimer is indicative of ongoing fibrinolysis, and circulating, soluble, fibrin polymer [thrombus precursor protein (TppP)] represents thrombogenic activity. 52

The D-dimer test will tell you if you may have a clot somewhere in your body, or if you are at risk of forming a clot. 0-1 is good and denotes that no clot is indicated. The higher above 1 you get, the greater the likelihood of a clot. The
Fibrinogen is another very relative test to access the likelihood of cancer developing or progressing. It also is a good predictor of thrombosis risk and blood clots.\(^{3-6}\) Fibrinogen levels are best kept below 350.

Also factor V Leiden and prothrombin 20210A are both linked to thrombosis. Carriers of the factor V Leiden mutation, who also had cancer, had a 12-fold increased risk vs. individuals without cancer and factor V Leiden. Similar results were indirectly calculated for the prothrombin 20210A mutation in patients with cancer.\(^{65}\) But rather than screen for factor V Leiden or the prothrombin 20210A mutation, it may be more cost-effective to consider D-Dimer, CRP, Fibrinogen, and risk markers for blood clots.

HEMEX laboratories (www.Hemex.com) offers a boutique menu of coagulation panels, including eg soluble fibrin monomer, as well as a host of enzyme/polymerisms to determine hereditary predispositions.

The growth of a primary tumor depends on its proliferation potential, activity of the immune system, and ability of tumor angiogenesis. Botanical agents such as Curcuminoids, Resveratrol, and Gingerols; Omega-3 fatty acids; and specific enzymes such as Lumbrokinase, Nattokinase, and Bromelian, assist in maintaining normal hemo-dynamic balance, inhibiting coagulation, suppressing cancer.

**Urokinase Plasminogen Activator**

Urokinase type plasminogen activator (uPA) activates plasminogen to plasmin and is often associated with cancer and other diseases where tissue remodeling is essential.\(^{67}\) The role of uPA is that it binds on the cell surface bringing about two events relative to its biological functions: (1) a conformational change of the receptor which, in turn, affects its interaction with other proteins; (2) a signal transduction which modulates the expression of apoptosis-related genes. Besides its applications as a thrombolytic agent and as a prognostic marker for tumors, uPA may provide the basis for other therapies as the structure of the receptor-binding domain of uPA has become a model for the design of anti-cancer molecules.\(^{68}\)

The p75 neurotrophin receptor (p75(NTR)) has been characterized as a metastasis and tumor suppressor in prostate cancer. The metastasis suppressor activity of p75(NTR) is mediated, in part, by down-regulation of both uPA and type IV collagenases, both of which are implicated in cell migration and metastasis.\(^{69}\)

The expression of uPA in 36 human prostate cancer specimens by immunohistochemistry was evaluated. A total of 71% of cancer specimens with extracapsular extension showed increased expression of uPA, vs 26.6% of those without capsular invasion. Increased expression was localized to the glandular cytoplasm, with tumor stroma yielding predominantly negative results. The increased expression of this marker may signal the presence of aggressive tumors.\(^{70}\)

Plasma levels of uPA were measured in patients who underwent radical prostatectomy for clinically localized PC (preoperative, \(n = 429\); postoperative, \(n = 76\)); 44 healthy men, 19 patients with metastases to regional lymph nodes, and 10 patients with bone metastases. Elevation of plasma uPA in PC patients was associated with features of biologically aggressive PC, disease progression after radical prostatectomy, and metastasis.\(^{71}\)

Overexpression of uPA was detected in 53% and 64% of primary PC tissues, and in more than 90% of lymph node metastases, but not in normal prostate or benign tissues. Of the uPA positive tumors, 76% and 68% were Gleason score 7 or higher. The overexpression of uPA was highly related to tumor differentiation in patients with PC.\(^{72}\)

Insulin-like growth factor binding protein-3 (IGFBP-3), a major IGF-binding protein in human serum, regulates the growth of several cancers, including prostate, through IGF-dependent and IGF-independent mechanisms. IGFBP-3 effectively blocks uPA- and matrix metalloproteinase-2-stimulated invasion pathways, ultimately reducing cancer cell metastasis. IGFBP-3 may be a key pathway as an anti-invasive and antimetastatic therapeutic agent for cancer.\(^{73}\)

**Nutraceutical compounds that inhibit uPA**

From >1,000 compounds tested, several potential uPA inhibitors have been identified such as antipain, leupeptin, folic acid, **rosmarinic acid (from rosemary)**, lavendustin A, fisetin, myricetin, and tolfenamic acid. Some of these were subject to further tests for inhibitory activity and inhibition of sprout formation. These natural compounds inhibit uPA and sprout formation and thus reduce angiogenesis. Both a proper diet rich in uPA-inhibiting
nutraceuticals and plant-based concentrated supplements can become a supportive tool in prostate cancer treatment.\textsuperscript{74} Part of the antitumor and antiangiogenic mechanisms of \textit{soy isoflavones} involves an ability to down-regulate uPA.\textsuperscript{75} Genistein has also demonstrated effective reductions in uPA expression.\textsuperscript{76}

**Nuclear Factor-kappaB is Activated in Prostate Cancer**

The transcription factor nuclear factor-kappaB (NF-kB) promotes the production of angiogenic, antiapoptotic, and prometastatic factors that are involved in carcinogenesis. The presence of NF-kB DNA binding has been identified in all prostate cancer cell lines tested. The binding was inhibited by many natural compounds such as parthenolide, curcumin, EGCG, and resveratrol which have decreased multiple gene transcripts under the control of NF-kB and inhibited proliferation of prostate cancer cells.\textsuperscript{77}

A study was conducted of the expression of NF-kappaB/p65 protein in six histologically normal prostates, 13 high-grade prostatic intraepithelial neoplasias (PIN), and 86 prostate adenocarcinoma specimens. Nuclear localisation of p65 was used as a measure of NF-kappaB active state. Nuclear localisation of NF-kappaB was only seen in scattered basal cells in normal prostate glands. Prostatic intraepithelial neoplasias exhibited diffuse and strong cytoplasmic staining but no nuclear staining. In prostate adenocarcinomas, cytoplasmic NF-kappaB was detected in 57 (66.3%) specimens, and nuclear NF-kappaB (activated) in 47 (54.7%). Nuclear and cytoplasmic NF-kappaB staining was not correlated (P=0.19). By univariate analysis, nuclear localisation of NF-kappaB was associated with biochemical relapse (P=0.0009; log-rank test) while cytoplasmic expression was not. On multivariate analysis, serum preoperative prostate specific antigen (P=0.02), Gleason score (P=0.03), and nuclear NF-kappaB (P=0.002) were independent predictors of biochemical relapse. These results provide novel evidence for NF-kappaB/p65 nuclear translocation in the transition from PIN to prostate cancer, and that nuclear localisation of NF-kappaB is an independent prognostic factor of biochemical relapse in prostate cancer.\textsuperscript{78}

**KI-67 and Prostate cancer**

The expression of the human Ki-67 protein is strictly associated with cell proliferation. During interphase, the antigen can be exclusively detected within the nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. The fact that the Ki-67 protein is present during all active phases of the cell cycle (G(1), S, G(2), and mitosis), but is absent from resting cells (G(0)), makes it an excellent marker for determining the so-called growth fraction of a given cell population. The fraction of Ki-67-positive tumor cells (the Ki-67 labeling index) is often correlated with the clinical course of the disease. The best-studied examples in this context are carcinomas of the prostate and the breast. For these types of tumors, the prognostic value for survival and tumor recurrence has repeatedly been proven in uni- and multivariate analysis. Ki-67 protein expression is an absolute requirement for progression through the cell-division cycle.\textsuperscript{79}

Two hundred and eleven patients treated by radical prostatectomy for localized prostate cancer were clinically followed up for a mean of 7.3 years. The primary, histopathological specimens were re-analysed to ensure uniform histopathological grading and pT classification. The expression of Ki-67, cyclin D1, and a high apoptotic rate are related to a malignant phenotype in prostate cancer; and high expression of Ki-67 (p=0.03), as well as high apoptotic rate (p=0.04), were related to a high risk of cancer death.\textsuperscript{80}

Ki-67 expression is a strong predictor of distant metastasis and mortality for men with prostate cancer treated with radiotherapy plus androgen deprivation. There were 537 patients (35.5%) in Radiation Therapy Oncology Group (RTOG) 92-02 who had sufficient tissue for Ki67-SI analysis. Median follow-up was 96.3 months. Ki-67 was the most significant determinant of distant metastasis and cause-specific death, and was also associated with overall death. The Ki-67 marker should be routinely checked in men diagnosed with prostate cancer.\textsuperscript{81}

**Bcl-2**

Bcl-2 is a normal human protein that is found in the mitochondrial membrane where it regulates the release of a substance known as cytochrome C. Once released from the mitochondria, cytochrome C triggers the activation of a number of enzymes (known as caspases) which ultimately result in cell death. Bcl-2 and its family members play a pivotal role in the normal process of cell death known as \textit{apoptosis}. In mature individuals, apoptosis is necessary to accommodate the billions of new cells produced daily and to eliminate aged or damaged cells. The regulation of this process—i.e., the decision to initiate the process of cell death—is mediated primarily by the Bcl-2 protein family.

**Bcl-2 Link to Cancer**

Prostate Cancer – Donald Yance
High levels of Bcl-2 are associated with most types of human cancer. In these diseases, Bcl-2 blocks the release of cytochrome C, which would ordinarily be triggered by cancer therapy. Bcl-2 also appears to be a major contributor to both inherent and acquired resistance to current anticancer treatments.\textsuperscript{82-84}

Bcl-2 is known to:

1. Prevent programmed cell death,
2. Enhance metastatic potential,
3. Promote resistance to anticancer therapy,
4. Indicate poor prognosis in many cancers.

\textbf{Bcl-2 and Prostate cancer}

Patients with metastatic hormone refractory prostate cancer (HRPC) have limited treatment options, and new therapies are needed. Advances in the understanding of the molecular mechanisms implicated in prostate cancer progression have identified many potential therapeutic gene targets including Bcl-2, an important pro-survival regulator of apoptotic cell death. Bcl-2 is overexpressed in a variety of human malignancies, including prostate cancer where it has also been associated with androgen independent progression and treatment resistance. Oblimersen is a phosphorothioate antisense oligonucleotide complimentary to the Bcl-2 mRNA, and a potent inhibitor of Bcl-2 expression which, in pre-clinical testing, can significantly enhance the therapeutic effect of chemotherapy, hormone, and radiation therapy. Clinical trials evaluating oblimersen in combination with chemotherapy in a variety of cancers have shown good tolerability and promising response rates. Randomized trials are required to determine if oblimersen can enhance the effectiveness of docetaxel in patients with HRPC.\textsuperscript{85}

One of the multi-target pathways in which natural compounds have shown to suppress PC is through Bcl-2. \textit{Curcumin and Green tea extract} inhibit Bcl-2 expression.\textsuperscript{86-88} \textit{Scutellaria baicalensis extract}, rich in many phenolic compounds, including \textit{baicalin, baicalein, wogonin oroxylin}, was found to inhibit Bcl-2-overexpression, prostaglandin E(2) synthesis, COX-2 gene expression, and block nuclear factor-kappaB (NF-kappaB) binding and transcriptional activation.\textsuperscript{89,90} \textit{Hibiscus protocatechuic acid (PCA)}, a phenolic compound isolated from the dried flower of \textit{Hibiscus sabdariffa L.} (Malvaceae), demonstrated antioxidant and antitumor promotion effects in part through Bcl-2 inhibition mechanism.\textsuperscript{91,92} \textit{Carnosol}, a phenolic compound extracted from the herb \textit{rosemary} has been reported to have anti-cancer activity. Carnosol may be useful as a novel chemotherapeutic agent against B-lineage leukemias, and possibly other types of cancers that express high levels of the protective protein Bcl-2.\textsuperscript{93} \textit{3,3'-Diindolylmethane (DIM)} is a major in vivo derivative of the putative anticancer agent indole-3-carbinol (I3C), which is present in vegetables of the Brassica genus. In a recent study DIM treatment decreased total transcript and protein levels of the apoptosis inhibitory protein Bcl-2, and the amount of Bcl-2 bound to the pro-apoptotic protein.
Bax. DIM treatment also caused an increase in Bax protein levels, but did not affect the level of Bax that was bound to Bcl-2. As a functional test of the role of Bcl-2 down-regulation in the DIM-induced apoptotic response, ectopic expression of Bcl-2 in MCF-7 cells was shown to attenuate the apoptotic effect of DIM. DIM can induce apoptosis in breast cancer cells independent of estrogen receptor status by a process that is mediated by the modulated expression of the Bax/Bcl-2 family of apoptotic regulatory factors.94

**Beta-sitosterol**, a main dietary phytosterol found in adaptogenic herbs, suppresses Bcl-2 expression,95 as does EPA from fish oil.96 A lectin extract of *viscum album* (mistletoe) has demonstrated an ability to induce apoptosis by effecting Bcl-2.97 **Theophylline**, a component of Green Tea and a phosphodiesterase inhibitor, resulted in downregulation of bcl-2 concomitant with induction of apoptosis.98 Theophylline works through an indirect increase in cAMP. Direct cAMP inducers, such as dibutyl-cAMP (db-cAMP) and **Forskolin** (*Coloeus forskolii*) induced moderate apoptosis. **6-Gingerol**, a naturally occurring plant phenol and one of the major components of fresh ginger, induced cell death in promyelocytic leukemia HL-60 cells; caused DNA fragmentation; and inhibited Bcl-2 expression in HL-60 cells. The inhibition of Bcl-2 expression in HL-60 cells appears to account for the mechanism of 6-gingerol-induced apoptosis.99 **Grape seed extract** was also shown to regulate the bcl-2 gene and downregulates the oncogene c-myc.100

Other important, multi-tasking, cancer-fighting compounds that suppress cancer-related Bcl-2 include **Rersveratrol**;101, 102 **Quercetin**;102, 103 **Echinocystic acid (EA)**;104, 105 a natural triterpene enriched in various herbs including **Panax ginseng**; **Parthenolide**;106 a sesquiterpene lactone responsible for the bioactivities of **Feverfew**; **Beta-lapachone**;107, 108 a quinone obtained from the bark of the Lapacho tree (*Tabebuia avellanedae*); **Oridinon**;109, 110 an extract from the Chinese herb **Rabdosia rubescens**; **Eurycoma longifolia extract**;111 **Andrographolide**;112 a diterpenoid lactone isolated from a traditional herbal medicine **Andrographis paniculata**; the alkaloid **Chelidione**;113 from **Celandine** (*Chelidonium majus L.*); and the flavonoid **Casticin**;114 from **Yarrow** (*Achillea millefolium*).

**PTEN** (phosphatase and tensin homologue)

PTEN (phosphatase and tensin homologue) is an important tumor suppressor protein gene that suppresses cancer. Lost expression of PTEN is associated with several important cancer-related events including:

- PTEN regulates the phosphatidylinositol-3'-kinase (PI3K) signaling pathway;
- PTEN has potent tumor suppressing abilities, including inhibition of the PI3K/Akt signaling pathway;
- Loss of PTEN causes activation of AKT, which is associated with increased proliferation, resistance to death, and increased angiogenesis in tumors;
- Loss of PTEN activates Epidermal growth Factor Receptors;
- Loss of PTEN activates COX-2;
- Active PTEN results in decreased phosphorylation of Akt and MAPK, the up-regulation of p27, and down-regulation of cyclin D1 protein levels resulting in decreased proliferation and an increase in apoptosis;
- Inactivating mutations or deletions of the PTEN gene result in hyper-activation of the PI3K/Akt signaling pathway, and are increasingly being reported in human malignancies, including breast cancer. They are related to features of poor prognosis and resistance to chemotherapy, hormone therapy, and herceptin therapy for her-2 neu-related cancers;
- Under conditions of PTEN deficiency, the PI3K/Akt signaling pathway becomes a fundamental proliferative and survival pathway; pharmacological inhibition of this pathway results in tumor growth inhibition.114-119

In prostate cancer, inhibition of EGFR signaling can result in a significant growth reduction and in increased apoptosis in EGFR-overexpressing PCa cells with different modalities which are regulated by PTEN status and this may have relevance in the clinical setting of PC.120

“Ad-PTEN and Ad-p27 Kip1 inhibited the growth and proliferation of PC-3 cells. The progression of the cell cycle of PC-3 cell was arrested in G(0)-G(1) phase, meanwhile the apoptosis rate of PC-3 was also affected after Ad-PTEN or/and Ad-p27 Kip1 infected.”121

**COXs expression and PGE-2 synthesis activates when PTEN becomes mutated.**122

**PTEN** suppresses NF-kB and induces apoptosis.123-125

**PTEN** and p53 down-regulate NF-kB and AP-1 suppressing UV induced cancer.126

Prostate Cancer – Donald Yance
Well known activators of PTEN and/or inhibitors of PTEN mutation include Quercetin, Resveratrol, Lutiolin, and Phytoestrogens.127-130

**p53 mutation**

Mutation of the p53 tumor suppressor gene is the most common genetic alteration in human cancer. The p53 protein is often called the guardian of the genome; p53 prevents replication of damaged DNA in normal cells and promotes suicide or apoptosis of cells with abnormal DNA.131 Faulty p53 molecules allow cells (carrying damaged DNA) to survive when they would normally die, and to replicate when they would normally stop. Cell cycle constraints are when pass, repair, and apoptotic mechanisms falter and disturbed cells pass mutations down to offspring. Thus, a lack of p53 regulation promotes the spontaneous emergence of mutant cells, a cellular distortion that is an invitation to cancer.132

Normal p53 function has been demonstrated to be crucial in the induction of apoptosis in human and murine cells following DNA damage. This result was further supported by the findings that p53 is the most commonly mutated tumor suppressor gene. Lack of p53 expression or function is associated with an increased risk of tumor formation.133-138

Two studies provide new information about mutations of the p53 gene, seen in two out of three prostate cancers that develop androgen independence. A gene called Id-1 is a feature of androgen-independent tumors in people with p53 mutations.139

There are many natural agents that reduce or reverse p53 mutation. Some of these include: Resveratrol,189-192 Resveratrol and Curcumin,197 OPCs from Grape seed extract,194 Quercetin,195-197 6-Gingerol,198 Vitamin E,199 and Vitamin E with N-acetylcysteine.200

**Diet and p53 Gene Expression**

The p53 mutational status was determined for a total of 1458 cases of colon cancer using single strand conformational polymorphism/sequencing of exons 5-8. The associations between those with mutations and those without were compared with a population-based group of controls (n = 2410). Comparisons were also made between cases with p53 mutations compared with cases without p53 mutations. Subjects with a p53 mutation were more likely to consume a Western-style diet compared with controls than were cases who were p53 wild type. Specific components of the diet were also found to be strongly associated with p53 mutations, including a diet with a high glycemic load, as well as foods high in red meat, fast food, and trans-fatty acid (mutation vs control, odds ratio = 1.92 95% CI = 1.47-2.50). Diets with a high glycemic load relative to the lowest intake were found to be significantly associated with missense mutations (OR = 1.69; 95% CI = 1.23-2.33, comparing p53+ to controls, and OR = 1.72; 95% CI = 1.19-2.50, comparing cases p53+ to cases of p53 wild type). Similar findings were seen with diets high in red meat, fast food and trans-fatty acid.

Components of the Western diet -- namely, red meat and foods that increase glycemic load -- appear to play an important role in the process of the p53 mutation that then causes cancer.201

**p21 and p27 Expression**

The p21 gene has been identified as a key factor for the regulation of cell growth by modulating the threshold of apoptosis in prostate cancer. The p21 protein induces G1 arrest by inhibiting the activity of the cyclin-dependent kinases and interacting with the proliferation of cell nuclear antigen, thereby directly preventing DNA synthesis. There is an association between p21 expression and the progression of prostate cancer to androgen independence.140-143

The molecular events leading to progression toward androgen-independent prostate cancer involve the p21 gene. The expression of p21 was examined by immunohistochemical studies in 105 prostate cancer samples: (a) 7 of 30 (23%) androgen-dependent tumors; and (b) 36 of 75 (48%) androgen-independent tumors stained positive for p21 (P < 0.02). Androgen deprivation reduced p21 expression to undetectable levels after 14 days. Tumor relapse, defining androgen-independent prostate cancer, was associated with increased expression of p21 to levels comparable with those found before castration. p21 expression at relapse was also correlated with a high Ki-67 index. p21 expression is therefore associated with the progression to androgen-independent prostate cancer.143
Also, low levels of p27 expression in pre-prostatectomy biopsies correlates with patients who are at high risk for recurrence.\(^{144-146}\)

A combined gene therapy that targets PTEN and p27 showed a synergistic role in inhibiting the invasiveness of PC-3 cells and angiogenesis.\(^{146}\)

Many natural plant compounds have demonstrated cancer-suppressing activity through cell cycle arrest and apoptotic pathways such as p27. Recently, Silymarin and one of its constituents, silibinin, exerted strong efficacy against prostate cancer in part by increasing p27 expression.\(^{147}\)

**Genetic Alterations (Polymorphisms) Cause the Development and Progression of PC**

Quantitative and structural genetic alterations cause the development and progression of prostate cancer. A number of genes have been implicated in prostate cancer by genetic alterations and functional consequences of the genetic alterations. Identification and characterization of these genes will be a key step for improving the predisposition, detection, and treatment of prostate cancer.\(^{148, 149}\)

**Polymorphisms of the P450 Super Gene Family**

**CYP17 gene**

CYP3A4, a member of the cytochrome P450 super gene family, is involved in androgen metabolism resulting in the oxidation of testosterone to 2b-, 6b-, or 15b-hydroxytestosterone. CYP17 encodes the enzyme cytochrome P-450c17 alpha, which mediates both 17 alpha-hydroxylase and 17, 20-lyase in the steroid biosynthesis pathway. Polymorphisms in genes involved in the androgen metabolism affect the risk of prostate cancer. A case-control study was conducted of 63 patients with untreated histologically proven prostate cancer, and 126 age-matched control men with benign prostatic hyperplasia (BPH) to determine whether a polymorphism in the CYP17 gene is associated with prostate cancer risk. After stratification by median age (66 years) at time of diagnosis, a marked increased risk was found in carriers of the A2/A2 genotype older than 66 years (OR = 8.93, 95%CI = 1.78-49.19, P = 0.01). These results, although small, suggest that the CYP17A2/A2 genotype may be a biomarker for prostate cancer risk, especially for older men.\(^{150}\)

**CYP1B1**

Men also with a polymorphism in the CYP1B1 gene may be more susceptible to environmental or hormonal factors that increase the risk of prostate cancer. Mutations in CYP1B1 have already been implicated in smoking-related head and neck squamous cell, colorectal, breast, ovarian, and now prostate cancer. The scientists pinpointed the variations in the gene by studying more than 400 prostate cancer patients and 220 healthy men. After looking at 13 variations in CYP1B1, they discovered that one frequent haplotype was more common in the men who had a family history of the disease, while another was more prominent in the healthy men. CYP1B1 may prevent, as well as cause, cancer due to variations in the gene that determine whether it will work to prevent prostate cancer or to activate it. This study suggests men with a particular gene variant have an increased risk of prostate cancer. It’s an exciting finding because we know the gene interacts with certain cancer-causing chemicals, -- and studying this more closely will bring us closer to finding out what factors in the environment or within the body may trigger the disease.\(^{151, 152}\)

**(SHBG) D356N**

In another recent study in which 14 single nucleotide polymorphisms in genes involved in hormone regulation or metabolism (AKR1C3, CYP1A1, CYP1B1, CYP3A4, ESR1, GNRH1, HSD173B, HSD3B2, SHBG, and SRD5A2) in 488 prostate cancer cases and 617 matched controls were accessed for their connection to PC. In this study gene alteration at sex hormone binding globulin (SHBG) D356N were found to be associated with an increased risk of prostate cancer compared, particularly among non-Hispanic whites (odds ratio, 1.54; 95% confidence interval, 1.13-2.09; P = 0.006).\(^{153}\)

**MnSOD**

A polymorphism [valine (V) --> alanine (A)] of manganese superoxide dismutase (MnSOD), the primary antioxidant enzyme in mitochondria, has been recently associated with prostate cancer.\(^{154, 155}\)
Free radicals cause DNA damage within the prostate

Free radicals produce changes in the DNA of prostate cells that have opposing effects on the risk of prostate cancer development. At around 60 years of age, the pro-cancer alterations start to outweigh the anti-cancer changes. There are a number of studies that indicate that intake of foods rich in antioxidants, such as phenols, carotenoids, and selenium reduce the risk of developing prostate cancer.\textsuperscript{156}

Histone Deacetylase and PC: Silencing of IFI16 Protein

Acetylation and deacetylation of chromatin histone protein by histone deacetylase (HDA) alters chromatin structure and dynamically affects transcriptional regulation. Many lines of evidence indicate that histone hypo-acetylation induces repression of tumour suppressor gene expression.\textsuperscript{157}

Increased expression of IFI16 protein (encoded by the IFI16 gene) in normal human prostate epithelial cells is associated with cellular senescence-associated cell growth arrest. Consistent with a role for IFI16 protein in cellular senescence, the expression of IFI16 protein is either very low or not detectable in human prostate cancer cell lines. Treatment of DU-145 and LNCaP prostate cancer cell lines with HDA, inhibitor trichostatin A (TSA), or CGK1026 resulted in transcriptional activation of the IFI16 gene. Histone deacetylase-dependent transcriptional silencing of the IFI16 gene in prostate epithelial cells contributes to the development of prostate cancer.\textsuperscript{158}

Using natural, multi-targeting compounds that that reduce HAD has shown to enhance the effectiveness of other agents against refractory prostate cancer.\textsuperscript{159,162}

Cell Adhesion Molecules (CAM)

Cancer cells communicate with each other and proliferate because of certain cell surface receptor molecules called cell adhesion molecules (CAM). In order for tumor invasion to take place, there must be a breakdown in the extracellular matrix. CAMs are complex protein-carbohydrate molecules that occur on the plasma membrane of all cell surfaces. They control both intracellular and extracellular (cell-to-cell) communication; they act as the eyes, ears, and nose of each cell. CAMs regulate organ architecture, cell migration, differentiation, apoptosis, mitosis, platelet aggregation, and the activity of the immune system. It has become evident that CAMs are actively involved in mediating the recruitment of specific lymphocyte subsets into different tissues. There are four main types of CAMs: cadherins, integrins, cell-surface lectins, and Immunoglobulin Super-family Cell Adhesion Molecules (ISCAMs).

E-Cadherin

Cadherins are calcium ion-dependent molecules that mediate cell-to-cell binding. Cadherins inhibit both invasion and metastasis, and reduce the expression of tumor cells. Several subtypes such as E-, N-, and P-cadherins have been named according to their tissue distribution. E-cadherin functions as a potential tumor suppressor gene. E-cadherin is expressed on the cell surface of most, if not all, epithelial tissues. It functions as a mediator of cell-to-cell interactions, and it has been well characterized as a suppressor of invasive epithelial tumor cells in vitro. E-cadherin maps to 16q22, a region that is subject to allelic deletion in carcinomas of the prostate, ovary, breast, and liver. LOH for 16q in the region of the E-cadherin gene was observed in 20% to 40% of breast carcinomas, and a significant inverse correlation was reported between E-cadherin expression and tumor grade, stage, and overall survival in prostate cancer patients.\textsuperscript{163,164}

E-cadherin is closely related to invasion and metastasis of ductal breast cancer, suggesting that it is an important tumor marker in predicting lymphatic metastasis of invasive ductal breast cancer.\textsuperscript{165} When considered in combination with the other markers, low levels of E-cadherin identified a group with an even lower long-term disease-free survival rate, 44%. Loss of E-cadherin expression appears to be a major determinative step in the metastatic progression.

For patients with prostate cancer, it is now well documented that decreased expression of E-cadherin is associated with a poor prognosis.\textsuperscript{166} The relation between loss of E-cadherin expression and acquisition of invasive behavior has also been well documented, however the restoration of E-cadherin may in fact reduce the invasive behavior. There is also a correlation between decreased expression of E-cadherin and increased expression of N-cadherin in high-grade PC.\textsuperscript{167-172}

E-cadherin is strengthened by tangeretin, a flavon found in tangerines.\textsuperscript{173} 8-Prenylnaringenin, the phytoestrogen
in hops and beer, upregulates the function of E-cadherin. Curcumin exhibits antimetastatic properties by modulating integrin receptors, collagenase activity, and the expression of Nm23 and E-cadherin. Also, Omega-3 fatty (n-3) acids and Gamma linolenic acid (GLA) both increase the expression of E-cadherin.

E-CaHerin and Nm23

The Nm23 gene is a metastasis suppressor gene, although it is really a family of genes. When nm23 is lost, the cell loses its ability to stay in one place and starts moving throughout the body. Nm23, encoded by the non-metastatic 23 gene, plays a key role in differentiation of many kinds of epithelium. Loss or dysfunction of E-cadherin and nm23 is frequently identified in many types of human cancers and is considered to correlate with invasive/metastatic phenotype. Damaged nm23 genes are frequently found in a variety of tumors including breast, colon, pancreatic, and prostate cancers (along with CD44). The overexpression of the nm23 gene resulted in the formation of excessive amounts of basement membrane Extracellular matrix (ECM), which in turn inhibited cell growth. The production of basement membrane initiates a cascade of cellular responses that lead to growth arrest.

Curcumin enhances the expression of antimetastatic proteins, tissue inhibitor metalloproteinase (TIMP)-2, and nonmetastatic gene 23 (Nm23). Lycopene may inhibit cancer cell metastasis by upregulating the expression of nm23-H1.

Osteonectin Promotes PC Bone Metastasis

Osteonectin is an antiadhesive protein known to be involved in cell-matrix interactions, migration, and angiogenesis. Osteonectin attracts prostate cancer cells and promotes invasiveness, and is a specific inducer of collagenase activity in those cancer cells that preferentially metastasize to the bone. It is well known that MMP activity shows a correlation with the invasive and metastatic ability of cancer cells. Osteonectin is a general chemo-attractant for bone-metastasizing epithelial cells, such as those of prostate and breast origin. Antibodies to osteonectin reduced the invasiveness of prostate cancer and breast cancer cells, suggesting potential therapeutic applications.

Down-regulates tNOX

Cancer specific cell surface oxidase tNOX is a novel cell surface protein related to unregulated growth and drug response of cancer cells. tNOX has been proposed as the cellular target for the anticancer action of various quinone site inhibitors with anticancer activity including naturally occurring polyphenols exemplified by the principal green tea catechin (-)epigallocatechin gallate (EGCG) alone, or even better in combination with other catechins in green tea. This protein is uniquely associated with all forms of cancer and is absent from normal cells and tissues. Its activity is correlated with cancer growth. When blocked, cancer cells fail to enlarge after division and eventually die.

Among the most potent and effective inhibitors of tNOX are EGCG and the vanilloid capsaicin. Catechin-vanilloid combinations are 10 to 100 times more effective than either catechin alone. EGCG required to inhibit tNOX was reduced 10 times by combination with inactive catechins such as (-)-epicatechin (EC), (-)-epigallocatechin (EGC), or (-)-epicatechin-3-gallate (ECG). Various synthetic mixtures based on purified catechins and decaffeinated tea extracts treated enzymatically to reduce the ester bond-containing catechins, varying in EGCG content from 0.065 to 40%, were of comparable efficacy to decaffeinated green tea extracts as long as EGCG was present and the ratio of total catechins to EGCG + EGC was about 1.5. Such mixtures appear to offer potential cancer protection and therapeutic advantages over those of EGCG alone through lowered toxicity of the mixture to normal cells and for more efficient blood delivery of orally-administered catechins to a tumour site.

An in vitro culture model of prostate cancer cells (LNCaP) with human osteoblasts (hFOB) was utilized to define the efficacy of the tNOX inhibitors EGCG against bone metastasis of prostate cancer alone, and in combination with Taxol and cisplatin. The LNCaP cells were more resistant to treatment with EGCG and Taxol when grown in co-culture than when grown in monoculture.

Telomerase

The ends of human chromosomes are protected from the degradation associated with cell division by 15-20 kb long segments of hexameric repeats of 5’-TTAGGG-3’ termed telomeres. In normal cells telomeres lose up to 300 bp of DNA per cell division that ultimately leads to senescence; however, most cancer cells bypass this lifespan restriction through the expression of telomerase; an enzyme found within the cell that is responsible for strengthening a cell.
hTERT, the catalytic subunit essential for the proper function of telomerase, has been shown to be expressed in approximately 90% of all cancers, including prostate cancer.  

**Telomerase inhibition in Prostate cancer**

To examine in vivo effects, researchers treated the cancer cells with ISIS 14691, then transplanted them into nude mice. When LNCaP cells were treated for 21 days prior to implantation, tumors grew significantly less over time than did control treated cells. When cells were exposed to the inhibitor for 35 days prior to implantation, no tumors developed. PSA levels averaged 1.2 compared with 37 for control cells. On its own, the inhibitor exerted less dramatic effects on the DU145 tumors. Thus, "cells expressing wild-type Rb and p53 proteins may be more susceptible to telomerase inhibition," the investigators suggest. Contrasting results were observed in experiments testing the synergistic effects of ISIS 14691 with chemotherapy drugs. After treatment with ISIS 24691 for at least 55 days, DU145 cells, but not LNCaP cells, were sensitized to cisplatin and carboplatin in liquid culture.

**Telomerase inhibition with natural compounds**

Because telomerase genes are often activated in cancer and are associated with enabling cancer cells to being much stronger and even immortal, agent that target this have an attractive mechanism in chemotherapy research. Some chemotherapeutic drugs, for example etoposide (VP-16), specifically target Telomerase activity. Leading biotechnology companies are developing methods to inactivate telomerase genes in cancer cells. Many natural plant compounds also, in part, inhibit cancer through a mechanism that involves the down-regulation of telomerase. Some of these plant compounds include: Podophyllum alkaloids (May apple), silibinin, from Milk thistle, Baicalein, from Scutellaria baicalensis, Oridonin from Rabdosia, EGCG, from Green tea, beta-Lapachone, from Pau de arco, the Lapacho tree, and Genistein.

Genistein, the most abundant isoflavone present in soybean has antiproliferative effects on a variety of cancer cells, including prostate cancer. Genistein represses telomerase activity in prostate cancer cells not only by repressing hTERT transcriptional activity via c-Myc but also by posttranslational modification of hTERT via Akt.

A recent study investigated the hTERT inhibiting effects of (-)-epigallocatechin-3-gallate (EGCG), the major polyphenol found in green tea catechins, in MCF-7 breast cancers cells and HL60 promyelocytic leukemia cells. Exposure to EGCG reduced cellular proliferation and induced apoptosis in both MCF-7 and HL60 cells in vitro, although hTERT mRNA expression was decreased only in MCF-7 cells when treated with EGCG. Furthermore, down-regulation of hTERT gene expression in MCF-7 cells appeared to be largely due to epigenetic alterations. Treatment of MCF-7 cells with EGCG resulted in a time-dependent decrease in hTERT promoter methylation and ablated histone H3 Lys9 acetylation. In conjunction with demethylation, further analysis showed an increase in hTERT repressor E2F-1 binding at the promoter. From these findings, we propose that EGCG is effective in causing cell death in both MCF-7 and HL60 cancer cell lines and may work through different pathways involving both antioxidat effects and epigenetic modulation.

Also, all-trans retinoic acid, a vitamin A related compound, inhibits telomerase as well.

**The Importance of Accessing Pathological Markers**

A number of molecular and cellular changes associated with the malignant progression of cancer are identifiable, and should be used as markers for metastatic ability of histological localized prostate cancer cells. They should also be used for gathering information that gives clues to what targeted treatments might be most effective. This way we are able to possibly predict which patients have acquisition of metastatic ability: increased cellular motility and loss of metastasis-suppressor gene function; and treat them more aggressively with targeted botanical-based compounds, as well as low-toxic, low dosage drug therapies when appropriate.

All of this in-depth analytical research into the biological characteristics of the Cancer as an energetic entity, both in-and-of itself, and in relationship to our energetic make-up, is vitally important to both gain an understanding of the potential aggressive behavior, “the IQ of the Cancer,” and it can also help us target certain abnormalities we discover in the pathology workup. This information can contribute to the development of innovative approaches for predicting the metastatic ability of individual tumors, and help the practitioner be aware of how aggressive the protocol needs to be, as well as what agents might be most useful. This bit of investigative work falls under the III branch, which involves a in-depth understanding of the “Cancer Energy.” Put together all clues before you set up a treatment plan.
“I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories instead of theories to suit facts.” Sherlock Holmes.

Section IV

The Eclectic Triphasic Medical System
A Systematic Wholistic Approach to Treating and Preventing Cancer

Within the Eclectic Triphasic Medical System (ETMS), accessing the Cancer Energy is a vitally important branch, but no less or no more then the other two branches. Accessing the individual with cancer, building their vitality, and accessing the external environment all together complete the picture. This re-visioning of cancer, repositioning it firmly in the body rather than external to the body and thus subject to influences from both the internal and external environment, is fundamental in the ETMS. When we approach a case of cancer, whatever type it may be, and when we design customized treatment plans, there are three core criteria we are examining:

1) The **Human Energy** within - An *endogenous* component comprising the personal energetic processes, or the core constitution of the individual patient (spirit, mind, and body), and evaluated from a highly individualized perspective;
2) The **External Energy** around - An *exogenous* component comprising the external environment in which the patient lives and operates, their perceptions of it, and its influences upon them, both psychic and physical;
3) The **Cancer Energy** - A *mixed endogenous / exogenous* component comprising the energetic and physiological processes of the cancer itself, which both responds to and alters the environment.

