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REVIEW ARTICLE

# Perspectives for Cancer Prevention With Natural Compounds

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## ABSTRACT

Cancer is the second leading cause of death in the United States. Despite the estimated 565,650 deaths in 2008 of Americans as a result of cancer, it is mostly a preventable disease. Simply by modification of diet, maintenance of optimum body weight, and regular physical activity, 30% to 40% of all instances of cancer could be prevented. Modification of diet alone by increasing vegetable and fruit intake could prevent 20% or more of all cases of cancer and may potentially prevent approximately 200,000 cancer-related deaths annually. Because of their safety, low toxicity, antioxidant properties, and general acceptance as dietary supplements, fruits, vegetables, and other dietary elements (phytochemicals and minerals) are being investigated for the prevention of cancer. Extensive research over the past several decades has identified numerous dietary and botanical natural compounds that have chemopreventive potential. In this review, we discuss promising natural chemopreventive compounds, their molecular targets, and their mechanisms, which may help the further design and conduct of preclinical and clinical trials.

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## INTRODUCTION

Cancer is the second leading cause of death in the United States with 565,650 projected cancer deaths and 1,437,180 new cases of cancer in 2008.[1] In 2005, the global incidence of cancer was 11 million with more than 7.6 million deaths, and is expected to increase to an incidence of 15.5 million with 11.5 million deaths by 2030.[2] The lifetime probability of being diagnosed with an invasive cancer is more than 40%.[1] However, cancer is mostly a preventable disease.[3] The two most important ways to reduce cancer risk are the avoidance of cancer-causing biologic, chemical, and physical agents and the habitual consumption of diets high in foods that protect against cancer. Approximately, 30% to 40% of cancer incidents are preventable by consuming a healthy diet, regular physical activity, and maintenance of optimum body weight, and more than 20% by consuming vegetables and fruits.[3]

Chemoprevention, by definition, is a means of cancer control by which the occurrence of the disease can be entirely prevented, slowed down, or reversed by the administration of one or more naturally occurring and/or synthetic agents. The concept of chemoprevention is gaining increasing attention because it is a cost-effective alternative to cancer treatment. The involvement of multiple factors and developmental stages and our increased understanding of cancer at the epigenetic, genetic, molecular, and cellular levels is opening up enormous opportunities to interrupt and reverse the initiation and progression of the disease and provide scientists with numerous targets to arrest by physiological and pharmacologic mechanisms, with the goal of preventing end-stage, invasive disease and impeding or delaying the development of cancer.[4]

## WHY NATURAL COMPOUNDS?

Chemoprevention began in the 1920s with Berenblum[5] and, after a period of relative dormancy, reentered the cancer research mainstream in the 1970s through the work of Sporn.[6] Because of their excessive toxicity and inadequate biodistribution, natural retinoids were replaced with more potent and less toxic synthetic retinoids. The first limited clinical trial with the vitamin A analog 13-cis-retinoic acid (13-cRA) showed a significant decrease in the size of oral premalignant lesions and reversal of dysplasia.[7] The follow-up phase III trial in patients with leukoplakia using initial high-dose 13-cRA followed by either low-dose 13-cRA or $\beta$-carotene suggested that low-dose 13-cRA was better than $\beta$-carotene as maintenance therapy.[8] Another phase III trial with high-doses of 13-cRA showed significant reduction in the incidence of second primary tumor (SPT) after 1 year of treatment and the protection lasted for 2 to 3 years.[9,10] A number of retinoid trials with mixed results followed.[11-13] The combination

 

**Table 1.** Information About Ongoing Clinical Trials With Natural Compounds

| Agent and Trial No. | Trial Type | Cancer Type | Location/Site | Status | Phase |
|---|---|---|---|---|---|
| Green tea | | | | | |
| NCT00363805 | Prevention | Lung | University of Arizona | Recruiting | II |
| NCT00134381 | Prevention | Skin | University of Medicine and Dentistry New Jersey and Rutgers University | Recruiting | II |
| NCT00721890 | Maintenance | Ovarian | Centre hospitalier universitaire de Québec | Recruiting | II |
| NCT00685516 | Therapy | Prostate | Jonsson Comprehensive Cancer Center | Recruiting | II |
| NCT00003197 | Therapy | Solid tumors | Memorial Sloan-Kettering Cancer Center | Active | I |
| NCT00005828 | Therapy | Prostate | North Central Cancer Treatment Group | Completed | II |
| NCT00253643 | Prevention | Prostate | Oregon Health and Science University Cancer Institute | Recruiting | |
| NCT00303823 | Prevention | Cervical | University of Arizona | Recruiting | II |
| NCT00516243 | Therapy | Breast | M. D. Anderson Cancer Center | Recruiting | I |
| NCT00459407 | Therapy | Prostate | University of Arizona | Recruiting | I |
| NCT00176566 | Therapy | Oral leukoplakia | University of Medicine and Dentistry New Jersey | Completed | II |
| NCT00666562 | Therapy | Bladder | University of Wisconsin, Madison | Recruiting | II |
| NCT00088946 | Therapy | Bladder | Jonsson Comprehensive Cancer Center | Active | II |
| NCT00091325 | Prevention | Solid tumors | University of Arizona | Completed | I |
| NCT00573885 | Prevention | Lung | British Columbia Cancer Agency | Recruiting | II |
| NCT00611650 | Prevention | Lung | British Columbia Cancer Agency | Recruiting | II |
| NCT00233935 | Prevention | Osophageal | M. D. Anderson Cancer Center | Recruiting | I |
| NCT00262743 | Therapy | Leukemia | Mayo Clinic | Recruiting | I/II |
| NCT00003367 | Therapy | Prostate | Memorial Sloan-Kettering Cancer Center | Active | III |
| NCT00676780 | Basic science | Prostate | Louisiana State University | Active | II |
| NCT00455416 | Therapy | Lymphoma | Rikshospitalet HF | Recruiting | II |
| NCT00676793 | Basic science | Breast | Louisiana State University | Recruiting | II |
| NCT00744549 | Therapy | Prostate | University Health Network, Toronto | Recruiting | II |
| NCT00707252 | Therapy | Lung | Louisiana State University | Recruiting | I/II |
| Curcumin | | | | | |
| NCT00113841 | Therapy | Multiple myeloma | M. D. Anderson Cancer Center | Active | Pilot |
| NCT00745134 | Therapy | Rectal | M. D. Anderson Cancer Center | Recruiting | II |
| NCT00365209 | Prevention | Colon | Chao Family Comprehensive Cancer Center | Active | II |
| NCT00689195 | Therapy | Osteosarcoma | Tata Memorial Hospital | Recruiting | I |
| NCT00192842 | Therapy | Pancreatic | Rambam Health Care Campus | Recruiting | II |
| NCT00094445 | Therapy | Pancreatic | M. D. Anderson Cancer Center | Completed | II |
| NCT00295035 | Therapy | Colon | Tel-Aviv Sourasky Medical Center | | III |
| NCT00641147 | Therapy | FAP | Johns Hopkins University | Recruiting | II |
| NCT00248053 | | FAP | Johns Hopkins University | Terminated | II |
| NCT00486460 | Therapy | Pancreatic | Tel-Aviv Sourasky Medical Center | Recruiting | III |
| NCT00027495 | Prevention | Colon | University of Michigan Cancer Center | Completed | I |
| NCT00176618 | Prevention | Aberrant crypt foci | University of Medicine and Dentistry New Jersey | Completed | |
| NCT00003365 | Prevention | Colorectal | Rockefeller University | Suspended | |
| NCT00118989 | Prevention | Adenomatous polyps | University of Pennsylvania | Recruiting | II |
| Resveratrol | | | | | |
| NCT00256334 | Therapy | Colon | University of California, Irvine | Recruiting | I/II |
| NCT00098969 | Prevention | Solid tumors | University of Michigan Cancer Center | Completed | I |
| NCT00433576 | Therapy | Colorectal | University of Michigan Cancer Center | Recruiting | I |
| NCT00578396 | Prevention | Colon | University of California, Irvine | Recruiting | I |
| NCT00455416 | Therapy | Follicular lymphoma | Rikshospitalet HF | Recruiting | II |
| Genistein | | | | | |
| NCT00244933 | Therapy | Breast | Barbara Ann Karmanos Cancer Institute | Active | II |
| NCT00290758 | Prevention | Breast | Robert H. Lurie Cancer Center | Active | II |
| NCT00546039 | Basic science | Prostate | University Hospital, Aker | Active | II |
| NCT00005827 | Therapy | Prostate | University of North Carolina Lineberger Comprehensive Cancer Center | Completed | I |
| NCT00001696 | PK | Cancer | National Cancer Institute | Completed | I |
| NCT00276835 | Therapy | Kidney cancer<br>Melanoma (skin) | Robert H. Lurie Cancer Center | Active | II |
| NCT00118040 | Therapy | Bladder | University of Wisconsin, Madison | Active | II |
| NCT00058266 | Therapy | Prostate | Robert H. Lurie Cancer Center | Active | II |
| NCT00769990 | Therapy | Cancers | Masonic Cancer Center, University of Minnesota | Suspended | I/II |
| NCT00584532 | Therapy | Prostate | University of California, Davis | Completed | II/III |

