Garlic

Species (Family)

Allium sativum L. (Amaryllidaceae/Liliaceae)

Synonym(s)

Ajo, Allium

Part(s) Used

Bulb (clove)

Pharmacopoeial and Other Monographs

BHP 1996[G9]
BP 2001[G15]
BPC 1949[G11]
Complete German Commission E[G3]
ESCOP 1997[G52]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO year volume 1[G63]

Legal Category (Licensed Products)

GSL[G37]

Constituents[1–3,G6,G41,G52,G56,G64]

Enzymes Allinase, peroxidases, myrosinase and others (e.g. catalases, superoxide dismutases, arginases, lipases).[2,3]

Volatile oils 0.1–0.36%. Sulfur-containing compounds including alliin, compounds produced enzymatically from alliin including allicin (diallyl thiosulfinate), allylpropyl disulfide, diallyl disulfide, diallyl trisulfide; ajoene and vinyldithiines (secondary products of alliin produced non-enzymatically from allicin); S-allylmercaptocysteine (ASSC) and S-methylmercaptocysteine (MSSC); terpenes include citral, geraniol, linalool, α- and β-phellandrene.

Other constituents Proteins (e.g. glutamyl peptides), amino acids (e.g. arginine, glutamic acid, asparagic acid, methionine, threonine), minerals, vitamins, trace elements, lipids, prostaglandins (A_2, D_2, E_2, $F_{1\alpha}$, F_2).[2,4]

Allicin and other sulfur-containing compounds are formed from alliin by the enzyme alliinase when garlic is crushed or chopped. (Alliin and alliinase are separated while the cells of a garlic bulb are intact, but crushing and chopping damage the cells of the bulb, allowing alliin and alliinase to come into contact with each other.[G56]) It is considered that 1 mg alliin is equivalent to 0.45 mg allicin.[G52] Commercial garlic preparations are often standardised on content of sulfur-containing constituents, particularly to alliin, or on allicin yield.

Garlic powder contains not less than 0.45% allicin calculated with reference to the dried drug.[G28]

Food Use

Garlic is used extensively as a food and as an ingredient in foods. It is listed by the Council of Europe as a natural source of food flavouring (category N1). This category indicates that there are no restrictions on the use of garlic in foods.[G16] In the USA, garlic is listed as GRAS (Generally Recognised As Safe).[G41]

Herbal Use

Garlic is stated to possess diaphoretic, expectorant, antispasmodic, antiseptic, bacteriostatic, antiviral, hypotensive and anthelmintic properties, and to be a promoter of leukocytosis. Traditionally, it has been used to treat chronic bronchitis, respiratory catarrh, recurrent colds, whooping cough, bronchitic asthma, influenza and chronic bronchitis.[G2,G6,G32,G34,G49,G64] Modern use of garlic and garlic preparations is focused on their reputed antihypertensive, anti-atherogenic, antithrombotic, antimicrobial, fibrinolytic, cancer preventive and lipid-lowering effects.

Dosage

Dried bulb 2–4 g three times daily;[G6] fresh garlic 4 g daily.[G3]

Tincture 2–4 mL (1 : 5 in 45% alcohol) three times daily.[G6]

Oil 0.03–0.12 mL three times daily.[G6]

Juice of Garlic (BPC 1949) 2–4 mL.[G11]

Syrup of Garlic (BPC 1949) 2–8 mL.[G11]

Clinical trials assessing the effects of garlic powder tablets on various parameters, including total serum cholesterol concentrations, triglyceride concentrations, blood pressure, platelet aggregation, vascular resistance, fibrinolysis and measures of peripheral arterial occlusive disease, have generally involved the administration of doses of 600–900 mg daily for 4–24 weeks.[G56] For prophylaxis of atherosclerosis, ESCOP (European Scientific Co-operative on Phytotherapy) states a dosage 0.5–1.0 g dried garlic powder daily (approximately equivalent to alliin 6–10 mg and allicin 3–5 mg).[G52]

Pharmacological Actions

In vitro and animal studies

Many pharmacological properties have been documented for garlic and its constituents *in vitro* and *in vivo* (animals), including antihypertensive, lipid-lowering, anti-atherogenic, antithrombotic, fibrinolytic, antioxidant, anticarcinogenic, antitumorigenic, immunomodulatory and antimicrobial activities. The pharmacological properties of garlic are attributed mainly to its sulfur-containing compounds. An extensive review of the pharmacological properties of garlic and its constituents is beyond the scope of this monograph, although several studies are described in brief below. The pharmacological activities of garlic and its constituents have been summarised in many reviews.[3,5–21,G5,G56]

Pharmacokinetics The available literature on the metabolism and pharmacokinetics of the constituents of garlic in animals has been reviewed.[3,G18]

In an *ex vivo* study, allicin showed a marked first-pass clearance effect in isolated perfused rat liver.[3] In rats, alliin and allicin were administered orally at doses of 8 mg/kg.[22] Absorption of alliin and allicin was complete after 10 minutes and 30–60 minutes, respectively. The mean total urinary and faecal excretion of allicin after 72 hours was 85.5% of the dose. No unchanged alliin or allicin was detected in urine, suggesting rapid and extensive metabolism of these constituents.[3] Pharmacokinetic studies of the garlic constituent *S*-allyl-L-cysteine administered orally to rats at doses of 12.5, 25 and 50 mg/kg have reported bioavailability of 64%, 77% and 98%, respectively.[23] Peak plasma concentrations of *S*-allyl-L-cysteine occurred at one hour, and the half-life of *S*-allyl-L-cysteine was 2.33 hours following oral administration of 50 mg/kg to rats.

