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Review article

Garlic: Health benefits and actions

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ABSTRACT

Recent years have seen an increasing emphasis on foods and food components in disease prevention. Garlic (*Allium sativum* L.), one of the best-researched herbal remedies, holds a unique position in history, traditionally employed to treat infection, colds, diabetes, heart disease, and a host of other disorders. Clinically, it has been evaluated for lowering blood pressure, cholesterol, and glucose concentration, as well as for the prevention of arteriosclerosis and cancer. Epidemiologically, garlic consumption inversely correlates with the risk of oral, stomach, esophageal, colon, and prostate cancers. In addition, the biological activities of garlic, including antibacterial, antithrombotic, antioxidant, immunomodulatory, and antidiabetic actions and modulation of drug metabolism, have been extensively investigated. Here, we briefly summarize the recent findings on garlic and its sulfur-containing compounds in preventing cardiovascular diseases and cancer, along with its modulation of drug-metabolizing enzymes and membrane transporter activities. Finally, garlic safety and drug interaction are discussed.

1. Chemicals and bioactive components of garlic

The unique flavor and health-promoting functions of garlic are generally attributed to its rich content of sulfur-containing compounds, i.e., alliin, γ-glutamylcysteine, and their derivatives. Processing a fresh and intact garlic bulb by crushing, grinding, or cutting induces the release of the vacuolar enzyme alliinase, which very quickly catalyzes alliin to allicin [1,2]. Allicin is, however, a very unstable compound, soon rearranged and transformed into numerous lipid-soluble sulfur-containing byproducts, mostly diallyl disulfide (DADS) but also diallyl sulfide (DAS), diallyl trisulfide (DATS), allylmethyl trisulfide, and diallyl tetrasulfide [1]. These compounds emit strong odors and are kept in garlic oil. Under appropriate conditions, allicin can be transformed into other lipid-soluble products such as ajoene and vinyldithiin. Ajoene is identified as a principal product in garlic extract prepared by using ether as a solvent [3].

In contrast to the processes stated above, alternative pathways occur in case of different means of garlic storage. An aging process caused by immersing intact or sliced raw garlic in alcohol or vinegar for several months results in sulfur-containing compounds in this aged product dramatically different from those found in garlic oil. This aging process is supposed to cause considerable loss of allicin. Meanwhile, with the action of γ-glutamyltranspeptidase, the other sulfur-containing precursor γ-glutamylcysteine is transformed into water-soluble *S*-allylcysteine (SAC) and subsequent metabolites, including *S*-allylmercaptocysteine (SAMC)

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and S-methylcysteine. Unlike the oily sulfur compounds, these water-soluble compounds are odorless but have a more delicate and less characteristic flavor [4].

In addition to sulfur-containing compounds as stated above, garlic is also rich in trace elements. In raw garlic, the amounts of zinc, manganese, copper, selenium, and iodine in 100 g fresh weight of garlic are 556.1, 446.9, 143.3, 5.5 and 2.5 μg, respectively [5]. The protein content of raw garlic ranges from 2.6% to 3.0%, depending on the variety of garlic. The average content of free amino acids is 2.13%. Concentrations of dietary fiber and total tocopherols in raw garlic are 2310 and 103.1 mg/100 g fresh weight, respectively. Ascorbic and total polyphenols levels are 73.6 and 1.9 mg in 100 g dry weight [6]. Over 70 fatty acids have been determined, with linoleic (46–53%), palmitic (20–23%), oleic (4–13%), and α-linolenic (3–7%) acids being most abundant, accounting for 80% of the total lipids [7].

2. Garlic preparations and supplements

Because of the complex chemistry of garlic, variations in processing methods can yield quite different preparations. Raw garlic homogenate, the major preparation of garlic, is the most common form of garlic consumed, and allicin the main compound present in fresh raw garlic homogenate. There are currently many garlic supplements on the market, garlic oil, powder, and aged extract being the most popular.

Garlic oil is mostly obtained by steam distillation, with a yield around 2.5–3.0 g/kg fresh garlic. In garlic oil, DAS, DADS, and DATS, differing in their number of sulfur atoms, and allylmethyl sulfide are the four most abundant volatile allyl sulfides [8]. Garlic power is generated from garlic cloves that have been dehydrated and pulverized into powder. Due to deactivation of alliinase by heat during dehydration, the major active constituents of garlic powder are alliin and a small amount of oil-soluble sulfur compounds.

To overcome the strong and irritant odor and the possible side effects of raw garlic and garlic oil, including growth retardation and destruction of gut microflora, an “aging” process has been applied to garlic. Aged garlic is prepared by soaking whole or sliced garlic cloves in alcohol or vinegar solution for 6–20 months, which removes the several irritant sulfur-containing compounds and also stabilizes some unstable compounds such as allicin [4,9]. The water-soluble compounds SAC and SAMC are the most abundant sulfur-containing components, and trace amounts of oil-soluble allyl sulfides exist in aged garlic. In contrast to odoriferous garlic oil and raw garlic, garlic powder and odorless aged garlic product are currently the most popular garlic supplements on the market.

3. Garlic and cardiovascular disorders

Cardiovascular disease is a common human chronic disease, and it is the leading cause of morbidity and mortality in the USA [10]. The etiology of cardiovascular disorders is multifactorial, with, for example, hypercholesterolemia, hypertension, diabetes mellitus, heredity, hyperhomocysteinemia, increase in oxidative damage, and smoking as well-demonstrated risk factors [11].

