NUTRITION REVIEWS

Special Article

Dietary phytochemicals in cancer prevention and therapy: a complementary approach with promising perspectives

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The population is aging. Over the coming years, the incidence of age-related chronic diseases such as cancer is expected to continue to increase. Phytochemicals, which are non-nutritive chemicals found in plants and food, have emerged as modulators of key cellular signaling pathways exerting proven anticancer effects. The challenge now is to develop personalized supplements comprised of specific phytochemicals for each clinical situation. This will be possible once a better understanding is gained of the molecular basis explaining the impact of phytochemicals on human health. The aim of the present literature review is to summarize current knowledge of the dietary phytochemicals with proven antitumor activity, with a special emphasis placed on their molecular targets. Also discussed are the limits of existing research strategies and the future directions of this field.

INTRODUCTION

The number of people over the age of 60 years is estimated to be increasing twice as fast as it did just 4 years ago. Longer life expectancy is associated with a high risk of nutrition-related chronic diseases such as obesity, cardiovascular disease (CVD), type II diabetes, or cancer. These conditions are approaching epidemic status in many parts of the world,[1,2] and nutrition is the most important non-genetic contributor to them.[3] Indeed, several food components have been identified as promoters or inhibitors of these diseases. In this sense, phytochemicals constitute the major group with beneficial effects. The challenge now is to develop dietary supplements that can help prevent or delay the onset of nutrition-related diseases in specific population groups. This will be possible once a better understanding is gained of the molecular basis for the ways in which these components affect human health, as well as of the specific populations or conditions to which they apply. In this context, the following areas of research are gaining special relevance: 1) application of the -omics technologies (nutrigenomics, nutriproteomics, or nutrimetabolomics) to gain a deeper understanding of the role of dietary components in biological processes; 2) analysis of the impact of dietary components on epigenetics and the relationship with human health; 3) biomarker identification and validation to monitor the effect of dietary components on chronic diseases; and 4) clinical intervention studies in specific population groups, based on existing molecular scientific evidence.

The present literature review summarizes current knowledge of the effect of dietary phytochemicals in cancer prevention and treatment, with a particular focus on their molecular targets; it also addresses existing research strategies for phytochemical application and future directions of this field. To that end, various databases were consulted, mainly within a timeframe covering 1994–2012. The following key words were used in the initial search strategy: phytochemical, plant, diet, natural product, cancer, tumor, and chemoprevention; the search was augmented by a profound exploration of each specific phytochemical compound.

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PHYTOCHEMICALS APPLIED TO CANCER PREVENTION AND THERAPY

Phytochemicals are non-nutritive compounds with disease-preventive properties that are found in plants. Their health-promoting effects have been conventionally revealed by different epidemiological studies, which initially found a consistent relationship between abundant consumption of fruits and vegetables and reduction in the risk of developing several diseases, including various types of cancer.[4] Subsequent studies led to the identification of specific dietary phytochemicals possessing anticancer properties (Table 1).

Cancer is one of the leading causes of death worldwide. It has been reported that a significant proportion of cancer patients use herbs as complementary therapies,[5] and many of the commonly used antitumor drugs are derived from natural compounds, which are either directly extracted from plants or other natural sources or chemically derived from naturally occurring compounds.[6] The cases of camptothecin (from *Camptotheca acuminate* Decne), vinblastine and vincristine (from *Catharanthus roseus*), or paclitaxel (from *Taxus brevifolia*) are some of the most successful examples of plant-based anticancer agents.[7]

It has also been estimated that one-third of all cancer deaths are preventable by lifestyle changes including appropriate nutrition.[8] Even though promising results have been found in vitro in several cell systems, no mechanism-based preclinical studies have been performed to date; this lack of preclinical data led to the failure of the first large-scale clinical studies of phytochemicals performed in the 1990s.[9,10] Because phytochemicals may display efficient and selective effects explained by their specific molecular targets, strategies for researching them should mimic those used in the development of new targeted antitumor drugs. The approach might begin with the selection of phytochemical candidates for cancer prevention or therapy based on the results of screening assays, such as antiproliferative activity assays, cell-transformation assays, and antitumorigenic activity assays (Figure 1). The next step would be the identification of molecular target candidates for select compounds using the -omics technologies, among others, to identify the specific population and patient groups that might benefit from the selected compounds. The strategy would be further validated using animal models and might also benefit from computation of molecular docking to determine binding interactions. Finally, specific clinical trials would have to be designed that consider the targeted pathways that are altered in patients with specific types of cancer. Following this approach, success expectancy in the evaluation of phytochemicals as antitumor agents will be increased significantly.

According to the book *Fundamentals of Cancer Prevention*, cancer prevention research can be categorized into three main types: primary (mainly avoidance of carcinogens), secondary (detection and elimination of premalignant lesions), and tertiary (preventing cancer recurrence, tumor progression, and disease-related complications).[11] Phytochemicals are able to contribute to cancer prevention by acting at different stages of the carcinogenic process, from tumor initiation through all the hallmarks of cancer,[12,13] i.e., cell proliferation, apoptosis, invasion and metastasis, angiogenesis, immortality, inflammation, immunity, genome instability and mutation, and cell energetics and metabolism (Figure 2).[14–24]

MOLECULAR TARGETS OF PHYTOCHEMICALS IN CANCER CARE

Initial in vitro studies found that phytochemicals may help prevent the tumorigenic action of carcinogens, blocking their mutagenic activity and suppressing cell proliferation.[25] In addition, it was found that phytochemicals protect against lipid peroxidation[26] and modulate immune[27] and inflammatory[28] responses. These effects of phytochemicals, in combination with their lack of toxicity, make them potentially efficient agents in the fight against cancer. However, each compound's mechanism of action and its effectiveness in each type of cancer must be studied in order to properly apply the compound to the appropriate clinical situation.

The term "nutritional genomics" was coined to describe work at the interface of plant biochemistry, genomics, and human nutrition.[29] It is now known that certain nutrients strongly influence genetic processes and metabolic pathways through interactions with specific molecular targets,[30–32] including those relevant to the process of carcinogenesis.[33] The main cancer-related biological activities attributed to phytochemicals and, accordingly, the principal molecular targets of these compounds are summarized in Table 2.

MAIN PHYTOCHEMICALS STUDIED FOR INTEGRATIVE CANCER CARE

Dietary phytochemicals can be classified depending on their chemical structure, botanical origin, biological properties, biosynthesis, etc. General classifications and key data fields were recently reported summarizing the available specific phytochemical databases,[34] including online databases of agents and diets ranked by efficacy in experimental studies of chemoprevention.