Anti-atherosclerotic and cholesterol- and lipid-lowering effects The effects of garlic and its constituents on cholesterol biosynthesis *in vitro* and in animal models of hypercholesterolaemia are well documented.[3]

Several *in vitro* studies have shown that garlic and its sulfur-containing constituents inhibit cholesterol biosynthesis in cultured hepatocytes.[24–28] In other *in vitro* studies, garlic extracts were shown to inhibit fatty acid and triglyceride synthesis.[29,30]

The step(s) in the cholesterol biosynthetic pathway inhibited by garlic, and the constituents of garlic causing inhibition have not been definitively established. Several mechanisms of action for the effects of garlic constituents on cholesterol and lipid synthesis have been proposed, including inhibition of hydroxymethylglutaryl-CoA (HMG-CoA) reductase activity and other enzymes, such as lanosterol-14-demethylase, involved in cholesterol biosynthesis.[3] Other proposed mechanisms include reduction in triacylglycerol biosynthesis via a reduction in tissue concentrations of NADPH, increase in hydrolysis of triacylglycerols via increased lipase activity and inactivation of enzymes involved in lipid synthesis via an interaction with enzyme thiol groups.[6,8,31] More recently, fresh garlic extract and the constituents *S*-allylcysteine, diallyl trisulfide and diallyl disulfide were shown to inhibit human squalene monooxygenase, an enzyme catalysing a step in cholesterol biosynthesis.[32] Another *in vitro* study reported that *S*-allylcysteine, *S*-propylcysteine and *S*-ethylcysteine inhibit triglyceride biosynthesis in part by decreasing *de novo* fatty acid synthesis via inhibition of fatty acid synthase.[30]

The anti-atherogenic, anti-atherosclerotic and cholesterol- and lipid-lowering effects of garlic and its constituents have been documented in several animal models (e.g. rabbits, rats, chickens, pigs) of atherosclerosis, hypercholesterolaemia and hyperlipidaemia.[3] For example, a reduction in both blood and tissue lipid concentrations in hypercholesterolaemic animals fed a diet supplemented with dried garlic powder, garlic oil, or allicin has been documented.[6,33] Garlic has also been reported to reduce hepatic triglyceride and cholesterol concentrations in rats, and to reduce aortic lipid deposition and atheromatous lesions in rabbits fed a high-fat diet.[6] Several studies have reported hypolipidaemic effects for garlic oil following administration to rats and rabbits fed a fat-rich diet to induce hyperlipidaemia.[3] Administration of aged garlic extract to rabbits fed a 1% cholesterol-enriched diet for six weeks reduced the surface area of the thoracic aorta covered

by fatty streaks (atherosclerosis) and significantly reduced aortic arch cholesterol, although plasma cholesterol concentrations were not reduced.[34] Allicin administration has been reported to reduce significantly the formation of fatty streaks in mice fed a cholesterol-rich diet, compared with control mice (no allicin treatment).[35]

The cholesterol-lowering effect of garlic is thought to be dose-related; proposed mechanisms of action include inhibition of lipid synthesis and increased excretion of neutral and acidic sterols.[6,8] An *in vitro* study reported that aged garlic extract may exert its anti-atherogenic effects via inhibition of smooth muscle proliferation and phenotypic change, and by an effect on lipid accumulation in the artery wall.[34,]

Antithrombotic and fibrinolytic activities Antithrombotic activity is well documented for garlic in both *in vitro* and *in vivo* (animal) studies.[3] Antithrombotic effects have been documented for fresh garlic, garlic powder and garlic oils.[3]

Increased serum fibrinogen concentrations together with a decrease in blood coagulation time and fibrinolytic activity are associated with a high-fat diet and enhance thrombosis.[6] Garlic has been shown to have a beneficial effect on all of these parameters. Garlic has been shown to inhibit platelet aggregation[36,37] caused by several inducers such as ADP, collagen, arachidonic acid, adrenaline (epinephrine) and calcium ionophore A23187.[38] Antiplatelet activity has been documented for garlic in *in vitro* studies using human platelets.[5,39]

Several mechanisms have been proposed by which garlic is thought to exert an anti-aggregatory action. These include inhibition of thromboxane synthesis via cyclooxygenase and lipoxygenase inhibition,[8] inhibition of membrane phospholipase activity and incorporation of arachidonic acid into platelet membrane phospholipids,[40] intraplatelet mobilisation of calcium uptake and inhibition of calcium uptake into platelets.[38] Garlic oil has been reported to reduce artificial surface adhesion of platelets *in vitro*.[41] Certain garlic constituents also affect processes preceding platelet aggregation, such as activation of platelets.[3]

Garlic is thought to contain more than one inhibitor of platelet aggregation and release; allicin is considered to be the major inhibitor.[3,42] Other studies have investigated the role of ajoene (a secondary degradation product of alliin) as an inhibitor of platelet aggregation and release.[3,43] Ajoene inhibits platelet aggregation caused by various inducers.[44,45] Its action is noted to be dose-dependent and reversible both *in vitro* and *in vivo*.[43] It has been suggested that this latter feature may be of clinical significance in instances where a rapid inhibition of platelet aggregation is required with subsequent reversal, such as chronic haemodialysis and coronary bypass surgery.[43] It has been proposed that ajoene exerts its anti-aggregatory effect by altering the platelet membrane via an interaction with sulfhydryl groups.[46] The inhibitory action of ajoene on granule release from platelets is thought to involve alteration of the microviscosity in the inner part of the plasma membrane.[47] Ajoene is reported to synergistically potentiate the anti-aggregatory action of prostacyclin, forskolin, indomethacin and dipyridamole,[48] and to potentiate the inhibitory action of prostaglandin I_2 (PGI_2) on platelet aggregation.[21] Approximately 96% inhibition of prostaglandin synthetase and 100% inhibition of lipoxygenase has been described for ajoene *in vitro*.[40] Structure–activity investigations suggested that an allylic structure in the open disulfide ring is required for activity.[40]>

Antioxidant effects Antioxidant properties have been documented for garlic *in vitro* and *in vivo* (animals).[3] Garlic constituents inhibit the formation of free radicals, support endogenous radical-scavenging mechanisms, enhance cellular antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase), protect low-density lipoprotein from oxidation by free radicals, and inhibit the activation of the oxidant-induced transcription factor nuclear factor kappa B (NF-κB).[3,18]