Due to the accompanying inflammation in the plaque, cardiovascular disorders are regarded as chronic inflammation-related diseases [11]. The increased production and release of inflammatory mediators, such as reactive oxygen species (ROSs), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), arachidonic acid metabolites, and nitric oxide is noted in the atherosclerotic lesion [12]. This results in a greater expression of adhesion molecules, including P-selectin, E-selectin, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and monocyte chemotactic protein-1 on the cell surfaces of monocytes, leukocytes and vascular endothelial cells, which accelerates the adherence of monocytes and leukocytes to the vascular endothelium and their subsequent transmigration into the subendothelial space.

Within the intima, activated macrophages release ROSs, scavenge oxidized low-density lipoprotein (oxLDL), become foam cells, and lead to the development of the fatty streak in the early stage of atherosclerosis [13,14]. This explains why phytochemicals with anti-chronic inflammation, hypolipidemic, and antioxidative properties are thought to be capable of decreasing the incidence of atherosclerosis.

Garlic has been regarded as a potent antiatherogenic food [15]. Its lowering of blood cholesterol is believed largely due to a reduction in LDL-cholesterol [16,17], which may be due to inhibition of hepatic hydroxymethylglutaryl-CoA reductase activity by alliin and allicin [18]. Over the past decade, several intervention studies and systemic meta-analytic reviews have investigated the effectiveness and properties of garlic in preventing cardiovascular disease (Table 1).

A double-blind placebo-controlled randomized study including 51 patients with coronary conditions indicated that 12 months’ treatment with 300 mg/d garlic powder significantly decreased the total cholesterol and LDL-cholesterol levels [19]. A reduction of 32.9 and 27.3 mg/dL in LDL-cholesterol resulting from the garlic was observed in men and women, respectively.

A similar reduction in total cholesterol and LDL-cholesterol, along with an increase in high-density lipoprotein-cholesterol, were also reported in hypercholesterolemic adults who were administered 10 g/d garlic extract for 4 months, 5 g/d raw garlic for 6 weeks, or 600 mg/d garlic powder for 12 weeks [20–22]. Oily macerate of garlic (1620 mg/day for 30 days) was found to significantly lower the levels of total cholesterol, LDL-cholesterol, and triacylglycerides in 70 hypertensive adults [23]. However, Burggraaf and colleagues reported that 12 weeks of 2.1 g/d garlic powder administration did not change the lipid profiles in overweight subjects with normal blood lipid levels [24].

A meta-analysis including 29 trials recently revealed that garlic supplementation markedly reduced blood total cholesterol levels (−0.19 mmol/L; 95% CI −0.33 to −0.06 mmol/L) and triacylglyceride levels (−0.11 mmol/L; 95% CI −0.19 to −0.06 mmol/L), but exhibited no significant effect on LDL- or high-density lipoprotein-cholesterol [25]. A similar reduction in total blood cholesterol and triglycerides has been reported in systemic reviews [26,27]. Inconsistent clinical evidence warrants more study before reaching convincing conclusions.

Table 1 – Effect of garlic supplementation on human cardiovascular disorders.

Preparation	Subjects/dose	Effect	Reference
Garlic powder	51 patients with CVD, 300 mg/d, 12 mo	↓ total cholesterol and LDL-C	[19]
	42 mildly hypercholesterolemic men, 600 mg/d, 12 wk	↓ total cholesterol and LDL-C ↑ HDL-C	[22]
	90 normolipidemic and overweight adults, 2.1 g/d, 12 wk	No changes in blood total cholesterol, LDL-C, and TG	[24]
Raw garlic	30 hypercholesterolemic adults, 5 g/d, 42 d	↓ total cholesterol and TG ↑ HDL-C	[21]
Garlic extract	23 hypercholesterolemic adults (13 with hypertension), approximately 10 g/d, 4 mo	↓ total cholesterol, LDL-C, and TG ↑ HDL ↓ SBP and DBP	[165]
Aged garlic extract	11 healthy adults, methionine- induced hyperhomocysteinemia, 4 mL/d, 6 wk	↑ NO and endothelium-derived hyperpolarizing factor	[166]
	65 patients with intermediate CVD risk, 250 mg/d co-administered with B vitamins (B_{12}, B_6, and folic acid) and L-arginine, 12 mo	↓ total cholesterol, LDL-C, and homocysteine ↑ HDL	[140]
Garlic oil	20 hypertensive patients, 250 mg/d, 2 mo	↓ SBP, DBP, and oxLDL	[13]
Oil-macerated garlic	70 hypertensive adults, 1620 mg/d, 30 d	↓ total cholesterol, LDL-C, and TG	[23]

CVD = cardiovascular disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; NO = nitric oxide; oxLDL = oxidized LDL; SBP = systolic blood pressure; TG = triglycerides.

Garlic is reported to prevent cardiovascular disease by multiple effects, one of which is inhibition of platelet aggregation. A single intravenous dose of aqueous extracts of garlic (10–100 mg/kg) dose-dependently inhibited blood thromboxane B_2 concentration in rabbits [28]. Maximum inhibition of thromboxane B_2 occurred 0.5 hours after injection and lasted until 6 hours afterwards. In another study, oral administration of aqueous extract of fresh garlic inhibited cyclooxygenase (COX) activity in rabbit platelets, resulting in a suppression of thromboxane formation and blood aggregation [29]. Similarly, in eight males (aged 40–50 years), the consumption of one crushed clove of garlic daily for 16 weeks resulted in an 80% reduction in serum thromboxane B_2 levels [30].

Allicin and allicin-derived thiosulfinates are recognized as major compounds responsible for the antithrombotic activity of garlic [31]. Besides an inhibition of COX activity, other possible mechanisms for garlic's inhibition of platelet aggregation include suppression of intraplatelet Ca^{2+} mobilization, an increase in cyclic AMP and cyclic GMP levels, an increase in platelet-derived nitric oxide production, and a reduction in platelet binding to fibrinogen [32].

