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Effect of garlic on cardiovascular disorders: a review

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Abstract

Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes. Effectiveness of garlic in cardiovascular diseases was more encouraging in experimental studies, which prompted several clinical trials. Though many clinical trials showed a positive effect of garlic on almost all cardiovascular conditions mentioned above, however a number of negative studies have recently cast doubt on the efficary of garlic specially its cholesterol lowering effect of garlic. It is a great challenge for scientists all over the world to make a proper use of garlic and enjoy its maximum beneficial effect as it is the cheapest way to prevent cardiovascular disease. This review has attempted to make a bridge the gap between experimental and clinical study and to discuss the possible mechanisms of such therapeutic actions of garlic.

Introduction

Dietary factors play a key role in the development of various human diseases, including cardiovascular disease. Epidemiological studies have shown that diets rich in fruits, herbs and spices are associated with a low risk of cardiovascular disease. Garlic acquired a reputation in the folklore of many cultures over centuries as a formidable prophylactic and therapeutic medicinal agent. Garlic has attracted particular attention of modern medicine because of its widespread health use around the world, and the cherished belief that it helps in maintaining good health warding off illnesses and providing more vigor. To date, many favorable experimental and clinical effects of garlic preparations, including garlic extract, have been reported. These biological responses have been largely attributed to i) reduction of risk factors for cardiovascular diseases and cancer, ii) stimulation of immune function, iii) enhanced detoxification of foreign compound, iv) hepatoprotection, v) antimicrobial effect and vi) antioxidant effect. This review has been made indicating an overall view of the efficacy of garlic in cardiovascular disease conditions both in human and animals.

Historical perspective of garlic

It is fascinating to observe how cultures that never came into contact with one another came to the same conclusions about the role of garlic in health and disease. If folk wisdom is not ignored, it may teach us valuable lessons. Some of the earliest references to this medicinal and culinary plant are found on Sumerian clay tablets dating from 2600–2100 BC. Garlic was an important medicine to the ancient Egyptians listed in the medical text *Codex Ebers* (ca. 1550 BC) specially for the working class involved in heavy labor [1,2]. There is evidence that during the earliest Olympics in Greece, garlic was fed to the athletes for increasing stamina [1]. In ancient Chinese medicine, garlic

was prescribed to aid respiration and digestion, most importantly diarrhea and worm infestation [3]. Three ancient medical traditions in India i.e., Tibbi, Unani and Auryveda, made extensive use of garlic as a central part of the healing efficacy of plants [2]. The leading Indian ancient medical text, *Charaka-Samhita* recommends garlic for the treatment of heart disease and arthritis for over many centuries. In another ancient Indian medical textbook, *Bower Manuscript* (~300 AD), garlic was used for fatigue, parasitic disease, digestive disorder and leprosy [4]. With the onset of Renaissance, increasing attention was paid in Europe to the medical use of garlic. A leading physician of the 16th century, Pietro Mattiali of Siena, prescribed garlic for digestive disorders, infestation with worms and renal disorders, as well as to help mother during difficult childbirth [2]. In England, garlic was used for toothache, constipation, dropsy and plague [4]. In modern era scientists have been trying to validate many of these properties of garlic, specially in terms of the identity of the active components, their mechanisms of action and exploring the potential benefits as food supplements.

Garlic preparations and their chemical compounds

Raw garlic homogenate has been the major preparation of garlic subjected to intensive scientific study, as because it is the commonest way of garlic consumption. Raw garlic homogenate is essentially same as aqueous extract of garlic, which has been used in various scientific studies. Allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) is thought to be the principal bioactive compound present in aqueous garlic extract or raw garlic homogenate. When garlic is chopped or crushed, allinase enzyme, present in garlic, is activated and acts on alliin (present in intact garlic) to produce allicin. Other important sulfur containing compounds presents in garlic homogenate are allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate and γ-L-glutamyl-S-alkyl-L-cysteine. The adenosine concentration increases several-fold as the homogenate is incubated at room temperature. The enzyme allinase responsible for converting alliin (S-allyl cysteine sulphoxide) to allicin is inactivated by heat. Thus the water extract of heat-treated garlic contains mainly alliin. Since garlic powder is a simply dehydrated, pulverized garlic clove, the composition, especially allinase activity of garlic powder is identical to those of fresh garlic. However, dehydration temperature should not exceed 60°C, above which allinase is inactivated [1].

Another widely studied garlic preparation is aged garlic extract (AGE). Sliced raw garlic stored in 15–20% ethanol for 20 months is refereed to as AGE. This whole process is supposed to cause considerable loss of allicin and increased activity of certain newer compounds, like S-allyl-cysteine (SAC), S-allylmercaptocysteine, allixin and selenium which are stable, highly bioavailable and significantly antioxidant [5]. Another recently identified antioxidant compound of AGE is N-alpha-(1-deoxy-D-fructos-1-yl)-L-arginine (Fru-Arg) which is not present in raw or heat treated garlic [6].

Medicinally used garlic oil is mostly prepared by steam-distillation process. Steam-distilled garlic oil consists of the diallyl (57%), allyl methyl (37%) and dimethyl (6%) mono to hexa sulfides. A typical commercial preparation of garlic oil contains diallyl disulfide (DADS, 26%), diallyl trisulfide (DATS, 19%), allyl methyl trisulfide (15%), allyl methyl disulfide (13%), diallyl tetrasulfide (8%), allyl methyl tetrasulfide (6%), dimethyl trisulfide (3%), penta sulfide (4%) and hexa sulfide (1%). Oil-macerated garlic oil contains the vinyl-dithiins and ajoenes. Ether extracted garlic oil (essential oil) contains nine times as much of the vinyl-dithiins (5.7 mg/gm) and allyl sulfides (1.4 mg/g) and four times as much of the ajoenes (0.4 mg/g) [1].

