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RESEARCH REVIEW

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Health Promoting Properties of Natural Flavor Substances

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Abstract The study of health promoting and disease preventing compounds in food or by themselves, so called nutraceuticals or functional foods, has become a major field of research in food science. Natural flavor compounds are usually present in food, essential oils, spices, and herbs. These compounds can produce aroma, not only by themselves, but also in combination with other compounds. Today, however, greater interest is being paid to the health promoting properties of natural flavor substances rather than their flavoring properties. In fact, a number of naturally occurring flavor compounds that possess health promoting and disease preventing properties have been extensively studied and identified. The beneficial properties of natural volatile flavor compounds as well as non-volatile substances in spices and herbs discussed in this review include antioxidant, anticarcinogenic, anti-inflammatory, and immune enhancing activities.

Keywords: flavor, herb, spice, antioxidant, anticancer, anti-inflammatory, immune-enhancing

Introduction

Food is a complex mixture of biochemicals essential for the metabolic processes of life. Many natural food components have been reported to possess various health promoting properties (1, 2). Consequently, the study of health promoting and disease preventing compounds in food or the food itself, so called nutraceuticals and functional foods, respectively, has become a major field in food science.

Flavor is a major characteristic influencing the desirability of food, together with color, texture and nutrition, and it forms the cornerstone of contemporary food industries throughout the world (3). Flavor compounds are usually present in food materials, especially in spices and herbs. It was found that small amounts of spices and herbs could be used to enhance the flavor of a food and also serve to help preserve the food (4). Today, however, the health promoting properties of spices, rather than their flavoring properties, are of great interest. In this review, we discuss representative natural flavor substances including volatile flavor compounds, spices and herbs that are known to possess properties that are beneficial for health.

Antioxidant properties of natural flavor substances

Free radicals and/or reactive oxygen species (ROS) play an important role in over a hundred disease conditions in humans, including arthritis, hemorrhagic shock, atherosclerosis, aging, Alzheimer's disease, Parkinson's disease, gastrointestinal dysfunctions, tumor promotion, carcinogenesis, and acquired immune deficiency syndrome (AIDS) (5, 6). An antioxidant can be defined as a substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly prevents or delays a pro-oxidant initiated oxidation of the substrate (7). As of today, antioxidants from food sources, spices, and medicinal herbs have been extensively studied.

Naturally occurring antioxidants include vitamin E, vitamin C, carotenoids, phenolic compounds including flavonoids, and sulfur-containing antioxidants such as glutathione, carnosine, etc. Antioxidant properties are also found in several flavor compounds such as vanillin (8-10), allicin (11-13), *S*-allyl cysteine (14-16), eugenol (17, 18), thymol and carvacrol (19-22), gingerol (23-25), etc. (Fig. 1). Besides these flavor compounds, essential oils, spices and herbs with flavoring properties have been more extensively studied for their medicinal properties including antioxidant activity (22, 26-28).

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is one of the most widely used flavoring agents for sweet foods. Vanillin is reported to suppress protein oxidation and lipid

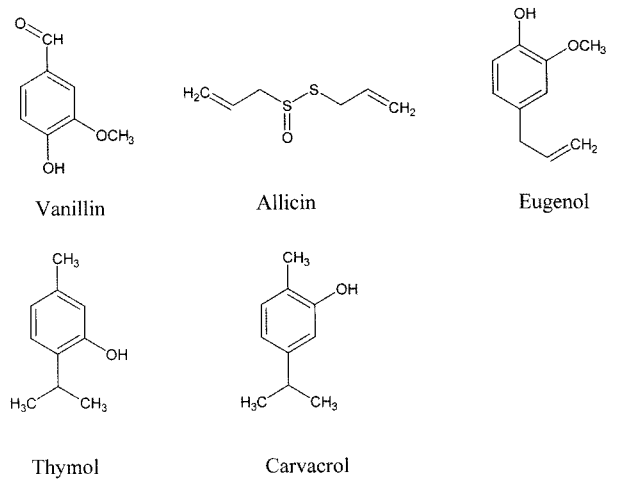

Fig. 1. Structures of natural flavor compounds with antioxidant properties.

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peroxidation induced by photosensitization in rat liver mitochondria (9). It also scavenges peroxynitrite and inhibits peroxynitrite-mediated reactions (10).