Garlic powder was reported to inhibit the production of superoxide by phorbol ester-activated human granulocytes *in vitro* (IC_{50} 390 μg/mL),[49] whereas alliin did not inhibit superoxide production in this model. It was suggested that allicin may be the constituent of garlic responsible for the observed oxygen-radical scavenging properties. *In vitro*, aged garlic extract and *S*-allylcysteine inhibited low-density lipoprotein oxidation and protected pulmonary artery endothelial cells against injury induced by oxidised low-density lipoprotein.[50] In subsequent studies using bovine pulmonary artery endothelial cells and murine macrophages, it was shown that aged garlic extract inhibited oxidised low-density lipoprotein-induced release of peroxides.[51] *In vivo* studies have reported reductions in liver lipid peroxidation and inhibition of ethanol-induced mitochondrial lipid peroxidation in rats fed garlic oil.[3]

The antioxidant properties are of interest in relation to the antiarteriosclerotic, antihepatotoxic and anticancer effects of garlic and its constituents. For

example, oxidation of low-density lipoprotein plays an important role in the initiation and progression of atherosclerosis.[50]

Antihypertensive effects Several studies involving animal models (e.g. dogs, rats) of hypertension have reported hypotensive effects of garlic preparations.[3] A hypotensive effect in dogs administered garlic extract has been documented; prior administration of antagonists to known endogenous hypotensive substances such as histamine, acetylcholine, serotonin and kinins did not affect the hypotensive effect.[52] Spontaneously hypertensive rats fed standardised dry garlic powder 1 mg/kg for nine months exhibited lower blood pressure than control rats (150 versus 205 mmHg, respectively).[53] By contrast, an ethanolic extract of garlic (1–2 g and 4–8 g daily) fed to spontaneously hypertensive rats did not lead to a reduction in blood pressure.[54]

Anticarcinogenic and antitumorigenic activities Many *in vitro* and animal studies have documented anticancer activities of garlic and its constituents.[3,14,15] These studies indicate that allicin, allicin-derived compounds and other compounds unrelated to allicin contribute to the anticancer effects of garlic.

In several animal models, garlic has been shown to inhibit carcinogenesis and to protect against the development of experimentally induced tumours.[3,14,15] For example, aged garlic extract significantly inhibited the growth of Sarcoma-180 and LL/2 lung carcinoma cells transplanted into mice.[55] Garlic powder and its constituents *S*-allylcysteine and diallyl disulfide inhibited *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis in rats,[56] and fresh garlic (250 mg/kg orally, three times weekly) suppressed 4-nitroquinoline-1-oxide–induced carcinogenesis in rat tongue.[57] Inhibition of benzo[*a*]pyrene-induced neoplasia of the forestomach and lung in female mice has been documented for four allyl group-containing derivatives in garlic.[58] Structure–activity requirements underlined the importance of the unsaturated allyl groups for activity. Saturated analogues containing propyl instead of allyl groups were devoid of activity.

In vitro studies using human tumour cell lines have reported that garlic powder and garlic extract inhibited the growth of a human lymphatic leukaemia cell line (CCRF CEM) in a concentration-dependent manner at concentrations down to 30 μg/mL.[59] Also, a combination of garlic extract and garlic powder inhibited the growth of human hepatoma (HepG2,) cells and human colorectal carcinoma (Caco2) cells in a concentration-dependent manner, although no activity was observed on these tumour cell lines with garlic extract or powder alone.[59] Synthetic diallyl disulfide inhibited tumour cell growth in four human breast cancer cell lines.[60] Growth inhibition occurred regardless of oestrogen receptor status.

Evidence indicates that there are several mechanisms by which garlic and its constituents may exert anticancer effects, such as inhibition of carcinogen formation, modulation of carcinogen metabolism, inhibition of mutagenesis and genotoxicity, increased apoptosis and inhibition of angiogenesis.[20]

Garlic has been shown to inhibit the synthesis of *N*-nitroso compounds (there is a view that *N*-nitroso compounds are possible carcinogens for humans).[14] Also, in rats pretreated with dimethylbenz[*a*]anthracene (DMBA) and fed a diet supplemented with garlic powder, the occurrence of DNA adducts in mammary tissue was significantly inhibited, compared with control.[61] (DMBA initiates and promotes cancer, and alkylation of DNA is thought to be an important step in carcinogenesis.) Dietary garlic has also been shown to suppress the occurrence of DNA adducts caused by *N*-nitroso compounds.[62]

Another possible explanation is that garlic constituents may modify drug-metabolising enzymes, which would have the effect of altering the bioactivation of carcinogens.[14] Glutathione-*S*-transferase activity has been shown to increase in rat and mouse tissues after administration of garlic powder or its sulfur-containing constituents.[3,14,15] Certain garlic constituents, e.g. diallyl sulfide, may depress the activity of some hepatic cytochrome P450 (CYP) enzymes, such as CYP2E1 and CYP2A6,[3,14,15,63] although other studies have shown that garlic constituents induce the activity of other CYP enzymes.[3,17] In rats, the antimutagenic properties of sulfur-containing compounds from garlic, e.g. diallyl disulfide and diallyl sulfide, against the carcinogens styrene oxide and 4-nitroquinoline-1-oxide and a benzo[*a*]pyrene compound have been shown to be associated with induction of phase II enzymes.[64]

A study in mice with transitional cell carcinoma (TCC) of the bladder reported that injection of liquid extract of garlic at the site of tumour transplantation led to a significant reduction in the incidence of TCC in this model.[65] Furthermore, garlic extract together with suicide-gene therapy significantly inhibited tumour growth (as determined by evidence of apoptosis following histomorphological and immunohistochemical studies) compared with control (no gene therapy).

