Chemoprevention in gastrointestinal physiology and disease. Targeting the progression of cancer with natural products: a focus on gastrointestinal cancer

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Cancer is one of the most important general public health and medical research issues in the world. The incidence of cancer is increasing globally; GLOBOCAN 2012 indicated that 14 million people were diagnosed with cancer and 8 million people have succumbed to cancer worldwide: the incidence and mortality of cancer is expected to increase to 27 million cases with 17 million deaths by 2030 (57, 79).

Studies are now beginning to unveil the vast complexity of cancer as a multifaceted disease, where dietary habits (high fat, meat vs. low fiber, fruits, vegetables), smoking, infection, chemicals (hormones, carcinogens), alcohol consumption, and solar radiation play significant roles in its formation (29, 47, 134). Cancer development comprises multiple steps, beginning with tumor cell initiation followed by promotion and progression. This results in an accumulation of genetic and epigenetic alterations abetted by increased expression of oncogenes and downregulation of tumor suppressor genes (166). According to gene ontology analysis, gastrointestinal cancers arise from disrupted systems regulating apoptosis, cell cycle, proliferation, differentiation, immune response, DNA repair, invasion, angiogenesis, and metastasis (166, 170, 177). Cancer generally defies precise specific categorization; its sheer biological complexity eludes innate mechanisms of resistance and thwarts effective medications that have been developed to treat less complex diseases. In a complex and heterogeneous disease such as gastrointestinal cancer, focusing on singular molecular target is not an optimal strategy and use of broader active agents have proven more effective in clinical treatments (5, 143). Investigators are now fully immersed in the questions: Can we call a drug effective if all it does is shrink the size of tumor? Can “partial responses” truly be counted as successes or are we delaying the inevitable? For these and other reasons cancer prevention may present an avenue for additional anticancer strategies: those that might correct the perturbed cell growth, differentiation, and disrupted apoptosis mechanism within the cancerous cells (5, 115, 116, 154). The promise of natural products in retarding cellular processes leading to advanced cancer is summarized in this review.

Cancer prevention is one of several strategies developed to address cancer. Some of the areas involved in cancer prevention are pharmacological interventions in the form of drugs, nutrients, and natural-derived products to prevent cancer development, while other areas include lifestyle changes and dietary modifications (68). Cancer prevention is defined as active measures to decrease the risk of cancer and/or its recurrence, whereas therapy is a treatment that is intended to cure a medical disease or precursor (15). Chemoprevention is generally defined as the effort to inhibit carcinogenesis with natural and synthetic compounds (141). Phytoprevention, a subset within the chemoprevention realm, is the use of plant-derived compounds often called phytochemicals. Cancer prevention with natural products has attracted worldwide attention. The adoption of traditional medicines (many derived from...
plants in the form of tonics or teas), those used for centuries by healers, shamans, etc., into the research environment has broadened the scope of chemoprevention (34, 177). It is important to note that drawing clear lines between natural medicines and remedies, on the one hand, and “drugs” or pharmaceutical products, on the other, can often be fraught with confusion, since many therapeutic drugs are derived from plant components. Two of the most well-known and successful drugs that fit this description are aspirin (from willow tree bark) and taxol (from Pacific yew bark). Most natural components from plants are seen as safer forms of therapeutic intervention compared with pharmaceuticals (5, 30, 117, 136, 154, 177). For instance, there has been some level of success in attenuating cancer risk through diet and lifestyle changes; in particular colorectal cancer (CRC) risk can be reduced through these changes and is possibly preventable (68, 90). It is very promising that the original ideological barriers between “prevention” and “therapy” have been eroded: preventive compounds are now being used adjuvantly with current chemotherapies [compounds such as epigallocatechin-3-gallate (EGCG), curcumin, quercetin, and genistein increase cytotoxic effects (78, 120, 150, 183, 213)]; therapeutic targets are now being investigated as targets for natural products. This promise does come with caution. Although the in vitro and animal research results have shown beneficial results, dosing problems, single vs. complex compound mixtures, diet vs. supplement form, and duration of study are all factors that have proved of great concern in adaption in the clinical research (136).

CRC has been the focus of many prevention studies because of its long precancerous development and defined windows of opportunity when agents can exert their preventive effects (10, 17, 19, 24, 26, 45, 68, 136). Maintaining a healthy diet and subsequently gastrointestinal homeostasis plays an important role in slowing CRC development. Disruption of a cancer-promotive environment, for instance through intervention on chronic inflammation, is an important contributor to CRC, as well as other cancers (87, 115). One of the most prominent and challenging aspects of colon cancer prevention studies lies in the identification of people who are at risk for CRC. To overcome this limitation, one can utilize biomarker testing. Several well-studied markers for CRC are K-ras, p53, APC mutation, and COX2 upregulation (9, 23, 26, 31, 140, 141). Along with these markers, perturbations in DNA methylation, DNA oxidative damage, dysfunctional apoptosis, and formation of aberrant crypt foci are other genetic and biological changes that correlate with CRC (117, 119, 126, 168). Recently, several prospective trials have combined these compounds to assess the changes in the previously mentioned markers and cellular processes and demonstrated the potential of natural product interventions in slowing CRC development (5). Also, the latest research suggests that certain phytochemicals may mitigate biological events characterizing late-stage cancer. In this review we will highlight the basic research, the early intervention trials, and how dietary and lifestyle interventions can impact the development of CRC and how this enhances our understanding of prevention research in other cancers.