Each of these can be addressed through carefully considered, individualized programs of botanical medicine, nutritional supplements, diet, exercise, meditation, visualization, and other therapeutic agents.

The Endogenous Component – The Patient

All over the world, indigenous systems of medicine have included a core analytical or diagnostic model that is based on energetic (non-tangible) qualities. In Ayurveda these are the *doshas* (*vata*, *pitta*, *kapha*); in Traditional Chinese Medicine (TCM) it is the concepts of earth, fire, metal, wood, and wind; in Humoral medicine from ancient Europe it is the *sanguine*, *melancholic*, *phlegmatic*, or *choleric* temperaments; in Native American lore it is the phases of our day, week, year, or lifetime as represented by the *four directions*. I have pulled from many of these traditional systems, in particular TCM and Eclectic Medical system, as well as put forth many of my own discoveries and insights to form a new Energetic Model.

In the Triphasic model the endogenous component equates to the core constitution of the patient. The first and most important step is to build vitality, and/or the vital energy(s) using Adaptogenic formulas, Nutritional compounds, diet, exercise, and lifestyle modifications. It isn’t until after this has been done that you would ever consider the specifics of the treatment program. In the ETMS we often may choose to do several weeks of nutritive and strengthening work to build the person up before attempting a more interventionist strategy using more potent anti-cancer compounds. Herbal agents are given to boost, nourish, tonify, and support the metabolism at its base, or foundation, in order to help the body in having the wherewithal to overcome cancer. Using Adaptogenic remedies, the building blocks to good health, are the most important and often only step you need to take to stabilize cancer and promote health and wellness. Adaptogenic remedies are given to all patients, and many of these plant medicines possess cancer-suppressing ability as well.

The three Energies within the Human Energy Branch:

1. The **Neuroendocrine and endocrine system**, referred to as the “Vital Essence,” channels through the *Kidney Network*;
2. The efficiency of the digestive system and lungs to create energy, blood, and tissue, the “Vital Force,” through the *Spleen Energy Network*;
3. The spiritual everlasting energy, the God within, The “Vital Spirit,” through the *Heart and Soul*.

With normal aging, together with the impact of modern day stress, it is inevitable that our Vital Essence and Vital Force deplete, although we do what we can to fortify them; but our spirit should always be growing and getting closer to the Creator. The endocrine system energetically emanates through our Vital Essence and relates to the metabolic model of aging and chronic diseases, including cancer. Endocrinology (Vital Essence) has had a profound impact on other branches of medicine with the consequence that the frontiers of classical endocrinology are slowly
vanishing. It is time to ask what the future demands of patients will be and whether there will be an appropriate number of specialists in endocrinology in the near future; and based on the complex, interwoven, and responsive system it is, other than adaptogenic plant medicine, what else can ultimately help us? As endocrine health diminishes, so do many other important pathways involved in cancer, including mitochondrial enzyme activities, inflammation, and the role redox cycling plays.

In forming a treatment, using plant extracts that both target/inhibit cancer growth and address the condition of the individual is vitally important within the Triphasic model. A person stressed out, prone to anger, or who has lost God’s ever-dwelling presence within, may need their Vital Spirit lifted. Plants such as Poria cocos, Reishi, and Bacopa, along with Prayer and Mediation can greatly change this. Poria, Reishi, and Bacopa also possess potent immune enhancing, anti-cancer, and detoxifying effects as well. Bacopa is one of the most effective chelators of toxins in the body. It possesses adaptogenic, and potent redox/anti-oxidant actions; and can detoxifiy heavy metals including aluminum and cadmium.\textsuperscript{1,2}

Oxidative damage from free radicals is a contributing cause of cancer. One of the substances that is essential for life, oxygen, is also harmful and becomes more so as we age. How does this happen? Oxygen in its various metabolic reactions in the body can be converted to undesirable by-products, called oxygen-derived free radicals, that are highly reactive and relatively indiscriminate in their destruction of protein, fat, and DNA molecules, all of the molecules upon which our bodies’ functions depend. Although the reduced exposure to free radicals in the food we eat and in the environment, along with free radical protection, is vital for the prevention of disease and for slowing down the aging process, it is for the most part secondary to anabolic decline, increased catabolic activity related to diminished effects of the endocrine system. If we are breaking down faster than we can build up and our energy system is not efficient, we generate excessive amounts of free radicals. So, before we deal directly with the oxidative damage created, we must first improve anabolic metabolism and energy transfer. Stress and aging; the pervasive effects of stimulants; and exposure to environmental, hormone-mimicking agents called endocrine disruptors increases catabolic activity and reduces endocrine health, which leads to enhancement of the aging process, and age-related cancers and a shorter lifespan.

In determining constitution, we don’t play by any single set of rules. Each of the medical models around the world has many valuable insights and important lessons to be learned. But in clinical practice, people are so unique that no single system can describe all the possibilities. In addition to strong training in certain disciplines or methodologies, holistic clinicians eventually develop their own ways of seeing patients and knowing how they function in the bigger picture, not just in their disease process. This may be done by evaluating many criteria. The ability to synthesize this disparate information and come to an understanding of the metabolic state of the patient is the hallmark of an experienced practitioner. It is the art of medicine. Knowing how to translate this into a clinical plan is the science of medicine.

Criteria for evaluating constitution

Stature
Build
Height
Coloring
Tongue: Coating, color, cracks etc.
Fullness or emptiness of the radial pulse
Fingernail analysis
Texture and temperature of skin
Extent of mucus secretions
Food and beverage preferences
The health of specific areas of the body: eye, ear, bone etc.
Digestive capacity and bowel habits
Temperature preferences
Mood and affect
Sleep
Age
Energy and exertion patterns
History of personal relations / social history
Past medical history
Drug use (prescription & street)

Prostate Cancer – Donald Yance
The two fundamental objectives of the ETMS is to (1) strengthen the person and (2) weaken the cancer. We strive to effect the internal environment for the promotion of optimal cellular health, and make it the least conducive for cancer. Another vitally important objective is not always to focus on the cancer but to promote wellness with only two goals in mind, (1) increase quality-of-life, and (2) lifespan. Sometimes you can get rid of the cancer but what did it cost you? And in the end did you live longer or better because of it?

The Endogenous Component: The Individual Constitution Itself Comprises Three Major Systems.


The primary role of the Kidney Network is the storage of Essence. This understanding of the body, Kidney Network, and Essence, is rooted in TCM. Essence is one of the most important substances in the body, and is responsible for birth, growth, development, and maturation. It is also the foundation for all other substances in the body and is the neuroendocrine/endocrine regulatory system. The Kidney Network is also related to the bones and, by extension, the teeth. It also governs marrow, which relates to actual bone marrow, and also to the brain, which is considered the “sea of marrow.” In Chinese medicine, each organ nourishes one of the senses, and the sense associated with the Kidney is hearing. The depletion of Kidney Essence is the mechanism responsible for aging. Weak and brittle bones, loss of teeth, hearing loss, confusion and neurological diseases, loss of both sexual desire and ability to perform, are all signs of loss of Kidney Essence. The Kidney Network also does include the physiological Kidneys and is responsible for fluid balance and the production and elimination of urine.

Stress exhausts us physically, disrupts relationships between all branches of the human energy systems creating unhealthy imbalances, and strains our neuroendocrine and endocrine systems, depleting Essence. Equally exhausting to our internal organs, especially the Kidney and the Spleen Networks, is overwork, too much exercise, and lack of good food and sleep. Therefore moderation and getting adequate rest is essential to preserving Essence.

Management of endocrine balance is critical to good health and perhaps most especially so in the case of cancer. Oxidative stress, dysglycemia, imbalanced HPA axis, thyroid dysfunction, pineal gland dysfunction, impaired ATP production and energy balance, and depleted vitality are contributing factors in the development of cancer. Estrogen, progesterone, testosterone, thyroid, insulin, prolactin, and other endocrine influences are also implicated in the development and causation of cancer. Adaptogenic and tonic herbs, blood sugar normalizing herbs, thyroid tonics, hormone balancers, and specific nutritional supplements are used to treat these problems.

2. The “Spleen” nutritive and immune system – connects to the “Vital Force”

The quality and quantity of the food we eat and our ability to adequately digest, absorb, metabolize, and assimilate it, ultimately dictates our fundamental health. In Chinese medicine, digestive health equals immune health through the transformative activities of the spleen acting on food and forming jing (life force) and wei chi (protective energy roughly equating to the western concepts of the immune system). This of course vastly pre-dates even Hippocrates who is famous for saying “Let food be your medicine and medicine be your food.”

Diet therapy offers a vast opportunity to introduce healing agents. For the cancer patient in particular, often nauseated by drug treatments, their throats sore from vomiting, perhaps unable to take solids, suffering from wasting and cachexia, food therapies become critical. Avoiding foods which undermine good health (sugars, trans fats, artificial flavors and preservatives etc) and emphasizing nutritious whole foods (fruits, vegetables, fish etc) can offer enormous benefit.

The Spleen Network relates to the efficiency of creating energy and building healthy tissue, blood, and a healthy responsive immune system. It is how we optimize the food we ingest and absorb. The Lungs are also important to energy transfer in that they relate to oxygen efficiency. Certain Adaptogens, including Panax ginseng, are traditionally classified as Spleen-energy tonics according to TCM.
Since the mitochondria are the major site of free radical damage, more efficient use of cellular energy (The Spleen and Kidney Network) plays a significant role in redox balance. Aging contributes to this process and this is also why certain anabolic adaptogens, like schisandra seed extract, that can both enhance mitochondrial energy transfer and assist in hepatic detoxification and free radical sequencing, are building blocks in the Triphasic Model.

Anabolic agent and nutrients, like Undenatured Whey Protein Concentrate (WPC), creatine, magnesium chelate, and branch chain amino acids (BCAA), promotes rapid improvement in protein metabolism and are critical to building up all branches within the Triphasic system; including assistance to hepatic detoxification and regeneration, which itself requires adequate energy and nutrition.

Smoothies are often used as way to get 2 or 3 servings of fruit, plus some good protein, concentrated nutrition, and even some of the botanical compounds into a person. Even people having trouble swallowing can take these and they can be sipped slowly so a hearty appetite is not needed. WPC, colostrum, and other healthy agents can all be added. Herbs can be used to increase anabolic metabolism, strengthen the digestion, and improve the flow of digestive juices, including proteolytic, lipolytic and glycolytic enzymes, pancreatic juices, and protective mucus. Attention to bowel health, including management of constipation and balancing of gut flora is also helpful.

In addition to eating really well, and maximizing the intake of protective phyto-nutrients, it may be necessary to use specific botanicals to nourish and strengthen the immune function itself. Deep immune tonics such as Astragalus membranaceous (Milk vetch), Uncaria tomentosa (Cat’s claw), Ganoderma lucidum (Reishi), Grifolia fronderosa (Maitake), and other medicinal mushrooms can be taken over the long term to optimize bone marrow function and white blood cell activity. Lymphatic agents such as Galium aparine (Cleavers) or Phytolacca sp. (Poke root) can help to maintain immune health through removal of metabolic wastes. Specific anti-microbials may also be employed on occasion including Tabebuia impeteginosa (Taheebo / Pau d’arco), Echinacea sp. (Purple cone flower), and Allium sativum (Garlic).

3. The “Liver” redox/anti-oxidant regulation and detoxification system

The Liver network is responsible for redox/antioxidant balance and quenching of oxygen free radicals. Oxygen-free radicals, more generally known as reactive oxygen species (ROS), along with reactive nitrogen species (RNS), are well recognized for playing a dual role as both deleterious and beneficial species. The “two-faced” character of ROS is substantiated by growing body of evidence that ROS within cells act as secondary messengers in intracellular signaling cascades, which induce and maintain the oncogenic phenotype of cancer cells. However, ROS can also induce cellular senescence and apoptosis and can therefore function as anti-tumorigenic species.

The cumulative production of ROS/RNS through either endogenous or exogenous insults is termed “oxidative stress” and is common for many types of cancer cells that are linked with altered redox regulation of cellular signaling pathways. Oxidative stress induces a cellular redox imbalance which has been found to be present in various cancer cells compared with normal cells; the redox imbalance thus may be related to oncogenic stimulation. DNA mutation is a critical step in carcinogenesis and elevated levels of oxidative DNAlesions (8-OH-G) have been noted in various tumors, strongly implicating such damage in the etiology of cancer. DNA damage is predominantly linked with the initiation process of cancer as well as contributing to progression, and more aggressive changes, in established cancer.

Free radical oxidative stress has both endogenous and exogenous sources of generation, the metal (iron, copper, chromium, cobalt, vanadium, cadmium, arsenic, nickel)-mediated formation of free radicals (e.g. Fenton chemistry), the DNA damage (both mitochondrial and nuclear), the damage to lipids and proteins by free radicals, the phenomenon of oxidative stress, cancer and the redox environment of a cell, the mechanisms of carcinogenesis and the role of signaling cascades by ROS; in particular, ROS activation of AP-1 (activator protein) and NF-kB (nuclear factor kappa B) signal
transduction pathways, which in turn lead to the transcription of genes involved in cell growth regulatory pathways. Enzymatic (superoxide dismutase (Cu, Zn-SOD, Mn-SOD), catalase, glutathione peroxidase) and non-enzymatic antioxidants (Vitamin C, Vitamin E, carotenoids, thiol antioxidants (glutathione, thioredoxin and alpha lipoic acid), flavonoids, selenium, cysteine, isothiocyanates, and others) have a role here as well.

The Paradoxical Effects of Natural Compounds as Redox Agents

It is well known that ROS stimulate cell proliferation and induce genetic instability, and their increase in cancer cells is often viewed as an adverse event. Interestingly and paradoxically, it has been shown that such abnormal increases in ROS can be exploited to selectively kill cancer cells using many natural compounds, including the isothiocyanates such as b-phenylethyl isothiocyanate (PEITC).

“Oncogenic transformation of cancer causes elevated ROS generation and renders the malignant cells highly sensitive to PEITC, which effectively disables the glutathione antioxidant system and causes severe ROS accumulation preferentially in the transformed cells due to their active ROS output. Excessive ROS causes oxidative mitochondrial damage, inactivation of redox-sensitive molecules, and massive cell death. In vivo, PEITC exhibits therapeutic activity and prolongs animal survival.”

The liver is the primary organ in terms of redox/antioxidant activity, but not the only one. In traditional Chinese medicine (TCM), the eyes are considered the gateway to the liver, therefore eye health correlates with redox balances. Macular degeneration and cataracts are diseases that are mostly caused by prolonged oxidative stress and a possible inability of the Liver Network to redox balance.

The physiological liver is one of the largest and most metabolically active organs in the body. At any given time, 25% of the total volume of blood is in the liver, where it filters through millions of lobules and is cleansed of metabolic wastes and unwanted exogenous compounds that are ingested through food, air, water, or even transdermally. Some people say that we are not so much what we eat but rather what we don’t excrete. This references the fact that inadequately or improperly metabolized compounds damage the liver and reduce its capacity to clear, so risking entering a vicious cycle. Phase I and Phase II detoxification pathways must be synchronized with the rate of phase I and never exceeding that of phase II. Tests can be done to evaluate the efficiency of these of specific detoxification pathways.

Herbalists work extensively with the channels of elimination. Traditionally sweats and purges were used to remove noxious influences such as epidemic fevers and plagues. Now we know that the skin can excrete the same compounds as the kidneys and that immune cells like a warm environment, so fevers serve a purpose and can be encouraged through specific protocols (Diaphoretic-Fever Treatment protocol). Fever is also effective in cancer therapies, enabling a more effective cancer-killing immune response.

Regular detoxification protocols are useful and customized to the needs of the patient. These alleviate stress and strain in the liver and encourage elimination of toxic elements. Specific herbs and supplements can be used to up-regulate liver clearance, and promote tissue detoxification. Milk thistle (Silybum marianum), a classic herb associated with liver benefits, also possess powerful cancer inhibiting and suppressing effects as well.

In general, I don’t believe in any doing any heroic therapies such has fasting and/or colonic therapy. By implementing the Triphasic model, using the various botanical and nutritional formulas together with a diet that both builds and assist in detoxification, you will achieve the best outcome you could hope for.

The Exogenous Component - the Environment

Our cumulative annual or lifetime exposure to environmental toxins is unquantifiable but undeniably high. We are exposed through multiple vectors. Industrial smoke; emissions; effluent and other wastes; car exhausts and all the petroleum damage done in the sake of everyone having the right to drive a car;
agricultural chemicals used as growth promoters; herbicides, pesticides, fungicides, and antibiotics; agents used in food processing such as preservatives, flavoring agents, coloring agents, processing agents, stabilizers, thickeners, sweeteners, aerators, and other chemicals; cosmetics and beauty care products; pharmaceutical and recreational drugs; and innumerable other sources. There are even geographic ‘hot spots’ of cancer incidence that correlate to known toxic sites or wind plumes.

According to a report from The Lowell Center for Sustainable Production at Boston University School of Public Health and Environment, the Environmental Health Initiative, released in September 2005, presented a strong causal link between environmental and occupational exposures and incidence of several cancers, including prostate cancer. Another 2005 study concluded similar findings, and more specifically the results suggest a negative association between occupational exposure to pesticides and prostate cancer.

Endocrine Disruptors and Prostate Cancer

Endocrine disruptors are synthetic chemicals found in pesticides and some plastics that can enter the body through the food chain, and interfere with hormone balance and disturb proper endocrine health. When levels go up, so too does body mass index and the risk of several cancers, fibroid tumors, endocrine-related diseases, and infertility to name a few. Breast cancer in men is becoming more and more common as a result of these hormone toxins. Many of these chemicals mimic estrogen (xenoestrogens) and lead to a reduction in male hormones, leading to higher levels of fat and estrogens, both of which contribute to prostate cancer.

Levels of these man-made chemicals in the environment have increased. Xenoestrogens, which have been implicated in a variety of medical problems act, in part, as false messengers disrupting the process of reproduction. Studies have implicated observations of disturbances in wildlife with estrogenic exposure. Reproductive issues of concern in humans are fetal exposure (perhaps leading to hypospadia) and decreased reproductive ability in men (i.e. decrease in sperm numbers). Xenoestrogens, because of their effects on estrogens receptors, are cancer activating and proliferating, and are implicated in breast, prostate, and other hormone-related cancers.

The levels of dioxins, polychlorinated biphenyls, and other organohalogen compounds in adults, children, and even infants through nursing mothers are all going up yearly. The reason why nursing mothers need to be careful is because the amount of polybrominated biphenyl ether concentration in women’s breasts continues to go up yearly. The fat tissue in the breast becomes a site where xenoestrogens congregate. Continuing evidence of the feminizing effects of xenoestrogens on a range of wildlife species increases the need to assess the human health risk of these estrogen mimics.

Occupational exposure to urban pollutants including endocrine disruptors causes alterations in plasma 17beta-estradiol (E2) levels and related diseases (adverse pregnancy outcome and mental health disorders) in female traffic police compared to a control group. In male traffic policemen, occupational exposure to urban pollutants causes alterations on 17-alfa-hydroxy-progesterone plasma levels and related diseases.

The xenoestrogen bisphenol A (BPA) activates a tumor-derived Androgen receptor (AR) mutant (T877A), leading to androgen-independent prostate cancer cell proliferation. BPA can serve as a potential “hormone sensitizer” of the mutant ARs present in advanced prostate adenocarcinomas, thereby possibly contributing toward therapeutic relapse in advanced prostate cancer patients and supporting the notion that nonsteroidal environmental compounds can alter the function of nuclear receptor complexes.

All of these are attempts to replace hormones rather than enhance and support the natural harmony within the system underneath it all. Although many people may assume that when a certain hormone is low, for example DHEA, it would warrant supplementing that hormone; this is not at all what is optimal for the body. Everything is in motion and changing all the time. What we need to start thinking about is lending a helping hand to the neuroendocrine and endocrine system first, using primary and secondary adaptogens and supportive nutrients. After that, we can proceed to more specific herbal and nutritional agents, and use any kind of hormone-treatment intervention as a last resort, using the lowest dosage possible. Even if,
essentially, you need some hormone replacement therapy, an example is the case of treating hypothyroidism with thyroid medicine, you may over time, by using adaptogenic formulations with some specific herbs and nutrients, together with diet and lifestyle changes, slowly wean them off the medicine. Those of use that promote a more natural way to optimal wellness need to look more to the plant world for enhancement of health rather then drugs and hormones.

There are herbs, nutritional supplements, foods, and other approaches to protect the body and rid it of at least some of these noxious influences. Supporting liver function through the use of alteratives, depuratives, and the use of Adaptogens; phenolic-rich plant extracts, such as resveratrol, and isothiocynate-rich compounds including Sulforaphane, are especially indicated.

Of course the chemical world we are exposed to constantly is not the only environmental influence. There are also the circumstances of our life. Are we happy? Are we fulfilled? Are we surrounded by friends, and family, and community? Are we giving love, receiving love, and feeling a sense of belonging? These also constitute environment because the way we perceive our reality, as a threat or as a safe place, dictates which endocrine glands function and what receptors are activated, which can ultimately adjust the expression of different genes just like pollutants and toxic agents can. This is eloquently explained by Bruce Lipton PhD in his book, *The Biology of Belief* (Elite Books 2005), in which he describes how genes don’t spontaneously choose when to switch on or off, but are prompted to do so by signals from the environment. Primitive danger signals and food signals that single celled organisms respond to are hard wired into our DNA behavior since the dawn of time. As cells coalesced, formed multi-cellular organisms, and eventually developed into complex bodies that comprise utterly interdependent communities of trillions of cells, now the chemical signals that cells respond to are hormones. If you live with a lot of stress or suffering then the hormone messages are danger signals and the cells respond by developing protective and defensive behavior. Inflammatory mediators released in this process contribute to the progression of cancer. In this way the total environmental experience of a person includes both their physical situation and their mental/emotional response to it.

**The Endogenous / Exogenous Component – the Cancer Energy**

Fundamentally, cancer occurs due to errors of DNA replication. This happens several thousand times each day in a normal person; but protective mechanisms within the cell, for example those mediated by the proteins p 27, p29, and p53, the “intra-cellular quality control engineers,” cause apoptosis and the cell dies. Even when endogenous cell signals fail and a faulty cell is allowed to get through the intra-cellular surveillance system, there are extra-cellular mechanisms that are intended to recognize and neutralize aberrant cells such as leukocytes and lymphocytes. However, if an aberrant cell gets through even these shields and survives to perpetuate into daughter cells, and if the gene error codes for resistance to apoptosis, then a cancer is born.

Thus cancer is inherently of the same tissue as the patient, and yet it behaves autonomously and has evaded the innate system of protection. The immune system doesn’t attack it wholeheartedly because the tissue is still recognizably ‘self’ so triggers are blunted. Left to develop, the cancer will soon start to put out stimulatory signals, growth factors that influence both its own behavior and that of neighboring cells. Now the cancer is influencing its environment and changing it to better suit its needs. It has gone from being endogenous to now almost being exogenous where it sets the environmental tone for the surrounding tissues. No wonder people feel invaded or taken over by some alien energy. This beast is capable not only of ignoring all the normal cellular control signals, but it is also now pumping out compounds which promote its growth and suppress immune resistance.

**The Triphasic Model in Action**

In addressing cancer through the Triphasic model, we must endeavor to acknowledge all these endogenous and exogenous qualities both within the cancer, and in the person and their environment. The Triphasic practitioner identifies the constitutional pattern in the individual and their cancer, and their particular ways of expressing imbalance; then works to address those core patterns. In some people this may lead to a protocol more heavily weighted towards hormone balancing, in others detoxification may predominate, or
nourishing and building may be prioritized. In many cases symptomatic intervention is required, for example, to manage the squeal of surgery, chemotherapy, or radiation, and the practitioner is required to address these critical issues as a priority, sometimes at the expense of also treating the core constitutional imbalances. In some cases this is unavoidable but every attempt should be made to maintain a truly wholistic approach that equally acknowledges body, mind, and spirit.

Alongside other interventions as needed, the therapeutic intention of the Triphasic model is:

- To weaken and suppress the cancer directly by disrupting its metabolism: e.g *Podophyllum peltatum* (May apple), *Thuja occidentalis* (Cedar), *Chelidonium majus* (Celandine), *Larrea divaricata* (Chaparral), or *Viscum album* (Mistletoe);
- To support and enhance the coding of onco suppressor genes: e.g phenolic compounds including flavonoids and catechins, and methyl donor molecules such as folic acid, B-12, and B-6;
- To strengthen blood vessel linings and increase vascular integrity: *Vitis vinifera* (grape seed & skin), *Vaccinium myrtillus* (Blueberry), *Achillea millefolium* (Yarrow), *Crataegus sp.* (Hawthorn), and *Centella asiatica* (Gotu kola);
- To modulate angiogenesis: e.g *Panax ginseng*, *Polygonum cuspidatum* (Knotweed), *Centella asiatica* (Gotu kola), *Aesculus hippocastanum* (Horse chestnut);
- To promote liver detoxification pathways and protect the liver from transiting metabolites: e.g Isothiocynates, DIM, Calcium D-glucarate, NAC, *Silybum marianum* (Milk thistle), *Cynara scolymus* (Artichoke), *Chionanthus virginicus* (Fringe tree), *Taraxacum offic.* (Dandelion) and *Peumus boldo* (Bolcho);
- To support immune response and bone marrow health: e.g *Astragalus membranaceus*, *Ganoderma lucidum*, *Cordyceps sinensis* and other medicinal mushrooms, *Echinacea sp*, *Uncaria tomentosa* (Uno de gato), *Atractylodes macrocephala* etc…;
- To act as partial agonists for estrogen receptors and thus provide a muted response to more proliferative estrogens: e.g *Glycyrrhiza glabra* (Licorice), *Trifolium pratense* (Red clover), *Medicago sativa* (Alfalfa)> and *Glycine max* (soy).

Practical applications of the Triphasic model require a multi-functional approach. Addressing body, mind, and spirit is a delicate art and cannot be rushed or crowded. Individual programs are carefully balanced to achieve optimum response and are adjusted as needed, and judged by progressive clinical responses. In a few types of cancer, notably breast and prostate, there is a clear physical type that is more prone and this can be correlated to constitutions. But in most cases, the practitioner is left to do individual patient analysis and evaluation to determine the constitutional type of the unique person presenting this time.

In breast cancer, the ‘apple’ shape has long been recognized as a risk factor. This belly fat has an ancient historical role as being good food storage for times of hunger; it also serves as the site of much post-menopausal, aromatase-mediated conversion of androgens to estrogen. Women get that middle age spread to ease the transition through menopause and that is why it is so hard to lose. However, in the case of breast cancer this fat becomes an estrogen factory. These women tend to be metabolically slower, they may have cold extremities and cool or clammy skin, have heavy menstruation, copious or easy mucus discharges, gain weight easily, and they often tend to internalize anger and hold grudges. Their constitution is cooler and damper and they need warming, drying, and stimulating herbs such as *Cinnamonum zeylandica* (warming) or *Rhodiola rosea* (Primary Adaptogen with an astringent drying action).

In thin women with breast cancer, the stress hormones tend to predominate. These women are hurried and often harried, and they take things seriously and worry about doing well enough. They are hard on themselves and hold others to unrealistic expectations. They may be quite warm at the surface but often feel chilly because they lose heat easily. They tend to scanty menstruation, drier stools, dry coughs, and acid indigestion. They may be irritable and flare up easily but rarely hold grudges and can go from scowls to smiles quite quickly. Their constitution is drier and warmer so they need cooling, moistening herbs to balance them. Demulcents (Althea off., Ulmus fulvis, Trigonella foenum-graecum) and nutritive agents like *Medicago sativa*, *Avena sativa*, and *Fucus vesiculosus* are indicated.
In prostate cancer, as well as most of the common cancers, a known risk factor is increased abdominal fat. With increased abdominal fat come several endocrine alterations, which can initiate or drive prostate cancer. These include insulin resistance, leptin resistance, and estrogen dominance. Abdominal fat in men, as in women, relates to more estrogen and, while men do need some and hence have the enzymes to make it, too much can disrupt normal prostate cell function and initiate a malignancy. Estrogen also serves as a driver of prostate cancer and this is the reasoning behind the use of Lupron (an FSH and LH (and hence estrogen) suppressor) in palliative prostate cancer care. The more feminine the features, e.g. higher voice, softer skin, and especially development of breasts, the more estrogen driven the cancer is likely to be.

Specific Herbs Useful for Prostate Cancer Prevention and Treatment

Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years; and have served humans well as valuable components of foods, seasonings, beverages, cosmetics, dyes, and medicines. In traditional foods and herbs there are a wide variety of active phytochemicals including the flavonoids, terpenoids, lignans, sulfides, polyphenolics, carotenoids, coumarins, saponins, plant sterols, curcuminoids, and phthalides; which have been recently researched and found to possess important actions in health promotion and cancer prevention. A more detailed study of these compounds has led to the science of nutrigenomics.

One approach to reducing Prostate cancer (PC) incidence, growth, and metastasis is prevention and intervention targeted towards mitogenic and survival signaling and cell-cycle regulation. Many of the herbs and phytoceutical compounds intervene at multiple targets of cancer suppression and are multifactorial, not single reductionist. PC progression has also been associated with transition from a paracrine to an autocrine relationship between receptors and growth ligands as the malignancy progresses to an advanced, androgen-independent, aggressive stage. The enormous research studies conducted to date suggest that targeting receptor tyrosine kinases (RTKs)-mediated signaling pathways, along with cell-cycle regulators, could be a practical and translational approach for PC prevention and intervention; and this is why herbal medicine should be the foundation to PC treatment.

Primary Adaptogens

Humans, like all living things, are in a constant flux, adapting so as to harmonize within and around their environment. We are continually adjusting to a multitude of slight or extreme changes, some of which are obvious while others go unnoticed. Good health can be measured by our ability to adapt. A healthy person with a strong adaptive capacity will survive and/or maintain good health whereas an unhealthy person with a weak adaptability will fall, become ill, or even perish. Adaptogens help us to combat the negative effects of stress and improve resistance, thus improving our health and well-being. They increase the body’s vitality and reserve, a key component to any comprehensive longevity program. They are revered because they enhance the life-force, encourage natural harmony, enhance one’s adaptability, and as a result generate “radiant health.”

The discovery of adaptogens actually came from the observation of certain plants that were able to endure harsh environments because of their well-developed adaptability. Rhodiola rosea, for example, is known to thrive in frigid weather conditions. Soviet scientist discovered that these plants could improve the adaptability of ordinary people or animals, and make them more fit and better equipped to acclimate to all forms of stress while maintaining balance and harmony. Through physiological and behavioral adaptation to our environments, we are able to sustain our equilibrium while attempting to meet all the energy requirements demanded for life’s processes. However, when demands become chronic, the neuro-endocrine system adapts at essentially all levels of organization, altering wide-spread changes in set points. Maintenance of such altered set points and their expanded physiological range is a necessary event in adaptation. A healthy system has a certain amount of intrinsic variability but an over reliance on these adaptive processes leads to the loss of physiological "flexibility" in the tissues and organ systems. So, as demands continue over time, the flexibility to maintain stability through change (allostasis) is diminished and leads to total body breakdown, which then leads to disease and a shortened life-span.

The antitumor effect of adaptogens is associated with immunomodulation - they can activate macrophages,
natural killer cells, antigen-dependent T lymphocytes, and interferonogenic actions. They also have the ability to suppress experimental tumor growth, to enhance tissue differentiation, to improve intercellular adhesion, and to reduce the likelihood of metastasis spreading.

In Oncology, adaptogens have scientifically proven to benefit cancer patients in the following ways:
1. As biological response modifiers, restoring immune surveillance, increasing non-specific human resistance;
2. Building bone marrow and blood counts, while reducing infections;
3. Protect and detoxify organs and cells throughout the body including liver, kidney, heart, and GI tract;
4. Increase anti-tumor/cytotoxic effects of chemotherapy and radiation therapy
5. Inhibit multi-drug resistance
6. Systemic enhanced anabolic and cellular energy effect: Improve recovery and healing after surgery, chemotherapy, and/or radiation therapy;
7. Inhibit cancer metastasis and/or reoccurrence;
8. Suppress angiogenesis;
9. Reduce levels of immune dysfunctional stress hormones (cortisol), which is associated with cancer growth;
10. Reduce cancer-related inflammation and gene proteins (NF-kB, COX-2 etc.).

In advanced prostate cancer, like most other cancers, loss of skeletal muscle mass is a result from cancer itself, and/or cancer treatments such as hormone blockage therapy, radiation, or chemotherapy causing depression in protein synthesis and an increase in protein degradation. This leads to a total system breakdown in health. Adaptogens, and in particular the adaptogens with enhanced anabolic activity such as *Rhaponticum carthamoides* and Mumie together with highly specific nutritional agents, including magnesium creatine and glutamine chelates, undenatured whey protein, and omega-3 fatty acids, will build healthy skeletal muscle mass and provide vital energy needed for an effective immune response. This is an often over-looked area of need for people with cancer until it is too late. My protocols, right from the start, address enhancing the neuroendocrine system and shifting systemic metabolism and organ systems throughout the body from the catabolic state to anabolic.

At the center of the Triphasic Model is the usage of adaptogenic formulas; foundational for health and healing. It is my belief, both from a conceptual point of view, and based on years of subjective clinical usage, that creating protocols built on combining adaptogens along with other complementary and more specific herbal remedies offers superior and lasting results. Adaptogens, secondary to their non-specific ability to enhance adaptation, are also highly effective as immune modulators and cancer-suppressing agents. Taking an approach that integrates adaptogenic remedies and life-style changes will serve to strengthen the “vital energy” and weaken the “cancer energy.” Examples of primary adaptogens that have demonstrated specific prostate cancer inhibiting actions include *Panax ginseng* and *Withania sommifera*.

**Panax ginseng**

Ginseng is a medicinal herb widely used in Asian countries, and many of its pharmacological actions are attributed to the ginsenosides. Prolonged usage of this king adaptogen has been associated with a reduction in the incidence of several cancers including gastric, liver, colon, lung, breast, and prostate. When ginseng was tested in animal models, a reduction in cancer incidence and multiplicity at various sites was noted.

A recent study evaluated the associations of ginseng use with survival and quality of life (QOL) in a cohort of 1,455 breast cancer patients who were recruited to the Shanghai Breast Cancer Study between August 1996 and March 1998 in Shanghai, China. The relation of ginseng use and QOL was evaluated by using multiple linear regression models. Approximately 27% of study participants were regular ginseng users before cancer diagnosis. Compared with patients who never used ginseng, regular users had a significantly reduced risk of death; adjusted hazard ratios associated with ginseng use were 0.71 (95% confidence interval: 0.52, 0.98) for total mortality and 0.70 (95% confidence interval: 0.53, 0.93) for disease-specific mortality/recurrence. Ginseng use after cancer diagnosis, particularly current use, was positively associated with QOL scores, with the strongest effect in the psychological and social well-being domains.
Publications on Panax ginseng and its relation to cancer on the Medline database (1983-2004) cover experimental models and human studies on cancer-preventive activity, cancer-treatment potential, and other beneficial effects. Panax ginseng, and specifically the active compounds, Ginsenosides, have been tested for their inhibiting effect on putative carcinogenesis mechanisms, including:

1) Inhibition of cell proliferation, anti-tumor,

2) Induction of apoptosis, induction of differentiation in cancer cells,

3) Enhancement of immunosurveillance, including antibody response, natural killer (NK) cell activity, interferon production, and the proliferation and phagocytic ability of leukocytes,

4) Regulates the gap junction-mediated intercellular communication (GJIC),

5) Increase cancer-fighting response of Dendritic cells: Dendritic cells play a pivotal role in the initiation of T-cell-mediated immune responses, making them an attractive cellular adjuvant for use against cancer,

6) Anti-inflammatory (suppresses COX-2, NF-kB, AP-1),

7) Enhancement of the antioxidative defense system; antimutagenic, and anti-toxin,

8) Endocrine system enhancement.

In most ginseng experiments, cancer inhibitory effects were found and a greater effect was demonstrated as use increased.

The use of cancer vaccines as a treatment for prostate cancer is growing with a very small amount of success. Dendritic cells (DCs) play a pivotal role in the initiation of T-cell-mediated immune responses, making them an attractive cellular adjuvant for use in cancer vaccines. Panax ginseng increases the effectiveness of vaccines in part through the enhanced effects it has on DCs.

**Ginseng and Prostate cancer:**

**Increases p21 and p27**

Ginseng shows anti-proliferative activity against a human prostate cancer cell. Ginsenoside Rg3 activated the expression of cyclin-kinase inhibitors, p21 and p27, often found down-regulated in prostate cancer. Ginsenoside Rg3 arrested LNCaP cells at G1 phase, and subsequently inhibited cell growth through a caspase-3-mediated apoptosis mechanism, leading to a reduction in the androgen receptor and 5 alpha-reductase enzyme. PSA levels were also reduced.