In this review, a general classification is proposed that properly summarizes the dietary phytochemicals

Table 1 **Classification and sources of dietary phytochemicals possessing antitumor activities.**

Group, subgroup, and functional component	Dietary source
Polyphenols	
Phenolic acids	
Anacardic acid	Cashew (*Anacardium occidentale*)
Caffeic acid	Coffee, olive oil
Chlorogenic acid	Coffee
Ellagic acid[a]	Pomegranate, berries
Gallic acid	Green tea
Rosmarinic acid	Rosemary
Flavonoids	
Apigenin	Parsley and celery
Butein	Indian cashew (*Semecarpus anacardium*)
Catechin gallate	Green tea
Cyanidin	Wild blueberry (*Vaccinium myrtillus*)
Daidzein	Soybean
Delphinidin	Cranberry, strawberry, pomegranate
(-)-Epigallocatechin-3-gallate[a]	Green tea
Epicatechin gallate	Green tea
Fisetin	Strawberry, apple
Genistein[a]	Soybean
Isoliquiritigenin	Licorice (*Glycyrrhiza glabra*)
Kaempferol	Tea, broccoli, grapes
Licochalcone-A	Licorice (*Glycyrrhiza glabra*)
Luteolin[a]	Parsley, celery, pepper, dandelion
Myricetin	Grapes, onions, tea
Naringenin	Grapes, citrus
Quercetin[a]	Onion, apple, broccoli
Silibinin	Milk thistle (*Silybum marianum*)
Tangeretin	Citrus fruits
Xanthohumol	Beer (from *Humulus lupulus*)
Stilbenes	
Piceatannol	Grapes
Pterostilbene	Blueberries
Resveratrol[a]	Red grapes, berries, plums, peanuts
Curcuminoids	
Bisdemethoxycurcumin	Turmeric (*Curcuma longa*)
Curcumin[a]	Turmeric (*Curcuma longa*)
Demethoxycurcumin	Turmeric (*Curcuma longa*)
Terpenoids	
Carotenoids	
Crocetin	Saffron (from *Crocus sativus*)
Lutein	Spinach
Lycopene[a]	Tomato, watermelon, red grapes
β-carotene	Carrots
Non-carotenoid terpenoids	
Anethole	Sweet fennel (*Foeniculum vulgare*)
Bisacurone	Turmeric (*Curcuma longa*)
Carnosol[a]	Rosemary
Ginsenoside Rg3	Ginseng
Limonene	Citrus fruits, cherries, grapes
Lupeol	Mango, strawberry
Ursolic acid	Rosemary, basil
Organosulfur compounds	
Glucosinolate-derived organosulfur compounds	
Allyl isothiocyanate	Cruciferous vegetables
Benzyl isothiocyanate	Cruciferous vegetables
Indole-3-carbinol	Cruciferous vegetables
Phenethyl isothiocyanate	Cruciferous vegetables
Sulforaphane[a]	Cruciferous vegetables
Allyl sulfur compounds	
Allicin	Garlic
Allyl mercaptan	Garlic
Diallyl disulfide[a]	Garlic
Diallyl sulfide	Garlic
Diallyl trisulfide	Garlic
S-Allylcysteine	Garlic
Phytosterols	
(Non-classified)	
β-Sitosterol[a]	Nuts, grains, seeds

[a] Phytochemicals with anticancer properties that are representative of their group/subgroup and discussed in this review.

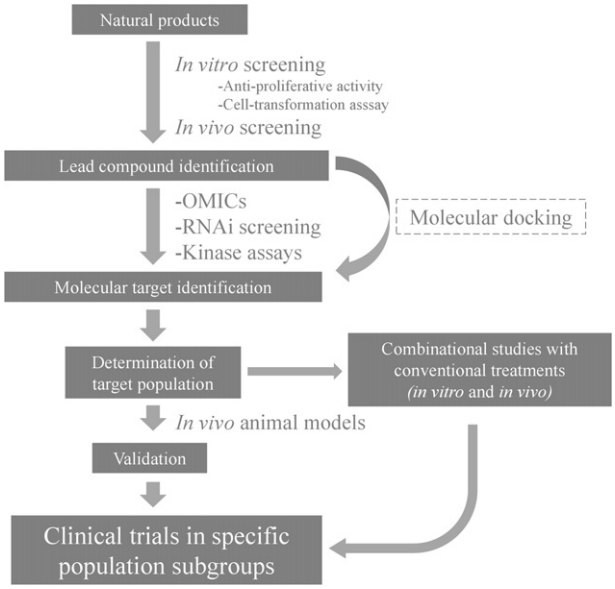

Figure 1 **Proposed process for developing new targeted antitumor agents from natural products.**

with antitumor activities. The key phytochemicals from each group and the pathways and cancer subtypes they target are shown in Table 3.

POLYPHENOLS

Polyphenols are plant secondary metabolites that contain one or more hydroxyl groups attached to a benzene ring in their chemical structure.[35] More than 8,000 different polyphenols from edible plants are present in the human diet,[35] and long-term diets rich in plant polyphenols showed protection against diabetes, osteoporosis, CVD, neurodegenerative disease, and cancer in epidemiological studies.[36] They may be classified into different groups according to their number of phenol rings and the structure that links these rings.[36] Several polyphenols showed the capacity to block initiation of the carcinogenic process and to suppress promotion and progression of cancer[37]; in this context, the groups of phenolic acids, flavonoids, stilbenes, and curcuminoids are the most important.

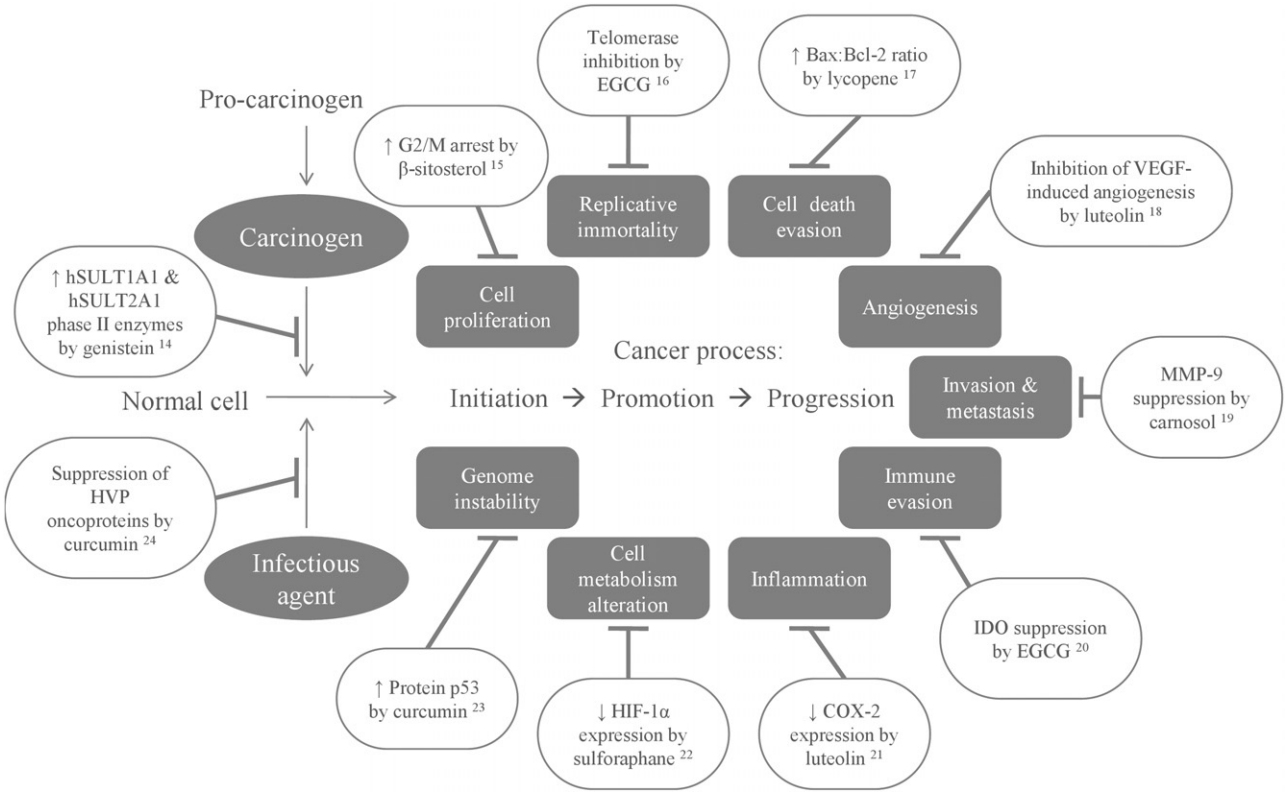

Figure 2 **Stages of the cancer process inhibited by phytochemicals.** The multiple molecular targets of the phytochemicals with antitumor activity indicate they are capable of interfering in every stage of cancer development. Illustrated here is one example for each stage.