Garlic (*Allium sativum*) has several flavor compounds and has been widely studied for its medicinal effects, such as antioxidant and anticancer activities, for several decades. Allicin (thio-2-propene-1-sulfinic acid *S*-allyl ester) is a known antioxidant in garlic and is produced by an enzymatic reaction when fresh garlic is crushed or injured. Allicin inhibits the formation of hydroxy radical adducts by more than 90% in liver homogenate (conc. 36 μg/mL) (11). Allicin and its precursor, alliin (*S*-allyl-L-cysteine sulfoxide), exhibit significant antioxidant activity against lipid hydroperoxide (LOOH) formation in human low-density lipoprotein (LDL) (13) and in the Fenton oxygen-radical generating system. The biological activity of allicin is attributed to either antioxidant activity or thiol disulfide exchange. Allicin displays inhibitory activity against three thiol-containing enzymes which possess very reactive or unshielded SH-groups: SH-protease papain, $NADP^+$-dependent alcohol dehydrogenase, and the NAD^+-dependent alcohol dehydrogenase from horse liver (12). Thiosulfinates including allicin seem to be primarily responsible for the antioxidant activity of garlic whereas they seem to have little or inverse effect on metal chelating ability of garlic (29).

The antioxidant activities of *S*-allyl cysteine (SAC), an organosulfur compound of aged garlic, and a commercial garlic tablet, Kyolic (Wakunaga Pharm. Co., Ltd., CA, USA), were demonstrated by using three different antioxidant assay systems involving the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, superoxide-mediated autoxidation of pyrogallol and 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) induced lipid peroxidation (14). In addition to its radical scavenging ability, SAC has been shown to regulate oxidative stress in cells. SAC suppressed nitric oxide formation by inhibiting inclucible nitric oxide (iNOS) mRNA and protein expression in murine macrophage RAW264.7 cells induced with lipopoly-saccharides (LPS) and interferon-gamma (IFN-γ) (15). Diallyl polysulfides such as diallyl trisulfide (DATS), diallyl tetrasulfide, diallyl pentasulfide, and diallyl hexasulfide, are also strong antioxidants found in garlic (28). Diallyl polysulfides from aged garlic extract protect biological membranes from lipid peroxidation both *in vitro* and *in vivo* (30). Diallyl sulfide (DAS) and diallyl disulfide (DADS) seem to have significantly greater oxidative-delaying properties than cysteine-containing compounds (SAC; *S*-ethyl cysteine, SEC; *S*-methyl cysteine, SMC; *S*-propyl cysteine, SPC) in both oxidized LDL and plasma samples (16).

Thymol is present in quantities of up to 50% in the essential oils of *Monarda punctata, Satureia thymera, Origanum floribundum, Ocimum viride, Ocimum gratissimum*, and particularly in thyme (*Thymus vulgaris* L., *T. capitatus, T. serpillum* L., *T. zygis* L. subsp. *Sylvestris, T. herba barona* L.) (3, 31-33). In *Lamiaceae* plants, thymol is always accompanied by its isomer carvacrol (22). An early study showed that thymol and carvacrol inhibited peroxidation of liposome phospholipids in the presence of iron (III) and ascorbate (20). Thymol and carvacrol are also effective inhibitors of lipid autoxidation in lard and sunflower oil (19, 22). However, these compounds differ in the mechanism of their inhibition, which depends on the character of the lipid medium. Thymol is a better antioxidant in sunflower oil than in lard, whereas the antioxidant activity of carvacrol in the two lipid systems does not differ significantly. The inhibition of oxidation by essential oils from plants of the oregano species depends highly on the content of carvacrol and thymol.

Eugenol is found in several volatile oils such as clove oil, laurel, and cinnamon leaf oil (3). It possesses a strong antioxidant activity with regard to hydroxy radical formation (17, 18, 34). Nagababu and Lakshmaiah (34) reported that eugenol inhibits hydroxy radical formation through its inhibitory effect on OH-mediated deoxyribose degradation. Eugenol also inhibited lipid peroxidation of human erythrocyte membranes catalyzed by hydrogen peroxide (H_2O_2) or benzoyl peroxide in the presence of copper ions (17). Eugenol also suppressed enzymatic lipid peroxidation catalyzed by soybean lipoxygenase, not by inactivating the enzyme directly, but by interfering with fatty acid radical intermediates due to its hydroxy radical scavenging ability, and thus plays a role in inhibiting the propagation of lipid peroxidation. (18)

The antioxidant properties of spices and their compounds have been widely studied. The total antioxidant activities of 12 common spice extracts are summarized in Fig. 2. The term 'total antioxidant activity' involves the 'ability' of an antioxidant substance to scavenge 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) free radicals, which can be derived from the enzymatic oxidation of metmyoglobin (35). Trolox (6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid), a synthetic water soluble tocopherol analog, is commonly used as a standard antioxidant in this assay. Any material having a Trolox equivalent number of more than one is considered to have superior free radical scavenging activity compared to Trolox. As shown in Fig. 2, seven out of the twelve spice extracts tested have better free radical scavenging capabilities than Trolox. These spices include oregano, thyme, sage, mint, huajiao, cinnamon, and rosemary. However, it should be noted that the free radical scavenging assay is not the only antioxidant test. There are many other antioxidant assays, and frequently, one assay does not necessarily correlate with another.