Atherosclerosis and lipid metabolism

Atherosclerosis is a complex disease, characterized by an excessive inflammatory, fibro-fatty, proliferative response to damage of the artery wall involving several cell types, particularly smooth muscle cells, monocyte-derived macrophages, T-lymphocyte and platelets [7]. Hyperlipidemia constitutes a major etiopathological factor for atherosclerosis. The medicinal value of garlic is best known for its lipid lowering and antiatherogenic effects.

Animal studies

Several groups of investigators [8–14] studied the effects of long term (2–9 months) feeding of garlic and garlic preparations (2% garlic powder in diet) on experimental atherosclerosis induced by a high-cholesterol diet in rabbits. Most of these studies reported a statistically significant reduction in atheromatous lesions, particularly in the aorta, that averaged about 50%.

The chronic effects of garlic on lipid metabolism in rats were also encouraging. The duration of these studies was at least 4 weeks. Garlic (1–4% in diet) and garlic protein administration in hypercholesterolemic rats induced by a high-cholesterol diet, significantly reduced serum cholesterol, triglyceride and LDL cholesterol [11,15–20] but there was no effect on serum HDL. Total lipid content and cholesterol levels in liver were also decreased in rat after chronic garlic consumption. Abramoviz et al. (1999) investigated the effect of allicin as an active component of garlic on the formation of fatty streaks in aorta and lipid profile in mice [21]. While no significant differences were observed between blood lipid profiles, the microscopic evaluation of formation of fatty streaks in the aortic sinus

Table 1: Studies showing no cholesterol lowering effect:

References	Preparation	Duration	Dose
Ziaei et al., 2001 [26]	Garlic powder (Garlet)	3 months	800 mg/day
Gardner et al., 2001 [27]	Garlic powder	12 weeks	500, 1000 mg/day
Rahman et al., 2000 [28]	Aged garlic extract	13 weeks	5 ml/day
Superko et al., 2000 [29]	Garlic powder	3 months	900 mg/day
Byrne et al., 1999 [30]	Garlic powder (Kwai)	6 months	900 mg/day
McCrindle et al., 1998 [31]	Garlic powder (Kwai)	8 weeks	900 mg/kg
Berthold et al., 1998 [32]	Steam-distilled garlic oil	12 weeks	10 mg/day
Isaacsohn et al., 1998 [33]	Garlic powder (Kwai)	12 weeks	900 mg/day
Simons et al., 1995 [34]	Garlic powder (Kwai)	12 weeks	900 mg/day
Luley et al., 1986 [25]	Commercial dried garlic	6 weeks	600 mg/day
Lutomski, 1984 [24]	Commercial garlic preparation	12 weeks	–

showed that values for mice in the allicin treated groups were significantly lower by nearly 50%.

Aged garlic extract 'Kyolic' also significantly inhibited the development of thickened, lipid-filled lesions in the preformed neointimas produced by balloon-catheter injury of the right carotid artery in cholesterol-fed rabbits [22,23].

Human studies

Since 1975 there have been more than 46 (from medline search) human studies on lipid-lowering effects of garlic and garlic preparations. These studies, were mostly randomized, double blind, placebo-controlled using garlic powder rather than raw garlic of 4–16 weeks, in hyperlipidemic patients. Most of these studies showed significant decrease in serum cholesterol and serum triglyceride. Only about one-third of these studies measured lipoproteins, where significant favorable changes in LDL-cholesterol level (11–26% decrease) were consistently observed. A few studies using garlic powder (having low allicin yields) failed to show any lipid lowering effects [24,25]. During the last one decade (1993–2002), 18 clinical studies have been published regarding the hypolipedemic effect of garlic. Nine studies showed negative results and garlic powder was used in seven of these studies (Table- 1) [26–34]. The different composition and quantity of sulfur components of different garlic preparations used in various studies could account for the inconsistent findings. It highlights the need for standardization of different garlic preparations and to arrive at a valid conclusion. Other factors might include the subject recruitment, duration of study, dietary control, lifestyle and methods of lipid analyses [35,36].

Four meta-analysis of randomized, placebo-controlled human studies on hypocholesterolemic effects of garlic are available [35–38]. The analyses further detected that the extent of cholesterol-lowering properties of garlic differed markedly from one study to another. Warshafsky and his colleagues deduced from five randomized clinical trials that hypercholesterolemic patients treated with garlic had a mean plasma cholesterol concentration, that was 9% lower than that of patients treated with placebo [36]. Silagy and Neil (1994) analyzed sixteen trials, with data from 952 subjects in the meta-analysis [35]. Garlic, in powder and non-powder form, significantly lowered serum lipid levels over a 1–3 month period. Serum cholesterol fell by 8% with dried powder preparations and 15% with non-powder preparations. Serum triglyceride level also dropped significantly, while HDL-cholesterol was essentially unchanged. Amongst the garlic powder preparations these effects appeared to be similar across the daily dose range of 600–900 mg. Another meta-analysis [37] revealed that there was no significant difference in the mean concentrations of serum lipids, lipoproteins or apo A1 or B amongst the groups receiving garlic (900 mg/day of dried garlic powder standardized to 1.3% allicin) and placebo. In this meta-analysis, garlic was less effective in reducing total cholesterol than suggested by previous meta-analyses. However, in a more recent meta-analysis of thirteen trials [38], garlic reduced total cholesterol level from baseline significantly more than placebo, while six diet-controlled trials with the highest scores for methodological quality revealed a nonsignificant difference between garlic and placebo groups. The available data suggests that garlic is superior to placebo in reducing total cholesterol levels. However, the size of the effect is modest, and the robustness of the effect is debatable. Therefore, the hypocholesterolemic effect of garlic remains to be firmly established.

