

•Reviews•

Therapeutic effects of garlic in cardiovascular atherosclerotic disease

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[ABSTRACT] Garlic (*Allium sativum*) is a widely known medicinal plant, potential of which remains to be fully evaluated. Its wide-range beneficial effects appear to be relevant for treatment and prevention of atherosclerosis and related diseases. It is generally believed that garlic-based preparations are able to improve lipid profile in humans, inhibit cholesterol biosynthesis, suppress low density lipoprotein oxidation, modulate blood pressure, suppress platelet aggregation, lower plasma fibrinogen level and increase fibrinolytic activity, thus providing clinically relevant cardioprotective and anti-atherosclerotic effects. It is important to assess the level of evidence available for different protective effects of garlic and to understand the underlying mechanisms. This information will allow adequate integration of garlic-based preparations to clinical practice. In this review, we discuss the mechanisms of anti-atherosclerotic effects of garlic preparations, focusing on antihyperlipidemic, hypotensive, anti-platelet and direct anti-atherosclerotic activities of the medicinal plant. We also provide an overview of available meta-analyses and a number of clinical trials that assess the beneficial effects of garlic.

[KEY WORDS] Atherosclerosis; Dyslipidemia; Cardiovascular disease; Natural medicines; Garlic

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Introduction

The medicinal properties of garlic (*Allium sativum* L.) that are known for thousands of years, have not been scientifically proven until recently, when the concepts of evidence-based medicine and controlled clinical trials were established. The beneficial effects of garlic in treatment of cardiovascular diseases (CVD) were especially challenging to prove due to the mild effect, long time frame and complex pathogenesis of atherosclerosis and related CVD. Garlic-based preparations are believed to have cardioprotective

and anti-atherosclerotic effects, such as improving blood lipid profile, inhibiting cholesterol biosynthesis, suppressing low density lipoprotein (LDL) oxidation, modulating blood pressure, suppressing platelet aggregation, lowering plasma fibrinogen level and increasing fibrinolytic activity^[1-2]. These potential effects appear to be very promising given the extent of challenge that atherosclerosis puts on modern medicine and the need for novel and safe medications. Coronary artery disease (CAD) and stroke are the main clinical manifestations of atherosclerosis and the leading global causes of death, adding up to 65% in total mortality rates^[3]. Atherosclerosis is a multifactorial disease, which is not entirely dependent on conventional cardiovascular risk factors. The pathology can be regarded as an excessive fibro-fatty, proliferative, inflammatory response to the arterial wall damage, which involves several cell types, such as smooth muscle cells, monocyte-derived macrophages, lymphocytes and platelets^[4]. It is

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therefore important to distinguish between indirect and direct anti-atherosclerotic effects of therapies, including garlic-based preparations. Indirect effects reduce the risk of atherosclerosis development, while direct effects target the cellular and molecular pathways of the disease pathogenesis. Among the outcomes of direct anti-atherosclerotic effects are plaque stabilization, reduction of the lipid core mass and re-

gression of existing plaques (Table 1). Although numerous reviews of preclinical and clinical studies evaluating the effects of garlic in CVD have been published, these reports present heterogeneous information, and are sometimes contradictory. In this review we will discuss the available evidence of beneficial effects of garlic in atherosclerosis and possible mechanisms that confer these effects.

Table 1 Anti-atherosclerotic effects of garlic

Anti-hyperlipidemic activity	Hypotensive effect	Anti-platelet activity	Direct anti-atherosclerotic effect
Diallyl disulfide: HMG CoA inhibition, reduction of cholesterol synthesis; <i>S</i> -allyl cysteine: Reduction of TG, cholesterol; antioxidant	Inhibition of ACE; down-regulation of angiotensin II receptor; stimulation of NO and H ₂ S; regulation of the growth suppressor p27 and attenuation of ERK1/2 phosphorylation	Inhibition of cyclooxygenase; decreased synthesis of thromboxane B ₂ , decreased production of leukotriene C ₄ , prostaglandin E ₂ by platelets; regulation of membrane phospholipases; regulation of serotonin and coagulation factor IV liberation; inhibition of GPIIb/IIIa receptor	Inhibit cIMT thickening; inhibit cellular proliferative activity, synthesis of extracellular matrix, antioxidant activity, reduce LDL oxidation, anti-inflammatory properties