Rosemary (*Rosemarinus officinalis* L.) extracts are good sources of various antioxidant compounds such as carnosol,

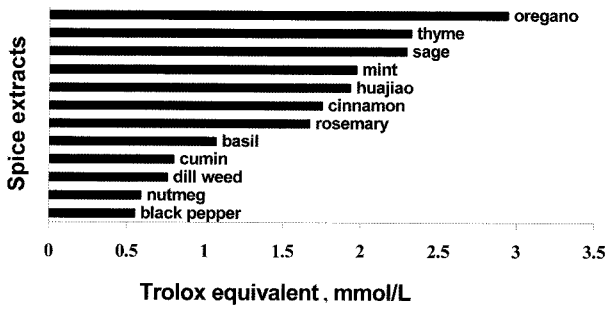

Fig. 2. Antioxidant activities of spice methanol extracts against $ABTS^{+}$ free radicals.

carnosic acid, rosmanol, epirosmanol, isorosmanol, rosmaridiphenol, rosmadial, miltirone, and ursolic acid (36-41). The structures of the representative compounds in rosemary extracts are presented in Fig. 3. Hexane, acetone, and methanol extracts from rosemary leaves have been reported to contain strong antioxidants (42). Rosemary extracts seem to strongly inhibit lipid oxidation as well as soybean lipoxygenase activity. Carnosol and carnosic acid are responsible for over 90% of the antioxidant activity of rosemary (43). The antioxidant activities of carnosol and carnosic acid were reported as early as the 1960s (44). Studies by Nakatani *et al.* (37, 45) showed that rosmanol, epirosmanol, isorosmanol, and carnosol all have remarkably high antioxidant capabilities when evaluated in lard using the Active Oxygen Method. Among these, rosmanol, epirosmanol, and isorosmanol were more than four times as effective as butylated hydroxytoluene (BHT), and carnosol was twice as active. A number of the compounds in rosemary have been found in the closely related sage (*Salvia officinalis* L.) and summer savory (*Satureja hortenis* L.) plants (46). Carnosol, carnosic acid, rosmadial, rosmanol, epirosmanol, and methyl carnosate were also identified from sage leaves and shown to have antioxidant activity (42, 47).

The antioxidant effect of capsanthin on the chlorophyll-sensitized photooxidation of soybean oil and several flavor compounds has also been reported (48). Capsanthin is the most abundant carotenoid in paprika spice and its concentration is about 1590 mg/kg of dry matter. In other spices, flavonoids, alone or together with other phenolic compounds, have been found to contribute to antioxidant activity. For example, the antioxidant activity of pepper (*Piper nigrum* L.) can be ascribed to the presence of glycosides of the flavonoids kaempferol, rhamnetin, and quercetin and at least five different phenolic amides (46).

[6]-Gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone), a major pungent flavor component of ginger (*Zingiber officinale* Roscoe), has been shown in numerous assays to possess substantial antioxidant properties including 1) DPPH radical scavenging activity, 2) oxidation of methyl linoleate by the Oil Stability Index (OSI) method, 3) liposome oxidation induced by AAPH, 4) oxidation of ROS detecting comopound, dichlorofluorescin, and 5) phospholipid peroxidation induced by $FeCl_3$-ascorbate (20, 23, 25). Gingerol is also known to suppress xanthine oxidase activity and decrease 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced superoxide formation in human promyelocytic leukemia (HL-60) cells (25, 49).

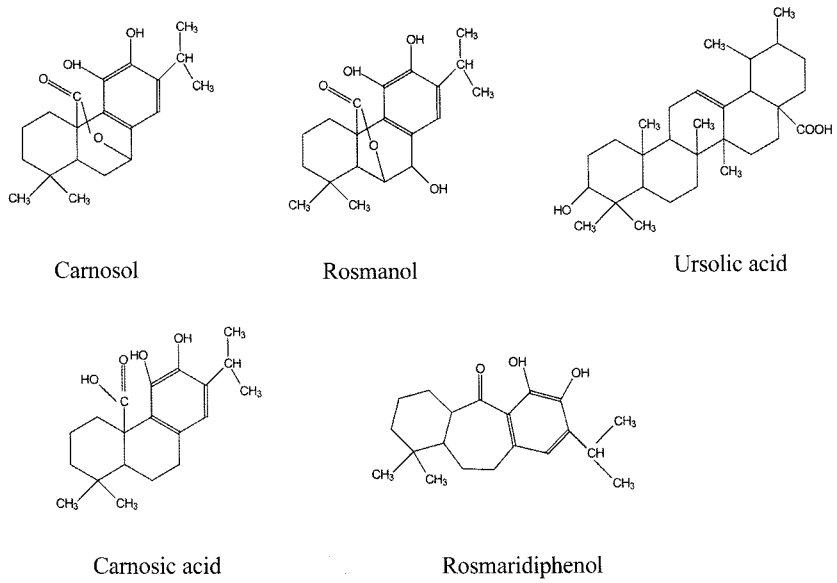

Fig. 3. Structures of major components in rosemary extracts.

