

## SPECIAL GUEST EDITOR SECTION

# Health Benefits of Culinary Herbs and Spices

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**Spices and herbs have been in use for centuries both for culinary and medicinal purposes. Spices not only enhance the flavor, aroma, and color of food and beverages, but they can also protect from acute and chronic diseases. More Americans are considering the use of spices and herbs for medicinal and therapeutic/remedy use, especially for various chronic conditions. There is now ample evidence that spices and herbs possess antioxidant, anti-inflammatory, antitumorigenic, anticarcinogenic, and glucose- and cholesterol-lowering activities as well as properties that affect cognition and mood. Research over the past decade has reported on the diverse range of health properties that they possess via their bioactive constituents, including sulfur-containing compounds, tannins, alkaloids, phenolic diterpenes, and vitamins, especially flavonoids and polyphenols. Spices and herbs such as clove, rosemary, sage, oregano, and cinnamon are excellent sources of antioxidants with their high content of phenolic compounds. It is evident that frequent consumption of spicy foods was also linked to a lower risk of death from cancer and ischemic heart and respiratory system diseases. However, the actual role of spices and herbs in the maintenance of health, specifically with regards to protecting against the development of chronic, noncommunicable diseases, is currently unclear. This review highlights potential health benefits of commonly used spices and herbs such as chili pepper, cinnamon, ginger, black pepper, turmeric, fenugreek, rosemary, and garlic.**

Spices have been an integral part of culinary culture around the world and have a long history of use for flavoring, coloring, and preserving food, as well as for medicinal purposes. The increased use of spices as flavorings in foods is a major trend worldwide (1). Spices not only enhance the flavor, aroma, and color of food and beverages, but they may also protect against the development of acute and chronic, noncommunicable diseases and help people maintain health. The long historical use of herbs and spices

for their medicinal benefits is fully acknowledged, and there is a growing amount of literature concerning the potential/purported benefits of these foods from a health perspective. These benefits include their possible role in conferring protection against cardiovascular and neurodegenerative diseases, cardiovascular disease, cancer, and type 2 diabetes mellitus (T2DM; 1–3).

Spices and herbs have been extensively studied in different countries because of their beneficial effects on human health (1, 4). However, the interest in spices has only recently grown in the Western world (5, 6). Greater awareness of ethnic spices for disease prevention and health promotion is needed in this population.

## Use and Knowledge of Spices and Herbs

The U.S. Department of Agriculture reports that the consumption of spices in the United States has climbed exponentially over the course of the last half-century, with spices such as ginger and chili pepper being used more frequently than ever before (6). According to the U.S. National Health and Nutrition Examination Survey, 5–10% of adults in the United States use botanical supplements such as spices, for health benefits (7, 8). Such increased use could in part be because of the lack of side effects from spices, greater availability than traditional medicines, and the consideration of known health benefits of spices (6–8).

It is evident that more Americans are considering the use of spices and herbs for medicinal and therapeutic uses, especially to remedy various chronic conditions, reduce disease symptoms, and aid in treatment and management of common health problems. A recent cross-sectional survey study involving 703 adults in the Midwestern United States examined consumers' perceptions about spices and their use and predictors of spice use (9) found that almost half of the participants were interested in learning about health benefits of spices (48%) and were willing to use spices as complementary and alternative medicine therapies (51%). Most (>50%) of the participants were familiar with or had used 8 out of the 10 listed spices. The majority of participants (54%) was currently using one or more spices on a daily basis and believed that ginger (64%), garlic (58%), and cinnamon (56%) could promote good health and wellness (Table 1). Furthermore, the majority of the participants listed 7 out of 10 spices as effective in preventing a specific disease with ginger (72%), garlic (68%), and cinnamon (67%) listed as effective by more than two-thirds of the participants. In addition to the adult population use, spices have also been explored in pediatric populations. For example, more than 1/10 of the infants and children were given spices, primarily to remedy minor ailments such as fussiness or stomach complications, coughs, and colds.

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**Table 1. Perceived efficacy of spices in promoting health and wellness (9)**

Spice	Effective <i>n</i> <sup>a</sup> (% <sup>b</sup> agreement)
Ginger	450 (64)
Garlic	404 (58)
Cinnamon	392 (56)
Chili pepper	300 (43)
Turmeric	251 (36)
Cilantro	168 (24)
Cloves	163 (23)
Black pepper	163 (23)
Curry leaves	108 (15)
Fenugreek	76 (11)

<sup>a</sup> *n* = 703.<sup>b</sup> % = Percent of individuals who believe that a certain spice can promote health and wellness.

### Biological Activities of Spices and Herbs Constituents

Culinary herbs and spices are foods that are a rich source of bioactive molecules such as sulfur-containing compounds, tannins, alkaloids, phenolic diterpenes, and vitamins, especially flavonoids and polyphenols (4, 10). Spices and herbs such as clove, rosemary, sage, oregano, and cinnamon are excellent sources of antioxidants with their high content of phenolic compounds (10, 11).

Research over the past decade has reported that bioactive constituents of spices possess the diverse range of health benefits (1, 5, 11, 12). There is now ample evidence that culinary herbs and spices are sources of constituents that possess antioxidative, anti-inflammatory, antitumorigenic, anticarcinogenic, and glucose- and cholesterol-lowering activities as well as properties that affect cognition and mood, which are actively used in preclinical, clinical, and therapeutic trials investigating new treatments of diseases. In addition, there is now a growing amount of literature on how polyphenols confer health benefits via their action on gut microbiota (13, 14), which, in humans, have been recently related to risks of diabetes, cardiovascular disease, liver cirrhosis, etc.

### Effect of Spices on Human Health

Culinary herbs and spices have been reported to have various beneficial effects on human health. There is ample research evidence to suggest that spice consumption is particularly related to the reduced risk of mortality as a result of cancer, ischemic heart diseases, and respiratory diseases. A recent observational study assessed consumption of spicy foods as part of a daily diet and the total risk and causes of death in 487 375 participants, aged 30–79 years, during a median follow-up of 7.2 years in China and concluded that people eat spicy food to improve health (15). Compared with participants who ate spicy foods less than once a week, those who consumed spicy foods 1 or 2 days a week were at a 10% reduced risk of death (hazard ratios for death was 0.90). And those who ate spicy foods three to five and six to seven days a week were at a 14% reduced risk of death (the hazard ratios for death were both 0.86). In other words, participants who ate spicy

foods almost every day had a relative 14% lower risk of death compared with those who consumed spicy foods less than once a week. It was found that frequent consumption of spicy foods was also linked to a lower risk of death from cancer, ischemic heart diseases, and respiratory diseases, and this was more evident in women than in men. People who consumed fresh chili tended to have a lower risk of death from cancer, ischemic heart disease, and diabetes (16, 17).

In addition, subjects with a high spice preference had a lower salt intake and blood pressure than subjects who disliked spicy food. The enjoyment of spicy flavors enhanced salt sensitivity and reduced salt preference. Salt intake and salt preference were related to the regional metabolic activity in the insula and orbitofrontal cortex (OFC) of participants. A more recent multicenter, double-blind observational and interventional study showed that administration of capsaicin, the major spicy component of chili pepper, enhanced the insula and OFC metabolic activity in response to high-salt stimuli, which reversed the salt intensity-dependent differences in the metabolism of the insula and OFC (18). It was concluded that enjoyment of spicy foods may significantly reduce individual salt preference, daily salt intake, and blood pressure by modifying the neural processing of salty taste in the brain. Application of spicy flavor may be a promising behavioral intervention for reducing high salt intake and blood pressure.