Possible mechanism/s

Protective effect of garlic on atherosclerosis has been attributed to its capacity to reduce lipid content in arterial wall. Garlic causes direct antiatherogenic (preventive) and antiatherosclerotic (causing regression) effects at the level of artery wall [39]. Garlic depressed the hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acid synthase, glucose-6 phosphate dehydrogenase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase [40]. Garlic also increased the excretion of cholesterol, as manifested by enhanced excretion of acidic and neutral steroids after garlic feeding [20]. LDL isolated from human subjects given AGE [41] and aqueous garlic extract [42] was found to be significantly more resistant to oxidation. These data indicate that suppressed LDL oxidation may be one of the powerful mechanisms accounted for the benefits of garlic in atherosclerosis [43]. Allicin was identified initially as the active compound responsible for antiatherosclerotic effect. However, recent *in vitro* studies revealed that water-soluble organosulfur compounds, especially S-allyl cysteine (SAC), present in aged garlic extract and diallyl-di-sulfide (DADS), present in garlic oil are also potent inhibitors of cholesterol synthesis [40,44].

Fibrinolytic activity

Inhibition of fibrinolytic activity (FA) or deficiency of the factors involved might upset the hemostatic balance and allow excessive fibrin deposition. In diabetes, hypertension, hypercholesterolemia etc, it is possible that disturbance in the coagulation-fibrinolytic system may be an important factor leading to the development of thrombosis and ischemia. Accordingly, the greater the FA, the more favorable is the antithrombic effect. FA is generally determined by euglobulin lysis time. The patients who died with acute or old myocardial infarction showed the highest values of plasma fibrinogen, euglobulin lysis time and antiplasmin. This suggests that prognosis in myocardial infarction is partly influenced by the degree to which plasma fibrinolysis is impaired [45].

Animals studies

Marked rise in blood coagulability of rabbits that followed 3 months of cholesterol feeding (0.2 g/kg/day) was significantly reduced by the essential oils of garlic. Fibrinolytic activity was actually increased even above the normal control levels. The essential oils of garlic (equivalent to 1 g/kg/day of raw bulbs) proved effective in mediating fibrinolytic activity [10,46]. Experimental study also revealed that garlic juice (raw garlic; 250 mg/day) had significant effect in enhancing the fibrinolytic activity in rabbit after receiving a cholesterol rich diet for 13 weeks [47]. The plasma fibrinolytic activity in rabbit, which was decreased on cholesterol feeding, was considerably increased when this diet was supplemented with garlic [48].

Human studies

Almost all human studies on fibrinolytic activity of garlic have been found to have positive effect (Table- 2). Acute as well as chronic intake of garlic oil and raw garlic increased fibrinolytic activity (FA). In 1975, Bordia first demonstrated that garlic oil increased FA after 3 hours of administration. Bordia also reported that chronic (3 weeks to 3 months) administration of garlic oil (dose: equivalent to 1 gm/kg of fresh garlic) increased FA significantly ranging from 36% to 130% in healthy as well as acute myocardial infarction patients [49–52]. Some other investigators also found the same results [53–55]. Dried garlic powder has been also tested for its fribinolytic activity. While two studies [24,25] showed no difference in FA, one study [56] showed increased FA as well as tissue plasminogen activator activity after acute and chronic garlic powder intake. Chutani and Bordia (1981) designed one study to show that both raw and fried garlic significantly enhance FA [53]. Frying removes the strong acrid smell of garlic, but preserves it useful effects on FA. The rise in FA has been observed within 6 hours of garlic administration, which showed that garlic has a rapid onset of action and the effect is well maintained as long as garlic is being taken. Recently Bordia (1998) found that intake (3 months) of ethyl acetate extract of crushed raw garlic also increased FA [57].

Platelet aggregation

Platelet aggregation superimposed on an atherosclerosis vessel is an antecedent event causing total blockage of blood flow leading to myocardial infarction and thromboembolic diseases. Platelets adhere to the exposed collagen, laminin and von Willebrand factor in the injured vessel wall. This process is called platelet activation. Activation can also be produced by ADP and thrombin. The activated platelets change shape, put out pseudopodia, discharge their granules, and stick to other platelets, initiating the process of platelet aggregation. Aggregation is also fostered by platelet activating factor (PAF), a cytokine secreted by neutrophil and monocytes as well as platelets [59]. Studies have shown that garlic has great potential in inhibiting platelet aggregation.

Animal studies

Pretreatment of rabbits with an aqueous extract of garlic (500 mg/kg) significantly inhibited thromboxane-B2 (TXB2) synthesis (a potent platelet aggregator) and protected against thrombocytopenia induced by collagen or arachidonate infusion. These observations indicate that garlic may be beneficial in the prevention of thrombosis [60]. Aqueous extract of garlic was found to inhibit platelet aggregation induced by ADP, epinephrine, collagen and arachidonate in a dose-dependent manner *in vitro* and inhibited biosynthesis of prostacyclin in rat aorta [61]. A dose-dependent inhibition of cyclooxygenase ac-

Table 2: Fibrinolytic activity in human:

References	Preparation	Duration	Effect
Bordia et al., 1975 [46]	Essential garlic oil	Acute effect	Increased FA
Bordia et al., 1977 [10]	Essential garlic oil	3 month	Increased FA
Bordia et al., 1978 [50]	Essential garlic oil	20 days	Increased FA
Bordia et al., 1978 [58]	Essential garlic oil	3 month	Increased FA
Chutani and Bordia, 1981 [52]	Fresh and fried garlic	acute effect and 4 weeks	Increased FA
Arora and Arora, 1981 [54]	Essential garlic oil	Acute effect	Slightly increased FA
Arora et al., 1981 [55]	Essential garlic oil	12 weeks	Increased FA only after 4 weeks
Bordia et al., 1982 [51]	Essential garlic oil	3 weeks	Increased FA
Lutomski, 1984 [24]	Dried garlic powder	12 weeks	No increased in FA
Luley et al., 1986 [25]	Dried garlic powder	6 weeks	No increased in FA
Legnani et al., 1993 [56]	Dried garlic powder	Acute and 14 days	Increased FA
Bordia et al., 1998 [57]	Ethyl acetate extract of garlic	3 months	Increased FA

tivity and collagen-induced platelet aggregation was observed in rabbit platelets treated with raw garlic *in vitro*. The concentration required for 50% inhibition of the platelet aggregation for garlic was calculated to be approximately 6.6 mg/ml plasma. But boiled garlic was found to be of little effect. This finding indicates that garlic may be beneficial in the prevention of thrombosis if ingested raw rather in a cooked form [62,63]. Garlic extract containing diallyl disulfide and diallyl trisulfide, prevented acute platelet thrombus formation in stenosed canine coronary arteries [64]. Fresh garlic extract is effective in reducing thromboxane formation by platelets both *in vivo* and *in vitro* animal models of thrombosis. It was observed that garlic inhibits thrombin-induced platelet synthesis of TXB2 in a dose-and time-dependent manner in rabbits. Maximum inhibition of TXB2 occurred between 0.5 h and 6 h at 25 and 100 mg/kg garlic. The rapid recovery of platelet cyclooxygenase activity after infusion of a single dose of garlic suggests that garlic should be taken more frequently in order to achieve beneficial effects in the prevention of thrombosis [65]. Garlic was also capable of delaying hyperthermia-induced platelet aggregation in mouse pial arterioles, *in vivo*, which was comparable to acetyl salicylic acid [66,67]. Ajoene, a constituent of essential oil of garlic, has been shown to inhibit *in vitro* platelet aggregation in different species of animals i.e., cow, dog, guinea-pig, horse, monkey, pig, rabbit and rat [68]. Under *in vivo* flow conditions and in the presence of physiological calcium levels, ajoene prevented thrombus formation induced by severe vascular damage, mainly in arterial sites with local low shear stress [69,70]. Makheja and Bailey (1990) identified three main antiplatelet constituents, namely adenosine, allicin and polysulfides in garlic [71]. Adenosine and allicin both inhibited platelet aggregation without affecting cyclooxygenase and lipoxygenase metabolites of arachidonic acid. The polysulfides inhibited platelet aggregation as well as thromboxane synthesis. The observed *in vivo* antiplatelet effects of ingesting garlic are attributable more to adenosine than to allicin and polysulfide constituents.

Human Study

In human studies a positive response to garlic has been observed. Like enhancement of fibrinolysis, garlic also has a beneficial effect on platelet adhesion or aggregation in human (Table- 3). Bordia (1978) first showed the dose-dependent inhibition of platelet aggregation by garlic [72]. Raw garlic, garlic oil and other extract of garlic have been shown to inhibit platelet aggregation in *in vitro* induced by ADP, collagen, arachidonate, epinephrine and calcium ionophore [57,61,73–75]. Chronic intake of garlic powder and garlic oil also inhibits platelet aggregation [28,50,55,76–79]. Single dose of garlic has also been shown to inhibit platelet aggregation [54,56,80].

Possible mechanism/s

The antiplatelet mechanism of garlic is much more established than its any other biological effects. Aqueous extract of garlic inhibited platelet aggregation induced by ADP, collagen, arachidonate, epinephrine and calcium ionophore A23187 in a dose-dependent manner [75]. It was found that garlic reduced the formation of thromboxane, inhibited the phospholipase activity and lipoxygenase products formed in platelets. These effects may explain, in part, inhibition of platelet aggregation. Further, since garlic was also effective in inhibiting aggregation induced by calcium ionophore A23187 it may be suggested that the antiaggregation effect may be related to intraplatelet mobilization of calcium. Inhibition of epinephrine-induced aggregation by garlic extract may suggest that it may be inhibiting uptake of calcium into platelets thereby lowering cytosolic calcium concentrations [75].

Table 3: Inhibition of Platelet aggregation (PA) in human:

References	Preparations	Duration	Effect
Bordia, 1978 [72]	Garlic	In-vitro	Dose-dependent Platelet aggregation
Vanderhock et al., 1980 [73]	Garlic oil	In vitro	Inhibit PA
Boullin, 1981 [80]	Fresh garlic	Single Dose	Inhibit PA
Ariga et al., 1981 [85]	Methyl allyl trisulfide	In vitro	Inhibit PA
Arora and Arora, 1981 [54]	Ether extract of garlic	Single Dose	Increased coagulation time
Bordia et al., 1982 [51]	Ether extract of garlic	3 weeks	Inhibit PA
Samson, 1982 [76]	Essential garlic oil	10 days	No PA activity
Apitz-Castro et al., 1983 [74]	Garlic extract and 3 pure component	In vitro	Inhibit PA
Block et al., 1984 [86]	Ajoene	In vitro	Inhibit PA
Srivastava, 1984 [61]	Aqueous extract of garlic	In vitro	Inhibit PA
Srivastava, 1986 [75]	Aqueous extract of garlic	In vitro	Inhibit PA
Harenberg et al., 1988 [77]	Dried garlic powder	4 weeks	No PA activity
Kiesewetter et al., 1991 [78]	Garlic powder	4 weeks	Inhibit PA
Kiesewetter et al., 1993 [87]	Garlic powder	4 weeks	Inhibit PA
Legnani et al., 1993 [56]	Garlic powder	Single Dose and 14 days	Inhibit PA
Morris et al., 1995 [88]	Oil extract (equivalent to 15 gm of raw garlic)	In-vitro and in-vivo (5 days)	Inhibit PA in in-vitro No in-vivo PA activity
Bordia et al., 1998 [57]	Ethyl acetate extract of garlic	In-vitro study	Inhibit PA
Sreiner and Lin, 1998 [79]	Aged garlic extract	10 months	Inhibit PA
Rahman and Billington, 2000 [28]	Aged garlic extract	13 weeks	Inhibit PA
Steiner and Li, 2001 [89]	Aged garlic extract	6 weeks	Dose dependent inhibition of PA