Table 1. Active phytochemicals found in herbs

Herbal source	Active phytochemicals
Allium sp. (Garlic, onions, leeks, and chives)	Diallyl sulfide, disulfides, and trisulfides
Labiatae family (Basil, dill, fennel, marjoram, mint, rosemary, oregano, sage, and thyme)	Monoterpenes, sesquiterpenes, and flavonoids. Rosemary and sage contain diterpenoids (rosmanol, carnosol, carnosic acid, rosmarinic acid, epirosmanol, and isorosmanol), and ursolic acid (a triterpenoid)
Umbellifereae family (Anise, caraway, celery seed, cilantro, coriander, cumin, dill, fennel, and parsley)	Coumarins, phthalides, polyacetylenes, and terpenoids
Zingiberaceae family (Tumeric and ginger)	Curcumin, gingerols, and diarylheptanoids

Table adapted from Craig (2).

Anticarcinogenic properties of natural flavor substances

The National Cancer Institute has identified several commonly used herbs as possessing cancer preventive properties (Table 1). These herbs include members of the *Allium* sp. (garlic, onions, and chives); members of the Labiatae (mint) family (basil, mints, oregano, rosemary, sage, and thyme); members of the Zingiberaceae family (turmeric and ginger), etc. (50). In addition to the antioxidant activities of the 12 spices extracts listed in Fig. 2, the anticarcinogenic properties of these spice extracts have been demonstrated using HL-60 cells as well (Fig. 4). HL-60 cells are genetically derived human leukemia cells that have lost reproductive control like other naturally occurring cancer cells. The anticancer properties of these spices were determined by measuring their inhibition of DNA synthesis in HL-60 cells. The extracts of basil, rosemary, sage, and mint exhibited very strong anticancer activities in the HL-60 assay (Fig. 4). Beneficial substances found in spices and herbs act as antioxidants and electrophile scavengers, stimulate the immune system, inhibit nitrosation and the formation of DNA adducts with carcinogens, inhibit hormonal actions and metabolic pathways associated with the development of cancer, and induce phase I or II detoxification enzymes (2).

Some of the substances from spices and herbs are known to stimulate Glutathione S-transferase (GST) activity (2). GST is a detoxifying enzyme that catalyzes the reaction of glutathione with electrophiles to form compounds that are less toxic, more water-soluble, and therefore, more easily excreted. Beneficial substances that induce GST activity include phthalides in umbelliferous herbs; sulfides in garlic and onions, curcumin in turmeric and ginger; and terpenoids, i.e. limonene, geraniol, menthol, and carvone found in commonly used herbs (Table 2).

Among terpenoids, monoterpenes are non-nutritive dietary compounds found in the essential oils of citrus fruits, including sweet orange, mandarin, grapefruit, lemon, lime, bitter orange, and many other plants (Fig. 5). The anticarcinogenic properties of monoterpenes have been systematically reviewed (51). d-Limonene comprises over 90% of orange peel oil and is used as a chemical intermediate in flavorings and fragrances. d-Limonene possesses chemopreventive activity against rodent