(continued on following page)

**Table 1.** Information About Ongoing Clinical Trials With Natural Compounds (continued)

| Agent and Trial No. | Trial Type | Cancer Type | Location/Site | Status | Phase |
|---|---|---|---|---|---|
| NCT00099008 | Prevention | Breast and endometrial pancreatic | University of North Carolina Lineberger Comprehensive Cancer Center | Completed | I |
| NCT00376948 | Therapy | Prostate | Barbara Ann Karmanos Cancer Institute | Suspended | II |
| NCT00269555 | Therapy | Leukemia | University of California, Davis | Active | |
| NCT00004858 | Therapy | Lymphoma | Parker Hughes Cancer Center | Active | I |
| NCT00499408 | Therapy | Prostate | Wake Forest University | Recruiting | II |
| Pomegranate | | | | | |
| NCT00413530 | Therapy | Prostate | M. D. Anderson Cancer Center | Recruiting | |
| NCT00719030 | Prevention | Prostate | University of California, Los Angeles | Recruiting | |
| NCT00732043 | Prevention | Prostate | Radiant Research | Recruiting | II |
| NCT00731848 | Therapy | Prostate | Radiant Research | Recruiting | II |
| NCT00336934 | Therapy | Prostate | Roll International Corporation | Recruiting | III |
| NCT00381108 | Therapy | BPH | University of California, Irvine | Recruiting | I |
| NCT00060086 | Therapy | Prostate | Jonsson Comprehensive Cancer Center | Active | II |
| NCT00455416 | Therapy | Follicular lymphoma | Rikshospitalet HF | Recruiting | II |
| NCT00433797 | Therapy | Prostate | University of Oslo | Recruiting | I/II |
| Lycopene | | | | | |
| NCT00042731 | Therapy | Prostate | H. Lee Moffitt Cancer Center and Research Institute | Completed | |
| NCT00416325 | Prevention | Prostate | University of Illinois | Completed | I |
| NCT00178113 | Prevention | Prostatic intraepithelial neoplasia | University of Pittsburgh | Completed | I |
| NCT00093561 | Prevention | Prostate | University of Illinois | Completed | I |
| NCT00416390 | Therapy | Precancerous/nonmalignant condition | University of Illinois | Active | |
| NCT00450749 | Therapy | Prostate | M. D. Anderson Cancer Center | Recruiting | II |
| NCT00006078 | Prevention | Prostate | University of Illinois | Completed | I |
| NCT00322114 | Prevention | Prostate | University of Illinois | Recruiting | II |
| NCT00402285 | Therapy | Prostate | University of California San Francisco Helen Diller Family Comprehensive Cancer Center | Active | |
| NCT00450957 | Prevention | Prostate | University of Illinois | Active | I |
| NCT00068731 | Therapy | Prostate | North Central Cancer Treatment Group | Active | II |
| NCT00744549 | Therapy | Prostate | University Health Network, Toronto | Recruiting | II |
| NCT00501371 | Therapy | BPH | Health Ever Bio-Tech Ltd | Recruiting | III |
| NCT00669656 | Therapy | Prostate | Norris Comprehensive Cancer Center | Recruiting | II |
| n-3 poly unsaturated fatty acids | | | | | |
| NCT00402285 | Therapy | Prostate | University of California San Francisco Helen Diller Family Comprehensive Cancer Center | Active | |
| NCT00114296 | Prevention | Breast | Cedars-Sinai Medical Center | Active | |
| NCT00003077 | Supportive | Soft tissue | Cancer and Leukemia Group B | Completed | I/II |
| NCT00627276 | Therapy | Breast | Oregon Health and Science University Cancer Institute | Recruiting | II |
| NCT00559156 | Therapy | Head and neck | Centre Regional de Lutte Contre le Cancer-Centre Val d'Aurelle | Active | II |
| NCT00723398 | Prevention | Breast | Penn State University | | |
| NCT00458549 | Treatment | Prostate | Dana-Farber Cancer Institute | Recruiting | |
| NCT00488904 | Prevention | Colorectal | Aalborg Hospital | Recruiting | IV |
| NCT00253643 | Prevention | Precancerous/nonmalignant condition, prostate | Oregon Health and Science University Cancer Institute | Recruiting | |
| NCT00168987 | Therapy | Colorectal neoplasm<br>Hepatocellular carcinoma<br>Cholangiocarcinoma | Charite University, Berlin, Germany | Completed | IV |
| NCT00798876 | Diagnostic | Prostate | University of California, Los Angeles | Recruiting | |
| NCT00533078 | Prevention | Colitis, mucositis, AML | University Hospital Inselspital, Berne | Recruiting | II |
| NCT00398333 | Supportive | Colorectal neoplasm | Hospital Clinic of Barcelona | Terminated | IV |
| NCT00145015 | Diagnostic | Colorectal neoplasm, ulcerative colitis, polyps | Institute of Food Research | Completed | |
| NCT00455416 | Therapy | Follicular lymphoma | Rikshospitalet HF | Recruiting | II |
| NCT00790140 | Therapy | Esophageal | University of Dublin, Trinity College | Recruiting | IV |
| NCT00510692 | Prevention | Familial adenomatous polyposis coli, FAP | S.L.A. Pharma AG | Completed | II/III |

Abbreviations: FAP, familial adenomatous polyposis; PK, pharmacokinetics; BPH, benign prostate hyperplasia; AML, acute myelocytic leukemia.