The Value of Natural Products for Cancer Prevention Studies

Medical historians now suggest that use of natural products for their pharmaceutical properties goes back at least 6,000 years (187). The use of natural products to treat parasites in the intestine has been documented for at least 5,000 years; long-held beliefs in natural medicines have informed modern cancer chemoprevention. Morphine, for example, isolated from opium and discovered in 1808, was among the very first naturally derived medications. In the mid-19th century acetylsalicylic acid or aspirin was developed from willow and to this day is one of the most prevalent anti-inflammatory drugs in the market. Natural product science is defined as discovering new and effective biologically active, naturally derived compounds, understanding their biosynthesis, and elucidating their modes of action (187). Although most natural product compounds are from plant sources, beneficial constituents can come from a wide variety of nonplant organismal sources including endophytic fungi, insect products, marine life, and agents from animals (187). For instance, a number of plant-derived compounds currently under investigation include curcumin (tumeric), EGCG (green tea), resveratrol (red grapes, peanuts, and berries), sulforaphane (SFN) (cruciferous vegetables), indole-3-carbinol (cruciferous vegetables), genistein (soybean), dihydrosulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), 6-gingerol (ginger), ellagic acid (pomegranate), ursoic acid (apple, pears, prunes), silymarin (milk thistle), eugenol (cloves), polyphenols, rosmarinic acid, naringenin, nobiletin, naringin, apigenin, hesperidin, morin, flavonoids, tocopherols, and ascorbates (5, 24, 30, 58, 68, 70, 87, 106, 114, 116, 117, 136, 149, 151, 168, 172, 205). The great wealth of chemical diversity found in natural products is best explained as a very long evolutionary process of adaptive development with respect to the environmental, insecticidal, and microbial pressures. And it is the sheer diversity that is seen as the greatest strength driving both the pharmaceutical industry and the growing natural product market, now upward of 7 billion dollars in the US alone (24). Today, more than 60% of therapeutic products on the market are derived from natural sources (43). The optimism concerning future discoveries is bolstered by the ability to determine the mechanism of action for natural-derived components (the specific identity of the targets that produce the desired therapeutic effects) is now possible at the molecular and genomic level (43).

Natural Products vs. Pharmaceuticals in Cancer Prevention

Phytochemicals have extraordinary biological action. They can have impact as anti-inflammatories, antioxidants, antiproliferatives, apoptosis inducers, cell cycle arrest agents, and antiangiogenesis and antimetastasis enhancers (1, 6, 20, 34, 55, 100, 105, 107, 112, 118, 129, 143, 147, 157, 160, 165, 179, 180, 184, 197, 199, 208). This array of action makes it very difficult to prove the specific efficacy of these natural products in a conclusive fashion, and comparing their effectiveness with that of pharmaceutical agents is equally if not more complex and challenging. This is likely due to the complexity of natural products and lack of information on their specific absorption, chemical alterations in the gut, and whole body metabolism. In many instances the isolated parent compound from plants may not even be the ultimate effector compound. Studying the
pharmacokinetics and pharmacodynamics is more complicated for plant extracts and food-derived products compared with synthetic drugs (5). In the frontier of cancer prevention research, it is now speculated that some natural phytochemicals impact carcinogenesis from initiation through metastasis, and recently the term small molecule natural products (SMNPs) has come into use (5, 143). Some of these are illustrated in Fig. 1. The foundation for cancer prevention efficacy is that critically designed experiments have shown suppression of carcinogenesis in animal models with mechanistic studies primarily constructed in vitro models (2, 5, 15, 23, 51, 71, 152, 153, 192, 203).

However, as suggested above, especially for natural products variable results are found in vitro and in vivo, often accounted for by problems in bioavailability. There can be activity discrepancies in phytochemical concentration between in vitro and in vivo efficacy, and this may be suggestive that low doses (in vitro) of phytochemicals affect different biology compared with higher doses used in vivo (149). In addition, hormesis might be a factor when undertaking pharmacological studies involving natural products, further clouding the transition from in vitro to in vivo to clinical models. Consider that some phytochemicals are very likely quickly metabolized and degraded in various human organs. This depends on an individual person’s genetic variation, which affects the biological mechanisms related with absorption, metabolism, gut microbiome makeup, and delivery of phytochemicals, thus affecting the concentration at serum and tissue level (36). And the impact of the environment, especially the construct of the diet, can moderate adsorption of these promising SMNPs.

To illustrate, curcumin and tea catechins are two natural products that have been well studied in cell lines, animal models, and humans (2, 6, 8, 12, 13, 20, 22, 34–37, 50, 54–56, 59, 60, 64, 70, 89, 100, 101, 105, 106, 117–119, 121, 123, 127, 130, 133, 140, 149, 154, 157, 161, 163–165, 167, 169, 171, 174–176, 178, 179, 184, 192–195, 197, 201, 203, 205–208). Curcumin is a cancer-preventive polyphenolic derivative of turmeric isolated from Curcuma longa with antioxidant and anti-inflammatory properties that inhibit cell growth and proliferation of cancer cells (5, 30, 121, 151, 176). Green tea and black tea are abundant sources of polyphenol catechins, many of which have been shown to inhibit cancer in model systems by the same mechanisms as curcumin. Yet epidemiological studies using dietary surveys have shown conflicting results in the correlation between tea consumption and CRC risk and concentrations of active agents may be a log order less in serum compared with cell line studies (8, 22, 64, 127, 174, 175, 178, 194, 195, 206, 207). Several studies have suggested that serum concentration levels of EGCG after tea drinking range between ~0.1 and 1 μM, yet high micromolar concentrations of EGCG are usually needed in in vitro studies to activate the beneficial proapoptosis mechanisms (149, 203). In clinical studies, the reported concentration of EGCG in plasma after an oral dose of 800 mg EGCG was reported in the range of ~0.6 to 3.3 μM (35, 37, 92). These are ineffective doses in cell culture assays (92). Bioavailability is a problem for natural product research, especially with tea, but probably encompassing many natural products. Some investigators have reported that nanotechnological procedures might improve the bioavailability of phytochemicals, but this technology is still in its
infancy (168). And there is the promise of using “assistor” compounds to accelerate uptake and distribution of anticancer phytochemicals; examples include black pepper, citrus juice, and chilies.

Despite increasing recognition of the potential of natural products, there are special challenges with respect to a variety of natural products’ composition. For example, whole tea has several: the uncertainty of causative constituents, concentration of specific catechins, and often scant of knowledge of causative constituent pharmacokinetics (24). Conventional chemotherapeutic drugs have some limitations as well: high cost and severe side effects due to toxicity. The current chemopreventive compounds (i.e., “drugs”) on the market are categorized into four main classes: selenium supplementation, calcium carbonate supplementation, hormone replacement therapy, and nonsteroidal anti-inflammatory (NSAIDs) drugs.