In regard to a specific mechanism of ajoene's antiplatelet action, several suggestions have been made. Ajoene strongly inhibits the metabolism of arachidonic acid by both cyclooxygenase and lipoxygenase pathways [81,82], thus inhibiting the synthesis of thromboxane A2 and 12-HETE. Antiaggregatory effect of ajoene may also be causally related to its direct interaction with the putative fibrinogen receptor (GPIIb/IIa) [83]. The studies of Jamaluddin et al (1988) demonstrated that ajoene interacts with a purified hemoprotein implicated in platelet activation [84]. Ajoene modifies the binding of the hemoprotein with ligands deemed to be physiologically relevant as effectors. Allicin inhibits human platelet aggregation in vitro without affecting cyclooxygenase or thromboxane synthase activity or cyclic adenosine monophosphate (AMP) levels. Allicin also inhibits platelet aggregation but does not alter the activity of vascular prostacyclin synthase. However, it inhibits ionophore A23187-stimulated human neutrophil lysosomal enzyme release. Thus garlic appears to be in possession of components which might exert their effects at various stages involved in the process of platelet aggregation.

Blood pressure lowering effect

A general definition of hypertension is a systolic blood pressure (SBP) of 140 mm Hg or higher or a diastolic blood pressure (DBP) of 90 mm Hg or higher or both. Prevention and proper management of hypertension decreases the incidence of related morbidity and mortality. A downward shift of 3 mm Hg in SBP decreases the mortality from stroke by 8% and from ischemic heart disease by 5% (Joint National Committee, 1993). Life style modification are definitive therapy for some and adjunctive therapy for all persons with hypertension (Joint National Committee, 1997). Diets that are high in fruits, vegetables and low-fat dairy products; have been shown to reduce hypertension. Increased consumption of garlic is associated with lower incidence of hypertension in population. Based on current information, garlic powder preparations are considered for recommendation as adjuncts in the treatment of hypertensive patients [90].

Animal Studies

In experimental animals, intravenous injection of garlic extracts produced slight reductions in both systolic and diastolic pressures [91,92]. Oral administration of garlic reduced experimentally induced hypertension, bringing blood pressure back to the normal range. For example 2.5 to 25 mg per kg of alcoholic garlic extract reduced blood pressure by 10 to 50 mm Hg [93]. Blood pressure in dogs has been significantly reduced for several hours following intragastric administration of a small dose of garlic pow-

Table 4: Blood pressure lowering effect in Human

References	Preparation	Duration	Dose	Effect
Ziaei et al., 2001 [26]	Garlic tablet (Garlet)	3 months	800 mg/day	↓ hypertension
Qidwai, 2000 [115]	Garlic in diet	Chronic intake	134 gm/month	↓ SBP
McCrindle et al., 1998 [31]	Kwai	8 weeks	900 mg/day	No changes
Steiner et al., 1996 [116]	Aged garlic extract	6 months	7.2 gm/day	↓ SBP & DBP
Simons et al., 1995 [34]	Kwai	12 weeks	900 mg/day	No changes
Jain et al., 1993 [117]	Kwai	12 weeks	900 mg/day	No changes
Mcmahan & Vargas, 1993 [118]	Garlic powder	Acute	2400 mg	↓ BP
Kiesewetter et al., 1991 [78]	Garlic powder	4 weeks	800 mg/day	↓ DBP
Auer et al., 1990 [119]	Kwai	12 weeks	600 mg/day	↓ SBP & DBP
Zimmerman et al., 1990 [120]	Kwai	3 weeks	900 mg/day	No changes
Vorberg et al., 1990 [121]	Kwai	16 weeks	900 mg/kg	↓ SBP & DBP
Piotrowski, 1948 [108]	Alcoholic extract of garlic	1 week	0.6–1.2 gm/day	↓ SBP

der (as low as 2.5 mg/kg b.wt) [94]. Other animal experiments on rats and dogs also indicate a 'normalizing' effect of garlic on elevated blood pressure [93,95–98]. The antihypertensive effect of garlic in these studies has been repeatedly confirmed.

Allicin, a major constituent of garlic, was also evaluated for its antihypertensive effects. Chronic oral administration of allicin lowered blood pressure in hypertensive rats [99,100]. Allicin also caused pulmonary vasodilatation in isolated lung of rat [101]. Single as well as multiple doses of aqueous garlic extract reduced thromboxane B2 and prostaglandin E_2 level and thereby reduced hypertension in '2 kidney 1-clip' model of hypertension in rat [102]. Garlic also inhibited endothelin-1 induced contraction in a dose-dependent manner in isolated rat pulmonary arteries [103].

Garlic (100 mg/kg) administration for 5 days resulted in a complete inhibition of acute hypoxic pulmonary vasoconstriction in rat [104]. There was a marked decrease in systolic blood pressure in spontaneously hypertensive rats after oral administration of single dose of garlic [97]. Prolongation of life span was also found in hypertensive rats by dietary supplementation with garlic [105].