  

**Table 2.** Source, Mechanism of Action, Synergistic Interactions With Other Drugs, and Molecular Targets of Promising Natural Compounds

| Agent | Natural Source | Mechanism of Action | Organ Site | Synergistic Interaction | Molecular Targets |
|---|---|---|---|---|---|
| Green tea polyphenols and EGCG | *Camellia sinensis* (green tea) | Antioxidant, anti-mutagenesis, anti-proliferation (cell cycle arrest, apoptosis), anti-inflammation, anti-angiogenesis, immunomodulation | Skin, lung, oral cavity, head and neck, esophagus, stomach, liver, pancreas, small intestine, colon, bladder, prostate, mammary glands | Curcumin, erlotinib, luteolin, genistein, atorvastin, TRAIL, tamoxifen, celecoxib, cisplatin, sulindac, dacarbazine, adriamycin | p53, p73, p21, Bax, EGFR, AKT, NF-κB, Bcl-2, cyclin D1, COX-2, VEGF, MMP-2/9, STAT3, ERK1/2, AP-1, IL-12, $CD8^+$ T-cell |
| Curcumin | *Curcuma longa* (turmeric powder) | Anti-oxidant, antiproliferation (cell cycle arrest, apoptosis), anti-inflammation, anti-angiogenesis, immunomodulation | Skin, lung, oral cavity, head and neck, esophagus, stomach, liver, pancreas, small intestine, colon, bladder, prostate, mammary glands, lymphoma, soft palate, cervix | Genistein, green tea, embelin, FU, vinca alkaloid, vinorelbine, gemcitabine, soy isoflavone, oxaliplatin, paclitaxel, TRAIL, celecoxib, retinoic acid | EGFR, IGF-1R, AKT, NF-κB, Bcl-2, COX-2, ERK, AP-1, Sp, VEGF, VEGFR1, MMP-2/9, p53, p21, Bax, STAT3/5 |
| Luteolin | Artichoke, broccoli, celery, cabbage, spinach, green pepper, pomegranate leaves, peppermint, tamarind, and cauliflower | anti-inflammation, anti-allergy, anti-proliferation (G1 and G2/M arrest, apoptosis), antioxidant, pro-oxidant | Ovarian, gastric, liver, colon, breast, oral, oesophageal adenocarcinoma, prostate, lung, nasopharyngeal, cervix, leukemia, skin, and pancreatic | Cisplatin, doxorubicin, TRAIL, TNF-α | JNK, p53, DR5, BAX, p21, PUMA, EGFR, IGF-1R, AKT, NF-κB, Bcl-2, CDK, ERK, STAT3 |
| Resveratrol | Red wine, grapes (mainly in the skin), mulberries, peanuts, vines, pines | Antioxidant, antiproliferation (cell cycle arrest and apoptosis), antiangiogenesis, antiinflammation | Ovarian, breast, prostate, liver, uterine, leukemia, lung, gastric | EGCG, indole-3-carbinol, vitamin E analogue, methylseleninic acid, quercetin, genistein, TRAIL, cisplatin, doxorubicin, ellagic acid, platinum compounds, FU, paclitaxel | SOD, catalase, glutathione, ↑ glutathione, AKT, NF-κB, iNOS, COX-2, STAT3, survivin, p53, p21, BAX, BAK, DR |
| Genistein | Soybeans and soy products, red clover (*Trifolium pretense*), sicilian pistachio *(Pistacia vera)* | Antioxidant, antiproliferation (growth inhibition, cell cycle arrest, apoptosis), anti-angiogenesis, anti-inflammation | Prostate, breast, skin, colon, stomach, liver, ovary, pancreas, oesophagus, head and neck | EGCG, letrozole, docetaxel, arsenic trioxide, resveratrol, lycopene, vitamin D, tamoxifen, paclitaxel, cisplatin, erlotinib, gemcitabine, doxorubicin, FU, camptothecins, adriamycin, bleomycin | AKT, NF-κB, Bcl-2, survivin, cyclin D1, COX-2, MMP-2/9, p53, p21, GADD153, Bax, STAT3/5, ERK1/2, CDK1, AP-1, IGF-1R |
| Pomegranate | *Punica granatum* (pomegranate fruit, pomegranate juice, pomegranate seed and seed oil) | Antioxidant, antiproliferation (growth inhibition, cell cycle disruption and apoptosis), antiangiogenesis, anti-inflammation | Prostate, skin, breast, lung, colon, oral, leukemia | | NF-κB, Bcl-2, COX-2, VEGF, ERK, JNK, p38, AKT, mTOR, iNOS, cyclin, CDK, p21, p27, BAX, BAK |
| Lycopene | Tomatoes, guava, rosehip, watermelon, papaya, apricot and pink grapefruit; most abundant in red tomatoes and processed tomato products | Antioxidant, antiproliferation (growth inhibition, cell cycle arrest, apoptosis), anti-angiogenesis, anti-inflammation, immunomodulator | Prostate, lung, breast, gastric, liver, pancreas, colotectal, head and neck, skin | Genistein, adriamycin, cisplatin | Cyclin D1, Bcl-2, Bcl-xL, AKT, BAD, NF-κB, MMP-9, Sp-1, IGF-BP3 |
| Ellagic acid | Pomegranate juice, and seed oil, different nuts, blue honeysuckle (*Lonicera caerulea*), strawberries and other berries, bark of arjun (*Terminalia arjuna*), leaves and fruits of *T. bellerica* and bark, leaves and fruits of *T. muelleri* | Antioxidant, anti-proliferation (growth inhibition, cell cycle arrest, apoptosis), anti-inflammation | Neuroblastoma, skin, pancreas, breast, prostate, colon, intestine, esophagus, bladder, oral, leukemia, liver | Cisplatin, vinorelbine, quercetin, resveratrol, cyclosporine A, 6-gingerol, seleno-methionine | p53, p21, JNK, p38, ↓CDK2, glutathione, glutathione-peroxidase, catalase, SOD, NF-κB, COX-2, PDGF, VEGF, MMP-2/9 |
| Lupeol | Mango, olive, fig, strawberry, red grapes | Antioxidant, anti-mutagenesis, anti-inflammation, antiproliferation (cell cycle arrest, apoptosis, induction of differentiation | Skin, lung, leukemia, pancreas, prostate, colon, liver, head and neck | Cisplatin | 14-3-3-σ, BAX, p21, Fas, Bcl-2, cyclin D1/2, Ras, NF-κB, COX-2, NOS, AKT |
| Betulinic acid | Widely distributed in plant kingdom; most abundant sources are *Betula* spp (birch tree), *Ziziphus* spp, *Syzigium* spp, *Diospyros* spp, and *Paeonia* spp | Anti-inflammation, apoptosis, immunomodulation | Skin, ovary, colon, brain, renal cell carcinoma, cervix, prostate, leukemia, lung, breast, head and neck | Bleomycin, FU, irinotecan, oxaliplatin, doxorubicin, cisplatin, taxol, dactinomycin, TRAIL, vincristine | PPAR-γ, p21, p38, JNK, topoisomerase I, NF-κB, COX-2, Bcl-2, cyclin D1/3, ↓Sp1,3 and 4 |

(continued on following page)

**Table 2.** Source, Mechanism of Action, Synergistic Interactions With Other Drugs, and Molecular Targets of Promising Natural Compounds (continued)

| Agent | Natural Source | Mechanism of Action | Organ Site | Synergistic Interaction | Molecular Targets |
|---|---|---|---|---|---|
| n-3 polyunsaturated fatty acids | Corn oil, sunflower oil, safflower oil, and olive oil, soybeans, walnuts, dark green leafy vegetables such as kale, spinach, broccoli, and brussels sprouts, and seeds or their oils such as flaxseed, mustard seed, and rapeseed (canola) | Anti-inflammation, apoptosis, cell cycle arrest, lipid peroxidation | Colorectal, prostate, breast, colon, gastric, pancreatic, head and neck, esophageal, hematologic malignancies | Sodium butyrate | NF-κB, Bcl-2, STAT3, p53, Bax, p21, Fas/FasL, PPAR-γ, RXR, Ras, ERK 1/2 |
| Ginkolide B | *Ginko biloba* | Antioxidant, anti-angiogenic, apoptosis | Ovary, breast, brain | Ethanol | PAFR, NO, iNOS, eNOS, JNK |

Abbreviations: EGCG, epigallocatechin-3-gallate; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; EGFR, epidermal growth factor receptor; NF-κB, nuclear factor-κB; COX-2, cyclo-oxygenase-2; VEGF, vascular endothelial growth factor; MMP-2/9, matrix metalloproteinases; IL-12, interleukin 12; FU, fluorouracil; IGF-1R, insulin-like growth factor-1 receptor; Sp, stimulating protein; VEGFR1, vascular endothelial growth factor receptor 1; TNF-α, tumor necrosis factor α; JNK, Jun-N-terminal kinase; CDK, cyclin-dependent kinase; ERK, extracelluar signal–regulated kinase; SOD, superoxide dismutase; mTOR, mammalian target of rapanycin; iNOS, inducible nitric oxide synthase; DR, death receptor; IGF-BP3, insulin-like growth factor binding protein 3; PPAR-γ, peroxisome proliferator-activated receptor-γ; PAFR, platelet activating factor receptor; NO, nitric oxide; eNOS, endothelial nitric oxide synthase.

of 13-cRA, α-interferon, and α-tocopherol appeared to be very effective in delaying SPT,[14] and a phase III trial with this combination versus no treatment has been initiated. However, because of patient accrual issues, this trial is currently delayed.