Of these, NSAIDs have the potential for overt toxicity yet paradoxically provide some of the highest benefit for protecting against advanced cancer. NSAID toxicity mostly refers to their effect on harming the intestine by ulceration, enhanced bleeding times, and altered kidney function among other deleterious symptoms. To circumvent these toxicities assigned to COX-1 inhibition, several COX-2-selective inhibitors such as celecoxib and rofecoxib were synthesized in the 1990s but were withdrawn (or medically limited) worldwide because of their adverse cardiovascular events (145). COX-2 antagonists illustrate that off-target toxicity may not be observed until well after a drug has been marketed, even in the face of safety as gauged by preclinical studies. Traditional chemotherapy involves some of the oldest chemical therapies for advanced CRC, such as 5-flurouracil + leucovorin; in 1996, topoisomerase I inhibitor irinotecan emerged but with many harsh side effects. Later oxaliplatin, a platinum-based drug, was introduced to the market in 2004, which significantly improved the overall survival rate from 6 mo with no treatment to 20 mo in advanced CRC. More recently, angiogenesis inhibitors have been under investigation for the treatment of metastatic CRC (145). Treatment-related toxicity is gauged by preclinical studies. Traditional chemotherapy indicates that oxidative stress (which plays an important role both in causation and treatment of some cancers) is attenuated when antioxidants are administered as a proxy for protective fruit and vegetable consumption, several large-scale chemoprevention trials were conducted that revealed either no effect of antioxidant compounds on the prevention of cancer or exacerbation of cancer (Table 1). Recently, other trials of vitamin supplements, notably long-term supplementation by vitamin E, were associated with negative effects (42). This was alarming to the field because of the careful in vitro studies of antioxidant compounds; their validation in preclinical animal models prioritized these agents as “safe” prior to implementation in human trials (58).

What went awry in the once-held consideration that antioxidant natural agents would translate, in humans, to an excellent way to prevent cancer? For many years it has been speculated that oxidative stress (which plays an important role both in causation and treatment of some cancers) is attenuated when the diet is rich in antioxidants. Indeed epidemiological studies and preclinical research was largely supportive of this notion, yet prospective trials have not confirmed the hypothesis (30, 45, 144, 151, 152, 166). One potential explanation often offered is that antioxidant vitamins (β-carotene; vitamins C

### Antioxidants and Cancer Chemoprevention

Over the last decade and a half the use of antioxidant compounds to prevent aerodigestive and gastrointestinal cancer was enthusiastically pursued (114, 136, 151, 204). On extensive epidemiological evidence that the consumption of certain antioxidant-rich foods associated with a reduced risk of cancer, it was theorized that using antioxidants in concentrated form (pills) and in rather pure form (vitamins vs. food-based interventions) would prospectively reduce cancer risk. Thus large-scale trials were designed and implemented. Originally designed as a proxy for protective fruit and vegetable consumption, several large-scale chemoprevention trials were conducted that revealed either no effect of antioxidant compounds on the prevention of cancer or exacerbation of cancer (Table 1). Recently, other trials of vitamin supplements, notably long-term supplementation by vitamin E, were associated with negative effects (42). This was alarming to the field because of the careful in vitro studies of antioxidant compounds; their validation in preclinical animal models prioritized these agents as “safe” prior to implementation in human trials (58).

### Table 1. Clinical trial outcomes using interventional antioxidants

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Intervention</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Linxian General Population Intervention</td>
<td>15 mg BCAT; 30 mg ATOC</td>
<td>No effect on gastric or esophageal cancer</td>
<td>142</td>
</tr>
<tr>
<td>1994</td>
<td>ATBC Trial</td>
<td>20 mg BCAT; 50 mg ATOC</td>
<td>Increase in risk for lung cancer</td>
<td>4</td>
</tr>
<tr>
<td>1996</td>
<td>CARET Trial</td>
<td>15 mg BCAT; 25000 IU retinol</td>
<td>Increase in risk for lung cancer</td>
<td>132</td>
</tr>
<tr>
<td>1996</td>
<td>Physician’s Health Study I</td>
<td>50 mg BCAT</td>
<td>No effect on cancer incidence and mortality</td>
<td>75</td>
</tr>
<tr>
<td>1999</td>
<td>Women’s Health Study</td>
<td>50 mg BCAT; 600 IU VITE 100 mg ASA</td>
<td>No effect on cancer incidence</td>
<td>97, 98</td>
</tr>
<tr>
<td>2007</td>
<td>Aspirin/Folate Polyp Prevention Study</td>
<td>1 mg folic acid</td>
<td>No effect on colorectal adenoma recurrence</td>
<td>39</td>
</tr>
<tr>
<td>2009</td>
<td>Physicians Health Study II</td>
<td>400 IU VITE; 500 mg VITC</td>
<td>No effect on cancer incidence and mortality</td>
<td>61</td>
</tr>
<tr>
<td>2010</td>
<td>SU.VI.MAX Trial</td>
<td>120 mg VITC; 30 mg VITE 6 mg BCAT; 100 µg Se</td>
<td>No effect on cancer incidence and mortality</td>
<td>61</td>
</tr>
<tr>
<td>2011</td>
<td>SELECT Trial</td>
<td>200 µg Se; 400 IU VITE</td>
<td>Increased risk for prostate cancer</td>
<td>91</td>
</tr>
</tbody>
</table>

BCAT, beta carotene; ATOC, alpha tocopherol; ASA, aspirin; VITE, vitamin E; VITC, vitamin C; Se, selenium.

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and E) were given in pure pill form as a matter of convenience. This after all was the practice for delivery of medications in treatment trials, and both patients and clinicians were familiar with the study designs. But pure antioxidant vitamins at best are only an approximation, or proxy, of the many compounds in vegetables and fruits (5, 47, 90, 149, 154). It is possible that convenience of vitamins substituted for lack of knowledge of actual plant antioxidants responsible for the epidemiological evidence, or they were not those forms found in nature (144). For example, natural vitamin E is different from the synthetic form and is composed of at least a handful of other isoforms (30). Along with the vitamin A compounds, it is now conjectured that the high-dose cancer prevention trials of the 1980s may have engaged biology in which a prooxidant effect was created (131). This again underscores the importance of careful dose and duration parameters when utilizing these SNMPS in basic and clinical research. Recently, a study from Sweden found that two antioxidants, vitamin E and N-acetylcysteine, can fuel the growth of lung cancers in mice (158). It has been long thought that antioxidants protect cells from the effects of DNA-damaging reactive oxygen species. However, natural antioxidants may not be discriminatory and may protect cancer cells from further DNA damage (83, 113, 216). These results fit with those from earlier human clinical trials, in which antioxidants failed to prevent disease or accelerated risk for cancer. The first of these was published in the New England Journal of Medicine in 1996 and showed that male smokers who took β-carotene supplements were more likely to develop and die of lung cancer than those who did not (75). Other trials found similar results for other antioxidants and other cancers, and some of those studies were stopped early. In 2012, the Cochrane Collaboration analyzed the results of 78 human trials and, on the basis of critical analysis, concluded that people who took antioxidant supplements (including both healthy people and those with chronic diseases) were more likely to die prematurely than those who did not (21).