**Modulated MAP kinases**

A study was conducted to characterize active constituents of ginseng and their effects on proliferation of prostate cancer cell lines, LNCaP, and PC3. Among 11 ginsenosides tested, ginsenosides Rg3 and Rh2 inhibited the proliferation of prostate cancer cells. Both ginsenosides induced cell detachment, and modulated three modules of MAP kinases activities differently in LNCaP and PC3 cells. These results suggest that ginsenosides Rg3 and Rh2-induced cell detachment and inhibition of the proliferation of prostate cancer cells.

**Ginsenoside RH2 enhances chemotherapy (Taxol) against PC cells**

The combination of Rh2 and paclitaxel has an effect on growth inhibition that is greater and synergistic, as demonstrated in a cultured LNCaP cell line.

**The “yin/yang” effects of Ginsenosides on angiogenesis**

Existing literature reports both wound-healing and antitumor effects of ginseng extract through opposing activities on the vascular system. A mass spectrometric compositional analysis of American, Chinese,
Korean, and Sanqi ginseng revealed distinct "sterol ginsenoside" fingerprints, especially in the ratio between a triol, Rg1, and a diol, Rb1, the 2 most prevalent constituents. This present study explains, for the first time, the ambiguity about the effects of ginseng in vascular pathophysiology based on the existence of opposing active principles in the extract. In addition, this study also unraveled the adaptability of ginseng extract as it demonstrated its ability to promote angiogenesis for wound healing while inhibiting cancer-related angiogenesis.46

Panax ginseng should be administered to any cancer patient undergoing surgery to promote healing and inhibit cancer metastasis. There isn’t a single patient I see that isn’t getting some form of Panax ginseng, together with other primary adaptogens. I use both the fluid extract, as well as a super concentrated form containing 80% ginsenosides.

Ashwagandha (Withania somnifera)

Withania extract has shown to possess potent adaptogenic, antioxidant, and anticarcinogenic effects; and it inhibits angiogenesis.47-49

Potent inhibitor of cancer angiogenesis

Withaferin A is also a potent inhibitor of cancer angiogenesis by suppression of human umbilical vein endothelial cell (HUVEC) sprouting in three-dimensional collagen-I matrix at doses which are relevant to NF-kB-inhibitory activity. Withaferin A inhibits cell proliferation in HUVECs (IC50 =12 nM) at doses that are significantly lower than those required for tumor cell lines through a process associated with inhibition of cyclin D1 expression.50

Enhances chemotherapy & radiation therapy

Withinia extract potentiates both chemotherapy and radiation, while protecting vital organs and improving immune system recovery.51, 52

Withania and Prostate cancer

One of the steroidal lactones, known as Withaferin A (WA), induced Par-4-dependent apoptosis in androgen-refractory prostate cancer cells and regression of PC-3 xenografts in nude mice. Interestingly, restoration of wild-type AR in PC-3 (AR negative) cells abrogated both Par-4 induction and apoptosis by WA. Individually, WA and anti-androgens induced neither Par-4 nor apoptosis in androgen-responsive prostate cancer cells, yet in combination, WA and anti-androgen synergistically induced Par-4 and apoptosis in androgen-responsive prostate cancer cells. Thus, when judiciously combined with anti-androgens, WA inhibits survival of both androgen-responsive and androgen-refractory prostate cancer cells by a Par-4-dependent mechanism. Par-4 up-regulation induces apoptosis in most tumor cells.53

Chinese Skullcap (Scutellaria baicalensis)

Scutellaria baicalensis is a member of the mint family that grows in China and Russia. The root of this plant is used in traditional Chinese herbal medicines and has been the focus of most scientific studies on skullcap. Chinese skullcap is anti-microbial, antipyretic, and anti-inflammatory. It is used for treating high fevers and accompanying irritability, thirst, cough, and expectoration of sputum.

The root of Chinese skullcap contains a wide range of flavonoid compounds, of which the most well known is baicalin. Most of the research on Chinese skullcap as an anti-cancer agent has focused on baicalin. The contents of baicalin are 6%-9%, wogonin 2%-8%, baicalein 0.1%-1.6%, neobacalein 0.01%-0.2%, wogonin 0.01%-0.3%, visidulin, and oroxylin are trace amounts or undetected. The ratio of baicalin to wogonin is under three. The ratio of baicalin to baicalein and baicalin to wogonin is between twenty and fifty.54
Modern research:
- Redox regulating/Anti-oxidative;
- Anti-inflammatory, in part by COX-2 inhibition;
- Anti-allergenic, antihistamine, treats allergies such as hay fever (allergic rhinitis);
- Cardiovascular tonic;
- Liver protective, anti-viral – effective against Hep B;
- It has been shown to have broad antimicrobial effects;
- **Anti-cancer – multi-factorial mechanisms and pathways:**
  - inhibits NK-kB,
  - inhibits COX-2,
  - inhibits LOX-5,
  - reduces PG$_2$,
  - binds to androgen receptor reducing cancer-cell proliferative ability,
  - inhibits beta-glucuronidase,
  - induction of apoptosis,
  - inhibition of angiogenesis: down regulates bFGF & MMP-2.

Prostate cancer inhibition

*Scutellaria baicalensis* (SB) and *Glycyrrhiza uralensis* (Chinese licorice) inhibited cell growth of prostate cancer and down-regulated PSA levels. Characterization of SB resulted in the isolation of baicalein.

**Baicalein effectively suppressed growth and PSA expression, and induced G(1)/S arrest in LNCaP cells.** Baicalein suppresses prostate cancer by effecting multiple changes in target cells to intervene in prostate cancer progression.\(^55\)

In another study the *in vitro* effects of baicalin on the growth, viability, and induction of apoptosis in several human prostate cancer cell lines, including DU145, PC-3, LNCaP, and CA-HPV-10 was studied. The results showed that baicalin could inhibit the proliferation of prostate cancer cells. Baicalin caused a 50% inhibition of DU145 cells at concentrations of 150 microM or above. The inhibition of proliferation of prostate cancer cells after a short period of exposure to baicalin was associated with induction by apoptosis, DNA fragmentation, activation of caspase-3, and cleavage of poly-ADP-ribose polymerase (PARP). **The results indicate that baicalin has direct anti-tumor effects on human prostate cancer cells.**\(^56\)

A study was conducted whereby researchers used transgenic adenocarcinoma of the mouse prostate (TRAMP), which mimics tumor progression in human prostate cancer providing a relevant pre-clinical model. In the study, researchers determined the extent of apoptosis (cell death) and necrosis (tissue death), as well as palpable tumor formation. Results of culturing the cancer cells with SB for two hours suggested that two hours is the optimal incubation time for SB to induce apoptosis in TRAMP-C1 cells. Mice were fed daily in random groups, either receiving sterile water as placebo or experimental doses of 8 milligrams and 16 milligrams of sterile SB aqueous extracts. In the placebo group, palpable tumors developed at 19 weeks of age, and by 32 weeks, all of the mice had palpable tumors. By comparison, 20 per cent and 30 per cent of the mice in the 8mg and 16mg SB groups respectively, were free of tumors. At 27 weeks, fewer than 30 per cent of the placebo animals were free of palpable tumors; in the low- and high-dose groups, 50 per cent and 70 per cent of the mice were tumor-free. The data demonstrates that SB extract modulates apoptosis of the TRAMP mouse prostate cancer cells *in vitro* and delays tumor development *in vivo*. Recent research data demonstrates that SB has a similar effect in the induction of apoptosis in a human prostate cancer cell line LNCaP (lymph node carcinoma of the prostate), and also modulates the PARP (Poly ADP-Ribose Polymerase, an enzyme required for the detection of DNA strand interruptions) of the same cell line.\(^57\)

The *in vitro* effects of baicalein and baicalin on human umbilical vein endothelial cells (HUVECs), and on human prostate tumor cells (DU-145 and PC3), as well as the effect of orally administered baicalein on the growth of DU-145 cells after subcutaneous injection into SCID mice, was studied. In studying the in *in vitro* effects of baicalein and baicalin treatment on human prostate cancer cell lines, *in vitro* anti-proliferative and anti-angiogenic properties of baicalein and baicalin were studied on HUVECs by sprout assay. The effect of orally administered baicalein on tumor growth in SCID mice was studied in four groups (n=10) of
animals injected subcutaneously with DU-145 cells and treated daily for 28 days. The control group received only vehicle (carboxymethylcellulose), whereas the other three groups received escalating doses of baicalein (10, 20, and 40 mg/kg per day). Baicalein and baicalin exhibit dose-dependent growth inhibitory effects on human prostate cancer cells and umbilical vein endothelial cells in vitro. Also, treatment by these two flavonoid compounds significantly decreased the average number and length of sprouts formed by the endothelial cell aggregates in a dose-dependent manner (anti-angiogenic). In vivo, treatment of mice with baicalein demonstrated a statistically significant tumor volume reduction (p<0.01) when compared to the control.58

A high-performance liquid chromatography was used to fractionate SB and identified four compounds capable of inhibiting prostate cancer cell proliferation, baicalein, wogonin, neobaicalein, and skullcapflavone. Individual compounds exhibited antiandrogenic activities, with reduced expression of the androgen receptor and androgen-regulated genes. In vivo, baicalein (20 mg/kg/d p.o.) reduced the growth of prostate cancer xenografts in nude mice by 55% at 2 weeks compared with placebo, and delayed the average time for tumors to achieve a volume of approximately 1,000 mm(3) from 16 to 47 days (P < 0.001). Most of the anticancer activities of SB can be recapitulated with four purified constituents that function in part through inhibition of the androgen receptor-signaling pathway.59

Baicalin has shown to induce apoptosis and inhibit proliferation of prostate cancer cells, and has direct anti-tumor effects on human prostate cancer cells.60

Decreases cancer-induced upregulation of MMP-2 and bFGF

In this study, baicalein and baicalin, were assessed for their potential as anti-angiogenic agents in vivo employing chicken chorioallantoic membrane (CAM) assay and in vitro human umbilical vein endothelial cells (HUVECs) culture. When CAMs were treated with either baicalein or baicalin for 48 hr, basic fibroblast growth factor (bFGF) was markedly reduced in a dose-dependent manner. Further characterization showed that both flavonoids exhibited dual antiproliferative (at low dose) and apoptogenic (at high dose) effects on HUVECs. In biochemical analysis, treatment of HUVECs with baicalein and baicalin for 24 hr resulted in a dose-dependent decrease in the matrix metalloproteinase (MMP)-2 activities. Moreover, the migration of endothelial cells and the differentiation of endothelial cells into branching networks of tubular structures in vitro were also inhibited by these 2 flavonoids in a dose-dependent manner. Taken together, the results of our study provide evidence that baicalein and baicalin possess an anti-angiogenesis potential that is a previously unrecognized biologic activity.61

Turmeric (Curcuma longa)

Turmeric's active constituents are yellowish-orange, volatile oils called curcuminoids. Curcumin, being the most active and researched, has demonstrated anti-inflammatory, antioxidant, antineoplastic, antiviral, and immune-modulation activity in vitro, in animals and in some human studies as well. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, and target multiple pathways some of which include the following:

1) down-regulate transcription factors NF-kappa B, AP-1, STAT-3, and Egr-1;
2) down-regulate the expression of COX-2, LOX-5/12, NOS;
3) reduce MMP-2 and -9, uPA;
4) reduce cancer-promoting cytokines: TNF, chemokines;
5) reduce cell surface adhesion molecules and cyclin D1;
6) down-regulate growth factor receptors (such as EGFR, HER2, bFGF, TGF-B1, and VEGF);
7) inhibit several cancer-inducing pathways (kinases) including c-Jun N-terminal kinase, protein tyrosine kinases, and protein serine/threonine kinases;
8) In several systems, curcumin has been described as a potent redox cycling agent, as regulating anti-oxidant and pro-oxidant actions, and as a modulator of inflammation.

Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion, and metastasis. Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no
dose-limiting toxicity when administered at doses up to 10 g/day. All of these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer.\textsuperscript{62}

**Curcumin and Prostate Cancer Inhibition**

1. **Inhibits proliferation, induces apoptosis, and inhibits angiogenesis in prostate cancer**
   Curcumin was shown to decrease the proliferative potential and induce the apoptosis potential of both androgen-dependent and androgen-independent prostate cancer. The action of curcumin was largely by modulating the apoptosis suppressor proteins and by interfering with the growth factor receptor signaling pathways, as exemplified by the EGF-receptor. Curcumin causes a marked decrease in the extent of cell proliferation as measured by the BrdU incorporation assay and a significant increase in the extent of apoptosis as measured by an in situ cell death assay. Moreover, a significant decrease in the microvessel density as measured by the CD31 antigen staining was also seen. Curcumin is a therapeutic anti-cancer agent, as it significantly inhibits prostate cancer growth, as exemplified by LNCaP in vivo, and it has the potential to prevent the progression of this cancer to its hormone refractory state.\textsuperscript{63}

2. **Inhibition of NK-kappa B**
   Curcumin induced cytotoxicity in the LNCaP prostate cancer cell line. LNCaP cells express constitutively active NFkB, which is inhibited by curcumin. Pretreatment with curcumin inhibited the activation of NFkB and sensitized LNCaP cells to TRAIL. A similar increase in the sensitivity of LNCaP cells to TRAIL-induced apoptosis was observed following the inhibition of NFkB by dominant negative mutant IkappaBalpha, an inhibitor of NFkB. Finally, curcumin was found to inhibit NFkB by blocking phosphorylation of IkappaBalpha. We conclude that NFkB mediates resistance of LNCaP cells to TRAIL and that curcumin enhances the sensitivity of these tumor cells to TRAIL by inhibiting NFkB activation by blocking phosphorylation of IkappaBalpha and its degradation.\textsuperscript{64}

3: **Inhibition of bone metastasis: Inhibition of NFkB**
   There is increasing evidence that the stringent selective pressure imposed by androgen ablation therapy on the residual prostate cancer cells may actually accelerate the development of the hormone refractory and bone metastatic phenotype. The highly metastatic C4-2B prostate cancer cell line is already "programmed" to exhibit the bone-like properties that would at least in part explain its affinity to set up osseous metastases. Curcumin is able to interfere with the osteoblastic component, as well as the osteoclastic component of this phenotype, by interfering with the growth factor receptor pathways and by inhibiting the NFkB activation process. It is concluded that curcumin may inhibit the growth factor collaboration between the prostate cancer cells and the osteoblast/stromal cells, thus exhibiting a potential to prevent the establishment of bony metastases.\textsuperscript{65}

4. **Inhibits cancer, angiogenesis, and metastasis**
   Curcumin exerts significant effects on the actin cytoskeleton in prostate cancer cells, including altering microfilament organization and function. This is a novel observation that may represent an important mechanism by which curcumin functions as a chemopreventative agent, and as an inhibitor of angiogenesis and metastasis.\textsuperscript{66}

5. **Induction of apoptosis**
   Study results indicate that curcumin is a novel and potent inducer of apoptosis in both androgen-dependent and androgen-independent prostate cancer cells; this was accomplished by down-regulating apoptosis suppressor proteins and other crucial proteins such as the androgen receptor. It is concluded that curcumin may provide an alternative, nontoxic modality by which the clinician may prevent the progression of prostate cancer to its hormone refractory state or to treat advanced prostate cancer by forcing cells to undergo apoptosis.\textsuperscript{67}

6. **Down-regulates MMP-2 and 9**
   Matrix metalloproteinases (MMPs) are important prerequisites for tumor invasion and metastasis. The effects of curcumin on prostate cancer cell (DU-145) invasion were tested in both in vitro and in vivo. Zymography and ELISA were utilized in order to determine the MMP-2 and MMP-9 activity. Matrigel...
invasion assay was performed to assess cellular invasion. A xenograft model was developed to examine tumorigenicity. Curcumin treatment resulted not only in a significant reduction in the expression of MMP-2 and MMP-9, but also effected the inhibition of invasive ability in vitro. Curcumin was also shown to induce a marked reduction of tumor volume, MMP-2, and MMP-9 activity in the tumor-bearing site. The metastatic nodules in vivo were significantly fewer in the curcumin-treated group than untreated group. Curcumin appears to constitute a potential agent for the prevention of cancer progression, or at least of the initial phase of metastasis in prostate cancer.\(^{68}\)

7. Curcuminoids and the isothiocynate PEITC from cabbage sprouts, synergistic against PC

Curcuminoids reduced the development of cancers in lab mice - as did a naturally-occurring substance called phenethyl isothiocyanate (PEITC). It is particularly abundant in the group of vegetables that includes watercress, cabbage, broccoli, Brussels sprouts, turnips, and cauliflower, the richest source being cabbage sprouts. When curcumin and PEITC are combined, the effect is even more pronounced. The bottom line is that PEITC and curcumin demonstrate significant cancer-preventive qualities in laboratory mice, and the combination of PEITC and curcumin are effective in treating established prostate cancers.

Mice were injected with curcumin or PEITC three times a week for four weeks, beginning a day before the introduction of the prostate cancer cells. The injections were found to significantly slow the growth of cancerous tumors. Using both together produced "even stronger effects." When the therapeutic potential of the substances on mice with well-established tumors was evaluated, they found that while PEITC or curcumin alone had little effect, combined they "significantly reduced" tumor growth.\(^{69}\)

8. Reduces prostate cancer: down-regulates androgen receptor

To study the effect of curcumin on the expression of prostate specific antigen (PSA), the AXSYM system-chemical luciferase method was used to examine the content of PSA in prostate cancer cell lines, LNCap after treatment with different doses of curcumin. pGL3-PSA luciferase expression vector, containing 640 bp DNA of PSA gene 5' promoter region was constructed and transfected into LNCap cell with lipofectin. Through detecting the activity of luciferase, the effect of curcumin on the promoter of PSA was studied. Western blotting was used to detect expression of androgen receptor (AR) in LNCap cell with different concentrations of curcumin. The results were that the expression of PSA was inhibited, and activity of luciferase was reduced by curcumin. There was also significant difference in AR expression as shown by Western blotting experiments after treatment of different doses of curcumin. Through inhibiting AR expression, curcumin reduced the function of PSA promoter and inhibited PSA protein expression.\(^{70}\)


Inflammation emerges as a risk factor for prostate cancer (PC) and mitogen activated protein kinase phosphatase-5 (MKP5), which is an important gene-regulator in PC, is enhanced by curcumin, as well as resveratrol and [6]-gingerol. The cytokines tumor necrosis factor (TNF)-alpha and interleukin (IL)-1beta increased p38-dependent nuclear factor kappa-B (NFkappaB) activation and expression of pro-inflammatory genes cyclooxygenase (COX)-2, IL-6, and IL-8, which is associated with the progression of prostate cancer. MKP5 over-expression decreased cytokine-induced NFkappaB activation, COX-2, IL-6, and IL-8 in normal prostatic epithelial cells, suggesting potent anti-inflammatory activity of MKP5. Pretreatment of cells with a p38 inhibitor mimicked the results observed with MKP5 over-expression, further implicating p38 inhibition as the main activity of MKP5. Curcumin regulated MKP5, subsequently decreasing cytokine-induced p38-dependent pro-inflammatory changes. Resveratrol and [6]-gingerol, also up-regulated MKP5. Moreover, the prostate cancer cell lines DU 145, PC-3, LNCap and LAPC-4 retained the ability to up-regulate MKP5 following curcumin, resveratrol and [6]-gingerol exposure.\(^{71}\)

10. Arrest the cell cycle of LNCap and PC3 cells at G(2), M phase and then induce cell apoptosis

After LNCap and PC3 cells were affected by 10, 25, 50, 75, 100 micromol/L curcumin respectively, the cell activity was assayed with methyl thiazolyl tetrazolium (MTT) method at 5, 12, and 24 hours. After 5 hours, the expression of IkappaBalpha in LNCap and PC3 cells were observed, and curcumin suppressed the proliferation of LNCap and PC3 cells in dose-dependent and time-dependent manners. Curcumin could
arrest the cell cycle of LNCaP and PC3 cells at G(2), M phase, and then induce cell apoptosis. The expression of IkappaBalpha in LNCaP cells had no significant difference after using curcumin (F = 0.129, P > 0.05). However, the expression of IkappaBalpha in PC3 cells increased gradually with the inducement of concentration-increased curcumin (F = 31.618, P < 0.05).

11. Blocks 12-LOX
Curcumin is an effective inhibitor of 12-LOX. Using a homology model of the three-dimensional structure of human 12-LOX, we did computational docking of curcuminoids to identify inhibitors superior to curcumin. Docking of the known inhibitors curcumin and NDGA to P-12-LOX was used to optimize the docking protocol for the system in study. Over 75% of the compounds of interest were successfully docked into the active site of P-12-LOX, many of them sharing similar binding modes. Curcuminoids that did not dock into the active site did not inhibit P-12-LOX. From a set of the curcuminoids that were successfully docked and selected for testing, two were found to inhibit human lipoxygenase better than curcumin. Additionally, the curcuminoids inhibiting 12-LOX were tested for their ability to reduce sprout formation of endothelial cells (in vitro model of angiogenesis). Only curcuminoids inhibiting human P-12-LOX and the known inhibitor NDGA reduced sprout formation. At IC(50), a substantial amount of 12-HETE can be produced by lipoxygenase, providing a stimulus for angiogenic sprouting of endothelial cells. Increasing the concentration of lipoxygenase inhibitors above IC(50), thus decreasing the concentration of 12(S)-HETE produced, greatly reduced sprout formation for all inhibitors tested.

12. Down-regulates Bcl-2, AKT, caspase-3, induced p53 apoptosis, & increases PTEN
In a recent study, curcumin inhibited growth and induced apoptosis in androgen-dependent and -independent prostate cancer cells, but had no effect on normal human prostate epithelial cells. Curcumin downregulated the expression of Bcl-2, and Bcl-XL and upregulated the expression of p53, Bax, Bak, PUMA, Noxa, and Bim. Curcumin upregulated the expression of p53 as well as its phosphorylation at serine 15, and acetylation in a concentration-dependent manner. Acetylation of histone H3 and H4 was increased in cells treated with curcumin, suggesting histone modification may regulate gene expression. Treatment of LNCaP cells with curcumin resulted in translocation of Bax and p53 to mitochondria, production of reactive oxygen species, drop in mitochondrial membrane potential, release of mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/HtrA2), activation of caspase-3 and induction of apoptosis. Furthermore, curcumin inhibited expression of phosphatidylinositol-3 kinase (PI3K) p110 and p85 subunits, and phosphorylation of Ser 473 AKT/PKB. Downregulation of AKT by inhibitors of PI3K (Wortmannin and LY294002) and AKT, or by dominant negative AKT increased curcumin-induced apoptosis, whereas transfection of constitutively active AKT attenuated this effect. Similarly, wild-type phosphatase and tensin homolog deleted from chromosome 10 (PTEN) enhanced curcumin-induced apoptosis and, in contrast, inactive PTEN (G129E and G129R) inhibited curcumin-induced apoptosis. Overexpression of constitutively active AKT inhibited curcumin-induced p53 translocation to mitochondria, and Smac release to cytoplasm, whereas inhibition of AKT by dominant negative AKT enhanced curcumin-induced p53 translocation to mitochondria and Smac release. Our study establishes a role for AKT in modulating the direct action of p53 on the caspase-dependent mitochondrial death pathway and suggests that these important biological molecules interact at the level of the mitochondria to influence curcumin sensitivity. These properties of curcumin strongly suggest that it could be used as a cancer chemopreventive agent.

The oncoprotein MDM2, a major ubiquitin E3 ligase of tumor suppressor p53, has been suggested as a novel target for human cancer therapy based on its p53-dependent and p53-independent activities. We have identified curcumin, which has previously been shown to have anticancer activity, as an inhibitor of MDM2 expression. Curcumin down-regulates MDM2, independent of p53. In a human prostate cancer cell lines PC3 (p53(null)), curcumin reduced
MDM2 protein and mRNA in a dose- and time-dependent manner, and enhanced the expression of the tumor suppressor p21 (Waf1/CIP1). The inhibitory effects occur at the transcriptional level and seem to involve the phosphatidylinositol 3-kinase/mammalian target of rapamycin/erythoblastosis virus transcription factor 2 pathway. Curcumin induced apoptosis and inhibited proliferation of PC3 cells in culture, but both MDM2 overexpression and knockdown reduced these effects. Curcumin also inhibited the growth of these cells and enhanced the cytotoxic effects of gemcitabine. When it was administered to tumor-bearing nude mice, curcumin inhibited growth of PC3 xenografts and enhanced the antitumor effects of gemcitabine and radiation. In these tumors, curcumin reduced the expression of MDM2. Down-regulation of the MDM2 oncogene by curcumin is a novel mechanism of action that may be essential for its chemopreventive and chemotherapeutic effects. Our observations help to elucidate the process by which mitogens up-regulate MDM2, independent of p53, and identify a mechanism by which curcumin functions as an anticancer agent.

Green Tea (Camellia sinensis)

In Green tea (Camellia sinensis), numerous biological activities have been reported including antimutagenic, antibacterial, hypcholesterolemic, antioxidant, antitumor, and cancer preventive activities. Evidence from epidemiologic studies indicate that frequent consumption of green tea is inversely associated with the risk of several types of human cancer, including prostate cancer, and studies with animal and in vitro cell culture models have revealed Green tea extract (GTE) with 95% polyphenols, and 40% EGCG, is an effective compound against cancer. Like curcuminoids, and resveratrol, the list of anti-cancer actions of GTE is endless. Some important specific actions against prostate cancer include:

- Induced apoptosis in a wide-range of cancer-cell lines: elevation of caspase 8 activity, activation of caspase-3,
- Inhibition of NFkB,
- Inhibits cancer-inducing inflammation and PG2: COX-2 inhibition,
- Inhibits angiogenesis: Binds tissue-type plasminogen activator (t-PA), an enzyme that facilitates tumor invasion in PC and other cancers,
- Inhibits Protein Kinase C, and reduces VEGF expression, suppression of VE-cadherin tyrosine phosphorylation and inhibition of Akt activation,
- Suppresses the activity of matrix metalloproteinase (MMP)-2 and MMP-9,
- Inhibits topoisomerase 1,
- Mediates mitogen-activated protein kinases (MAPKs)
- Reduces oxidative damage and tumor development as a result, producing enzymes that speed carcinogen removal and enhance DNA repair activity,
- Inhibition of phenol sulfotransferase,
- Induces p21, p21 and p27,
- Counteracts carcinogen-induced damage to the gap junction, and improves gap junction communication,
- Modulates insulin-like growth factors and receptors, down-regulating cancer growth,
- Inhibits aromatase activity,
- Down-regulates tNO.

The anti-cancer effects of GTE appear to be greatly enhanced by other anti-cancer compounds including curcumin, selenium, lycopene, and Grape skin and seed.

Ongoing research is demonstrating that the anti-cancer effects of GTE together with pomegranate concentrate (40%ellagic acid) against prostate cancer are synergistic and very promising.

Prostate cancer
Several epidemiological studies have correlated green tea consumption with reduced risk of prostate cancer. Evidence from epidemiological studies, by animal studies, and in vitro evidence suggest that consumption of tea is associated with decreased risk or progression of prostate cancer. Ongoing human, animal, and cultured studies are confirming this as well.\textsuperscript{123-128}

Emerging evidence and potential biological mechanisms for the role of green tea in prostate cancer prevention is reviewed.

**Prostate cancer (PC) 1**

Oral infusion of a polyphenolic fraction isolated from green tea at a human achievable dose (equivalent to six cups of green tea per day), significantly inhibits prostate cancer (PCA) development and metastasis in transgenic adenocarcinoma of a mouse prostate (TRAMP) model that closely mimics the progressive form of human prostatic disease.\textsuperscript{127}

**PC 2**

Five days before they were to undergo radical prostatectomy, 20 men with prostate cancer were randomly assigned to consume daily either five cups of green tea, five cups of black tea, or diet or regular soda containing no tea polyphenols. Their blood serum was then collected and added to prostate tissue samples from a commercially available prostate cancer cell line called LNCaP. When the scientists compared the level of total polyamine to the total polyphenol content, the tea drinkers showed a significant negative correlation - the more tea components in the tissue, the less of the polyamines associated with malignancy. When the scientists measured the proliferation of prostate cancer cells, there was a significant decrease in how fast new cancer cells appeared for the men who had consumed either green or black tea.\textsuperscript{123}

**Green Tea and soy synergistically inhibit PC 3**

The objective of the present study was to identify possible synergistic effects between soy and tea components on prostate tumor progression in a mouse model of orthotopic androgen-sensitive human prostate cancer. Soy phytochemical concentrate (SPC), black tea and green tea were compared with respect to tumorigenicity rate, primary tumor growth, tumor proliferation index and microvessel density, serum androgen level, and metastases to lymph nodes. SPC, black tea, and green tea significantly reduced tumorigenicity. SPC and black tea also significantly reduced final tumor weights. The combination of SPC and black tea synergistically inhibited prostate tumorigenicity, final tumor weight, and metastases to lymph nodes in vivo. The combination of SPC and green tea synergistically inhibited final tumor weight, metastasis, and significantly reduced serum concentrations of both testosterone and DHT in vivo. Inhibition of tumor progression was associated with reduced tumor cell proliferation and tumor angiogenesis. This study suggests that further research is warranted to study the role of soy and tea combination as effective nutritional regimens in prostate cancer prevention.\textsuperscript{129}

**PC 4**

To investigate whether green tea consumption has an etiological association with prostate cancer, a case-control study was conducted in Hangzhou, southeast China, during 2001-2002. The cases were 130 incident patients with histologically confirmed adenocarcinoma of the prostate. The controls were 274 hospital inpatients without prostate cancer or any other malignant diseases, and matched to the age of cases. Information on duration, quantity and frequency of usual tea consumption, as well as the number of new batches brewed per day, were collected by face-to-face interview using a structured questionnaire. The risk of prostate cancer for tea consumption was assessed using multivariate logistic regression adjusting for age, locality, education, income, body mass index, physical activity, alcohol consumption, tobacco smoking, total fat intake, marital status, age at marriage, number of children, history of vasectomy, and family history of prostate cancer. Among the cases, 55.4% were tea drinkers compared to 79.9% for the controls. Almost all the tea consumed was green tea. The prostate cancer risk declined with increasing frequency, duration, and quantity of green tea consumption. The adjusted odds ratio (OR), relative to non-tea drinkers, were 0.28 (95% CI = 0.17-0.47) for tea drinking, 0.12 (95% CI = 0.06-0.26) for drinking tea over 40 years, 0.09 (95% CI = 0.04-0.21) for those consuming more than 1.5 kg of tea leaves yearly, and 0.27 (95% CI = 0.15-
0.48) for those drinking more than 3 cups (1 litre) daily. The dose response relationships were also significant, suggesting that green tea is protective against prostate cancer.  

PC 5

Men at a high risk of contracting prostate cancer had their risk slashed after taking green tea extract for a year. After a year’s oral administration of GTE, only one man in a group of 32 at high risk for prostate cancer developed the disease, compared to nine out of 30 in a control. The researchers said that earlier studies demonstrated primarily that green tea catechins were safe for use in humans; while they have newly identified that EGCG targets prostate cancer cells specifically for death without damaging the benign controls.

Scientists added that they had identified Clusterin, the most important gene involved in apoptosis, or programmed cell death in the prostate, as a possible mediator of catechins action. “EGCG induced death in cancer cells, not normal cells, inducing Clusterin expression.” The patients used in the study were men aged between 45 and 75 with high-grade prostatic intraepithelial neoplasia – premalignant lesions that presage invasive prostate cancer within one year in nearly a third of cases and for which no treatment was given. Of the 62 volunteers, 32 received three tablets per day of 200 mg GTEs, while the remainder was given a placebo. The researchers carried out follow-up biopsies after six and 12 months. Only one case of prostate cancer was diagnosed among those receiving 600 mg daily of GTEs, while nine cases were found in the untreated group. The 30 percent incidence rate among controls is consistent with previous findings, as was the absence of significant side effects or adverse reactions. The 600 mg-per-day dosage of GTE given to the participants in the study was two times the amount of green tea consumed daily in China, where 10 cups a day is normal.

PC 6

The present study investigated the degradation of EGCG and its effect on prostate cancer cell in the presence of Cu2+. EGCG was incubated with prostate cancer cells, LNCaP, and pretreated with or without Cu2+. EGCG in F-12 medium was quantified using HPLC and the viability of cells was assessed by gel electrophoresis, flow cytometry, and electron microscope. The results of HPLC showed that EGCG degraded completely within 12 h in F-12 medium with or without Cu2+. Gel electrophoresis and flow cytometry did not detect apoptosis of LNCaP cells when they were incubated with EGCG. Electron microscopy examination revealed that EGCG-Cu2+ complex led to damage of cytoplasm membrane in LNCaP cells. It was speculated that not EGCG, but its oxide and complex with Cu2+, are the bioactive components responsible for its cytotoxicity to LNCaP prostate cancer cells.

PC 7: Inhibits IGF-1

The polyphenols present in green tea help prevent the spread of prostate cancer by targeting molecular pathways that shut down the proliferation and spread of tumor cells, as well as inhibiting the growth of tumor nurturing blood vessels. A team of researchers from the University of Wisconsin and Case Western Reserve University in Cleveland, Ohio, have documented the role of green tea polyphenols in modulating the insulin-like growth factor-1 (IGF-1)-driven molecular pathway in prostate tumor cells in a mouse model for human prostate cancer. EGCG, present in green tea, inhibits IGF-1 and also may interact specifically with a component of a leptin-independent appetite control pathway. Endocrine changes induced by parenteral administration of EGCG may relate to the observed growth inhibition and regression of human prostate and breast tumors in athymic mice treated with EGCG as well as play a role in the mechanism by which EGCG inhibits cancer initiation and promotion in various animal models of cancer.

Prostate cancer 8:

One of the primary signal transduction pathways activated by IGF-1 binding to its receptor is the Akt pathway. This study determined that phosphorylated Akt levels are very low in serum-starved human normal prostate epithelial cells (PrEC) and Du145 prostate carcinoma cells, and that treatment of these cells with IGF-I results in a rapid and sustained phosphorylation of Akt. Pre-treatment of PrEC and Du145 cells
with doses as low as 20 microg/ml of a mixture of black tea polyphenols (BTP) substantially reduced IGF-I-mediated Akt phosphorylation. This effect of BTP appears to be due partially to the reduced autophosphorylation of IGF-I receptor-1 in BTP-treated cells. BTP pre-treatment also decreased downstream effects of Akt activation including phosphorylation of glycerol synthase kinase-3, increased cyclin D1 protein levels and increased DNA synthesis. Our results indicate that polyphenols from black tea inhibit the IGF-I signal transduction pathway, which has been linked to increased prostate cancer incidence in human populations and, therefore could prevent prostate cancer.\textsuperscript{134}

**PC 9 and 10**

Prostate cancer cells treated with EGCG, stabilized the p53 protein, and NF-kB transcription activity was inhibited.\textsuperscript{135} In another experimental study, the anti-apoptotic function of Bcl-2 proteins was also inhibited.\textsuperscript{136}

**PC 11: Synergistic with Lycopene**

Green tea and Lycopene consumption significantly reduce the risk of prostate cancer. An investigation was conducted that looked at the possible joint effect of lycopene and green tea on prostate cancer risk. A case-control study was conducted in Hangzhou, China, with 130 prostate cancer patients and 274 hospital controls. Information on tea and dietary intakes, and possible confounders, was collected using a structured questionnaire. The risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed using multivariate logistic regression models. Prostate cancer risk was reduced with increased consumption of green tea. The protective effect of green tea was significant (odds ratio 0.14, 95% CI: 0.06-0.35) for the highest quartile relative to the lowest after adjusting for total vegetables and fruits intakes and other potential confounding factors. Intakes of vegetables and fruits rich in lycopene were also inversely associated with prostate cancer risk (odds ratio 0.18, 95% CI 0.08-0.39). Interaction analysis showed that the protective effect from tea and lycopene consumption was synergistic (p<0.01). This study suggests that habitual drinking of tea and intakes of vegetables and fruits rich in lycopene could lead to a reduced risk of prostate cancer.\textsuperscript{137}

**PC 12**

Green Tea Catechins (GTCs) which have proven effective at inhibiting cancer growth in several laboratory studies were recently studied in a pilot clinical trial in HG-PIN subjects showing that only 1/30 tumor was diagnosed in subjects treated for 1 year with 600 mg/die GTCs, while 9/30 cancers were found in placebo-treated men.\textsuperscript{138}

**PC 13: Synergistic with COX-2 inhibitor**

EGCG was tested alone and in combination with specific COX-2 inhibitors on the growth of human prostate cancer cells both in vitro and in vivo. Human prostate cancer cells LNCaP, PC-3, and CWR22Rnu1 were treated with EGCG and NS398 alone and in combination, and their effect on growth and apoptosis was evaluated. In vivo, athymic nude mice implanted with androgen-sensitive CWR22Rnu1 cells were given green tea polyphenols (0.1% in drinking water) and celecoxib (5 mg/kg, i.p., daily, 5 days per week), alone and in combination, and their effect on tumor growth was evaluated. Combination of EGCG (10-40 micromol/L) and NS-398 (10 micromol/L) resulted in enhanced (a) cell growth inhibition; (b) apoptosis induction; (c) expression of Bax, pro-caspase-6, and pro-caspase-9, and poly(ADP)ribose polymerase cleavage; (d) inhibition of peroxisome proliferator activated receptor gamma; and (e) inhibition of nuclear factor-kappaB compared with the additive effects of the two agents alone, suggesting a possible synergism. In vivo, combination treatment with green tea polyphenols and celecoxib resulted in enhanced (a) tumor growth inhibition, (b) lowering of prostate-specific antigen levels, (c) lowering of insulin-like growth factor-I levels, and (d) circulating levels of serum insulin-like growth factor binding protein-3 compared with results of single-agent treatment.\textsuperscript{139}

Dosage: It is more efficacious to take powder green tea extract (95% polyphenols/40% EGCG) rather than drinking tea as a cancer adjuvant therapy. An appropriate dose for cancer inhibition including VEGF blockade would be 3-4 grams of standardized green tea extract (95% polyphenols/60% catechins). Caffeine
has been shown to potentiate tea polyphenols, such as EGCG, so it is preferable not to decaffeinate the tea.