The identification of several biomarkers, including epidermal growth factor receptor (EGFR), cyclo-oxygenase-2 (COX-2), and Ras, which are associated with disease progression, and the discovery of novel targeted inhibitors for these biomarkers has opened new opportunities for chemoprevention.[4] Subsequently, several targeted agents, such as the COX-2 inhibitors celecoxib and refecoxib, the EGFR inhibitors erlotinib and gefitinib, and farnesyltransferase inhibitors have been discovered.[15-18] However, because of a lack of long-term safety data in patients without the evidence of active cancer, two proposed clinical trials to examine gefitinib and tipifarnib in the reversal of premalignant lesions of the lungs have been discontinued.

Safety is always a primary consideration in studies involving human subjects, particularly patients without evidence for overt cancer. An ideal chemopreventive agent should be nontoxic, effective at lower doses, economical, and easily available. Patient accrual to chemoprevention trials is sometimes a challenge, partly due to the toxicity of the pharmaceuticals investigated. In recent years, natural dietary agents have drawn a great deal of attention both from researchers and the general public because of their potential ability to suppress cancers as well as reduce the risk of cancer development. From multiple epidemiological and animal studies, it was clear that consumption of food rich in fruits and vegetables decreases the occurrence of cancers.[19-23] Clinicians are also paying increasing attention to diet-derived chemopreventive agents as a result of the willingness of patients to use over-the-counter diet-derived agents. Cell culture and animal studies over the past several decades have suggested the cancer-preventive potential of several nutritional compounds, including those found in green and yellow vegetables, citrus fruits, and spices. Since the first primary tumors and SPTs share common host factors (genetic abnormalities, immune function, and hormone imbalances), environmental and/or occupational exposures, lifestyle factors, and gene-environment interactions, these agents should also be effective in the prevention of SPT. However, clinical trials have only recently started to investigate these compounds (Table 1). The chemopreventive properties and molecular targets of selected promising natural compounds are discussed later and summarized in Table 2.

### *Tea Polyphenols*

Tea is one of the most widely consumed beverages and is rich in substances with antioxidant properties. Different processing techniques yield different types of tea. Although both black tea and green tea have been studied for their chemopreventive potential, green tea showed higher promise and greater efficacy against multiple types of cancer. Epigallocatechin-3-gallate (EGCG) (Fig 1A) is the most abundant polyphenol in green tea and has gained the most attention with respect to anticarcinogenic activity.

Epidemiological studies from different countries and many animal model studies have yielded promising results of green tea and its constituents in reducing human cancer risk in multiple organ

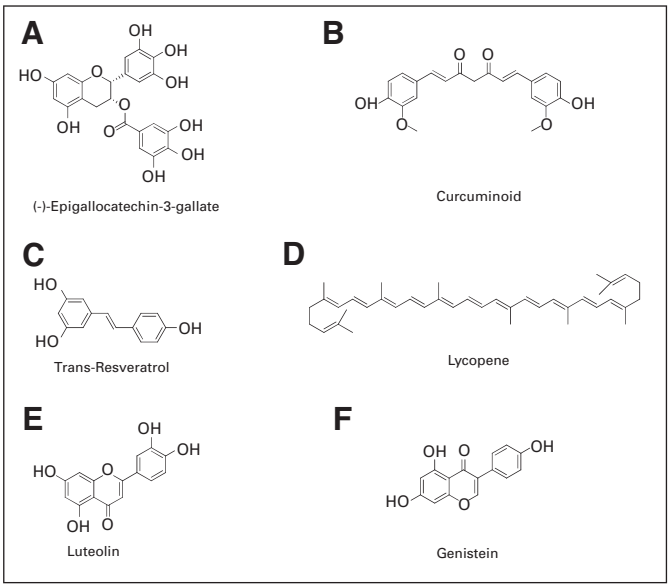


**Fig 1.** Chemical structures of natural chemopreventive agents. Most of these compounds are polyphenols containing multiple phenol rings in their structures.

  

sites.[24-29] In xenograft models, green tea polyphenols (GTP) inhibited tumor growth and suppressed metastasis of metastasis-specific mouse mammary carcinoma 4T1 cells[30] and reduced tumor blood vessel formation in estrogen receptor–negative breast cancer.[31] GTP extract (PPE) reduced the risk of colon carcinogenesis after azoxymethane insult in rats.[32] These results are consistent with previously published results.[33] A case control study at Mayo Clinic in patients with chronic lymphocytic leukemia (CLL) and other low-grade lymphomas who used over-the-counter products containing tea polyphenols showed that four of these patients had evidence of clinical benefit from these products.[34] On the basis of these findings, Mayo Clinic has initiated an National Cancer Institute–sponsored phase I/II clinical trial of decaffeinated green tea extracts for patients with asymptomatic, early-stage CLL.[34] Several phase I trials of healthy volunteers have also been conducted to define the basic biodistribution patterns, pharmacokinetic parameters, and preliminary safety profiles for short-term oral administration of various green tea preparations.[35-37] The consumption of green tea appears to be relatively safe. A phase I study suggested that up to 1 g of green tea solids (equivalent of approximately 900 mL of green tea) could be safely consumed by patients with solid tumors.[38]

EGCG was also found to synergistically increase the efficacy of other drugs in cell culture and animal models. Our own study showed that EGCG synergistically increased the efficacy of erlotinib in head and neck cancer models[39] and could "resensitize" erlotinib-resistant lung cancer cells to erlotinib (J. Cardelli, personal communication, August 2008). Accordingly, a phase I/II trial has been opened exploring the possibility that GTP together with erlotinib will be more effective than erlotinib alone as a second-line treatment approach for patients with non–small-cell lung cancer (NSCLC). EGCG also sensitized the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) –resistant prostate cancer cell line LnCaP to TRAIL-mediated apoptosis.[40] Because of these promising in vitro and in vivo results, several clinical trials are currently ongoing involving green tea alone or in combination with other drugs (www.clinicaltrials.gov).

