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Assessment of the Impact of Garlic in Heart-related Diseases

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Abstract

Atherosclerosis, hyperlipidemia, thrombosis, hypertension, and diabetes are just a few of the metabolic illnesses that garlic and its derivatives have been shown to prevent and treat. Experimental investigations on the effectiveness of garlic in heart-related disorders were more encouraging, which led to the initiation of multiple clinical trials. The effectiveness of garlic, particularly its cholesterol-lowering impact, has recently come under scrutiny despite the fact that numerous clinical investigations have demonstrated a favorable effect of garlic on practically all of the cardiovascular disorders listed above. As the least expensive method of preventing heart-related disease, using garlic properly and reaping its full benefits is a significant problem for scientists around the world. This review has made an effort to discuss the mechanisms of such therapeutic effects of garlic and to bridge the gap between experimental and clinical investigation.

Keywords

Garlic, Heart-related diseases, animal experiment, clinical trial

1. Introduction

Cardiovascular disease is just one of the many human diseases that are greatly influenced by dietary variables. Diets high in fruits, herbs, and spices have been linked to a lower incidence of cardiovascular disease, according to epidemiological research. Over many ages, the folklore of many civilizations developed a reputation for garlic as a potent preventative and curative medicine. disease is just one of the many human diseases that are greatly influenced by dietary variables. Diets high in fruits, herbs, and spices have been linked to a lower incidence of cardiovascular disease, according to epidemiological research. Over many ages, the folklore of many civilizations developed a reputation for garlic as a potent preventative and curative medicine. Garlic has drawn the attention of medical researchers in particular due to its widespread use in food and medicine around the world and the widely held idea that garlic promotes health by fending off disease and boosting vitality. Garlic products, including garlic extract, have been shown to have numerous positive experimental and clinical effects thus far.

These biological reactions have been generally linked to the following mechanisms: i) decreased risk factors for cancer and cardiovascular disease, ii) immune system activation, iii) improved foreign substance detoxification, iv) hepatoprotection, v) antibacterial impact, and vii) antioxidant effect. This review was written to provide a comprehensive analysis of garlic's effectiveness in treating cardiovascular disease in both humans and animals.

1.2 Historical Perspective of Garlic

It is remarkable to see how societies that had never interacted arrived to the same understandings about the function of garlic in health and sickness. Folk knowledge may provide us with useful lessons if it is not disregarded. On Sumerian clay tablets from 2600 to 2100 BC, this medicinal and culinary plant is mentioned for the first time. In particular for the working class engaged in hard labor, garlic was a significant remedy to the ancient Egyptians as documented in the medical text Codex Ebers (about 1550 BC) [1,2]. There is proof that participants were given garlic to increase stamina at the first Olympics in Greece [1]. Garlic was recommended in traditional Chinese medicine to help with breathing, digestion, and, most critically, diarrhea and worm infestation [3]. Garlic was used extensively in three ancient Indian medical systems, including Tibbi, Unani, and Auryveda, as a key component of plants' therapeutic potential [2]. Garlic has long been recommended for the treatment of heart disease and arthritis by the most important ancient medical treatise in India, the Charaka-Samhita. Garlic was prescribed for weariness, parasite illness, digestive disorders, and leprosy in the Bower Manuscript (c. 300 AD), an early Indian medicinal manual [4]. With the advent of the Renaissance, the medicinal use of garlic began to receive more attention in Europe. Pietro Mattiali of Siena, a renowned physician of the 16th century, recommended garlic for renal problems, worm infestation, and digestive issues in addition to supporting mothers during challenging labors [2]. Garlic was used to treat toothaches, constipation, dropsy, and plague in England [4]. In the intervening years, scientists have worked to confirm many of these characteristics of garlic, particularly in regards to the composition of the active ingredients, the mechanisms underlying their actions, and the potential advantages as dietary supplements.

1.2 Garlic preparations and their chemical compounds

The primary method of preparing garlic that has been the subject of extensive scientific research is raw garlic homogenate, as it is the most popular way to consume garlic. The aqueous garlic extract that has been employed in numerous scientific investigations is very similar to raw garlic homogenate. Aqueous garlic extract or raw garlic homogenate are believed to contain the main bioactive component allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate). The allinase enzyme, which is present in garlic, is activated when it is diced or crushed and reacts with the alliin (present in intact garlic) to form allicin. Allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate, and -Lglutamyl-S-alkyl-L-cysteine are other significant sulfur-containing compounds found in garlic homogenate. As the homogenate is incubated at room temperature, the concentration of adenosine multiplies several-fold. Heat inactivates the enzyme allinase that transforms alliin (S-allyl cysteine sulphoxide) into allicin. As a result, the primary component of the heat-treated garlic water extract is alliin. Garlic powder's composition, particularly its allinase activity, is the same as that of fresh garlic because it is basically a dehydrated, ground garlic clove. Dehydration temperatures, however, should not rise above 60°C because allinase becomes inactive at that point [1].