Garlic's protection against cardiovascular diseases has been partly attributed to its potent anti-inflammatory activity [33]. The ethyl acetate-soluble fraction of garlic is proven to be effective in inhibiting nuclear factor κB (NF-κB) activation, as well as expression of COX-2 and inducible nitric oxide synthase in IL-3-dependent murine pro-B-cells Ba/F3 through the Toll-like receptor-dependent pathway [34]. Thiacremonon, a novel organosulfur compound of garlic, inhibits 12-O-tetradecanoylphorbol-13-acetate-induced ear edema in ICR mice, and carrageenan- and *Mycobacterium butyricum*-induced inflammatory and arthritic responses in the paws of Sprague-Dawley rats [35]. Garlic oil reportedly suppresses 1-chloro-2, 4-dinitrobenzene-induced contact hypersensitivity as determined by ear swelling [36].

After 30 days of administration of 600 mg/kg garlic powder, an increase in interferon-γ and a decrease in IL-4 in phytohemagglutinin-activated splenocytes were noted, suggesting that garlic treatment may favor a T-helper type 2 cell or humoral immune response [37]. 1,2-Vinyldithiin was recently reported to significantly suppress IL-6 and monocyte chemoattractant protein-1 secretion by macrophage-secreted factors stimulated human preadipocytes isolated from the subcutaneous adipose tissue of nonobese young women [38]. DAS has been reported to prevent COX-2 upregulation and prostaglandin E_2 (PGE_2) secretion in primary human synovial fibroblasts and articular chondrocytes induced by IL-1β and monosodium urate crystal, and ameliorates crystal-induced synovitis, potentially through the NF-κB signaling pathway [39].

The presence of proinflammatory cytokines initiates numerous physiological changes in vessel walls, such as enhanced adhesion of leukocytes to the endothelium. A recent *in vitro* study indicated that the chloroform extract of aged black garlic attenuated TNF-α-induced VCAM-1 expression via an NF-κB-dependent pathway in human umbilical vein endothelial cells (HUVEC), hence decreasing the adhesiveness of monocytes on endothelial cells [40]. In primary human coronary artery endothelial cells, aqueous extract of garlic (0.25–4.0 mg/mL) dose-dependently curbs ICAM-1 and VCAM-1 expression induced by IL-1α [41]. When stimulated by oxLDL, DADS and DATS suppress VCAM-1 and E-selectin expression in HUVEC and the subsequent adhesion of HL-60 to endothelial cells [42].

Taken together, although solid clinical evidence that garlic's effect in protecting blood vessels can be attributed to its anti-inflammatory properties is lacking, the potent anti-inflammatory action of garlic and its sulfur-containing compounds obtained from *in vitro* and animal studies supports the potential value of garlic in preventing atherogenesis.

Evidence indicates that garlic also acts to maintain vascular tone and cardiac function. Experiments on laboratory animals and investigations of humans has proved that diets supplemented with garlic can restore endothelial functions. Allicin is believed to be the active component of raw garlic protecting coronary endothelial function and

vasoreactivity in pulmonary hypertensive rats [43]. Enhancement of nitric oxide synthase activity and greater nitric oxide production partly explained this hypotensive action.

Our recent work demonstrated that DADS and DATS protect the activity and protein expression of endothelial nitric oxide synthase in response to an oxLDL insult to the endothelial cells [44]; this is partly attributable to the mediation of phosphatidylinositol 3-kinase/protein kinase B signaling and prevention of eNOS degradation caused by DADS and DATS [44]. SAC supplementation reduces the incidence of stroke in stroke-prone spontaneously hypertensive rats [45], and lowers mortality and infarct size in a rat model of acute myocardial infarction induced by coronary artery ligation [46].

In an animal experiment inducing diabetes by streptozotocin, rats were orally administered 0–100 mg/kg/d garlic oil for consecutive 16 days; streptozotocin-induced cardiac contractile dysfunction and apoptosis were markedly improved by the garlic oil [47]. In a hypercholesterolemic animal experiment, rats were fed a 1.0% garlic- and 0.5% turmeric-supplemented diet for 10 weeks. Enhanced vasorelaxation in the aortic ring response to adenosine, acetylcholine, and isoproterenol, along with attenuation of the contractile response to 5-hydroxytryptamine, was seen in animals given the garlic- and turmeric-supplemented diet, thus lowering their blood pressure [48].

In a randomized, placebo-controlled, cross-over design involving 15 patients with angiographically proven coronary artery disease, brachial artery flow-mediated endothelium-dependent dilation was improved by aged garlic extract [49]. Similarly to aged garlic extract, garlic oil in a dose of 250 mg/d for 2 months demonstrably improved both systolic and diastolic blood pressure in 20 hypertensive patients [13].

4. Garlic and cancer

The past few decades have seen many epidemiological studies on the correlation between garlic consumption and incidence of cancer, from which an inverse relationship has emerged. Setiawan et al observed a negative dose–response relationship between the monthly intake of garlic and the risk of stomach cancer in Shanghai and Qingdao, China [50]. A recent study found an odds ratios among individuals with a high versus a low intake of garlic and onions that correlated with a starkly reduced risk of colorectal adenoma [51]. In persons who consume a high proportion of garlic, a decreased susceptibility to stomach and colon cancers has also been reported [52].