### Overview of Selected Herbs and Spices

#### *Chili Pepper*

**Bioactive components.**—Red pepper contains 0.2–2% capsaicinoids, which are responsible for the pungency or bite in capsicums. Capsaicin, an alkaloid, accounts for about 50–70% of the total capsaicinoids and dihydrocapsaicin for 20–25%, which, together with capsaicin, provides the fieriest notes from midpalate to throat. Red pepper also contains newly discovered, nonpungent compounds called capsinoids (e.g., capsiate and dihydrocapsiate).

The beneficial effects of red pepper have long been documented. The habitual consumption of spicy foods was inversely associated with total and certain cause-specific mortality (cancer, ischemic heart diseases, and respiratory diseases), independent of other risk factors of death. A recent large population-based prospective study analyzed the association between consumption of hot red chili peppers and mortality, using a population-based prospective cohort from the National Health and Nutritional Examination Survey III. The frequency of hot red chili pepper consumption was measured in 16 179 participants at least 18 years of age. Total and cause-specific mortality were the main outcome measures. Total mortality for participants who consumed hot red chili peppers was 21.6% compared with 33.6% for those who did not (absolute risk reduction of 12%; relative risk of 0.64). Consumption of hot red chili peppers was associated with a 13% reduction in the instantaneous hazard of death. It is documented that the consumption of hot red chili pepper was associated with reduced mortality. The findings are in line with previous evidence showing potential protective effects of spicy foods on human health (16).

**Antioxidant anti-inflammatory effects.**—Red pepper capsaicin has antioxidant potential in mitigating oxidative stress in various tissues or organs in both in vitro and animal models (19–21).

Capsaicin-inhibited neutrophil (inflammatory cells) migration toward the inflammatory focus reduced vascular permeability and proinflammatory cytokine production in an animal study (21). Capsaicin may also suppress obesity-induced inflammation by modulating messenger molecules released by obese mice fat cells and inactivating macrophage to release proinflammatory mediators in vitro (22).

**Cardiovascular health.**—The antioxidant and antiplatelet properties of capsaicin and the important role of capsaicin in regulating energy metabolism may also contribute to its beneficial effects on the cardiovascular system (23–26). An animal study showed that 3 mg/kg/day capsaicin reduced low-density lipoprotein (LDL) levels, increased high-density lipoprotein (HDL) levels, and reduced oxidative stress levels measured as malondialdehyde in various tissues (27). In another animal study, when capsaicin was used alone (0.015% in the diet) or combined with curcumin, dietary high-fat–induced excess of triglycerides in the blood was countered by 14 and 12%, respectively; the total cholesterol was reduced 23 and 21%, respectively (28). In addition, capsaicin preferentially inhibited arachidonic acid-induced platelet aggregation in vitro (29). Capsaicin may also defend against heart disease via a transient receptor potential (TRP)-mediated modulation of coronary blood flow (30). Two randomized crossover intervention studies revealed 4 weeks of regular consumption of a chili blend (55% cayenne chili) at 16 g a day increased the resistance of serum lipoproteins to oxidation and reduced resting heart rate. It also increased effective myocardial perfusion pressure time in men but not women (31, 32). A randomized, double-blind, placebo-controlled trial in 44 pregnant women with gestational DM (GDM) documented that capsaicin-containing chili supplementation (5 mg/day capsaicin) regularly improved postprandial hyperglycemia and hyperinsulinemia as well as fasting lipid metabolic disorders in women with GDM, and it decreased the incidence of large-for-gestational-age newborns (33).

**Blood glucose control.**—Human trials found that 5 g or more of chili pepper (*Capsicum frutescens*) was associated with a decrease in blood glucose level and maintenance of healthy insulin levels (34–36). Animal studies suggested that red pepper may affect insulin secretion from beta-cells and/or peripheral insulin resistance, reduce liver glucose output and increase glycogen (the main form of body fuel) storage, as well as activate the peroxisome proliferator-activated receptors in vitro, which involve cell glucose and fat metabolism (37–39). Furthermore, dietary capsaicin may provide beneficial effects on glucose homeostasis via activating the TRP vanilloid type 1 (TRPV1; 40).

**Thermogenesis, satiety, and weight management.**—Short-term consumption of red pepper may have the potential to assist in body weight management by increasing satiety and fullness, reducing energy and fat intake, increasing body heat production (thermogenesis), raising the body's metabolic rate (41–43), preventing fat cells from growing into mature cells (adipogenesis; 44), and increasing the rate of fat burn-off (fat oxidation; 45). TRP channels, which are primary receptors for pungent agents such as capsaicin, may in part be responsible for lipid catabolism and thermogenesis; activating of TRPV1 appears to stimulate cellular mechanisms against obesity (40).

Human studies suggest that red pepper enhances thermogenesis and fat oxidation but also affect blood pressure and heart rate (45–47). The longer-term use of capsaicin may be also limited by its strong pungency. However, a certain type of

red pepper (*C. annuum*; CH-19 sweet, a nonpungent cultivar of red pepper, containing capsate at 0.1 mg/kg dry weight) could enhance thermogenesis but have no impact on blood pressure and heart rate (47, 48). A 12 week placebo-controlled human trial confirmed that consumption of capsinoids from *C. annuum* was associated with abdominal fat loss (49). Furthermore, Janssens et al. (50) investigated the 24 h effects of capsaicin on energy expenditure, substrate oxidation, and blood pressure during 25% negative energy balance and found that consuming 2.56 mg capsaicin per meal supports negative energy balance by counteracting the unfavorable negative energy balance effect of decrease in components of energy expenditure as well as promotes fat oxidation in negative energy balance.

**Gut health.**—Evidence suggests capsaicin is a gastroprotective agent in peptic ulcer disease (51, 52). Capsaicin inhibits acid secretion and stimulates alkali and mucus secretions (particularly gastric mucosal blood flow), which help in the prevention and healing of ulcers (53). Red pepper sauce (which is high in capsaicin) helps with issues swallowing by increasing the contractility and motility response of the human esophagus. An acute administration of capsaicin seems to improve the motor performance of the esophageal body in patients with ineffective esophagus motility (54).

The antimicrobial activity of spices, has been highlighted by inhibitory effects against *Helicobacter pylori* and other bacteria and fungi (55, 56). Chili pepper has long been recognized to have a beneficial effect on the gut microbiota in humans. In recent years, rapidly emerging evidence has implicated gut microbiota as a novel and important metabolic factor that affects the health of the host (57), and several studies in humans have related abundance, composition, and metabolites of gut microbiota to risk of obesity (58, 59), diabetes (60), liver cirrhosis (61), and cardiovascular disease (62). In a 6 week, controlled feeding trial, subjects were given the weight maintenance diet sequentially contained with up to 10 mg/day capsaicin from chili powder (63). Dietary capsaicin increased the Firmicutes:Bacteroidetes ratio and *Faecalibacterium* abundance, accompanied with increased plasma levels of glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide and decreased plasma ghrelin level. Further enterotype analysis revealed that these subjects could be clustered into Bacteroides enterotype (E1) and Prevotella enterotype (E2), and the above beneficial effects were mainly obtained in E1 subjects. Moreover, E1 subjects had significantly higher fecal *Faecalibacterium* abundance and butyrate concentration after capsaicin interventions than those in E2 subjects.