Aged garlic extract (AGE) is another frequently studied garlic preparation. AGE is the term used to describe raw, sliced garlic that has been kept for 20 months in ethanol at a 15% to 20% concentration. Allicin is expected to be largely lost during this process, whereas the activity of newer molecules like selenium and stable, highly bioavailable antioxidants S-allylcysteine (SAC), S-allylmercaptocysteine, and allixin is expected to increase [5]. N-alpha-(1-deoxy-Dfructos-1-yl)-L-arginine (Fru-Arg), which is absent from raw or heat-treated garlic, is a new antioxidant component of AGE [6].

Most garlic oil used in medicine is created by the steam distillation technique. Diallyl (57%), allyl methyl (37%),

and dimethyl (6%) mono to hexa sulfides make up steam-distilled garlic oil. 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%). Vinyl-dithiins and ajoenes are found in garlic oil that has been macerated. The amount of vinyl-dithiins (5.7 mg/gm), allyl sulfides (1.4 mg/g), and ajoenes (0.4 mg/g) in ether extracted garlic oil (essential oil) is nine times higher [1].

1.3 Atherosclerosis and Lipid Mwetabolism

Atherosclerosis is a complicated condition marked by an excessive inflammatory, fibro-fatty, proliferative response to arterial wall damage involving a variety of cell types, especially smooth muscle cells, monocyte-derived macrophages, T lymphocytes, and platelets [7]. A significant etiopathological contributor to atherosclerosis is hyperlipidemia. The lipid-lowering and antiatherogenic properties of garlic are its most well-known therapeutic benefits.

1.3.1 Animal Studies

The effects of long-term (2-9 months) feeding of garlic and garlic preparations (2% garlic powder in diet) on experimental atherosclerosis produced by a high-cholesterol diet in rabbits were investigated by several groups of researchers [8–14]. In the majority of these trials, atheromatous lesions, notably in the aorta, showed a statistically significant reduction that, on average, was roughly 50%.

Additionally encouraging were the long-term effects of garlic on the lipid metabolism in rats. These trials lasted at least four weeks. In hypercholesterolemic rats created by a high-cholesterol diet, garlic (1–4% in diet) and garlic protein injection dramatically decreased blood cholesterol, triglyceride, and LDL cholesterol [11,15–20], but there was no change in serum HDL. Following prolonged garlic ingestion, rats' livers also had lower cholesterol and total lipid contents. Allicin, an active ingredient in garlic, was studied by Abramoviz et al. (1999) for its impact on mice's lipid profiles and the development of fatty streaks in the aorta [21]. Although there were no discernible variations in blood lipid profiles, microscopic analysis of the development of fatty streaks in the aortic sinus revealed that values for mice in the allicin-treated groups were noticeably lower by almost 50%. A thickened, lipid-filled lesion caused by balloon-catheter damage to the right carotid artery in cholesterol-fed rabbits was greatly prevented by the aged garlic extract "Kyolic" [22,23].

1.3.2 Human Studies

Over 46 human investigations on the lipid-lowering properties of garlic and garlic products have been conducted since 1975 (according to a medline search). Most of these trials involved hyperlipidemic individuals and were randomized, double-blind, placebo-controlled, and used garlic powder rather than raw garlic over a period of 4–16 weeks. In the majority of these investigations, serum cholesterol and triglycerides significantly decreased. Only roughly a third of these trials examined lipoproteins, where considerable positive changes in LDL-cholesterol level (decreases of 11-26% were frequently seen). A few trials utilizing garlic powder, which has minimal allicin yields, were unsuccessful in demonstrating any benefits on lipid levels [24,25]. 18 clinical investigations on the hypolipedemic effects of garlic have been published in the past ten years (1993-2002). Garlic powder was utilized in seven of the nine investigations that produced negative findings (Table 1) [26–34]. The contradictory results could be explained by the varied garlic preparations employed in various trials having varying sulfur component compositions and quantities. It emphasizes the necessity of standardizing various garlic preparations in order to draw a reliable conclusion. Other elements could be the selection of the subjects, the length of the study, dietary restrictions, way of life, and lipid analysis techniques [35,36].