Based on the US Food and Drug Administration's evidence-based review system for scientifically evaluating the risk of diverse types of cancer, 19 human studies revealed garlic's antitumorigenic potential in stomach, colon, rectal, breast, lung, and endometrial cancers. Very limited evidence supports a relation between garlic consumption and reduced risk of colon, prostate, esophageal, larynx, oral, ovary, or renal cell cancer [53].

Several human intervention studies have plotted garlic's anticarcinogenic traits. A preliminary double-blind, randomized clinical trial using high-dose aged garlic extract (2.4 mL/d) as the active treatment and low-dose aged garlic extract (0.16 mL/d) as the control was performed involving 51 patients with colorectal adenomas/precancerous lesions of the large bowel [54]. After 12 months of treatment, 37 patients (19 in the active and 18 in control group) completed the study, the size and number of colon adenomas in the high-dose group being significantly lower ($p = 0.04$).

An earlier double-blind intervention study of 5033 subjects (2526 in the intervention and 2507 in the control group) was performed in China. A dose of 200 mg/d DATS in combination with 100 μg/d selenium was taken by the intervention group each month for 3 years. The results showed that DATS offered protection against gastric cancer for males [55]. In this study, it is interesting to note that no such protection occurred in females.

Numerous animal model studies found in the literature were carried out using either garlic extract or individual garlic-derived compounds. The development of aflatoxin B1- or diethylnitrosamine-induced liver cancer in rats was limited by fresh garlic [56] and garlic oil [57]; the latter also protected against ferric nitrilotriacetate-induced kidney cancer growth in rats [58]. DADS suppressed 7,12-dimethylbenzo[*a*]anthracene (DMBA)-induced rat mammary tumor [59]. DAS and DATS protected against DMBA-, phorbol ester-, and benzo[*a*]pyrene-induced skin tumorigenesis in mice [60–63]; DATS also inhibited the growth of PC-3 human prostate cancer xenografts in male nude mice [64]. Similarly, ajoene significantly inhibited B16/BL6 melanoma growth and metastasis to the lung in C57BL/L mice [65]. Aside from oil-soluble organosulfur compounds, water-soluble SAC inhibited the growth and malignant progression of highly metastatic human nonsmall-cell lung carcinoma in nude mice [66].

Although the precise mechanism of garlic's anticancer efficacy is still not clear, molecular action such as regulation of cell proliferation, increase in tumor apoptosis, blocking of the cell cycle, inhibition of carcinogen activation, increase in phase II drug-metabolizing enzymes, enhanced antioxidation capacity, change in proteasome-dependent protein degradation, and modulation of immune response have been proposed and extensively probed in recent years (Table 2).

In many cancer cells, garlic organosulfur compounds display potential for suppressing the growth of cancer cells and producing cell cycle arrest. DAS increases the accumulation of sub-G1 DNA and the concomitant accumulation of cells in the G2/M phase in a dose-dependent manner in human anaplastic thyroid carcinoma cells [67], as well as in human colon cancer cells [68]. DAS, DADS, and DATS further exhibit differential effects in terms of lowering cyclin-dependent kinase-Cdk7 and

Table 2 – Mechanisms underlying the anti-cancer actions of garlic.

1. Induces apoptosis/arrests the cell cycle
2. Blocks invasion/metastasis
3. Suppresses cell proliferation
4. Inhibits activation of carcinogen
5. Enhances antioxidation
6. Decreases histone deacetylase activity
7. Interrupts tubulin polymerization
8. Changes proteasome activity

raising cyclin B1 protein levels in J5 human liver tumor cells, thus arresting the cells in the G2/M phase [69]. Among those lipid-soluble allyl sulfides, which differ in their number of sulfur atoms, DATS revealed a better growth inhibition of human melanoma A375 cells and skin basal cell carcinoma cells than was seen with DADS and DAS [70]. The induction of apoptosis and cell cycle arrest by garlic allyl sulfides have also been reported in different types of cancer cell, e.g., human lung adenocarcinoma [71], glioblastoma [72], prostate cancer [73,74], neuroblastoma [75], gastric cancer [76], bladder cancer [77], colon cancer [78], and mammary cancer [79].

Garlic organosulfur compounds resulting in cell cycle arrest and apoptosis can be linked to the modulation of several key elements in cellular signal transduction. It has been demonstrated that DATS-induced apoptosis of PC3 human prostate cancer cells involves c-Jun N-terminal kinase (JNK) and extracellular-signal-regulated kinase-mediated phosphorylation of Bcl-2 [80]. Inactivation of the Akt signaling pathway also likely plays a role in DATS-induced mitochondrial translocation of Bad and caspase-mediated apoptosis in PC3 and DU145 human prostate cancer cells [81]. Likewise, the DATS arrest of DU145 cells in G2/M phase is effected by hyperphosphorylation of Cdc25C [82] and delayed cdk1 translocation into the nucleus [83], as well as by oxidative modification of beta-tubulin in human colon cancer cells, which impedes the polymerization of tubulin [84].

A similar interruption of tubulin polymerization has been reported by treating SW480 and NIH3T3 fibroblasts with SAMC; this subsequently arrests the cells in mitosis and triggers the JNK1 and caspase-3 signaling pathways, leading to apoptosis [85]. In B16F-10 melanoma cells, DADS-induced apoptosis is attributed to the mitochondrion-dependent pathway by upregulating p53 and caspase-3 while downregulating NF-κB-mediated Bcl-2 activation [86]. Recently, both the extrinsic and intrinsic death pathways have been shown to be involved in allicin induction of apoptosis in gastric SGC-7901 cancer cells [87].