### *Curcumin*

Curcumin (Fig 1B), isolated from the roots (rhizomes) of the plant *Curcuma longa*, is the major yellow pigment present in turmeric, widely used as a spice. Although turmeric and its chemical components have been used in traditional medicine for thousands of years, it was not until the 1980s that curcumin attracted much attention because of its antitumorigenic activity. Kuttan et al[41] reported that turmeric extract inhibited the growth of Chinese hamster ovary cells, and was cytotoxic to lymphocytes and Dalton's lymphoma cells in vivo. The same group used an ethanol extract of turmeric and curcumin ointment in patients with external cancerous lesions with promising results.[42] Curcumin was shown to interrupt the carcinogenesis process by inhibiting the initiation step or suppressing the promotion and progression stages in animal models.[43,44] Several studies in rodent models demonstrated the inhibitory effects of curcumin in colon carcinogenesis.[45,46] Curcumin has been shown to inhibit the initiation and promotion of chemically induced skin cancer[47] and DMBA-induced oral carcinogenesis.[48] Curcumin also inhibits the growth of cancer cells from multiple organ sites in vitro and in xenograft models by inducing cell cycle arrest and apoptosis.[28,49-51]

Curcumin was also reported to exhibit synergistic chemopreventive effects with other diet-derived polyphenols, such as genistein,[52] green tea,[53] and embelin,[54] and increased the efficacy of many anti-cancer drugs including fluorouracil (FU),[55] vinca alkaloid,[56] vinorelbine, and gemcitabine.[57] Encouraged by the results of these cell culture and animal model studies, curcumin was brought to clinical trials. In a pilot study, 100% of patients showed a decreased polyp number and size after a mean of 6 months of treatment with curcumin and quercetin.[58] Another phase I clinical trial conducted in patients with high risk or premalignant lesions showed that curcumin was safe up to 8 g/day.[59] A pharmacodynamic and pharmacokinetic study of oral Curcuma extract was also carried out in patients with colorectal cancer.[60] Several phase I and phase II clinical trials are now ongoing in multiple centers to study the chemopreventive efficacy of curcumin (www.clinicaltrials.gov).

### *Resveratrol*

Resveratrol (Fig 1C) is a phytoalexin, a major constituent of red wine, and abundant in the grape skin. Table 3 shows the resveratrol content in different wines, juices, and foods. The cardioprotective and chemopreventive activities have brought resveratrol to public and scientific attention. Resveratrol prevented skin cancer development in mice treated with carcinogen and was effective in all three major stages of cancer development.[61] Topical application of resveratrol in mice, both before and after UVB exposure, inhibited skin damage and decreased skin cancer incidence.[62] Prophylactic use of resveratrol reduced the number and size of esophageal, intestinal, and colon tumors.[62,63] Resveratrol prevented the development of DMBA-induced mammary carcinogenesis, inhibited the growth of MDA-MB-231 xenografts, induced apoptosis of prostate cancer cell lines PC-3, DU145, and LNCaP, and suppressed the progression of prostate cancer in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice.[64-68]

In preclinical studies, resveratrol was also effective against a number of other cancer types, including liver, pancreatic, gastrointestinal, lung, and some soft tissue tumors.[28,69-73] Besides its in vitro effects, resveratrol also exerts antitumor activity in vivo and enhances the therapeutic effects of FU in a murine model of liver cancer.[74] It also significantly abrogated benzo[a]pyrene diol epoxide–DNA adduct induction by Benzo[a]pyrene (B[a]P) in the lungs of BALB/c mice.[75] A phase I study showed that even 5 g resveratrol was safe after oral administration.[76] Several clinical trials to study the chemopreventive potential of resveratrol are now ongoing (www.linicaltrials.gov).

**Table 3.** Resveratrol Content in Different Beverages and Foods

| Food and Beverage | Serving Size | Total Resveratrol (mg) |
|---|---|---|
| Muscadine wine | 5 ounce glass | 2.12-6 |
| Red wine | | |
| Global | 5 ounce glass | 0.30-1.07 |
| Spanish | 5 ounce glass | 0.29-1.89 |
| Red grape juice (Spanish) | 5 ounce glass | 0.17-1.30 |
| Rose wine (Spanish) | 5 ounce glass | 0.06-0.53 |
| Pinot noir | 5 ounce glass | 0.06-0.30 |
| White wine (Spanish) | 5 ounce glass | 0.01-0.27 |
| Peanuts | | |
| Raw | 146 g | 0.01-0.26 |
| Boiled | 180 g | 0.32-1.28 |
| Peanut butter | 258 g | 0.04-0.13 |
| Red grapes | 160 g | 0.24-1.25 |

### Lycopene

Lycopene (Fig 1D) is a natural antioxidant that imparts red color to tomatoes, guava, rosehip, watermelon, and pink grapefruit, and is found abundantly in red tomatoes and processed tomato products. Table 4 shows the lycopene content of several dietary sources. Because of its strong antioxidant properties, lycopene has drawn much attention as a cancer preventing agent. Epidemiological studies have shown that high intake of lycopene-containing vegetables is inversely associated with the incidence of certain types of cancer including digestive tract, prostate, and cervix.[77-81] Initial evidence suggests that tomato products may help to prevent disease progression in benign prostate hyperplasia, and increases apoptosis in benign prostate hyperplasia and carcinoma.[82,83] A combination of vitamin E, selenium, and lycopene dramatically inhibited prostate cancer development and increased disease-free survival.[84] A reduction in Dunning *R*-3327H prostate cancer growth rate was observed in rats fed with diets containing broccoli, tomato, lycopene, and a combination of tomato plus broccoli.[85] A phase II randomized clinical trial of lycopene supplementation before radical prostatectomy suggested that lycopene supplementation may decrease the growth of prostate cancer.[86] Another phase II trial suggested that the combination of lycopene with soy isoflavones more strongly stabilized serum prostate-specific antigen (PSA) levels than lycopene alone in men with prostate cancer.[87] In a cell culture model, lycopene strongly inhibited proliferation and induced apoptosis of prostate and breast cancer cell lines.[88,89]

A reduction in the incidence of aberrant crypt foci after lycopene treatment suggested its role in colon cancer prevention.[90] Lycopene also strongly suppressed the growth of lung cancer cells and was found to be more potent than either $\alpha$-carotene or $\beta$-carotene.[91] Administration of lycopene during the postinitiation stage reduces the incidence of lung adenocarcinoma in mice.[92,93] In two large cohort studies, $\alpha$-carotene and lycopene intake were found to be significantly associated with a lower risk of lung cancer.[94] Dietary tomato powder and lycopene supplementations were also found to prevent leiomyoma of the oviduct in the Japanese quail.[95]

### Pomegranate

Pomegranate is widely consumed as both fresh fruit and juice. Although pomegranate fruit was used for various medicinal purposes in ancient times, its chemopreventive property was reported only at the beginning of the current century and has drawn much attention thereafter. The polyphenol-rich fractions from fermented juice, aqueous pericarp extract, or supercritical CO2-extracted seed oil inhibited growth of breast cancer cells,[96] and decreased new blood vessel formation in the chicken chorioallantoic membrane model in vivo.[97] It has also been shown that the pomegranate constituents cyanidin, delphinidin, and petunidin can inhibit the growth of MCF-7 breast cancer cells.[98]

Pomegranate seed oil significantly inhibited skin tumor development and promotion in CD1 mice.[99] Treatment with pomegranate fruit extract was shown to induce cell cycle arrest and apoptosis of human lung carcinoma A549 cells, significantly inhibited A549 tumor growth in nude mice after oral administration,[100] and protected A/J mice from carcinogen-induced lung carcinogenesis.[101]

A number of in vitro and in vivo studies suggest that pomegranate has strong potential for prostate cancer chemoprevention. Pomegranate fruit extract dose dependently inhibited the growth of PC-3 prostate cancer cell lines with the induction of apoptosis, and inhibited CWR22Ru1 xenografts with concomitant decrease in serum PSA levels.[102] Pomegranate extract was found to significantly inhibit the proliferation of LNCaP and human umbilical vein endothelial cells and decrease xenografted prostate cancer size, tumor vessel density, vascular endothelial growth factor (VEGF) peptide levels, and HIF-1$\alpha$ expression in severe combined immunodeficiency mice.[103] A phase II clinical trial conducted to assess the effects of pomegranate juice consumption on PSA progression in men with rising PSA after primary surgery or radiation showed significant increase in mean PSA doubling time.[104] The statistically significant prolongation of PSA doubling time, coupled with corresponding laboratory effects on prostate cancer cell proliferation and apoptosis, warrant further testing in a placebo-controlled study.