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**	**–**

There are four meta-analyses on the hypocholesterolemic effects of garlic that were conducted on randomized, placebo-controlled human studies [35–38]. The analysis also revealed that there were significant variations between studies in how much garlic lowers cholesterol. A mean plasma cholesterol with placebo was observed in hypercholesterolemic individuals treated with garlic, according to five randomized clinical trials conducted by Warshafsky and his colleagues [36]. In the meta-analysis conducted by Silagy and Neil in 1994, data from 952 subjects were used to examine sixteen trials [35]. Over the course of one to three months, garlic, both in powder and non-powder form, dramatically reduced serum cholesterol levels. With dried powder preparations, serum cholesterol decreased by 8%, whereas non-powder preparations reduced it by 15%. The level of serum triglycerides decreased dramatically as well, although HDL cholesterol remained practically same. These effects appeared to be consistent across the daily dose range of 600-900 mg among the garlic powder preparations. Another meta-analysis [37] found no statistically significant difference between the groups receiving garlic (900 mg/day of dried garlic powder standardized to 1.3% allicin) and placebo in terms of the mean concentrations of blood lipids, lipoproteins, or apo A1 or B. Garlic's ability to lower total cholesterol was found to be less effective in this meta-analysis than it had been in prior meta-analyses. Though six diet-controlled trials with the highest methodological quality scores showed no significant difference between the garlic and placebo groups, a more recent meta-analysis of thirteen trials found that garlic significantly reduced total cholesterol level from baseline more than placebo [38]. The information at hand indicates that garlic reduces total cholesterol levels more effectively than a placebo. The magnitude of the effect is moderate, and its robustness is in question. Therefore, it is still unclear whether garlic has a real hypocholesterolemic impact.

1.3.4 Possible Mechanism

Garlic's ability to lower the lipid content of artery wall has been linked to its protective impact against atherosclerosis. At the level of the arterial wall, garlic has direct antiatherogenic (preventive) and antiatherosclerotic (inducing regression) actions [39]. The hepatic activities of lipogenic and cholesterogenic enzymes, such as 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase, fatty acid synthase, glucose-6-phosphate dehydrogenase, and malic enzyme, were inhibited by garlic [40]. As evidenced by higher excretion of acidic and neutral steroids following garlic ingestion, garlic also increased the excretion of cholesterol [20]. LDL was observed to be considerably more oxidation resistant in human individuals who received AGE [41] and aqueous garlic extract [42]. These findings suggest that one of the potent mechanisms behind garlic's anti-atherosclerotic effects may be decreased LDL oxidation [43]. The chemical ingredient responsible for the antiatherosclerotic action was initially identified as allicin. Recent in vitro investigations, however, have shown that water-soluble organosulfur compounds, particularly S-allyl cysteine (SAC) and diallyl-di-sulfide (DADS) found in old garlic extract and garlic oil, are also powerful inhibitors of cholesterol formation.

1.4 Fibrinolytic Activity

The hemostatic equilibrium may be disrupted by the inhibition of fibrinolytic activity (FA) or a lack of one or more of the necessary components, which would permit excessive fibrin deposition. It is probable that a disturbance in the coagulation-fibrinolytic system may be a significant factor causing the development of thrombosis and ischemia in conditions such as diabetes, hypertension, hypercholesterolemia, etc. Therefore, the antithrombic action is more favorable the higher the FA. The time it takes for euglobulin to lyse usually determines FA. The highest levels of plasma fibrinogen, euglobulin lysis time, and antiplasmin were

seen in the patients who died from acute or elderly myocardial infarction. This shows that the degree of decreased plasma fibrinolysis affects the outcome in myocardial infarction [45].

1.4.1 Animal Studies

The essential oils of garlic considerably decreased the dramatic increase in blood coagulability that occurred in rabbits after three months of consuming 0.2 g/kg/day of cholesterol. In fact, fibrinolytic activity was elevated even above typical control levels. Garlic essential oils, which are present in raw bulb quantities of 1 g/kg/day, were successful in mediating fibrinolytic activity [10,46]. After ingesting a diet high in cholesterol for 13 weeks, an experimental investigation found that garlic juice (raw garlic; 250 mg/day) significantly increased the fibrinolytic activity in rabbits [47]. Garlic was added to this diet, which significantly enhanced the plasma fibrinolytic activity in rabbits, which had been reduced by cholesterol feeding [48].

1.4.2 Human Studies

Nearly all investigations on the effects of garlic's fibrinolytic action on humans have been good (Table 2).

Garlic oil and raw garlic consumption both acutely and over time increased fibrinolytic activity (FA). The first time that garlic oil enhanced FA after 3 hours of administration was by Bordia in 1975. Furthermore, Bordia observed that continuous (3 weeks to 3 months) treatment of garlic oil (dose: equivalent to 1 gm/kg of fresh garlic) dramatically elevated FA ranging from 36% to 130% in both healthy individuals and acute myocardial infarction patients [49–52]. The similar findings were made by a few other researchers as well [53–55]. The fribinolytic potential of dried garlic powder has also been investigated. One study [56] found increased FA and tissue plasminogen activator activity after acute and chronic garlic powder use, while two studies [24,25] found no differences in FA. One study was designed by Chutani and Bordia (1981) to demonstrate that both raw and fried garlic significantly increase FA [53]. Garlic's unpleasant smell is eliminated when it is fried, but it keeps its beneficial effects on FA. The increase in FA was noticed within six hours of garlic administration, demonstrating that the effect of garlic is well maintained for as long as it is consumed. Bordia (1998) recently discovered that consuming crushed raw garlic ethyl acetate extract for three months similarly raised FA [57].