## Cinnamon

**Bioactive components.**—Cinnamon's key components are essential oils and other derivatives such cinnamaldehyde, cinnamic acid and cinnamate (bark oil; 60–80%), eugenol (leaf oil; 10%), and water soluble polyphenols (4–10%), e.g., catechin, epicatechin, procyanidin, quercetin, kaempferol, and polyphenolic polymers. The flavonoids are primarily proanthocyanidins and oligomers of cinnamtannins. The doubly linked phenol type A polymers are believed to be the bioactive component for glucose metabolism (64).

**Antibacterial and antifungal activity.**—Extracts of cinnamon and its major components, cinnamaldehyde and eugenol, have

been shown to attack major respiratory and gastrointestinal tract pathogens *in vitro* (65, 66). An anecdotal report suggests that cinnamon may have beneficial effects on chronic salmonella infection (67). Further, an *in vitro* study suggested cinnamon may have some bactericidal activity against *H. pylori* (68), but there is a lack of evidence to support the use of cinnamon for *H. pylori* infection eradication in humans.

**Anti-inflammatory and antioxidant effects.**—Cinnamon polyphenol extract suppressed inflammation processes through the regulation of anti- and proinflammatory gene expression *in vitro* (69, 70). Cinnamaldehyde-inhibited cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), two major inflammation systems (70). In a double-blind, placebo-controlled trial involving 22 overweight subjects with impaired fasting blood glucose, 500 mg/day aqueous extract of cinnamon (high in type A polyphenols) for 12 weeks reduced oxidative stress as measured by plasma malondialdehyde (MDA) levels (71).

**Cardiovascular health.**—Cinnamon and cinnamon extract (high in type A polyphenols) lowered sugar-induced blood pressure increase in one study with rats predisposed to hypertension (72). Cinnamaldehyde has been reported to inhibit platelet aggregation *in vitro* in human and rabbit cells as well as reduce blood clots formed within a blood vessel in an animal study (73). By regulating gene expression involving inflammatory, insulin, and lipoprotein metabolism signaling pathways, a cinnamon extract (high in type A polyphenols) inhibited the overproduction of lipoproteins and serum triglycerides after a meal, suggesting that this extract may be beneficial in the control of lipid metabolism (74–76). In a recent systematic review and meta-analysis, Maieran et al. (77) assessed 13 randomized controlled trials with 750 participants investigating the effect of cinnamon supplementation on blood lipid concentrations. Cinnamon supplementation significantly reduced blood triglycerides and total cholesterol concentrations without any significant effect on LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C). Moreover, cinnamon may have protective effects against metabolic syndrome aspects in various ways, and the use of cinnamon can be effective in reducing metabolic syndrome complications (78, 79). Consumption of cinnamon (short term) is associated with notable reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP; 80).

**Blood glucose control.**—The consumption of cinnamon is associated with a statistically significant decrease in fasting plasma glucose (FPG) levels. Cinnamon thus has been suggested to help patients with T2DM achieve better glycemic control, although conclusions from meta-analyses are mixed (81–84). Eleven randomized, controlled trials that met the inclusion criteria were identified and enrolled 694 adults with T2DM both receiving and not receiving hypoglycemic medications. In 10 of the studies, participants continued to take their hypoglycemic medications during the cinnamon intervention period. The studies ranged from 4 to 16 weeks in duration, and 7 of the studies were double-blind. Cinnamon doses ranged from 120 to 6000 mg/day. All 11 of the studies reported some reductions in FPG during the cinnamon intervention, and of the studies measuring hemoglobin A1c (HbA1c), very modest decreases were also apparent with cinnamon, whereas changes in the placebo groups were minimal. However, only four studies achieved the American Diabetes Association treatment goals [FPG < 7.2 mmol/L (130 mg/dL) and/or HbA1c < 7.0]. It was concluded that cinnamon supplements added to standard

hypoglycemic medications and other lifestyle therapies had modest effects on FPG and HbA1c (81).

Proanthocyanidins are considered active ingredients in cinnamon aqueous extracts. Preclinical animal studies provide evidence that components of cinnamon may decrease blood glucose levels and increase insulin sensitivity (85). Cinnamaldehyde is another active component derived from cinnamon. Accumulating evidence supports the notion that cinnamaldehyde exhibits blood glucose-lowering effects in diabetic animals by increasing glucose uptake and improving insulin sensitivity in adipose and skeletal muscle tissues, improving glycogen synthesis in liver, restoring pancreatic islets dysfunction, slowing gastric emptying rates, and improving diabetic renal and brain disorders (86). Cinnamaldehyde exerts these effects through its action on multiple signaling pathways, including PPARs, AMPK, PI3K/IRS-1, RBP4-GLUT4, and ERK/JNK/p38MAPK, TRPA1-ghrelin, and Nrf2 pathways (87). Additionally, obese mice fed for 5 weeks with a cinnamon-containing diet significantly reduced their cumulative body weight gain and improved glucose tolerance without detectable modification of insulin secretion (87).

Although evidence of glucose control in humans is inconsistent, there is evidence of dose-related hypoglycemic effects. Recent human studies showed that cinnamon supplements of 3 g/day or more had improved glucose control and insulin sensitivity in both healthy and diabetic subjects (88–92). In addition, consuming 500 mg/day aqueous extract of cinnamon (approximately 10 g cinnamon ground powder/day) for 12 weeks led to improvements in several metabolic features (i.e., fasting blood sugar, SBP, and body composition; 93). However, most human studies did not show any improvements in blood glucose control or insulin sensitivity when cinnamon was used at <3 g/day doses (92, 94–97).

**Hepatoprotective effect.**—One study found the ethanol extract of cinnamon showed hepatoprotective action against carbon tetrachloride-induced lipid peroxidation and liver injury in rats by elevating antioxidant enzyme activities (98). Cinnamon bark extract reduced the hepatic lipid accumulation and protected the liver from acute alcohol-induced fatty liver in mice (99).

**Neuroprotective property.**—Various cinnamon species and their biologically active ingredients have renewed the interest toward the treatment of patients with mild-to-moderate Alzheimer's disease (AD) through the inhibition of tau protein aggregation and the prevention of the formation and accumulation of amyloid- $\beta$  (A $\beta$ ) peptides into the neurotoxic oligomeric inclusions, both of which are considered to be the AD trademarks. An aqueous extract of cinnamon inhibits tau protein activity (a protein that becomes toxic when it accumulates and twists inside nerve cells in the brain), and A $\beta$  insult of neuronal cells in an *in vitro* model (100, 101). Indeed, cinnamon possesses neuroprotective effects by interfering with multiple oxidative stress and proinflammatory pathways. Additionally, cinnamon modulates endothelial functions and attenuates the vascular cell adhesion molecules. Cinnamon polyphenols may induce AD epigenetic modifications. Cinnamon, particularly cinnamaldehyde, seems to be effective and safe approaches for treatment and prevention of AD onset and/or progression. However, further molecular and translational research studies as well as prolonged clinical trials are required to establish the therapeutic safety and efficacy in different *Cinnamon* spp.

## Ginger

**Bioactive components.**—Ginger contains the following nonvolatile pungent components: gingerols, shogaols, paradols, and zingerone.

**Nausea and vomiting.**—Clinical trials show ginger (1 g/day) may be safe and effective for decreasing nausea and vomiting during pregnancy (102–105) or when induced by chemotherapy (106). Furthermore, 500 mg oral ginger 1 h before surgery in women who were undergoing laparoscopic cholecystectomy is effective in decreasing the severity of postoperative nausea and vomiting (107). In a double-blinded study, 500 mg ginger 2 times per day was effective in ameliorating antiretroviral-induced nausea and vomiting (108). However, ginger with prescription drugs may not reduce chemotherapy-induced nausea as evidenced by a randomized, double-blind, placebo-controlled trial in 162 patients (109).