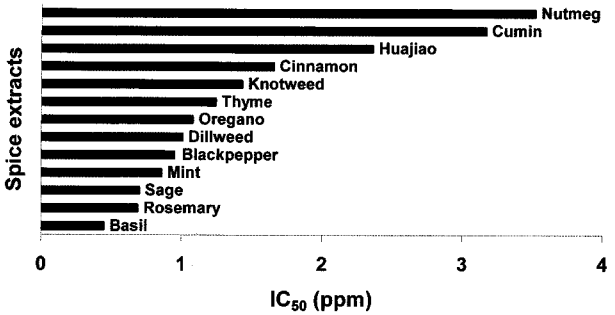

Fig. 4. Anticarcinogenic activities of various spices methanol extracts. Pellets of human leukemia HL-60 cells after centrifugation were suspended in RPMI medium at a concentration of 5×10^5 cells/mL. Each 1 mL of the cell suspension was transferred to test tubes and treated with 2 μL of vehicle (DMSO) or various concentrations of spice extracts. Three microliters of [^{3}H]thymidine (50 μCi/mmol) was added to each tube followed by incubation at 37°C for 2 hr. The reaction was terminated by the addition of 1 mL of ice cold phosphate buffer saline and centrifuged for 10 min at 1000 *g*. The precipitated cells were collected, lysed with 1 mL of ice cold deionized water and 1 mL of 10% trichloroacetic acid (TCA) solution. After washing the macromolecular substances with TCA and acetone, the dry filtrates were transferred to scintillation vials with 5 mL of Scient Varse fluid (Fisher Scientific, Springfield, NJ, USA) and radioactive emissions from each vial were measured in a scintillation counter.

mammary, skin, liver, lung, and forestomach cancers (52-54). Recently, limonene has been found as the most abundant volatile compound in *Zanthoxylum piperitum* (*Chopi*) (55). Perillyl alcohol (POH) and geraniol also display inhibitory properties against various cancers. POH suppresses the growth of breast and pancreatic cancer cells *in vitro*, and inhibits their growth and metastasis *in vivo* (56-59). POH also induces cell cycle arrest, causes apoptosis and inhibits cell proliferation in human carcinoma cell lines (BroTo and A549) *in vitro* (60). Geraniol suppresses MCF-7 human breast cancer cell proliferation and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity, which catalyzes the formation of mevalonate, a precursor of cholesterol that is required for cell proliferation (61). In addition, geraniol inhibits colon, lung, and prostate cancers (62-65). Structurally diverse isoprenoids, such as d-limonene,

Table 2. Terpenoids known to inhibit tumors

Terpenoids	Herbs that contain the active terpenoid
Carvone	Caraway, spearmint, and dill
Cineole	Coriander, lavender, rosemary, sage, and thyme
Farnesol	Lemongrass, chamomile, and lavender
Gerniol	Lemongrass, coriander, melissa, basil, and rosemary
Limonene	Caraway, mints, cardamom, dill, celery seed, coriander, and fennel
Menthol	Peppermint
Perillyl alcohol	Lavender, spearmint, sage
α-Pinene	Caraway, coriander, fennel, juniper berry, rosemary, and thyme

Table adapted from Craig (2).

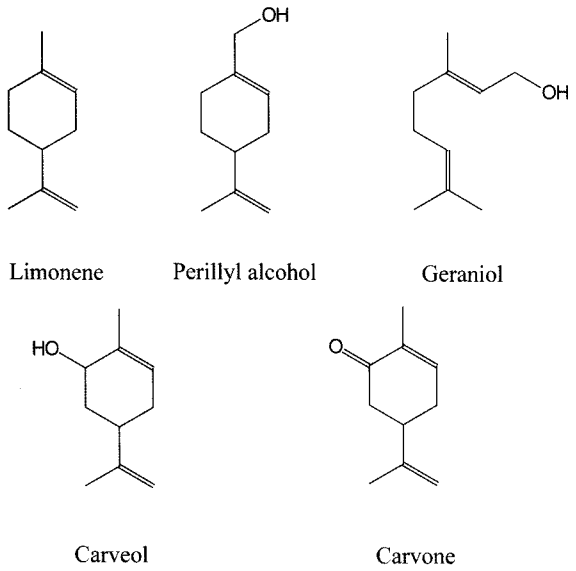

Fig. 5. Structures of anticarcinogenic monoterpenes.

perillyl alcohol, cyclic monoterpenes (perillaldehyde, carvacrol, and thymol), and acyclic monoterpene (geraniol) decrease the proliferation of murine B16 (F10) melanoma cells (66). Bioassay-guided fractionation of clove terpenes from the plant *Eugenia caryophyllata* revealed that eugenol significantly induces the detoxifying enzyme GST in mouse liver and small intestine (67). Essential oil of *Chrysanthemum boreale* Makino, which contains aromatic monoterpenes such as camphor, α-thujone, *cis*-chrysanthenol, 1,8-cineole, α-pinene, etc., inhibits cell proliferation and induces apoptosis through the induction of poly-ADP-ribose polymerase (PARP) cleavage and caspase-3 activation in a human oral epidermal carcinoma KB cell line (68).

The antitumor activities of monoterpenes may be explained by several mechanisms, which include 1) the induction of phase II carcinogen-metabolizing enzymes, resulting in carcinogen detoxification, 2) the induction of apoptosis and/or inhibition of the post-translational isoprenylation of cell growth-regulating proteins, and 3) tumor redifferentiation concomitant with increased expression of the mannose-6-phosphate/insulin-like growth factor II receptor and transforming growth factor β1 (51).