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

1.5 Platelet aggregation

Myocardial infarction and thromboembolic disorders are caused by total stoppage of blood flow, which is caused by platelet aggregation superimposed on an atherosclerotic channel. Platelets cling to the exposed von Willebrand factor, collagen, and laminin in the damaged vessel wall. The term "platelet activation" refers to this action. ADP and thrombin can also result in activation. The process of platelet aggregation is

started when active platelets transform, exude pseudopodia, release their granules, and adhere to other platelets. Platelet activating factor (PAF), a cytokine released by platelets as well as neutrophils and monocytes, also promotes aggregation [59].

1.5.1 Animal Studies

Garlic has a strong ability to prevent platelet aggregation, according to studies. A 500 mg/kg dose of an aqueous garlic extract dramatically reduced the production of thromboxane-B2 (TXB2), a powerful platelet aggregator, in rabbits before collagen or arachidonate infusions caused thrombocytopenia. These findings suggest that using garlic to prevent thrombosis may be advantageous [60]. ADP, epinephrine, collagen, and arachidonate were reported to reduce platelet aggregation in a dose-dependent manner in vitro and to decrease the formation of prostacyclin in rat aorta when garlic extract was used [61]. In rabbit platelets treated with raw garlic in vitro, cyclooxygenase activity and collagen-induced platelet aggregation were both inhibited in a dose-dependent manner. It was determined that 6.6 mg/ml of plasma was the concentration needed for garlic to suppress platelet aggregation by 50%. But it was shown that boiling garlic had little impact. This result suggests that raw garlic, as opposed to cooked garlic, may be helpful in the prevention of thrombosis [62,63]. In canine coronary arteries with stenosis, garlic extract containing diallyl disulfide and diallyl trisulfide inhibited the formation of acute platelet thrombus [64]. Both in vivo and in vitro animal models of thrombosis, fresh garlic extract reduces platelet production of thromboxane. The synthesis of TXB2 by thrombin-induced platelets is inhibited by garlic in rabbits, and this inhibition is dose- and time-dependent. At 25 and 100 mg/kg garlic, the maximum inhibition of TXB2 occurred between 0.5 and 6 hours. In order to achieve positive results in the prevention of thrombosis, garlic should probably be taken more frequently, according to the quick recovery of platelet cyclooxygenase activity after a single dose was infused [65]. Similar to acetyl salicylic acid, garlic was similarly effective at postponing hyperthermia-induced platelet aggregation in mouse pial arterioles in vivo [66,67]. Ajoene, an ingredient in garlic's essential oil, has been found to prevent platelet aggregation in a variety of animal species, including cows, dogs, guinea pigs, horses, monkeys, pigs, and rats [68]. Ajoene inhibited thrombus formation caused by severe vascular injury under in vivo flow circumstances and in the presence of physiological calcium levels, primarily at arterial regions with local low shear stress [69,70]. Adenosine, allicin, and polysulfides were the three primary antiplatelet components in garlic that Makheja and Bailey (1990) found [71]. Both adenosine and allicin prevented platelet aggregation while having no effect on the arachidonic acid metabolites cyclooxygenase and lipoxygenase.

1.5.2 Human Studies

Studies on humans have shown that garlic has a favorable effect. Garlic has a positive impact on platelet adhesion or aggregation in humans, similar to how it increases fibrinolysis (Table 3). Garlic's dose-dependent ability to suppress platelet aggregation was initially demonstrated by Bordia in 1978 [72]. In vitro platelet aggregation caused by ADP, collagen, arachidonate, epinephrine, and calcium ionophore has been demonstrated to be inhibited by raw garlic, garlic oil, and various garlic extracts [57,61,73-75]. Garlic powder and oil consumption for an extended period of time also prevents platelet aggregation [28,50,55,76-79]. Garlic has also been demonstrated to prevent platelet aggregation in a single dose [54,56,80].