Effects of garlic constituents on the immune system have been documented *in vitro* and *in vivo*; these effects may contribute, at least in part, to the anticancer effects of garlic (*see* Immunomodulatory activity).

Immunomodulatory activity Immunostimulant activity has been described for a high molecular weight protein fraction obtained from an aged garlic extract.[66] The fraction was found to strongly stimulate mice peritoneal macrophages *in vitro*, and to stimulate carbon clearance in mice *in vivo*. It has been suggested that garlic may suppress tumour cell growth by the stimulation of immunoresponder cells.[55,66,67]

In vitro and/or *in vivo* (animal) studies have found that garlic has several immune-enhancing effects, such as stimulation of lymphocyte proliferation and macrophage phagocytosis, induction of macrophage- and lymphocyte-infiltration into transplanted tumours, and stimulation of interferon-γ release.[67] Other effects on the immune system documented for garlic and/or its constituents include increased natural killer cell activity and increased interleukin-2 production by garlic fractions *in vitro*,[68] and increased numbers of antibody-forming cells in mice spleens following administration of standardised garlic powder.[3] Other studies demonstrated that, *in vitro*, aged garlic extract, compared with control, enhanced the proliferation of spleen cells in a concentration-dependent manner, increased production of cytokines (including interleukin-2 and tumour necrosis factor α) and enhanced natural killer cell activity of a T cell fraction of mouse splenic cells against YAC-1 after incubation for 24 hours.[55] Also, compared with control, aged garlic extract significantly inhibited the growth of sarcoma-180 and LL/2 lung carcinoma cells transplanted into mice, and significant increases in natural killer cell activity of spleen were observed in splenic cells from sarcoma-bearing mice treated with aged garlic extract, compared with those from control mice.[55,69]

Antimicrobial activity Antimicrobial activity (including antibacterial, antiviral, antifungal, antiprotozoal and antiparasitic activites) is well documented for garlic.[3,7] The *in vitro* antimicrobial activity of garlic is considered to be mainly due to allicin.[3]

In vitro studies have demonstrated that bacteria sensitive to garlic include species from *Staphylococcus*, *Escherichia*, *Proteus*, *Salmonella*, *Providencia*, *Citrobacter*, *Klebsiella*, *Hafnia*, *Aeromonas*, *Vibrio* and *Bacillus* genera.[7,70] In these studies, *Pseudomonas aeruginosa* was found not to be sensitive to garlic.[7,70] *In vitro* studies have also shown that allicin has significant antibacterial activity against several species, including *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, *Salmonella typhi* and *Vibrio cholerae*.[70]

In other *in vitro* studies, garlic oil and four diallyl sulfide constituents, including diallyl disulfide, showed activity against antibiotic-resistant *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*,[71] and against *S. aureus*, methicillin-resistant *S. aureus*, *Candida* spp. and *Aspergillus* spp.[72]

Garlic has also been documented to inhibit growth in 30 strains (consisting of 17 species) of mycobacteria, including *Mycobacterium tuberculosis*.[73] *In vitro*, both aqueous garlic extract and ethanolic garlic extract inhibited the growth of *M. avium* complex (MAC) strains isolated from patients with or without acquired immune deficiency syndrome (AIDS).[74] Aqueous garlic extract at concentrations of 2–5 mg/mL inhibited the growth of clinical isolates of *Helicobacter pylori* from patients with chronic gastritis or duodenal ulcer.[75] The minimum inhibitory concentration to inhibit 90% of growth (MIC_{90}) was 5 mg/mL. Sulfur-containing compounds from garlic (diallyl sulfide and diallyl disulfide, produced from alliin) were shown to decrease growth of *H. pylori* isolates from patients with peptic ulcer.[76] It has been proposed that garlic inhibits bacterial cell growth by primarily inhibiting RNA synthesis.[77]

Broad-spectrum activity against fungi has been documented for garlic including the genera *Microsporum*, *Epidermophyton*, *Trichophyton*, *Rhodotorula*, *Torulopsis*, *Trichosporon*, *Cryptococcus neoformans* and *Candida*, including *Candida albicans*.[7]

Garlic extract has been reported to be more effective than nystatin against pathogenic yeasts, especially *Candida albicans*.[7] Inhibition of lipid synthesis is thought to be an important factor in the anticandidal activity of garlic, with a disulfide-containing component such as allicin thought to be the main active component.[78] Garlic has been found to inhibit the growth and toxin production of *Aspergillus parasiticus*.[79]

Allicin produced from synthetic alliin with alliinase isolated from garlic cloves inhibited the destruction of baby hamster kidney cells by trophozoites of the protozoan parasite *Entamoeba histolytica in vitro*.[80] Allicin also inhibited the cysteine proteinase activities of intact *E. histolytica* trophozoites. *In vitro* activity against *Giardia intestinalis* has also been documented for whole garlic extract (IC_{50}

0.3 mg/mL) and for several of its constituents, particularly allyl alcohol and allyl mercaptan (IC_{50} 7 μg/mL and 37 μg/mL, respectively).[81]

In vitro antiviral activity against parainfluenza type 3, herpes simplex type 1 and influenza B has been documented.[82,83] Activity was attributed to allicin or an allicin derivative. Garlic was reported to be ineffective towards coxsackie B1 virus.[84]

Antihepatotoxic effects Antihepatotoxic activity *in vitro* and *in vivo* has been reported for garlic and its constituents.[3] Garlic oil[85] and some of its constituents, namely alliin, *S*-allylmercaptocysteine (ASSC) and *S*-methylmercaptocysteine (MSSC) reduced carbon tetrachloride (CCl_4)- and galactosamine-induced hepatotoxicity *in vitro*.[85] Other *in vitro* studies have shown that *S*-allylcysteine, *S*-propylcysteine and *S*-allylmercaptocysteine neutralised CCl_4-induced hepatotoxicity, and that *S*-allylcysteine and *S*-allylmercaptocysteine prevent liver damage induced by hepatotoxins in acute hepatitis in mice.[3,86]

An *in vitro* study in rat hepatocytes found that diallyl sulfide (0.5 and 2 mmol/L) and diallyl disulfide (0.5 and 1 mmol/L) protected against DNA damage induced by aflatoxin B_1, compared with control.[87] In this model, diallyl sulfide and diallyl disulfide appeared to exert a hepatoprotective effect via increased activity of glutathione-*S*-transferase and glutathione peroxidase activity.

