Role of Botanicals in the Prevention of Cancer

Michael J. Wargovich

Division of Basic Research, South Carolina Cancer Center, Columbia, SC 29203

Abstract

Many cultures have traditions that encompass the use of herbs, spices, and other plants for medicinal purposes. From the ancient past to the present medicinal knowledge has been passed down to new generations in the form of shamans, medicine men, healers, and the like. In the past decade there has been a surge of scientific interest in complementary and alternative medicine, much of which has its origins in traditional medicine. It has been recognized for some time that dietary patterns and content affect cancer risk. Epidemiological studies have strongly suggested that the fruit and vegetable content of the diet associates with reduced risk for colon, lung, prostate, and other cancers. Many different types of cellular mechanisms have been postulated by which compounds in botanicals can prevent cancer. Mechanisms particular to the prevention of colon cancer will be addressed in this review.

Colon Cancer

In the developed world, colon cancer is a very common disease. Although historically the disease has not been found in high incidence in developing countries, that pattern is changing. In Asia particularly, the incidence of colon cancer is rising in Japan, Singapore, Taiwan[1-3]. This pattern is suspected to apply to other countries throughout the world, especially in populations who are adopting a more Western diet and lifestyle. Colon cancer now ranks as the fourth most common cancer in the world. Much has been written about the etiology of colon cancer. Risk factors include a sedentary, non-active lifestyle, a diet rich in total fat, a diet in which fruits and vegetables are sparsely consumed; for other dietary factors such as cereal fiber intake, alcohol use, or protein intake the data are inconsistent. By far, the great majority of studies of diet and colon can-

Address for correspondence: Michael J. Wargovich, Ph.D., Division of Basic Research, South Carolina Cancer Center, 14 Medical Park, Suite 500, Columbia, SC 29203

Table 1[4]. Epidemiological Evidence for Colon Cancer Protection by Fruits and Vegetables

Cancer Site	Type of Study	Protection Observed?
Colon	Cohort	2/3
	Case-Control	17/21
Colorectal	Case-Control	5/6

cer associate a reduced risk for the disease when the diet contains adequate or high levels of fruits and vegetables and some of these studies are reflected in Table 1.

The preponderance of the evidence favors the hypothesis that natural compounds in fruits and vegetables protect against the development of cancer[5]. Colon cancer manifests a stepwise development in its pathogenesis, from initial mutations in the colonic epithelium, through stages denoted by aggressive proliferation, the development of premalignant lesions, such as the adenomatous polyp, and finally, malignant disease[6,7]. Over 90% of colon cancers are adenocarcinomas developing from the glandular crypts lining the large bowel. Our understanding of the molecular biology of colon cancer is now well understood involving the accumulation of genetic changes in tumor suppressor genes with activation of oncogenes providing a growth advantage for the incipient tumor[8,9]. Like many human cancers, colon cancer corrupts growth regulatory pathways via mutations in cell signaling cascades, engaging inappropriate expression of growth factors, co-opting angiogenic factors for nutrients and oxygen, and evading apoptotic signals to become invasive[10].

Phytochemicals and Cancer Prevention: Basic Mechanisms

As alluded to above the strongest association with diet and prevention of colon cancer is persistent exposure to plant foods. Phytochemicals in plants have their own functions in plants, often providing a survival benefit for the plant. Phytochemicals in plants can be antibacterial, anti-viral, anti-fungal, protect plants from oxidative damage, and ensure the propagation of the plant. In fruits and vegetables some of these mechanisms provide a collateral benefit when eaten by humans. Generally phytochemicals provide cancer protection through one of five mechanisms. Examples are presented in Table 2.

Plants have developed a strong armamentarium of antioxidants to cope with growth in an envi-

Table 2. Mechanisms of Cancer Protection by Phytochemicals

Mechanism of Action	Dietary Example
Antioxidants	Tea polyphenols; grape anthocyanins
Activation of Carcinogen Metabolism	Isothiocyanates from crucifers
Detoxification of Carcinogen Metabolism	Organosulfides from garlic
Anti-hormone Activity	Phytoestrogens in soy
Anti-inflammatory Activity	Flavonoids from spices

ronment constantly exposed to ionizing radiation. Some of these compounds continue to provide antioxidant benefits when used as foods. Among the most actively investigated phytochemicals in this class are the polyphenols found in green tea, anthocyanins in grapes, and curcumin from the spice turmeric[11-13]. It should be noted that antioxidant phytochemicals may also affect other mechanisms of inhibition. For instance, curcumin modulates the cyclooxygenase pathway and tea catechins can affect certain intracellular signaling pathways.

Phytochemcials in plants have been shown to influence the cytochrome P450 metabolic activation of drugs and carcinogens (Phase 1 reactions) as well as stimulate detoxification systems such as glutathione-S-transferase activity (Phase 2 reactions). When studied in isolation this may lead to the conclusion that certain plant foods may cause harm, but in reality, diets contain complex mixtures of a variety of plant compounds, each capable of stimulating or inhibiting metabolic activation schemes in vivo. Isothiocyanates (ITCs) are found as glycoside conjugates called glucosinolates in cruciferous vegetables of the genus *Brassica* (Brassicaceae). They include cabbage, broccoli, Brussels sprouts, cauliflower, kohlrabi, Chinese cabbage, among others. ITCs are known to modify the activity of several important Phase 1 enzymes includes Cyps 1A1, 1A2, 2E1, and 3A4 thus modulating the activation of a broad range of substrates that include important and potential human carcinogens such as polycyclic aromatic hydrocarbons (cyp 1A1) heterocyclic amines (cyp 1A2) and nitrosamines (cyp 2E1) and a variety of drugs (through cyp 3A4)[14]. Allium vegetables, on the other hand, are potent inducers of the glutathione-S-transferase enzyme system which might assist in the detoxification of certain carcinogens[15,16]. Often, phytochemicals in certain foods can modulate both Phase 1 and 2 systems.