1.5.3 Possible mechanism

Garlic's antiplatelet mechanism is significantly more well-established than any other biological impacts it may have. In a dose-dependent way, calcium ionophore A23187, collagen, arachidonate, epinephrine, and aqueous extract of garlic reduced platelet aggregation [75]. It was discovered that garlic decreased the production of thromboxane, hindered the action of phospholipase, and prevented the creation of lipoxygenase products in platelets. These consequences could partially account for the suppression of platelet aggregation. Additionally, since calcium ionophore A23187-induced aggregation was successfully inhibited by garlic, it is possible that the antiaggregation activity of garlic is connected to intraplatelet calcium mobilization. Garlic extract may be reducing calcium uptake into platelets by preventing epinephrine-induced aggregation, which would lower 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**

Numerous hypotheses have been put out regarding the precise mechanism of ajoene's antiplatelet activity. The synthesis of thromboxane A2 and 12HETE is inhibited by ajoene's potent inhibition of the metabolism of arachidonic acid via the cyclooxygenase and lipoxygenase pathways [81,82]. The putative fibrinogen receptor (GPIIb/IIa), which ajoene directly interacts with, may have a causal role in the antiaggregatory effect [83]. Ajoene interacts with a purified hemoprotein linked to platelet activation, according to research by Jamaluddin et al. from 1988 [84]. Ajoene alters the hemoprotein's affinity for ligands that are thought to be physiologically significant as effectors. Without changing cyclooxygenase, thromboxane synthase, or cyclic adenosine monophosphate (AMP) levels, allicin prevents human platelet aggregation in vitro. Although it does not affect the activity of vascular prostacyclin synthase, allicin also prevents platelet aggregation. However, it prevents the release of the lysosomal enzyme from human neutrophils when ionophore A23187 is present. Thus, it appears that garlic contains elements that could have an impact at different points during the platelet aggregation process.

1.6 Blood pressure lowering effect

A systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic blood pressure (DBP) of 90 mm Hg or higher, or both, are considered to be indicative of hypertension. The incidence of associated morbidity and mortality lowers with adequate hypertension management and prevention. According to the Joint National Committee (1993), a 3 mm Hg decrease in SBP reduces stroke and ischemic heart disease mortality by 8% and 5%, respectively. According to the Joint National Committee (1997), lifestyle changes are an adjuvant therapy for everyone with hypertension and a definitive therapy for others. It has been demonstrated that diets rich in fruits, vegetables, and low-fat dairy products can lower blood pressure. Garlic consumption is linked to lower rates of hypertension in the general population. Garlic powder preparations are taken into

consideration for suggestion as adjuncts in the treatment of hypertension patients based on the most recent data [90].

1.6.1 Animal Studies

Garlic extracts administered intravenously to laboratory animals resulted in small decreases in both systolic and diastolic pressures [91,92]. Garlic supplementation decreased experimentally generated hypertension and returned blood pressure to normal. For instance, alcoholic garlic extract at 2.5 to 25 mg per kg lowered blood pressure by 10 to 50 mm Hg [93]. After giving dogs a tiny amount of garlic powder (as little as 2.5 mg/kg b.wt) intragastrically, blood pressure was dramatically lowered for several hours [94]. Garlic appears to have a 'normalizing' impact on high blood pressure in other animal studies done on rats and dogs [93,95-98]. Garlic's antihypertensive effect in these investigations has been amply supported. A key component of garlic called allicin was also examined for its potential to lower blood pressure. Allicin was given orally to hypertensive rats over an extended period of time to reduce blood pressure [99,100]. In a rat's isolated lung, allicin also led to pulmonary vasodilatation [101]. In the '2 kidney 1-clip' model of hypertension in rats, single as well as multiple doses of aqueous garlic extract decreased thromboxane B2 and prostaglandin E2 levels, consequently reducing hypertension [102]. In isolated rat pulmonary arteries, garlic similarly reduced endothelin-1-induced contraction in a dose-dependent manner [103]. Acute hypoxic pulmonary vasoconstriction in rats was completely inhibited by garlic (100 mg/kg) treatment for 5 days [104]. After a single dose of garlic was administered orally to spontaneously hypertensive rats, the systolic blood pressure significantly decreased [97]. Garlic supplementation in the diet was also observed to increase life expectancy in hypertensive rats [105].

1.6.2 Human Studies

Table 4 shows how garlic lowers blood pressure in people. The hypotensive properties of garlic were discovered in 1921 by Leoper and DeBray [106]. Damrau (1941) conducted his own research on 26 patients and evaluated the preceding literature [107]. Over one-quarter of the subjects saw a fall in SBP of 20 mm Hg or more. Blood pressure was reduced in 85% of the patients, with an average decline of 12.3 mm Hg for SBP and 6.5 mm Hg for DBP. Some of the earliest clinical experiments in which hypertension patients received garlic under strictly controlled circumstances have been examined by Piotrowski (1948) [108]. Within a week of starting treatment with 0.6 to 1.2 g of a dialyzed, alcoholic garlic extract daily, around half of 100 patients showed a reduction in SBP of at least 20 mm Hg. Studies using dried garlic powder (Kwai tablets) showed a blood pressure reduction of about 9% on average with 0.6 g of garlic powder daily [77,109], and a beneficial effect of garlic on blood pressure and blood lipids in mildly hypertensive subjects was shown in a randomized double-blind trial [110]. All of those results suggest that garlic can, at least in some circumstances, be helpful in the management of moderate hypertension.