**Antioxidant and anti-inflammatory effects.**—Ginger and its extracts, such as 6-gingerols and 6-shogaol, exhibited substantial free-radical scavenging activities and inhibited production of inflammatory mediators [e.g., NO and Prostaglandin E<sub>2</sub>]. They also suppressed proinflammatory transcription factor (NF- $\kappa$ B) and activity of inflammatory cytokines [e.g., tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )] and inhibited COX-2 (an enzyme responsible for biochemical pathways activated in chronic inflammation) during in vitro studies (110–114). 6-Shogaol was found to have much stronger inhibitory effects on arachidonic acid release and NO synthesis than 6-gingerol (112–114). In a recent human clinical trial, participants with osteoarthritis (OA) received capsules containing 500 mg of ginger powder for 3 months, and their serum levels of TNF- $\alpha$  and interleukin-1 $\beta$  (IL-1 $\beta$ ) were decreased (115). Ginger also significantly lowered COX-1 protein expression in participants at increased risk for early event in colorectal cancer (116).

**Cardiovascular health.**—Ginger has been reported to have anti-inflammatory, antioxidant, antiplatelet, antihypertensive, and hypolipidemic effects (117–121). Although the relatively few human trials involving ginger generally used low doses yielding inconclusive results, dosages of 5 g or more demonstrated significant antiplatelet (anticoagulation) activity (117, 121). Early human studies suggested that up to 2 g dried ginger is unlikely to cause platelet dysfunction when used therapeutically (122). However, there is a synergistic effect on antiplatelet aggregation when 1 g ginger per day was combined with nifedipine (a BP-lowering drug; 123). A double-blind, placebo-controlled trial with 85 hyperlipidemic subjects showed 3 g/day ginger for 45 days markedly lowered blood levels of triglyceride, cholesterol, and LDL, with increased HDL, when compared with a placebo control (120). In addition, a study with rats indicated that ginger may prevent fat storage and reduce body weight (124). More clinical trials are necessary before definitive conclusions can be made about the cardiovascular effects of ginger in humans.

**Joint and muscle health.**—Animal studies suggest that ginger can reduce joint swelling, cartilage destruction, and serum levels of inflammatory cytokines associated with rheumatoid arthritis and joint and muscle pain (125, 126). In a randomized human trial, 11 days of oral administration of 2 g raw or heat-treated ginger prior to exercise reduced muscle pain induced by eccentric exercise and slightly reduced markers of inflammation and muscle function (127). It was also reported that 4 g ginger supplementation can accelerate muscle strength

recovery following intense exercise in a randomized trial on 20 nonweight-trained participants (128).

**Antiglycation and antiglycemic effects.**—The accumulation of advanced glycation endproducts (AGEs) as a result of nonenzymatic reaction between proteins and sugar has been implicated in unhealthy conditions associated with aging and diabetes. Thus, inhibiting AGEs formation is believed to play a role in the prevention of diabetic complications. In vitro studies showed ginger extract could prevent and/or inhibit protein glycation (129, 130). Animal data also indicated a hypoglycemic effect for ginger extract (131–134). In randomized clinical trials, it was found that supplementation of ginger (1.6–3.0 g daily) improved insulin sensitivity and some fractions of lipid profile and reduced C-reactive protein (CRP) and prostaglandin E<sub>2</sub> in type 2 diabetic patients. Glycemic indexes (lowering blood glucose and HbA1c), insulin sensitivity, and lipid profile, as well as total antioxidant capacity, MDA, CRP, and paraoxonase-1 activity were improved in patients with T2D (135–137).

**Weight management potential.**—It is evident that oral ingestion of ginger could induce thermoregulatory function and fat oxidation in humans. Serum levels of free fatty acids were significantly elevated at 120 min after intake of 1.0 g dried ginger root powder in both the morning and afternoon. Morning ginger intake also significantly reduced respiratory exchange ratios and elevated fat oxidation by 13.5% 120 min after ingestion. These results suggest that the effect of a single oral ginger administration facilitate fat use (138). Mansour et al. (139) measured resting state energy expenditure for 6 h after consumption of a breakfast meal with or without 2 g ginger powder dissolved in a hot-water beverage. There was a significant effect of ginger on thermic effect of food (ginger versus control =  $42.7 \pm 21.4$  kcal/day,  $P = 0.049$ ). Visual analog scale ratings showed lower hunger ( $P = 0.002$ ), lower prospective food intake ( $P = 0.004$ ), and greater fullness ( $P = 0.064$ ) levels with ginger consumption versus the control. These results, which show enhanced thermogenesis and reduced feelings of hunger with ginger consumption, suggest a potential role of ginger in weight management. Furthermore, ginger consumption (2 g/day ginger powder) for 12 weeks in obese women showed a significant decrease in body mass index (BMI), serum insulin and homeostatic model assessment–insulin resistance (HOMA-IR) index, and total appetite score, demonstrating a minor beneficial effect of ginger supplementation on weight loss and some metabolic features of obesity (140). Overall, ginger consumption has the potential in managing obesity; however, additional studies are necessary to confirm these findings.

**Neuroprotective effect.**—In vitro studies found that ginger extract inhibited the expression of a wide range of inflammation-related genes in microglial-like cells (nonneuronal brain cells) and protected brain cells from Abeta insult (too much Abeta protein in the brain is linked to the development of AD), suggesting that ginger may have neuroprotective effects (141, 142). More research on the proposed health benefits of ginger in this area is warranted.

## Black Pepper

**Bioactive components.**—Black pepper contains from 5 to 9% piperine, the major active constituent. Black pepper also contains alkaloids, piperidine, wisanine, and dipiperamide (143).

**Antioxidant effect.**—Piperine, the active compound of black pepper, has been demonstrated within in vitro studies to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species. Both the oil and oleoresins showed strong antioxidant activity in comparison with butylated hydroxyanisole and butylated hydroxytoluene (143–145). Black pepper or piperine treatment has also been evidenced to lower lipid peroxidation in vivo and beneficially influence cellular antioxidant status in a number of experimental situations of oxidative stress (146, 147).

**Anti-inflammatory effect.**—Piperine has revealed remarkable anti-inflammatory and analgesic activities (148). The anti-inflammatory activity of piperine has been confirmed in many rat models (149). Both in vitro and in vivo rat models found that piperine inhibited 5-lipoxygenase and COX-2, two key enzymes involved in biosynthesis of proinflammatory mediators that cause inflammation, pain and fever (150–152). Piperine also reduced the levels of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels and inhibited activation of NF- $\kappa$ B within in vitro and in vivo animal studies (152–154). In addition, piperine relieved pain in an arthritis animal model (152, 155). Curcumin and piperine supplementation before and after exercise can attenuate some aspects of muscle damage (156).

**Antiallergic effect.**—An animal model found that piperine inhibited both histamine release and eosinophil infiltration and also suppressed allergic airway inflammation and airway hyperresponsiveness (157). Asthma is an inflammatory disease caused by irregular immune responses in the airway mucosa. Piperine has shown deep inhibitory effects on airway inflammation in a murine model of asthma from suppressing type 2 helper T cells (Th2) cytokines (IL-4, IL-5, and IL-13), immunoglobulin E, eosinophil CCR3 expression, and by enhanced transforming growth factor- $\beta$  (TGF- $\beta$ ) gene expression in the lungs. Therefore, it can be considered as a possible immunomodulator by downregulating Th2 cytokines (157).