Table 2 **Antitumor activities and molecular targets of phytochemicals.**

Activity	Molecular targets[a]
Anti-inflammatory	IL-1RI, CCL2, NF-kB, IKK, COX-1, COX-2, PGE_2, iNOS, PPARγ
Antioxidant/carcinogen metabolism	hSULT1A1, hSULT2A1, UGT1A, QR, GST, Nrf2, ARE, CYP1A1, metallothionein
Antiproliferative	
Cell cycle	Aurora-A, Cdc2, Cdc25a, Cyclin B1, Cyclin D1, E2F4, RB, FoxM1, Skp2, p16, p21, p27
Growth factor signaling	EGFR, IGF-I, IGF-II, IGF-1R, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-5, ERK, JNK/c-Jun, p38, Akt, mTOR, PI3K, PTEN, 4E-BP1, G3BP1, Ras, ErbB2
Hormone signaling	AR, ERα, ERβ
Non-classified targets	FOXO, C/EBPα, BTG3, PHB, Pin1, PKCα, PKCδ, RARα, RARβ, VDR, telomerase
Apoptosis	Apaf-1, GDF15, BAD, Bax, Bcl-2, Bcl-xL, Bcl-xS, caspase 3, caspase 8, caspase 9, caspase 10, cIAP1, XIAP, DR5, Fas, Hsp70, survivin
Cell metabolism modification	SphK1, HIF-1α, FASN, HMG-CoA reductase, AMPK, PFKFB4
Drug resistance inhibition	MRP5, BCRP, P-glycoprotein
Genome stability	ATM/Chk1, BRCA1, BRCA2, p53, topoisomerase-II
Inhibition of immune evasion	IL-10, IDO, TGFβ
Inhibition of invasion, metastasis & angiogenesis	E-cadherin, CXCL1, CXCL2, CXCL12, CXCR4, EMMPRIN, connexin 43, KAI1, c-Met, endoglin, VEGF/VEGFR, vimentin, ZEB1, MMP-2, -7, -9, PAK1
Stemness inhibition	Gli1, WIF-1, Wnt/β-catenin, Notch-1, Notch-2, Twist-1

[a] Additional information and references are available online in the Supporting Information (Table S1a).

Abbreviations: 4E-BP1, 4E-binding protein 1; AMPK, AMP-activated protein kinase; Apaf-1, apoptotic peptidase activating factor 1; AR, androgen receptor; ARE, antioxidant response element; ATM/Chk1, ataxia–telangiectasia-mutated/check point kinase-1; BAD, BCL2-associated agonist of cell death; Bax, BCL2-associated X protein; Bcl-2, -xL, -xS, B-cell lymphoma protein-2, -xL, -xS; BCRP, breast cancer resistance protein; BRCA-1, -2, breast cancer-1, -2; BTG3, B-cell translocation gene 3; C/EBPα, CAAT-enhancer binding protein α; CCL2, CC motif ligand 2; Cdc2, cyclin-dependent kinase 1; Cdc25a, cell division cycle 25 homolog A; cIAP-1, -2, cellular inhibitor of apoptosis protein-1, -2; COX-1, -2, cyclooxygenase-1, -2; CXCL-1, -2, -12, chemokine (C-X-C motif) ligand-1, -2, -12; CXCR4, chemokine (C-X-C motif) receptor 4; CYP1A1, cytochrome P450 1A1; DR5, death receptor 5; E2F4, E2F transcription factor 4; EGFR, epidermal growth factor receptor; EMMPRIN, extracellular matrix metalloproteinase inducer; ERK, extracellular signal-regulated kinase; ER-α, -β, estrogen receptor -α, -β; FASN, fatty acid synthase; FoxM1, forkhead box M1; FOXO, forkhead transcription-factor O; G3BP1, GTPase activating protein (SH3 domain) binding protein 1; GDF15, growth differentiation factor 15; Gli1, glioma-associated oncogene 1; GST, glutathione transferase; HIF-1α, hypoxia inducible factor 1, alpha; HMG-CoA, hydroxy-methylglutaryl-coenzima A; Hsp70, heat shock 70 kDa protein; hSULT1A1, human simple phenol sulfotransferase; hSULT2A1, human dehydroepiandrosterone sulfotransferase; IDO, indole amine 2,3-dioxygenase; IGF-1R, insulin-like growth factor -1 receptor; IGFBP-1, -2, -3, -5, insulin-like growth factor binding protein -1, -2, -3, -5; IGF-I, -II, insulin-like growth factor -I, -II; IKK, Ikappa beta kinase; IL-10, interleukin 10; IL-1RI, IL-1 receptor type I; iNOS, inducible nitric oxide synthase; JNK, c-Jun NH(2)-terminal kinase; KAI1, kangai 1; MMP-2, -7, -9, matrix metallopeptidase-2, -7, -9; MRP5, multi-drug resistance-associated protein 5; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor-kappa B; Nrf2, nuclear factor erythroid 2 related factor 2; PAK1, p21-activated protein kinase 1; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; PGE_2, prostaglandin-E2; PHB, prohibitin; PI3K, phosphatidylinositol 3-kinase; Pin1, peptidyl prolyl cis/trans isomerase; PKC-α, -δ, protein kinase C -α, -δ; PPARγ, peroxisome proliferator-activated receptor-gamma; PTEN, phosphatase and tensin homolog; QR, quinone reductase; RAR-α, -β, retinoic acid receptor-α, -β; RB, retinoblastoma; Skp2, S-phase kinase-associated protein 2; SphK1, sphingosine kinase 1; TGFβ, Transforming growth factor-β; UGT1A, uridine 5′-diphosphate-glucuronosyltransferase 1A; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; WIF-1, Wnt inhibitory factor-1; XIAP, X-linked inhibitor of apoptosis; ZEB1, zinc finger E-box binding homeobox 1.

Phenolic acids

Phenolic acids account for 30% of dietary polyphenols.[38] They contain in their structure a phenolic ring and a carboxylic acid function, and those derived from hydroxybenzoic or hydroxycinnamic acids are the most common in plants.[39] Among them, ellagic acid is one of the most studied in relation to cancer therapy.