ACE: angiotensin-converting enzyme; cIMT: carotid intima-media thickness; HMG CoA: 3-hydroxy-3-methylglutaryl CoA; LDL: low-density lipoprotein TG: triglycerides

Hypolipidemic effects of garlic-based preparations

Normalization of the blood lipid profile is one of the basic current therapeutic approaches to reduce the risk of CVD [5]. Data from several epidemiologic studies have shown that certain diets with high garlic consumption were associated with reduced risk of cardiovascular disease, and hence garlic was considered as potentially lipid-lowering dietary constituent [6].

Biological mechanisms of lipid-lowering effects of garlic have been studied extensively by several groups. Diallyl disulfide, which is a component of garlic oil, was found to inhibit 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase in a concentration-dependent manner and therefore have an effect similar to that of statins [7]. Treatment with diallyl disulfide irreversibly inactivated microsomal and a soluble 50 kDa form of HMG-CoA reductase by forming an internal protein disulfide that became inaccessible for reduction by dithiothreitol, thereby retaining the inactive state of the enzyme [8]. Exposure of primary rat hepatocytes and human HepG2 cells to water-soluble garlic extract resulted in a concentration-dependent inhibition of cholesterol biosynthesis at several different enzymatic steps [9]. At very high concentrations, garlic extract inhibited cholesterol biosynthesis causing accumulation of the precursors lanosterol and 7-dehydrocholesterol. Studies in cultured rat hepatocytes suggested that garlic components inhibit cholesterol synthesis by deactivating HMG-CoA reductase *via* enhanced phosphorylation, but not by changing the levels of mRNA or the amount of the enzyme [10]. Synthetic diallyl disulfide analogs were found to be effective for reducing total lipid levels in a rodent model, which was accompanied by a significant decrease in HMG-CoA reductase activity mRNA levels. Diallyl disulfide analogs also significantly inhibited the activation of sterol regulatory element-binding protein-2 and interfered with

DNA binding activity of cAMP response element-binding protein, but not nuclear Factor- κ B, which upstream regulatory sequences of HMG-CoA reductase [11]. The main active constituent of aged garlic extract, *S*-allyl cysteine, was evaluated as antioxidant and hypolipidemic agent in rats, and caused significant decrease of triglycerides, total cholesterol, AST, ALT, malondialdehyde, glutathione peroxidase enzyme activity, total glutathione and oxidized glutathione in rat serum. The protective effects were superior for aged garlic extract compared to *S*-allyl cysteine, indicating that other active constituents may be present in the extract [12]. Effects of garlic on lipid profile and the expression of related genes in rats fed on a high-fat diet included significant changes in the levels of mRNA of sterol regulatory element binding protein-1c (SREBP-1c), acetyl-CoA carboxylase, fatty acid synthase, and glucose-6-phosphate dehydrogenase. Hepatic expression of HMG-CoA reductase and Acyl-CoA cholesterol acyltransferase mRNA was also significantly lowered. As a result, blood levels of total lipids, triglycerides and cholesterol were decreased [13].

In clinical trials, the effects of garlic preparations on blood lipid profile were rather heterogeneous. Early systematic reviews and meta-analyses of randomized controlled trials of garlic preparations have shown an evident but moderate lipid-lowering effect of garlic, despite the fact that many of the included trials had methodological shortcomings. Analysis of 16 trials (952 subjects in total) conducted in 1998 showed a reduction in total cholesterol and serum triglycerides and total cholesterol reduction of 12% compared to placebo. The size of the effect did not depend significantly on the dose within the range of 600–900 mg·d⁻¹ of dried garlic powder standardized by allicin content [14]. However, the results of own double-blinded randomized 6-month parallel trial performed by the same authors showed no significant differences between the groups receiving garlic (900 mg·d⁻¹ of dried

garlic powder standardized to 1.3% allicin) and placebo with respect to mean concentrations of serum lipids, lipoproteins, apo-A1 and apo-B. Updated meta-analysis still showed association of garlic with a mean reduction in total cholesterol by $0.65 \text{ mmol}\cdot\text{L}^{-1}$ [15].