Garlic and its extracts appear to have antihypertensive activity, according to Pektov (1979) and a number of other research, the majority of which came from the Soviet Union and Bulgaria [111]. These studies' findings also showed a mild hypotensive impact, with drops in SBP of 20–30 mm Hg and DBP of 10–20 mm Hg, in addition to subjective relief. 47 of the 70 hypertensive patients in different research conducted in China in 1986 who received garlic oil equivalent to 50 g of raw garlic per day exhibited a modest to significant drop in blood pressure [112]. Silagy and Neil (1994) conducted just one meta-analysis [113]. Eight experiments with the same dried garlic powder formulation (Kwai) were found. 415 subjects' data were used in the analysis. There were just three experiments that were particularly done on hypertensive people.

Three studies indicated a significant decrease in systolic blood pressure (SBP) and four in diastolic blood pressure (DBP) in the seven trials that evaluated the impact of garlic with that of a placebo. The patients who received garlic treatment experienced a higher absolute change in SBP (from the baseline to the final assessment) than the subjects who received a placebo. The associated decrease in DBP was slightly less in the garlic-treated participants. According to this meta-analysis, "garlic powder preparation may be useful clinically in subjects with mild hypertension." To now, there is not enough data to support its use as a standard therapeutic therapy for the treatment of hypertension patients. For a definitive conclusion, more well planned and analyzed studies are required.

1.6.3 Possible Mechanism

According to Rashid and Khan (1985), the prostaglandin-like actions of garlic's antihypertensive impact are what lower peripheral vascular resistance [92]. Garlic contains substances called gamma-glutamylcysteines that have been shown to be able to block angiotensin-converting enzyme in vitro [114], suggesting that they may reduce blood pressure. Garlic has a preventive effect against hypoxic pulmonary vasoconstriction via modulating the synthesis and activity of both endothelium-derived relaxing and constricting factors [103]. In pulmonary arteries, garlic causes nitric oxide-dependent relaxation. This theory was supported by the finding that the NOS inhibitor L-NAME completely eliminated the vasodilatory effects of garlic [103,104]. However, according to a different study, the pulmonary vasodilatory effects of allicin are unrelated to the production of NO, the activation of ATP-sensitive (K+) channels, or the cyclooxygenase enzyme [101].

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

1.7 Diabetes Mellitus

A collection of illnesses known as diabetes mellitus are characterized by excessive blood sugar levels brought on by deficiencies in insulin secretion, action, or both. There are also anomalies in the metabolism of fat, protein, and carbohydrates [122]. The major factor in controlling blood glucose levels and subsequent complications is nutrition.

1.7.1 Animal Studies

Both streptozotocin- and alloxan-induced [123–126] and alloxan-induced [127–132] diabetes mellitus in rats and mice were successfully treated with garlic to lower blood glucose levels. Garlic can lower blood glucose levels in diabetic mice [127,133], rats [124,129,130], and rabbits [131,132], according to the majority of research. Sallyl cysteine sulfoxide (alliin), an amino acid in garlic that contains sulfur (200 mg/kg b.wt.), has been regularly demonstrated by Augusti and Sheela to have the ability to ameliorate diabetes state in rats virtually to the same extent as glibenclamide and insulin [128–130]. Garlic oil treatment reduced serum levels of alanine and aspartate transferases, acid and alkaline phosphatase, and amylase in diabetic rats [123]. In hyperglycemic mice brought on by immobilization stress, aged garlic extract is also useful for preventing adrenal hypertrophy, hyperglycemia, and corticosterone increase [133]. In streptozotocin-induced diabetic mice, consuming garlic for 12 days (6.25% of the weight of the diet) decreased hyperphagia and polydipsia but had no effect on hyperglycemia and hypoinsulinemia [125]. In a rabbit glucose tolerance test, consumption of garlic juice improved glucose utilization [132,134]. The blood sugar levels of rabbits significantly decreased when treated with the garlic ethyl alcohol, petroleum ether, and ethyl ether extracts [131]. In an alloxan-induced diabetic rabbit model, allicin at a dose of 250 mg/kg is 60% as efficacious as tolbutamide [132].

1.7.2 Human Studies

There is little research on garlic's hypoglycemic effects in people. While some studies [57,117,136] found no

change in blood glucose levels after chronic administration of garlic oil and garlic powder, [78,135] demonstrated a considerable reduction in blood glucose levels. With the exception of one or two investigations on animals, all human studies (Table 5) suggest that garlic lowers blood glucose levels in healthy, normal persons but not in diabetic patients. Thus, it is still uncertain whether garlic has any effect on diabetes.