Ellagic acid. Ellagic acid, a dimer of gallic acid (hydroxybenzoic acid derivative),[40] is the main polyphenol in pomegranate.[41] It is responsible for more than 50% of the antioxidant activity of pomegranate juice and for the beneficial effects of pomegranate in atherosclerosis and cancer.[41] It is usually present in foodstuffs as ellagitannins or conjugated with a glycoside moiety, such as glucose,[41] and released during digestion and metabolism.[42] Moreover, it is metabolized by human intestinal microbiota to yield urolithins A and B, which reportedly possess estrogenic and antiestrogenic activities.[43] It has mainly been studied in relation to prostate cancer, showing antiproliferative activity,[41] but it was also found to induce

Table 3 **Representative anticancer phytochemicals, their main target pathways, and the cancer subtypes they have been reported to inhibit.**

Phytochemical	Target pathways[a]	Cancer subtypes[a]
Ellagic acid	Apoptosis, cell cycle, hormone signaling, IGF signaling, NF-kB signaling, p53 signaling, telomerase	Bl (cells), Br (cells), Ce (cells), Co (cells), Pa (cells), Pr (cells)
EGCG	Antioxidant/detoxification enzymes, apoptosis, cell cycle, cytokine signaling, folate biosynthesis, Hedgehog signaling, hormone signaling, JAK/Stat signaling, lipid metabolism, mTOR signaling, multidrug resistance, NF-kB signaling, PI3K/Akt signaling, telomerase, VEGF signaling, Wnt signaling	Ad (cells), ATC (cells), Bl (rats), Br (cells), Ce (cells), Co (mice), Cs (mice), GIST (cells), HCC (mice), HNSCC (cells), Lu (cells), Or (cells), Ov (cells), Pa (cells), Pr (mice), Sk (cells), St (cells)
Genistein	Akt signaling, antioxidant/detoxification enzymes, apoptosis, cell cycle, cytokine signaling, EMT signaling, Gap junction, Hedgehog signaling, hormone signaling, MAPK signaling, NF-kB signaling, p53 signaling, telomerase, VEGF signaling, Wnt signaling	Bl (mice), Br (cells), Ce (cells), Gl (cells), OSCC (cells), Pa (cells), Pr (mice), R (cells), Th (cells)
Luteolin	Akt signaling, apoptosis, cell cycle, EMT signaling, hormone signaling, IGF signaling, lipid metabolism, NF-kB signaling, VEGF signaling	Br (cells), Co (cells), HCC (cells), Lu (cells), NPC (cells), OSCC (mice), Ov (cells), Pa (cells), Pr (mice), St (cells)
Quercetin	Antioxidant/detoxification enzymes, apoptosis, cell cycle, ErbB2 signaling, Gap junction, Hedgehog signaling, hormone signaling, IGF signaling, lipid metabolism, NF-kB signaling, PI3K/Akt signaling	Br (mice), Ce (cells), Co (rats), Gl (cells), HCC (cells), Lu (humans), Me (cells), Ov (cells), Pr (mice), Th (cells)
Resveratrol	Akt signaling, apoptosis, cell cycle, ErbB2 signaling, hormone signaling, lipid metabolism, NF-kB signaling, Notch signaling, p53 signaling, PI3K/Akt signaling, telomerase	Bl (mice), Br (mice), Ce (cells), Co (cells), HNSCC (cells), HCC (cells), MTC (cells), NSCLC (cells), Ov (mice), Pa (mice), Pr (cells), R (cells), Th (cells), St (cells)
Curcumin	Akt/mTOR signaling, antioxidant/detoxification enzymes, apoptosis, cell cycle, cytokine signaling, Hedgehog signaling, IGF signaling, MAPK signaling, multidrug resistance, NF-kB signaling, Notch signaling, p53 signaling, VEGF signaling, Wnt signaling	Bl (cells), Br (cells), Ce (cells), Cg (cells), Co (humans), Es (cells), Ew (cells), Gl (mice), HCC (mice), HNSCC (cells), Lk (cells), Lu (mice), Mb (mice), Or (cells), Os (cells), Ov (cells), Pa (mice), Pr (mice), SSCC (mice), St (cells), UL (cells)
Lycopene	Akt signaling, antioxidant/detoxification enzymes, cell cycle, Gap junction, IGF signaling, lipid metabolism, Ras signaling	Br (cells), Co (mice), En (cells), Lu (cells), Or (cells), Pa (humans), Pr (humans)
Carnosol	Antioxidant/detoxification enzymes, AMPK signaling, apoptosis, hormone signaling, MAPK signaling, multidrug resistance, NF-kB signaling	Br (rats), Co (cells), Lk (cells), Me (cells), NSCLC (cells), Ov (cells), Pr (mice)
Sulforaphane	Apoptosis, cell cycle, EMT signaling, hormone signaling, telomerase, Wnt signaling	Br (cells), Ce (cells), Co (mice), HCC (cells), NSCLC (cells), Ov (cells), Pa (mice), Pr (mice), TSCC (cells)
Diallyl disulfide	Antioxidant/detoxification enzymes, apoptosis, cell cycle, ERK signaling, JNK/c-Jun signaling, NF-kB signaling, p53 signaling	Br (cells), Ce (cells), Co (cells), Lk (mice), Me (cells), Nb (cells), NSCLC (cells), Pr (cells), St (cells)
β-sitosterol	Apoptosis, Gap junction, lipid metabolism, MAPK signaling, multidrug resistance	Br (cells), Co (rats), Fs (cells), Lk (cells), Pr (cells), St (cells)

[a] Additional information and references are available online in the Supporting Information (Table S1b).
Abbreviations: Ad, adrenal cancer; ATC, anaplastic thyroid carcinoma; Bl, bladder cancer; Br, breast cancer; Ce, cervical cancer; Cg, cholangiocarcinoma; Co, colorectal cancer; Cs, chondrosarcoma; EMT, epithelial-mesenchymal transition; En, endometrial cancer; Es, esophageal cancer; Ew, Ewing sarcoma; Fs, fibrosarcoma; GIST, gastrointestinal stromal tumor; Gl, glioma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; JAK/Stat, Janus kinase/signal transducer and activator of transcription; Lk, leukemia; Lu, lung cancer; MAPK, mitogen-activated protein kinase; Mb, medulloblastoma; Me, melanoma; MTC, medullary thyroid carcinoma; Nb, neuroblastoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small-cell lung carcinoma; Or, oral cancer; Os, osteosarcoma; OSCC, oral squamous cell carcinoma; Ov, ovarian cancer; Pa, pancreatic cancer; Pr, prostate cancer; R, renal cancer; Sk, skin cancer; SSCC, skin squamous cell carcinoma; St, stomach cancer; Th, thyroid cancer; TSCC, tongue squamous cell carcinoma; UL, uterine leiomyosarcoma.

cell cycle arrest, antiproliferative effect, and apoptosis on cells from several cancer types (Table 3) at concentrations that are within or below those found in plasma after oral intake (5×10^{-8}–5×10^{-5} M).[44] These effects were principally related to the inhibition of NF-κB[41] and IGF-II,[45] the induction of p53/p21 expression, and the modulation of pro- and anti-apoptotic proteins.[41]