**Grape seed extract (GSE)**

Grape seeds contain mainly phenols, such as proanthocyanidins (oligomeric proanthocyanidins). Scientific studies have shown that the antioxidant power of proanthocyanidins is 20 times greater than vitamin E and 50 times greater than vitamin C. Extensive research suggests that grape seed extract is beneficial in many areas of health because of its antioxidant effect to bond with collagen, promoting youthful skin, cell health, elasticity, and flexibility. Studies have shown that proanthocyanidins help to protect the body from sun damage; to improve vision; to improve flexibility in joints, arteries, and body tissues such as the heart; and to improve blood circulation by strengthening capillaries, arteries, and veins. The most abundant phenolic compounds isolated from grape seed are catechins, epicatechin, procyanidin, and some dimers and trimers. GSE contains an important group phenolic compounds referred to as oligomeric proanthocyanidin complexes (OPCs) which are primarily known for their antioxidant activity. However, these compounds have also been reported to demonstrate antibacterial, antiviral, anticarcinogenic, anti-inflammatory, anti-allergic, and vasodilatory actions. In addition, they have been found to inhibit lipid peroxidation, platelet aggregation, capillary permeability and fragility, and to affect enzyme systems including phospholipase A2, COX, and LOX. Based on these reported findings, OPCs may be a useful component in the treatment of a number of conditions.  

**General multi-mechanistic, anti-cancer actions:**

- Anti-Aging/Antioxidant - scavenge oxygen free radicals 20-50x greater than that of vitamin C or E,
- Down-regulates NF-kB,
- Increase Cip1/p21,
- Anti-angiogenic via VEGF inhibition; upregulates IGF binding protein-3,
- Inhibition: IGF-II,
- MMP-2 and 9 inhibition,
- Regulates tumor suppressor genes: downregulates bcl-2 and oncogene c-myc,
- Inhibition of tNOX (combined with Green tea extract),
- Chemotherapy sensitizer,
- Inhibits aromatase,
- Protects vital organs: protects against acetaminophen induced liver and kidney damage, ameliorates chronic pancreatitis,
- Cytoprotective: Removes toxins and heavy metals from the body.

**GSE and Prostate cancer (PC)**

**PC 1: Apoptosis induction**

GSE induced both caspase-dependent and caspase-independent apoptosis as evidenced by cytochrome c and apoptosis-inducing factor release into cytosol. Additional studies revealed that GSE causes DNA damage-induced activation of ataxia telangiectasia mutated kinase and Chk2, as well as p53 Ser(15) phosphorylation and its translocation to mitochondria, suggesting this to be an additional mechanism for apoptosis induction. GSE-induced apoptosis, cell growth inhibition, and cell death were attenuated by pretreatment with N-acetylcysteine and involved reactive oxygen species generation.

**PC 2: Upregulates p21**

Gallic acid, a major active agent responsible for grape seed extract activity, in the treatment of DU145 prostate cancer cells, resulted in a strong cell growth inhibition, cell cycle arrest, and apoptotic death in a dose- and time-dependent manner; together with a decrease in cyclin-dependent kinases and cyclins, but strong induction in Cip1/p21.

**PC 3: MMP-2 and -9, and NF-kB inhibition**
Treatment of androgen-sensitive LNCaP cells with a synthetic androgen R1881 resulted in an increase of MMP-2 and -9, which were completely abrogated in the presence of GSE (20-60 microg/ml). The inhibition of metastasis-specific MMPs in tumor cells by proanthocyanidins from grape seeds is associated with the inhibition of activation of MAPK and NF kappa B pathways, and thus provides the molecular basis for the development of GSP as a novel chemopreventive agent for both androgen-sensitive and -insensitive prostate cancer therapies.\(^\text{145}\)

PC 4: Aromatase inhibition

GSE contains high levels of procyanidin dimers that have been shown to be potent inhibitors of aromatase. GSE down-regulates of two transcription factors, cyclic AMP-responsive element binding protein-1 (CREB-1) and glucocorticoid receptor (GR). CREB-1 and GR are known to up-regulate aromatase gene expression. \(^\text{146}\)

PC 5: Procyanidin B2-3,3'-di-O-gallate from GSE potent inhibitors of PC

The focus of this study was to purify 14 procyanidins from the fractions and to identify those with highest activity toward growth inhibition, cell death, and apoptosis in DU145 cells. The most active procyanidin was identified by mass spectrometry and enzymatic hydrolysis as the 3,3'-di-O-gallate ester of procyanidin dimer B2 (Epi-Epi). B2-digallate exhibited dose-dependent effects on DU145 cells over the range 25-100 \(\mu\)M, whereas gallic acid (GA) exhibited comparable activity at lower doses but was highly lethal at 100 \(\mu\)M. Structure-activity studies demonstrated that all three hydroxyl groups of GA are necessary for activity, but a free carboxylic acid group is not required even though esterification reduced the activity of GA. These data, and the fact that non-esterified B2 exhibited little or no activity, suggest that the galloyl groups of B2-digallate are primarily responsible for its effects on DU145 cells. Taken together, these data identify procyanidin B2-3,3'-di-O-gallate as a novel, biologically active agent in GSE that should be studied in greater detail to determine its effects against prostate cancer. \(^\text{147}\)

Daily dosage should be 200-800 mg.

Milk thistle (Silymarin marianum)

Milk Thistle (Silybum marianum, Family Asteraceae) is one of the earliest known herbal medicines with hepatoprotective effects, and it has been documented in ancient literature as a plant specifically for liver ailments, and removing obstructions of the liver as well as the spleen.

The extract of milk thistle is basically a concentrate of the flavolignan silymarin (80%), which itself represents a mixture of four isomeric flavonoids: silibinin, isosilibinin, silydianin and silychristin. Silibinin is the major active and most studied constituent in silymarin. \(^\text{148}\)

Silibinin inhibits prostate cancer through multiple mechanisms:

1) NF-kappaB (nuclear factor-kappa B) pathways,
2) VEGF modulation,
3) EGFR modulation,
4) Insulin-like growth factor-1 receptor (IGF-1R) signaling,
5) Modulates cell-cycle regulators, including cyclin-dependent kinases (CDKs), Kip1/p27 and Cip1/p21, and cyclins for its anticancer efficacy against PCA,
6) Telomerase inhibition.

Silymarin and PC inhibition

The underlying mechanisms of silibinin/silymarin efficacy against PCA involve alteration in cell cycle progression, and inhibition of mitogenic and cell survival signaling, such as epidermal growth factor receptor, insulin-like growth factor receptor type I, and nuclear factor kappa B signaling. Silibinin also synergizes the therapeutic effects of doxorubicin in PCA cells, making it a strong candidate for combination chemotherapy. \(^\text{149}\)
PC 1: Apoptosis induction

Silymarin and silibinin (50-100 microg/ml) inhibited cell proliferation, induced cell death, and caused G1 and G2-M cell cycle arrest in a dose/time-dependent manner in prostate cancer cells. Also noted was a decrease in cyclin D1, cyclin D3, cyclin E, cyclin-dependent kinase (CDK)4, CDK6 and CDK2 protein levels, and CDK2 and CDK4 kinase activity, together with an increase in CDK inhibitors (CDKIs) Kip1/p27 and Cip1/p21. Further, both agents caused cytoplasmic sequestration of cyclin D1 and CDK2, contributing to G1 arrest.150

PC 2: Anti-angiogenic – inhibits VEGF

The antiangiogenic effects of silymarin were also exemplified in a study whereby exposure of DU145 prostate, as well as MCF-7 and MDA-MB-468 breast cancer cells to silymarin resulted in a dose-dependent decrease in the secreted vascular endothelial growth factor (VEGF).151

PC 3: Anti-angiogenic – inhibits VEGF

Another recent animal study confirmed anti-tumor/anti-angiogenic effects when silibinin decreased lung tumor expression of VEGF, and of inducible nitric oxide synthase and cyclooxygenase-2, two enzymes that promote tumor growth and progression by inducing expression of VEGF.152 In a squamous cell carcinoma (OSCC) study, the anti-metastatic effect of silibinin showed a marked inhibition of invasion and motility, with 89% and 66.4% of inhibition, reducing the expression of MMP-2 and u-PA, known contributors to cancer metastasis.153

PC 4: Inhibits chemical-induced PC

In a recent animal study administration of silymarin at 100 or 500 ppm dose level for 40 weeks significantly reduced the incidence of prostatic adenocarcinoma in 3, 2-dimethyl-4-aminobiphenyl (DMAB) induced prostate carcinogenesis.154 There was no toxicity observed in the animals fed with silymarin.

PC 5: Inhibits DHT telomerase

The androgen sensitive prostate cancer cell line LNCaP is strongly positive for dihydrotestosterone (DHT) dependent telomerase activity, which is an important factor in cellular immortality and carcinogenesis. In a recent study, the potential of silibinin as an anticancer agent was examined. It demonstrated an ability to down-regulate telomerase activity and PSA levels. The down-regulation of PSA by silibinin, and its counteraction on DHT effects, indicates that this compound can interact with the expression of genes that are regulated through the androgen receptor.155

PC 6: Tumor suppression

Silibinin inhibits growth of prostate cancer cells from human and animal origins, and also suppresses human prostate tumor xenograft growth in nude mice. Silibinin also inhibits prostate cancer growth in the transgenic adenocarcinoma of mouse prostate (TRAMP) mouse model. Now, silibinin has been entered into phase I/II clinical trials in human PCA patients where preliminary observations were suggestive of its further study in a larger base of the patient population.156

PC 7: Isosilybin A and B suppress PC via cell cycle arrest and apoptosis induction

The anticancer efficacy of two pure compounds, isosilybin B and isosilybin A from silymarin, in human prostate carcinoma LNCaP and 22Rv1 cells was tested. Treatment with isosilybin B and isosilybin A resulted in growth inhibition and cell death, together with a strong G1 arrest and apoptosis in both the cell lines. In the studies examining changes in cell cycle and apoptosis regulators, both isosilybin B and A resulted in a decrease in the levels of both cyclins (D1, D3, E and A) and CDKs (Cdk2, Cdk4 and
Cdc25A), but caused an increase in p21, p27, and p53 levels, except in 22Rv1 cells where isosilybin B caused a decrease in p21 protein level. Isosilybin B- and isosilybin A-induced apoptosis was accompanied with an increase in the cleavage of PARP, caspase-9, caspase-3, and a decrease in survivin levels. Compared to LNCaP and 22Rv1 cells, the antiproliferative and cytotoxic potentials of isosilybin B and isosilybin A were of much lesser magnitude in non-neoplastic human prostate epithelial PWR-1E cells suggesting the transformation-selective effect of these compounds. Together, this study for the first time identified that isosilybin B and isosilybin A, two diastereoisomers isolated from silymarin, have anti-prostate cancer activity that is mediated via cell cycle arrest and apoptosis induction.\textsuperscript{157}

**PC 8: Potent antiproliferative, proapoptotic, and antiangiogenic efficacy**

In this present study, the effect of silybin feeding [0.05% and 0.1% (w/w) in the diet for 60 days] on the prognostic biomarkers (namely, proliferation, apoptosis, and angiogenesis) in the prostate tumor xenografts was investigated. Immunohistochemical analysis of the tumors for proliferating cell nuclear antigen and Ki-67 showed that silybin decreases proliferation index by 28-60% and 30-60% (P<0.001) as compared with their controls, respectively. There was a 7.4-8.1-fold (P<0.001) increase in apoptotic cells in silybin-fed groups over that of control group. Silybin also increased activated caspase 3-positive cells by 2.3-3.6-fold (P<0.001). CD31 staining for tumor vasculature showed a significant decrease (21-38%; P<0.001) in tumor microvessel density in silybin-fed groups of tumors as compared with control group of tumors. Vascular endothelial growth factor and insulin-like growth factor-binding protein 3 protein expression were both slightly decreased in the silybin-fed groups compared with the control group, respectively. Silybin, based on this and other studies done in vivo, possesses potent antiproliferative, proapoptotic, and antiangiogenic efficacy against prostate cancer.\textsuperscript{158}

**PC 9: Human study**

In a recent human study involving a supplement that included Silymarin, soy isoflavones concentrate, and lycopene; 42 men with at least 5 PSA measurements were tested. Per protocol analysis showed a significant decrease in PSA slope (p = 0.030) and (2) log PSA slope (p = 0.041). This translates into a 2.6 fold increase in the PSA doubling time from 445 to 1150 days for the supplement and placebo periods.\textsuperscript{159}

**PC 10: Inhibiting effect on androgen hormone imbalances: DHT and estrogens**

The different effects of dihydrotestosterone (DHT) and testosterone represent a rational basis for specific herbal extracts to target 5 alpha-reductase inhibition. 5 alpha-reductase is most active in the prostate, but is also active in other organs and tissues, with different distribution of at least two 5 alpha-reductase isoenzymes. Progesterone-5 alpha-reductase is another enzyme with 5 alpha-reductase activity that is present in human tissues including the prostate. Acknowledging the several 5 alpha-reductase activities present, basic 5 alpha-reductase inhibitors that are synthetic steroids (e.g. finasteride--Proscar) are being tried for prostate cancer prevention. Non-steroidal 5 alpha-reductase inhibitors (e.g. polynsaturated fatty acids from pumpkin seeds) are effective components, but their effects are mild. Extracts of several well-known plants, such as Serenoa repens seeds (saw palmetto), Pygeum africanum, Urtica (nettles) roots, and catequine structures from the green tea belong to this group. Beside androgens, participation of estrogens in the origin and development of benign prostatic hyperplasia and prostate cancer is evident. Inhibition of the "aromatase" complex, which catalyzes transformation of androgens to estrogens, most likely contributes to the complexity of phytotherapeutic effects.\textsuperscript{160}

**PC 11: Increases secreted levels of insulin-like growth factor binding protein 3 (IGFBP-3)**

Silybin possesses anticancer activity against both hormone-dependent and -independent prostate cancer. Studies aiming at testing in vivo efficacy of silymarin/ silybin revealed that dietary feeding of silybin to animals bearing prostate cancer significantly inhibits tumor growth and increases secreted levels of insulin-like growth factor binding protein 3 (IGFBP-3) in plasma without any toxicity symptoms in the animals fed.\textsuperscript{161} Other \textit{in vitro} studies confirms that silybin upregulates the expression of IGFBP-3, and thus causes increased secreted IGFBP-3 in conditioned medium.\textsuperscript{162} Cell survival signaling and proliferation is partially mediated by IGFBP-insulin like growth factor-1 (IGF-1)/IGF-1R (insulin like growth factor-1 receptor) and
Prostate Cancer is often constitutively upregulated in human prostate carcinoma cell lines and is often implicated in advanced and androgen independent stage of prostate cancer.163

Reishi (Ganoderma lucidum)

Reishi (Ganoderma lucidum), as a 15:1 powdered extract (RPE), whereby both the water-soluble polysaccharides are pulled out, followed by an alcohol extraction to pull out the triterpenes. It should be then concentrated to yield 10% polysaccharides and 4% triterpenes. RPE has shown radiation and chemotherapy-protective ability due to its stimulating effects on bone marrow. Reishi can also alleviate many negative symptoms such as weakness, dizziness, and sleeplessness. Ganoderma polysaccharides promote the production of IL-2 and markedly enhance the cytotoxicity of T lymphocytes.164 RPE has also demonstrated strong activity against a wide range of prostate cancer cell lines.165

Reishi’s effects against PC

PC 1: Inhibition of NFkappaB and AP-1: down-regulating uPA

Recently it has been demonstrated that RPE inhibits constitutively active transcription factors NF-kB and AP-1 which resulted in the inhibition of expression of urokinase-type plasminogen activator (uPA) and its receptor uPAR, important targets for prostate cancer inhibition. RPE also suppressed cell adhesion and cell migration of highly invasive prostate cancer cells, suggesting its potency to reduce tumor invasiveness. Thus, RPE clearly demonstrates anticancer activity in experiments with cancer cells, and has possible therapeutic potential as a dietary supplement for an alternative therapy for prostate and other cancers. In one experiment conducted, RPE inhibited constitutively active NF-kB, demonstrating strong inhibition of cancer cell migration. RPE induces apoptosis, inhibits cell proliferation, and suppresses cell migration of highly invasive human prostate cancer cells PC-3.165,166

PC 2: Down-regulates PI 3-kinase & NF-jB through the suppression of uPA

Phosphatidylinositol 3-kinase (PI 3-kinase) and nuclear factor-j B (NF-jB) regulate motility of highly invasive human breast cancer cells by the secretion of urokinase-type plasminogen activator (uPA). Ganoderma lucidum inhibited constitutively active transcription factors AP-1 and NF-jB in breast MDA-MB-231 and prostate PC-3 cancer cells. Furthermore, Ganoderma inhibited the expression of uPA and uPA receptor (uPAR), as well secretion of uPA, resulted in the suppression of the migration of MDA-MB-231 and PC-3 cells.167

PC 3: Increases p21: resulting in cancer cell apoptosis

In one experiment, RPE significantly showed an inhibitory effect, in a dose- and time-dependent manner, on cell proliferation, cell cycle, and apoptosis in human prostate cancer cells (PC-3). Mechanisms involved included down-regulation of the expression of cyclin B and Cdc2, and by the up-regulation of p21 expression. The inhibition of cell growth was also demonstrated by cell cycle arrest at G2/M phase. Furthermore, RPE induced apoptosis of PC-3 cells with a slight decrease in the expression of NF-kappaB-regulated Bcl-2 and Bcl-xl. Thus RPE, like all other botanical agents, exerts its effect on cancer cells by multiple mechanisms and may have potential therapeutic use for the prevention and treatment of cancer.168

PC 4: Inhibition of angiogenesis - Down-regulates VEGF & TGF-B1

RPE inhibited angiogenesis related to prostate cancer. It inhibits the early event in angiogenesis, capillary morphogenesis of the human aortic endothelial cells, by the inhibition of constitutively active AP-1 in prostate cancer cells, resulting in the down-regulation of secretion of VEGF and TGF-beta1 from PC-3 cells. Thus, RPE modulates the phosphorylation of Erk1/2 and Akt kinases in PC-3 cells, which in turn inhibits the activity of AP-1.169,170

Testing of various samples of Ganoderma lucidum demonstrate a wide range of effectiness: some showed a strong inhibition of cancer cell migration comparable to the inhibition of constitutively active NF-kappaB,
whereas other samples showed less or no activity in highly invasive estrogen receptor-negative breast cancer cells or androgen receptor-negative prostate cancer cells, respectively.\textsuperscript{171}

**PC 5: Reduces DHT within the prostate: 5alpha-reductase inhibition**

The inhibitory effects of methanol extracts of 19 edible and medicinal mushrooms on 5alpha-reductase activity were examined. The extract of Ganoderma lucidum showed the strongest 5alpha-reductase inhibitory activity. The treatment with the fruit body of Ganoderma l. or the extract prepared from it significantly inhibited the testosterone-induced growth of the ventral prostate in castrated rats. This effect can have a beneficial effect on inhibiting both benign and cancerous growths within the prostate.\textsuperscript{172}

Because of the availability of *Ganoderma lucidum* from different sources, it is advisable to test for its biologic activity.\textsuperscript{173}

The therapeutic dosage of the 15:1 extract concentration is 3-6 grams daily.

**Rabdosia (Rabdosia rubescens Hora)**

Rabdosia is used traditionally to treat many forms of cancer, especially breast and esophageal cancers. The herb contains several terpenes which have anticancer activity, including oridonin, rubescensine B, and ponicidin. The diterpenoids, oridonin, and ponicidin possess significant antiangiogenic activity.\textsuperscript{174}

This herb is widely used in the province of Hunan to treat esophageal cancer. From August 1974 to January 1987, 650 cases of moderately and advanced esophageal carcinoma were treated with a combination of chemotherapy and Rabdosia rubescens, or Rabdosia rubescens and/or traditional Chinese medicinal prescription. After treatment, 40 patients survived for over 5 years (5-year survival rate 6.15%): 32 for over 6 years, 23 for more than 10 years, 5 for more than 15 years, and 20 died of tumors (16 cases) or other diseases (4 cases). There were 20 patients who are still living and some of them have been living for more than 18 years.\textsuperscript{175}

**Rabdosia has shown to inhibit many forms of cancer through multiple mechanisms including:**

- Inhibition of NFkB;
- Up-regulation of p21;
- Down-regulation of Bcl-2;
- Inhibition of Telomerase;
- Anti-angiogenic: Inhibition of VEGF.\textsuperscript{176-181}

**Inhibition of Prostate Cancer**

Rabdosia has potent anti-prostate cancer actions. Oridonin induced apoptosis and G0/G1 cell cycle arrest in LNCaP prostate cancer cells. In addition, expression of p21waf1 was induced in a p53-dependent manner. Taken together, oridonin inhibited the proliferation of cancer cells via apoptosis and cell cycle arrest with p53 playing a central role in several cancer types which express the wild-type p53 gene. Oridonin may be a novel, adjunctive therapy for a large variety of malignancies.\textsuperscript{182,183}

**Licorice, (*Glycyrrhiza glabra* & other spp.)**

Licorice, (*Glycyrrhiza glabra* & other spp.), a member of the pea family (Fabaceae) is one of the oldest and most frequently employed botanicals in Chinese medicine. Licorice increases overall vitality while it moderates and harmonizes the characteristics of other plants, to bring the formula together energetically. In Traditional Chinese Medicine (TCM) it is considered, because of this action, to be a synergist and is used in many classic formulas as a supporting and harmonizing agent. A number of pharmaceutical effects of licorice are known, which include anti-inflammatory, antiviral, antibacterial, antiulcer, anticarcinogenesis, and others. Inappropriate use of licorice can produce pseudoaldosteronism by inactivating 11beta-hydroxysteroid-dehydrogenase and by binding to mineralocorticoid receptors. Licorice possesses many other therapeutic properties as to potentiate the action of cortisol.\textsuperscript{184}
Licorice extract protects against carcinogen-induced DNA damage and may be a suppressive agent as well against cancer.\textsuperscript{185}

Glycyrrhizic acid, a major component in licorice, is an inhibitor of lipoxygenase (LOX), cyclooxygenase (COX), and protein kinase C. It also down-regulates when over-active, the epidermal growth factor receptor (EGF). Licorice polyphenols also induce apoptosis in cancer cells.\textsuperscript{186}

The angioinhibitory activity of Licorice (\textit{G. glabra}) extract was confirmed by its inhibition of angiogenesis in in vivo assays, peritoneal, and chorioallantoic membrane assay. Reduction in the levels of VEGF and microvessel density count in mice treated with Licorice extract indicated that the plant extract decreased VEGF production and the induction of neovascularization.\textsuperscript{187}

Isoliquiritigenin, a chalcone isolated from licorice root, significantly reduced pulmonary metastasis.\textsuperscript{188} Glabridin, an isoflavanoid in licorice, exhibited varying degrees of estrogen receptor agonism in different tests and demonstrated growth-inhibitory actions on breast cancer cells.\textsuperscript{189}

\textbf{Inhibition of Prostate cancer}

\textbf{PC 1}

Recent studies have shown that licorice possesses prostate cancer inhibiting ability especially when combined with other herbs including Chinese skullcap, and rabdosia r.\textsuperscript{190}

\textbf{PC 2: Induction of apoptosis- Licochalcone, an estrogenic-like flavonoid suppresses PC}

Licochalcone (LA) is a novel estrogenic-like flavonoid isolated from licorice root suppressed, androgen-independent p53-null PC-3 prostate cancer cells. LA induced modest level of apoptosis, but had more pronounced effects on cell cycle progression, arresting cells in G2/M, accompanied by suppression of cyclin B1 and cdc2. It also inhibited phosphorylation of Rb, specifically phosphorylation of S780 with no change of phosphorylation status of T821; it decreased expression of transcription factor E2F concurrent with reduction of cyclin D1; and showed down-regulation of CDKs 4 and 6, but increased cyclin E expression.\textsuperscript{191}

\textbf{PC 3: Induction of apoptosis}

Isoliquiritigenin (ISL), a simple chalcone derivative, 4,2',4'-trihydroxychalcone found in licorice, inhibits prostate cancer cell growth by the induction of apoptosis. This is mediated through mitochondrial events which are associated with an evident disruption of the mitochondrial membrane potential along with the release of cytochrome c and Smac/Diablo, and the activation of caspase-9.\textsuperscript{192}

\textbf{PC 4: Inhibits cancer cell proliferation}

DU145 and LNCaP prostate cancer cell lines were used as targets. We examined the effects of isoliquiritigenin on cell proliferation, cell cycle regulation, and cell cycle-regulating gene expression. Further, we investigated the effects of isoliquiritigenin on the GADD153 mRNA and protein expression, and promoter activity. Isoliquiritigenin significantly inhibited the proliferation of prostate cancer cell lines in a dose-dependent and time-dependent manner.\textsuperscript{193}

\textbf{Frankincense (\textit{Boswellia serrata})}

\textit{Boswellia serrata}, contains gum-like resinous active triterpenoids referred to as boswellic acids, which exhibit potent anti-inflammatory, analgesic, ulcer protective, lipid-lowering, and anti-cancer activity. Extract strength up to 75% boswellic acids are available, and are what is recommended to use an anti-cancer effect. Boswellic acids preferentially inhibit COX-2 and 5, 12, and 15-LOX; making it a potent natural anti-inflammatory and anti-cancer compound, by reduction of key inflammatory mediators of the AA cascade.\textsuperscript{194, 195}
**Down-regulation of the expression of NF-kB**

Boswellic acids (Acetyl-11-keto-beta-boswellic acid) potentiate the apoptosis induced by TNF and chemotherapeutic agents, while suppressing TNF-induced invasion, and inhibiting receptor activator of NF-kappaB ligand-induced osteoclastogenesis, all of which are known to require NF-kB activation. These observations corresponded with the down-regulation of the expression of NF-kB-regulated antiapoptotic, proliferative, and angiogenic gene products.196

**Inhibits topoiserase I and II & increases p21**

Boswellic acids have also been shown to inhibit topoisomerase I and II, and increase p21, which also contribute to the anti-cancer effects.197

Boswellic acids have shown to modulate the immune system and inhibit a number of cancers including glioblastoma, melanoma, colon, several forms of leukemia, and prostate cancer.198-204 Boswellic acids inhibit Pgp, resensitizing drug therapies to cancer cells, and effectively crosses the blood-brain barrier.205

**Boswellic acids even inhibit androgen independent prostate cancer by inhibiting NF-kB signaling by intercepting the IkappaB kinase (IKK) activity; signaling through an interferon-stimulated response.206**

In another study, boswellic acids inhibited the growth of chemotherapy-resistant human PC-3 prostate cancer cells in vitro and induces apoptosis as shown by activation of caspase 3 and the induction of DNA fragmentation. In addition, compound 1 is active in vivo as shown by inhibition of proliferation and induction of apoptosis in PC-3 prostate cancer cells xenotransplanted onto the chick chorioallantoic membrane.207

**Inhibition of 5-LOX: a major pathway for PC growth**

5-lipoxygenase (5-LOX) acts as biological fuel for cancer cells by stimulating EGF (epidermal growth factor), VEGF (vascular endothelial growth factor), and other growth factors. The inhibition of 5-LOX has consistently been shown to induce cancer cell apoptosis.208-211 5-LOX inhibition is a targeted pathway for many botanical compounds most notably the pentacyclic triterpene, Acetyl-11-keto-beta-boswellic acid (AKBA).212 The specific constituent in boswellia responsible for suppressing 5-LOX is AKBA. Boswellia-derived AKBA binds directly to 5-LOX and inhibits its activity.213

AKBA inhibits 5-LOX in a selective, enzyme directed, nonredox, and noncompetitive manner.197 AKBA has been shown to induce apoptosis through topoisomerase inhibition, and 5-LOX inhibition in several cancer cell lines including HL-60 and CCRF-CEM cells.198

**Nettles (Urtica dioica & Urens)**

I consider nettles leaf to be equal or superior to all of the super green foods that can be found in the market place today. Nettles leaf is highly nutritive, being very high in chlorophyll, protein, and minerals. There are many benefits from eating nettles regularly. It is especially good for anemia, upper respiratory diseases, allergies, and poor lymphatic function. Like many great cancer-inhibiting plants, nettles is a weed that grows freely and abundantly once planted. As a healing food, it can be cooked and eaten like spinach or dried and mixed in salad dressings, soups, smoothies, or taken as a tea alone or with other herbs.

Nettles has been traditionally used in many parts of the world to treat various forms of cancer including prostate cancer.214 Although the root of nettles is the primary part used for prostate health and prostate cancer inhibition, one recent study looked at the effects of the aqueous extract of nettle leaves on adenosine deaminase activity in prostate tissue from patients with prostate cancer. Ten prostate tissues from patients with pathologically proven, localized prostate cancer (Gleason scores 4 to 7) were used in the study. In the tissues, ADA activities with and without preincubation with different amounts of nettles extracts were performed. The nettles extract resulted in a significant inhibition on ADA activity of prostate tissue, and
this might be one of the mechanisms in the observed beneficial effect of nettles in prostate cancer.\textsuperscript{215}

The phytosterols B-sitosterol and sitosterol B-glucoside are found in the root, and lignans are found in the seed. The phytosterols found in the root are potent immune-activators and possess anti-inflammatory activity as well.\textsuperscript{216}

**Nettles root extract inhibits PC**

Extracts of nettle roots are highly effective in the treatment of benign prostatic hyperplasia (BPH) and this has been confirmed by numerous clinical trials.\textsuperscript{217-220}

Nettle root extract increases the androgen binding capacity, possessing a unique ability to modulate the binding of sex hormone-binding globulin to its receptor on human prostatic membranes, thus inhibiting proliferation within the prostate.\textsuperscript{221}

Nettle root extract has shown significant anti-proliferative activity against human prostatic epithelial (LNCaP) and stromal (hPCPs) cells. This was evaluated using a colorimetric assay. The inhibition was time-dependent, with the maximum of growth reduction (30\%) at a concentration of 1.0E-6 mg/ml on day 5 compared to the untreated control. The antiproliferative effect of nettles root extract has been observed in both an in vivo and in vitro model.\textsuperscript{222}

I utilize primarily the root extract 6:1, or the fluid extract for early prostate cancer, although the seed extract is wonderful as to use when there is kidney stress present.

Nettles root 6:1 extract dosage: 2 – 7 grams daily

**Pygeum (Pygeum africanum)**

Pygeum africanum is an evergreen tree that grows in the mountainous forests of Africa. Unfortunately, it has become an endangered species due to its popularity for prostate problems. High quality extract is still being produced using farmed trees grown on plantations for medicinal use (Euromed). The bark extract helps preserve prostate health and promote a man's overall well being. Pygeum not only helps common prostate problems and is a potent inhibitor of oxidative damage within the prostate, it contains a variety of active compounds that synergistically aid prostate health. Many studies have shown the effectiveness of Pygeum extract in treating BPH, including reduction of the frequency of nighttime urination, and relief of symptoms associated with genito-urinary problems resulting from BPH.\textsuperscript{223,224}

**Inhibit PC: blocks EGF**

Pygeum africanum extract (PAE) has shown an ability to inhibit prostate cancer proliferation. The incubation with PAE of prostate cancer cells significantly, and in a dose-dependent manner, inhibited the proliferation of prostate cancer derived cells LnCaP, PZ-HPV-7, and CA-HPV-10. In the PZ-HPV-7 cells PAE counteracted the mitogenic action of EGF and blocked the transition from G1 to S in the cell cycle. PAE also exerts a potent antimitogenic action on the epithelial cells derived from benign prostatic hyperplasia explants. The anti-cancer effect is associated with the inhibition of the mitogenic action of EGF, and it is accompanied by a decrease of cells entering the S Phase of the cell cycle.\textsuperscript{225}

**Inhibits prostate growth by down-regulating bFGF, EGF, and IGF-I**

The effect of PAE inhibited the proliferation of rat prostatic stromal cells stimulated by different growth factors. EGF, bFGF, and IGF-I but not KGF are mitogenic for prostatic fibroblasts. PAE is a potent inhibitor of rat prostatic fibroblast proliferation in response to direct activators of protein kinase C, the defined growth factors bFGF, EGF, and IGF-I, and the complex mixture of mitogens in serum depending on the concentration used. The therapeutic effect of PAE is due at least in part to the inhibition of growth factors responsible for the prostatic overgrowth in man.\textsuperscript{226}
Only use ethically harvested pygium. Euromed is in the process of producing pygium that will be farmed, which I am excited about.

**Red Clover (Trifolium pratense)**

Red clover is an excellent alterative, and traditionally has been used to retard the growth of cancer. Recently, high potency extracts have been produced that concentrate the isoflavones present in red clover. These extracts have been shown to suppress prostate and other cancers.

**Biochanin A, an isoflavone from red clover inhibits PC in animals**

A study was conducted that used LNCaP cells and xenografts to investigate the mechanisms of the antiproliferative effects of biochanin A, the major isoflavone present in red clover. Biochanin A induced a dose-dependent inhibition of proliferation and [(3)H]thymidine incorporation that correlated with increased DNA fragmentation, indicative of apoptosis. Biochanin A significantly decreased expression of cancer cell proliferation and eleven genes were up-regulated, including 9 that were undetectable in controls. In mice with LNCaP xenografts, biochanin A significantly reduced tumor size and incidence. These results indicate that biochanin A inhibits prostate cancer cell growth through induction of cell cycle arrest and apoptosis. Biochanin A-regulated genes suggest multiple pathways of action. Biochanin A inhibits the incidence and growth of LNCaP xenograft tumors in athymic mice.227

**PC Human study: Increases apoptosis**

A nonrandomized, nonblinded trial, with historically matched controls from archival tissue, was conducted that was designed to determine the effects of acute exposure to a dietary supplement of isoflavones from red clover in men with clinically significant prostate cancer before radical prostatectomy. Thirty-eight patients were recruited to the study upon diagnosis of prostate cancer. Before surgery, 20 men consumed 160 mg/day of red clover derived dietary isoflavones containing a mixture of genistein, daidzein, formononetin, and biochanin A. Serum PSA, testosterone, and biochemical factors were measured, and clinical and pathological parameters were recorded. The incidence of apoptosis in prostate tumor cells from radical prostatectomy specimens was compared between 18 treated and 18 untreated control tissues. There was no significant difference between pre- and posttreatment serum PSA, Gleason score, serum testosterone, or biochemical factors in the treated patients (P > 0.05). Apoptosis in radical prostatectomy specimens from treated patients was significantly higher than in control subjects (P = 0.0018), specifically in regions of low to moderate-grade cancer (Gleason grade 1-3). No adverse events related to the treatment were reported. This report demonstrates that dietary isoflavones may halt the progression of prostate cancer by inducing apoptosis in low to moderate grade tumors, potentially contributing to the lower incidence of clinically significant disease in Asian men.228

**Human study: Reduces circulating levels of androgen in PC patients**

Red clover extract was tested on the hypothalamic-pituitary-testicular (HPT) axis in prostate cancer patients. 40 men were recruited who were about to undergo radical prostatectomy for prostate cancer. They received either 240 mg of red clover isoflavones or placebo daily for 2 weeks. Serum hormone levels were measured before and after treatment. In addition, recombinant cell bioassay was used to measure serum androgen bioactivity. Red clover extract treatment increased serum LH from mean of 3.4-5.2 IU, P = 0.03. Concomitantly, a non-significant trend towards decline in serum T, cfT and ABA values was noted. However, mean serum LH/T ratio was upregulated from 0.20 to 0.48 IU/nM, P = 0.004, suggesting compensated hypogonadism. During the course of treatment, serum concentration of equol correlated strongly with the concomitant decrease in ABA (r = -0.586, P = 0.022). Red clover extract rich in isoflavones, which act as phytoestrogen compounds, interferes with HPT axis in prostate cancer patients by inducing testicular resistance to LH, reducing circulating levels of androgen, and thus decreasing prostate cancer proliferation.229

Red clover extract has also shown to inhibit COX activity in several cancer cell models.230
Saw palmetto (*Serenoa repens*)

Saw palmetto is an herb most commonly used for the treatment of symptoms of BPH, although it really has many wonderful uses and is a good nutritive tonic herb as well. In vitro studies have found that saw palmetto inhibits growth of prostatic cancer cells and may induce apoptosis, although a recent prospective cohort study of 35,171 men aged 50-76 yr in western Washington State found no association with its use and the risk of prostate cancer. The use of commercial saw palmetto varies widely in dose and constituent ratios so it is difficult to access as meaningful.