**Digestion aid.**—Black pepper may accelerate the overall digestive process by enhancing the activity of digestive enzymes, increasing gastric acid and bile acid secretion, and reducing food transit time (145). In animal studies, piperine was found to enhance the activities of pancreatic amylase, lipase, and chymotrypsin by 87, 37, and 30%, respectively, when consumed through the diet (158).

**Cardiovascular health.**—Piperine has been shown to inhibit lipid droplet accumulation in mouse macrophages that are converted to foam cells in an animal study, suggesting it may help retard the progression in which fatty deposits build up in the arterial wall (159). Piperine also reduced plasma lipid and lipoprotein levels in rats (160), inhibited platelet-derived growth factor-BB-induced proliferation and migration of vascular smooth muscle cells in blood vessels (161), and lowered blood pressure in animals (162). More research is necessary to verify the cardiovascular benefits of black pepper.

**Weight management.**—Piperine may enhance energy expenditure or thermogenesis through the sympathetic nervous system by increasing levels of catecholamine and activating the adrenal sympathetic nerves in animal studies (163). Zanzer et al. (164) recently examined the postprandial effect of a black pepper-based beverage (BPB) on glycaemia, appetite, gastrointestinal well-being, gut hormones (peptide tyrosine-tyrosine and GLP-1), and thyroid hormones postprandially after a white wheat bread challenge in healthy adults, and concluded

that BPB appears to have the potential to modulate perceived appetite by lowering ‘hunger,’ ‘desire to eat,’ and ‘prospective consumption’ and increasing ‘satiety’ and ‘fullness’ without affecting gastrointestinal wellbeing. Further experiments are needed to establish the relevant dose and mode of intake to optimize the effects.

**Enhancing nutrient bioavailability.**—Piperine has a passive diffusion mechanism, high apparent permeability coefficient, and short clearance time (165). It was suggested that piperine promotes its efficient permeation through the epithelial barrier in the intestine (166). Piperine enhances the absorption of various nutrients and drugs and functions as a bioavailability enhancer of various substances such as coenzyme Q10, curcumin, and tea polyphenols (145). For example, when curcumin was administered with piperine at 20 mg/kg, its bioavailability increased by 154% in an animal study (167). Bioavailability enhancing of curcumin could be a preventive effect of piperine on the intestinal and hepatic metabolism of curcumin (168). Studies have shown that piperine remarkably increased the in vivo bioavailability of resveratrol by inhibiting its metabolism and decreasing the required dose of resveratrol in a clinical setting (169).

**Mood and cognitive function.**—Black pepper may exhibit antidepressant-like activity and have a cognition-enhancing effect via the regulation of neurotransmitter metabolism in animals (170, 171).

### Turmeric

**Bioactive components.**—The major active constituents of turmeric are curcuminoids including curcumin (diferuloylmethane), demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin. Curcumin is the active compound most commonly studied using in vitro and in vivo (animal and human) studies.

**Antioxidative and anti-inflammatory effects.**—Curcumin preparations in vitro have scavenged free radicals, inhibited lipid peroxidation and LDL oxidation, and prevented deoxyribonucleic acid (DNA) oxidative damage. Turmeric also has exhibited powerful anti-inflammatory activity, possibly by inhibiting COX-2, prostaglandins, leukotrienes, and other inflammatory mediators such as TNF- $\alpha$ , and NF- $\kappa$ B (2, 3). In a randomized controlled trial (172), it was shown that curcumin supplementation (daily dose of 1 g/day) over 8 weeks significantly decreased serum concentrations of proinflammatory cytokines in 59 subjects with a metabolic syndrome. There were significant reductions in serum concentrations of TNF- $\alpha$ , IL-6, TGF- $\beta$ , and MCP-1 following curcumin supplementation ( $P < 0.001$ ).

**Cardiovascular health.**—A number of laboratory, animal, and human studies suggest that curcumin may have protective effects on cardiac function, vascular health, and lipid profiles (173, 174). In an uncontrolled study, 10 healthy human volunteers who received a dose of 500 mg curcumin per day for 7 days had a 12% decrease in total serum cholesterol levels and a 29% increase in HDL-C levels (175). Curcumin also reduced cholesterol levels in acute coronary syndrome patients in a clinical trial in which curcumin was administered in various doses (45, 90, or 180 mg/day). It appeared that lower doses of curcumin were more effective than higher doses in this regard, in which 45 mg/day of curcumin reduced LDL and total

cholesterol levels with increased HDL concentrations (176). In a 12 week randomized, double-blind, placebo-controlled trial (177), subjects with T2D ( $n = 118$ ), curcuminoid (1000 mg/day plus piperine 10 mg/day) supplementation revealed significant reductions in serum levels of total cholesterol, non-HDL-C and lipoprotein(a) with elevations in serum HDL-C levels in the curcuminoids group as compared with the placebo group. Thus, curcuminoids supplementation could contribute to a reduced risk of cardiovascular events in dyslipidemic patients with T2D. Moreover, 12 weeks of curcumin (2000 mg/day Longvida<sup>®</sup>; Verdure Sciences) supplementation improved resistance of arterial endothelial function by increasing vascular NO bioavailability and reducing oxidative stress, while also improving conduit artery endothelial function in healthy middle-aged and older adults (178). In addition, curcumin can improve metabolic profiles in patients with metabolic syndrome (179).

*Gastrointestinal health.*—A pilot trial examined the effect of standardized turmeric extract on symptoms of irritable bowel syndrome (a functional bowel disorder) in 207 otherwise healthy adults. Administering a dose of either 72 or 144 mg turmeric extract for 8 weeks reduced the pain/discomfort score significantly (22–25%), and approximately two-thirds of the subjects reported an improvement in symptoms after treatment (180). A randomized, double-blind trial in patients with ulcerative colitis suggested that consumption of 2 g/day curcumin reduced recurrence rates and improved the clinical activity index (181). In addition, *in vitro* and *in vivo* animal studies suggested that curcumin has anti-*H. pylori* activity and eradicated *H. pylori* from infected mice (182, 183). In a recent randomized trial (184), it was shown that an addition of curcumin (500 mg/day) on top of the standard antihelicobacter regimen in patients with peptic ulcers is safe and improves dyspepsia symptoms but has no enhancing effect on the eradication of *H. pylori* infection.

Curcumin has been shown to be effective against development of hepatic steatosis and its progression to steatohepatitis (185, 186). In a randomized trial, an 8 week supplementation of curcumin was associated with a significant reduction in liver fat content (78.9% improvement in the curcumin versus 27.5% improvement in the placebo group) in patients with nonalcoholic fatty liver disease (NAFLD; 186). There were also significant reductions in BMI and serum levels of total cholesterol, LDL-C, triglycerides, liver enzymes, and uric acid when compared with the placebo group (185, 186).

*Brain health and cognitive function.*—Preventing the accumulation of A $\beta$  aggregation is an important factor in maintaining healthy brain function. The accumulation of A $\beta$  occurring in the brain is one of the leading causes of neurodegeneration (187). Curcumin enhanced A $\beta$  clearance and reduced A $\beta$  and plaque burdens in animal studies (188, 189). Animal studies with curcumin also found that this bioactive ingredient has improved memory retention and prevented oxidative damage (190, 191). In addition, a mouse study showed that curcumin protected against the development of brain blood vessel spasm and limited secondary brain tissue death as a result of an inadequate blood supply (192). A population-based cohort study in Singapore involving over 1000 mentally competent Asian subjects aged 60–93 years showed that regular turmeric consumption helped preserve cognitive function even when low-to-moderate curry levels were consumed (193).