Flavonoids

Flavonoids represent the 60% of dietary polyphenols with more than 4,000 varieties. Their chemical structure consists of two benzene rings linked by three carbon atoms that form an oxygenated heterocycle.[38] They are classified into seven groups: flavones, flavonols, flavanones, isoflavones, catechins, anthocyanins, and chalcones.[46] They have the potential to protect from viral infections as well as several diseases, such as diabetes and cardiovascular, inflammatory, and neurological diseases.[47] Moreover, the results of many in vitro, in vivo, and epidemiological studies suggest flavonoids have a protective effect against a wide range of cancer types.[38]

(-)-Epigallocatechin-3-gallate (EGCG). This is the major catechin found in green tea (*Camellia sinensis*).[48] The frequent consumption of green tea has been related to several health benefits, and it is now recognized as the most effective cancer-preventive beverage. Shimizu et al.[49] showed that consumption of 10 Japanese-size cups of green tea daily, supplemented with green tea extract tablets, significantly decreased recurrence of colorectal polyps in humans. It is generally assumed that the antitumor effects of green tea are mediated by its polyphenols and, concretely, by the flavonoid EGCG.[48] The antitumor efficacy of EGCG was confirmed on multiple cancer types (Table 3), including less common tumors, such as anaplastic thyroid carcinoma, which is one of the most aggressive malignancies. The chemopreventive activity required in most cases a concentration of EGCG that is higher than that achieved in plasma after two or three cups of tea (0.1–0.3 μM).[50] Therefore, alternative methods of administration may be necessary in order to increase its biodisponibility in some situations. The numerous pathways targeted by EGCG are reported in Table 3 and are related to the following processes: cancer cell proliferation, apoptosis, immune evasion, invasion, metastasis, and angiogenesis. The antiangiogenic effect occurs via activity on tumor-associated endothelial cells and endothelial progenitor cells,[51] as well as inhibition of the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis.[52] Recently, EGCG was reported to inhibit hepatocyte growth factor (HGF)/c-Met signaling in cells from several types of cancer,[53–56] thus inhibiting the cells' potential to invade and metastasize. A wide description of the molecular mechanisms of EGCG was previously reported by Khan et al.[48] Combinations with antitumor drugs, such as raloxifen[57] or bortezomib,[58] as well as other phytochemicals, such as quercetin,[59] resulted in a potentiation of the antitumor effect in vitro. Regarding the inhibition of immune evasion, EGCG downregulated the expression of indoleamine 2,3-dioxygenase, a protein involved in the antiproliferative and apoptotic effect on T cells in the tumor microenvironment.[20] The wide range of antitumor effects demonstrated that EGCG is a potential tool for cancer prevention and therapy, both alone and in combination with other antitumor drugs or phytochemicals.

Genistein. This is the predominant isoflavone of soybean. Consumption of soy, the principal dietary source of isoflavones, appears to be responsible for the lower relative incidence of prostate and breast cancers in Asian compared to Western countries.[60] Because genistein possesses weak estrogenic activity, it is included in the group of phytoestrogens. Its binding affinity is 4% for ERα and 87% for ERβ compared to estradiol.[60] Studies of genistein have focused mainly on hormone-related cancers, such as prostate and breast cancer, but inhibitory effects on other tumor types have also been observed (Table 3). Moreover, genistein has shown other beneficial health effects, such as decreasing CVD incidence, preventing osteoporosis, relieving postmenopausal problems, and decreasing body mass and fat tissue. The antitumor activities of genistein include effects on prevention and progression.[60] Regarding prevention, it inhibits 7,12-dimethylbenz-[alpha] anthracene (DMBA)-induced genotoxicity.[61] Moreover, it exerts antitumor effects in several cancer types in vitro and in vivo (Table 3), and a concentration near 50 μM is required to significantly inhibit the proliferation of most tumor cell types. Taking into account that normal average plasma concentrations of genistein in Japanese men is 0.28 μM,[62] the intake of supplements, or administration via other routes, would be necessary to achieve the chemopreventive effect. The pathways underlying the antitumor effects of genistein are included in Table 3. A detailed description of the multitargeted effect of genistein in tumor cells was reported previously by Banerjee et al.[60] Genistein showed a synergistic effect in vitro in combination with chemotherapeutic drugs, such as cisplatin, erlotinib, doxorubicin, bleomycin, docetaxel, and gemcitabine,[60] and with phytochemicals, such as indole-3-carbinol.[63] Docetaxel and gemcitabine synergized with genistein in tumor models as well. Furthermore, genistein enhanced the effect of radiotherapy.[60] The combination of genistein with tamoxifen, however, showed controversial results. Some studies concluded

that genistein may interfere with the inhibitory effects of tamoxifen on tumor growth,[64] while others reported a synergistic effect of the combination on breast cancer inhibition.[65,66] Most epidemiological, in vivo, and in vitro studies demonstrated that genistein inhibits carcinogenesis,[67] but there are some exceptions. Genistein increased the growth of human breast cancer cells in a postmenopausal animal model with low plasma estradiol concentrations,[68] and its use in breast cancer is sometimes questioned because of genistein's estrogen-like effects and its possible interaction with tamoxifen.[69]

Luteolin. This is one of the most effective antitumor flavones, and is found in many medicinal herbs and vegetables such as parsley, celery, pepper, and dandelion. Plants rich in luteolin were used in traditional Chinese medicine to treat hypertension, inflammatory disease, and cancer.[70] Diets rich in flavones correlate with a lower risk of breast cancer, and luteolin intake has been reported to significantly decrease the incidence of ovarian cancer.[71] The concentration of luteolin in standard daily nutrition is relatively low (<1 mg/day), but it is available at low cost in higher amounts from plants that are not traditionally consumed, such as *Reseda luteola*.[71] Luteolin is usually glycosylated in plants, and it is released from dietary components during absorption.[70] It inhibits the proliferation of various tumor cell types, including nasopharyngeal and oral squamous cancers (Table 3). At the molecular level, it inhibits several tumor-related signaling pathways such as Akt and NF-κB pathways (Table 3). The antitumor mechanisms of luteolin were extensively described by Lin et al.[70] This flavone also decreased the protein expression of Cox-2 and PGE_2 in macrophage-like cells,[21] thus exerting an anti-inflammatory effect that could potentially be beneficial in cancer therapy. Some mechanisms of luteolin were specific for tumor cells. For instance, it induced the expression of DR5 on malignant tumor cells, but not on normal human peripheral blood mononuclear cells.[70] Likewise, luteolin increased the resistance of normal keratinocytes against UVB-induced apoptosis, but not of malignant cells.[72] Moreover, it induced apoptosis in multidrug-resistant cancer cells expressing P-glycoprotein and ATP-binding cassette, sub-family G member 2 (ABCG2), without affecting their transport functions.[73] Furthermore, it inhibited the expression of CD74 in gastric epithelial cells. This molecule was constitutively expressed in a gastric carcinoma cell line, and it has been identified as an adhesion molecule for *Helicobacter pylori*.[74] The decreased expression of CD74 may inhibit the infection of gastric cells, thus potentially decreasing gastritis and gastric cancer. The antioxidant capacity of luteolin was inferior to that of quercetin in cell-free systems, but superior in systems with biological membranes, owing to its higher lipophilicity.[71] This property would also allow luteolin to penetrate into human skin and to cross the blood-brain barrier, thus being potentially useful in both skin and brain cancers. Interestingly, the antitumor effect of luteolin was correlated with an intracellular increase in levels of reactive oxygen species (ROS). A proteomic approach based on 2D electrophoresis and Western blot analysis showed the induction of PRDX6 and PHB proteins, involved in ROS metabolism and apoptosis, after luteolin treatment in human hepatoma cells. These results suggest that luteolin may exert pro-oxidant activity in tumor cells.[75]