Other activities Garlic oil and juice have been reported to protect against isoprenaline-induced myocardial necrosis in rats.[88] Oral administration of garlic extract 100, 200 or 400 mg/kg to rats given oral lead acetate 5 mg/kg daily for six weeks was found to reduce tissue lead concentrations, compared with those in control rats.[89] A diet containing 2% aged garlic extract was reported to protect against intestinal damage induced by oral methotrexate and 5-fluorouracil administered to rats for 4–5 days, compared with a control diet.[90]

A study in senescence-accelerated mice found that *S*-allylcysteine, present in aged garlic extract, administered in the diet for eight months (40 mg/kg/diet daily) significantly attenuated the decrease in the conditioned avoidance response, compared with a diet lacking *S*-allylcysteine.[91] It was suggested that the findings indicate that dietary supplementation with *S*-allylcysteine may reduce age-related learning disabilities and cognitive disorders in senescence-accelerated mice.

Hypoglycaemic activity has been documented for an alcoholic garlic extract following oral administration to rabbits (dose equivalent to 50 g dry garlic powder). Fifty-nine per cent activity compared to that of 500 mg tolbutamide was observed.[92]

Garlic has been documented to cause both smooth muscle relaxation and contraction.[37,52,84] Garlic oil has been reported to depress gastrointestinal movements induced by charcoal meal and castor oil.[84] In mice, garlic has also inhibited acetylcholine- and PGE_2-induced contraction of the rat gastric fundus, with the most active components exhibiting the weakest antiplatelet aggregatory activity.[37] Garlic has also elicited contractions on the rat uterus and the guinea-pig ileum *in vitro*.[52] Both actions were blocked by flufenamic acid, but not by atropine or cyproheptadine, indicating a prostaglandin-like mode of action.

In vitro, ajoene was found to inhibit the release of lipopolysaccharide-induced prostaglandin E_2 in macrophages in a concentration-dependent manner.[93] This effect was reported to be due to inhibition of cyclooxygenase 2 (COX-2) activity by ajoene.

Clinical studies

Pharmacokinetics The available literature on the metabolism and pharmacokinetics of the constituents of garlic in humans has been reviewed.[3,94,G18]

Addition of allicin to fresh whole blood results in conversion of allicin to allyl mercaptan and other compounds produced from allicin, such as diallyl trisulfide and ajoene, have also been shown to form allyl mercaptan in blood.[3] Sulfur-containing compounds, such as diallyl disulfide, diallyl sulfide, dimethyl sulfide and mercapturic acids, have been isolated and identified in human urine following the ingestion of garlic.[3,95] A subsequent study detected *N*-acetyl-*S*-allyl-L-cysteine (allylmercapturic acid) in the urine of volunteers ($n = 6$) who had ingested two garlic tablets containing 100 mg garlic extract (Kwai).[96] The mean (standard deviation) elimination half-life of allylmercapturic acid was estimated to be 6 (1.3) hours.

It has been reported that the flavour of human breast milk is altered when lactating women consume foods containing sulfur-containing compounds, such as garlic (*see* Contra-indications, Warnings; Pregnancy and lactation).[97] Also, garlic ingestion by pregnant women significantly alters the odour of their amniotic fluid (*see* Contra-indications, Warnings; Pregnancy and lactation),[98] suggesting that the odorous components of garlic are present. Evidence for this comes from a placebo-controlled study involving 10 healthy pregnant women undergoing routine amniocentesis. The odour of samples of amniotic fluid from women who ingested capsules containing garlic extract was judged to be 'stronger'

or more 'garlic-like' than that of samples from women who had ingested placebo capsules.

Pharmacodynamics Several of the pharmacological activities documented for garlic and its constituents *in vitro* and *in vivo* (animals) have also been reported in clinical studies (*see* Clinical studies, Therapeutic effects).

Numerous studies have assessed the effects of the administration of garlic preparations in hypercholesterolaemia.[3] Many, but not all, of these studies have documented the effects of garlic administration in lowering serum cholesterol and triglyceride concentrations. Clinical studies have also documented fibrinolytic activity associated with garlic administration and effects on platelet function.[99,100]

Therapeutic effects

Anti-atherosclerotic and cholesterol- and lipid-lowering effects Numerous studies have investigated the effects of garlic preparations in lowering raised serum cholesterol concentrations, and the findings of these studies have been reviewed in several meta-analyses.[101–104]

A meta-analysis of five randomised, placebo-controlled trials involving mostly patients with serum cholesterol concentrations greater than 5.17 mmol/L who received preparations of garlic extract at doses of 600–1000 mg daily for 8–24 weeks reported that garlic significantly reduced total serum cholesterol concentrations by about 9% (net reduction over placebo), compared with placebo ($p < 0.001$).[101] Another meta-analysis included 16 trials involving patients with a range of disorders (such as hyperlipidaemia, coronary heart disease and hypertension) as well as healthy volunteers, and compared garlic preparations (e.g. fresh garlic, garlic oil, garlic extract, dried garlic powder) with garlic-free diet, placebo or other agents (two studies used bezafibrate or a reserpine/diuretic combination as the comparator treatment).[102] This analysis reported a mean difference of −0.77 mmol/L (95% confidence interval (CI) −0.65, −0.89) in reduction of total serum cholesterol concentrations between garlic recipients and those receiving placebo or a garlic-free diet (net reduction over placebo: 12%). Analysis of data from the eight trials that assessed garlic powder preparations indicated that garlic powder administration significantly reduced serum triglyceride concentrations, compared with placebo (net reduction: 13%). It was stated, however, that several trials had methodological flaws, and that there was not enough evidence to recommend garlic as an effective lipid-lowering agent for routine use. The results of a subsequent randomised placebo-controlled trial involving 115 patients with moderate hyperlipidaemia (which showed no difference between garlic and placebo)[103] were included in a re-analysis[103] of the meta-analysis described above.[102] This analysis showed that the effect of garlic in reducing serum cholesterol concentrations remained statistically significant, compared with placebo, but that the size of the effect was reduced.