Human study

Blood pressure lowering effect of garlic on human is given in Table- 4. Leoper and DeBray recognized the hypotensive effect of garlic in 1921 [106]. Damrau (1941) has reviewed the earlier literature, including his own investigations on 26 patients [107]. Blood pressure reduction was observed in 85% of the patients, the average decline being 12.3 mm Hg systolic (SBP) and 6.5 mm Hg diastolic (DBP) blood pressure, over one-quarter of the subjects experienced a decline in SBP of 20 mm Hg or more.

Piotrowski (1948) has reviewed some of the early clinical studies in which garlic was administered under controlled conditions to hypertensive patients [108]. Two-fifths of 100 patients exhibited a 20 mm Hg or greater decline in SBP generally within 1 week after initiation of treatment with 0.6 to 1.2 g daily of a dialyzed, alcoholic garlic extract.

Studies with a dried garlic powder (Kwai tablets) showed an average decrease in blood pressure of about 9% with 0.6 g garlic powder per day [77,109] and in a randomized double blind trial, a beneficial effect of garlic on blood pressure and blood lipids in mildly hypertensive subjects was demonstrated [110]. Those reports point in the same direction, that garlic can be useful in the control of mild hypertension in many if not all cases.

Pektov (1979) has also cited several studies, mostly from the Soviet Union and Bulgaria, which indicate that garlic and its extracts exhibit antihypertensive activity [111]. Besides subjective improvement, the results of these studies indicated a moderate hypotensive effect involving a drop in SBP of 20–30 mm Hg and in DBP of 10–20 mm Hg. Another study in China (1986) on 70 hypertensive patients who were given garlic oil equivalent to 50 gm of raw garlic/day, 47 patients showed moderate to marked reduction in blood pressure [112].

There is only one meta-analysis done by Silagy and Neil (1994) [113]. Eight trials were identified all using the same dried garlic powder preparation (Kwai). Data from 415 subjects were included in the analysis. Only three trials were specifically conducted in hypertensive subjects.

Of the seven trials that compared the effect of garlic with that of placebo, three showed a significant reduction in systolic blood pressure (SBP) and four in diastolic blood pressure (DBP). The overall pooled mean difference in the absolute change (from baseline to final measurement) of SBP was greater in the subjects who were treated with garlic than in those treated with placebo. For DBP the corresponding reduction in the garlic-treated subjects was slightly smaller. This meta-analysis suggest that this "garlic powder preparation may be of some clinical use in subjects with mild hypertension". However, there is still insufficient evidence to recommend it as a routine clinical therapy for the treatment of hypertensive subjects. More rigorously designed and analyzed trials are needed for firm conclusion.

Possible mechanism/s

Rashid and Khan (1985) have postulated that mechanism of antihypertensive action of garlic is due to its prostaglandin like effects, which decreases peripheral vascular resistance [92]. The gamma-glutamylcysteines are the compounds in garlic that may lower blood pressure, as indicated by their ability to inhibit angiotensin-converting enzyme in *in vitro* [114]. Garlic modulates the production and function of both endothelium derived relaxing and constricting factors and this may contribute to its protective effect against hypoxic pulmonary vasoconstriction [103]. Garlic elicits nitric-oxide-dependent relaxation in pulmonary arteries. This hypothesis was explained by the fact that NG-nitro-L-arginine methyl ester (L-NAME, a NOS inhibitor) abolished the vasodilatory effect of garlic [103,104]. But another study reported that pulmonary vasodilatory effect of allicin are independent of the synthesis of NO, ATP-sensitive (K+) channel, activation of cyclooxygenase enzyme [101].

Diabetes mellitus

Diabetes mellitus is a group of diseases characterized by high blood glucose levels resulting from defects in insulin secretion, insulin action, or both. Abnormalities in the metabolism of carbohydrate, protein, and fat are also present [122]. Nutrition plays a primary role to control blood glucose level and further complication.

Animal studies

Garlic was effective in reducing blood glucose in streptozotocin-induced [123–126] as well as alloxan-induced [127–132] diabetes mellitus in rats and mice. Most of the studies showed that garlic can reduce blood glucose level in diabetic mice [127,133], rats [124,129,130], and rabbit [131,132]. Augusti & Sheela consistently showed that S-allyl cysteine sulfoxide (alliin), a sulfur containing amino acid in garlic (200 mg/kg b.wt.) has a potential to reduce diabetic condition in rat almost to the same extent as did glibenclamide and insulin [128–130]. Treatment of diabetic rats with garlic oil decreased serum acid and alkaline phosphatase, serum alanine and asparate transferases, as well as serum amylase in diabetic rats [123]. Aged garlic extract is also effective to prevent adrenal hypertrophy, hyperglycemia and elevation of corticosterone in hyperglycemic mice induced by immobilization stress [133]. Garlic intake (6.25% by weight in diet) for 12 days reduced hyperphagia and polydipsia but did not alter hyperglycemia and hypoinsulinaemia in streptozotocin-induced diabetic mice [125]. Ingestion of garlic juice resulted in better utilization of glucose in glucose tolerance test performed in rabbits [132,134]. The ethyl alcohol, petroleum ether and ethyl ether extracts of garlic produced a significant fall in blood sugar levels in rabbits [131]. Allicin at a dose of 250 mg/kg is 60% as effective as tolbutamide in alloxan-induced diabetic rabbit [132].

Human study

Hypoglycemic effect of garlic in human is not well studied. Chronic feeding of garlic oil and garlic powder [78,135] showed significant decrease in blood glucose level whereas some other studies [57,117,136] showed no change of blood glucose level. All human studies (Table-5), except one or two, showing effect of garlic on blood glucose level on normal healthy individuals but not in diabetic patients. Thus the role of garlic in diabetic condition is yet to be confirmed.