**Inhibited PC in an animal model**

The antiproliferative effects of saw palmetto, in vivo, on nude mouse xenografts, and in vitro, on PC-3 and DU-145 human prostate cancer, were recently tested. Treatment with saw palmetto in vitro resulted in a 33% decrease of PC-3 cell proliferation at 72 hours and a 23% reduction of DU-145 cell proliferation at 24 hours (P<.01). The difference in reduction is likely due to the specific doubling time of each cell line. In vivo, prostate tumor xenograft size was significantly reduced in saw palmetto-treated mice compared to untreated controls (P=.012). This study clearly demonstrates a biologic response to saw palmetto treatment as manifested by cell proliferation and tumor growth.

**Unique 5alpha-reductase inhibiting effect**

Saw palmetto is an effective dual inhibitor of 5alpha-reductase isoenzyme activity in the prostate. Unlike other 5alpha-reductase inhibitors, saw palmetto induces its effects without interfering with the cellular capacity to secrete PSA. Saw palmetto, unlike other 5alpha-reductase inhibitors, does not inhibit binding between activated AR and the steroid receptor-binding consensus in the promoter region of the PSA gene. This was shown by a combination of techniques: assessment of the effect of saw palmetto on androgen action in the LNCaP prostate cancer cell line revealed no suppression of AR and maintenance of PSA protein expression at control levels.

**IGF-I signaling mediation: Induction of JNK**

Treatment of starved cells with Saw palmetto extract (SPE) alone induced phosphorylation of the pro-apoptotic protein JNK. SPE treatment may relieve symptoms of BPH, in part, by inhibiting specific components of the IGF-I signaling pathway and inducing JNK activation, thus mediating anti-proliferative and pro-apoptotic effects on prostate epithelia. This effect would also contribute another cancer suppressing mechanism from saw palmetto.

**COX-2 suppression**

Various concentrations of saw palmetto were analyzed for cytotoxic effects on prostate cell lines and generic cancer cells. The extract inhibited proliferation of prostate-derived cell lines in a dose-dependent fashion. The berry extract also reduced Cox-2 expression and Cox-2 expression is associated with an increased incidence of prostate cancer. So, saw palmetto further suppresses prostate cancer by reducing COX-2 expression and this would provide basis for prostate cancer chemoprevention and justify long-term consumption of saw palmetto extract-containing formulations.

Traditionally, saw palmetto was used, among other things, by the Eclectic Physicians as a anabolic nutritive tonic. I believe saw palmetto is very well suited for the prevention of the catabolic state caused by prolonged periods of stress, aging, and advanced cancer (Cancer-related-cachexia). Prolonged catabolic states cause muscle loss, fatigue, susceptibility to injury, immune suppression, and eventually disturbance of weight, and even heart disease. I would classify saw palmetto as a nutritive anti-catabolic agent with many applications in health promotion, and specifically as a general prostate tonic. I use small amounts and combine it with several other appropriate herbs.

**Feverfew (*Tanacetum parthenium L*)**
Feverfew is well known for its ability to prevent migraine headaches. Most researchers attribute the herb’s anti-migraine/anti-inflammatory properties to the presence of the sesquiterpene lactone, parthenolide, which hinders the inflammatory process, or to the release of serotonin from certain white blood cells and platelets, which in turn can reduce the frequency and severity of migraines by keeping the blood vessels toned. Feverfew also interferes with the actions of arachidonic acid, reducing PG2 by regulating LOX and COX-2, NF-kB, and histamine as well, all of which contribute to feverfew’s ability to suppress cancer. Parthenolide is the active compound in feverfew which has received most of the attention. Parthenolide-mediated cell death signaling pathway also involves the Bcl-2 family members.

Parthenolide has a strong ability to trigger the death of human acute myeloid leukemia (AML) cells as well as chronic myelogenous leukemia (CML) cells. In fact, this agent was found to be much more specific to leukemia cells than the standard chemotherapy drug Ara-C. Further analysis revealed that parthenolide selectively targets stem cell populations.

Oxidative stress may contribute to parthenolide-induced apoptosis and to GADD153 overexpression in a glutathione-sensitive manner. The sensitivity of tumor cells to parthenolide appears to result from the low expression level of the multifunctional detoxification enzyme glutathione S-transferase.

**Inhibition of NF-kB**

Nuclear Factor kappa B (NF-kB) can be inhibited by several botanical compounds including parthenolide. Several studies have confirmed the NF-kB is an important target for parthenolide’s anti-cancer activity.

**Enhances therapeutic effectiveness of chemotherapy (Taxol)**

NF-kB-inducible genes protect cancer cells against paclitaxel as MDA-MB-231 breast cancer cells, modified to overexpress IB, required lower concentrations of paclitaxel to arrest at the G2/M phase of the cell cycle and undergo apoptosis when compared to parental cells. The effect of NF-B on paclitaxel-sensitivity appears to be specific to cancer cells because normal fibroblasts derived from embryos lacking p65 subunit of NF-B, and wild type littermate embryos, were insensitive to paclitaxel-induced G2/M cell cycle arrest. Parthenolide, mimicked the effects of IB by inhibiting NF-kB DNA binding activity and Mn-SOD expression, and increasing paclitaxel-induced apoptosis of breast cancer cells.

Parthenolide exerted in vitro stimulatory activity on tubulin assembly by inducing the formation of well-organized microtubule polymers and potentiating the anti-cancer effects of paclitaxel against MCF-7 breast cancer cells. The antimicrotubular and antiproliferative effects of parthenolide, a well known microtubule-stabilizing anticancer agent, increase paclitaxel activity.

Human prostate cancer demonstrates overexpression of the active subunit of NF-kappaB, p65, and that this occurs at an early stage in the genesis of prostate cancer. This work supports the rationale for targeting NF-kappaB for the prevention and/or treatment of prostate cancer.

**Parthenolide inhibits PC-1: NF-kB inhibition**

The in vitro effects of parthenolide were assessed using the androgen independent cell line CWR22Rv1, and human umbilical endothelial cells (HUVECs). The in vivo activity of P as a single agent and its ability to augment the efficacy of docetaxel, and the anti-androgen bicalutamide, were determined using the CWR22Rv1 xenograft model. Parthenolide, at low micromolar concentration, inhibited proliferation of CWR22Rv1 and HUVEC cells, promoted apoptosis, and abrogated NF-kB-DNA binding. Parthenolide downregulated antiapoptotic genes under NF-kB control, TRAF 1 and 2, and promoted sustained activation of c-Jun-NH2 kinase (JNK). Parthenolide also augmented the in vivo efficacy of docetaxel and restored sensitivity to anti-androgen therapy. These studies demonstrate parthenolide's antitumor and anti-angiogenic activity, and its potential to augment the efficacy of chemotherapy and hormonal therapy.
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Section V

Nutraceutical Compounds from the Plant Kingdom for Prostate Cancer Treatment/Prevention

Resveratrol

Resveratrol is one of a group of compounds called phytoalexins, which are polyphenols, a natural product occurring in the skins of grapes and various other plants, such as peanuts, which have medicinal properties. Resveratrol is produced by the plant under times of stress, such as unfavorable weather, or insect or pathogenic attack. Resveratrol is a kind of immune-enhancing cytokine that protects the plant from fungal attack.

Japanese Knotweed (Polygonum cuspidatum), Hu Zhang, is the richest known source of resveratrol, has traditionally been used in traditional Chinese Medicine (TCM) to treat cancer.

In TCM cancer is generally believed to be caused by physiologically 3 factors: (1) phlegm (this is an accumulation of excess fluid which has congealed in a particular part of the body) and (2) blood stasis (this is a partial or complete obstruction of blood circulation in a particular part of the body). In addition to tumors or masses, cancer also involves (3) tissue destruction (necrosis), which is viewed in TCM as being caused by the presence of heat toxins in the body. So we have phlegm, blood stasis and heat toxins as the 3 factors, and in TCM, Hu Zhang is said to influence all 3 of those factors.

Polygonum c., according to TCM, activates the blood circulation and removes blood stasis. Its secondary functions include draining heat and transforming (eliminating) phlegm, and clearing heat and eliminating toxins.

Modern research has discovered potential applications of this herb for cancer -- several compounds have shown possible usefulness, including resveratrol, emodin, and chrysophanol. These compounds have shown antitumor, antimitastatic, chemopreventive, chemical carcinogenesis-inhibitive, oncogene signal transduction-inhibitive, and immune-modulating properties. One study also demonstrated that Hu Zhang was able to increase white blood cells (WBC's, aka leukocytes) in patients with lowered WBC levels due to radiation treatment.

Aside from cardioprotective effects, resveratrol suppresses proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of p21cip1/WAF1, p53, and Bax; down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL, and cIAPs; and activation of caspases. Resveratrol has been shown to suppress the activation of several transcription factors, including NF-kB, AP-1, and Egr-1; to inhibit protein kinases including I kappaB alpha kinase, JNK, MAPK, Akt, PKC, PKD, and casein kinase II; and to down-regulate products of genes such as COX-2, 5-LOX, VEGF, IL-1, IL-6, IL-8, AR, and PSA. These activities account for the suppression of angiogenesis.

Resveratrol also has been shown to potentiate the apoptotic effects of cytokines, chemotherapeutic agents, and gamma-radiation. Pharmacokinetic studies revealed that the target organs of resveratrol are the liver and kidney, where it is concentrated after absorption, and is mainly converted to a sulfated form and a
glucuronide conjugate. In vivo, resveratrol blocks the multistep process of carcinogenesis at various stages: it blocks carcinogen activation by inhibiting polymorphisms such as aryl hydrocarbon-induced CYP1A1 expression and activity, and suppresses tumor initiation, promotion, and progression. Besides chemopreventive effects, resveratrol exhibits therapeutic effects against cancer and is pharmacologically safe.1

At therapeutic doses (400-500 mg.) this chemopreventive agent is effective against cancer, including PC. Resveratrol is perhaps the most exciting compound studied and is a diverse multi-tasker as it relates to human health. Here is a more detailed list of some of the anti-cancer mechanisms:

- Reduces COX-2 expression, 2-5
- Suppresses prostaglandin (PG) biosynthesis from arachidonic acid, inhibiting prostaglandin E2 formation. Enhances the effects of radiation: Pretreatment with resveratrol enhanced tumor cell killing (in two cervical tumor cell lines) by radiation in a dose-dependent manner; 6
- Reduces ornithine decarboxylase (ODC) and protein levels; and protein levels of proliferating cell nuclear antigen (PCNA), which are established markers of tumor promotion; 7
- Modulates immune response: induction of cytotoxic T lymphocytes (CTLs), lymphokine activated killer (LAK) cells, and the production of the cytokines interferon (IFN)-[gamma], interleukin (IL)-2, and IL-12; 8
- Modifies gene protein behavior, eg. up-regulates more than 80 genes, most profoundly p21 CIPI/WAF1, 9 which is associated with growth arrest of cancer cells,
- Activates p27 and PTEN; 9
- Induces cancer-cell apoptosis through a p53-mediated mechanism; 11-13
- Induces caspase-3 activation (NF-kB); 14
- Enhances gap-junctional intercellular communication (GJIC), 15, 16
- A powerful redox regulator and free radical scavenger, via hydroxyl-radical scavenging, inhibition of lipid peroxidation, and a glutathione-sparing mechanism. Apples dipped in a resveratrol solution had a greatly increased shelf life; 17
- Inhibits DNA synthesis in cancer; 18
- Inhibits cancer angiogenesis; 19 Inhibits VEGF angiogenesis; 20, 21
- Reduces Hypoxia-inducible factor-1alpha (HIF-1alpha) and VEGF; 22, 23
- Inhibits EGFR; 24, 25
- Inhibits protein kinase C (PKC) at high concentrations in prostate cancer; 26, 27
- Triggers apoptosis: Activation of caspases 9 and 3; 28
- Inhibit tumor cell division and induce an early S phase and G2 cell cycle arrest; 30, 31
- Decreases the expression of CyclinD1 and p34cdc2 protein; 32
- Down-regulates Bcl-2, 33 Down-regulates NFkB, 34-36 Down-regulation of NF-kB, COX-2, and MMP-9 expression; 37
- Down-regulates IL-8; 8
- Down-regulates AP-1; 39
- Down-regulates telomerase; 40
- Inhibits tumor-promting inflammatory cytokines IL-6 and TNF-alpha; 41
- In the presence of 17-beta-estradiol resveratrol reduced breast cancer formation; 42 also reduced cancer proliferation through estrogen-dependent and -independent mechanisms. 43 In animal models, carcinogen-induced preneoplastic lesions and mammary tumors are inhibited by resveratrol (COX-2 and p53 mediated). 34
- Modulates of AMPK signaling & the induction of ROS induces apoptosis in chemoresistant cancer cells; 45
- Binds ER-beta and ER-alpha with comparable affinity, but with 7,000-fold lower affinity than estradiol (E2). Thus, resveratrol differs from other phytoestrogens that bind ER-beta with higher affinity than ER-alpha. 46, 47
- Inhibits cancer-inducing polymorphisms. Cytochrome P450 1B1 (CYP1B1) catalyzes the bioactivation of numerous procarcinogens and it is expressed in tumor cells, including human breast and prostate cancer. Resveratrol alters CYP1B1 gene expression, and reduces bioactive metabolites that trigger cancer; 38

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• One enzyme that is able to affect both the mitogenic and mutagenic characteristics of estrogens is cytochrome P450 1A2 (CYP1A2), which is principally responsible for the metabolism of 17β-estradiol. Resveratrol was shown to inhibit CYP1A1 and CYP1B1. 49
• In breast cancer cells, resveratrol normalizes gene expression. 51 Human study is being conducted involving resveratrol’s ability to inhibit ER breast cancer, 52 and anti-aromatase activity. 52, 53
• Cytotoxic to Adriamycin resistant breast cancer cells, 54, 45
• Inhibits cancer inducing MMP2 and 9, 45, 55-57
• Increases the effects of chemotherapy (Taxanes), 58, 59
• Radiation sensitizer, 60
• Inhibit cancer metastasis, 61
• Raises GSH, inhibits oxidative damage selective to healthy cells, 62
• Inhibits blood clotting through PAF modulating effects and platelet aggregation inhibition, 63 and significantly altered platelet-adhesion to fibrinogen, 64, 65
• Lowers Homocysteine. 66

Prostate Cancer and Resveratrol:

**Inhibits proliferation and induces apoptosis:**
Resveratrol inhibits proliferation and induces apoptosis of DU145 and LNCaP cells in concentrations exceeding 5 micromol/L, and altered cell cycle distribution of all prostate cancer cell lines in concentrations as low as 0.5 micromol. 67

Resveratrol suppressed the proliferation of human prostate cancer cells with a typical apoptotic feature, interfering with the expression of HSP70. 68

Caspase-Mediated, hormone-sensitive LNCaP cells and hormone-insensitive DU 145 cells were treated with resveratrol and resveratrol was toxic to cells regardless of whether the cells were hormone-responsive or –unresponsive. 69

Resveratrol-induced apoptosis and proliferation arrest were evidenced in prostate derived cells PZ-HPV-7 (non-tumorigenic line), LNCaP (androgen-sensitive cancer line), and PC-3 (androgen-insensitive cancer line). Resveratrol induced a decrease in proliferation rates and an increase in apoptosis in cancer cell lines in a dose- and time-dependent manner. These effects were coincident with cell accumulation at the G0/G1 phase. In LNCaP and PC-3, the apoptosis induced by resveratrol was mediated by activation of caspases 9 and 3 and a change in the ratio of bax/bcl-2. Expressions of cyclin D1, E, and Cdk4, as well as cyclin D1/Cdk4 kinase activity were reduced by resveratrol only in LNCaP cells. In contrast, cyclin B and Cdk1 expression and cyclin B/Cdk1 kinase activity were decreased in both cell lines in the presence of resveratrol. However, modulator proteins p53, p21, and p27 were increased by resveratrol only in LNCaP cells. These effects probably result in the observed proliferation arrest and disruption of cell cycle control. In addition, the specific differences found between LNCaP and PC-3 suggested that resveratrol acts through different mechanisms upon the androgen or estrogen receptor cell status. 70

**Inhibits Bcl-2:**
Treatment with resveratrol (0-50 micromol/L for 24 hours) resulted in a significant (a) decrease in cell viability, (b) decrease of clonogenic cell survival, (c) inhibition of androgen (R1881)-stimulated growth, and (d) induction of apoptosis in androgen-responsive human prostate carcinoma (LNCaP) cells. Resveratrol causes an inhibition of phosphatidylinositol 3'-kinase/Akt activation that, in turn, results in modulations in Bcl-2 family proteins in such a way that the apoptosis of LNCaP cells is promoted. 71

**Inhibits EGF/TGFalpha- down-regulates PKC:**
The development of androgen-independent prostate cancer (AI PrCa) involves constitutive Erk1/2 activation sustained by the EGF/TGFalpha/EGFR axis and other trophic signaling mechanisms in neoplastic human prostate epithelial cells in vivo. Resveratrol demonstrated an ability to reduce protein kinase C (PKC), the major cellular receptor for phorbol esters (EGF/TGFalpha) by suppression of TPA-induced Erk1/2 activation. This shows resveratrol can even be useful in treating advanced prostate cancer.
in which this pathway is often up-regulated.\textsuperscript{72, 73} In a study of hormone-insensitive DU145 prostate cancer cells, resveratrol induced p53 phosphorylation in LNCaP prostate cancer cells. Resveratrol induced apoptosis in two cell lines through different PKC-mediated and MAPK-dependent pathways.\textsuperscript{74}

**Increases effectiveness of chemotherapy (vinorelbine):** Both Resveratrol and propolis, which modulate cell cycle distribution, alone or in combination with vinorelbine, act as potentially useful agents for prostate cancer therapy by effecting cell cycle control, and through the modulation of heat shock proteins (HSPs) expression.\textsuperscript{75} In another study resveratrol and propolis extract in human prostate cancer, exerting their cytotoxicity through two different types of cell death: necrosis and apoptosis respectively, and potentiated chemotherapy in combination with a very low dosage of vinorelbine (5 microM).\textsuperscript{76}

**Anti-Proliferative Effect: Inhibition of D-type Cyclins and (Cdk) 4 expression:** Resveratrol treatment in DU145 cells resulted in a dose-dependent inhibition of cell growth and induced apoptotic cell death. The anti-proliferative effect of resveratrol was associated with the inhibition of D-type cyclins and cyclin-dependent kinase (Cdk) 4 expression, and the induction of tumor suppressor p53 and Cdk inhibitor p21. Moreover, the kinase activities of cyclin E and Cdk2 were inhibited by resveratrol without alteration of their protein levels. Resveratrol treatment also up-regulated the Bax protein and mRNA expression in a dose-dependent manner.\textsuperscript{77}

**Resveratrol derivatives potent anti-PC activity:**
Several resveratrol derivatives were synthesized and investigated in the search for an anticancer agent with higher efficacy than resveratrol. During the examination of cancer cell lines, compounds C, F, and G evidenced higher inhibitory activity than resveratrol with regard to the growth of PC-3 and LNCaP human prostate cancer cells. Moreover, four derivatives of resveratrol evidenced potent growth inhibitory activity (IC\textsubscript{50} 0.01-0.04 microM) in LNCaP cells. The levels of activity in these derivatives were 25-100 times stronger than that associated with resveratrol (IC\textsubscript{50} 1.0 microM).\textsuperscript{78}

**Binds to the AR receptor and reduces the cancer antigen PSA:**
Grape (Red wine) consumption reduces prostate cancer by more than 50%: Men who consumed four to seven glasses of red wine per week reduced their risk of prostate cancer by more than 50 per cent. There was also a 60% lower incidence of the more aggressive types of prostate cancer. The more clinically aggressive prostate cancers were where the strongest reduction in risk was observed.\textsuperscript{79}

**Down-regulates AR and ER receptors, markedly decreased PKB/AKT**
Using androgen receptor (AR)-positive LNCaP and oestrogen receptor alpha (ERalpha)-expressing PC-3 prostate tumour cells, we have analysed whether the antiproliferative activity of resveratrol (RES) takes place by inhibition of the AR- or ERalpha-dependent PI3K pathway. RES inhibited AR- and ERalpha-dependent PI3K activities in LNCaP and PC-3, respectively. Consistently, lower PI3K activities correlated with decreased phosphorylation of downstream targets protein kinase B/AKT (PKB/AKT) and glycogen synthase kinase-3 (GSK-3). GSK-3 dephosphorylation could be responsible for the decreased cyclin D1 levels observed in both cell lines. Importantly, RES markedly decreased PKB/AKT phosphorylation in primary cultures from human prostate tumors, suggesting that the mechanism proposed here could take place in vivo. Thus, RES has antitumoral activity in androgen-sensitive, and androgen-non-sensitive, human prostate tumours by inhibiting survival pathways such as that mediated by PI3K.\textsuperscript{80}

**Anti-inflammatory activity: increases MKP5:**
Mitogen activated protein kinase phosphatase-5 (MKP5) reduces anti-inflammatory activities. MKP5 is increased by curcumin, resveratrol, and [6]-gingerol, which leads to decreased cytokine-induced NFkappaB activation, COX-2, IL-6, and IL-8 in normal prostatic epithelial cells reducing PC activation and progression.\textsuperscript{81}

**Prostate cancer inhibition:**
Researchers at the University of Alabama at Birmingham (UAB) came to the conclusion after a study of male mice that were fed resveratrol. The findings were published Saturday in the online edition of Carcinogenesis. The nutrients in red wine have shown anti-oxidant and anti-cancer properties. In the study...
resveratrol-fed mice showed an 87 percent reduction in their risk of developing prostate tumors that contained the worst kind of cancer-staging diagnosis. The mice that proved to have the highest cancer-protection effect earned it after seven months of consuming resveratrol in a powdered formula mixed with their food. Other mice in the study, those fed resveratrol but still developed a less-serious form of prostate cancer, were 48 percent more likely to have their tumor growth halted or slowed when compared to mice who did not consume the compound, according to the study. 124

Resveratrol and Grape (Muscadine) Skin Extract – down-regulate Akt activity & up Bcl-2
Muscadine grapes contain unique phytochemical constituents compared with other grapes and are potentially a source for novel compounds with antitumor activities. This study compared the antitumor activities of muscadine grape skin extract (MSKE), which we show contains no resveratrol, with that of resveratrol using primary cultures of normal prostate epithelial cells (PrEC) and the prostate cancer cell lines RWPE-1, WPE1-NA22, WPE1-NB14, and WPE1-NB26, representing different stages of prostate cancer progression. MSKE significantly inhibited tumor cell growth in all transformed prostate cancer cell lines but not PrEC cells. Prostate tumor cell lines, but not PrEC cells, exhibited high rates of apoptosis in response to MSKE through targeting of the phosphatidylinositol 3-kinase-Akt and mitogen-activated protein kinase survival pathways. The reduction in Akt activity by MSKE is mediated through a reduction in Akt transcription, enhanced proteosome degradation of Akt, and altered levels of DJ-1, a known regulator of PTEN. In contrast to MSKE, resveratrol did not induce apoptosis in this model but arrested cells at the G(1)-S phase transition of the cell cycle associated with increased expression of p21 and decreased expression of cyclin D1 and cyclin-dependent kinase 4 proteins. 125

Resveratrol, from the medicinal plant Polygonum cuspidatum, shows higher efficiency, less toxicity, and regulated mRNA expression of several genes involved in cell cycle control, apoptosis, metastasis, cell-cell adhesion, and ER and AR signaling pathway. 82, 83

Ellagic acid
Pomegranate (Punica granatum L.) fruits are widely consumed as juice. The potent antioxidant and antiatherosclerotic activities of PJ are attributed to its polyphenols including punicalagin, the major fruit ellagitannin, and ellagic acid, of which pomegranates are the richest source. 84 Pomegranate extract, standardized to ellagic, was recently tested in humans for absorption and was found high absorbable. 85 However the superior bioactivity of pomegranate compared to its purified polyphenols illustrated the multifactorial effects and chemical synergy of the action of multiple compounds compared to single purified active ingredients. 84 This is why it is important not to simply isolate out a compound, but to use a concentrate that is standardized to an active compound or group of compounds, which still contains a whole-plant/food concentrate.

Ellagic acid (EA) suppresses cancer: VEGFR-2 inhibition
Ellagic acid (EA) inhibits VEGF-induced phosphorylation of VEGFR-2 in endothelial cells (EC) as well as PDGF-induced phosphorylation of PDGFR in smooth muscle cells, leading to the inhibition of downstream signaling triggered by these receptors. Ellagic acid also specifically inhibits angiogenesis of cancer by inhibiting VEGF-induced migration and abolished PDGF-dependent smooth muscle cell migration. Ellagic acid also presented a greater selectivity for normal cells than for tumor cells “The identification of EA as a naturally occurring dual inhibitor of VEGF and PDGF receptors suggests that this molecule possesses important antiangiogenic properties that may be helpful for the prevention and treatment of cancer.” 87

Pomegranate extract inhibits aromatase
Pomegranate extract (PE) demonstrated an ability to block endogenous, active, estrogen biosynthesis and inhibited aromatase activity by 60-80%. PE inhibits 17-beta-hydroxysteroid dehydrogenase. PE also showed a 47% inhibition of cancerous lesion formation induced by the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA). 88

PE extract has shown to have anti-leukemic activity through a differentiation-promoting action against human HL-60 promyelocytic leukemia cells. 89
**Induction of caspase 3: Induction of apoptosis synergistic with other phytonutrients**

Alterations in cell cycle kinetics, proliferation, and apoptosis (caspase-3 activity) were examined after incubation with **ellagic acid, quercetin, and resveratrol**, as single compounds and in combination. Results showed a more than additive interaction for the combination of ellagic acid with resveratrol, and furthermore significant alterations in cell cycle kinetics induced by single compounds and combinations were observed. An analysis was performed to assess the apparent synergistic interaction for the combinations of ellagic acid with resveratrol, and quercetin with resveratrol, in the induction of caspase 3 activity, confirming a synergistic interaction.  

**Inhibits PC: multi-mechanisms**

Ellagic acid, from PE has shown to inhibit cancer through down regulation of IGF-II, activation of p21 (waf1/Cip1), and prevention of the destruction of p-53 gene by cancer cells.  

Ellagic acid showed a synergistic effect against hormone refractory PC with chemotherapy.  

Ellagic acid and resveratrol demonstrated a synergistic effect against PC.  

**Human study: Drinking pomegranate juices suppressed PC**

A daily glass of pomegranate juice can hold back prostate cancer and could even prevent men dying of the disease, new research has shown. Recently researchers at the University of Wisconsin showed that pomegranate juice dramatically slows down prostate cancer in mice. The new three-year pilot study from the University of California at Los Angeles involved 50 prostate cancer patients who had undergone surgery or radiotherapy. All the men had experienced a post-treatment increase in blood levels of PSA (prostate-specific antigen), indicating that cancer was still present in their bodies. Over a period of three years, scientists measured the men's PSA levels to calculate how fast they were taking to double. Prostate cancer patients who have short doubling times are more likely to die from their illness. The average doubling time for the disease is about 15 months. But drinking pomegranate juice extended this period to 54 months - an almost four-fold increase. The study showed that the speed at which PSA levels rose in the men fell by an average of 35% after they started drinking pomegranate juice. There was also evidence that pomegranate juice was actually killing prostate cancer cells. Just one 8oz glass of juice per day increased the stability period of prostate cancer four-fold, scientists found. Simply by drinking pomegranate juice, a man of 65 to 70 with prostate cancer could complete his normal life span without having to undergo harsh medical treatments.  

**Inhibit prostate cancer growth – new study**

The new study suggests that the **ellagitannins** may also play a role in prostate cancer protection. Seeram and co-workers looked at the effect of ellagitannins and its metabolites to accumulate in the tissues in C57BL/6 wild-type male mice. Ellagitannins are hydrolyzed to release **ellagic acid**, which is then converted by gut microflora to urolithin A (UA) derivatives. “It is unclear why pomegranate ellagitannin metabolites localize at higher levels in prostate, colon, and intestinal tissues relative to the other organs studied,” wrote the authors. The researchers also investigated the potential of the pomegranate extract to inhibit the growth of prostate cancer cells (LAPC-4) grafted onto mice with impaired immune function. Compared to the control, the pomegranate extract was found to significantly inhibit the growth of the grafted tumors.  

**Isothiocyanates (ITCs)**

Several epidemiologic studies suggest that consumption of cruciferous vegetables may be particularly effective (compared with total fruit and vegetable consumption) in reducing cancer risk at several organ sites. In the 1980s, there had been an explosion of research showing anti-cancer properties of cruciferous vegetables: cabbage, broccoli, and Brussels sprouts, for example. Crucifers that are widely consumed are especially rich in glucosinolates, which are converted by plant myrosinase and gastrointestinal microflora to isothiocyanates (ITCs). These compounds activate genes that regulate enzymes that detoxify certain cancer-causing substances; that aid in DNA repair; that affect proliferation of cells; and that program death of damaged cells. A recent study conducted found that polish immigrants in the United States who ate a lot
of cabbage, rich in ITCs, when they were 12 or 13 years old -- more than three servings a week -- had a breast cancer risk about 70 percent lower than those who ate little cabbage during their adolescence and adulthood. Organic cabbage sprouts are the richest source of ICT phenethyl isothiocyanate, which when combined with curcumin has shown to be a potent suppressor of PC.

A number of ICTs effectively block chemical carcinogenesis in animal models by enhancing glutathione S-transulfurase, which help in carcinogen excretion. Substantial evidence supports the view that phase 2 enzyme induction is a highly effective strategy for reducing susceptibility to carcinogens. These vegetables are also high in vitamins A, C, and E; some contain anticancer minerals, and most are high in fiber. However this works, cruciferous vegetables have proved to contain terrific anticancer nutrients.

Many isothiocyanates (ITCs) such as sulforaphane (SFN), phenethyl isothiocyanate (PEITC), allyl isothiocyanate (AITC), and 6-(methylsulfinyl) hexyl isothiocyanate (6-MITC) are highly effective in chemoprevention, or reduction of the risk of cancer, and other chronic diseases including neurological diseases.

ITCs function as indirect redox cycling free radical scavenging agents. As such, these compounds do not directly neutralize free radicals, as direct redox cycling compounds do, but rather they induce (or boost) the activity of the Phase 2 detoxification enzymes which act as a defense mechanism, triggering broad spectrum activity neutralizing various free radicals before they can cause cell damage that may instigate mutations leading to cancer. The effect of indirect redox cycling agents remains even after they have left the body. The indirect free radical scavenging effects are long-lasting, triggering an ongoing process that remains in action for several days. ITCs and phenolic compounds are the most important compounds in nature for maintaining cell behavior and for inhibiting cancer. They are crucial for the maintenance of glutathione homeostasis and possess a selective ability to deplete glutathione, increasing reactive oxygen species (ROS), in cancer cells. They have recently been shown to inhibit neurological diseases by controlling inflammation, and through the enhancement of levels of glutathione in the brain, which reduces oxidative stress.

ICTs buttress the enzyme systems responsible for metabolizing carcinogens and increase the action of glutathione compounds.

ITCs inhibit activator protein 1 (AP-1) and MAPK signalling pathways, which are believed to play an important role in cancer chemoprevention and chemotherapy due to their involvement in tumor cell growth, proliferation, apoptosis, and survival.

ITCs blocked lung cancer progression in both animal studies and in human lung cancer cells. Two studies were conducted further confirming isothiocyanates cancer-inhibiting effects. One of the two new studies tested naturally occurring ITCs’ impact on the stages of cancer development specifically after exposure to cancer-causing chemicals. The researchers induced lung tumor development in experimental mice by exposing them to tobacco carcinogens, and then they fed one group of mice the ITCs. The ITCs feed group had a reduced development of malignant, as well as non-malignant tumors, compared to mice that did not receive the compound. The second study looked at the effect of ITCs on human lung cancer cells, which were forced to grow quickly. The test showed that ITCs significantly induced apoptosis of the human lung cells compared to cells that did not have the gene, suggesting that its use may stop fast growing lung cancer cells from the outset.

In one experiment where ITCs were added to the diets of mice before and during the administration of carcinogens (like those in cigarettes), the isothiocyanates stopped the growth of tumors developing in the stomach and lung.

**PC Inhibition by ITCs**

**AP-1 and MAPK suppression**

The activator protein 1 (AP-1) and MAPK signaling pathways are believed to play an important role in cancer chemoprevention and chemotherapy due to their involvement in tumor cell growth, proliferation,
apoptosis, and survival. In the present study, we determined the effects of SFN, PEITC, and AITC on AP-1 activation, and investigated the roles of ERK and JNK signaling pathways in the regulation of AP-1 activation and cell death, elicited by these ITCs in human prostate cancer PC-3 cells. **SFN, PEITC, and AITC** each caused a significant elevation in the phosphorylation of ERK1/2, JNK1/2, Elk-1, and c-Jun. Transfection with ERK2 and upstream kinase DNEE-MEK1 activated AP-1 activity, and transfection with dominant-negative mutant ERK2 (dnERK2) potently decreased AP-1 activation induced by SFN, PEITC, and AITC. Transfection with JNK1 and upstream kinase MKK7 activated AP-1 activity, and transfection with dominant-negative mutant JNK1-APF significantly attenuated AP-1 activation induced by SFN, PEITC, and AITC. Pretreatment with MEK1-ERK inhibitor U0126 and JNK inhibitor SP600125 substantially attenuated the decrease in cell viability induced by SFN, PEITC, and AITC. Transfection with dnERK2 and JNK1-APF significantly reversed the decrease of Bcl-2 expression elicited by these ITCs. Furthermore, transfection with dnERK2 and JNK1-APF blocked the apoptosis induced by these ITCs in PC-3 cells. Taken together our results indicate that the activation of the ERK and JNK signaling pathways is important for transcriptional activity of AP-1, and is involved in the regulation of cell death elicited by ITCs in PC-3 cells. 

**Sulforaphane (SFN)**

Sulforaphane (SFN) is an isothiocynate, found abundantly in ORGANIC broccoli sprouts, and to a much less extent in cruciferous vegetables. Little to no SFN is found in non-organic commercial broccoli. SFN is a potent inducer of Phase II enzyme activity and has demonstrated diverse cancer-suppressing effects. SFN induces p53-independent apoptosis and modulates Bcl-2 family protein expression. **SFN, in one experiment, blocked the formation of mammary tumors in rats treated with a potent carcinogen. The number of rats that developed tumors was reduced by as much as 60%; the number of tumors in each animal was reduced by 80%; and the size of the tumors that did develop was reduced by 75%. Furthermore, the tumors' appearance was delayed and they grew more slowly.** Several other studies have confirmed that SFN is a potent inhibitor of breast cancer and an effective compound against breast cancer.

In another experiment, SFN inhibited the growth of human prostate cancer cells, and another showed it stopped the growth of colon cancer cells. Several recent studies also showed that SFN kills Helicobacter pylori, the bacteria that cause stomach ulcers and can lead to stomach cancer.

**Induction of apoptosis: through ROS and JNK-mediated signaling to G2/M arrest**

DU145 human PCa cell culture model was used to investigate the role of protein kinase signaling pathway(s) in SFN-induced cell cycle arrest and apoptosis. The results showed that SFN exposure for 24 h or longer significantly decreased the number of viable DU145 cells in a dose-dependent manner with an IC50 of asymptotically equal to 10 microM. The decreased cell number was associated with G2/M phase arrest and apoptotic cell death, with the latter being evidenced by caspase-mediated cleavage of poly (ADP-ribose) polymerase and increased release of histone-associated DNA fragments. SFN decreased viable DU145 cell number in large part through the generation of ROS and JNK-mediated signaling to G2/M arrest and caspase-dependent apoptosis.