Quercetin. This is a flavonol found in apple, onion, and broccoli, among other plants, and with an average concentration near 10 mg/kg, represents the most abundant flavonoid in vegetables and fruits.[76,77] Onion is one of the major sources, containing 300 mg/kg.[77] In plants, quercetin usually occurs in glycosylated forms (e.g., rutin, quercetrin).[46] Quercetin has shown a free radical-scavenging effect and activity against many age-related disorders, such as CVD, neurodegenerative disease, and cancer.[78] Indeed, supplements of quercetin are commercially available in Europe and the United States. The anticancer effects of quercetin include antimutagenic, antioxidant, and antiproliferative activities, as well as regulation of several cell-signaling pathways, cell cycle, and apoptosis.[46] Quercetin has exerted inhibition of azoxymethane-induced colorectal carcinogenesis in rats, while its glycosylated form, rutin, did not produce the same effect[46]; this indicates quercetin probably represents the active form inhibiting cancer. However, according to this study, extrapolation to humans of the daily doses producing an antitumor effect in rats was not achievable by dietary intake alone, thus suggesting supplementation may be necessary. Even though quercetin is mainly metabolized in the liver, its highest concentration in rats fed a quercetin-rich diet was found in the lung. Accordingly, epidemiological studies demonstrated its effect on decreasing the incidence of lung cancer,[79] but inhibition of other cancer types has also been demonstrated in both in vitro assays and animal models (Table 3). The anticancer molecular mechanisms of quercetin and luteolin are very similar, probably due to their chemical similarity. Quercetin has also demonstrated an ability to inhibit the PI3K/Akt survival signaling pathway,[80] COX-2 and PGE2 production,[81] as well as CD74 expression in gastric cells, thus inhibiting the adhesion of *Helicobacter pylori*.[74] Additionally, it was reported to inhibit Hedgehog signaling, among other pathways (Table 3), and it sensitized prostate,[82] colon,[83] and lung[84] cancer cells to TRAIL-induced cytotoxicity as a result of the upregulation of DR5 and downregulation of survivin. It also sensitized head and neck cancer cells to cisplatin.[85] The combination

of quercetin with EGCG produced a synergistic effect on the inhibition of prostate cancer stem cell characteristics and epithelial-mesenchymal transition (EMT), which are closely related to invasion and metastasis.[59]

Stilbenes

Stilbenes are stress metabolites produced by plants in response to fungal infection. They are chemically characterized by a core of 1,2-diphenylethylene. Small fruits are particularly rich sources of bioactive stilbenes such as resveratrol and pterostilbene. They possess several pharmacological activities such as lowering cholesterolemia, increasing insulin sensitivity, preventing cancer, and extending lifespan.[86]

Resveratrol. This is the most important stilbene related to cancer, and it is mainly present in the human diet in red wine and grapes. It possesses a natural antiproliferative activity, due to its role as a phytoalexin (plant antibiotic).[87] Its consumption has been associated with the inhibition of age-related illnesses, including cancer, diabetes, arthritis, and neurodegenerative, coronary, and pulmonary diseases. The main molecular mechanism attributed to resveratrol is the activation of sirtuin proteins, which is suggested to be responsible for its ability to mimic caloric restriction and to interfere in the aging process.[87] In animal models, resveratrol has been shown to inhibit proliferation of a wide range of human cancer cells, and to suppress carcinogenesis in several organ sites (Table 3). Moreover, in clinical studies, resveratrol consumption from grapes led to decreased breast cancer incidence.[88] Surprisingly, resveratrol from wine did not yield the same result, and the difference was not explained by either the alcohol content of the wine or by a non-specific beneficial effect of fruit intake.[88] Interestingly, resveratrol appeared to be more potent in inhibiting already established lung cancer than in its prevention, while the opposite occurred in skin and breast cancers.[87] According to a phase I pilot study in eight colon cancer patients, grape powder containing resveratrol had the ability to suppress the Wnt signaling pathway in normal colonic mucosa, suggesting it may have a role to play in colon cancer prevention.[89] Many other cancer-related signaling pathways are regulated by resveratrol, such as those under the control of Akt, PI3K/Akt, NF-κB, and ER, thus controlling proliferation, apoptosis, cell cycle progression, inflammation, angiogenesis, invasion, and metastasis in multiple cancer cells (Table 3). Interestingly, it was reported that the specificity of resveratrol against cancer cells might be due to the lower pH environment of tumors compared to normal cells.[90] On the other hand, resveratrol downregulated ErbB2 in estrogen-free medium, while it upregulated it in the presence of estrogens.[91] This suggests resveratrol might differentially affect pre- and post-menopausal women. Besides the environment, the genetic background of the cell also influences the activity of resveratrol. For instance, resveratrol decreased the susceptibility of ER- breast cancer cell lines to paclitaxel-induced cell death, while it did not have a similar effect on the ER+ breast tumor cell line MCF-7.[92] Moreover, resveratrol could synergize or antagonize 5-FU depending on the concentration and the p53 status of the cell.[93] It also increased the antitumor activity of several other drugs, such as rapamycin in breast cancer[94] and gemcitabine in both in vitro and in vivo models of pancreatic cancer.[95]

Curcuminoids

Curcuminoids are obtained from turmeric as a yellow crystalline powder and are used to provide flavor and color to spice blends, such as curry.[96] They are derived from curcumin, which is structurally characterized by two ortho-methoxylated phenols and a β-diketone moiety with conjugated double bonds.[97] In Ayurvedic medicine, turmeric powder is used to treat biliary and hepatic disorders, anorexia, sinusitits, rheumatism, and wound healing. The major curcuminoids present in turmeric are curcumin, demethoxycurcumin, bisdemethoxycurcumin, and the recently discovered cyclocurcumin.[96] Most of them were reported to possess anticancer properties, with curcumin being the most deeply studied.

Curcumin. This curcuminoid inhibits cell growth in a wide range of cancers, including some uncommon types, such as cholangiocarcinoma, medulloblastoma, and uterine leiomyosarcoma (Table 3). It has also shown anti-inflammatory, antioxidant, and antitumor effects. Much of its beneficial effect was due to the inhibition of NF-κB and the consequent inhibition of pro-inflammatory pathways.[96] Additional molecular mechanisms of curcumin include inhibition of the mTOR signaling pathway,[98] cell cycle progression (Cyclin D1), proliferation (EGFR), survival pathways (β-catenin), transcription factors such as AP-1,[96] other molecules related to metabolism (HIF-1[99]) and invasion and metastasis (CCL2,[100] MMPs), the modulation of apoptosis-related molecules (caspases and Bcl-2 family),[96] and the upregulation of p53.[23] With regard to immunity, curcumin decreased the activity of T regulatory cells by inhibiting the expression of TGF-β and IL-10; it also increased the capacity of T effector cells to kill cancer cells.[101] Interestingly, curcumin inhibits human papilloma virus oncoproteins, which are responsible for cervical cancer.[24] The multiple molecular targets of curcumin make it capable of inhibiting most of the stages and hallmarks of cancer (see Figure S1 in