Several randomised, double-blind, placebo-controlled trials[105–108] have been published since the meta-analyses described above. One of these studies[105] has been criticised for its choice of garlic preparation.[109]

Several of these trials[105–107] were included in the most recent meta-analysis of randomised clinical trials of garlic preparations involving patients with hypercholesterolaemia.[104] This meta-analysis included 13 randomised, double-blind, placebo-controlled trials of garlic monopreparations involving 796 patients with coronary heart disease ($n = 1$ trial), hyperlipoproteinaemia (2), hypercholesterolaemia (7), hypertension (1), familial hyperlipidaemia in children (1) and healthy volunteers (1). Ten of the trials assessed the effects of a standardised garlic powder preparation (Kwai) at doses of 600–900 mg daily for 8–24 weeks; the other three trials tested garlic oil or spray dried powder. Ten trials reported differences favouring garlic over placebo in the reduction of total serum cholesterol concentrations, although these differences were statistically significant in only three studies. Overall, meta-analysis indicated a significant difference in the reduction of total cholesterol concentrations favouring garlic over placebo (−0.41 mmol/L; 95% CI −0.66 mmol/L, −0.15 mmol/L; $p < 0.01$), equivalent to a net reduction in total cholesterol concentrations of 5.8%. It was stated that although these findings indicated that garlic is more beneficial than placebo in reducing serum cholesterol concentrations, the size of the effect is small. Furthermore, several studies had methodological limitations.[104]

Another randomised, double-blind, placebo-controlled trial has been published since the meta-analysis described above. This study assessed the effects of garlic powder (tablets) 500 mg and 1000 mg daily, or placebo, for 12 weeks in 53 patients with moderate hypercholesterolaemia (baseline low-density lipoprotein cholesterol (LDL-C) 130–190 mg/dL).[108] At the end of the study there were no significant differences in the absolute mean change in LDL-C between the three groups (mean (SD) values were: 0.0 (4.3) mg/dL, 1.4 (4.8) mg/dL and −10.1 (6.8) mg/dL for the placebo, garlic powder 500 mg and garlic powder 1000 mg groups, respectively).

Another meta-analysis, which aimed to summarise the evidence for the effects of garlic on several cardiovascular-related factors, considered 45 randomised controlled trials of at least four weeks' duration.[110] It was reported that after one and three months, garlic treatment may lead to small reductions in total cholesterol concentrations (0.03–0.45 mmol/L and 0.32–0.66 mmol/L, respectively). However, no effect was noted for pooled six-month data. Changes in cholesterol concentrations were paralleled by changes in low-density lipoprotein and triglyceride concentrations.

A randomised, double-blind, placebo-controlled trial explored the anti-atherosclerotic effect of garlic powder 900 mg daily for 48 months in 280 patients with advanced atherosclerotic plaques and an established risk factor for arteriosclerosis (e.g. high systolic blood pressure, hypercholesterolaemia, diabetes mellitus, smoking).[111] It was reported that continuous garlic intake significantly reduced the increase in arteriosclerotic plaque volume, compared with placebo. However, the robustness of the findings of this study is difficult to assess independently as no exact *p*-value is given.

A Cochrane systematic review of garlic for the treatment of peripheral arterial occlusive disease identified only one eligible randomised, placebo-controlled trial.[112] The trial involved 78 participants with peripheral arterial occlusive disease (lower limb atherosclerosis) who received garlic, or placebo, for 12 weeks. At the end of the study, the difference in the increase in pain-free walking distance between the two groups was found to be statistically non-significant.

An open study involved 101 healthy adults aged 50–80 years who had taken a standardised garlic powder preparation at a dose of at least 300 mg daily for at least two years and 101 age- and sex-matched subjects.[113] Measures of the elastic properties of the aorta were compared for the two groups. Pulse-wave velocity and elastic vascular resistance were reported to be reduced significantly in the garlic group, compared with the control group. These findings suggest that long-term use of garlic powder to attenuate age-related increases in aortic stiffness is worth further study.

Antithrombotic and fibrinolytic effects Several placebo-controlled studies have documented fibrinolytic effects for garlic preparations in clinical studies involving patients with coronary heart disease, hyperlipidaemia and hypercholesterolaemia, and healthy volunteers.[3] Several studies involved the administration of ether-extracted garlic oil 20 mg daily for up to 90 days, whereas several others involved the administration of garlic powder 600–1500 mg daily for up to 28 days. Most, but not all, of these studies reported significant increases in fibrinolytic activity in garlic recipients, compared with placebo recipients.

An open, uncontrolled study explored the effects of garlic consumption (one fresh chopped clove daily for 16 weeks) in eight healthy male volunteers.[114] After 16 weeks, garlic consumption was reported to reduce significantly serum thomboxane B_2 and cholesterol concentrations, compared with baseline values.

Antioxidant effects Blood samples from 31 individuals who participated in a randomised, placebo-controlled trial involving 115 patients with moderate hyperlipidaemia who received a standardised garlic powder preparation 900 mg daily for six months (which showed no difference between garlic and placebo)[103] were analysed to explore the effects of garlic treatment on the resistance of low-density lipoprotein to oxidation.[115] There were no significant differences between garlic and placebo recipients in low-density lipoprotein composition. Thus, garlic administration did not reduce the susceptibility of low-density lipoprotein to oxidation. This finding contrasts with some of the results of a double-blind, placebo-controlled study involving 23 patients with coronary artery disease who received a standardised garlic powder preparation (Kwai tablets) 300 mg three times daily, or placebo, for four weeks.[116] The study reported that garlic powder administration reduced the atherogenicity of low-density lipoprotein. At the end of the study, the ability of low-density lipoprotein to induce intracellular cholesterol accumulation was decreased by 38%, compared with baseline values. Decreases in the susceptibility of low-density lipoprotein to oxidation and in low-density lipoprotein-stimulated cell proliferation (an indicator of low-density lipoprotein atherogenicity) were also documented.