Subsequent studies delivered undecisive results. In several studies, treatment with garlic in one or another form (raw, extract or powder) was associated with decreases in total blood cholesterol up to 11.5%, and in LDL-cholesterol up to 15% [16-18]. At the same time, double-blind placebo-controlled studies demonstrated no significant effect of garlic powder tablets (Kwai, 900 mg daily) on plasma cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triglycerides, and lipoprotein (a) in subjects with hypercholesterolemia [19-20]. Similarly, a double-blinded randomized placebo-controlled study failed to show any effect of steam-distilled garlic oil preparation (5 mg twice per day for 12 weeks) on serum lipoproteins [21].

More recent studies with garlic preparations continued delivering contradictory results. For instance, the study of Tapsell and co-authors published in 2006 demonstrated that consuming a half to one clove of garlic (or equivalent) daily may have a cholesterol-lowering effect of up to 9% [22]. A study that evaluated the effect of raw garlic consumption on human blood biochemical factors in 30 hyperlipidemic individuals (blood cholesterol higher than $245 \text{ mg}\cdot\text{dL}^{-1}$) showed that after 42 days of garlic consumption, mean blood total cholesterol and triglycerides were reduced, and HDL-cholesterol was increased significantly [23]. Treatment with enteric-coated garlic powder tablets equal to 400 mg (1 mg allicin) twice daily decreased total cholesterol by 12%, and LDL-cholesterol by 17%, while HDL-cholesterol increased by nearly 16%, along with a statistically insignificant decrease in serum triglycerides [24]. Treatment with oily macerate of garlic (270 mg of garlic macerate suspended in rape seed oil, containing 0.27 mg of allicin derivatives standardized for allicin) was associated with a 9% reduction in total cholesterol and 14% reduction in LDL-cholesterol [25]. A double-blind placebo-controlled study showed that time-released garlic powder tablets (Allicor, 600 mg daily) allowed reducing total cholesterol by 7.6% and LDL-cholesterol by nearly 12%, while increasing HDL-cholesterol by 11.5% in subjects with hyperlipidemia [26]. The same preparation was tested in other controlled studies that sometimes confirmed its moderate hypolipidemic effect [27-28], and sometimes failed to do so [29].

A meta-analysis published in 2009 evaluated the results of 13 randomized controlled trials of garlic ranging from 11 to 24 weeks in duration, reporting the effects of garlic on cholesterol levels in 1056 healthy or hypercholesterolemic subjects [30]. It was found that administration of garlic was not associated with any significant difference in any of the examined outcome measures compared with placebo, including serum total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides or apo-B levels. The authors concluded that the

available evidence from randomized controlled trials did not support any beneficial effects of garlic on serum lipids. Another meta-analysis of 29 randomized, placebo-controlled trials of garlic conducted the same year demonstrated that garlic significantly reduced total cholesterol and triglycerides but had no significant effect on LDL- or HDL-cholesterol [31]. A more recent meta-analysis conducted in 2012 included a total of 26 studies and demonstrated that garlic was superior to placebo in reducing serum total cholesterol and triglyceride levels, but had no effect on other lipid parameters, including LDL-cholesterol, HDL-cholesterol, apo-B, and cholesterol/HDL-cholesterol ratio [32]. The most comprehensive meta-analysis conducted to date included 39 primary trials evaluating the effect of garlic preparations on total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides [33]. The authors showed that garlic was effective in reducing total serum cholesterol and LDL-cholesterol in individuals with elevated total cholesterol levels, if used for longer than 2 months. The observed mean reduction of total serum cholesterol by 8% was of clinical relevance and was associated with a 38% reduction in risk of coronary events at 50 years of age. At the same time, HDL-cholesterol levels improved only slightly, and triglycerides were not influenced significantly. A random-effect meta-analysis performed on 22 trials published in 2014 reported that garlic powder intake significantly reduced blood cholesterol and LDL-cholesterol by 0.41 and $0.21 \text{ mmol}\cdot\text{L}^{-1}$, respectively [34].