**Cell Signaling Prevention Targets**

Phytoprevention strategies maybe have more suitability in colon cancer due to the intestinal tract constant exposure to toxins and conversely the beneficial SNMP proposed to have beneficial effects (185). It is important to reiterate that dose, duration of treatment, and single compound vs. mixture are equally important factors in prevention regimes (42, 70, 117, 152, 185). Here we highlight some advances in targeting processes involved in the progression of colon cancer (Fig. 2). The colon is a complicated tissue comprised of millions of test-tube-shaped structures called crypts. The gastrointestinal epithelium cells practice homeostasis maintenance that is reflected through balance of stem cells proliferation, differentiation, migration, and death (86). Colon cancer initiates with the formation of polyplike outgrowths of the tissue as a result of genetic abnormalities or the disruption of subcellular signaling pathways in the individual compromised crypt.

Most cancer cells share 10 common characteristics as summarized by Hanahan and Weinberg (69): sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, deregulating cellular energetics, avoiding immune destruction, tumor promoting inflammation, and genome instability and mutation. Aberrant cells such as cancer cells have been deregulated as a result of genetic mutations. The main subcellular mechanisms leading to CRC are the Wnt signaling pathway, the Notch signaling pathway, the NF-κB pathway, PI3K/Akt, the transforming growth factor (TGF)-β pathway, and the Ras-MAPK signaling pathway (86). In the end, for the colon, the innate homeostatic balance is overwhelmed by too many mutations and epigenetic events that lead to progressive cancer.

A broad scope of work including mathematical and computational analyses has been conducted in an effort to better understand CRC initiation and development. Studies have identified a mutation in Smad, involved in TGF-β signaling, as a key event in CRC progression (62). Other results suggest that colorectal tumorigenesis initiates with a loss of adenosomatous polyposis coli (APC), involved in Wnt signaling, followed with KRAS mutation and TP53 inactivation. Multiscale modeling, a mathematical approach that addresses the interplay between various hallmarks of cancer, suggests that the sustained proliferative signaling of CRC cells through cell cycle alteration is an important role in tumor initiation (86). Thus targeting these pathways is a prime avenue for prevention as well as therapeutic studies (86). Drug design for effective prevention studies requires the development of agents with specific therapeutic effects that occur during these pathway perturbations, switching a normal cell into a precancerous lesion (or cancer stem cells). Certain SMNPs have shown potential in disrupting these deleterious effects.

**Wnt Signaling Pathways**

The Wnt signaling pathway plays multiple important roles such as stem cell maintenance, cell proliferation, differentiation, and apoptosis (Fig. 3). The normal growth process of the crypt is mostly controlled through regulating the transcription factor (TF) β-catenin. Wnt target genes are c-myc, axin2, and asci. ASCL plays a significant role in stem cell maintenance and is restricted to crypts. Disruption of the Wnt signaling pathway via downregulation of ASCL2 leads to hyperplasia and loss of the stem cell compartment (189). The critical initiating steps in malignant transformation are inactivation of the apec gene and/or activating mutations of β-catenin, which are reported for almost all CRCs (49). Current clinical studies and drug development approaches for the Wnt signaling pathway fall into two principal categories: first a direct targeting approach of Wnt signaling pathway constituents and second an indirect targeting approach of downstream elements in the signaling cascade (Fig. 3).

Two inhibitors of this pathway have been identified by Chen and colleagues in 2007 (34). One molecule disrupted Wnt production and secretion and the second served to stabilize Axin2, targeting β-catenin for degradation in APC mutated CRCs. Axin 2 is part of the β-catenin destruction box and poly-ADP-ribosylating enzymes tankyrase 1 and 2 (TNKS) degrades Axin2 (34, 49, 53a, 156, 170). This role in the Wnt pathway suggests that it is a good target with potential therapeutic benefits and as such may be an important target for SMNPs, especially those that are epigenetic modulators. For instance, a viable target for epigenetic modulators in the canonical pathway is secreted Fzd-related proteins (SFRP), since hypermethylation, leading to lower expression, of this gene is implicated in CRC (77, 191). Another potential area to target is the TF, T cell factor
(TCF)/β-catenin complex, which can corrupt cell growth when unregulated. Emami and colleagues discovered a leading compound, ICG-001, that targets the CBP/P300, a coactivator of the TCF/TCF, reducing the dysregulation of this complex (99). The role of the Wnt signaling pathway in normal proliferation, however, suggests that the direct targeting strategy may be associated with adverse side effects. So it is important to note the importance of the compounds’ specific therapeutic effects within a specific time frame of carcinogenesis. With respect to CRC prevention, preventing the transformation of normal colonic crypt cells into cancerlike stem cells (49) would be the most worthy target of any intervention, preventive or therapeutic. But in the real world, researchers often take an indirect approach, one that simply aims to target already aberrant Wnt signaling target genes like COX2 and their downstream biological consequences.

One example of Wnt-pathway SMNP inhibition, Banerjee and colleagues (14) employed a rat colon cancer model to show that extracts from the pomegranate fruit, which contain polyphenols such as ellagitannins and flavonoids, inhibit targets in the Wnt signaling pathway. The plant flavonoid isorhamnetin has shown chemopreventive activity through β-catenin signal inhibition (156). A phenyl propanoid isolated from the bark of cinnamon cassia (2-hydroxycinnam aldehyde) has been found to suppress β-catenin signaling and lead to downregulation of target genes c-myc and cyclin D1 (99). Finally, a natural lignan, hydnocarpin, isolated from loncera japonica, has also been found to inhibit the activation of β-catenin through disruption of the Wnt pathway.