Garlic organosulfur compounds may also act epigenetically and exert anticarcinogenic activity. Histone acetylation notably increases in colonocytes isolated from DADS-treated rats and also in erythroleukemia cells from SAMC-treated mice, suggesting that histone deacetylase is the target of garlic allyl compounds [88, 89]. In addition to DADS, other garlic organosulfur compounds have been tested; allyl mercaptan, a metabolite of DADS, has been shown to exert the most potent inhibitory effect on histone acetylase in assays with HeLa nuclear extracts, lysates from human colon cancer cells, or purified human histone deacetylase-8 [78,90]. Allyl mercaptan inhibition of histone deacetylase activity results in increasing histone acetylation and Sp3 transcription factor binding to the p21WAF1 gene promoter region, elevating p21 expression and producing cell cycle arrest in HT29 colon cancer cells [90]. Enzyme kinetics assays further reveal an inhibition of allyl mercatpan on histone deacetylase via a competitive mechanism ($Ki = 24\ \mu M$) [90].

Evidence indicates that tumor invasion and metastasis are suppressed in the presence of garlic and its organosulfur compounds. DATS administration retards the growth of PC-3 human prostate cancer xenograft cells in athymic mice [64], and prevents progression to invasive carcinoma and lung metastasis in transgenic adenocarcinoma of mouse prostate (TRAMP) cells [91]. In *in vitro* experiments, the DADS-suppressed invasion of human prostate cancer LNCaP cells was attributed to an inhibition of matrix metalloproteinase-2 (MMP-2) and MMP-9 activity and to a tightening of the tight junctions [92].

Garlic's suppression of tumor invasion may also be attributed to its action on E-cadherin expression. SAC and SAMC restoration of E-cadherin expression suppresses the proliferation and invasion of prostate cancer cells [93]. This increase in E-cadherin expression and inhibition of cell proliferation are also noted in oral squamous cancer CAL 27 cells in the presence of SAC [94]. The invasive activities of SW480 and SW620 colorectal cancer cells are inhibited by aged garlic extract, whereas aged garlic extract has no effect on the invasion of HT29 cells, suggesting that the anti-invasive action of aged garlic extract is cancer cell-dependent [95]. In the presence of ajoene, human leukemia HL60 cells were arrested in the G2/M phase; both trypsin- and chymotrypsin-like proteasome catalytic activities were inhibited [96].

Taken together, most animal and cell studies suggest that garlic is a potent chemopreventive agent for several types of cancer, acting by inhibiting cell proliferation, arresting the cell cycle, inducing cell apoptosis, and blocking invasion and metastasis.

5. Garlic and the detoxification system

The cancer-chemopreventive effect of garlic organosulfur compounds is believed to be associated with the modulation of carcinogen metabolism, including effects on phase I and II detoxification enzymes. Phase I enzymes, mainly cytochrome P450 (CYP), detoxify a variety of endogenous and exogenous chemicals and activate many carcinogens [97]. Phase II enzymes catalyze the conjugation of phase I metabolites to various water-soluble molecules, such as glutathione (GSH), glucuronic acid, or sulfate, accelerating the metabolite excretion rate. The efficacy of DAS, DADS, and DATS in the transcriptional regulation of phase I and II detoxification enzyme expression positively correlates with the suppression of aflatoxin B1- and benzo[*a*]pyrene-induced liver and forestomach neoplastic formation in mice and rats [98,99].

Decreased 7,12-dimethylbenzo[*a*] anthracene-induced DNA adduct formation in rat mammary tissue by DADS [59], protection against benzo[*a*]pyrene-induced skin tumorigenesis and micronucleated reticulocyte formation in mice by DAS [63], and the suppression of aflatoxin B1-induced DNA breaks by allicin, DAS, DADS, and SAC in HepG2 cells [100] can also be explained by their effectiveness in modulating metabolism of carcinogens.

Among the CYP isozymes, a decrease in CYP2E1 activity and protein levels has been reported in rats fed a diet containing 5% garlic powder [101]. This downregulation of CYP2E1 by garlic suppresses the formation in rats of hepatic preneoplasia induced by diethylnitrosamine [102]. The formation of lycidamide, an active metabolite of acrylamide, in rat liver tissues falls because of the inhibition of CYP2E1 by DAS [103]. In addition to DAS, a reduction in the activity and expression of CYP2E1 results from garlic oil, DADS, and allyl methyl

sulfide [104,105]. In contrast to downregulation of CYP2E1, the activities of isozymes CYP1A1, CYP1A2, CYB2B1, and CYP3A2, as well as their protein and mRNA levels, are upregulated by garlic organsosulfur compounds. Dosing rats with 200 mg/kg DAS and allyl methyl sulfide raises CYP1A1, CYP1A2, and CYP3A2 protein levels in a time-dependent manner, a rise being noted 24 hours after treatment [105]. A dose-dependent increase in rat liver CYP1A1, CYP2B1, and CYP3A1 activities and gene transcription is also caused by garlic oil (30–200 mg/kg body weight), probably from the combined effect of the three major allyl sulfides, DAS, DADS, and DATS, in the garlic oil [104,106,107].

Besides acting at the stage of gene transcription, the constituents of garlic may bind to CYP and change its enzyme activity. Using human liver microsomes, the activity of CYP2C9, CYP2C19, CYP3A4, CYP3A5, and CYP3A7, but not CYP2D6, is inhibited by incubation with garlic oil or extracts of fresh garlic, garlic powder, or aged garlic [108]. In the case of CYP2E1, diallyl sulfone and diallyl sulfoxide, metabolites of DAS, act as suicide substrates [109]; this inhibited CYP2E1 activity explains partly the action of DAS in attenuating acetaminophen-, carbon tetrachloride- and ischemic-reperfusion-induced toxicity in rat livers [110,111].