The observed controversy in the results of studies evaluating the hypolipidemic effect of garlic can have several explanations. First, the doses of garlic used in the trials were usually far lower than those used in animal studies. Next, differences in the organosulfuric composition of different types of garlic preparations may hinder interpretation of the results. Moreover, biological availability of garlic products was not taken into account in many studies. Finally, the response to garlic may differ between the individuals considerably, and the agent may be more beneficial for some specific groups of patients. To evaluate hypolipidemic activity of garlic preparations, more accurate meta-analyses are necessary, that only include studies with standardized preparations and rigorous methodology.

Effects of garlic on arterial hypertension

Together with dyslipidemia, arterial hypertension is a potent risk factor of atherosclerosis and related cardiovascular diseases. Possible blood pressure-lowering effects of garlic-based preparations have been evaluated in a number of pre-clinical and clinical studies. Molecular mechanisms of hypotensive effects of garlic remain to be fully understood. Among the reported biological pathways of garlic hypotensive activity are inhibition of angiotensin-converting enzyme [35], reduction of vasoconstrictor prostanoids synthesis [36], stimulation of NO and H_2S [37], up-regulation of the growth suppressor p27 and attenuation of ERK1/2 phosphorylation [38],

and down-regulation of angiotensin II receptor [39]. Garlic-derived polysulfides may stimulate production of hydrogen sulfide (H₂S) and enhance the regulation of endothelial nitric oxide (NO), which induces smooth muscle cell relaxation, vasodilation, and blood pressure reduction [40]. Sulfur deficiency that contributes to hypertension can be alleviated by supplementation of organosulfur compounds derived from garlic. Other experimental explanations of hypotensive effects of garlic include prevention of NO synthesis inhibition by *N*-omega-nitro-L-arginine-methyl-ester, combination of endothelium-dependent and endothelium-independent mechanisms, direct relaxant effect on smooth muscles, a depressant effect on automaticity and tension of myocardium via beta-adrenoreceptor blocking action, diuretic and natriuretic inhibitory response of kidney Na, K-ATPase, and the opening of potassium ion channels causing membrane hyperpolarization that closes the part of L-type Ca²⁺ channels [41].

An early systematic review evaluating the effect of garlic powder preparation (Kwai) included 8 trials and a total of 415 subjects suggested that garlic powder preparation may be of some clinical use in subjects with mild hypertension [42]. The major limitation of that work was that only 3 of the included trials were conducted in hypertensive subjects. A later meta-analysis of 10 randomized controlled trials of the effects of garlic on blood pressure in patients with and without elevated systolic blood pressure brought more decisive results. In patients with elevated blood pressure, garlic reduced both systolic and diastolic blood pressure by 16.3 and 9.3 mmHg, respectively, however, in patients without hypertension, no significant effect was detected [43]. An updated systematic review and meta-analysis of 11 studies published in 1955–2007 tested the associations between blood pressure outcomes and duration of treatment, dosage, and blood pressure at the treatment start [44]. Mean overall decrease of systolic blood pressure in the garlic group as compared to placebo was 4.6 mm Hg, while mean decrease in the hypertensive patients was 8.4 mm Hg. There was a strong association between blood pressure at the start of the intervention and the level of blood pressure reduction. Therefore, garlic preparations were found to be superior to placebo in reducing blood pressure only in individuals with mild hypertension. This conclusion was in line with the results of our own study of two garlic-based preparations standardized by allicin content (Kwai and Allicor) that had a statistically significant hypotensive effect on both systolic and diastolic blood pressure in men with mild and moderate arterial hypertension [45]. Taken together, these findings showed that the mechanisms of hypotensive action of garlic-based preparations may be quite different from those of conventional pharmacological agents used for treatment of arterial hypertension, and may be referred to complex biological regulation of blood pressure.

During the recent years, the interest to garlic's therapeutic potential was renewed, which resulted in a series of comprehensive meta-analyses. The random-effects model