**Table 4.** Lycopene Content of Different Foods

| Source | Lycopene Content ($\mu$g/g) |
|---|---|
| Raw tomato | 8.8-42 |
| Tomato juice | 86-100 |
| Tomato sauce | 63-131 |
| Tomato ketchup | 124 |
| Watermelon | 23-72 |
| Pink grapefruit | 3.6-34 |
| Pink guava | 54 |
| Papaya | 20-53 |
| Rosehip puree | 7.8 |
| Apricot | $< 0.1$ |

### Luteolin

Luteolin (Fig 1E) is a flavonoid abundant in several green vegetables, such as broccoli, celery, cabbage, spinach, green pepper, and cauliflower, that exhibits a wide array of pharmacologic properties ranging from anti-inflammation to anticancer effects.[105] Luteolin is capable of inducing anticancer effects by inducing cell cycle arrest, senescence, or apoptosis in oral squamous cancer cells,[106] human esophageal adenocarcinoma cells,[107] lung carcinoma cells,[108] human colon cancer cells,[109] and human hepatoma cells.[110] Luteolin inhibited proliferation and induced apoptosis of prostate cancer cells in vitro and in xenografts[111] and increased the efficacy of cisplatin in gastric cancer cells.[112] In an animal model, the flavonoid also inhibited tumor promotion against DMBA-induced mammary tumors.[113] Luteolin was also found to significantly decrease colon cancer incidence and the number of tumors per rat when administered at the initiation and the postinitiation stages of carcinogenesis.[114] Well-controlled clinical trials are now warranted to evaluate the chemopreventive potential of luteolin in human subjects.

### Genistein

Genistein is a phytoestrogen (Fig 1F) abundant in soybeans and soy products. Multiple lines of compelling evidence from a number of epidemiological studies support an inverse correlation between dietary soy consumption and the risk of prostate,[115] breast,[116,117] and endometrial[118] cancer. The consumption of dietary genistein decreased tumor multiplicity and diminished the incidence of adenocarcinoma in the DMBA model of mammary cancer in rats.[119] The soybean isoflavone mixture consisting of 74% genistein and 21% daidzein was found to inhibit DMBA-induced adenocarcinoma in the

  

prostate and seminal vesicles in rats.[120] Genistein inhibited PCa cell growth in culture by inducing G2/M arrest and apoptosis, inhibited the secretion of PSA, and increased the radiation effect against prostate cancer in cell culture and in orthotopic and metastatic in vivo models.[121,122] Genistein also potentiated the antitumor activity of cisplatin in BxPC-3 tumor xenografts.[123] On the basis of these observations, several early clinical trials either with genistein or soy products have been completed. A pilot study conducted in patients with prostate cancer and rising serum PSA levels suggested that soy isoflavones may benefit some patients with prostate cancer.[124] Another phase II trial was carried out in PSA-recurrent prostate cancer after previous local therapy, which showed a decrease in serum PSA level from 56% to 20%.[125] Other clinical trials are ongoing to study the efficacy of soy products and genistein in cancer prevention (www.clinicaltrials.gov).

### Other Promising Natural Agents

Besides the aforementioned dietary agents, other natural compounds are being actively investigated for their chemopreventive potential, many of which show strong promise. These include ellagic acid, some triterpenes (such as lupeol, betulinic acid, ginsenosides, oleanolic acid), polyunsaturated fatty acids (PUFAs), and ginkolide B. Ellagic acid is an antioxidant polyphenol present in many fruits and vegetables including grapes, strawberries, raspberries, pomegranates, and nuts, that exhibited chemopreventive activity against skin, lung, esophageal, colon, bladder, prostate, and breast cancers.[126,127] Among the triterpenes, lupeol[128] and betulinic acid[129] have been extensively investigated for their chemopreventive activities and showed a broad spectrum of activity against multiple cancer types in both cell culture and animal models. Among the PUFAs, the n-3 PUFAs (linoleic acid and its derivatives) have been extensively studied and exhibited chemopreventive potential in animal models of prostate, breast and colon carcinogenesis, and currently several preventive trials are ongoing against these cancers.[130] *Ginko biloba* extracts and its constitutent ginkolide B have also been studied for their chemopreventive activities and showed some promise against several cancer types.[131,132]

## MOLECULAR TARGETS FOR NATURAL CHEMOPREVENTIVE AGENTS

The cell signaling pathways activated by natural dietary agents are numerous and different for different agents. Moreover, the same compound activates different signaling pathways depending on the cell types. The main signaling pathways activated by dietary chemopreventive agents are illustrated in Figure 2 and Table 1, and described in the following part of this article.

### p53 Family Members

The tumor suppressor p53 plays a pivotal role in controlling the cell cycle, apoptosis, genomic integrity, and DNA repair in response to various genotoxic stresses.[133,134] After activation, p53 can bind to regulatory DNA sequences and activate the expression of target genes, which can be grouped into four categories: cell cycle inhibition (p21, reprimo, cyclin G1, GADD45, 14-3-3), apoptosis (PERP, NOXA, PUMA, p53AIP1, ASPP1/2, Fas, BAX, PIDD), genetic stability (p21, DDB2, MSH2, XPC) and inhibition of angiogenesis (TSP1, Maspin, BAI1, GD-AIF).[135-137] In addition to its transactivation function, p53 can also act as a transrepressor.[138,139] Because of these roles, p53 has been considered a molecular guardian of the genome.

Many natural chemopreventive agents induce cell cycle arrest or apoptosis by activating p53 and its target genes. EGCG induced the expression of p53 and its target p21 and BAX in prostate cancer cells with wild-type p53, but not with inactive p53.[140] EGCG also activated p53 and BAX in breast carcinoma cells.[141] Luteolin also induced cell cycle arrest and apoptosis and increased chemosensitization by activating p53 and its targets p21, BAX, and PUMA (unpublished data from Munna L. Agarwal).[112] In human breast cancer and bladder cancer cells, curcumin was shown to induce apoptosis through p53-dependent BAX induction.[142,143] Curcumin also induced p53-mediated apoptosis by activating its mitochondrial translocation.[144] Huang et al[145] reported that resveratrol induced apoptosis only in cells expressing wild-type p53, but not in p53-deficient cells. Resveratrol activates the expression of p21, p27, BAX, PUMA, MDM2, and cyclin G, all important downstream targets.[146] The dietary chemopreventive agent genistein also activates p53 in multiple cell types. For example, genistein induced G2/M arrest and apoptosis in human malignant glioma cell lines by activating p53 and p21.[147]

Many natural compounds can also induce cell cycle arrest and apoptosis in cells lacking functional p53. In addition to p53, mammalian cells contain two closely related proteins, p63 and p73.[148,149] We have previously reported that EGCG induces apoptosis by activating p73-dependent expression of a subset of p53 target genes including *p21*, *reprimo*, *cyclin G1*, *PERP*, *MDM2*, *WIG1,* and *PIG11*.[150] p73 is also activated in response to EGCG in multiple myeloma cells.[151] Our unpublished results also suggest that the dietary agents curcumin and luteolin activate p73.

### Nuclear Factor-Kappa B

Nuclear factor-kappa B (NF-κB) is a master transcription factor consisting of closely related proteins that generally exist as dimers and bind to a common DNA sequence within the promoters/enhancers of target genes, called the κB site, to promote transcription of target genes through the recruitment of coactivators and corepressors.[152] The NF-κB family of transcription factors consists of five members, p50, p52, p65 (Rel A), c-Rel, and Rel B, which share an N-terminal Rel homology domain responsible for DNA binding and homo- and heterodimerization. NF-κB is activated by free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, γ-radiation, ultraviolet (UV) light, and x-rays and induces NF-κB target genes important for cellular growth and transformation, suppression of apoptosis, invasion, metastasis, chemoresistance, radioresistance, and inflammation.