**Induction of apoptosis: stabilization of p53 protein, suppression of inhibitors of apoptosis, and increase in BAX activation**

SFN suppresses proliferation of cancer cells by causing apoptosis. In this study, LNCaP (wild-type p53) and PC-3 (p53 deficient) human prostate cancer cells were examined to gain further insights into the mechanism of SFN-induced apoptosis. The LNCaP cell line was relatively more sensitive to SFN-induced apoptosis compared with PC-3. The SFN treatment caused stabilization of p53 protein in LNCaP cells, but SFN-mediated apoptosis was not attenuated by knockdown of p53 protein. Instead, the differential sensitivity of these cells to SFN-induced apoptosis correlated with difference in kinetics of Bax conformational change. Ectopic expression of Bcl-2 failed to confer protection against SFN-induced cell death.
death in LNCaP cells. Treatment of PC-3 cells with SFN resulted in a marked decrease in the levels of inhibitor of apoptosis (IAP) family proteins (cIAP1, cIAP2 and XIAP), which was accompanied by inhibition of nuclear translocation of p65-nuclear factor kappaB (NFkB). The effect of SFN on levels of IAP family proteins as well as transcriptional activity of NFkB was biphasic in LNCaP cells. The SFN-treated LNCaP and PC-3 cells exhibited a marked increase in protein level of Apaf-1, which was accompanied by an increase in transcriptional activity of E2F1. The SFN-induced apoptosis in both cell lines was significantly attenuated by Apaf-1 protein knockdown. This recent study reveals a complex signaling mechanism involving Bax activation, downregulation of IAP family proteins and Apaf-1 induction in regulation of SFN-induced cell death.112

**Induces apoptosis: Induction of autophagy**

The present study reports a novel response to SFN in PC-3 and LNCaP human prostate cancer cells. Treatment of cells with SFN, a specific inhibitor of autophagy (3'-methyladenine), attenuated localization of LC3 to autophagosomes but exacerbated cytosolic release of cytochrome c as well as apoptotic cell death as revealed by analysis of subdiploid fraction and cytoplasmic histone-associated DNA fragmentation. SFN causes autophagy to inhibit release of cytochrome C and induced apoptosis in human prostate cancer cells.113

**Inhibition of Histone Deacetylase (HDA).**

A novel mechanism of SFN in human colon cancer cells is the inhibition of HDA. Here, we show that the addition of 15 microM SFN also inhibited HDAC activity by 40, 30 and 40% in BPH-1, LnCaP and PC-3 prostate epithelial cells, respectively. The inhibition of HDAC was accompanied by a 50-100% increase in acetylated histones in all three prostate cell lines, and in BPH-1 cells treated with SFN there was enhanced interaction of acetylated histone H4 with the promoter region of the P21 gene and the bax gene. A corresponding 1.5- to 2-fold increase was seen for p21Cip1/Waf1 and Bax protein expression, consistent with previous studies using HDA inhibitors, such as trichostatin A. The downstream events included cell cycle arrest and activation of apoptosis, as evidenced by changes in cell cycle kinetics and induction of multi-caspase activity. These findings provide new insight into the mechanisms of SFN action in benign prostate hyperplasia, androgen-dependent prostate cancer, and androgen-independent prostate cancer cells, and they suggest a novel approach to chemoprotection and chemotherapy of prostate cancer through the inhibition of HDAC.114 An older study was done that also demonstrated that SFN inhibits cancer by suppressing HDAC. 115

**Inhibition of HDA by Broccoli sprouts, rich in SFN**

This anticarcinogen was first identified as a potent inducer of Phase 2 enzymes, but evidence is mounting that SFN acts through other cancer chemopreventive mechanisms. SFN has demonstrated both in human colon cancer cells and prostate epithelial cells, to inhibit HDA. SFN was tested to see if it might inhibit HDA activity in vivo. When consumed in the diet at an average daily dose of 7.5 mumol per animal for 21 days, SFN suppressed the growth of human PC-3 prostate cancer cells by 40% in male nude mice. There was a significant decrease in HDAC activity in the xenografts, as well as in the prostates, and mononuclear blood cells (MBC) of mice treated with SFN, compared to controls. There also was a trend towards increased global histone acetylation in the xenografts, prostate, and MBC. In human subjects, a single dose of 68g broccoli sprouts inhibited HDA activity significantly in peripheral blood mononuclear cells (PBMC) 3 and 6 hrs following consumption. These findings provide evidence that one mechanism of cancer chemoprevention by SFN is via epigenetic changes associated with inhibition of HDAC activity. Other dietary agents such as butyrate, biotin, lipoic acid, garlic organosulfur compounds, and metabolites of vitamin E have structural features compatible with HDA inhibition. The ability of dietary compounds to de-repress epigenetically silenced genes in cancer cells, and to activate these genes in normal cells, has important implications for cancer

Donald Yance  
Prostate Cancer
Potent immune booster/modulator

The effect of SFN on the immune system was studied using mice. Intraperitoneal administration of five doses of Sulforaphane (500 mg/dose/animal/day) was found to enhance the total WBC count (12,950 cells/mm^3) on 9th day. Bone marrow cellularity was also increased and treatment with Sulforaphane along with the antigen, sheep red blood cells (SRBC), produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen. SFN also showed an enhancement in the phagocytic activity of peritoneal macrophages. Moreover administration of SFN significantly reduced the elevated level of TNF-a production by LPS stimulated macrophages. These results indicate the immunomodulatory activity of SFN.

Boost NK cells, IL-2, INF gamma etc.

The effect of sulforaphane on cell-mediated immune (CMI) response was studied in normal as well as Ehrlich ascites tumor-bearing BALB/c mice. Administration of sulforaphane significantly enhanced natural killer (NK) cell activity in both normal as well as tumor-bearing animals, and the activity was observed earlier than in tumor-bearing control animals. Antibody-dependent cellular cytotoxicity (ADCC) also was enhanced significantly in both normal as well as tumor-bearing animals after sulforaphane administration compared with untreated control tumor-bearing animals. An early antibody-dependent complement-mediated cytotoxicity (ACC) also was observed in sulforaphane-treated normal and tumor-bearing animals. Administration of sulforaphane significantly enhanced the production of Interleukin-2 and Interferon-gamma in normal as well as tumor-bearing animals. In addition, sulforaphane significantly enhanced the proliferation of splenocytes, bone marrow cells, and thymocytes by stimulating the mitogenic potential of various mitogens such as concanavalin A, phytohaemagglutinin, poke weed mitogen, and lipopolysaccharide.

Paradoxal redox cycling effects of PEITC and other ITCs

PEITC, like other natural compounds, and other ITCs, acts as a redox-regulating agent that can behave paradoxally and selectively by increasing oxidative stress in transformed cells, such as cancer cells, possibly by generating reactive oxygen species (ROS), and also by undermining the ability of the cells to detoxify oxidants. PEITC does this by depleting cellular levels of reduced glutathione, and by inhibiting the activity of glutathione peroxides, a key cellular enzyme involved in the degradation of hydrogen peroxide.

SFN and PEITC suppress PC: NF-kB inhibition & regulation of VEGF expression

In this study, the effects and molecular mechanisms of SFN and PEITC on NF-kappaB transcriptional activation and NF-kappaB-regulated gene expression in human prostate cancer PC-3 C4 cells were studied. Treatment with SFN (20 and 30 microM) and PEITC (5 and 7.5 microM) significantly inhibited NF-kappaB transcriptional activity, nuclear translocation of p65, and gene expression of NF-kappaB-regulated VEGF, clycin D1, and Bcl-X(L) in PC-3 C4 cells. SFN and PEITC also strongly inhibited NF-kappaB transcriptional activity as well as VEGF, clycin D1, and Bcl-X(L) expression. Furthermore, SFN and PEITC also inhibited the basal and UVC-induced phosphorylation of IkappaBalpaha and blocked UVC-induced IkappaBalpaha degradation in PC-3 C4 cells. Taken together, these results suggest that the inhibition of SFN and PEITC on NF-kB transcriptional activation as well as NF-kB-regulated VEGF, clycin D1, and Bel-X(L) gene expression is mainly mediated through the inhibition of IKK phosphorylation, particularly IKKbeta, and the inhibition of IkappaBalpaha phosphorylation and degradation, as well as the decrease of nuclear translocation of p65 in PC-3 cells.

Regulation by AP-1

Another study examined the effects of SFN, PEITC, and AITC on AP-1 activation; and investigated the roles of extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling
pathways in the regulation of AP-1 activation and cell death elicited by these ITCs in human prostate cancer PC-3 cells. SFN, PEITC, and AITC each induced AP-1 activity potently and caused a significant elevation in the phosphorylation of ERK1/2, JNK1/2, Elk-1, and c-Jun. The results indicated that the activation of the ERK and JNK signaling pathways is important for transcriptional activity of AP-1 and is involved in the regulation of cell death elicited by ITCs in PC-3 cells.  

**Phenethyl isothiocyanate (PEITC)**

The ICT phenethyl isothiocyanate (PEITC) is found abundantly in cabbage sprouts, although most cruciferous vegetables contain it. PEITC not only affords significant protection against chemically induced cancer in animal models but also inhibits growth of cancer cells in culture and in vivo by causing cell cycle arrest and apoptosis induction. PEITC is a strong suppressor of the androgen receptor and has shown to inhibit PC.

**Induction of apoptosis: mediated by ROS-dependent disruption**

The PEITC-induced cell death in PC-3 cells was associated with disruption of the mitochondrial membrane potential, release of apoptogenic molecules (cytochrome c and Smac/DIABLO) from mitochondria to the cytosol and generation of reactive oxygen species (ROS). Administration of 12 micromol PEITC/day (Monday through Friday) by oral gavage significantly retarded growth of PC-3 xenografts in athymic mice. For instance, 31 days after the initiation of PEITC administration, the average tumor volume in control mice (721 +/- 153 mm3) was approximately 2-fold higher compared with mice receiving 12 micromol PEITC/day. The PEITC-mediated inhibition of PC-3 xenograft growth was associated with induction of Bax and Bid proteins. In conclusion, the present study indicates that the PEITC-induced apoptosis in PC-3 cells is mediated by ROS-dependent disruption of the mitochondrial membrane potential and regulated by Bax and Bid.

**Inhibition of angiogenesis: down-regulates VEGF**

PEITC recently demonstrated potent inhibition of angiogenesis in vitro and ex vivo at pharmacologically achievable concentrations. The PEITC treatment caused a decrease in survival of human umbilical vein endothelial cells (HUVEC) in a concentration- and time-dependent manner. The capillary-like tube structure formation (in vitro neovascularization) and migration (invasion potential) by HUVEC was also inhibited significantly in the presence of PEITC at pharmacologically relevant concentrations (<1 mumol/L). The PEITC-mediated inhibition of angiogenic features of HUVEC in vitro was associated with suppression of vascular endothelial growth factor (VEGF) secretion, down-regulation of VEGF receptor 2 protein levels, and inactivation of prosurvival serine-threonine kinase Akt. The PEITC treatment reduced migration by PC-3 human prostate cancer cells, which correlated with inactivation of Akt and suppression of VEGF, epidermal growth factor (EGF), and granulocyte colony-stimulating factor (G-CSF) secretion. The PEITC-mediated inhibition of PC-3 cell migration was statistically significantly attenuated by ectopic expression of constitutively active Akt. Most importantly, PEITC treatment inhibited ex vivo angiogenesis as revealed by chicken egg chorioallantoic membrane assay.

**Activates glutathione S-transferase gene (GSTP1), which is typically inactivated in PC**

PC is characterized by the silencing of pi-class glutathione S-transferase gene (GSTP1), which encodes a detoxifying enzyme. The silencing of GSTP1, due to aberrant methylation at the CpG island in the promoter/5'-UTR, occurs in the vast majority of prostate tumors and precancerous lesions. It is a pathologic marker and probably an underlying cause of oxidative damage and inflammation at tumor initiation. Inhibition of the aberrant promoter methylation could therefore be an effective mean to prevent carcinogenesis. The effects of PEITC to re activate GSTP1 were investigated. Exposure of prostate cancer LNCaP cells to PEITC inhibited the activity and level of histone deacetylases (HDACs), and induced selective histone acetylation and methylation for chromatin unfolding. Concurrently PEITC demethylated the promoter and restored the unmethylated GSTP1 in both androgen-dependent and -independent LNCaP cancer cells to the level found in normal prostatic cells, as quantified by methylation-specific PCR and pyrosequencing. The PEITC-mediated cross-talk between the DNA and chromatin in demethylating and reactivating GSTP1 genes, which is critically inactivated in prostate carcinogenesis, underlines a primary mechanism of cancer chemoprevention.
Regulation of the Androgen Receptor

PEITC induced a significant growth inhibition, with equal IC(50), in both Androgen Receptor (AR) positive and Androgen Independent (AI) cells. PEITC represses AR transcription and expression, and mediates growth arrest in androgen dependent and independent prostate cancer cells. With the AR modulation and growth attenuation, PEITC and possibly other isothiocyanates, may prevent and inhibit hormone sensitive and refractory prostate cancer.\textsuperscript{123}

Inhibition of EGFR signaling

A study was conducted that looked at the combined effects of PEITC and curcumin in PC-3 human prostate cancer cells and in PC-3 cells that were stably transfected with an NF-kB luciferase plasmid (PC-3 C4). In this study it was found that there was a synergistic effect of PEITC and curcumin for the induction of apoptosis. PEITC and curcumin additively inhibited NF-kB activity. Furthermore, the combined treatment significantly increased the activity of poly(ADP-Ribose) polymerase and cleavage of caspase-3 in correlation with apoptotic cell death. Studying upstream signaling events, the phosphorylations of IkappaBalpha and Akt (Ser473, Thr308) were significantly attenuated by the combination of PEITC and curcumin. As these events can be downstream of the activation of epidermal growth factor receptor (EGFR), we pretreated PC-3 cells with PEITC and curcumin and then stimulated them with EGF. EGFR phosphorylations (Y845 and Y1068) were dramatically suppressed by PEITC or curcumin, and more so by the combination. Importantly, the degree of Akt and PI3K phosphorylations induced by EGF were also significantly suppressed. PEITC and curcumin exert synergestic inhibitory effects on cell proliferation and ultimately lead to programmed cell death of tumor cells.\textsuperscript{124}

6-(methylsulfinyl)hexyl isothiocyanate (6-MITC)

Wasabi contains a diversity of unique ISTs which are effective inhibitors of cancer. Extracts from Wasabi have been shown repeatedly to be effective against stomach, breast, prostate, colon, and melanoma cancers.\textsuperscript{125-134}

Recently, attention has focused on the anticancer properties of an aromatic component 6-(methylsulfinyl)hexyl isothiocyanate (6-MITC), isolated from wasabi. The anticancer activity of 6-MITC in vitro was studied by using a human cancer cell (HCC) panel. 6-MITC directly affected the cells in the HCC panel and inhibited their growth in culture. The mean concentration required to inhibit 50% of control cell growth was 3.9 microM, which is a sufficiently low dosage for practical use. The suppression influenced not only the cell growth, but also the survival of these cells. The mean concentration to suppress cells to a 50% survival was 43.7 microM.\textsuperscript{135}

6-MITC has shown to suppress cancer by down-regulating COX-2.\textsuperscript{136}

In a melanoma model wasabi extract rich in 6-MITC appeared to inhibit not only tumor cell growth but also tumor metastasis.\textsuperscript{137}

DIM (3,3'-diindolylmethane)

Indole-3-carbinol (I3C) is a compound that occurs naturally in Brassica vegetables such as cabbage and broccoli. 3,3'-diindolylmethane (DIM) is a dimer of I3C that is formed under acidic conditions and unlike I3C is more stable with higher anti-cancer effects. DIM modify cytochrome p450 enzyme and carcinogen metabolism. These in turn help produce healthy hormonal balance, promoting normal cell growth and division, and inducing programmed cell death (apoptosis).

One of the many beneficial effects of DIM supplementation is on estrogen metabolism. The ratio of hydroxylation of estrogen at the 2- and 16- positions may therefore control the proportions of carcinogenic and anti-carcinogenic metabolites formed. Women who metabolize a larger proportion of endogenous or exogenous estrogen through 16-hydroxylation pathway may be at higher risk for breast cancer than women who metabolize more estrogen through 2-hydroxylation pathway. DIM promotes healthier estrogen
metabolism by preventing the receptor binding of “stronger” more stimulating estrogens. DIM induces Phase I and II enzyme-pathways involved in carcinogen metabolism. They shift metabolism to the 2-hydroxylation excretory pathway of estradiol and not the 16α-hydroxylation excretory pathway, which contains 17-Keto metabolites that are more strongly estrogenic, and that stimulate proliferation of the terminal ductolobular acinar epithelium.\textsuperscript{139-146}

With 13C there is a risk that estrogen is preferentially metabolized to its 4-hydroxy metabolite, which may play a much more active role in initiating DNA strain breaks and apurinic reactions with DNA that could result in potent carcinogenicity; whereas DIM does not lead to a 4-hydroxy metabolite.\textsuperscript{147}

But yet, DIM does much more including normalization of cell behavior, free radical scavenging,\textsuperscript{148-151} it inhibits the expression of cyclin-dependent kinase-6 and induces a G1 cell cycle arrest in ER negative breast cancer,\textsuperscript{152} and is an inhibitor of MDR.\textsuperscript{153}

DIM can induce apoptosis in breast cancer cells independent of estrogen receptor status by a process that is mediated by the modulated expression of the Bax/Bcl-2 family of apoptotic regulatory factors and NF-kappaB pathways.\textsuperscript{154, 155}

DIM can induce a G1 cell-cycle arrest; a mechanism identified as selective inhibition of cyclin-dependent kinase 6 (Cdk6) expression and stimulation of p21 (Waf1/Cip1) gene expression.\textsuperscript{156} DIM also has shown to cause a marked reduction in EGFR.\textsuperscript{157}

**DIM inhibits PC**

**Downregulates Akt, p-Akt, and PI3 kinase**

DIM is a potent anti-proliferative agent, compared to I3C, in the hormone independent DU 145 CaP cells. The anti-prostate cancer effect is mediated by the inhibition of the Akt signal transduction pathway as DIM, in sharp contrast to I3C, induces the downregulation of Akt, p-Akt, and PI3 kinase. DIM also induced a G1 arrest in DU 145 cells by flow cytometry and downstream concurrent inhibition of cell cycle parameters such as cyclin D1, cdk4, and cdk6. This data suggest a need for further development of DIM as a chemopreventive agent for CaP, which justifies epidemiological evidences and molecular targets that are determinants for CaP dissemination/progression. The ingestion of DIM may benefit CaP patients and reduce disease recurrence by eliminating micro-metastases that are often present in patients who undergo radical prostatectomy.\textsuperscript{158}

**Down-regulates Akt activation, NF-kB, and AR phosphorylation**

The molecular mechanism of action of DIM has not been investigated in androgen receptor (AR)-positive hormone-responsive and -nonresponsive prostate cancer cells. DIM significantly inhibited Akt activation, NF-kb DNA binding activity, AR phosphorylation, and the expressions of AR and prostate-specific antigen, targeting multiple pathways involved in prostate cancer. DIM inhibited AR nuclear translocation, leading to the down-regulation of AR target genes. Moreover, DIM significantly inhibited prostate cancer bone metastasis. These results suggest that DIM-induced cell proliferation, inhibition, and apoptosis induction are partly mediated through the down-regulation of AR, Akt, and NF-kB signaling. These observations provide a rationale for devising novel therapeutic approaches for the treatment of hormone-sensitive, but more importantly, hormone-refractory prostate cancer by using DIM in combination with other therapeutics.\textsuperscript{158}

**Reduces androgen-binding to the AR receptor and lowers DHT**

DIM acts as a powerful anti-androgen, inhibiting the spread of human prostate cancer cells. In this study, the researchers compared the effects of DIM on androgen-dependent human prostate cancer cells as well as on cancer cells that were independent of androgen. It was found that androgen-dependent cancer cells treated with a solution of DIM grew 70 percent less than untreated cells. However, androgen-independent cells were not affected by the DIM solution. Further tests showed that DIM inhibits the actions of
dihydrotestosterone (DHT), the primary androgen involved in prostate cancer. DHT works by stimulating the expression of prostate specific antigen (PSA). PSA acts as a growth factor for prostate cancer, however when androgen-dependent cells were treated with DIM, the level of PSA decreased, which suggests that DIM functions at a gene expression level. DIM significantly halted proliferation of androgen-dependent human prostate cancer cells.\textsuperscript{159}

**Induction of apoptosis: AR, Akt, and NF-kB pathways**

DIM was studied in another experiment on AR, Akt, and NF-kB signaling in hormone-sensitive LNCaP (AR+) and hormone-insensitive C4-2B (AR+) prostate cancer cells. DIM was found to significantly inhibit cell proliferation and induce apoptosis in both cell lines. Importantly, DIM significantly inhibited Akt activation, NF-kB DNA binding activity, AR phosphorylation, and the expressions of AR and prostate-specific antigen, suggesting that DIM could interrupt the crosstalk. Confocal studies revealed that DIM inhibited AR nuclear translocation, leading to the down-regulation of AR target genes. Moreover, DIM significantly inhibited C4-2B cell growth in a severe combined immunodeficiency-human model of experimental prostate cancer bone metastasis. These results suggest that DIM-induced cell proliferation, inhibition, and apoptosis induction are partly mediated through the down-regulation of AR, Akt, and NF-kB signaling.\textsuperscript{160}

**Inhibits MDR**

In another experiment I3C was used rather than DIM and showed a PC suppressive effect through a mechanism involving the androgen receptor (AR) expression in LNCaP cells. I3C expression of exogenous AR was prevented by I3C.\textsuperscript{161}

DIM synergizes with chemotherapeutic agents by inhibiting multi-drug resistance through down-regulation of P-glycoprotein (P-gp), and is a potent chemopreventive agent for hormonal-dependent cancers such as breast, prostate, and cervical cancer.\textsuperscript{162}

Dosage: 200-600 mg.

**Quercetin**

Quercetin is a flavone, a sub category of flavonoids, and is found in apples, onions, broccoli, eucalyptus, green, black and red tea, and blue-green algae. Quercetin possesses anti-allergenic, anti-viral, redox-regulating, anti-inflammatory, and anticancer abilities. Quercetin has been shown to prevent mast cell degranulation and histamine release more effectively than the anti-allergy drug, Cromoglycate. Also, quercetin helps inhibit the action of two enzymes involved in allergic reactions and inflammation - phospholipase A2 and lipoxygenase.

In a double-blind trial, 67% of patients taking quercetin had an improvement of prostatitis symptoms, compared to a 20% response rate in the placebo group.\textsuperscript{163}

Quercetin has been shown to inhibit the growth of several human cancer cell lines including breast (Estrogen receptor positive and ER-negative), prostate, ovarian, squamous cell, cervical, bladder and gastric cancers, acute myeloid and acute lymphoid leukemia, and some lymphomas. Quercetin has been found to be a potent inhibitor of cyclin-dependent kinases; it inhibits the activity of angiogenic mediators, and induces apoptosis by a diversity of mechanisms that are still not fully understood.\textsuperscript{164}

Quercetin, by blocking pro-inflammatory reactions in the body that release arachidonic acid into the cells, acts as a powerful inhibitor of the tumor-promoting prostaglandin PGE-2. It also stabilizes mast cell walls by prolonging the health of lipids, by blocking lipoxygenase activity, and through stabilization of capillary beds by decreasing capillary fragility. This is why quercetin is one of the most effective natural anti-allergenic agents.\textsuperscript{165-167} It should be taken in a sub-lingual form where it can be effectively absorbed.

**Quercetin and Cancer Inhibition: Pleotrophic/multi-tasking in review:**
Redox/antioxidative;
Modulates inflammatory pathways including COX and LOX pathways, inhibiting PGE-2;
Inhibits cancer-related angiogenesis;
Down-regulates tumor promoting growth factors including EGF and Her II neu;
Down regulates NFKB and AP-1;
Activates PTEN;
Inhibits mutation of p53;
Down regulates Bcl-2;
Down regulates TNF-alpha;
Activated caspase-3, Bax, and Bak;
Elevates p21 and p27;
ER regulation - down-regulating estrogen binding;
Reduces circulating IGF, increasing IGFBP;
Down-regulates MMP-2 and 9;
Down-regulates cyclin D and E;
Down-regulated the expression of heat shock protein 70;
Chemosensitize;
Radiosensitize.

Quercetin and PC

PC 1: Inhibits oncogenes and up-regulates tumor suppressor genes

Quercetin at concentrations of 25 and 50 micro M significantly inhibited the growth of the highly aggressive PC-3 prostate cancer cell line and the moderately aggressive DU-145 prostate cancer cell line. Quercetin significantly inhibited the expression of specific oncogenes and genes controlling G(1), S, G(2), and M phases of the cell cycle. Moreover, quercetin reciprocally up-regulated the expression of several tumor suppressor genes.\textsuperscript{167}

PC 2: Down-regulates Her II neu

Because the ErbB-2 receptor is involved in hormone-independency for growth and metastasis of prostate cancer cells, the aim was to investigate the effects of quercetin on ErbB-2 and ErbB-3 expression and its critical components such as MAP kinase and PI-3 kinase. Co-treating PC-3 cells with quercetin significantly attenuated EGF- and TGF-alpha-induced growth and phosphorylation of ErbB-2, ErbB-3, c-Raf, MAPK kinase 1/2 (MEK1/2), MAPK, Elk-1 and Akt-1.\textsuperscript{168}

PC 3: Inhibits Metastasis: Down-regulates MMP-9

Matrixmetalloproteinases (MMP) 2 and 9 are enzymes known to be involved in tumor invasion and metastasis. PC-3 cells were treated with quercetin at various concentrations (50 and 100 muM) for a 24h period and then subjected to western blot analysis to investigate the impact of quercetin on MMP-2 and 9 expressions. Quercetin treatment decreased the expressions of MMP-2 and MMP-9 in dose-dependent manner. Inhibition of metastasis-specific MMPs in cancer cells may be one of the targets for anticancer functions of quercetin, and thus provides the molecular basis for the development of quercetin as a novel chemopreventive agent for metastatic PC.\textsuperscript{169}

PC 4: Inhibits AR binding: Reduces overexpression of c-Jun

Prostate cancer cells treated with quercetin or without treatment were used for checking protein expression levels of c-Jun and cAMP response element binding protein (CREB)-binding protein (CBP). Regulatory effects of c-Jun and CBP on the function of androgen receptor (AR) were examined by cotransfection experiment. Quercetin dramatically induced the protein expression of c-Jun which in turn inhibited the AR function. Overexpression of c-Jun induced by quercetin had inhibitory effect on the function of AR protein, leading to an inhibitory effect on prostate cancer.\textsuperscript{170}
PC 5: Potentiates and sensitizes TNF-related apoptosis-inducing ligand (TRAIL): inhibits Akt

TNF-related apoptosis-inducing ligand (TRAIL) is a promising cancer therapy that preferentially induces apoptosis in cancer cells. However, many neoplasms are resistant to TRAIL by mechanisms that are poorly understood. Human prostate cancer cells, but not normal prostate cells, are dramatically sensitized to TRAIL-induced apoptosis and caspase activation by quercetin. Quercetin can potentiates TRAIL-induced apoptotic death. Human prostate adenocarcinoma DU-145 and LNCaP cells were treated with various concentrations of TRAIL (10-200 ng/ml) and/or quercetin (10-200 microM) for 4 h. Quercetin, which caused no cytotoxicity by itself, promoted TRAIL-induced apoptosis. Quercetin also induced potent inhibition of Akt phosphorylation. Quercetin enhances TRAIL-induced cytotoxicity by activating caspases and inhibiting phosphorylation of Akt.171

PC 6: Inhibits AR expression and down-regulation of c-Jun

Cell extracts treated with quercetin or without treatment were used for checking protein expression levels of c-Jun and cAMP response element binding protein (CREB)-binding protein (CBP). Quercetin dramatically induced the protein expression of c-Jun which in turn inhibited the AR expression.172

Another mechanism whereby quercetin suppressed PC was through the modulation of AP-1. 173

PC 7: Inhibits Benzo(a)pyrene toxicity induced PC

Benzo(a)pyrene (BaP)-mediated toxicity in prostate cancer and the chemopreventative potential of quercetin were studied. Quercetin inhibited both BaP-mediated effects on peroxiredoxin (Prx) I and II, in 22Rv1 human prostate cancer cells. In prostate cancer cells, quercetin inhibited BaP-mediated upregulation of Prx I and had tendency to neutralize BaP-mediated downregulation of Prx II. Quercetin also inhibited BaP-induced concentrations of reactive oxygen species as well. These results suggest that Prx I and II may be involved in BaP-mediated toxicity and the potential chemopreventative mechanisms of quercetin.174

Modified Citrus Pectin

Modified citrus pectin (MCP) is a complex polysaccharide obtained from the peel and pulp of citrus fruits. Modified citrus pectin is rich in galactoside residues, giving it an affinity for certain types of cancer cells. Metastasis is one of the most life-threatening aspects of cancer and the lack of effective anti-metastatic therapies has prompted research on MCP’s effectiveness in blocking metastasis of certain types of cancers, including melanomas, prostate, and breast cancers.

Modified citrus pectin powder is produced from citrus pectin via pH and temperature modification that breaks it into shorter, non-branched, galactose-rich, carbohydrate chains; which dissolve more readily in water and are better absorbed and utilized by the body than ordinary long-chain pectins. It is believed the shorter polysaccharide units afford MCP its ability to access and bind tightly to galactose-binding lectins (galectins) on the surface of certain types of cancer cells. Galactose-binding lectins (selectins) fall under the category of cell adhesion molecules.

Cell adhesion molecules (CAM)

Cancer cells communicate with each other and proliferate because of certain cell surface receptor molecules called cell adhesion molecules (CAM). In order for tumor invasion to take place, there must be a breakdown in the extracellular matrix. CAMs are complex protein-carbohydrate molecules that occur on the plasma membrane of all cell surfaces. They control both intracellular and extracellular (cell-to-cell) communication. They act as the eyes, ears, and nose of each cell. CAMs regulate organ architecture, cell migration, differentiation, apoptosis, mitosis, platelet aggregation, and the activity of the immune system. It has become evident that CAMs are actively involved in mediating the recruitment of specific lymphocyte subsets into different tissues. There are four main types of CAMs: cadherins, integrins, selectins (cell-surface lectins), and Immunoglobulin Super-family Cell Adhesion Molecules (ISCAMs).
Selectins, also called cell-surface lectins, act as receptors by binding to cell surface carbohydrates and glycoproteins. In order for metastasis to occur, cancerous cells must first clump together; Selectins, including galactins, serve as the cement that allows cancer cells to clump together and form metastatic tumors. I often use the analogy of velcro balls, or burdock burrs easily sticking together. Galectins (β-galactosidase lectins) are binding proteins that sometimes have increased activity in metastatic cancers of the breast, prostate, colon, and melanoma. Certain dietary lectins may be able to bind to the tumor cell and inhibit tumor cell-to-cell adhesion, thereby prohibiting completion of the metastatic process. Galactose-rich, modified citrus pectin has a binding affinity for galectins on the surface of cancer cells, resulting in an inhibition, or blocking, of cancer cell aggregation, adhesion, and metastasis.\(^{175-178}\)

Peinta et al examined modified citrus pectin’s effectiveness against prostate cancer metastasis in the Dunnin rat model. Rats were injected with prostate adenocarcinoma cell lines and given drinking water containing various MCP concentrations. Oral MCP did not affect primary tumor growth, but significantly reduced metastases when compared to control animals.\(^{179}\)

In one human study, Strum et al examined the effect of MCP on prostate specific antigen (PSA) doubling time in seven prostate cancer patients. PSA is an enzymatic tumor marker, and its doubling time reflects the speed at which the cancer is growing. MCP was administered orally at a dosage of 15 grams per day in three divided doses. Four of seven patients exhibited more that 30-percent lengthening of PSA doubling time. Lengthening of the doubling time represents a decrease in the in the cancer growth rate.\(^{180-182}\)

**Dosage**

Modified citrus pectin dosages are usually expressed in grams, with a typical adult dosage ranging between 10-30 grams daily in divided doses.

**Lycopene**

Several epidemiological studies have shown an inverse association between tomato consumption and prostate cancer. The carotenoid lycopene, which is found abundantly in tomatoes and tomato products, has been shown to reduce the risk of prostate cancer. Health benefits of lycopene from tomato products are in part related to lycopene antioxidant activity. Consumption of tomato products with olive oil significantly raises the plasma antioxidant activity of lycopene.\(^{183}\)

Lycopene has the ability to suppress HMG-COA reductase by post-transcriptional mechanisms, reducing dolichyl phosphate production, causing a reduction in cell surface expression of IGF-I receptors. The substantial cancer protection associated with tomato consumption (rich in lycopene), as evidenced in epidemiological studies, reflects the ability of lycopene to interfere with endogenous synthesis of isoprenoids. Carotenoids are effective antioxidants that quench free radicals, provide protection against oxidative damage to cells, and also stimulate immune function. Persons with high levels of carotenoids have reduced risk of cancer.\(^{184,185}\)

The following studies take a further look at this phenomenon by analyzing the effects of key tomato carotenoids on prostate cancer cell cultures and the association of plasma levels of tomato carotenoids with prostate cancer.

A recent study involving twenty-six men with newly diagnosed, clinically localized prostate cancer were divided in half and either given 15 mg. of lycopene or no supplementation three weeks prior to surgery. The men in the group all had a radical prostatectomy and then retested their prostate-specific antigens (PSAs). The lycopene group had an 18% reduction in PSAs while the control group had a 14% increase. Overall the investigators found that the treated group had smaller tumors, which were more likely to be confined to the prostate. Levels of serum, PSA (Prostate Specific Antigen, a common marker used to detect prostate cancer) were found to decline in the patients who received Lycopene tomato extract. In addition, the tumors in patients who consumed the natural Lycopene showed signs of regress and decreased malignancy.\(^{186}\)
Researchers at the University of Illinois in Chicago recently published these results of one study in the 2001 December issue of the Journal of the National Cancer Institute. The researchers found that men with prostate cancer who ate daily pasta dishes with tomato sauce had a significant reduction in DNA damage to prostate cancer cells and reduced PSA--prostate-specific antigen--levels. Thirty-two African-American men ate tomato-based pasta dishes, including lasagna and stuffed shells, daily for 3 weeks before their scheduled cancer surgery. The amount of lycopene in each meal was carefully measured. An examination of the prostate tissue after surgery found that lycopene had accumulated in the tissue and that prostate DNA damage was 28.3% lower in the men who had eaten the tomato sauce than in a control group. PSA levels decreased 17.5%.\textsuperscript{187}

Researchers found that the tomato carotenoids \textbf{phytofluene, zeta-carotene, and lycopene} significantly reduced growth of prostate cancer cells.\textsuperscript{188} I do not believe in supplementing with synthetic lycopene which is what is widely found in health food stores. Here is a good example of the importance of the whole food source of carotenoids from tomatoes.

This case-control study was conducted to investigate the effects of plasma lycopene, other carotenoids, retinol, and alpha- and gamma-tocopherols on the risk of prostate cancer. The study included 65 patients with prostate cancer and 132 cancer-free controls. All of them were interviewed using a standard epidemiological questionnaire at the Memorial Sloan-Kettering Cancer Center from 1993 to 1997. Plasma levels of carotenoids, retinol, and tocopherols were measured by high performance liquid chromatography. Significant inverse associations with prostate cancer were observed with plasma concentrations of lycopene and zeaxanthin. The higher the plasma concentration of carotenoids the lower the incidence of prostate cancer.\textsuperscript{189}

Polyphenols from tomato products counteract the ability of IGF-1 to stimulate proliferation and prevent apoptosis via inhibition of multiple intracellular signaling pathways involving tyrosine kinase activity.\textsuperscript{190}

\textbf{Acts on male hormones by lowering DHT to inhibit PC}

In this study, rats were fed lycopene, vitamin E, a combination of both, or a placebo mixture for four weeks, and were then injected with prostate cancer cells into their prostates. These cancer cells grew into tumors in the following two weeks. Lycopene as well as vitamin E from feedings caused an enhanced killing rate of tumor cells, which was shown by larger areas of dead tissue in the prostate tumors. Both nutrients affected gene expression directly in the tumors: lycopene interfered with local androgen activation by down-regulating 5-alpha-reductase, the key enzyme for the transformation of testosterone to its most active form dehydrotestosterone (DHT). As a consequence, the expression of androgen-regulated target genes was also reduced.\textsuperscript{191}

In addition, lycopene decreased the expression of two prostatic cytokines, IGF-I and IL-6, both regarded as risk factors for prostate cancer. Vitamin E reduced androgen signaling without affecting androgen metabolism.\textsuperscript{192}

\textbf{Anti-mitotic/proliferative effects: LNCaP and PC3 cells suppression}

LNCaP and PC3 cells treated with lycopene undergo mitotic arrest, accumulating in G0/G1 phase. Immunoblot screening indicated that lycopene's antiproliferative effects are likely achieved through a block in G1/S transition, mediated by decreased levels of cyclins D1 and E, decreased cyclin dependent kinase 4, and suppressed Retinoblastoma phosphorylation. These responses correlated with decreased insulin-like growth factor-1 receptor expression and activation, increased insulin-like growth factor binding protein 2 expression, and decreased AKT activation. Exposure to lycopene at doses as low as 10nM for 48h induced a profound apoptotic response in LNCaP cells. In contrast PC3 cells were resistant to apoptosis at doses up to 1muM. Lycopene exposure suppressed phosphatidylinositol 3-kinase-dependent proliferative and survival signaling in androgen-responsive LNCaP and androgen-independent PC3 cells through the induction of G0/G1 cell cycle arrest.\textsuperscript{193}
Human study in androgen independent PC patients

Don’t expect Lycopene by itself to stop progressive androgen independent PC. This study explored the efficacy of a lycopene-rich tomato product in androgen-independent prostate cancer and the reasons patients participated in an "alternative medicine" study. This Phase II study evaluated 46 patients with androgen-independent prostate cancer. All were asymptomatic and had serum prostate-specific antigen elevation despite hormonal manipulation. All patients completed a questionnaire on their motivations for enrolling in an "alternative medicine" study. Patients were prescribed a lycopene-rich tomato supplement at a lycopene dose of 15 mg twice daily. Surprisingly one patient actually manifested a tumor response with a 50% or greater confirmed decline in serum prostate-specific antigen level.\(^{194}\)

A summary of the main proposed mechanisms of lycopene for the cancer inhibition:

1. Scavenger of oxidative damage, lowering damage to lipids, proteins, and DNA. In particular, oxidized DNA bases such as hydroxy-deoxyguanosine (80HdG) may cause mutations and hence are implicated in the development of cancer;
2. Enhances Gap-junction communication. Enhancement of Gap-junctional communication has shown to suppress tumor cell replication;
3. Inhibition of the mitogen pathway insulin-like growth factor (IGF)-1, increase in IGF-BP-2;
4. Inhibition of HMG CO-enzyme A reductase;
5. Down-regulates 5-alpha-reductase, reducing the production of DHT;
6. Inhibits inflammatory cytokine IL-6;
7. Anti-mitotic/proliferative: G0/G1 cell cycle arrest.