Alcohol extract of rosemary and sage has also been shown to exhibit strong anti-tumorogenic properties (69). Application of rosemary extract to mice skin inhibited the covalent binding of benzo(a)pyrene [B(a)P] to epidermal DNA and inhibited tumor initiation by B(a)P and 7,12-dimethylbenz(a)anthracene (DMBA) (70). Carnosol or ursolic acid from rosemary inhibited TPA-induced ear inflammation and ornithine decarboxylase activity (70). When applied topically, sage oil, which has similar constituents to rosemary, not only delayed tumor appearance but also inhibited tumor incidence and the yield (19 and 61 %, respectively) of DMBA-initiated and TPA-promoted SP-1 skin papillomas (IC_{50}: 50 μg/mL) (71).

Carnosol was shown to prevent DMBA-induced DNA damage and tumor formation in rat mammary tissue (72). A recent study reported that carnosol suppressed β-catenin tyrosine phosphorylation and prevented intestinal tumor multiplicity by 46% in C57BL/6J/Min/+ (Min/+) mice (73). In addition, carnosol inhibited the invasion of highly metastatic mouse melanoma B16/F10 cells *in vitro* by suppressing metalloproteinase-9 through down-regulation of nuclear factor kappa B (NF-κB) and c-Jun (74).

Curcumin (diferuloyl methane), a naturally occurring yellow pigment in turmeric and curry, is present in the rhizomes of the plant *Curcuma longa* Linn (75). Chemopreventive properties of curcumin have been widely studied and reviewed in several previous publications (26, 27, 76-79). Curcumin exhibits antimutagenic activity in the Ames assay and inhibits chemically induced preneoplastic lesions in breast, colon, and neoplastic lesions in the skin, forestomach, duodenum, and colon of rodents (80, 81). Curcumin also modulates arachidonic acid metabolism by blocking phosphorylation of cytosolic phospholipase A_2 ($cPLA_2$), decreasing the expression of cyclooxygenase-2 (COX-2) and inhibiting the catalytic activity of 5-lipoxygenase (5-LOX) (82). It also enhances glutathione content and GST activity in the liver and inhibited arachidonic acid metabolism in mouse skin, protein kinase C activity in TPA-treated NIH 3T3 cells, tyrosine protein kinase activity in rat colon, and 8-hydroxyguanosine formation in mouse fibroblasts (75). Curcumin enhances tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-mediated apoptosis by ROS-mediated DR5 up-regulation in human renal cancer cells (83). It inhibits the activity of specific receptor tyrosine kinases (RTKs) and the activity of the transcription factors activator protein-1 (AP-1) and NF-κB, thus inhibiting cell proliferation and enhancing apoptosis (84).

Many researchers have examined the anticarcinogenic potential of garlic and its components. Recent reports demonstrated that allylsulfide derivatives inhibit the growth of transplantable tumors and also inhibits a number of different tumor cell lines such as those derived from canine breast, human melanoma, human neuroblastoma, human prostate, and human breast (85). Oral administration of garlic extract inhibits two-stage chemical carcinogenesis induced by DMBA in mice transplanted intraperitoneally with Ehrlich ascites tumour (86). The inhibition of gastrointestinal cancer by organosulfur compounds in garlic has also been demonstrated (87). Onion and garlic oils have demonstrated abilities to inhibit tumor formation in mouse skin (88). Subsequently, diallyl sulfide and its analogues were shown to inhibit 1) 1,2-dimethylhydrazine (DMH)-induced colon tumorigenesis in mice and rats, 2) B(a)P-induced forestomach tumorigenesis in A/J mice, 3) nitrosomethylbenzylamine-induced formation of esophageal tumors in rats, 4) DMH-induced formation of liver tumors in mice, 5) 3-methylcholanthrene-induced uterine cervix tumors in mice, and 6) benzoyl peroxide-induced tumor promotion in Sencar mice previously initiated with DMBA (89, 90). Hong *et al.* (91) indicated that diallyl sulfide inhibits the formation of lung tumors in mice by reducing the metabolic activation of tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Other interesting compounds having biological activity in garlic are the *cis* and *trans* isomers of ajoene, which have been shown to be a potent inhibitor of platelet

aggregation (92).

Organosulfur compounds, including DAS, N-acetylcysteine, and SAC present in garlic and onion oil, have been shown to inhibit colon, forestomach, esophagus, mammary gland, and lung carcinogenesis in experimental animals (93-96). As previously stated, these compounds are known to induce phase II enzymes including GST, NAD(P)H-dependent quinone reductase 1 (NQO1), and UDP-glucuronosyl transferase, in the liver and colonic mucosa of experimental animals (26, 28). A recent study revealed that garlic organosulfur compounds induce phase II detoxifying enzymes such as NQO1 and heme oxygenase 1 (HO-1), through transcription factor Nrf2 and the antioxidant response element (ARE) (97).