Phase II detoxification enzymes are known to play a key role in accelerating the excretion rate of numerous xenobiotics. Induction of phase II enzymes such as glutathione S-transferase (GST), epoxide hydrolase (EH), UDP-glucuronyl transferase (UGT), sulfotransferase, and NAD(P)H quinone oxidoreductase 1 (NQO1) is considered to be a crucial mechanism protecting organisms against chemical insults. It is thus reasonable to speculate that the induction potency of phytocompounds on phase II enzymes is associated with their efficacy in chemoprevention [112,113].

GST is among the most important phase II enzymes, its vital role in cancer prevention being supported by the finding that the incidence of 7,12-dimethylbenzanthracene-induced skin cancer was significantly elevated in the pi form of GST (GSTP)-null mice [114]. The increase in GST activity caused by garlic organosulfur compounds, including allyl methyl trisulfide, allyl methyl disulfide, DATS and DAS, strongly correlates with the inhibition of benzo[*a*]pyrene-induced forestomach neoplasia [115]. The effect of DAS, DADS, and DATS on the transcriptional regulation of GST enzyme expression is also positively correlated with their suppression of aflatoxin B1- and benzo[*a*]pyrene-induced liver and forestomach neoplastic formation [98,99].The decrease in 7,12-dimethylbenz[*a*]anthraxcene-induced hamster buccal pouch carcinogenesis caused by SAC is also accompanied by enhanced GST activity and an increased GSH level [116].

Upregulation of phase II detoxification enzyme gene transcription involves a series of signaling pathways and transcriptional factors. Among these, the pivotal role of nuclear factor E2-related factor 2 (Nrf2) is well documented [112,117]. Activation and binding of Nrf2 to the promoter antioxidant response element/electrophile response element increases the transcription of GST, NQO1, UGT, and sulfotransferase. After treatment with garlic organosulfur compounds, Nrf2 nuclear translocation is increased and NQO1 expression is upregulated in HepG2 cells and in mice [118,119]. Increased hepatic NQO1 and GST activity helps to attenuate carbon tetrachloride-induced liver injury in rats orally dosed with 500 μmol/kg DATS for 5 consecutive days [120].

Dozens of organosulfur compounds have been identified in garlic products, and these appear to vary in their biological activity. It is interesting to ask what chemical characteristic of these garlic-derived compounds determines their potency to modulate drug metabolism. Evidence from structure–function relationship studies indicates that the number of both allyl groups and sulfur atoms in each organosulfur compound is a determining factor in the transcription of phase I and II enzymes.

With phase II detoxification enzymes, the number of sulfur atoms and allyl groups correlates positively with their potency to enhance gene transcription. DATS displays the best induction of NQO1, follows by DADS; DAS has only a minor effect [118]. Compared with DATS, DADS at a 10-fold higher dose (100 μmol/kg) increased the expression of GST and NQO1 in rat liver, whereas DAS did not [121]. Similar findings (DATS > DADS > DAS) have been reported for the induction of GSTP in rat liver [107,122]. An increase in UGT activity is also noted in HepG2 cells treated with DAS, dipropyl sulfide (DPS), and DADS; the effective concentration of DAS and DPS (50 μM) is much higher than that of DADS (2.5 μM) [123]. Feeding rats a diet containing 5% garlic powders markedly raises hepatic UGT activity in an alliin content-dependent manner [101].

A comprehensive study to examine the effect of the allyl sulfides DAS, DADS, DPS, and dipropyl disulfide (DPDS) on the hepatic, renal, intestinal, and pulmonary phase II enzymes GST, EH, UGT, and NQO, was performed by Guyonett et al [124]. After orally dosing Wistar rats with 1 mmol/kg of each of the compounds for 4 consecutive days, DADS exerted the greatest inducibility of all phase II detoxification enzymes, with pulmonary EH activity unchanged. In addition, induction of NQO activity was seen only in DADS-treated animals. The increases in GST and EH activity caused by DAS, DPS, and DPDS were only noted in liver. Later, the increase in hepatic GST and NQO1 expression and activity by treatment with allyl-containing compounds was demonstrably greater than that by propyl-containing ones: i.e., DADS > DPDS and DATS > dipropyl trisulfide [118,125,126]. These findings suggest that garlic alk(en)yl sulfides have different potencies for inducing phase II enzymes, and that such induction is tissue-specific.

As for phase I enzymes, garlic components with an allyl side chain are better at inducing most CYP isozyme expressions than are propyl- or methyl-containing ones. However, the effect of sulfur atom number on CYP expression differs from that seen in their action on phase II enzymes: garlic compounds with a higher number of sulfur atoms displayed lower inducibility [105,107,115,122,126]. This discrepancy suggests that the regulatory mechanism of garlic organosulfur compounds on phase II and CYP isozymes is different, and the precise active mechanism warrants further study.

6. Garlic and antioxidation

Oxidative stress is a state wherein the balance between radicals generated and the free radical- or oxidant-scavenging capacity of the endogenous antioxidant system is disrupted. Oxidative stress is documented as being involved in the

pathogenesis of chronic diseases, including cardiovascular disorders and cancer. Hence, compounds with antioxidant properties may be used to prevent oxidative stress-mediated diseases [127].