Most of the natural chemopreventive agents including curcumin,[153,154] resveratrol,[155] EGCG,[156] lycopene,[157] genistein,[158] and luteolin[108] act as potent inhibitors of NF-κB pathways. These compounds may block one or more steps in the NF-κB signaling pathway such as inhibition of the most upstream growth factor receptors that activate the NF-κB signaling cascade, translocation of NF-κB to the nucleus, DNA binding of the dimers, or interactions with the basal transcriptional machinery. The NF-κB target genes influenced by the natural chemopreventive agents include inhibition of Bcl-2 and Bcl-x(L), cyclin D1, matrix metalloproteinases (MMP), and VEGF.

### Activator Protein 1

Activator protein 1 (AP-1) is a group of dimeric basic region-leucine zipper proteins consisting of Jun (c-Jun, JunB, JunD), Fos (c-Fos, FosB, Fra-1, and Fra-2), Maf (c-Maf, MafB, MafA, MafG/F/K,

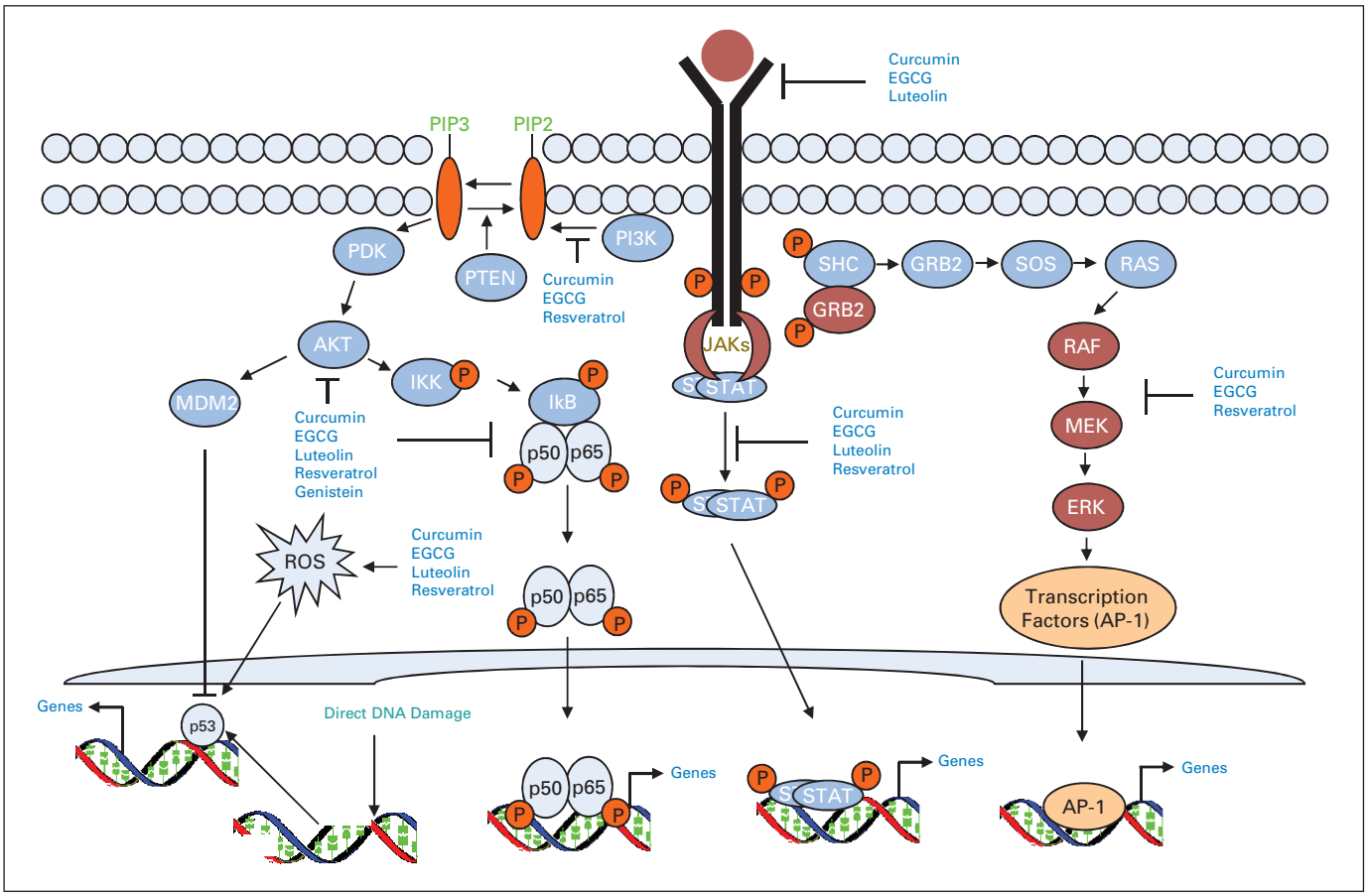


**Fig 2.** Molecular targets of natural chemopreventive agents. The cell signaling pathways activated by natural dietary agents are numerous and different for different agents. Multiple growth factor receptors (epidermal growth factor receptor, insulin-like growth factor 1 receptor, fibroblast growth factor, platelet-derived growth factor receptor) are activated at the cell surface in tumorigenesis. Activation of these receptors activates several downstream signaling pathways. Among these pathways, the Ras-MAPK (such as ERK and JNK) pathways, the JAK-STAT pathways, the PI3K-AKT pathways and the NF-κB pathways are important and are the targets of natural chemopreventive agents. Some natural agents inhibit the receptors at the cell surface either by dephosphorylating them or by inducing their degradation, which ultimately modulate the downstream signaling pathways important for proliferation, angiogenesis, and apoptosis. Inhibition of AKT and ERK signaling by natural agents is quite common, although in many cases this inhibition is the result of growth factor receptor inhibition. Inhibition of NF-κB signaling pathway by interfering with multiple targets of signaling is another common target of natural agents. Many natural compounds generate reactive oxygen species (ROS), which activate p53 family members and induce cell cycle arrest and apoptosis. EGCG, epigallocatechin-3-gallate; ERK, extracellular signal–regulated kinase.

and Nrl), and ATF (ATF2, LRF1/ATF3, B-ATF, JDP1, JDP2) subfamilies.[159] These proteins form either homo- or heterodimers and bind either to AP-1 DNA recognition elements (5‘-TGAG/CTCA-3‘) or to cAMP response elements (5‘-TGACGTCA-3‘) and activate their target genes. In addition to being transcriptional activators, an increasing body of evidence suggests that some of the biologic effects of AP-1 are mediated by gene repression.[159] AP-1–regulated genes include important modulators of invasion and metastasis, angiogenesis, proliferation, differentiation, and survival.[159]

Several natural chemopreventive compounds such as green tea,[160] resveratrol,[161] and curcumin[162] have been reported to suppress AP-1 activation and modulate AP-1 target genes, which is ultimately linked to their chemopreventive potential. Green tea polyphenols inhibit the transcriptional activity of AP-1 in multiple cells types, which is essential for their growth inhibitory effects.[160,163] Pretreatment with resveratrol inhibits TPA-induced AP-1 DNA binding by inhibiting the nuclear expression of c-Jun and c-Fos.[161] Multiple studies also suggest that suppression of AP-1 activity is important for mediating the proapoptotic function of curcumin. Curcumin reduced cell survival of human glioma cells, which was correlated with the inhibition of AP-1 and NF-κB signaling pathways.[162]