The effects of standardised garlic powder tablets (Sapec; alliin 1.3%, allicin 0.6%) 900 mg daily for two months on oxidative stress status were explored in an open, uncontrolled study involving 25 healthy volunteers.[117] At the end of the study, a reduction in serum malondialdehyde concentrations was observed, compared with baseline values. It was stated that this finding indicates that standardised garlic powder may have antioxidant activity in humans.

Antihypertensive effects A meta-analysis of randomised controlled trials of garlic preparations assessed the evidence for the effects of garlic on blood pres-

sure.[118] Eight trials involving 415 participants were included in the review, all of which had tested the effects of an allicin-standardised garlic powder preparation (Kwai tablets) at doses of 600–900 mg daily for 4–52 weeks. Overall, the absolute change in mean systolic blood pressure was 7.7 mmHg greater for the garlic group, compared with the placebo group (95% CI 4.3–11.0). However, only three trials specifically involved subjects with hypertension and, as reported by other meta-analyses of trials of garlic preparations, several trials had methodological limitations. Thus, it was stated that there was insufficient evidence to recommend garlic treatment for routine management of hypertension.

Another overview of trials reported that the effects of garlic treatment on blood pressure are 'insignificant'.[110]

Anticancer effects The protective effects of garlic consumption against various different cancers (including colon, stomach, larynx, breast and endometrial) have been explored in several epidemiological studies, and their findings have been summarised.[3,119] Most, but not all, of these studies suggest that garlic consumption may have a protective effect, particularly against cancers of the gastrointestinal tract.[3,119] However, the findings should be interpreted cautiously, as bias and/or confounding cannot be excluded, and there are other methodological issues, for example, most studies did not distinguish between consumption of raw or cooked garlic.

Antimicrobial effects An epidemiological study comprising a dietary interview and measurement of serum *H. pylori* antibodies was conducted among 214 adults in a low-risk area of Shandong Province in China.[120] The findings suggested a protective effect of garlic consumption against *H. pylori* infection.

An open, uncontrolled study involving 34 patients with tinea pedis explored the effectiveness of ajoene cream (0.4% w/w).[121] After seven days' treatment, complete cure of the infection was recorded for 27 (79%) participants. The remaining seven patients experienced complete cure after a further seven days' treatment. All patients were evaluated for recurrence of infection 90 days after the end of treatment; all found to be infection free as determined by negative cultures for the fungus.

Other effects A reduction in blood sugar concentrations and an increase in insulin have been observed following allylpropyl disulfide administration to normal volunteers, whereas another study reported that garlic exhibits hypoglycaemic actions in diabetic patients but not in controls.[5] It has also been reported that garlic can prevent tolbutamide- and adrenaline-induced hyperglycaemia.[5]

A randomised, placebo-controlled, crossover trial involving 100 Swedish participants working in a tick-endemic area found that administration of garlic powder 1200 mg daily for eight weeks resulted in fewer tick bites than did placebo administration.[122]

An open, uncontrolled study involving 15 patients with hepatopulmonary syndrome explored the effects of treatment with capsules containing a standardised garlic powder preparation for at least six months.[123] Improvements in arterial oxygenation and symptoms were documented for several participants. The effects of garlic powder treatment in patients with hepatopulmonary syndrome require further study.

Side-effects, Toxicity[G19,G58]

Side-effects Garlic is generally considered to be non-toxic.[8,124] Adverse effects that have been documented in humans include a burning sensation in the mouth and gastrointestinal tract, nausea, diarrhoea and vomiting.[8]

A meta-analysis of 13 randomised, double-blind, placebo-controlled trials of garlic monopreparations, 10 of which assessed the effects of a standardised garlic powder preparation (Kwai) at doses of 600–900 mg daily for 8–24 weeks (*see* Clinical studies, Therapeutic effects, Anti-atherosclerotic and cholesterol- and lipid-lowering effects) reported that few adverse events were documented in the included trials.[104] The frequency and nature of adverse events reported for garlic were similar to those for placebo. The most common adverse events reported were 'garlic breath', body odour and gastrointestinal symptoms.

The allergenic potential of garlic is well recognised, and allergens have been identified as diallyl disulfide, allylpropyl sulfide and allicin (the latter may be an irritant).[125] A garlic antigen in the serum of affected patients has also been identified.[43] Cases of contact dermatitis resulting from occupational exposure to garlic have been reported.[43,126,G51] A case of garlic allergy associated with ingestion of raw or cooked garlic has been documented.[127] There is an isolated report of multifaceted dermatitis artefacta associated with local application of garlic by a 19-year-old individual.[128] Garlic burns following local application of garlic have also been documented.[129,130]

Garlic may enhance existing anticoagulant therapy; a potential interaction between garlic and warfarin has been documented.[131,132] Case reports have suggested that garlic supplementation may increase

the risk of bleeding in patients undergoing surgery.[G21]