Dosage: 30 mg. daily, although I mostly promote eating a diet rich in lycopene and not to supplement

Carotenoids in general are very important compounds for cancer prevention. A case-control study involving men from the Physicians Health Study considered baseline beta-carotene plasma concentration and risk of prostate cancer. The investigators found a nonsignificant trend toward increased prostate cancer risk and the lowest quartile of baseline plasma beta-carotene concentration in 631 case patients and 2204 controls (OR 1.45, 95% CI 0.98–2.15). Men in the lowest quartile of plasma beta-carotene concentration assigned to supplementation with beta-carotene 50 mg every other day had a reduced risk of prostate cancer compared with those assigned to placebo (OR 0.68, 95% CI 0.46–0.99).\(^{195}\)

I don’t typically supplement lycopene or beta-carotene, but rather recommend people eat a diet rich in carotenoids.

Lumbrokinase

Lumbrokinase is a strong fibrinolytic enzyme from the earthworm (Lumbricus rubellus lysates) that not only directly degrades fibrin, but also activates plasminogen. Lumbrokinase, being a plasminogen activator, is similar to the tissue plasminogen activator from various sources which can convert the plasminogen into plasmin to carry out fibrinolysis, thus dissolving fibrin in thrombus. Lumbrokinase contains at least six lumbrokinase fractions (F1 to F6) with potent fibrinolytic activities.\(^{196-203}\)

Lumbrokinase is a new thrombolytic medicine which is safe, non-toxic, with no obvious side-effects, that effectively powers fibrinogen levels and reduces the risk of not only cardiovascular and cerebral diseases,\(^{200-203}\) but is also very useful in cancer therapies. Using Lumbrokinase together with botanical phytocemicals compounds and specific fatty acids to dissolve cancer-induced fibrin is an important target in my protocols.

Cocoa Polyphenols Extracts

Yes! In addition to all of the cardiovascular benefits, eating a small amount of organic chocolate (sweetened with whole-raw sugar) may also suppress cancer, including PC. Cocoa contains many different types of physiologically active components. It was shown that cocoa beans are rich in specific flavonoids, catechins, epicatechins, and proanthocyanidins. Cocoa also contains beta-sitosterol, the most common
Phytosterol, which plays a protective role against the development of cancer. A study was conducted to evaluate the inhibitory effect of different cocoa polyphenols extracts, alone or combined with beta-sitosterol, on two human prostate cancer cell lines (nonmetastatic 22Rv1 cells and metastatic DU145 cells) and a normal human prostate cell line (RWEP-1). A synergy between beta-sitosterol and cocoa polyphenols extract was also researched. At the highest tested concentration, cocoa polyphenols extracts induced a complete inhibition of growth of both metastatic and nonmetastatic cancer cell lines. In addition, cocoa polyphenols extracts were more active against local cancer cells than against metastatic cells. Moreover, at the highest tested concentration, cocoa polyphenols extracts are not effective on a normal prostate cell line. Beta-sitosterol induced low growth inhibition of both cancer cell lines. Cocoa polyphenols extracts, however, were significantly more active and showed a strong and fast inhibition of cell growth than beta-sitosterol alone. The results of this study show that "cocoa polyphenols extracts have an antiproliferative effect on prostate cancer cell growth but not on normal cells at the highest tested concentration."

**Honokiol (Magnolia spp.)**

Honokiol, a soluble nontoxic natural product derived from Magnolia spp., has been shown to induce apoptosis in malignant cells. Honokiol induces cell cycle inhibition, observed at lower doses of HNK, and induction of apoptosis, at a higher dose.

**Suppresses angiogenesis via VEGF**

Investigators at Emory University, separated the natural magnolia mixture chromatographically and tested the fractions for their ability to prevent the growth of an endothelial cell line in culture. Endothelial cells make up the walls of blood vessels. They identified honokiol, a compound previously studied by Japanese researchers in herbal medicines, as the active component of the magnolia extract. Honokiol reduced the growth of endothelial cells by driving them into apoptosis, a self-destruction program activated by cells when their growth signals are disrupted. Importantly for the specificity of its anti-tumor activity, honokiol inhibited the growth of endothelial cells more than other kinds of cells. In mice inoculated with tumor-promoting cells, honokiol reduced tumor growth by 50 percent over a control group of mice. Now, Arbiser's laboratory is working to more precisely determine the mechanism by which honokiol affects endothelial cell growth. The Emory team found that honokiol acts within the cell to stop growth signals from VEGF being heard. Honokiol may also act by activating a natural tumor defense, stimulating the production of a protein within the body that induces suicide by tumor cells.

**Inhibits the bone metastatic growth of human prostate cancer cells.**

In PCa cells honokiol induced apoptosis via the activation of caspases 3, 8, and 9 and the cleavage of polyadenosine diphosphate ribose polymerase in a dose- and time-dependent manner. Honokiol was shown to inhibit the growth and depress serum PSA in mice harboring C4-2 xenografts in the skeleton and the combination with docetaxel showed additive effects that inhibited further growth without evidence of systemic toxicity. Immunohistochemical staining confirmed honokiol exhibited growth-inhibitory, apoptotic, and antiangiogenic effects on PCa xenografts. The combination of honokiol and low-dose docetaxel may be used to improve patient outcome in androgen-independent prostate cancer with bone metastasis.

**Phytonutrients in combination become much more active as inhibitors of PC**

Preclinical and clinical data has been collected on phytochemicals such as genistein, lycopene, curcumin, green tea extract rich in epigallocatechin-gallate, and resveratrol, in terms of their effects as a potential treatment of prostate cancer. It is known that prostate cancer patients increasingly use complementary and alternative medicines in the hope of preventing or curing cancer. The preclinical data for the phytochemicals presented in this review show a remarkable efficacy against prostate cancer cells, with molecular targets ranging from cell cycle regulation to induction of apoptosis.
Section VI

Important Essential Fatty Acids for PC Prevention and Treatment: EPA/DHA (n-3) from fish oil and GLA

Essential fatty acids (EFAs) are vital components of human health that cannot be produced by the body and are therefore “essential.” The role of EFAs are vital for the development and proper maintenance of cell membrane behavior and cell signaling in all tissues, which are highly dependent on the lipid constituents of cells. EFAs are needed for normal brain function, growth, and development; bone health; stimulation of skin and hair growth; regulation of metabolism; and maintenance of reproductive processes. They play key roles in the structure of brain cells and of the eye, particularly the retina. They're vital for each neuron's membrane, both its outer protection and its means of accessing key nutrients. And it is these essential fats that regulate the growth of the long tendrils called axons that enable neurons to communicate with each other.

Unfortunately most people and pets obtain their EFAs from commercial foods and oils, which have been highly processed and are often in an oxidized, rancid state. Food manufacturers know about this propensity towards rancidity, and therefore highly refine their vegetable oils. Considerable research has shown that trans fatty acids, present when vegetable oils are highly refined (hydrogenated or partially hydrogenated), are especially damaging to cell tissue and can have a negative affect on all aspects of health. This makes them extremely unhealthy to consume. Linoleic acid (LA), the predominant omega-6 fatty acid found in most oils and foods such as corn and soy, is particularly prone to this rapid health hazard. This creates two problems: 1) acceleration of free radical damage (lipid peroxidation) and inflammation; 2) no available source of healthy EFAs to carry out important roles in the body. Increasing the level of omega-3 fatty acids, while eliminating commercial processed vegetable oils, will lower inflammatory precursors and may have a favorable effect on the Hypothalamus-pituitary-adrenal axis assisting in adaptation and energy efficacy.

Fish oil, rich in omega-3 fatty acids, eicosapentanoic acid (EPA) and docosa hexanoic acid (DHA), consumption is a strong factor in helping people live longer, and many experts believe that it is likely the predominant reason why the Japanese are the longest lived race on the planet. Omega (n) -3 fatty acids have been associated with numerous health benefits, from brain development and preventing memory loss, to suppressing tumors and cutting heart disease. N-3 fatty acids exert suppressive effects on cancer growth and are associated with impaired angiogenesis. Both EPA and DHA have shown in multiple experiments to inhibit metastasis of several cancers including breast, prostate, and colon cancer. Dietary n-3 fatty acids inhibit the growth of pre-existing breast cancer micrometastases when used as adjuvant nutritional therapy after excision of the primary tumor. Most likely the suppression of angiogenesis contributes to this therapeutic effect. Elsewhere, we have discussed in detail the potential for dietary n-3 fatty acid supplementation as an adjunct to surgery and conventional combination chemotherapy and for cancer prevention.

Not only is the typical American diet providing an abundance of omega-6 fatty acids, mostly commercial processed and in a highly oxidative form, but it is also low in n-3 fatty acids, which is associated with an increase risk of PC. On the other hand diets rich in n-3 fatty acids from fish have been shown to reduce risk of PC.

Another beneficial effect of n-3 fatty acids in cancer therapy is its ability to treat malnutrition and inhibit cachexia – wasting that occurs in late-stage cancer. N-3 fatty acids have shown to improve immune function, effect tumor necrosis factor, and most important improve the quality and prolong the life of patients with generalized malignancy.

N-3 fatty acids showed to impede tumor angiogenesis and invasiveness by down-regulating protein kinase C and modulating eicosanoid production. Induction of collagenase by protein kinase C plays an important role in the angiogenic process as well as in metastasis. Lipoxygenase products are required for endothelial cell mitosis, and also promote collagenase production, as I have mentioned previously. By down-regulating hormonal activation of protein kinase C and modulating eicosanoid metabolism, ingestion of n-3-rich fish oils may
impede angiogenesis and reduce tumor invasiveness, thus rationalizing the growth-retardant and anti-metastatic effects of fish oil feeding almost invariably seen in animal tumor models. Certain other anti-inflammatory agents-including cromolyn (similar in structure to quercetin, it is an inhibitor of protein kinase C activation, but is weaker than quercetin) and gamma-linolenic acid (GLA - indirectly inhibits lipoxygenase) may have analogous, tumor-retardant activities. This study concludes by saying clinical application of supplemental fish oil in cancer therapy is long overdue. In another earlier study, fish oil supplementation showed to inhibit breast cancer growth by reducing PGE\textsubscript{2} formation and lipid peroxidation. Fish oil also induced apoptosis in lymphoma cells, as well as in other cancer cell lines.

<table>
<thead>
<tr>
<th>EPA/DHA</th>
<th>Key functions or Effects of n-3 fatty acid</th>
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<tbody>
<tr>
<td>Readily incorporated into membranes, often at the expense of arachidonic acid</td>
<td>Antagonize production of inflammatory cell eicosanoids from the n-6 arachidonic acid</td>
</tr>
<tr>
<td>Subject to ready peroxidation due to high degree of unsaturation (therefore important to maintain appropriate antioxidant status)</td>
<td>Precursor of alternative family of eicosanoids, often with only weak biological effects</td>
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**Key Functions continued:**
- Induce apoptosis;
- Anti-inflammatory;
- Can prevent immunosuppression in some situations;
- Antiangiogenesis;
- Chemo-protective;
- Inhibit cachexia.

**Prostate cancer inhibition**

Most epidemiological studies indicate that the level of dietary fat intake and the nature of the constituent fatty acids influence both breast and prostate cancer risk, and disease progression. As stated earlier these observations derive support from the use of animal models, which demonstrate that commercial oils rich in polyunsaturated n-6 fatty acids stimulate breast and prostate carcinogenesis and tumor growth and metastasis, whereas long-chain n-3 fatty acids exhibit inhibitory effects. A multiplicity of biological actions of eicosanoids derived from tumor cell arachidonate metabolism appears to elicit responses, both in the tumor itself and in the host cells that subscribe to its microenvironment.

Men who consume moderate-to-high amounts of fatty fish, such as salmon, herring, and mackerel, which contain high levels of Omega-3 fatty acids, have a significantly reduced risk of developing prostate cancer. EPA and DHA intakes are related to both lower total prostate cancer risk and advanced prostate cancer risk. Men with the highest quintiles of EPA and DHA combined had an 11 percent lower total prostate cancer risk and advanced prostate cancer risk was 26 percent lower, according to the risk analysis.

**Dietary fatty acids correlate with PC biopsy grade and volume in Jamaican men**

A total of 148 men were enrolled in Kingston, Jamaica. Serum prostate specific antigen and erythrocyte membrane polyunsaturated fatty acids were analyzed. Men with prostate specific antigen 2.6 ng/ml or greater underwent biopsy. Histopathological and statistical analyses were performed on available data. Of the 54 men who underwent biopsy, 24 had prostate cancer, 17 had a Gleason score of 7 or greater, and 11 had a tumor volume of 50% or greater. There were significant positive correlations between linoleic acid and Gleason score ($p = 0.009$), and the linoleic acid-to-docosahexaenoic acid (n-3) ratio and tumor volume ($p = 0.03$). There was a significant negative correlation between the arachidonic acid (n-6)-to-docosapentanoic acid (Omega3) ratio and Gleason score ($p = 0.04$).

**Reduces PC Progression:** Down-regulates PG2, COX-2, VEGF
This study found that a diet rich in commercial n-6 fatty acids (soy, corn, and vegetable oils) increased the spread of prostate tumor cells into bone marrow, while n-3 fatty acids blocked the invasion. Mice were divided into two groups; one fed a diet comprised of 20 percent fat with a healthy one-to-one ratio of omega-6 to omega-3 fatty acids, while the second group of mice was fed the same diet but with the fat derived from mostly omega-6 fatty acids. N-6 fats are found in corn, soy, and other vegetable oils; nuts, seeds, and red meats. Corn oil is the backbone of the American diet. We consume up to 20-50 times more omega-6 fatty acids in our diet compared to n-3 acids. At the end of the intervention period, the researchers reported that tumor cell growth rates had decreased by 22 per cent and PSA levels by 77 per cent in the group receiving a healthier balance of fatty acids compared with the group that received predominantly omega-6 fatty acids. EPA, DHA, and n-6 acid compete to be converted by COX-1 and COX-2 into prostaglandins, which can become either pro-inflammatory and increase tumor growth, or anti-inflammatory and reduce growth. The researchers found that levels of the pro-inflammatory prostaglandin (PGE-2) were 83 per cent lower in tumors in the EPA and DHA n-3 group than in mice on the predominantly n-6 fatty acid diet. This suggests that higher levels of DHA and EPA may lead to development of more anti-inflammatory prostaglandins.²³

**DHA together with COX-2 inhibitor suppress PC**

Published in 2006, this study was undertaken to determine the effects of low doses of DHA in combination with celecoxib on the molecular targets at the proteins level in rat prostate cancer cells. The results showed the rate of cancer cell growth was inhibited more effectively (p < 0.01) by DHA in combination with celecoxib at lower doses (2.5 microM each). A total number of twelve proteins were differentially expressed by the combined action of DHA and celecoxib at low doses. These agents activate both HSP70 and p53 proteins and reveal a unique COX-2 independent mode of action against prostate cancer.²⁴

** Stops the spread of prostate cancer**

In another recent study, researchers found that the main metabolite of AA, prostaglandin E2, enables prostate cancer cells to spread to the bone marrow. However when EPA and DHA were present at just half the concentration of the n-6 fatty acid, this spread of cancer cells was stopped. Tumors appear to exploit the n-6 fats as a high-energy source – giving them the energy they need to maintain a high growth rate – and to create important signaling molecules. N-3 fats are known to interfere with the various functions of omega 6 fats.²⁵

One study showed tumor-bearing mice that were fed fish oil had a significantly slower growth of primary tumors, lower mortality rate, and lower metastatic spread, in contrast with mice fed soybean oil.²⁶

Dietary gamma-linolenic acid, found in oils of Pine seed, Primrose, Black current seed, and Borage seed, also inhibit prostate cancer via suppression of elevated generation of PGE(2) and 5S-HETE.²⁷-²⁹

A blended oil of super concentrate fish oil (EPA & DHA), a super-concentrate of Sea Buckthorn oil, and Pine seed oil (18% GLA), is what I use as a supplemental oil.

**Sea Buckthorn oil super concentrate** contains an array of important nutrients and bioactive substances such as vitamins (C and E), carotenoids (including lycopene & beta-carotene), flavonoids, tocotrienols, unique fatty acids including n-7’s, free amino acids, and elemental components. Numerous clinical trials and scientific studies during the 20th century confirm medicinal and nutritional value of Sea Buckthorn, and most importantly, its anti-carcinogenic properties.³⁰,³¹ Sea Buckthorn oil super concentrate possess unique protection from oxidative damage and toxicity.³²-⁴²

Dosage: EPA 1000-2000, DHA 750-1500, GLA 500-1000

**Vitamins and Minerals Useful for Prostate Cancer Prevention and Treatment**

**Vitamin D**

Donald Yance
Prostate Cancer

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19/21/07
In my practice vitamin D is one of the standard supplements I give both in prevention and in treatment of prostate cancer. I routinely monitor vitamin D levels and supplement accordingly. Several epidemiologic observations have found a link between Vitamin D levels, exposure to sun, and incidence of prostate cancer. The presence of vitamin D receptors in prostate cancers and the low level of vitamin D in the serum of prostate cancer patients suggest that vitamin D has potential as a chemopreventive agent. Recent laboratory and epidemiological studies indicate that a high circulating level of 1,25 (OH)2D vitamin D, the biologically active form of vitamin D, inhibits prostate carcinogenesis.44,45

**Deficiency contributes in incidence and mortality**

Low levels of vitamin D increases the risk of developing prostate cancer as well as contributes to the progression of existing prostate cancer. A PubMed database search yielded 63 observational studies of vitamin D status in relation to cancer risk; including 30 of colon, 13 of breast, 26 of prostate, and 7 of ovarian cancer, and several that assessed the association of vitamin D receptor genotype with cancer risk.47

A high frequency of vitamin D deficiency in black men contributes to prostate cancer incidence and mortality. Prostate cancer in black men tends to be more aggressive.48 Black men are also more frequently deficient in vitamin D because dark skin requires longer exposure to the sun to ensure optimal levels.

**Sunlight protective against PC**

Cumulative sunlight exposure during the summer months was a better predictor of survival in men with prostate cancer (as well as other cancers) compared to the winter months. This observation added to a growing body of evidence that vitamin D metabolites play an important role in cancer survival.49 A recent study found that a rise in PSA in men with untreated low-grade prostate cancer is slower during spring-summer.50

Vitamin D exerts an antiproliferative effect on prostate cancer in a pleotrophic manner, demonstrating multi-mechanisms.51-53

**Climatological factors and PC**

To evaluate if climatological factors (temperature, rainfall, and number of sunlight hours per year) may influence the mortality associated with prostate cancer over a five-year period, the trends of prostate tumor associated mortality in the period between January 1st, 1998, and December 31st, 2002, in the geographic area of Spain, was studied. Demographic and mortality data were obtained from the National Institute of Statistics (INE) and climatological data about temperature and rainfall were obtained from the National Institute of Meteorology (INM). Prostate cancer mortality presented statistically significant differences, being higher in provinces with higher Martonne index (p < 0.001) and lower in areas with a greater number of sunlight hours per year (p = 0.041). Mortality associated with prostate cancer was significantly superior in regions with less exposition to the sunlight. The climate change may lead to a modification of the main epidemiologic patterns and it may become associated with a modification of cancer mortality rates. Nevertheless, these results should be taken with caution and should be confirmed by prospective studies.54

**Vitamin D FokI ff genotype associated with increase rick of PC**

Vitamin D insufficiency is a common public health problem nationwide. Circulating 25-hydroxyvitamin D3 (25[OH]D), the most commonly used index of vitamin D status, is converted to the active hormone 1,25 dihydroxyvitamin D3 (1,25[OH]2D) which, operating through the vitamin D receptor (VDR), inhibits in vitro cell proliferation, induces differentiation and apoptosis, and may protect against prostate cancer. Data suggests that a large proportion of the US men had suboptimal vitamin D status (especially during the winter/spring season), and both 25(OH)D and 1,25(OH)2D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25(OH)D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population of this cohort) are more susceptible to this cancer in the
Inhibits angiogenesis: Suppression of IL-8

Interleukin (IL)-8 expression is often elevated during prostate cancer progression, and this suggests that IL-8 plays a role in tumor progression, mediated through its stimulation of angiogenesis. A recent study found that 1alpha, 25-dihydroxyvitamin D3 could prevent prostate cancer progression by interrupting the interleukin-8 signaling required in tumor angiogenesis.56

Reduced the expression of MMP-9 and cathepsins

Two recent studies showed that vitamin D3 (1,25-VD) inhibited the function of protease enzymes that are involved in tumor invasion in prostate cancer by decreasing matric metalloproteinases (MMP-9) and cathepsins (CPs), while it increased the activity of their counterparts, tissue inhibitors of metalloproteinase-1 (TIMP-1) and cathepsin inhibitors.57,58

Reduced blood clot formation in men with advanced PC

In men with advanced prostate cancer, vitamin D supplementation reduced blood clots, a common complication that occurs and contributes both to cancer progression and mortality.59

Reduced pain and improves muscle strength in advanced PC patients

Vitamin D deficiency develops in a significant percent of patients with advanced hormone refractory prostate cancer. Supplementation with vitamin D is a useful adjunct for improving pain, muscle strength, and quality of life, even in advanced prostate cancer. A phase II study was conducted to determine whether pain associated with prostate cancer bone metastasis would respond to vitamin D replacement, and if parameters of muscle strength would be improved by vitamin D replacement therapy. After a 4-week placebo period, eligible patients received orally 2,000 units vitamin D daily for 12 weeks. A total of 16 patients with advanced hormone refractory prostate cancer were enrolled in this phase II study, of whom 7 (44%) had decreased baseline vitamin D. With vitamin D treatment, 4 patients (25%) had improvement in pain scores and 6 (37%) had improvement in muscle strength measurements.60

Reduces the pro-cancerous PG-2

The combination of calcitriol and non-steroidal anti-inflammatory drugs (NSAIDs) resulted in a synergistic inhibition of PC cell growth. The combination of calcitriol and genistein also resulted in a synergistic inhibition of PC cell growth. In addition to inhibiting CYP24 enzyme activity, genistein has its own independent actions on the prostaglandin (PG) pathway in PCa cells. Like calcitriol, it inhibits COX-2 expression and activity leading to decreased synthesis of PGE(2). It also inhibits the EP and FP receptors, thereby reducing the biological function of PGE(2). Thus, the combination of calcitriol and genistein acts additively to inhibit the PG pathway. Calcitriol regulates myriad pathways that contribute to the potential chemopreventive and therapeutic utility of calcitriol in PC.61

Calcitriol, the hormonally active form of Vitamin D, inhibits the growth and development of many cancers through multiple mechanisms. New research has shown that several new and diverse pathways add to the mechanisms already established as playing a role in the actions of calcitriol to inhibit the development and progression of prostate cancer. Some of these include:

- Increases the expression of insulin-like growth factor binding protein-3 (IGFBP-3), which plays a critical role in the inhibition of PC cell growth by increasing the expression of the cell cycle inhibitor p21;
- Inhibits the prostaglandin (PG) pathway by three actions: (1) the inhibition of the expression of COX-2, the enzyme that synthesizes PGs; (2) the induction of the expression of 15-prostaglandin dehydrogenase (15-PGDH), the enzyme that inactivates PGs; and (3) decreasing the expression of EP and FP PG receptors that are essential for PG signaling;
• Induces mitogen activated protein kinase phosphatase 5 (MKP5) expression in prostate cells, leading to the selective dephosphorylation and inactivation of the stress-activated kinase p38. MKP5 is a member of a family of phosphatases that are negative regulators of MAP kinases. P38 activation is pro-carcinogenic and is a mediator of inflammation.;
• Mullerian Inhibiting Substance (MIS) has been evaluated for its inhibitory effect in cancers of the reproductive tissues, and is in development as an anti-cancer drug. Calcitriol induces MIS expression in prostate cells revealing yet another mechanism contributing to the anti-cancer activity of calcitriol in PC.62

Enhances radiation and chemotherapy

Vitamin D has also shown to enhance the anti-tumor effects of radiation and chemotherapy against prostate cancer.63-65

Combining calcitriol with docetaxel (Taxotere) improves prostate cancer survival without increasing toxicity. The results of a new study found that the combination vitamin D and taxotere added a survival advantage even more impressive than the PSA response rates might indicate. Also, the combining of calcitriol with docetaxel resulted in a reduction in the risk of death by approximately one third.66

Vitamin D measurement

There are two tests used for measuring the concentrations of vitamin D in your blood. The term vitamin D actually refers to a number of different but related chemical compounds (termed sterols), some of which are inactive and some of which are active in thier forms. The two most common vitamin D tests measure calcidiol (an inactive form) and calcitriol (the active form). The test for calcidiol (sometimes called 25-hydroxy-vitamin D) is used to assure that the body has adequate vitamin D supply. The test for calcitriol (sometimes called 1,25 dihydroxy-vitamin D) is used to assure that the kidney is converting an appropriate amount of calcidiol to the active hormone calcitriol.

Dosage range: 1000 IU-4000 IU

Selenium

Selenium is an essential trace element occurring in both organic and inorganic forms. The organic form is found predominantly in grains, fish, meat, poultry, eggs, and diary products, and enters the food chain via consumption of plants and plant-consuming animals. There is marked geographic variability of selenium content in food, which can be related to local soil content. It is widely distributed in body tissues and is an important constituent of many antioxidant enzymes.

Many epidemiologic observations support selenium as a protective agent against the development of cancer. Both case-control and randomized placebo-controlled trials in humans also suggest that selenium can decrease the risk of developing prostate cancer.67

There have been many studies showing a direct connection between selenium and prostate cancer. In the now famous Clark Study, a 63% reduction in prostate cancer was found in men who received 200 micrograms of selenium from selenium-enriched yeast containing mostly selenomethionine.68

Another study conducted at Stanford University found that low plasma selenium is associated with a 4 to 5-fold increased risk of prostate cancer.69

The strongest evidence for a protective effect of selenium comes from the Nutritional Prevention of Cancer Trial. 1,312 participants took the equivalent of 200 µg yeast per day vs placebo, and with a mean follow-up of 4.5 years the incidence of prostate cancer was reduced in the selenium arm by two-thirds compared to placebo. Reanalysis of the effect of selenium supplementation with a mean follow up of 7.5 years continues to show a marked reduction of the incidence of prostate cancer, with an RR of 0.48 (95% CI 0.29 to 0.87),
with the strongest effect for those with a PSA <4 ng/ml and the lowest serum levels of selenium at study entry.\textsuperscript{70}

Selenium inhibits tumorigenesis in a variety of experimental models, and a number of potential mechanisms have been proposed for its antitumorigenic effects. Accumulating evidence suggests that it works by inhibiting important early steps in carcinogenesis by inhibition of cellular proliferation, induction of apoptosis, and modulation of androgen-regulated genes.\textsuperscript{71-73}

\textit{In vivo} studies also support the antitumorigenic role of selenium in prostate cancer. In a dog model, Waters demonstrated that oral selenium in various forms, given over 7 months as a dietary supplement, resulted in lower levels of DNA damage in prostatic epithelial cells and increased intraprostatic apoptosis compared with controls. A study comparing 200 µg oral selenium per day with placebo in 51 men who underwent transurethral resection of the prostate for benign prostatic hyperplasia and who had normal pretreatment serum levels of selenium, demonstrated that selenium supplementation resulted in significantly higher levels of selenium in prostatic tissue.\textsuperscript{74, 75} Together, these studies demonstrate that orally ingested selenium reaches the prostate gland and modulates markers of oxidative stress relevant to the proposed molecular mechanisms of its protective effects.

Selenium is found in Brazil nuts, tuna, and sunflower seeds.

**Dosage:** 200-800 mcg.

**Copper and Zinc in PC**

High serum levels of copper correlates with certain cancers, and high copper appears to play a role in cancer promotion. Copper metabolism is profoundly altered in neoplastic development in human cancer and in tumor-bearing animals. The role of copper in cancer promotion through inflammation and angiogenesis is now well known. Serum copper levels correlate with tumor incidence, tumor burden, and malignant progression and recurrence in a variety of human cancers (Hodgkin's and non-Hodgkin’s lymphoma, sarcomas, leukemias, and cancers of the cervix, pancreas, breast, \textbf{prostate}, liver, and lung, and in brain tumors as well).

We are learning that copper status is critical to the function of many angiogenic growth factors. The concept of tumor growth driven by angiogenesis is well accepted, but what drives angiogenesis? Based on several lines of evidence, it is reasonable to hypothesize that angiogenesis is dependent on copper status. Copper is incorporated in the extra-cellular matrix that forms the very structure of blood vessels. Copper also acts as a co-factor to molecules known as bFGF, VEGF, and angiogenin; without it, they can not function and growth of new blood vessels stops.\textsuperscript{76, 77} The uptake of copper by tumors is a pathway easily effected through supplementation and is standardly targeted in my protocols.

**Copper and angiogenesis**

Copper stimulates the proliferation and migration of endothelial cells and is required for the secretion of several angiogenic factors by tumor cells. The angiogenic activity of bFGF, vascular endothelial growth factor (VEGF), TNF-alpha, and IL-1 were found to be copper dependent. It was shown that depletion of copper by Tetrathiomolybdate (TM) selectively repressed bFGF-induced sprout formation.\textsuperscript{78} Furthermore, copper repletion switches angiogenesis back "on" when a copper-sufficient diet is restored, providing evidence for a novel, physiologic, and metabolic control pathway of angiogenesis. Copper, but not other trace metals, stimulated the directional migration of endothelial cells. Serum copper levels are up-regulated in many human tumors and correlate with tumor burden and prognosis. Copper chelators reduce tumor growth and microvascular density in animal models. Using nutritional and botanical-based copper-chelation therapy, prostaglandin E-stimulated angiogenesis was suppressed.\textsuperscript{76-82}

A risk of a subsequent diagnosis of cancer has been found to be positively associated with elevated serum copper levels. It is believed that the presence of cancer may increase serum copper levels.\textsuperscript{83} The Cancer Energy appears to be able to manipulate the environment, altering the balance of several substances to
enable its growth, one of which is copper.

Also, high serum copper and ceruloplasmin, which is often combined with low serum zinc, is associated with increased mortality from all cardiovascular disease and higher risk of subsequent cancer diagnosis.83-86

Tetrathiomolybdate (TM) is a potent copper chelator which has shown remarkable ability to suppress angiogenesis. Although this may involve multiple mechanisms, the effects on vascular endothelial growth factor (VEGF) are pivotal. Long-term TM treatment on the growth and metastatic progression in an animal model was recently tested. The results showed that TM treatment is able to maintain effective inhibition of angiogenesis. TM lowered copper and significantly caused a reduction in tumor size and vascularity in TM-treated animals. These effects were highly correlated with suppression of human VEGF expressed in the developing tumors, as well as the mouse VEGF levels detected in the plasma. TM treatment also drastically suppressed the development of lung metastases. Taken together, these results show that copper chelation can act long-term as a suppressor of vascularity and inhibit the growth of metastasis in this model.87

Copper deficiency induced by TM significantly impaired tumor growth and angiogenesis in two animal models of breast cancer: an inflammatory breast cancer xenograft in nude mice, and Her2/neu cancer-prone transgenic mice.88

Copper deficiency induced by lowering copper with a chelating agent, such as TM decreases the production of five proangiogenic mediators:
(a) Vascular endothelial growth factor (VEGF);
(b) Fibroblast growth factor 2(FGF-2)/basic fibroblast growth factor(bFGF);
(c) Interleukin (IL)-1alpha;
(d) IL-6;
(e) IL-8;
(f) NF-kB levels and transcriptional activity.

A major mechanism of the antiangiogenic effect of copper deficiency is the suppression of NF-kB, contributing to a global inhibition of NF-kB-mediated transcription of proangiogenic factors.88

Copper reduction suppresses PC

Because copper often plays a role in the universal requirement for angiogenesis in solid tumor growth, the use of TM was tested for the efficacy of copper deficiency to retard tumor growth in the Dunning prostate cancer model. Significant reduction in size of the primary tumor was observed in mice rendered copper deficient. Improved survival, fewer metastatic lesions, and excellent tolerability were also observed.89

The underlying hypothesis of antiangiogenesis using copper-reduction therapy is that the level of copper required for angiogenesis is higher than that required for essential copper-dependant cellular functions. The assumption is that there is a copper deficient level that impedes angiogenesis but does not interfere with other copper-dependant cellular functions. The optimal range for ceruloplasmin (the copper storage value) for someone with cancer is between 10-20% of the normal range (20-25).

I have had a great deal of success using natural agents including molybdium, phenolic-rich companion adaptogens including green tea extract and grape seed extract, isothiocynates, NA-cysteine, cilantro, and most importantly zinc.

Zinc

Zinc is a trace mineral needed for some 300 enzyme-systems used by the body. It is not a direct copper chelator but rather it acts by blocking dietary copper in the intestines preventing additional absorption of copper, and assisting the excretion of it in the stool. This means that any newly ingested copper does not reach the blood stream.

Some of Zinc’s important roles in the body are:
• Produces carbonic anhydrase, which conjugates CO2;
• Is essential to the production of hydrochloric acid (HCL);
• Combined with copper in SOD, zinc acts as an antioxidant. This is why you do not want copper levels to fall below normal;
• Provides nutritional support to the bones, teeth, nails, hair, skin, eyes, and prostate;
• Is essential to the production of antibodies, WBC’s, and thymus function (T-cells);
• Is an essential co-factor in the production of seminal fluid;
• Essential for the conversion of Linoleic Acid (LA) to Gamma Linoleic Acid (GLA);
• Is involved with the metabolism of testes, pituitary, thyroid, and adrenals;
• Is essential to normal fetal growth. 89

Zinc induces cells of the intestinal tract to produce a metallothionein protein (MT) which has a very high affinity for copper and is excreted in the stool. This means that any newly ingested copper does not reach the blood circulation system. Zinc is a better alternative to older copper chelating agents, and Wilson's disease patients frequently use it in their maintenance programs with long-term success. 90, 91

Excessive supplemental zinc is not stored. The human body is extremely efficient in removing surplus zinc in fecal matter, urine, and sweat. Zinc supplementation can make some people nauseous so I recommend starting with low doses, with meals, and building up. Foods rich in Phytic acid, such as pasta and soy foods, reduce the absorption of zinc so try to avoid taking zinc along with these foods. 92 Absorption and excretion rates of zinc are subject to individual variability. The copper reduction protocol I developed for cancer is 20-40 mg zinc three times a day, checking levels every 4-8 weeks. I primarily use a “whole-food” zinc supplement together with a liquid zinc sulfate, and dose accordingly. I typically have people take a good dosage with their morning smoothie, a foundational aspect of my protocols.

**Zinc and PC**

Zinc deficiency, low zinc serum levels below the normal range of 60 to 150 mcg/dL, is common in cancer patients and causes immune suppression since zinc is a key component of many enzyme systems necessary for T-cell function and regulation, as well as prostaglandin regulation. 93-96

I routinely check zinc levels in men with PC, as well as all cancer patients, and more often then not they have zinc deficiency and copper excess. As a clinician, I have monitored copper, zinc, and ceruloplasin levels in many cancer patients and I am convinced it is an important bio-marker to access and target in cancer patients, particularly prostate cancer and lymphoma patients. By altering the microenvironment to reduce ceruloplasin below 25, yet keeping it in the normal range, and maintaining zinc in the mid to upper range of normal, is a contributing and effective piece in controlling cancer growth in many patients within the Triphasic model.

**Low zinc levels linked to PC spread**

Cancerous prostate cells contain less zinc than healthy prostate cells and this may lead to the cancer's ability to spread. In a recent experiment, cultured cells were exposed to zinc sulphate for two days. The cancerous cells accumulated about one-third less zinc than did the noncancerous cells. Also, the amount of one zinc transporter protein—ZIP1—was reduced in the cancerous cells. As a result, those cells had low ability to take in zinc. In addition, analysis showed that even though a second zinc transporter protein, ZIP3, was present in the cancerous cells, it was not in its correct location. Overexpressing ZIP1 significantly suppressed growth and spread of the cancerous cells. 97

**Zinc: An important component to Histone Deacetylase (HDA) regulation**

Altered zinc levels in PC patient disrupt carboxypeptidase A3 (CPA3), a gene which is involved in the inhibition of Histone Deacetylase (HDA). Butyric acid and sulfuraphane, two other agents I use, have shown to inhibit prostate and other cancers by down-regulating HDA. Also, p21 transactivation is required for the induction of CPA3. 98
Zinc and Molybdenum reduce copper levels

Zinc and molybdenum are the key supplements to implement into a protocol to target copper-chelation. Molybdenum is an essential trace mineral that is needed for the proper function of certain enzyme-dependant processes including the metabolism of iron. Unitary copper excretion will occur with daily molybdenum consumption of up to 1-5mg per day. In high doses, molybdenum can increase uric acid levels which can be helpful for people with low levels of uric acid, important for certain antioxidant functions. People with high levels need to monitor uric acid and be careful of gout-like symptoms.