Supporting Information online). Furthermore, it modulates the activity of ABCG2 in animal models, thus inhibiting multidrug resistance.[102] Clinical trials demonstrated that it exerted beneficial effects in neoplastic and preneoplastic diseases such as myelodysplastic syndromes, multiple myeloma, and pancreatic and colon cancers.[96] However, further studies in humans are required to confirm its antitumor effects in other types of cancer. Importantly, curcumin was reported to induce tumor-promoting effect in damaged lung epithelium; this should be taken into account in future clinical trials so that smokers and ex-smokers can be excluded.[103]

TERPENOIDS

Terpenoids can be isolated from plant, animal, and microbial species. They are synthesized from two five-carbon isoprene units. The number of units allows the classification of terpenoids as monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), tetraterpenes (C40), and polyterpenes.[104] Plant terpenoids are secondary metabolites that are mainly involved in the defense against insects and environmental stress, and are related to the repair of damage and wounding. They inhibit the NF-κB signaling pathway, and are thus potentially useful against cancer and inflammatory diseases.[105] Antitumor drugs such as taxanes (from *Taxus brevifolia*), and vincristine and vinblastine (from *Catharanthus roseus*) belong to the group of terpenoids.[104]

Carotenoids

Carotenoids are naturally occurring fat-soluble pigments that belong to the group of tetraterpenes. They are particularly abundant in yellow-orange fruits and vegetables, and leafy greens. This group includes both provitamin A carotenoids such as β-carotene and β-cryptoxanthin, and non-provitamin A carotenoids such as lutein and lycopene. They possess several health benefits such as immune system stimulation, protection from sunburn, and antitumor activity. Most of these effects are related to their antioxidant effect.[106] However, some carotenoids, such as lycopene, play a role in regulating hormone action, cell cycle, apoptosis, gap-junction communication, epigenetics, etc.,[107] suggesting that their antioxidant activity may not be solely responsible for their anticancer effect.

Lycopene. This is the most promising carotenoid in relation to cancer prevention and therapy. It provides the red color to tomatoes, which constitute the principal source of lycopene in the human diet.[106] Epidemiological studies, both prospective and retrospective, indicated an inverse correlation between lycopene intake and prostate cancer risk.[108] In addition, doses of 10 mg lycopene/day, administered for 3 months, decreased PSA, tumor grade, bone pain, and urinary tract symptoms in patients with hormone refractory metastatic prostate cancer.[109] Lycopene was also able to inhibit other cancer types (Table 3). Alteration of serum concentrations of components of the IGF system was found in both prostate[110] and colorectal[111] cancer patients after lycopene treatment. In vitro, lycopene has been found to modify the functionality of several pathways (Table 3). Due to its wide range of targets and the results of several epidemiological studies, lycopene appears to be a promising agent in cancer therapy, particularly for prostate cancer. Moreover, it was recently reported that lycopene supplementation increased the antitumor activity of docetaxel in castration-resistant prostate tumor models.[112] According to the WCRF/AICR report of 2007, foods containing lycopene probably protect against prostate cancer.[113] However, some epidemiologic and intervention studies did not demonstrate an inverse correlation between lycopene consumption and cancer risk.[114,115] These inconsistent results may be explained, in part, by interindividual variations with regard to genetic background. Indeed, polymorphisms in the X-ray repair cross-complementing protein 1 (*XRCC1*)[116] and manganese-containing superoxide dismutase (*MNSOD*)[117] genes were reported to determine the response to lycopene regarding prostate cancer risk.

Non-carotenoid terpenoids

Carnosol. This diterpenoid is naturally present in rosemary plants (*Rosmarinus officinalis*) and possesses several pharmacological activities, including antioxidant, anti-inflammatory, and anticancer effects.[118] It has shown antitumor effects in leukemia, colon, prostate, and other types of cancers (Table 3), which are explained by the regulation of NF-κB, AMPK, ER, and AR pathways, apoptotic proteins, and proto-oncogenes such as c-Jun.[118] In addition, it inhibits invasion of mouse melanoma cells by suppressing MMP-9,[19] as well as P-glycoprotein activity,[119] and is, thus, potentially useful for decreasing drug resistance. Its anti-inflammatory activity, which also represents a beneficial effect in cancer therapy, was explained by regulation of the NF-κB pathway[19] and inhibition of nitrite production by macrophages.[120]

ORGANOSULFUR COMPOUNDS

Organosulfur compounds are naturally occurring compounds that contain at least one atom of sulfur in their

structure, and are present in the human diet mainly in garlic (allyl sulfur compounds) and cruciferous vegetables (as glucosinolates). These compounds possess several biological properties such as antimicrobial effect, carcinogen detoxification, free radical scavenging, and induction of apoptosis and antiproliferative activity on tumor cells, among others. Moreover, epidemiologic studies have demonstrated an inverse correlation between the consumption of organosulfur compounds and the incidence of different types of cancer.[121]

Glucosinolate-derived organosulfur compounds

Cruciferous vegetables, including broccoli, cabbage, and cauliflower, among others, are the major sources of organosulfur compounds. Cruciferous vegetables contain over 120 glucosinolates that give rise after hydrolysis to different aglycone metabolic products, such as the group of isothiocyanates, which are principally responsible for the antitumor activities of cruciferous plants. The hydrolysis of glucosinolates requires the activity of myrosinase enzymes, which are present in the cruciferous plant itself and in the human gut.[122]

Sulforaphane. This compound results from hydrolysis of the glucosinolate glucoraphanin.[122] It has shown antitumor activities against cancer cells from multiple organs such as prostate, colon, breast, ovary, and pancreas, among others (Table 3). The molecular mechanisms responsible for the antitumor effects of sulforaphane include regulation of the JNK-,[123] HIF-1α-,[22] ER-,[124] AR-,[125] and Fas-[126] signaling pathways, which lead to cell cycle arrest and apoptosis. Some of these activities are associated with inhibition of histone deacetylase (HDAC).[125,126] Moreover, sulforaphane has been shown to inhibit EMT-related proteins and self-renewal of cancer stem cells from several organs, such as breast.[127] Interestingly, a proteomic approach revealed that the binding affinity of isothiocyanates to tubulin correlates with their ability to induce apoptosis.[128] Sulforaphane was able to induce both apoptosis and autophagy in highly therapy-resistant carcinoma cells, and these types of cell death were produced independently from each other and dependent on ROS.[129] Clinical trials in healthy volunteers showed that sulforaphane is safe and well tolerated by humans.[122] Moreover, it inhibited primary human colorectal cancer cells from five patients from Taiwan in both in vitro and animal models.[130]

Allyl sulfur compounds

Allium vegetables possess antimicrobial, antithrombotic, antitumor, hypolipidemic, antiarthritic, and hypoglycemic activities.[131] Case-control and cohort studies indicated a consistent inverse relationship between high garlic intake and colorectal cancer risk.[132] The therapeutic properties of garlic were attributed to its content of organosulfur compounds, among which diallyl disulfide is one of the most studied.