More recently, Rainey-Smith et al. (194) investigated the ability of a curcumin formulation to prevent cognitive decline in

a population of community-dwelling older adults. A significant time  $\times$  treatment group interaction was observed for the Montreal Cognitive Assessment (repeated-measures analysis; time  $\times$  treatment;  $F = 3.85$ ,  $P < 0.05$ ) in subjects who ingested 1500 mg/day Biocurcumax for 12 months. Subsequent analysis revealed that this association was driven by a decline in function of the placebo group at 6 months that was not observed in the curcumin treatment group. In addition, curcumin may have antidepressant effect. Chronic supplementation with curcumin (1000 mg/day) produced a significant antidepressant behavioral response in depressed patients by a reduction of 17 item Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale scores (195). Furthermore, curcumin decreases inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  levels, increases plasma brain-derived neurotrophic factor levels, and decreases salivary cortisol concentrations.

*Joint and muscle health.*—The anti-inflammatory activity properties of curcumin may also help this bioactive compound maintain healthy joint function (196). In a well-described animal model of rheumatoid arthritis, the arthritic index, a clinical measure of joint swelling, was used as the primary end point for assessing the effect of turmeric extracts on joint inflammation. The study showed turmeric extract containing 41% curcuminoids was effective in preventing joint inflammation in rats (197). A number of human clinical trials have demonstrated that curcumin acts as an analgesic and anti-inflammatory agent for the management of arthritis (198, 199). Kuptniratsaikul et al. (200) found that patients with primary knee OA who consumed a dose of 2 g/day turmeric extract for 6 weeks had similar pain relief as the patients who consumed 800 mg/day of ibuprofen (200). Haroyan et al. (201) compared the effects of CuraMed<sup>®</sup> (Terry Naturally) 500 mg capsules (333 mg curcuminoids) and Curamin<sup>®</sup> (Terry Naturally) 500 mg capsules (350 mg curcuminoids and 150 mg boswellic acid) taken orally 3 times a day for 12 weeks in 201 patients with OA in a three-arm, randomized, double-blinded, placebo-controlled trial. They found that curcumin complex reduced pain-related symptoms in patients with OA, and curcumin in combination with boswellic acid is more effective, presumably because of the synergistic effects of curcumin and boswellic acid.

*Blood glucose control.*—*In vitro* and *in vivo* animal studies have found that curcumin lowered blood glucose levels through the suppression of glucose in the liver (202), reversed insulin resistance in fat cell cultures (203), increased glucose uptake into skeletal muscle (204), and stimulated pancreatic beta-cell function (205). Turmeric supplementation has been shown to improve glucose indexes. A randomized clinical trial, in which patients with T2DM were given two 300 mg doses of curcuminoids daily for 8 weeks, found that curcumin had a favorable effect on endothelial dysfunction in association with reductions of inflammation and oxidative stress in a similar manner to those randomized to the prescription medication group (atorvastatin; 206). In a recent clinical trial, 46 patients with NAFLD were given 3 g turmeric in capsules each day for 12 weeks, and it was found that turmeric consumption decreased serum levels of glucose, insulin, and HOMA-IR (207).

*Weight management.*—In cell cultures and an animal model for obesity, curcumin inhibited the formation of new blood vessels (angiogenesis), decreased the transformation of young fat cells into mature fat cells (adipogenesis), and reduced the

buildup of fat in the mature cells, which has implications for lowering body fat and body weight gain in mice. Therefore, curcumin may have a potential benefit in weight control. In a human study on 40 subjects who had a weight loss <2% after 30 days of diet and intervention lifestyle, curcumin administration for an additional 30 days increased weight loss from 1.88 to 4.91%, enhanced body fat reduction percentage from 0.70 to 8.43%, and enhanced BMI reduction from 2.10 to 6.43% (208). Supplementation with curcumin (phytosomal form; 1000 mg/day) was associated with a reduction in BMI and waist circumference in patients diagnosed with NAFLD (209).

*Chemoprevention.*—Curcumin inhibited the proliferation of various tumor cells in culture, prevented carcinogen-induced cancers in rodents, and inhibited the growth of human tumors in various models (210). Numerous mechanisms for these outcomes have been implicated, and human data in this area are limited to a small number of study subjects. Large doses of oral curcumin have biological activity in some patients with pancreatic cancer and marked tumor regression (73%) was observed in one subject (211).

### Fenugreek

*Bioactive components.*—The chemical components of fenugreek seeds include a large carbohydrate fraction (mucilaginous fiber, galactomannan), steroidal saponins (e.g., diosgenin and trigogenin), free amino acids (e.g., hydroxyisoleucine and lysine), flavonoids, and alkaloids (e.g., gentianine and trigonelline). Three important chemical constituents with functionality are steroidal saponins (converted from saponin while passing through human intestinal tract), galactomannans, and 4-hydroxyisoleucine.

*Lipid metabolism and vascular health.*—Several animal and human studies have identified significant lipid-lowering activity with different fenugreek preparations (212–217). An animal study indicated that fenugreek fractions rich in steroid saponins decreased total plasma cholesterol but did not change triglyceride levels (212). The fiber content of fenugreek extract helped moderate the metabolism of lipids in the digestive tracts of rats (213, 214). In a hamster model of diabetes, a fenugreek-active compound (4-hydroxyisoleucine) decreased elevated plasma triglyceride by 33% and total cholesterol levels by 22% (215). Human data suggest that higher intakes may be required for lipid-lowering activity to become significant. An open label clinical trial using a daily dose of 12.5–18 g seed powder in healthy volunteers demonstrated significant reductions in total cholesterol and LDL-C levels (216). Another clinical trial study also showed that serum levels of triglycerides and VLDL-C were decreased significantly (30 and 30.6%, respectively) after taking 10 grams/day powdered fenugreek seeds soaked in hot water for 8 weeks in type 2 diabetic patients (217). Further well-controlled, double-blind research is warranted, especially to determine the optimum dosage levels.

*Blood glucose metabolism.*—Animal and in vitro studies have demonstrated that 4-hydroxyisoleucine, an amino acid extracted from fenugreek seeds, is a key component in supporting glucose and lipid metabolism (218). Administering fenugreek seed extract improved insulin signaling and sensitivity, which promoted the cellular actions of insulin in fructose-fed animals. This effect was comparable with that of metformin, a drug used to treat high blood sugar (219). The fiber content of fenugreek

extract also plays a role in its ability to moderate the metabolism of glucose in the digestive tract (220). Specifically, a soluble fiber in fenugreek, galactomannan, becomes viscous and thickens the intestinal contents, helping to maintain healthy glucose absorption (221). In a human study, when fenugreek was incorporated into food, it reduced the glycemic index (GI) by 21% compared with standard food not treated with fenugreek (222). Furthermore, a recent randomized, controlled crossover trial in healthy human subjects documented that replacing 10% of refined wheat flour with fenugreek seed powder significantly reduced the glycemic response and the GI of buns and flatbreads (223). It has been also reported that fenugreek seeds at 10 g/day significantly decreased fasting blood glucose and HbA1c, serum levels of insulin, homeostatic model assessment for insulin resistance, and total cholesterol and triglycerides, and it increased serum levels of adiponectin in type 2 diabetic patients (224).