Numerous studies have demonstrated garlic and its organosulfur compounds to be potent antioxidants by displaying radical-scavenging activity and modulating cellular antioxidant enzyme activity. Aged garlic extract and SAC have been shown to scavenge ROSs, protect endothelial cells from injury by oxLDL [128], and defend PC12 neuron cells from damage by hydrogen peroxide [129]. Garlic extract has been proven to be as effective as *N*-acetylcysteine in lessening ROS formation and GSH depletion induced by acetaminophen in rat primary hepatocytes [130]. Garlic pretreatment with 1 g/kg for 5 weeks reduces iron-catalyzed lipid peroxidation by lowering malondialdehyde levels in rat liver and colon, along with enhancing the status of the antioxidants [131]. Likewise, garlic reduces iron-induced cell proliferation and autophagy and protects mitochondrial membranes by lowering iron storage in the liver [131]. Garlic oil is effective in reducing tributyltin-induced oxidative damage in mice and human amniotic cells [132], as well as decreasing sodium nitrite-induced neurotoxicity in rats [133].

The aforementioned garlic protection against oxidant-induced damage can be attributed to an increase in the activities of superoxide dismutase, GSH reductase, γ-glutamate cysteine ligase, and GST, and also in GSH production [133–135]. Activated Nrf2 demonstrably plays a key role in garlic enhancement of both antioxidant defense capability and drug metabolism enzymes, as described above [134].

The antioxidant properties of garlic have been ascertained in animal models of disease. In the fructose-induced metabolic syndrome model in rats, aqueous garlic extract attenuates oxidative stress and prevents vascular remodeling by suppressing NAD(P)H-oxidase [136]. In db/db mice with type 2 diabetes, the consumption of 5% freeze-dried aged black garlic for 7 weeks significantly raised superoxide dismutase, catalase, and glutathione peroxidase activity and lessened lipid peroxidation in the liver [137]. In rats with streptozotocin induced-diabetes, garlic oil helps to normalize impaired antioxidant status [138]. Less neuron damage accompanied by increased levels of synaptophysin and presynaptic SNAP25 (synaptosomal-associated protein of 25 kDa, a member of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors, which play a key role in presynaptic vesicle fusion and exocytosis), have been seen in Alzheimer's APP transgenic (Tg) mice treated with a diet containing 2% aged garlic extract and its active component SAC (20 mg/kg diet) [129]. SAC also reduces lipid peroxidation and superoxide radical production, and elevates Cu-Zn-superoxide dismutase activity in 1-methyl-4-phenylpyridinium-induced parkinsonism in mice [139].

In recent years, several human intervention studies have examined the antioxidant potency of garlic in humans. Two months of garlic oil (250 mg/d) supplementation greatly reduced oxLDL and 8-iso-prostaglandin F_2 alpha levels, accompanied by a significant decline in both systolic and diastolic blood pressure, in hypertensive patients [13]. A similar fall in oxLDL production has been reported by dosing 70 hypertensive adults with 1620 mg/d oily macerate of garlic for 30 d [23]. In double-blind placebo-controlled study, plasma oxLDL levels sharply fell in those administered 200 mg/d aged garlic extract combined with multi-micronutrients (folic acid, vitamins B_6 and B_{12}, and L-arginine) for 1 year, compared with controls [140]. Taken together, these results suggest that garlic has potent antioxidant activity in delaying the onset and development of cardiovascular disease, cancer, diabetes, and neurodegenerative diseases caused by an imbalance between free radical production and antioxidant defense.

7. Garlic and drug interaction

As stated above, garlic definitely modulates drug-metabolizing enzyme activity and membrane transporter levels in the liver, lung, kidney, and intestinal tissues. This raises some possibility that garlic supplementation could cause interactions between food and drugs and change the therapeutic efficacy of any drugs administered. To resolve this question, *in vitro* and *in vivo* experiments have multiplied in recent years. Increased toxicity of the human immunodeficiency virus protease inhibitor ritonavir has been reported in patients with AIDS who were co-administered garlic [141]. This can be explained, at least in part, by its inhibition of the excretion of ritonavir: allicin, for example, has been reported to inhibit the p-glycoprotein-mediated efflux of ritonavir in Caco-2 cells [142].

However, examining the permeability of rat jejunum and the Caco-2 cell monolayer has shown that aged garlic extract raises saquinavir and darunavir efflux [143]. A higher efflux of darunavir after addition of aged garlic extract has recently been noted in rat liver slices and isolated hepatocytes, whereas the efflux of saquinavir decreases [144]. The authors propose the competitive binding at the same binding sites and a positive cooperative effect with distinct binding places is likely to be responsible for garlic's effect in altering the efflux of saquinavir and darunavir, respectively [144]. Greater multidrug resistance-associated protein 2 expression is also reported in kidney brush-border membranes with DADS, but not with SAC [145].

For *in vivo* models, the pharmacokinetics of the diuretic drug hydrochlorothiazide in rats has been calculated following 3 weeks' administration of garlic homogenate. The results show that garlic homogenate increases the bioavailability and half-life of hydrochlorothiazide while decreasing its clearance [146]. The diuretic effect of hydrochlorothiazide is concomitantly increased by garlic homogenate. Enhancement of the antihypertensive and cardioprotective efficacy of captopril in rats by garlic homogenate and SAC was also reported in a later work [147].

In our laboratory, the effect of garlic oil on the pharmacokinetics of atorvastatin has recently been determined. Rats were orally administered 50 mg/kg of garlic oil for 5 consecutive days, and then a single dose of atorvastatin (10 mg/kg) was given. The rise of p-glycoprotein levels in liver and 3A1/2 activity in both intestinal and liver tissue appear to be negatively correlated to the area under the curve (AUC) of plasma concentration of atorvastatin and its metabolite 2-OH-atorvastatin (unpublished data).

It would also be intriguing to learn whether and how garlic supplementation interacted with drugs in humans and changed their therapeutic efficacy. To date, limited research

Table 3 – Garlic and drug interactions.