The induction of apoptosis may be the major contributing factor for the anti-tumorigenic properties of diallyl sulfide (98). *S*-Allylmercaptocysteine (SAMC) has been evaluated for its inhibitory effects on the proliferation and viability of two erythroleukemia cell lines, HEL and OCIM-1, two hormone-responsive breast and prostate cancer cell lines, MCF-7 and CRL-1740, and normal human umbilical vein endothelial cells (99). Although there were variations in sensitivity to this organosulfur compound in the different cell lines examined, the two hormone-responsive cancer cell lines of breast and prostate were clearly much more susceptible to the thioallyl compound. SAC and raw garlic also have been reported to reduce B(a)P-DNA adduct formation in stimulated human peripheral blood lymphocytes *in vitro* (100).

COX-2, a major enzyme catalyzing the production of prostaglandins in response to inflammatory stimuli, has been recognized as a target of chemopreventive as well as anti-inflammatory agents. Extensive studies demonstrated that COX-2 is positively regulated by eukaryotic nuclear transcription factor NF-κB. Natural compounds derived from spices that can inhibit NF-κB pathways include curcumin, gingerol, capsaicin, eugenol, gingerol, ursolic acid, and diallyl sulfide, etc (27, 76, 101-103).

Anti-inflammatory properties of natural flavor substances

Inflammation is a necessary response of the host to counteract infectious agents and other foreign bodies (104). A number of mediators, including cytokines, ROS, and arachidonic acid metabolites produced by immune cells, play a key role in inflammatory responses. In chronic inflammation, cytokines induce the production of nitric oxide resulting in DNA damage and carcinogenic peroxynitrite and nitrite production. Uncontrolled production of these mediators can exacerbate inflammatory responses (105).

Salvia (Lamiaceae), which comprises about 500 species, including sage, has been reported to possess anti-inflammatory activity (106). Ethanol extract of *Salvia transsylvanica* (Schur ex Griseb) significantly decreased the weight of edema induced by carrageenan in rat paw in a dose-dependent manner. Rosemary extract and compounds in rosemary, such as carnosol and ursolic acid, exhibited antiinflammatory effects on TPA-induced and arachidonic acid induced inflammation in mice (70). Carnosol inhibited nitrite formation induced by lipopoly-saccharide (LPS) and IFN-γ in mouse peritoneal cells by more than 50% (2.5-10 μM) (107).

Oral administration of rosemary (*Rosmarinus officinalis* L.) prevents CCl_4-induced inflammation, necrosis, and vacuolation (108). It also enhances GST-dependent detoxification systems by increasing cytosolic GST activity and plasma GST activity in CCl_4-induced acute liver in rat (108). Carnosol was recently reported to suppress iNOS through the down-regulation of NF-κB signaling pathways in mouse macrophage cells (109).

Oral administration of curcumin from tumeric and capsaicin from red pepper is also known to inhibit paw inflammation in arthritic rats (110). The level of Gp A72, which precedes the onset of paw inflammation in arthritic rats and persists in the chronic phase, was lowered by curcumin and capsaicin (88 and 73%, respectively). In addition, curcumin and capsaicin could control the release of inflammatory mediators such as eicosanoids and hydrolytic enzymes secreted by macrophages, and thereby exhibit anti-inflammatory properties (111). Curcumin suppresses ultraviolet B-irradiated COX-2 expression in human keratinocytes (HaCaT) by inhibiting the activation of the nuclear transcription factor AP-1, and mitogen-activated protein kinases (MAPKs) such as p38 and JNK (112). Curcumin reduces the respiratory burst of Chlamydia pneumoniae-primed THP-1 cells (113). It also inhibits the expression of cyclin D1, which results in decreased cell growth (114). Topical application of curcumin significantly suppresses TPA-induced inflammation, hyperplasia, proliferation, and papilloma formation in mouse skin (75, 78).

ROS generated by activated macrophages play an important role in the initiation of inflammation. Capsaicin and curcumin at a concentration of 10 μM entirely inhibited ROS and nitrite radical production *in vitro* by activating rat peritoneal macrophages (110). Eugenol from clove and piperine from pepper required higher concentrations (500 μM) to completely inhibit ROS release. Eugenol supplementation (0.17 wt%) lowers carrageenan-induced inflammation in rats (93). However, curcumin as a feed supplement does not affect inflammatory responses in rats but instead, due to its poor absorption, inhibits inflammation after parenteral application. According to Huang *et al.* (115), the topical application of commercial grade curcumin (approximately 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxy-curcumin) and pure curcumin, demethoxycurcumin and bisdemethoxy-curcumin has a similar potent inhibitory effect on TPA-induced inflammation of mouse ears, as well as TPA-induced transformation of cultured JB6 (P+) cells. Eugenol and thymol also display marked inhibitory activities against neutrophil chemotaxis (116).