*Satiety and weight management.*—Because of its high fiber content, fenugreek could help promote satiety, which may potentially support weight management. Hydroxyisoleucine, a fenugreek extract, reduced body weight in obese mice (225). In a single-blind, randomized, crossover study, 8 g fenugreek fiber in a breakfast meal increased feelings of fullness and reduced hunger, as well as reduced energy intake at lunch in 18 healthy obese subjects (226). Another small-scale, double-blind, randomized, placebo-controlled human trial showed a consumption of 1200 mg fenugreek seed extract daily for 14 days significantly decreased fat consumption by 17% compared with a placebo in 12 healthy subjects (227).

*Exercise and physical performance.*—Prolonged exercise depletes muscle reserves of glycogen, which can place limitations on physical performance. The speed of glycogen resynthesis in muscle can, therefore, determine the rate of recovery after exercise. A recent study in trained male cyclists documented that those who ingested a glucose beverage with fenugreek extract (containing 2 mg/kg body weight of 4-hydroxyisoleucine) right after high-intensity exercise had a 63% greater rate of muscle glycogen resynthesis than those who consumed the glucose beverage without the fenugreek extract (228). However, in a subsequent study by the same research group using a low-intensity exercise protocol, the fenugreek extract had no effects on glycogen resynthesis (229). Nevertheless, an animal study suggested fenugreek extract may have beneficial effects on endurance capacity by increasing fatty acid use and sparing glycogen. An animal study found that mice that received a fenugreek extract (300 mg/kg) had increased exercise endurance compared with those who did not (230).

*Liver health.*—Animal studies suggest fenugreek may help protect against liver changes induced by chronic alcohol consumption. Administration of fenugreek seed extract to alcohol-fed rats (200 mg/kg) reduced the levels of lipid peroxidation products and protein carbonyl content, increased the activities of antioxidant enzymes, and restored the levels of thiol groups compared with the control (231). Animal experiments have also found that fenugreek reduced the triglyceride accumulation in the liver (232), a hallmark feature of hepatic steatosis, and regressed cholesterol gallstones formation (233); both effects were accompanied by significant reductions in blood lipid levels.

*Sexual health.*—Fenugreek seed extract has demonstrated hormone modulatory activity, providing biological plausibility

for relieving menopausal symptoms. In a randomized, placebo-controlled trial, treatment with fenugreek dehusked seed extract at 600 mg/day resulted in a significant reduction in menopausal symptoms; women aged 40–65 years in the treatment group reported significantly less daytime hot flashes and night sweats at 12 weeks (234). In addition to improvements on various postmenopausal discomforts and quality of life of women, there was a significant increase in plasma estradiol in the extract-treated group (235). Moreover, Rao et al. (236) reported that fenugreek extract supplementation resulted in a significant increase in blood-free testosterone and E2 levels as well as sexual desire and arousal, compared with the placebo. The results indicate that fenugreek extract may be a useful treatment for increasing sexual arousal and desire in women.

Recently, clinical studies also documented the effect of a specialized fenugreek seed extract (e.g., Testofen) on the symptoms of possible androgen deficiency, sexual function, and serum androgen concentrations in healthy aging males (237–240). Supplementation of the extract at a dose of 600 mg/day for 12 weeks improved the Aging Male Symptom questionnaire, a measure of possible androgen deficiency symptoms; sexual function; and increased both total serum testosterone and free testosterone in healthy middle-aged and older men (237). Testofen demonstrated a significant positive effect on physiological aspects of libido and may assist to maintain normal healthy testosterone levels (239). A protodioscin-enriched fenugreek seed extract (500 mg/day) increased serum-free testosterone levels up to 46% as well as sperm counts, and it improved mental alertness, mood, and libido in the male study population (238).

### Rosemary

*Bioactive components.*—Rosemary contains phenolic acids and diterpenes including carnosic acid, carnosol, caffeic acid and its derivatives (i.e., rosmarinic acid), flavonoids (apigenin, diosmin, luteolin), and tannins. Rosemary also contains volatile oils that consist of cineole, pinene, and camphor.

*Antioxidant and anti-inflammatory effects.*—Numerous laboratory tests indicate that rosemary has strong antioxidant properties. Carnosic acid and carnosol likely account for over 90% of its antioxidant activity (241). Carnosic acid and carnosol reduced membrane damage by 40–50% and inhibited lipid peroxidation by 88–100 and 38–89%, respectively, under oxidative stress conditions in a cell culture testing. Both compounds also lowered DNA damage induced by a dietary oxidant (242). Rosemary extract enhanced antioxidant defenses and improved antioxidant status in aged rats (243). Rosemary suppressed the activation of inflammatory cytokines such as NF- $\kappa$ B and IL-1 $\beta$  and shut down specific enzymes (COX-2) involved in inflammation during in vitro experiments (244, 245).

*Cognition, mental health, and neuroprotection.*—Inhalation of rosemary and lavender oils enhanced cognitive function in a randomized study of 140 subjects using a cognitive assessment battery test and self-assessment mood scale (246). The aroma of rosemary oil reduced test-taking stress in graduate students (247). Rosemary extract had an antidepressant-like effect through an interaction with the monoaminergic system in a rat study (248). There is emerging

evidence that rosemary may promote brain health by inhibiting both acetylcholinesterase and butyrylcholinesterase in vitro, which may help facilitate communication among cells in the brain (249, 250). A protective effect on dopaminergic neural cells (which involve behavior and cognition, mood, attention, and learning) has been observed in a number of rosemary constituents (251, 252). Furthermore, carnosic acid may improve cell viability and blood flow to the brain, based on in vitro experiments (251, 253).

*Vascular health.*—Evidence suggests that rosemary extract could inhibit LDL-C oxidation in a biologically relevant human cell culture system (254). Rosemary has shown antithrombotic activity and may improve endothelial function both in vitro and in vivo (255, 256). At a 5% concentration, rosemary significantly improved vascular function by inhibiting platelet reactivity and arterial blood clot formation as well as enhancing flow-mediated vasodilation in animals (256). Further, rosemary extract inhibited rabbit lung angiotensin I-converting enzyme (ACE) in vitro (257). This inhibition leads to less production of a chemical that causes arteries to constrict, suggesting that rosemary extract may have an antihypertensive effect. Clinical studies are needed to determine whether this effect is significant in humans.

*Blood glucose control.*—In an animal model, a high dose of rosemary extract (100 mg/kg or higher) significantly lowered blood glucose levels and increased serum insulin concentrations in diabetic rabbits compared with 50 mg/kg (258). Rosemary activated PPAR- $\gamma$ , which plays an essential role in the regulation of cellular functions and metabolism, leading to lower blood levels of fatty acids and glucose (259). Furthermore, rosemary is a potential inhibitor of alpha-glucosidase, which may help reduce sugar absorption (260). Rosemary may also inhibit AGE formation in vitro (261), which suggests it has the potential to protect against the development of diabetic complications. However, more studies are required in animals and humans to confirm this hypothesis.

*Skin care.*—Destruction of collagen is a hallmark of skin aging as a result of exposure to UV irradiation in which the matrix metalloproteinases (MMPs) play important roles in destructive processes. A water-soluble extract inhibited UV-induced MMP-1 and showed potential benefits for preventing skin photodamage in vitro (262). Further, carnosic acid has demonstrated photoprotective action on human skin cells exposed to UVA light in vitro. Rosemary extract inhibited oxidative damage to skin-surface lipids in both in vitro and in vivo studies (263). Rosemary may be a good candidate for an antiskin aging agent, but more human data are needed.