Toxicity Erratic pulse rates, abnormal ECGs, weight loss, lethargy and weakness, soft faeces, dehydration and tender skin on fore and hindlimbs have been observed in spontaneously hypertensive rats administered garlic extract at 0.25 and 0.5 mL/kg every 6 hours for 28 days.[133] The effects were most pronounced in animals receiving doses two or three times a day. Conversely, acute toxicity studies for garlic extract in mice and rats have reported LD_{50} values for various routes of administration (by mouth, intraperitoneal injection, intravenous injection) as all greater than 30 mL/kg.[124] Early studies, in 1944, reported LD_{50} values for allicin in mice as 120 mg/kg (subcutaneous injection) and 60 mg/kg (intravenous injection).[43] Results of chronic toxicity studies are stated to be conflicting.[43] High doses are reported to cause anaemia due to both decreased haemoglobin synthesis and haemolysis.[43] A chronic toxicity study in rats given a garlic extract (2 g/kg) five times a week for six months, reported no toxic symptoms.[134] High doses were found to decrease food consumption slightly, but did not inhibit weight gain. There were no significant differences in urinary, haematological or serological examinations, and no toxic symptoms in histopathological examinations. Genotoxicity studies using the micronucleus test have reported both positive[135] and negative[136] findings. No evidence of mutagenicity has been reported when assessed using the Ames and Ree assay.[135]

Slight cytotoxic signs have been observed at high doses in Hep2 and Chinese hamster embryo primary cultured cells.[135]

The literature relating to the toxicity of garlic has been reviewed.[3,G19,G20]

Contra-indications, Warnings

In view of the pharmacological actions documented for garlic, therapeutic doses of garlic may interfere with existing hypoglycaemic and anticoagulant therapies. There may be an increased risk of bleeding with use of garlic supplements in patients undergoing surgery.[G21] Garlic may potentiate the antithrombotic effects of anti-inflammatory drugs such as aspirin, and may be synergistic with eicosapentaenoic acid (EPA) in fish oils.[8] Gastrointestinal irritation may occur particularly if the clove is eaten raw by individuals not accustomed to ingesting garlic.

A study involving healthy volunteers detected *N*-acetyl-*S*-allyl-L-cysteine (allylmercapturic acid) in their urine following ingestion of garlic tablets (*see* Clinical studies, Pharmacokinetics).[96] As allylmercapturic acid is used as a biomarker for monitoring human exposure to allylhalides and other chemicals leading to allylmercapturic acid excretion, it was suggested that garlic consumption may interfere with and confound this monitoring process.

Pregnancy and lactation Garlic is reputed to act as an abortifacient and to affect the menstrual cycle, and is also reported to be utero-active.[G30] *In vitro* uterine contraction has been documented.[84]

Studies have shown that consumption of garlic by lactating women alters the odour of their breast milk and the suckling behaviour of their infants.[97] Further evidence for this comes from a blinded, placebo-controlled study involving 30 nursing women.[137] The results indicated that infants who had no prior exposure to garlic odour in their mothers' milk spent more time breast feeding after their mothers ingested garlic capsules than did infants whose mothers had repeatedly consumed garlic. Findings from a placebo-controlled study involving 10 healthy pregnant women undergoing routine amniocentesis indicate that the odorous components of garlic can be found in amniotic fluid following garlic consumption.[98] The odour of samples of amniotic fluid from women who ingested capsules containing garlic extract was judged to be 'stronger' or more 'garlic-like' than that of samples from women who had ingested placebo capsules. The effects of *in utero* exposure to garlic odour and on the neonate's behaviour towards exposure to garlic-flavoured human breast milk are not known.

There are no experimental or clinical reports on adverse effects during pregnancy or lactation.[G19] In view of this, doses of garlic greatly exceeding amounts used in foods should not be taken during pregnancy and lactation.

Pharmaceutical Comment

There is a vast scientific literature on the chemistry, pharmacology and clinical properties of garlic. Experimental studies have focused mainly on the cardiovascular and anticancer effects of garlic and its constituents, as well as its antimicrobial properties. Clinical studies have investigated mainly the anti-atherosclerotic and cholesterol- and lipid-lowering effects of garlic preparations. Generally, these studies report beneficial results for garlic, although the evidence at present is insufficient to recommend garlic as routine treatment for hypercholesterolaemia. *In vitro* and animal studies provide supporting evidence for some of the clinical properties of garlic and its constituents.

Garlic is characterised by its sulfur-containing constituents. Pharmacological activities documented for garlic are also associated with these compounds. It is recognised that allicin, the unstable compound formed by enzymatic action of allinase on alliin when the garlic clove is crushed, is required for the antimicrobial activity that has been demonstrated by garlic. However, serum concentrations of allicin achieved in humans following oral ingestion of garlic are unclear. The hypolipidaemic and antithrombotic actions documented for garlic have been attributed to many of the degradation products of alliin.

One of the difficulties in comparing studies that have investigated the efficacy of garlic, is establishing the concentration of active principles present in the garlic preparations used. It has been reported that the percentage of active constituents in fresh garlic may vary by a factor of 10.[43] Many commercial garlic preparations are standardised on content of sulfur-containing constituents, particularly to alliin, or on allicin yield. Dried garlic powder contains both alliin and allinase and therefore has an allicin-releasing potential. Garlic preparations produced by heat or solvent extraction processes are stated to contain alliin but to be devoid of allinase and therefore have no allicin releasing potential.[43] Garlic oil macerates and steam distillation products are rich in secondary alliin metabolites, such as ajoene. However, it is unclear to what extent these secondary compounds are formed in the body following the ingestion of garlic and whether, therefore, these products exhibit the pharmacological actions of fresh garlic.[43]

Fermented garlic preparations are considered to be practically devoid of the active sulfur-containing compounds.[43] Many 'odourless' garlic preparations are available: obviously one should establish if these products are odourless due to the formulation of the product or because they are devoid of the odoriferous, active principles. Further randomised controlled clinical trials with standardised preparations are required to establish the true usefulness of garlic in reducing serum lipids, blood pressure, platelet aggregation and exerting an antimicrobial effect. Therapeutic doses of garlic should not be given to those whose blood clots slowly and caution is recommended for patients on anticoagulant therapy.[G58]

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See also General References G3, G5, G6, G9, G16, G18, G19, G20, G21, G28, G31, G32, G36, G41, G43, G50, G51, G52, G56, G58, G61, G63 and G64.

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