Table 5: Hypoglycemic effect of garlic in Human

References	Preparation	Duration	Dose	Effect
Zhang et al., 2001 [135]	Garlic oil & Allicin	11 weeks	8.2 mg/day 7.8 mg/day	↓ blood glucose
Li et al., 2000 [137]	Garlicin	10 days	64 mg/day i.v. drip	↓ blood glucose
Bordia et al., 1998 [57]	Ethyl acetate extract	3 months	Eq to 1 gm raw garlic/day	No change
Ali & Thomson, 1995 [136]	Fresh garlic	16 weeks	3 gm/day	No change
Jain et al., 1993 [117]	Garlic powder	12 weeks	900 mg/day	No change
Kiesewetter et al., 1991 [78]	Garlic powder	4 weeks	800 mg/day	↓ blood glucose

Possible Mechanism

Though the exact mechanism/s of garlic as antidiabetic agent is still not clear but *in-vivo* [124,132] as well as *in-vitro* [128] studies showed that garlic acts as an insulin secretagogue in diabetic rats. Augusti & Sheela also proposed that antioxidant effect of S-allyl cysteine sulfoxide (isolated product from garlic) may also contribute for its beneficial effect in diabetes [128]. Another proposed mechanism is due to spare insulin from sulphydryl group. Inactivation of insulin by sulphydryl group is a common phenomenon. Garlic (allicin) can effectively combine with compounds like cysteine and enhance serum insulin [132]. Jain & Vyas proposed that garlic can act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the beta cells or its release from bound insulin [131].

Other cardioprotective properties of garlic

Animal study

Garlic has a significant antiarrhythmic effect in both ventricular and supraventricular arrhythmias. Garlic powder (1% added to a standard chow for an 8 week period) significantly reduced ischemia reperfusion-induced ventricular fibrillation (VF) in isolated perfused rat heart [138]. Garlic dialysate suppressed premature ventricular contractions and ventricular tachycardia in ouabain-intoxicated dogs as well as ectopic rhythms induced by isoprenaline and aconitine on electrically driven left rat atria [139]. Garlic dialysate decreased the positive inotropic and chronotropic effects of isoproterenol in a concentration dependent manner. β-receptor blocking action of garlic was also suggested by Martin et al [140]. The positive inotropism and chronotorpism induced by isoproterenol were partially antagonized by preincubation of the rat atria with the garlic dialysate. The ECG showed a regular sinus bradycardic rhythm in garlic dialysate fed anaesthetized rat [140]. Direct relaxant effect of cardiac muscles was reported by Aqel et al [141]. Garlic juice inhibited norepinephrine-induced contractions of rabbit and guinea pig aortic rings. It also inhibited the force of contraction of isolated rabbit heart in a concentration-dependent manner [141]. Only one study showed that aqueous garlic extract increased the amplitudes of atrial complex 'p' wave and the ventricular complex 'QRS' of the rat ECG. This is suggestive of increase in voltage output of the atria and ventricles probably in accordance with positive inotropism [142].

Raw garlic homogenate augmented endogenous antioxidants along with reduction of basal lipid peroxidation in rat heart, liver and kidney in a dose dependent manner [143,144]. Aged garlic extract (AGE) also exerted its antioxidant action by scavenging reactive oxygen species [145] and enhancing the cellular antioxidants, like reduced glutathione superoxide dismutase, catalase and glutathione peroxidase of vascular endothelial cells [146,147]. Augmented endogenous antioxidants on heart and endothelial cells have important direct cytoprotective effects, especially in the event of oxidant stress induced injury. Recently, in our laboratory, we found that chronic oral administration of garlic homogenate protected the rat heart from *in vitro* ischemic reperfusion injury [148] and oxidative stress induced by single dose of adriamycin [149]. AGE has been shown to offer protection against the cardiotoxic effects of doxorubicin, an antineoplastic agent used in cancer therapy [150]. Feeding of garlic powder in rats for 11 days had a protective effect on isoproterenol-induced myocardial damage [151]. In another study, the size of the ischemic zone was significantly reduced and the onset of arrhythmia after occlusion of the descending branch of the left coronary artery was significantly prolonged in rats fed with a standard chow enriched with 1% garlic powder for 10 weeks [152]. Aqueous garlic extract was also found to be effective in reducing Cu (+)-initiated oxidation of low density lipoprotein (LDL) as measured by photochemiluminescence method [42]. AGE also protected vascular endothelial cells from H_2O_2-induced oxidant injury [153].

Human Study

Aortic stiffening is as much an important risk factor in cardiovascular morbidity and mortality, as it serves as reliable surrogate marker for clinical endpoints like myocardial and cerebrovascular incidents. Elevated aortic stiffness induces high systolic blood pressure, augmented pulse pressure with increased ventricular afterload, reduced subendocardial blood flow and augmented pulsatile stress in the peripheral arteries [154]. In population, consuming garlic for long period, attenuation of age-related increase in aortic stiffness has been observed. This suggests a protective effect on the elastic properties of the aorta related to aging in human [155]. This study also showed that regular long term garlic powder intake protected endothelial cell from oxidative injury [155]. Twelve week therapy with garlic powder (800 mg/day) was effective in patients with peripheral arterial occlusive disease Stage II. There was a significant decrease of plasma viscosity. It is also quite interesting that the garlic-specific increase in walking distance did not appear to occur until the 5th week of treatment [87]. Microcirculation of skin increased by 48% after administration of 800 mg/day garlic powder over a period of four weeks. Plasma viscosity was decreased by 3.2% [78]. Kiesewetter also reported that garlic improved blood fluidity and increased capillary perfusion [156]. Decreased plasma viscosity and increased (55%) capillary skin perfusion were observed even after 5 hours of garlic powder administration [157]. All these studies are summarised in Table- 6.