1.7.3 Possible Mechanism

Garlic functions as an insulin secretagogue in diabetic rats, according to in-vivo [124,132] and invitro [128] research, even if the precise mechanism or mechanisms by which it prevents diabetes are yet unknown. The antioxidant properties of S-allyl cysteine sulfoxide, an isolated garlic compound, were also suggested by Augusti & Sheela as potentially contributing to its positive effects on diabetes [128]. Another theory is that this process protects insulin from the sulphydryl group. Sulphydryl group inactivation of insulin is a typical occurrence. Allicin, a component of garlic, can effectively mix with substances like cysteine to increase serum insulin [132]. Garlic may function as an anti-diabetic medication by boosting either the release of insulin from bound insulin or the secretion of insulin from beta cells in the pancreas [131].

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**

1.8 Other Heart-related protective properties of garlic

1.8.1 Animal Studies

Both ventricular and supraventricular arrhythmias are significantly reduced by garlic's antiarrhythmic effects. In an isolated perfused rat heart over an 8-week period, garlic powder (1% added to a conventional chow) significantly decreased ischemia reperfusion-induced ventricular fibrillation (VF) [138]. Intoxicated dogs with ouabain had premature ventricular contractions and ventricular tachycardia; isoprenaline and aconitine-induced ectopic rhythms on electrically driven left rat atria were also inhibited by garlic dialysate [139]. In a concentration-dependent manner, garlic dialysate reduced the beneficial inotropic and chronotropic effects of isoproterenol. Martin et al [140] also proposed that garlic may inhibit -receptors.

Preincubation of the rat atria with the garlic dialysate partially counteracted the positive inotropism and chronotorpism brought on by isoproterenol. In an anesthetized rat fed garlic dialysate, the ECG revealed a consistent sinus bradycardic rhythm [140]. Aqel et al. [141] showed that cardiac muscles had a direct relaxing action. The aortic rings of rabbit and guinea pigs did not contract when norepinephrine was present. Additionally, it reduced the force of the isolated rabbit heart's contraction in a concentration-dependent way [141]. Only one study found that aqueous garlic extract raised the rat ECG's ventricular complex 'QRS' and atrial complex 'p' wave amplitudes. This suggests an increase in the atria's and ventricles' voltage output, perhaps in line with positive inotropism [142].

In a dose-dependent manner, raw garlic homogenate increased endogenous antioxidants and decreased basal lipid peroxidation in the heart, liver, and kidney of rats [143,144]. In addition to increasing cellular antioxidants such reduced glutathione superoxide dismutase, catalase, and glutathione peroxidase of vascular endothelial cells, aged garlic extract (AGE) also had an antioxidant effect by scavenging reactive oxygen species [145]. In the event of oxidative stress-induced injury, enhanced endogenous antioxidants on heart

and endothelial cells have significant direct cytoprotective benefits. In our lab, we recently discovered that adriamycin-induced oxidative stress and in vitro ischemia reperfusion injury were both prevented by continuous oral administration of garlic homogenate [148, 149].

Doxorubicin, an antineoplastic drug used in cancer therapy, has been demonstrated to have cardiotoxic effects. AGE has been proven to provide protection against these effects [150]. Garlic powder was given to rats for 11 days, and this had a protective effect against the cardiac damage caused by isoproterenol [151]. In a different study, rats fed a regular diet enhanced with 1% garlic powder for 10 weeks saw a large reduction in the size of the ischemic zone and a significant delay in the start of arrhythmia following blockage of the left coronary artery [152]. According to research using the photochemiluminescence method, aqueous garlic extract was also observed to reduce Cu (+)-initiated oxidation of lowdensity lipoprotein (LDL) [42]. Additionally, AGE shielded vascular endothelial cells from oxidative damage brought on by H2O2 [153].

1.8.2 Human Studies

As a trustworthy surrogate measure for clinical outcomes including myocardial and cerebrovascular events, aortic stiffness is a significant risk factor for cardiovascular morbidity and mortality. High systolic blood pressure, augmented pulse pressure with higher ventricular afterload, decreased subendocardial blood flow, and increased pulsatile stress in the peripheral arteries are all caused by elevated aortic stiffness [154]. Long-term use of garlic in a population has been shown to reduce the age-related rise in aortic stiffness. This shows that aging in humans has a protective impact on the aorta's elastic characteristics [155]. This study also shown that consistent, long-term consumption of garlic powder protected endothelium cells from oxidative damage [155]. Patients with Stage II peripheral artery occlusive disease responded well to a twelve-week regimen of garlic powder (800 mg/day). The plasma viscosity significantly decreased. The fact that the increase in walking distance associated with garlic did not appear to materialize until the fifth week of treatment is also highly intriguing [87]. Following a four-week treatment with 800 mg/day of garlic powder, skin microcirculation increased by 48%. The viscosity of the plasma was reduced by 3.2% [78]. Garlic improved blood fluidity and boosted capillary perfusion, according to Kiesewetter [156]. Even five hours after the injection of garlic powder, there was a reduction in plasma viscosity and an increase (55%) in capillary skin perfusion [157]. Table 6 provides a summary of all these investigations.