**NOTCH Signaling Pathway**

The first Notch gene mutation was discovered in *Drosophila* in 1913 (196). The Notch signaling pathway is dysregulated in many cancers. In mammals there are 4 Notch genes expressed, which translate into a single-pass transmembrane receptor consisting of Jagged-1,–2 Delta-like 1–3 and 4 Notch intracel-
lular domain (NICD) activated by the gamma-secretase and translocated into the nucleus (212). Once they bind to CSL-MAML-1 and p300/CBP, these complexes activate the transcription factors HES-1-5-7, HEY-1-2, and HEY-L encoding helix-lo0-helix (bHLH)/transcriptional repressors (34). Cell signaling transduction from the ligand to the CSL-NICD-MAML-1 cascade is known as the “canonical” Notch signaling pathway. One of the NF-κB compartments P50/or RelA in the nucleus is another target of the NICD, which enhances NF-κB activity in the nucleus; this signaling pathway is known as the “noncanonical” pathway (167). Notch signaling plays an important role in colon crypt development and a key developmental role in cell fate determination and disrupting this process is associated with colon cancers (34, 104, 108, 154, 169). Antibodies were developed to antagonize the Notch extracellular regulatory region in an attempt to facilitate ADAM protease cleavage (11, 103, 200). These antibodies are still in preclinical studies (200). Although downregulation of γ-secretase activity to disrupt Notch signaling is promising, there is concern because some clinical trials on Alzheimer patients with secretase inhibitors resulted in increased incidences of squamous cell skin cancers (74). Although this might not apply to all secretases and consequently downregulation of the Notch pathway by other means, it does reveal that not all inhibition might be beneficial. So when utilizing natural products careful attention to both beneficial and deleterious, if any, effects must be paid.

The anti-Notch monoclonal Ab-OMP-5qR5/DLL 1 and DLL 4 inactivation of Notch signaling inhibits tumor growth in APCmin−/− mice (88, 102, 137). Studies have also shown that epigenetic modulation of the Notch ligand DLL1 through hypermethylation of the promotor promotes gastric cancer (84, 88). In 50% of diffuse gastric cancer cases, lack of DLL1 ligand was due to promoter methylation (88). Curcumin, a very promising SMNP from turmeric, modulated several important signaling pathways, including Notch-1 (162, 210). Diallyl trisulfide (DAT) is an organosulfur compound derived from garlic and a few other Allium plants. DATs have been show to
inhibit proliferation of osteosarcoma cells by triggering cell cycle arrest and apoptosis in vitro (108). The cancer-preventive effect of this compound was associated with downregulation of Notch-1 expression and its downstream genes such as vascular endothelial growth factor (VEGF) and matrix metalloprotei-
nases (MMPs) (108). Isothiocyanates (ITCs) are naturally occurring chemical groups from plants with cancer-preventive properties. They have shown a profound ability to cause growth arrest and cell death in cancer cells. Recent studies highlight downregulation of Notch activation by ITCs and ability to inhibit migration of cancer cells (170). Biochanin A, a soybean isoflavone, is a class of antioxidants, and other similar isoflavones can be found in biochanin A, alfalfa (for-
mononetin), and peanut (genistein) (104, 106, 143, 154) (Fig. 3). They have shown inhibitory effects on cancer development and progression in vitro and in vivo by regulating multiple corrupted cellular signaling pathways including Akt, NF-κB, MAPK, Wnt, androgen receptor (AR), p53 and Notch signaling (104). EGCG from green teas inhibits cancer by affecting a wide array of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt, and Notch (48, 133, 154, 169, 179). On the frontier of prevention research is the notion that combinatorial therapy, employing natural products to enhance current therapies by sensitizing cells, makes them more vulnerable to therapy (4, 138, 146, 148, 190).

**Anti-Inflammatory Compounds and Cancer Prevention**

The relationship between cancer and inflammation comprise two protective pathways: an intrinsic pathway, driven by ge-
netic alterations that promote inflammation and neoplasia (e.g., oncogenes); and an extrinsic pathway, driven by disease-specific inflammatory conditions that increase cancer risk (e.g., inflammatory bowel disease) (115). In the extrinsic pathway, reactive oxygen and nitrogen substances generated by immune responsive cells lead to DNA damages such as mutations and DNA strand breaks (115). Some phytochemicals prevent this carcinogenic process via antioxidant mechanisms and reinforcing protective mechanisms, such as increasing glutathione (GSH, a reactive species neutralizer) (81, 215). The important molecular events related to the intrinsic and extrinsic pathways include transcription factors [e.g., nuclear factor-κB (NF-κB), signal transducer activator of transcription-3 (STAT3), hypox-
ia-inducible factor (HIF1α)], cytokines (e.g., TNF-α, IL-1β, IL-6, IL-23), and chemokines (115, 116). Also, cancer-related inflammation (CRI) is a key factor of the tumor microenvironment (116). CRI induces the tumor microenvironment via producing growth factors (e.g., G-CSF, GM-CSF, M-CSF), chemokines (e.g., CCL2, CCL20, IL-8), chemokine receptors and adhesion molecules (CXCR4-CXCL12, L-selectin), and proteases (MMP7, MMP9, MMP10, UPA) (115). Finding SMNPs with the ability to disrupt any number of these targets can positively impact the future of inflammatory-driven dis-
esases.

COX-2 has a role in growth and progression of cancer and a major role in inflammatory response (125, 128). COX-2 expression was observed in many cancers from colon to prostatic to breast (7, 26, 27, 52, 215). Some NSAIDs, some of which are natural products or synthetics created from their natural counterparts, are potent COX-2 inhibitors. Clinical and epidemiological studies have shown the preventive effects of NSAIDs for precancerous lesions and malignant lesions regardless of cancer risk factors (16, 17, 32, 40, 41, 46, 71, 153). The selective COX-2 inhibitor celecoxib inhibits its expression and has also shown potential for preventing recurrence of premalignancy (10, 19, 139, 173). However, these drugs (NSAIDs and COXIBS) have limitations for long-term usage due to the side effects such as gastrointestinal bleeding and cardiovascular events (94, 135, 159), again underscoring the detailed observation needed when utilizing compounds for long duration prevention studies. Not to mention the financial burden of continued purchase one would incur during a long-term prevention regime. Therefore, any alternative preventative agent should have lower off-toxic effects and costs to be considered a more viable solution.