Preparation	Subjects/dose	Effect	Reference
Garlic extract	12 healthy males, 2 g/d (3.71 mg allicin/tablet), 2 wk	No changes in the pharmacokinetics of warfarin	[150]
Garlic extract	10 women with breast cancer, 600 mg/d (3.6 mg allicin/tablet), 17 d	No changes in the pharmacokinetics of docetaxel	[151]
Garlic extract	10 healthy males, 600 mg/d (12 mg γ-glutamyl- cysteine/4.8 mg alliin), 21 d	↑ duodenal p-glycoprotein level No change in CYP 3A4 expression No changes in bioavailability of simvastatin, pravastatin, and saquinavir	[148]

has been carried out (Table 3). In a clinical trial involving 10 healthy subjects, 600 mg garlic extract was given daily for 21 days, the results indicating that garlic extract increased intestinal p-glycoprotein expression and decreased the AUC of plasma concentration of saquinavir [148]. Our study evaluated the pharmacokinetics of two hypocholesterolemic drugs, simvastatin and pravastatin, whose AUCs were not changed.

Due to its antithrombotic activity, garlic ranks among the most widely used herbal medicines, typically ingested by people receiving warfarin [149]. Changes in the pharmacokinetics of warfarin as a result of garlic have been determined in a clinical trial involving 12 healthy male volunteers. The results showed that the plasma concentration–time profile of warfarin and platelet aggregation unaltered when warfarin was co-administered with garlic (2 g/d) for 2 weeks [150].

An influence of garlic on the pharmacokinetics of docetaxel was also rated in 10 women with metastatic breast cancer [151], treated with 30 mg/m^2 docetaxel given weekly for 3 of 4 weeks. Three days after the initial dose of docetaxel, patients received 600 mg of garlic twice daily for 12 consecutive days. The results indicated that the clearance of docetaxel and additional pharmacokinetic parameters including peak concentration, AUC, and half-life were not affected.

Although garlic had no significant effect on the pharmacokinetics of docetaxel, these authors found that patients with the CYP3A5*3C/*3C genotype had a lower mean AUC ratio than those with the CYP3A5*1A/*1A genotype [151]. This finding suggests that genetic background is a determining factor in the outcome of garlic and drug interaction. Understanding the genotype of each individual tested may help in evaluating whether garlic interacts with the particular drug and changes its therapeutic efficacy.

Although the results remain inconsistent and contradictory, the possibility that garlic will affect the therapeutic efficacy of certain drugs cannot be excluded based on its potency in terms of modulating drug-metabolizing enzymes and the activity and expression of membrane transporters.. More well-designed studies are warranted to clarify whether garlic affects the metabolism of drugs and alters their pharmacokinetics.

8. Safety of garlic

Consumed for hundreds of years, garlic is regarded as a safe food. However, in addition to the possible interaction with drugs cited above, several health risks have been reported to be associated with the excess consumption of garlic, or with contact with garlic it in the workplace. In particular, gastrointestinal tract injury and allergic reactions caused by garlic attract concern. Increased exfoliation of the gastric surface epithelial cells in healthy subjects has been reported after the intragastric infusion of a single dose of raw garlic of over 0.75 g [152]. By injecting 0.5 mL of raw garlic juice into the ligated duodenum of rats, injury to the duodenal mucosal lining followed 2 hours after exposure, with severe damage including ulcers and bleeding occurring after 24 hours [153].

Damage to the stomach and intestine may account for the decrease in body weight seen after rats were given aqueous extracts of garlic (300 or 600 mg/kg/d for 21 days) and garlic oil (200 mg/kg, three times a week for 6 weeks) [36,154]. In a chronic toxicity test, however, no differences in body weight gain and in urinary, hematological, serological, and histological examinations were observed in Wistar rats given garlic extract at doses of 2 g/kg five times a week for 6 months [155]. These inconsistencies require more careful experimental designs to clarify whether garlic displays an adverse effect on gastrointestinal tract and growth; for instance, differences in garlic species, garlic preparations, and the dosage tested merit consideration.

Over recent decades, the allergenic potential of garlic has become well recognized. Cases of allergic reactions – e.g., contact dermatitis, asthma, urticaria, pemphigus, and anaphylaxis – have been reported in association with garlic use [156]. Allergic contact dermatitis in response to garlic was initially reported in 1950; to date, most cases have appeared in chefs and housewives in frequent contact with garlic [157–161]. Among Fernández-Vozmediano et al.'s 13 curry chefs, four tested DADS-positive, all showing dermatitis of the nondominant hand, with hyperkeratosis and fissuring of the thumb, index, and middle finger [162]. Allergy of the hands in the case of a 58-year-old male taking garlic to treat his hyperlipidemia also related to his use of garlic tablets [163]. Based on such evidence, garlic is classified as a type I allergen [159], the allergens being identified as DADS, allylpropyl disulfide, allylmercaptan, and allicin [164].

9. Conclusions

Past decades have seen myriad studies, especially *in vitro* and in animal models, addressing the protective effect of garlic against cardiovascular disease and cancer. This protection can arise from its diverse biological activities: enhanced antioxidant defense, lowering of blood lipids, inhibition of blood aggregation, enhancement of cancer cell cycle arrest/apoptosis, inhibition of invasion and/or metastasis, and

modulation of drug metabolism and/or the immune response. However, the results observed in human clinical and intervention studies have been inconsistent. The risk of garlic–drug interactions is attracting increasing interest, especially in the elderly and in those with chronic diseases. Further experiments are warranted to understand the actual health benefits and impact of garlic.

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