*Hepatoprotective effects.*—Rosemary extract has reduced toxic chemical-induced liver damage and cirrhosis and has improved detoxification systems in an animal model (264). Consumption of 200 mg/kg leaf extract can limit weight gain induced by a high-fat diet and protect against obesity-related liver steatosis (build up of fat in the liver) in mice. However, administering a lower dose of the leaf extract at 20 mg/kg body weight was ineffective for this purpose (265).

*Chemopreventive and anticarcinogenic potential.*—In vitro studies suggest that rosemary extract may reduce the effects of carcinogenic or toxic agents in many human cell lines (266). One mechanism through which constituents in rosemary may exert anticancer effects is by reducing the expression of a number of proinflammatory genes (267).

## Garlic

**Bioactive components.**—Many of the biological effects of garlic are attributed to the allicin, ajoene, and other organosulfur constituents such as S-allyl-L-cysteine (SAC). Alliin, which is found predominantly in garlic, is cleaved by alliinase to form allicin when garlic is crushed or chopped. Allicin, which is unstable in an aqueous solution, rapidly decomposes nonenzymatically to other sulfur-containing compounds including allylpropyl disulfide, diallyl sulfide, diallyl disulfide, diallyl trisulfide, diallyl tetrasulfides, ajoene, and vinylidithiines. SAC is formed from  $\gamma$ -glutamylcysteines during long-term incubation of crushed garlic in aqueous solutions and is the primary organosulfur constituent in aged garlic extract. In addition, phytoalexin (e.g., allixin) is found to have certain biological activity. Allicin has been found to be the compound most responsible for the “hot” sensation of raw garlic.

**Anti-inflammatory activity.**—Garlic and its sulfur-containing compounds exert anti-inflammatory properties through the inhibition of NF- $\kappa$ B activation (a transcription factor that regulates inflammatory response genes), iNOS, and COX-2 expression during in vitro and animal studies (268–270). In a clinical trial, daily dose supplementation of a 1000 mg garlic tablet for 12 weeks significantly improved stiffness, pain, and physical function in overweight or obese women with OA (271).

**Cardiovascular health and endothelial function.**—Garlic has traditionally been used to promote cardiovascular health through a variety of mechanisms (268, 272–274). Evidence from in vitro, animal, and human research has shown that taking garlic may slow the development of atherosclerotic process (hardening of the arteries; 275, 276), a condition that can lead to heart attacks and strokes, by beneficially reducing fatty streak formation in blood vessels and atherosclerotic plaque size (277, 278), inhibiting oxidation of LDL-C (as oxidized LDL is what damages the blood vessels; 279, 280), suppressing inflammatory cell adhesion to endothelial cells (280), and improving impaired endothelial function (276, 281, 282). Some human trials showed that garlic slowed the development of atherosclerosis as measured by ultrasound (283) or increased brachial artery flow-mediated, endothelium-dependent dilation by 44% (284). More recently, Szulinska et al. (285) demonstrated that supplementation with 400 mg of garlic extract favorably modified endothelial biomarkers (e.g., CRP, and plasminogen activator inhibitor-1, and LDL-C) associated with cardiovascular risk. Furthermore, supplementation of garlic powder tablet (1200  $\mu$ g allicin/tab) twice daily could prevent carotid intima-media thickness progression in patients with coronary artery disease (286).

**Blood cholesterol-lowering effects.**—There is contradictory evidence about the effects of garlic on cholesterol and triglyceride levels. Animal and human cell lines studies have demonstrated that garlic may reduce blood lipids levels via inhibition of HMG-CoA reductase (similar to the mechanism by which statins work) or other key enzymes involved in cholesterol and fatty acid synthesis (287). A meta-analysis found garlic reduced blood total cholesterol (7.3 mg/dL) and triglycerides (9.7 mg/dL) but exhibited no significant effect on LDL or HDL (288). A later review documented that garlic supplementation reduced total cholesterol by 7.4–29.8 mg/dL in eight meta-analyses (289).

**Blood pressure-lowering effects.**—The antihypertensive effects of garlic and its constituents in vitro and in vivo are

well documented (290, 291). Garlic stimulates the synthesis of NO (292, 293) and inhibits ACE activity (294). Furthermore, garlic-derived organic polysulfides are converted by red blood cells into hydrogen sulfide gas, which leads to vasorelaxation via vascular smooth-muscle cell signaling pathway (295). This study demonstrated a new mechanism responsible for garlic-mediated attenuation of hypertension. A meta-analysis indicated that garlic reduced SBP by 16.3 mmHg and DBP by 9.3 mmHg in patients with an elevated SBP (296). A recent review documented that garlic supplementation reduced SBP by 7–16 mmHg and 5–9 mmHg for DBP based on four meta-analyses and two original studies (289).

**Antithrombotic and anticoagulant properties.**—Antithrombotic activity has been documented for garlic extract in both in vitro and in vivo human studies (297–299). Garlic has been shown to inhibit platelet aggregation (stickiness) by inhibiting COX-1 activity and thromboxane A2 formation (a clotting factor) during in vitro studies using human platelets (297, 299). Additionally, garlic extracts have the potential to activate fibrinolytic activity, increasing fibrinolysis (dissolving small blood clots; 300, 301). In a placebo-controlled study that involved 30 patients with coronary artery disease, administration of garlic extract (at the dose equivalent to 4 g garlic) increased markedly fibrinolytic activity (299). However, it seems that raw garlic or garlic oil does not impair platelet function or alter vasoreactivity and fibrinolytic potential in healthy volunteers (302–304).

**Hypoglycemic activity.**—Garlic has blood glucose-lowering properties in diabetic rats (305–307). When the rats were treated with a high dose (500 versus 50 mg/kg) of raw garlic, blood glucose, cholesterol, and triglyceride levels were markedly affected (308). Both garlic oil and diallyl trisulfide improved glycemic control in diabetic rats through increased insulin secretion and increased insulin sensitivity (309). In a human trial, it was demonstrated that treatment with time-released garlic product (Allicor) resulted in better metabolic control because of the lowering of fasting blood glucose and triglyceride levels (310). More recently, Wang et al. (311) systematically evaluated the clinical efficacy and safety of garlic supplement in the management of T2DM and found a significant reduction in the level of fasting blood glucose in from 1 to 2 weeks to 24 weeks, as well as significantly decrease in fructosamine and glycated hemoglobin (both in 12 and 24 weeks) were achieved in the garlic group. Thus, current data confirm that garlic supplements play a positive and sustained role in blood glucose and favorable lipoprotein regulation in the management of T2DM.

**Brain health.**—Experimental evidence has shown that some garlic-derived products have a protective effect against ischemic brain injury, thereby improving learning and memory retention (312–314). In vitro and animal studies also suggest garlic could protect neurons from A $\beta$ -induced neurotoxicity and apoptosis (315–317). These preclinical studies suggest that garlic helps prevent cognitive decline associated with AD (314–317). However, observation in humans is not available yet.

**Immunomodulatory activity.**—In vitro and in vivo (animal) studies have found that garlic and its constituents have several immune-enhancing effects such as stimulation of lymphocyte proliferation and interferon- $\gamma$  release and enhancement of macrophage phagocytosis and killer cell activity (318–321). However, more studies are needed to understand the significance of these emerging data.

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