There is an increasing array of nonsynthetic SMNPs (EGCG, resveratrol, DATs) that are suitable for cancer pre-
vention through inhibition of proinflammatory processes primarily targeting the components of the COX-2, NF-κB, and STAT pathways. The search for tolerable and efficacious suppressors of chronic inflammatory processes involved in cancer progression and recurrence is an increasing area of basic and clinical research. Curcumin downregulates NF-κB, disrupting COX-2 promoter activation (140). Xiao and colleagues (201) reported that curcumin suppressed PMA (phorbol 12-
myristate 13-acetate)-induced tumor progression by reducing COX-2 mRNA and protein expression level in H460 cells. Others investigated the inhibitory effect of curcumin on deoxycholic acid (DCA) induced cell proliferation in the colon cancer cell line (HT-29) through disruption of corrupted molecular mechanisms (193). They showed that curcumin sup-
pressed the cell proliferation via regulating COX-2 transcription, thus reducing COX-2 protein expression, and PGE2 synthesis induced by DCA (193). Treatment of curcumin combined with a selective COX-2 inhibitor (celecoxib) inhibited the colon cancer cell growth via suppression COX-2 expression (101). Resveratrol suppressed both COX-2 and PGE2 production in FGF (fibroblast growth factor)-stimulated fibroblasts (188). EGCG inhibited COX-2, PGE2, and IL-8 expression, which is induced by IL-1β in synovial fibroblasts, and the suppression of COX-2 through inhibition of NF-κB translocation (73, 81). SFN suppressed the expression of COX-2 and iNOS and inhibited the phosphorylation of ERK 1/2, JNK, and p38 activated by lipopolysaccharide (161). This shows that disruption of increased COX2 expression and activity by several SMNPs can be a promising preventative strategy, as long as the extended durations of use effects are carefully monitored.

NF-κB is a key organizer of inflammation and is an important endogenous tumor promoter (85). NF-κB activates the expression of inflammatory cytokines, adhesion molecules, and COX-2 and promotes cell survival by activating antiapoptotic genes (e.g., Bcl2) (116). Inhibition of COX-2 by curcumin involves inhibiting the IKK signaling complex, prohibiting the translocation of active NF-κB and also inhibiting the tumor-promoting function of TNF-α (2, 50, 163). Curcumin has been shown to inhibit IκB α phosphorylation and degradation, in effect blocking NF-κB activation (50). Shishodia and others (165) reported that curcumin inhibited NF-κB activation and downregulated the expression of transcription factor-controlled gene products (e.g., Bcl-2, Bcl-xl, cyclin D1, COX-2, TNF, IL-6, RANK, and RANKL) in human mantle cell lymphoma.
EGCG also inhibit NF-κB activation, MAPK pathway, and AP-1 activity (164). Some studies have suggested that EGCG inhibits Akt activation in both colon cancer cell lines and in vivo mouse models (23, 164). EGCG also prohibited the activation and expression of MMPs and increased the expression of tissue inhibitors of MMPs (TIMP1 and TIMP2) (6, 59, 60). EGCG also inhibited phosphorylation of IkB-α activation and nuclear translocation of NF-κB/p65 and the suppression induced downregulation of the expression of cyclin D1, MMP-9, IL-8, and iNOS (179). Many dietary phytochemical agents (e.g., emodin, gingerol, reveratrol, lycopene, indole-3-carbinol, vitamin C, SFN, and ellagic acid) have been found to be potent inhibitors of NF-κB (1, 87). Resveratrol was found to inhibit the activation of NF-κB, STAT3 signaling pathway, and have antioxidant activity (28, 54, 66). It blocked IL-1-induced activation of NF-κB, leading to inhibition of proliferation (54).

It also modulated TNF-α-mediated MMP-9 expression in HepG2 cells by downregulation of the NF-κB signaling pathway (211). Apigenin inhibited the LPS-induced COX-2 and NO synthase-2 activity expression in mouse macrophages. It also inhibited the 12-O-tetradecanoylphorbol-13-acetate (TPA)-mediated COX-2 expression through blocking Akt signal transduction and arachidonic acid release in HaCaT cells (12, 109). Apigenin inhibited NF-κB translocation to the nucleus and suppressed IkB-α phosphorylation and degradation in LPS-induced monocytes and CD4 T cells (130, 202). The inhibition of NF-κB correlated with a decreased expression of NF-κB dependent reporter gene and inhibited expression of NF-κB regulated genes, specifically Bcl 2, cyclin D1, COX-2, MMP-9, and iNOS-2 (167). Although promising, many SMNPs may be limited in their efficacy in vivo because of their low bioavailability (87). Enhancing the metabolic uptake of SMNPs, many of which are from the plant bioflavonoid chemical class, is an important challenge for use of these agents in the clinic. In addition to the increased uptake is to monitor how this higher concentration used in treatments affects the intended targets and possibly off-target effects (toxicity).

STAT proteins were identified with being latent cytoplasmic transcriptional factors translated to the nucleus upon Jak-mediated phosphorylation and dimerization through cytokine-induced activation of Jak2 (48, 122). Activation of Jak-STAT3 signal pathway has been frequently observed in many primary human malignancies (122, 186). Dysregulation in STAT3 is associated with increased proliferation, survival, and metastasis of breast cancer cells. Along with induced uncontrolled growth and survival via dysregulation of gene expression such as cyclin D1, c-Myc, Bcl-xl, Mcl-1, and surviving genes, which were contributed to oncogenes (25, 82, 155, 186), curcumin was shown to inhibit IL-6 induced Stat3 activation in human multiple myeloma cells (20). It was found to induce a time-dependent and dose-dependent suppression of constitutive IL-6 expression, and IL-6 induced Stat3 phosphorylation in gynecological malignancy (157). In glioma cells, low-dose curcumin antagonized Jak1, 2/Stat3 tyrosine-phosphorylation in a dose-dependent manner. Curcumin also inhibited transcription of Stat3 target genes c-Myc, MMP-9, Snail, and Ki-67, which are associated with cell proliferation through inducing G2/M phase arrest (197). EGCG suppressed Stat3 phosphorylation and inhibited the collagen production and proliferation of fibroblasts cells in keloid tissues (133). Also, it suppressed the activation of Stat3 in breast cancer cell (118). Resveratrol also regulated IL-6-induced ICAM-1 gene expression, which has an important role in metastasis. Resveratrol impacted tumorigenicity in an in vivo model and induced sensitivity of tumor-initiating cells to radiotherapy via the Stat3 pathway (209). SFN is another SMNP that modifies IL-6 inducible activation of STAT3 (67).