Table 6: Direct cardioprotective effect of garlic in Human

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

1.9 Adverse Effect

Given that garlic has been a staple of human diet for ages, it is assumed that garlic is safe in a variety of quantities. A few isolated instances, however, draw attention to some of the harmful and toxic consequences of garlic.

1.9.1 Animal Studies

It has been demonstrated that mice exposed to higher quantities of garlic extract exhibit clastogenic behavior

[158], which was noticeably diminished at lower concentrations. Rats fed high doses of raw garlic for an extended period of time developed anemia, lost weight, and failed to grow due to red blood cell lysis [159]. Rats that were given 5 ml/kg of raw garlic juice died as a result of stomach damage [160]. After 3 and 8 days, survivors showed swollen livers, enlarged spleens and adrenal glands, and decreased erythrocyte counts along with other morphological abnormalities. Due to liver damage, aqueous garlic extract (200 gm/l drinking water) for 10 days showed noticeably elevated levels of aspartate aminotransferase (AST). An analysis of the liver's histopathology revealed focal nonspecific damage and inflammatory cell infiltration in the hepatocytes [161]. In rats given fresh garlic homogenate for 7 days, Chen et al. (1999) found that doses of 2 and 4 gm/kg significantly reduced liver catalase activity [162]. After 30 days of feeding raw garlic homogenate at a dose of 1000 mg/kg/day, an ultrastructural examination performed in our lab revealed a considerable loss of normal cellular architecture of the heart, liver, and kidneys [143,144]. When rats were given allicin (100 mg/kg/day) for 15 days, liver lipase and alpha glucal phosphorylase activity increased whereas glucose-6-phosphatase activity decreased [163]. It is unclear how exactly garlic causes changes in cell structure and function.

Additionally, some toxicity with garlic powder has been recorded. Rat spermatogenesis was inhibited by a chronic treatment of garlic powder (50 mg/day). Garlic's antiandrogenic action is demonstrated by decreased leydig cell function and decreased sialic acid concentration in the testes, epididymis, and seminal vesicles [164]. In an isolated perfused rat liver, a higher concentration of garlic powder (200 mg/ml) or allicin from garlic caused significant cell damage in the porta hepatis zone [165], which were not seen at a lower concentration. Diallyl sulfide, an oxidized byproduct of allicin, dramatically reduced liver cell viability at 5 mM, according to another in vitro investigation [166].

It has also been discovered that feeding garlic oil at a dose of 100 mg/kg after a 24-hour fast is fatal. Acute pulmonary edema with significant congestion appeared to be the cause of death [161]. Rats were much less likely to acquire weight when given garlic oil and diallyl-disulfide (200 mg/kg b.w.) [167]. The natural chemical ajoene, which is generated from garlic and found in different varieties of garlic oil, is both an inhibitor and a substrate of human glutathione reductase and is predicted to increase oxidative stress in the corresponding cell [168].

The sulphoxides in garlic extract can undergo exchange reactions with the tritable SH-groups of enzymes and other proteins in the body spontaneously at physiological pH and temperature, inhibiting their activity. However, all the toxicity reports mentioned above cannot be fully explained. Alcohol dehydrogenase [169], papain [161], and alkaline phosphatase have all been shown to be inhibited by garlic. Its toxicity may be caused by these enzyme interactions with garlic's constituent parts.

1.9.2 Human Studies

Clinical research employing garlic and its compounds showed very few adverse effects. The majority of the side effects that were mentioned were vague. The most common complaint was discomfort in the gastrointestinal tract and nausea [170]. According to a study by Koch (1995), there were 39 publications that contained reports of allergic reactions to garlic between the years of 1938 and 1994 [171]. The majority of these instances had an allergic contact dermatitis, which has been associated with occupational exposure to garlic and can occasionally be severe [172]. Additionally, there have been infrequent reports of allergic reactions to garlic that result in rhinitis, bronchospasms, or allergic conjunctivitis [173, 174]. Bloating, headaches, vertigo, and excessive sweating were additional side effects that were described [170]. Garlic powder and fresh garlic consumption may interact with anticoagulants or platelet aggregation inhibitors in ways that are cumulative, in one case resulting in a life-threatening hemorrhage [175-179].

2. Conclusion

According to epidemiological research, eating garlic lowers the risk of cardiovascular disease progression [180–182]. The idea that eating garlic has a strong cardioprotective impact is supported by a multitude of scientific research, which includes both animal and human trials. However, certain aspects of using garlic correctly, such as the use of the many preparations available, dose, duration, and interaction with generic medications, should be optimized. Additionally,

more investigation should be done to pinpoint the precise chemicals found in garlic or garlic-related products that are largely accountable for its biological effects.

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