A terpene oxide, 1,8-cineole, possesses anti-inflammatory properties against paw edema induced by carrageenan and cotton pellet-induced granuloma (117). It is also known as eucalyptol or cajeputol, and is a major component of eucalyptus (up to 75%), rosemary (up to 40%), Psidium (40-60%), and many other essential oils. When tested on human blood monocytes *in vitro,* cineole was reported to inhibit cytokine production and arachidonic acid metabolism (118). Cineole also inhibits trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats (119). Colonic damage is associated with an increase in myeloperoxidase activity and by a decrease in glutathione. It also significantly reduces the myeloperoxidase activity and

causes repletion of glutathione. Cineole suppresses superoxide production in human peripheral blood leukocytes (120) and inhibits paw edema induced by carrageenan and cotton pellet-induced granuloma (117).

When given orally (33 mg/kg each, 26 days), a combination of ginger oil and eugenol significantly suppressed inflammation and/or rheumatism in male Sprague-Dawley rats (121). 6-Gingerol, a major pungent compound of ginger, has also been shown to suppress TPA-induced epidermal ornithine decarboxylase activity and inflammation (122).

Allicin inhibits tumor necrosis factor alpha (TNF-α) induced expression of interacellular adhesion molecule-1 (ICAM-1), a key mediator in inflammation, on human umbilical endothelial cells (123).

Cardamom oil, a widely using flavoring agent, is proven to have marked anti-inflammatory activity against acute carrageenan-induced planter edema in male albino rats in doses of 175 and 280 μL/kg (124).

Immune-enhancing properties of natural flavor substances

As discussed earlier, curcumin possesses various pharmacological properties including antioxidant, anti-carcinogenic and anti-inflammatory activities. It is also known to have inhibitory effects on human immuno-deficiency virus (HIV) type-1 (125). Curcumin inhibits the HIV-1 integrase protein, an effect which might be due to an intramolecular stacking of two phenyl rings that brings the hydroxyl groups into close proximity. Furthermore, curcumin blocks CyA-resistant PMA (cyclosporine A, a commonly used immunosuppressant) and the anti-CD28 pathway of T-cell proliferation, which demonstrates the immunosuppressive property of curcumin *in vitro* (126, 127).

Garlic is reported to boost immune function by stimulating lymphocytes and macrophages to destroy cancer cells. Oral administration of garlic oil (200 mg/kg of body weight) suppresses D6-desaturase activity and changes membrane arachidonic acid content, both of which display immuno-enhancing potential (128). Aged garlic extract was highly effective for immunotherapy in human bladder cancer and other malignancies (129-131). Allicin strongly inhibits the spontaneous and TNF-α-induced secretion of proinflammatory cytokines and chemokines such as interleukin (IL)-1β, IL-8, IP-10 (INF-γ-inducible protein of 10 kDa), and MIG (monokine induced by INF-γ) from HT-29 and Caco-2 cells, and suppresses the expression of IL-8 and IL-1β, mRNA as well. In addition, allicin inhibits the degradation of inhibitor of kappa B (IκB), indicating that allicin possesses immunomodulatory effects on intestinal epithelial cells and thus may have the potential to attenuate intestinal inflammation (132). Allicin markedly inhibits concanavalin A (Con A) induced liver damage in mice through its immunomodulatory effects on T cells and adhesion molecules, and the inhibition of NF-κB activation (133). Black seed oil from *Nigella sativa* (Ranunculaceae), a broadly used spice and food pre-servative, has antibacterial and antifungal effects. Black seed oil exhibits outstanding antiviral effects in BALB/c mice against murine cytomegalovirus that might be mediated by an increase in Mϕ number and function, and IFN-γ production (134).

Conclusion

Flavor substances have long been recognized as important components of food material as well as food additives. In addition to their primary role as flavoring agents in food, flavor substances have been studied for their heath promoting properties during recent decades. These properties include antioxidant, anticarcinogenic, anti-inflammatory, and immune-enhancing activities. Although numerous studies have been conducted on the biological activities of flavor substances, the molecular mechanisms of these substances in preventing chronic diseases are not fully understood. In addition, the bioavailability and pharm-acokinetics of these substances are poorly characterized. Therefore, further studies on their molecular roles as health promoting agents as well as their biological consequences including pharmacokinetics and *in vivo* effects are needed.

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