In the tumor microenvironment, TNF, IL-1β, IL-6, and chemokines have an important role between cancer and inflammation. TNF, like other cytokines, is released from macrophages that have responsibility of regulation in the immune system. However, overexpression or release of TNF is associated with disease progression (such as cancer) through NF-κB activation (87). Current research aims to determine whether bioactive phytochemicals can suppress tumor-associated inflammation by directly modulating production of key cytokines and chemokines.

Epigenetic Regulation by Natural Products

Research continues to define the importance of intervening in the process of chronic inflammation in the mitigation of diseases of the colon including colitis and cancer (45, 84, 89, 93, 152). However, many natural products intervene to reduce inflammation not only directly through attenuation of proinflammatory signaling pathways but also indirectly, through epigenetic pathways (70, 117, 123, 172, 199). Prevention of disease by reversing changes in the epigenome has the advantage, theoretically, to make an impact on the course of carcinogenesis by reactivating silenced regulatory genes. The processes by which certain natural products can reverse epigenomic changes lie in their capacity to modify DNA methylation, structural and conformational changes through histone modifications, and microRNA expression (70, 117, 172).

As in other molecular avenues of cancer chemoprevention, the pathways described for epigenetic regulators were paved with pharmaceuticals that, like NSAIDs for inflammation, were sullied by toxicity in humans. Nevertheless, the clinical use of DNA methyltransferase (DNMT) inhibitors 5-azacytidine and decitabine and the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA), which held initial promise in treatment of certain nonsolid tumors, were also associated with toxicities (18, 63). Inhibitions of DNMTs theoretically allow the reexpression of tumor suppressor genes in cancers whose expression is silenced by hypermethylation of a particular gene’s promoter. HDAC inhibitors, again, are believed to restore gene expression by preventing the deacetylation of histone proteins, allowing for a more open chromatin for gene transcription. An increasing number of natural products have the potential to act as epigenetic regulators and possibly without the above-observed toxicities.

Curcumin, as discussed earlier, is an antioxidant and anti-inflammatory polyphenol from the root of Curcuma longa (turmeric). Research has shown it to modify a wide range of epigenetic proteins. Docking experiments suggest that its structure could interfere with DNMT1 (119) and curcumin seems to have an affinity for modulating histones by inhibiting both histone acetyltransferase (HAT) and HDACs (13). At least one study associated anti-inflammatory activity of curcumin by repressing NF-κB expression while inhibiting HDACs 1 and 3 (34). Curcumin has been shown to upregulate a number of...
beneficial miRs while downregulating several believed to be involved in tumor progression (176, 208).

EGCG is one of the most thoroughly researched antioxidant and anti-inflammatory polyphenols with established epigenetic modifying activity. Our laboratory has found that EGCG represses both DNMT3a and HDAC1 activity in colon cancer cell lines while restoring the silenced expression of the important nuclear transcription factor RXRα in these cell lines (93, 123). RXRα is a master transcription factor and heterodimerizes with a number of other important transcription factors to regulate cell growth (examples are VDR, PXR, LXR, PPAR). Earlier research appears to link EGCG with inhibition of DNMT and reactivation of other silenced genes (56), including RARβ (106). EGCG treatment is also associated with modified expression of miRs in liver cancer cells (184).

Soy isoflavones including genistein have been heavily researched for the prevention of hormone-driven cancers. Epigenetic modulation has been reported for this isoflavone and other related isoflavones including the reactivation of silenced genes such as P16ink4a and RARβ in cell culture, with inhibitory activity reported against the expression of DNMT1 and DNMT3 (55). Genistein also stimulated HAT activity and acetylated histones in growth inhibited-prostate cancer cells; while this is associated with epigenetic action, it is difficult to dissociate the antiproliferative effect from genistein’s other known anticancer effects (112). As with other natural products, genistein modulated miR activity. Most notably for cancers of the gastrointestinal tract, genistein treatment of gemcitabine-resistant pancreatic cancer cells stimulated the downregulation of miR-200 and associated with markers involved in inhibition of epithelial-mesenchymal transition (EMT) (107).

Members of the Alliaceae family, especially garlic, have documented chemopreventive activity. Diallyl disulfide, one of the lipid soluble organosulfur compounds from garlic, has been shown to modify histone acetylation in mouse bone marrow cell precursors (95). Histone hyperacetylation associated with growth inhibition was reported in cancer cells treated with diallyl disulfide (DADS) (95) and SAMC (96), suggesting that these compounds may alter HDAC enzymes. Several garlic organosulfur compounds have been utilized in in vitro studies and identified allyl mercaptan (AM) as the most potent inhibitor of HDAC activity. In human colon cancer cells, AM induced the accumulation of acetylated histones and enhanced the binding of Sp3 and p53 transcription factors to the p21waf1 gene promoter with a corresponding increase in p21 mRNA and protein expression, resulting in cell cycle arrest and growth inhibition (129).

One of the polyphenols found in berries and grapes, resveratrol, has been reported to have pluripotent effects on cancer cells, ranging from interference with aberrant cell signaling, antioxidant, anti-inflammatory, and epigenetic effects (117). More evidence points to the ability of this natural compound to modulate HDAC and sirtuin activities; this feature might explain some of the antiaging action of resveratrol (147). Resveratrol is an activator of Sirt1 and has been shown to have an anti-inflammatory effect against colitis, and cancer erupting from colitis (45, 152), presumably by altering the epigenetic status of NF-κB. In colon cancer cells resveratrol has been found to depress the expression of oncogenic miRs, such as downregulating miR26 while upregulating miR22 (180).