Coriandrum sativum (coriander) has been documented as a traditional treatment for diabetes. Both coriander and cilantro (coriander leaf) are extremely effective chelators of toxic metals. Cilantro increases the elimination of copper, mercury, lead, and other heavy metals. Cilantro’s suppressive activity on lead deposition is most likely the result of the chelation of lead by some substances contained in cilantro. Coriander has antioxidant ability and improves glucose and insulin utilization. Recent research has demonstrated the presence of antihyperglycaemic, insulin-releasing, and insulin-like activity in Coriandrum sativum.99-101

I have my patients use cilantro like lettuce in a salad, or blend it and make a salad dressing, or to combine it with other vegetables and make a fresh juice.

Alpha and gamma-tocopheryl succinate

In a recent study, levels of vitamin A and E were significantly lower, and malondialdehyde (MDA) and copper levels were significantly higher (p<0.001) in patients with PC compared to controls. Serum vitamin C was significantly lower in patients with PC when compared to controls (p<0.01). Moreover, Selenium and Zinc levels were also significantly lower, in patients with PC than in controls.102

Alpha-tocopheryl succinate (dry vitamin E) has shown to reduce the abundance of androgen receptor (AR) in prostate cancer cells.103

A recent study found that increasing the quantity of gamma-tocopherol caused cancer cells to grow more slowly. The study also shows that the anticancer effect is enhanced when the mixed forms of tocopherols are used.104

The role vitamin E plays in preventing prostate cancer was assessed as a secondary end point in the ATBC cancer prevention study which reported a 34% relative risk reduction.105 High concentrations of gamma-tocopherol, the most common dietary form of vitamin E (found in seed oils such as Sea Buckthorn, walnut, pumpkin), are associated with a statistically significant reduction in the risk of PC.106 The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was started to evaluate the role of vitamin E and selenium supplementation in preventing prostate cancer.107 This prospective, randomized, double-blind, placebo-controlled prevention trial involves healthy men with a normal digital rectal examination and a serum PSA level below 4 ng/ml. Subjects were randomized to one of four treatment groups: vitamin E (400-mg racemic α-tocopherol) plus selenium (200-µg 1-selenomethionine), vitamin E plus placebo, selenium plus placebo, or placebo plus placebo. A minimum follow-up period of 7 years is planned. Enrollment of patients began in August 2001 and was closed in June 2004 with 35,534 participants; final study results are anticipated in 2013. Unlike trials with selenium and vitamin E reported so far, in which prostate cancer was a secondary end point, clinical diagnosis of prostate cancer is the primary end point of SELECT.

I only use the dry succinate form and dose it 200-400 IU. Often, redox cycling combination formulas provide 200 IU of dry E.

Dosage: 200-400 IU

Combinations of protective nutrients better than any single agent
A study was conducted that looked at the relationship between prostate cancer and the MnSOD polymorphism, and its interactions with baseline plasma antioxidant levels (selenium, lycopene, and alpha-tocopherol) and beta-carotene treatment among 567 cases and 764 controls nested in the prospective Physicians’ Health Study. We found little overall association between MnSOD polymorphism and prostate cancer risk; however, this polymorphism significantly modified risk of prostate cancer associated with prediagnostic plasma antioxidants (P(interaction) > or = 0.05). Among men with the AA genotype, high selenium level (4th versus 1st quartile) was associated with a relative risk (RR) of 0.3 [95% confidence interval (CI), 0.2-0.7] for total prostate cancer; for clinically aggressive prostate cancer, the RR was 0.2 (95% CI, 0.1-0.5). In contrast, among men with the VV/VA genotype, the RRs were 0.6 (0.4-1.0) and 0.7 (0.4-1.2) for total and clinically aggressive prostate cancer. These patterns were similar for lycopene and alpha-tocopherol and were particularly strong when these antioxidants and selenium were combined; men with the AA genotype had a 10-fold gradient in risk for aggressive prostate cancer across quartiles of antioxidant status. Men with AA genotype who were randomly assigned to beta-carotene treatment (versus placebo) had a RR of 0.6 (95% CI, 0.2-0.9; P(interaction) = 0.03) for fatal prostate cancer, but no significant association was observed in men with the VV/VA genotype. Both endogenous and exogenous antioxidants play an important and interdependent role in preventing clinically significant prostate cancer.108

Boron

Boron supplementation has an overall enhancing effect on several hormones and has shown ability to aid in bone health. Boron has also revealed in several studies to improve calcium bone absorption and enhance collagen synthesis. Medical studies have shown that participants taking boron supplements reap the benefits of harder and stronger bones.109 Boron is essential for animals and humans for bone metabolism and joint health, and is a popular supplement for the treatment and prevention of osteoporosis, and to a lesser extent osteoarthritis.110

Diets rich in boron are associated with lower PC occurrence.

Men who ate the greatest amount of boron were 64% less likely to develop PC compared to men who consumed the least amount of boron. The more boron-rich foods consumed, the greater the reduction in risk of being diagnosed with PC. Those men in the highest quartile of boron consumption had a 64% reduction in PC, while men in the second quartile had a 35% reduction in risk, those in the third quartile reduced their risk by 24%. Men in the lowest quartile of boron consumption ate roughly one slice of fruit a day, while those in the highest quartile consumed 3.5 servings of fruit a day plus one serving of nuts. Boron-rich foods include plums, grapes, prunes, avocados, and nuts such as almonds and peanuts. All of these foods have other constituents that are also associated with a reduce risk of cancer.111 However a closer look at boron in one study found that it inhibits the proliferation of prostate cancer cell lines DU-145 and LNCaP in a dose-dependent manner. Non-tumorigenic prostate cell lines PWR-1E and RWPE-1, and the cancer line PC-3 were also inhibited, but required concentrations higher than observed human blood levels.112

Boran cleaves IGFBP-3 and lowers IGF-1

It is thought that PSA cleaves insulin-like growth factor binding protein-3 (IGFBP-3), providing increased local levels of IGF-1 leading to tumor growth. Separately, there is data that suggests an enzymatic regulatory role for dietary boron, which is a serine protease inhibitor. In this study boron was studied as a PSA inhibitor in an animal study. Dietary supplementation with boron, as boric acid, inhibited PSA and reduced the development and proliferation of prostate carcinomas in an animal model. Two groups (10 animals/group) were dosed with boric acid solutions (1.7, 9.0 mgB/kg/day) by gavage. Control group received only water. Tumor sizes were measured weekly for 8 weeks. Serum PSA and IGF-1 levels were determined. The size of tumors was decreased in mice exposed to the low and high dose of boric acid by 38% and 25% respectively. Serum PSA levels decreased by 88.6% and 86.4% respectively, as compared to the control group. There were morphological differences between the tumors in control and boron-dosed animals, including a significantly lower incidence of mitotic figures in the boron-supplemented groups. Circulating IGFBP-3 levels were not different among groups, though expression of IGFBP-1 in the tumors was markedly reduced by boron treatment. This data indicates that low-level dietary boron supplementation...
reduced tumor size and content of a tumor trophic factor, IGF-1.\textsuperscript{113}

\section*{Section VI}

\textbf{Treatment strategies for advanced refractory PC}

Once you have learned the Triphasic System, the most important thing to do when approaching a more aggressive cancer, including prostate cancer, is to apply it piece by piece, layer by layer, and realize it is time to run a very in-depth investigation to uncover the nature of the cancer – what is up-regulated, was is down-regualted, what the energy of the person is, and how can we maximize the Vital Force.

Once you have built a protocol based on the Triphasic System, and yet have not fully inhibited the cancer, it is time to add the final layer, which is the stronger more cancer-targeted agents/botanicals. However, this is not done in place of everything else, but in addition. The foundation must remain in place; the importance of enhancing the Vital Force must still be central but now it is just not enough.

An example of a target to investigate is the androgen receptor. When men become hormone refractory, the cancer has usually become more aggressive and less responsive to gentle therapies. One approach I take is if they have not used hormone therapy yet, to first introduce the 5-\(\alpha\)-reductase inhibitor Avodart (dutasteride), which although not commonly used as a treatment, it has been considered for chemo-prevention of prostate cancer.\textsuperscript{1} This is because androgens are required for the development of prostate cancer, and men with lower 5-\(\alpha\)-reductase activity have a lower rate of prostate cancer.\textsuperscript{2}

A phase II, double-blind, placebo-controlled, dose-ranging, comparative trial clearly demonstrated that serum dihydrotestosterone (DHT) suppression was significantly greater with the dual (types 1 and 2) 5-\(\alpha\)-reductase inhibitor dutasteride 0.5 mg/day than with Proscar (finasteride) 5 mg/day in men with benign prostatic hyperplasia.\textsuperscript{3} There is presently a study (REDUCE) looking into the possible prostate suppressing effects of Avodart.\textsuperscript{4} More often then not, the botanical agents can lower 5-\(\alpha\)-reductase activity while also inhibiting cancer through other mechanisms; plus, they can potentiate the effects of Avodart. In addition, they are also free of the side effects that come with 5-\(\alpha\)-reductase inhibiting drugs.

If DHT is all ready very low, then it is time to investigate other pathways that may be up-regulated that could be the main culprit causing the cancer to proliferate. Each situation needs to be evaluated and treated based on the information you receive and the specifics of the situation. The other Allopathic option is to try Triple-drug, intermittent hormone blockage therapy, although I prefer to only use this approach if all else is not enough.

Before going down this avenue, it would be wise to have the tumor slide sample tested for growth factors, knowing that it is possible that the cancer could have changed and is now using transcription growth factors that years ago were not up-regulated in the original cancer.

\textbf{Metronomic dose using whole-plant extracts}

A phenomenon that may limit the advantages of low-dose metronomic, or continuous dose delivery, is a threshold effect for drug activity. The general utility of the maximum tolerated dose (MTD) paradigm, a strategy aimed at optimizing the chance of total tumor cell eradication, is here questioned. Evidence to date suggests that for many tumors the potential for eradication is in fact remote, with patients consistently demonstrating tumor cell presence subsequent to MTD treatments having eradicative intent. The failure to eradicate is attributed largely to the heterogeneous nature of the tumor. Heterogeneous cell populations demonstrate short-term refractoriness to up-front dose delivery, but “resensitize” as part of dose recovery, showing increased overall susceptibility to a given series of doses when delivered more evenly spaced. It is demonstrated: (1) that the minimization of total tumor burden, rather than complete eradication, may often be the more practical objective; and (2) that regularly spaced “metronomic” dosing is the best way to achieve this. As a corollary, it was found that the more efficient the ability of tumor endothelial cells to resensitize following dosing predicts a targeting bias towards the endothelial compartment of a tumor when metronomic dosing is employed. This lends theoretical support to recent empirical studies showing that regularly spaced dosing schedules with no extended rest periods act more antiangiogenically, thereby
Cytotoxic whole plant extracts contain a vast array of complimenting compounds that support and potentiate their actions. Some of the actions of these unique plant compounds include:

1) selective inhibition of complex I in the electron transport system in mitochondria;
2) inhibition of multi-drug resistance - P-glycoprotein (P-gp) inhibition;
3) inhibition of tubulin binding molecules;
4) telomerase inhibition;
5) induction of apoptosis;
6) selective inhibition of angiogenesis;
7) selective inhibition of insulin-like growth factor receptor binding;
8) “biological response modifying” actions (increasing host defense), enhancing cytotoxic T lymphocytes, natural killer cells etc.

Some Botanical Extracts and their Active Compounds for the Treatment of Advanced Refractory PC

Artemisinin and other related compounds from Artemisia annua

Artemisinin, the main sesquiterpene lactone from Artemisia annua, has potent cancer-suppressing effects and is best combined with a full spectrum extract of Artemisia annua, yielding a diversity of important synergistic compounds, including nine sesquiterpene lactones and various flavonoids. Studies suggest that components (mainly the flavonoids) found in the whole herb synergize with the effects of isolated Artemisinin, respecting the value and tradition of the whole-plant. Purified Artemisinin, however, is critical for therapeutic relevance.

Artemisinin is used as an alternative drug in the treatment of severe and multidrug-resistant malaria. The artemisinin molecule contains two oxygen atoms linked together in what is known as an ‘endoperoxide bridge’ which could react with an iron atom to form free radicals. Artemisinin is toxic to malaria parasites because the parasite contains a high amount of iron in the form of heme molecules. Free radicals cause macromolecular damages and kill the parasites. Artemisinin has been used as an antimalaria treatment in more than two millions patients.

Artemisinin and cancer

Rapid growth of abnormal cells sequesters relatively large amounts of iron, mainly in the form of holoalbumin. Artemisinin has been shown to cause rapid and extensive damage to these abnormal cells and to have relatively low toxicity to normal cells.

Recently, artemisinin has shown broad-spectrum cytotoxic activity against a variety of cancer cell lines. Artemisinin becomes cytotoxic to cancer cells in the presence of ferrous iron. Since iron influx is high in cancer cells, artemesinin selectively kills cancer cells under conditions that increase intracellular iron concentrations. Compared to normal cells, most cancer cells have high rates of iron intake and express a high cell surface concentration of transferrin receptors. Artemisinin reacts with the iron within the cancer cell causing a generation of free radicals to damage and induce death to the the cancer cell.

Some of the anti-cancer actions of Artemisinin

- Cytotoxic;
- Induction of apoptosis;
- Inhibition of NF-kB;
- Anti-angiogenic (down-regulates VEGF);
- Inhibits multi-drug resistance;
- The anti-cancer effects of Artemisinin are enhanced by butyric acid, a potent HAD inhibitor;
- Taking Artemisinin with grapefruit juice increases the bioavailability.
- One animal study demonstrated potent anti-prostate cancer activity from Artemisinin.
I recommend testing soluble transferrin receptors and ferratin prior to using the ART protocol. High soluble transferrin sometimes gives a clue to the possible cancer-fighting effects of ART. Ferratin levels must be over 40 in order for ART to be effective.

**Burdock seed (**Arctium lappa**)** **40% Lignans - Arctiin & Arctigenin**

Traditionally, Burdock seeds have been used to act upon the urinary tract in a direct way, relieving irritation and increasing renal activity, assisting at the same time in eliminating morbid byproducts and toxic waste. In chronic disorders, A. lappa may be used to remove worn-out tissues.

The highest levels of lignans are found in the seeds, the part of the plant I use most frequently. Methanol extracts of burdock seed have induced differentiation of myeloid leukemia cells and demonstrated potent anti-cancer action against lymphocytic leukemia.28

Burdock seed has a pronounced and direct effect of removing toxicity of the liver from various chemical toxins including carbon tetrachloride. Burdock seed lignans decrease the oxidative stress of hepatocytes.29

Burdock seed extract inhibited breast, colon, and pancreatic cancers in animals, partly through a mechanism involving the induction of glutathione S-transferase.30

Enterolactones obtained from the biotransformation of arctiin by human intestinal bacteria showed antiestrogenic activity and inhibited breast cancer.31

Arctiin (ARC) and arctigenin (ARC-G) from burdock seed exhibited remarkable anti-tumor-promoting effects on a two-stage carcinogenesis test of mouse skin tumors induced by 7, 12-dimethylbenz[a]anthracene as an initiator, and 12-O-tetradecanoyl phorbol-13-acetate as a promoter, by both topical application and oral administration. Furthermore, ARC-G exhibited potent anti-tumor-promoting activity on two-stage carcinogenesis test of mouse pulmonary tumors induced by 4-nitroquinoline-N-oxide as an initiator and glycerol as a promoter.32

In another experiment the lignan arctiin and its aglycone arctigenin demonstrated potent cytotoxicity against Chang liver cells.33

**Inhibits PC through an Anti-Adhesion Mechanism**

The effect of arctiin on growth regulation in prostate cancer PC-3 cells was that it was found to modulate the attachment/detachment of PC-3 cells. We then investigated the role of arctiin on MUC-1 expression. The expressions of MUC-1 and integrins alpha2, alpha5, and beta1 were detected. Treatment of PC-3 cells with arctiin decreased the cell number in a concentration- and time-dependent manner in serum-containing condition. Arctiin preferentially induced cell detachment effects in PC-3 cells. Arctiin increased the expression of the anti-adhesion mucin MUC-1. The arctiin-induced increase in MUC-1 protein expression was due to up-regulation of mRNA, as revealed by RT-PCR analysis. Arctiin significantly induces cell detachment and decreases cell numbers via the up-regulation of MUC-1 mRNA and protein in PC-3 cells.34

**Celandine (Chelidonium majus) and Chelidonium alkaloids including Chelidonine**

Celandine has traditionally been used when there is an enlargement of the liver, constipation, indigestion and a strong urinous odor. It is also particularly well-suited for cancers of viral origin. Celandine has been shown to possess anti-cancer and anti-microbial activity. The juice of celandine, when applied to the skin, produces inflammation, and even vesication, and has long been known as a caustic for the removal of warts; it can also be applied to indolent ulcers, fungous growths, etc… Hemorrhoids, hepatic and splenic congestion, and gastro-intestinal disorders due to capillary engorgement of the viscera, are conditions for its exhibition; and it is one of the best of remedies for biliary catarrh, the result of hepatic congestion, and for jaundice, due to obstruction of the bile ducts, the mucous membranes of which are swollen from the subacute inflammation present.35
Anti-cancer effects

Celandine has traditionally been used to treat cancer and recently has been tested for cytotoxic effects. It was found comparable to many commonly used chemotherapeutic drugs.36

The carcinostatic tumor inhibition of sarcoma 180 and Ehrlich carcinoma by chelidonine and protopine was associated with considerable cytotoxic activity. For chelidonine and sanguinarine this activity was shown in HeLa, normal rabbit kidney, and Ehrlich ascites carcinoma cell cultures. Sanguinarine and chelerythrine were both cytotoxic against KB cells at low doses, causing changes in cell shapes and inhibiting cell mitoses in HEp-2 cell cultures. Several Chelidonium alkaloids also exhibit cytotoxic activity against Eagle's KB carcinoma of the nasopharynx in cell culture.37-41

Chelidonium suppressed chemically-induced stomach and liver cancer, 42, 43 and also delayed progression of pancreatic cancer in humans, increasing lifespan and quality of life.44

Another mechanism celendine has shown to suppress cancer is by inducing apoptosis through a Bcl-2 controlled mitochondrial signaling pathway.46

Prostate Cancer: Increases p27

Exposure of LNCaP prostate cancer cells to Ukrain (NSC-631570), a novel semisynthetic drug from Chelidonium majus L., resulted in cell growth inhibition which was concomitant with apoptosis. After 24h treatment with 3.5 microM of Ukrain (a Celandine alkaloid preparation) as many as 73% cells were found in the G2/M phase. However, at higher drug concentrations (7 microM and 17.5 microM) the changes in cell phase distribution were less dramatic but cell accumulation in the G2/M phase was still evident. The rate of apoptotic cells rose steadily with increased drug concentration in a dose-dependent manner and reached 20% at a dosage of 17.5 microM. To investigate whether the cell cycle control mechanisms are affected in response to Ukrain, we analyzed the expression levels of some cyclins, cyclin-dependent kinases (CDK), and apoptosis-related proteins in drug treated cancer cells. Western blot experiments revealed alterations in levels of CDK1 and CDK2 after treatment. Up-regulation of the CDK inhibitor p27 was observed, which lead to G2/M cell accumulation.46

In another study ME180 and A431 carcinoma cells were exposed to Celandine alkaloids which resulted in cell growth inhibition, which is concomitant with reversible G2/M cell cycle arrest and apoptosis at doses as low as 7 microM. Alterations in levels of mitotic cyclins A and B1 and cyclin-dependent kinases CDK1 and CDK2 after treatment were seen. Also observed was an upregulation of the CDK inhibitor p27 in both cancer cell lines, which may lead to the G2/M cells accumulation.47

Pacific Yew (Taxus brevifolia)

The yew tree has been associated very closely with cancer treatment during the past twenty years. The yew tree contains a group of unique alkaloids referred to as taxans that have been shown to exhibit significant antineoplastic actions. Taxanes represent the most important class of antitumor agents introduced in cancer therapy in the last decade. In addition to 27 different diterpenes (Taxanes), many of which have proven anti-cancer properties, Taxus contains four flavonoids, including quercetin, along with three plant sterols, which include beta-sitosterol, daucosterol, and ponasterone A, all of which contribute to its overall anti-cancer effects.

The first member of the family isolated from the yew tree was paclitaxel (taxol), firstly isolated from Taxus brevifolia and found active as an antitumor agent at the end of the 1960's. In the mid-90's, a semi-synthetic taxane derived from 10-deacetylbbaccatin III was introduced and thereafter named docetaxel (taxotere). More recently, a liposomal form of Taxol, Abraxene, has been approached for the treatment of several cancers. Abraxane is less toxic and more effective than either Taxol or taxotere.48, 49
chemotherapeutic drugs are some of the most effective used today. They are used to treat many types of cancers including ovarian, breast, non-small cell lung, and refractory prostate cancer.\textsuperscript{50-52}

Taxanes, rather than inhibiting microtubulin formation at the M phase (the miotic phase of the cell during which time the cell is dividing) the way other plant alkoloids do, it inhibits cell division by decreasing the concentration of tubulin required for assembly. This keeps it in the Gap I phase longer than it should and does not allow the cell to get to the mitotic phase for division.\textsuperscript{53}

Some recent studies on taxanes suggest that these compounds have a synergistic effect, and that various taxanes were shown to reverse multi-drug resistance in breast cancer cells when co-administered with placitaxol.\textsuperscript{54-59}

Recently, taxotene, another taxane found within the yew, in combination with Taxol, has been found to have a synergestic effects against PC.\textsuperscript{60}

Whenever one of my patients is on a taxane drug, I use the yew extract in a combination formula that the patient takes daily throughout the chemo-cycle. I have seen miraculous results in many cases, even in very advanced cases, combining my protocols with low dose Abraxane, and sometimes low dose Avastin, a VEGF inhibiting drug.

**Vinca rosea** (*Catharanthus rosea*), Madagascar periwinkle

Rosy periwinkle (*Catharanthus rosea*), often referred to as vinca rosea, is a native plant to Madagascar. It contains a group of compounds, referred as Vinca alkaloids, which represent a chemical class of major interest in cancer chemotherapy. Anti-tumor Vinca alkaloids include the lead compounds vinblastine and vincristine, which have been employed in clinical practice for more than thirty years and remain widely used to this day. They are still standard therapy in the treatment of childhood leukemias, and for Hodgkin’s disease and in some solid tumors. The discovery of the plant’s anti-cancer compounds was serendipitous, and it happened when the plant was being investigated for the treatment of diabetes.\textsuperscript{51}

Many Vinca alkaloids are now firmly established as cytotoxic and chiefly block mitosis through metaphase arrest. Vincristine and viblastine are not only toxic to cancer cells but, like most chemotherapeutic agents, are highly toxic to normal cells as well. However, the plant extract is non-toxic because the level of these toxic alkaloids are minute and in combination with many other plant compounds toxicity is low.\textsuperscript{62}

Recent studies have demonstrated that certain newly identified properties, such as antiangiogenic activities, could enlarge the therapeutic usage of natural and semi-synthetic Vinca alkaloids. Thus, Vinca alkaloids remain a drug family with a continuing interest for future anticancer therapy.\textsuperscript{63-66}

**Gossypol, from cottonseed oil** (*Gossypium spp.*)

Gossypol, a natural polyphenolic compound present in cottonseeds, possesses antiproliferative and pro-apoptotic effects in in vivo and in vitro models. There are two enantiomers, (+)-gossypol and (-)-gossypol, the latter being a more potent inhibitor of cancer cell growth. Gossypol was previously tried and abandoned as a male contraceptive; it inhibits prostate cancer, and has shown to boost the effectiveness of other treatments for prostate cancer (radiation and chemotherapy) and possibly other common cancers as well. Gossypol in cotton is a natural toxin present in the plant that protects it from insects. Its name is derived from the scientific name of cotton (*Gossypium spp.*) and phenol, its main chemical structure.

**Inhibition of PC:**

A study in 1996 of the effect of gossypol on the growth of human androgen-independent prostate cancer cell line (PC3) found that gossypol “is a potent inhibitor of prostate cancer cell growth.”\textsuperscript{67}

In a more recent study, gossypol-induced apoptosis was both caspase-dependent and -independent. Furthermore, the release of apoptosis inducing factor (AIF), which triggers caspase-independent apoptosis,
from mitochondria to cytosol was observed in PC-3 cells exposed to gossypol treatment. Gossypol-induced apoptosis is, at least through inhibiting of Bcl-X(L)/Bcl-2 with pro-apoptosis molecules, followed by a caspase-dependent and -independent process which involves the release of AIF from the mitochondria to cytosol. 68

Bcl-2 inhibition

Researchers at the University of Michigan Comprehensive Cancer Center found that gossypol inhibited the function of Bcl-2 in human prostate tumors implanted in mice and makes the cancer more sensitive to radiation therapy, chemotherapy, and increased apoptosis. 69

TGF-B1 inhibition

The inhibitory effects of gossypol on human prostate cancer cells-PC3 are associated with transforming growth factor beta1 (TGF-B1) signal transduction pathway.70

In another more recent study (-) gossypol treatment down-regulated cyclin-D1, Rb, CDK4 and CDK6, and up-regulated p21 and TGF-beta1 at the mRNA and/or protein levels.71

Cotton root bark extract, what I use in my clinic, was traditionally used by the Eclectic Physicians, mostly for females as an emmenagogue. In King’s American Dispensatory cotton root bark extract is indicated for menstrual delay, with backache and dragging pelvic pain; fullness and weight in the bladder, with difficult micturition; hysteria, with anemic condition of the reproductive tract; and for sexual lassitude, with anemia. There is no traditional usage for cancer, nor is there any research on the bark extract.

Section VII

Immunonutrition

The potential to modulate the activity of the immune system by interventions with specific nutrients is termed immunonutrition. This concept may be applied to any situation in which an altered supply of nutrients is used to modify inflammatory or immune responses. Major surgery, radiation therapy, and/or chemotherapy is followed by a period of immunosuppression that increases the risk of morbidity and mortality due to allostatic overload which can lead to infection. Improving immune function during this period will improve a person’s ability to inhibit infection, recover quickly and fully, and reduce the risk of reoccurrence. Critically ill patients, those with aggressive, metastatic, advanced cancer are at greater risk of adverse outcomes that involve allostatic overload. In these patients, complex, variable, immune and inflammatory changes occur that are only now being well defined. A biphasic response, with an early hyperinflammatory response, followed by an excessive compensatory response associated with immunosuppression is seen in many such people. Here, early treatment is aimed at decreasing the inflammatory response rather than enhancing it, to abrogate the hyperinflammation and prevent the compensatory immunosuppression. Anabolic and Adaptogenic plant-based remedies, together with immunonutrition, foundations to building the 1st branch of the Triphasic Model, the “Internal Energy Force,” partner up and provide an effective treatment protocol to maximize healing.

Three potential targets exist for immunonutrition: (1) mucosal barrier function; (2) cellular defense; and (3) local or systemic inflammation. The nutrients most often studied for immunonutrition are arginine, glutamine, branched chain amino acids, creatine as magnesium creatine chelate, omega-3 fatty acids, and undenatured Whey Protein Concentrate. Individual components of immunonutrition have been reported to preserve or augment various aspects of cellular immune function and to modify the production of inflammatory mediators.

Enteral provision of glutamine decreased the incidence of sepsis in premature neonates and the incidence of pneumonia, bacteraemia, and severe sepsis in critically ill patients. Parenteral glutamine decreased the incidence of infections in recipients of bone marrow transplantation and changed the pattern of mortality in
patients in intensive care. These clinical benefits of glutamine seem to be associated with improvements in intestinal integrity and in cellular immune function.

Recent trials using parenteral omega fatty acids in surgical patients show immune benefits, anti-inflammatory effects, as well as anti-cancer effects.¹⁻¹²

**L-arginine**

Supplementation with L-arginine has significantly increased the quantity and cytotoxic activity of NK cells and lymphokine-activated cells in patients with breast cancer, one study showed. L-arginine possesses anti-atherogenic, lipid lowering, vascular dilation, cardio-tonic, Human Growth Hormone enhancement, antioxidant, and immunomodulatory actions. It also has wound-repair activity.

A positive study conducted by a team of German researchers showed that arginine contributed significantly to immune function by increasing levels of white blood cells. Scottish scientists added that dietary supplementation with arginine in breast cancer patients enhanced NK cell activity and lymphokine cytotoxicity. Various researchers have shown that increasing arginine increases neutrophils (white blood cells that remove bacteria, cellular debris, and solid particles), significantly upgrading host defense.

Studies have emerged regarding arginine or arginine analogs in cancer treatment. For example, infusions of arginine significantly reduced the incidence of liver and lung metastasis in laboratory mice. Earlier research found that supplemental arginine altered the number of tumor-infiltrating lymphocytes in human colorectal cancer, offering important implications for new strategies in cancer treatment. Arginine supplementation was found to inhibit chemically induced colon cancer.

Arginine has a positive impact on the healing of gastric ulcers, bone fractures, diabetic foot ulcers, second-degree burns, radiation enteritis, and ulcerative lesions of the small intestines.¹¹⁻²¹

**Glutamine: Covalent Bonded Glutamine & Magnesium Glycl Glutamine (MGG)**

Glutamine is very important for the maintenance of immune function, particularly when the body is under stress and not getting the nutrition and fuel it needs. When a person is sick, the body will pull glutamine from vital muscle tissue and use it to produce lymphocytes and macrophages. These cells consume glutamine at a high rate under normal conditions, but this process is greatly accelerated when the body is working to destroy pathogens. Glutamine appears to be required to support the proliferation of mitogen-stimulated lymphocytes, as well as the production of interleukin-2 (IL-2) and interferon-gamma (IFN-gamma). It is also required for the maintenance of lymphokine-activated killer cells (LAK). Glutamine can enhance phagocytosis by neutrophils and monocytes. Glutamine assists in the production of NK cells and can increase the synthesis of glutathione in the intestine, which may also play a role in maintaining the integrity of the intestinal mucosa by ameliorating oxidative stress. Glutamine can also enhance the utilization of the amino acid cysteine. When glutamine availability is below par, it will not only cause important muscle loss but it could also compromise glutathione synthesis.

Glutamine has multiple functions, including the following:
1. It is needed for nitrogen transfer between tissues;
2. It is a regulator of protein synthesis and the removal of renal ammonia;
3. It is an essential precursor for nucleic biosynthesis;
4. It is the fuel for intestinal mucosa and other rapidly divided cells such as renal tubular cells;
5. It is the primary energy source for gut enterocytes, lymphocytes, myocytes, and the brain;
6. It has specific stimulatory effects on collagen and cartilage synthesis.

Glutamine’s general effects include: immunomodulatory, anticatabolic/anabolic, gastrointestinal mucosal-protective actions, protectant against chemotherapy and radiation therapy. It may also have antioxidant activity being a precursor amino acid for the production of glutathione. Glutamine enhances chemotherapy and reduces toxicity. Glutamine’s ability to reduce toxicity includes mediation in glutathione metabolism.
Covalent bonded glutamine will be absorbed faster and probably more efficiently than L-glutamine in the human digestive system. Recent publications have stated that covalent bonded glutamine delivers up to 10 times more glutamine to the blood stream than L-glutamine. \(^{22-49}\)

**Whey Protein Concentrate**

Un-denatured **whey protein concentrate** (WPC) has the highest biological value of any protein source available and should be incorporated into programs for all types of people, including those with impaired gastrointestinal function, and those with cancer. WPC is a balanced source of essential amino acids and peptides with a high protein efficiency ratio. It is an excellent source of sulfur amino acids (methionine and cysteine), as well as the branched-chain amino acids (leucine, isoleucine, and valine). During strenuous exercise the body requires more protein to support its muscles and prevent muscle break down. \(^{50}\)

Some health benefits associated with WPC are: immune modulation, glutathione enhancement, intestinal health, anti-bacterial properties against pathogenic bacteria, weight management, liver health, and cardiovascular health. \(^{51}\) WPC has shown to enhance cellular glutathione levels, a vital aspect of our cells protective ability. \(^{52, 53}\) WPC is rich in lactoferrin, an iron binding protein that is a vital element to the human body. Lactoferrin also assists the production of alpha-interferon, which has profound immune-stimulating action. \(^{54}\) WPC has also been found to inhibit cancer. \(^{55, 56}\)

**Herbal Synergy**

Combining a broad spectrum of multiple herbal formulas from the various categories of adaptogens is much like creating a healthy, colorful, gourmet entrée with plenty of vegetables, raw and cooked, olive oil, a piece of fish, and a touch of aromatic culinary herbs, etc. As healthy as any one food is, you wouldn’t think of making it the only food you eat. As wonderful as any one herb may be, the same concept should apply. If you only eat some great foods but exclude others, you would be missing very important nutrients critical for health and vitality. For example, both **green tea extract** and **turmeric extract** (companion adaptogens) have shown to prevent cancer in animal and human studies. However, as single agents both have limitations, but when combined these herbs act synergistically to the enhancement of their beneficial effects. The combination of green tea extract and curcumin has shown to be more effective than either agent alone in decreasing the proliferation of squamous cell carcinoma, inhibiting oral carcinogenesis at the post-initiation, and inhibiting the invasion of B16F-10 melanoma cells by inhibition of metalloproteinases, thereby inhibiting lung metastasis. \(^{57}\) The combination of turmeric and resveratrol, a phenolic compound found in grape skin, have recently demonstrated synergistic effects against neuroblastoma cancer. \(^{58}\) Even grape seed and grape skin have synergistic effects against cancer. \(^{59}\)

An interesting point regarding Eleuthero is that this herb, when combined with other primary, secondary, and companion adaptogens, possesses an ability to enhance the normalizing adaptogenic effects while drastically decreasing any potential adverse reactions, even subtle ones. \(^{60}\) Many studies show that by combining Eleuthero with Rhaponticum, Schisandra, Rhodiola rosea, or Aralia manchurica the effects are greater than Eleuthero alone. \(^{61}\)

Research demonstrates that herbal extracts have significantly enhanced effects when used in combination. *Scutellaria baicalensis*, *Rabdosia rubescens*, *Panax-pseudo ginseng*, *Dendranthema morifolium*, *Glycyrrhiza uralensis*, and *Serenoa repens* extracts were found to be significantly more effective when used together than any of the individual extracts alone. Combining herbal extracts against cancer significantly enhances their activity in the cell lines tested compared with extracts alone. \(^{62}\)

In one other recent study, the combined prostate cancer inhibitory effects were most pronounced when several herbs were used together. *S. baicalensis, D. morifolium, G. uralensis*, and *R. rubescens* were tested and when the four extracts were tested together they were significantly more effective than any two-by-two combinations of the individual extracts alone. \(^{63}\)
Closing thoughts

A major advantage of implementing “The Triphasic Model,” a fundamentally natural healing system using such things as herbs and diet, is that it builds a trusting relationship with nature, in what God has given us. Nature has an innate intelligence that is directed not merely at controlling and removing superficial symptoms; nor working in a direction that our minds, or science, can completely understand; but rather it works in the direction of life-giving assistance, lending a helping hand. Yes, we have learned about how certain plant agents bind to hormone receptors while others detoxify hormones within the liver, up-regulate this gene, and down-regulate another, but do we really understand the vastness of what a single plant has to offer to our innate healing ability? We can only understand this if we begin to look within our hearts and souls along with our minds. Then, and only then, will we understand and see why we are sick and what we need to do to heal.

Only an herb, only Nature when we listen to Her, can bring us into balance, can lift our spirits, elevate our mood, and can be like music in concert within our inner most self. As in TCM it is only certain herbs that can build up Kidney Essence. Yet also within the plant are compounds that can have specific inhibitor effects against cancer, can bind to cancer promoting hormones and chemical mimicking hormones created by man; can detoxify our liver, strengthen our endocrine system, enhance our immune system, assist in regulating body temperature, remove obstructions, and eliminate accumulated toxins. Yes and it does all of this while, if we only use our minds to see, it goes unnoticed, because an herb works in collaboration with our innate healing “vital force.” And if through faith and trust we see, in communion with God, it is through faith and trust in nature we heal, and also see a face of God, and the love that is pouring out to us.

Physician’s Prayer

Dear Lord, the Great Healer, I kneel before you,
Since every perfect gift must come from You.
I pray, give skill to my hands, clear vision to my mind,
Kindness and meekness to my heart,
Give me singleness of purpose, strength to lift up a part
of the burden of my suffering fellow men, and a true
realization of the privilege that is mine.
Take from my heart all guile and worldliness,
that will the simple faith of a child, I may rely on You.

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