Table 6: Direct cardioprotective effect of garlic in Human

References	Preparation	Duration	Dose	Effect
Li et al., 2000 [137]	Garlicin	10 days	64 mg/day i.v. drip	↓ Unstable angina
Breithaupt-Grogler et al., 1997 [155]	Garlic powder	7 years	300 mg/day	↑ elastic property of blood vessels
Kiesewetter et al; 1993 [87]	Garlic powder	12 weeks	800 mg/day	↓ peripheral arterial occlusive disease
Kiesewetter et al., 1991 [78]	Garlic powder	4 weeks	800 mg/day	↓ plasma viscosity
Jung et al., 1991 [157]	Garlic powder	Single dose	900 mg/day	↓ plasma viscosity & ↑ skin perfusion
Kiesewetter et al; 1990 [156]	Garlic powder	Acute	–	↑ capillary perfusion

Adverse effects

Considering the fact that garlic has been an integral part of our diet for centuries, it is taken for granted that garlic is safe in a wide range of doses. But a few isolated reports highlight some of the adverse and toxic effects of garlic.

Animal study

Higher concentrations of garlic extract have been shown to be clastogenic [158] in mice, which was appreciably reduced at lower concentrations. Prolong feeding of high levels of raw garlic in rats has resulted in anemia, weight loss and failure to grow due to lysis of red blood cells [159]. Raw garlic juice at a dose of 5 ml/kg has resulted in death of rats due to stomach injury [160]. Surviving rats exhibited swelling of the liver, hypertrophy of the spleen and adrenal glands, and the decrease of erythrocyte count with various morphological changes after 3 and 8 days. Aqueous garlic extract (200 gm/l drinking water) for 10 days exhibited significantly higher levels of aspartate aminotransferase (AST) due to liver injury. Histopathological examination of liver showed focal nonspecific injury with inflammatory cell infiltration in hepatocytes [161]. Chen *et al.*, (1999) have reported that treatment of rats with fresh garlic homogenate for 7 days caused a significant decrease in liver catalase activity in doses of 2 and 4 gm/kg [162]. The ultrastructural study carried out in our laboratory revealed significant loss of normal cellular architecture of heart, liver and kidneys after 30 days feeding of raw garlic homogenate at 1000 mg/kg/day dose [143,144]. Feeding of allicin (100 mg/kg/day) for 15 days in rats increased the activity of liver lipase and alpha glucal phosphorylase and decreased glucose-6-phosphatase activity [163]. The exact mechanism of such garlic induced alteration in cell structure and function is not clear.

There is also some reported toxicity with garlic powder. Chronic administration of garlic powder (50 mg/day) resulted in inhibition of spermatogenesis in rats. Reduced concentration of sialic acid in the testes, epididymis and seminal vesicles together with decreased leydig cell function reflects antiandrogenic effect of garlic [164]. Higher concentration of garlic powder (200 mg/ml) or allicin isolated from garlic caused considerable cell injuries in the porta hepatis zone in isolated perfused rat liver [165], which was not observed at a lower concentration. Another *in vitro* study showed that diallyl sulfide (oxidized product of allicin) at 5 mM significantly decreased cell viability in liver [166].

Garlic oil fed at a dose of 100 mg/kg after 24 hour fasting has also been found to be lethal. The cause of death appears to be acute pulmonary edema with severe congestion [161]. Garlic oil and Diallyl-disulfide (200 mg/kg b.w.) significantly reduced body weight gain of rats [167]. Ajoene, a garlic derived natural compound, present in other types of garlic oil, is an inhibitor as well as a substrate of human glutathione reductase and expected to increase the oxidative stress of the respective cell [168].

All the above mentioned toxicity reports can not be explained to its fullest extent but the sulphoxides present in the garlic extract can undergo exchange reaction with the tritable SH-groups of enzymes and other proteins in the body spontaneously at physiological pH and temperature, inhibiting their activity. Garlic has been demonstrated to inhibit the alkaline phosphatase [161], papain, and alcohol dehydrogenase [169]. These enzyme interactions with garlic components may be a reason for its toxicity.

Human study

Relatively few side effects were reported in clinical studies using garlic and its preparations. Most of the reported side effects were non-specific. Gastrointestinal discomfort and nausea were the most frequent complaint [170]. A survey by Koch (1995) showed that allergic reactions to garlic were reported in a total of 39 publications between 1938 and 1994 [171]. Most of these cases involved an allergic contact dermatitis, sometimes severe [172], which has

been reported in people with occupational exposure to garlic. There have also been sporadic reports of allergic conjunctivitis, rhinitis, or bronchospasms occurring in response to garlic inhalation or ingestion [173,174]. Other reported side effects included bloating, headache, dizziness, and profuse sweating [170]. Ingestion of fresh garlic and garlic powder may have additive effects with anticoagulants or platelet aggregation inhibitors, leading in one case to a life-threatening hemorrhage [175–179].

Conclusions

Epidemiological study shows an inverse correlation between garlic consumption and reduced risk of cardiovascular disease progression [180–182]. The wealth of scientific literature supports the proposal that garlic consumption have significant cardioprotective effect, which include both animal and human studies. But certain issues regarding the proper use of garlic, i.e use of different preparations available, dose, duration and interaction with generic drugs should be optimized. Further research should also be carried out to identify specific compounds from garlic or garlic products that are responsible for most of its biological effects.

Authors' contributions

SKB carried out the extensive search and compilation of the review article. SKM participated in its design, coordination and drafting the manuscript.

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