A formulation of resveratrol SRT501 was in clinical trial for treatment of multiple myeloma but was halted because of unforeseen kidney failure in several patients. The dose used in this trial was 5 g/day; this increased amount might have impacted underlying renal issues in these patients. Although we tend to only report the desired beneficial direct effects of these compounds, diligence is required to monitor other maladies or exacerbation of them when studying these preventive compounds.

The pungent chemicals associated with cruciferous vegetables have been extensively researched for epigenetic modulation: indole-3-carbinol (I3C), its metabolite diindoylmethane (DIM), and SFN. In prostate cancer cells, DIM has been found to decrease HDAC activity, although the mechanism might involve instability in HDAC protein, stimulating its degradation (105). In the TRAMP mouse model DIM inhibited the progression of prostate cancer was found to demethylate and reexpresses Nrf2 and Nrf2-target genes (199).

SFN has been largely identified as an HDAC inhibitor although studies have also identified it as an inhibitor of DNMTs. In the colon cancer cell line Caco2 downregulation of DNMTs has been recorded following treatment with SFN (182). However, other studies in melanoma cell lines, for instance, found that chromatin was less acetylated in the presence of SFN (51), highlighting once again that SMNPs are not a panacea for all cancers but have specific effects in specific cells. The epigenetic effects of SFN have been studied in vivo. Oral treatment of C57BL/6J mice with SFN resulted in reduced HDAC activity in the colon mucosa. Continual treatment inhibited colon tumorigenesis in ApcMin+/- mice while stimulating global acetylation of chromatin and histone acetylation marks on repressed tumor suppressor genes (126). As a possible pathway for future research, SFN treatment resulted in a decrement in the ability of bladder cancer cells to become invasive by increasing levels of expression of E-cadherin (usually compromised in EMT) through a COX-2/MMP2-MMP-9-dependent pathway, but, importantly, through a miR200C/ZEB1-independent pathway (161).

Natural Products and Late-Stage Cancer

A mere 10 years ago it would have been impossible to conclude that natural products could be used to inhibit migrating cancer cells and their invasion. The research climate has changed and appropriately, since cancer patients often turn to natural product supplements in the belief that they are less toxic and may assist traditional therapy while also reducing unwanted side effects (Fig. 2). At the bench level a few natural products have surprisingly shown that even the late stages of cancer progression can be modulated. Curcumin, active in a number of possible mechanisms thwarting the development of cancer, has been shown to inhibit colon cancer metastasis in experimental models and maintain expression levels of the putative tumor suppressors (Ap-1) via miR 21 expression (124). It also inhibits MMP-2 activity as well as limiting the production of metastasis-permissive cytokines (72, 76). Likewise, the tea catechin EGCG has been shown to suppress metastatic bladder cancer by NF-kB modulated MMP2-expression, as well as sensitizing human oral squamous cancer cells to conventional therapy via similar effects on MMP-2 (33, 214). Resveratrol was recently shown to modulate key miRs
involved in the action of tumor suppressors and in modulating TGF-β receptors, explaining, in part, its antimetastatic effects (181). Flavonoids, a wide group of chemopreventive SMNPs, have considerable promise in inhibiting cancer invasion. These include not only agents in tea, but other phenolic acids found in plants such as caffeic acid, 6-gingerol, and capsaicin (198). In hormone-dependent cancers, such as breast and prostate, the soybean-derived SMNP genisteen may inhibit metabolic pathways involved in invasion through modulation of tumor suppressor activity and in pathways connected to NF-κB expression (53, 65).

It is not surprising that natural compounds with the potential to inhibit the metastatic process do so via their ability to interfere with processes involving angiogenesis. From Asia, several herbs used in treatment of medical conditions have stimulated research into their potential as anticancer agents. From Baikal skullcap (Scutellaria baicalensis), an herb used to treat inflammatory conditions, comes wogonin, which has documented anti-COX-2 activity and the ability to suppress VEGF phosphorylation (80, 110, 111). Coptis root (Coptidis rhizoma) yields berberine, which has been shown to inhibit MMP2 activity and reduced the propensity for epithelial to mesenchymal transition in human cervical cancer cells (38). Compounds from Artemisia annua have been shown to antagonize VEGFRs and MMPs 2 and 9 (44).

While this field is still in its infancy, there is the promise of using natural product as adjuvants to traditional cancer therapy in the hopes of 1) making therapy work better and 2) reducing the off-target side effects of cancer medicines. In the first scenario SMNPs can be marshalled to attack the same or collateral target(s) of conventional therapy. Two concepts that merit exploration are the aforementioned SMNPs that inhibit angiogenesis and modulate epigenetics. In the former concept cancer therapeutics targeting proliferation and growth factors would be augmented by SMNPs that restrict that neovascularature features acquired by many tumors. In the latter, natural compounds with the ability to modify DNMT and HDAC expression could desilence quiescent tumor suppressors to impart a better environment for therapeutic intervention. Cancer therapeutics often cause intolerable side effects that limit the duration of treatment. With judicious use it may well be possible to reduce the need for high-dose (and life-threatening) regimens. It must also be stated that careful consideration of dose and duration of the SMNPs, as well purified compound vs. dietary consumption as mode of delivery are just as crucial to the long-term success of these prevention regimes as is the initial antitumor effect.

Conclusions and the Path Forward

As evidenced in this review, natural product research has furrowed a number of new and potentially useful compounds not only for the prevention of primary cancer or its recurrence, but for use in late-stage cancers as well. In terms of cancer chemoprevention the lesson learned from COX-2 inhibition is that the purified drug route of intervention may imply an unacceptable level or risk for some, and this risk could be attenuated with judicious use of safer, efficacious SMNPs that might also be better choices for life-long interventions. Yet it should be emphasized that cancer chemotherapy is a different scenario where the propensity for troublesome side effects is acceptable in the race to kill cancer cells. Even in these circumstances it may be possible to achieve equal or greater therapeutic advantage by coadministration of SMNPs that enhance the cell-killing facet of therapeutics while sparing normal cells due to a reduced need for high-dose regimens.

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AUTHOR CONTRIBUTIONS


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Themes

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