Diallyl disulfide. In in vitro studies, diallyl disulfide inhibited colon and gastric cancers, among other tumor types, and this antitumor effect was also demonstrated in vivo with some cancers such as leukemia (Table 3). The compound has also been shown to induce G2/M arrest,[133] differentiantion,[134] and apoptosis[135] in cancer cells. The antiproliferative and antiapoptotic effects of diallyl disulfide have been associated with the generation of ROS,[135] with the increase of histone acetylation by decreasing HDAC activity,[136,137] as well as with the regulation of caspases and other pro- and anti-apoptotic proteins.[138] The signaling pathways altered by this compound are reported in Table 3.

PHYTOSTEROLS

Phytosterols are chemically classified as 4-desmethylsterols. Human intake levels are usually similar to cholesterol (150–450 mg/day) but the absorption is significantly lower.[139] The most common dietary phytosterols are β-sitosterol, campesterol, and stigmasterol, and they are principally found in nuts, whole grains, seeds, and the oils derived from them.[140] They play a role against dyslipidemias[141] and possess numerous antitumor activities that involve effects on transduction signaling pathways that regulate cell proliferation and apoptosis.[140]

β-sitosterol. This is the most abundant phytosterol in Western diets.[142] Due to its chemical similarity to cholesterol, most studies have focused on its role in CVD, finding that higher concentrations of plasma β-sitosterol are inversely related with coronary heart disease,[139] but it seems to play an antiproliferative role against several cancer types as well. While β-sitosterol has principally been studied on colon and breast tumors, findings with regard to leukemia, fibrosarcoma, and stomach and prostate cancers have also been reported (Table 3), with β-sitosterol inhibiting tumor cell proliferation and inducing apoptosis, mainly by activating caspase 3[143] and 8,[15] increasing Fas levels and MAPK activity,[143] and modulating the expression of molecules related to apoptosis, such as Bcl-2.[15] The pro-apoptotic signal seems to be the intracellular accumulation of ceramide, which is due to the activation of *de novo* ceramide synthesis by β-sitosterol.[144] Moreover, β-sitosterol was found to sensitize breast cancer cells to TRAIL-induced apoptosis.[145]

PRESENT LIMITATIONS AND FUTURE DIRECTIONS

Although understanding of the molecular aspects of cancer has been progressing in recent years, overall cancer incidence and mortality continue to increase worldwide. Thus, further research into cancer treatment remains critically important. Ancient medicines such as traditional Chinese medicine and Ayurveda have long used herbal remedies to treat a wide range of diseases. This ancient knowledge is presently being tapped to find bioactive molecules with potential utility in current cancer therapy. Indeed, phytochemical compounds derived from plants used in traditional Chinese medicine, such as emodin, berberine, artemisin, apigenin, as well as in Ayurvedic medicine, including ursolic acid, genistein, silymarin, resveratrol, indole-3-carbinol, curcumin, anethole, sulforaphane, ellagic acid, and quercetin, reportedly possess the ability to suppress multiple steps of the carcinogenic process. Consequently, it seems worthwhile to utilize the large body of knowledge from ancient medicines to undertake scientific investigations aimed at developing cost-effective and safe antitumor molecules that will improve existing cancer therapies.

Thanks to the advanced technologies currently available, it is now possible to discover the specific molecular mechanisms responsible for the antitumor effects of traditionally used phytochemicals. Thus, meticulous preclinical investigations will allow researchers to establish the scientific basis upon which more targeted human studies can be designed. This will potentially help resolve existing controversies with regard to certain epidemiological and clinical studies, such as those mentioned above regarding lycopene and genistein.

On the one hand, a compound should be characterized with regard to its effect on gene and protein expression (i.e., nutrigenomic and nutriproteomic effects, respectively) and modulation of its activity in light of the genetic background of each individual (i.e., nutrigenetic effect). Thus, the potential effects of different polymorphisms on the metabolism and activity of the selected compound can be considered, such as the single-nucleotide polymorphisms related to lycopene efficacy described above. Several factors can contribute to interindividual differences in the metabolism and disposition of phytochemicals and, consequently, to differences in their chemopreventive effects. One of these factors involves the genetic variation that influences the degree of absorption, metabolism, and excretion of these agents (e.g., polymorphisms in biotransformation enzymes). Different isoenzymes of the glutathione transferase family possess different degrees of catalytic efficiency. This may influence the tissue concentrations of isothiocyanates and, thus, the chemopreventive effect after cruciferous ingestion.[146] Another example involves the selectivity of each uridine diphosphate glucuronosyltransferase isoform for the conjugation of flavonoids, which depends on the structure of the compounds. Similarly, the sulfating activity of sulfotransferase depends on the flavonoid subtype and sulfotransferase variant.[146]

On the other hand, variations in the molecular targets (receptors and/or signal transducers) of the phytochemical may affect its chemopreventive response. For instance, mutations in the estrogen receptor gene can result in a lower binding affinity of phytoestrogens. The intestinal microbiota also contributes to interindividual differences in antitumor response after an identical intake of a particular phytochemical; this is because the microbiota metabolizes several phytochemicals, leading to either the degradation of the bioactive compounds or the production of more active molecules from their precursors (e.g., equol from daidzein, isothiocyanates from glucosinolates).[146] Consequently, more tailored studies need to be performed in order to better understand the role that each phytochemical can play in the prevention and therapy of each tumor type. In addition, more detailed knowledge of the metabolomic effects of phytochemicals (i.e., dose and temporal changes in cellular small-molecular-weight compounds[131]) will help researchers identify biomarkers in readily available fluids and tissues and differentiate responders and non-responders in clinical and epidemiological studies.

Research on the anticancer activities of traditionally used nutrient compounds will identify new antitumor molecules that can be used in cancer prevention and treatment, both alone and in combination with current chemotherapy, as well as new targets for the development of new anticancer molecules, which may be obtained by studying the molecular mechanisms of these compounds.

Despite the putative safety of phytochemical compounds, they should undergo the same analyses used for drug development. The results of such analyses are essential to determine the pharmacokinetic/pharmacodynamic profiles of the compounds, as well as to confirm putative interactions with other molecules. In this sense, several phytochemicals synergize with anticancer molecules and radiotherapy. Therefore, an appropriate combination therapy will potentially lead to a reduction in side effects without modifying or even increasing the chemotherapeutic effect. Furthermore, the safety and low cost of these compounds make them promising molecules for cancer prevention, particularly in subjects at increased risk of cancer development due to their genetic background or unavoidable and long-term exposure to carcinogens.

CONCLUSION

One of the main advantages of dietary phytochemicals stems from their relative pharmacological safety, as

proven by their use over time. They have also been shown to exert their antitumor effects through multiple targets. Because cancer development is driven by several signaling pathways, multitargeted therapies are theoretically more efficient and could potentially evade the drug resistance that occurs when cancer cells develop new mutations. However, more studies are required to find the first (directly binding) or the most important targets for these phytochemicals in order to perform tailored clinical studies that give rise to consistent results. Thus, the application of phytochemical supplements in target population and patients constitutes a very promising tool for the management of cancer prevention and treatment.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 **Stages of the cancer process inhibited by curcumin.** Most phytochemicals with anticancer activity have the capacity to inhibit several stages of cancer development. This figure shows curcumin as an example of a multitargeted phytochemical.

Table S1a **Antitumor activities and molecular targets of phytochemicals (with references).**

Table S1b **Representative anticancer phytochemicals, their main target pathways, and the cancer subtypes they have been reported to inhibit (with references).**