### *Signal Transducers and Activators of Transcription Pathway*

A novel signal transduction pathway to the nucleus has been uncovered through the study of transcriptional activation in response to interferon.[164] Activation of various tyrosine kinases leads to phosphorylation, dimerization, and nuclear localization of the signal transducers and activators of transcription (STAT) proteins, binding to specific DNA elements and direct transcription. So far, seven mammalian STAT family members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) have been cloned that share common structural elements. Constitutive activation of STAT3 and STAT5 has been implicated in multiple myelomas, lymphomas, leukemias, and several solid tumors.[165] Several dietary agents, such as green tea,[166] resveratrol,[167] and curcumin,[168] have been implicated to modulate STAT activation in tumor cells. Consumption of GTP substantially inhibited STAT3 expression in TRAMP mice, which may contribute

  

to growth inhibition and apoptosis in this autochthonous mouse prostate cancer model.[169] PPE also inhibits angiogenesis of breast cancer cells by inhibiting the expression of VEGF and MMP-9 via suppressing STAT3 activation.[166] Resveratrol has been reported to modulate interleukin (IL)-6–induced *ICAM-1* gene expression by attenuating STAT3 phosphorylation.[167] Several studies have also demonstrated a role for STAT signaling pathways in curcumin-mediated chemoprevention. Prevention of tumor-induced T-cell apoptosis by curcumin was mediated via STAT5A-induced expression of Bcl-2.[170] Selvendiran et al[110] reported that luteolin inhibited phosphorylation of STAT3, which targeted it for proteosomal degradation and inhibited the expression of cyclin D1, survivin, Bcl-x(L), and VEGF.

### Growth Factors and Their Receptors

Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Several growth factor signaling molecules, such as endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, transforming growth factor, insulin-like growth factor, and colony-stimulating factor are implicated in carcinogenesis. Abnormal growth factor signaling pathways lead to increased cell proliferation, suppression of apoptotic signals, and invasion, contributing to metastasis. As a consequence of growth factor receptor activation, several downstream signaling pathways, most important of which are PI3K-AKT and Ras-MAPK, are activated. These signaling pathways have significant impacts on tumorigenesis and become targets for many natural chemopreventive and chemotherapeutic agents.

Curcumin inhibits the ligand-stimulated activation of EGFR and enhances the growth inhibitory effects of FU and oxaliplatin through EGFR and insulin-like growth factor receptor pathways.[171,172] Decreased expression and activation (tyrosine phosphorylation) of EGFR, HER-2, HER-3, and IGF-1R as well as their downstream effectors such as AKT and COX-2 were observed after curcumin treatment together with FOLFOX (FOLFOX-FU plus oxaliplatin).[172]

Several studies have also demonstrated an essential role for the inhibition of growth factor signaling for the chemopreventive potential of GTP. EGCG treatment inhibited the phosphorylation of EGFR and its downstream targets AKT and ERK in head and neck cancer and potentiated the effects of the tyrosine kinase inhibitor erlotinib.[39,173] EGCG induced internalization and ubiquitin-mediated degradation of EGFR, ultimately undermining EGFR signaling. Adachi et al[174] reported that the inhibitory effect of EGCG on activation of EGFR was associated with altered lipid order in HT29 colon cancer cells. EGCG also inhibits the activation of IGF-1 receptor in human colon cancer cells.[175]

Inhibition of IGF-1-induced activation of IGF-1R and AKT were demonstrated in prostate cancer PC-3 and DU145 cells by luteolin. Inhibition of AKT by luteolin resulted in decreased phosphorylation of its downstream targets, including p70S6K1, GSK-3$\beta$, and FKHR/FKHRL1. Luteolin also inhibited IGF-1–induced activation of EGFR and MAPK/ERK signaling.[176] Growth inhibition and apoptosis of pancreatic tumor cells by luteolin was also associated with the inhibition of EGFR tyrosine kinase activity.[177]

### Host Factors/Immunoprevention

Immunoprevention is an approach to cancer prevention that aims to stimulate the host immune system to eliminate damaged cells before tumor onset. It is now established that the absence of functional T cells or T cell–derived cytokines, such as interferon (IFN)-$\gamma$, enhances the onset of spontaneous and carcinogen-induced tumor.[178] Thus, activation of functional T cells or production of several cytokines, such as INF-$\gamma$ or IL-12, might contribute to cancer prevention. Several natural agents have been found to modulate certain host factors, which were important for their chemopreventive potential. GTP prevented UV radiation–induced skin cancer by inducing IL-12–dependent DNA repair, activating cytotoxic (CD8+) T cells, inducing tumor cell apoptosis, and inhibiting angiogenic factors.[179,180] EGCG also enhanced CD8+ T cell–mediated antitumor immunity induced by DNA vaccination.[181] Tumor-induced immunodepletion caused apoptosis of thymic CD4+/CD8+ single/double positive cells as well as loss of circulating CD4+/CD8+ T cells. The administration of curcumin to tumor-bearing animals resulted in restoration of progenitor, effecter, and circulating T cells.[170] Genistein modulated immune responses and increased host resistance to B16F10 tumor, which may be related to increases in the activities of cytotoxic T cells and natural killer cells.[182] Resveratrol enhanced IFN-$\gamma$ expression in CD8+ T cells, leading to immune stimulation, and suppressed the CD4+CD25+ cell population, rendering the peritumoral microenvironment unfavorable to tumors in tumor-bearing mice.[183]

In addition to the tumor cells themselves, host components, including the stroma, an expanding vasculature, and often chronic inflammation, contribute to tumor growth. Thus, targeting these host factors might delay tumor progression. Some natural agents target these host factors. EGCG inhibited viability, capillary tube formation, and migration of human umbilical vein endothelial cells and inhibited angiogenic and metastasis markers (von Willebrand factor, VEGF, CD31, MMP-2, MMP-7, MMP-9, and MMP-12) in a xenograft model of pancreatic cancer.[184] Luteolin inhibited vascular VEGF-induced angiogenesis and tumor growth in vivo in a murine xenograft model.[185] A number of studies also suggest that angiogenesis is the target of chemoprevention by curcumin.[186,187]

## CONCLUSION AND FUTURE DIRECTIONS

Chemoprevention research has gained momentum through the US Food and Drug Administration approval of tamoxifen and raloxifene for breast cancer risk reduction. Various epidemiological and preclinical findings and the results of several early clinical studies convincingly argue for a definitive role of selected dietary products in the prevention and treatment of cancers. Many of these agents target multiple signal transduction pathways, which vary widely depending on cancer origin. The key challenge to researchers is how best to use this information for effective cancer prevention in populations with different cancer risks. Moreover, low potency and poor bioavailability of dietary agents pose further challenges to scientists. The introduction of synthetic analogs of natural compounds may be a solution for these potency and bioavailability limitations. For example, the synthetic curcumin analog EF24 exhibited approximately 10-fold greater potency than natural curcumin.[154] Some natural compounds have exhibited synergism with established chemopreventive agents or with other natural compounds. Since drug-associated toxicity remains a significant barrier for currently available chemotherapeutic and chemopreventive drugs, using natural compounds (which have better safety profiles) as adjuvant therapy with current chemotherapeutic agents may help to mitigate drug-associated toxicities. For example,

genistein was found to sensitize prostate cancer to radiation in animal studies[122] and a recent clinical trial suggested that soy isoflavones could prevent radiation-induced bladder and bowel adverse effects and erectile dysfunction.[188] Because of the advances in our understanding of multistep and field carcinogenesis, the introduction of new technologies for screening and early detection, and the emergence of promising molecularly targeted agents, prevention and therapy are beginning to converge at the level of early-phase clinical trials.[189] The future full convergence of prevention-therapy drug development will open new avenues for natural compounds in reducing the public health impact of major cancers. However, more preclinical studies and clinical trials are certainly needed to validate the usefulness of these agents either alone or in combination with existing therapies.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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