Isoflavones in soy and red clover are examples of phytochemicals which have endocrine disruptor activity activity, particularly as they function as weak antagonists of the estrogen receptor. There are two primary isoflavones in soy foods: genistein and daidzein. These compounds are

similar structurally to estradiol, the native female sex hormone. Isoflavones can weakly bind to estrogen receptors in hormone-dependent tissues such as the breast and perhaps the prostate. Isoflavones compete for receptor binding with the more potent, naturally occurring estrogens, disrupting their activity. There is evidence that breast cancer rates are significantly lower in Asian countries which routinely consume high amounts of soy. For example, the consumption of soy in Korea is approximately 20 grams per day. Death rates from breast cancer in the early 1990s in Korea were estimated at about 3/100,000. In the United States where soy consumption is not common, breast cancer death rates were about 23/100,000 during that decade. Daidzein and genistein, the principal isoflavones in soy have been shown to modify the growth of human breast cancers in vitro. Of great interest, genistein has been shown to anti-angiogenic properties, thus inhibiting the outgrowth and invasion of more aggressive forms of cancer[17-21]

The last, and perhaps most exciting mechanism by which botanicals inhibit cancer formation is through the mediation of the inflammatory process.

Phytochemicals as Mediators of Inflammation

Inflammation has long been noted to participate in the process of carcinogenesis. However, widespread interest began when it was reported that habitual consumption of aspirin and other NSAIDs was associated with a reduced risk of mortality from colon cancer. To date, over a dozen clinical studies have documented that use of pain relievers (i.e., non-steroidal anti-inflammatory drugs) is associated with an approximate halving of risk for colon cancer[22-25]. The most likely mechanisms of action involves the suppression of prostanoid generation by inhibition of the two enzymes responsible for the metabolic conversion of arachidonate to prostaglandins, leukotrienes, and thromboxanes, i.e., cyclooxygenases 1 and 2 (COX 1 and COX 2).

While there is promise for the use of aspirin and related NSAIDs in the prevention of colon cancer, the most common side effect for their continued use involves the generation of gastrointestinal ulcers[26]. This is more likely for NSAIDs that suppress COX 1 and while newer COX 2 selective inhibitors are less likely to cause ulcers, they are not completely innocuous. Many natural compounds in botanicals have anti-inflammatory activity and it remains to be seen whether or not they are effective chemopreventive agents. Table 3 lists some botanical products with reported anti-inflammatory activity.

Several of the botanicals listed above had been tested in our laboratory for their ability to sup-

Table 3. Botanicals With Anti-inflammatory Activity

Astragalus	Green Tea
Bilberry	Hawthorn
Black Cohosh	Horse Chestnut
Capsicum	Kava
Cats Claw	Licorice
Cordyceps	Milk Thistle
Chamomile	Onion
Dong quai	Reishi
Ephedra	Rosemary
Feverfew	Saw Palmetto
Ginger	Schisandra
Ginseng	St. Johns Wort
Grape Seed Extract	Turmeric

press the development of aberrant crypt foci (ACF) which are premalignant lesions for colon cancer in rodents in humans. In these experiments we have chosen to test purified constituents from these plants for chemopreventive activity. Though only beginning to examine the broad number of phytochemicals with anti-inflammatory activity, curcumin from turmeric, silymarin from milk thistle, and ginsenoside rich fractions from ginseng have significant cancer preventive effects in the ACF chemoprevention assays.

Conclusions

Plant abound in biologically active materials. By some estimates over half of present day medicines are botanical in origin and many chemotherapeutic agents are of plant origin. One discipline, emerging with bright promise over the last 20 years is the field of cancer chemoprevention, which has spawned intensive research into the role of botanical compounds as cancer inhibitors. Regarding colon cancer, substantial evidence is now in hand suggesting that inflammation plays a pivotal role in the conversion of benign lesions to invasive cancers. Second to this is the corruption of angiogenic pathways by colon tumors enabling them to achieve a growth advantage. Anti-inflammatory compounds may act to retard the biology of inflammation and angiogenesis. As discussed above, despite the overwhelming evidence in animal models for a cancer chemoprotec-

tive effect by NSAIDs, their widespread use as preventives in humans is limited by gastrointestinal toxicity. Our laboratory program has begun to identify natural compounds with NSAID-like activity. These may have utility in colon cancer specifically, and may have utility against other cancers where inflammation is part and parcel of the molecular pathway toward invasive cancer. For other human cancers it may well be that the mechanisms discussed in this review may be more important more relevant. Future directions of research will necessarily require investigations directed toward our understanding of how these mechanisms intersect and synergize given the complexity of phytochemicals in our diet.

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