meta-analysis published in 2014 included 9 trials assessing systolic blood pressure and 10 trials assessing diastolic blood pressure [34]. This analysis provided the evidence for reduction of both systolic and diastolic blood pressure in patients treated with garlic by 4.3 and 2.4 mmHg, respectively. Another systematic review included 9 randomized placebo-controlled trials that evaluated garlic preparation in 482 hypertensive patients and follow-up ranging 8–26 weeks and reported a difference of 9.1 mm Hg and 3.8 mm Hg, for systolic and diastolic blood pressure respectively [46]. Another meta-analysis of 17 trials showed that garlic intake caused a 3.8 mm Hg reduction in systolic blood pressure and a 3.4 mm Hg reduction in diastolic blood pressure, with the effect being prominent in hypertensive, but not normotensive patients [47]. Finally, a meta-analysis of 7 randomized placebo-controlled trials published before August 2014 reported a significant lowering effect of garlic on both systolic and diastolic blood pressure by 6.7 and 4.8 mmHg, respectively [48]. Therefore, most of clinical trials supported the assumption that garlic may moderately decrease arterial blood pressure in hypertensive subjects, thus providing a certain type of consensus. Tapsell with co-authors stated that there is level III-1 evidence that aged garlic extract is associated with modest reduction of blood pressure (an approximate 5.5% decrease of systolic blood pressure) [22].

Garlic and platelet function

Antithrombotic therapy is a necessary component of treatment of atherosclerosis patients. Long-term therapy with antiplatelet drugs is generally recommended, but has certain limitations due to possible adverse effects. Garlic is a known plant remedy with antithrombotic activity, which enhances fibrinolysis, inhibits platelet aggregation, and diminishes plasma viscosity [49]. Possible mechanisms of garlic antithrombotic activity include inhibition of cyclooxygenase [50], decreased synthesis of thromboxane B₂ and decreased production of vasoconstrictors like leukotriene C₄ and prostaglandin E₂ by platelets [51], regulation of activity of membrane phospholipases that prevents liberation of arachidonic acid from phospholipids [52], and regulation of serotonin and coagulation factor IV liberation from platelets [53]. Unlike aspirin, garlic does not affect the prostacyclin synthesis in the vascular wall, thus sustaining antithrombotic properties of endothelial cells [54]. Aged garlic extract was shown to reduce collagen-induced platelet aggregation in rats by increasing the amount of both the extracellular ATP and the extra- and intracellular TXB₂, and by suppressing the phosphorylation of collagen-induced ERK, p38 and JNK [55]. In human blood-derived platelets, this substance decreased ADP-induced aggregation by increasing cyclic nucleotides and inhibiting fibrinogen binding and platelet shape change [56]. It was also shown that garlic extract inhibited platelet aggregation *via* inhibiting the GPIIb/IIIa receptor and an increasing cAMP level [57].

Clinical evidence of antithrombotic effects of garlic is contradictory. A randomized double-blind placebo-controlled crossover study using solvent-extracted garlic oil, which earlier demonstrated the highest antiplatelet activity *in vitro*, showed a significant 12% reduction of adrenaline-induced platelet aggregation, but no effect on collagen-induced or ADP-induced aggregation [58]. By contrast, a double-blinded placebo-controlled randomized study in patients with cerebral atherosclerosis and chronic cerebrovascular insufficiency demonstrated that 14-day treatment with garlic powder pills (Allicor) significantly inhibited ADP-induced platelet aggregation by 25% and increased plasma fibrinolytic activity by 22%. At the same time, the observed trend to decrease plasma fibrinogen level did not reach statistical significance [59]. Therefore, garlic appears to inhibit platelet aggregation by multiple mechanisms and may have a role in preventing cardiovascular disease. A recent comprehensive review named garlic among the plants exhibiting anti-platelet activity that are of interest for developing drugs to treat diseases related to aggregation disorders [60].

Direct anti-atherosclerotic effects of garlic

Ideally, therapy of atherosclerosis should prevent the growth of existing atherosclerotic lesions and the formation of the new ones. The most intriguing property of garlic-based preparations is its direct anti-atherosclerotic activity, which is independent from the moderate reduction of cardiovascular risk factors associated with garlic. The components of garlic can regulate two main intracellular enzymes responsible for cholesterol intracellular metabolism. Additionally, garlic extract inhibits cellular proliferative activity and the synthesis of connective tissue matrix components, possesses antioxidant activity and lowers LDL susceptibility to oxidation [61–62]. Garlic-based preparations inhibited neointimal thickening in cholesterol-fed rabbits [63]. Garlic-based preparation Allicor prevented cholesterol accumulation in cultured cells treated with serum from atherosclerosis patients after a single dose, thus was shown to reduce serum atherogenic potential [61–63]. Atherogenesis is dependent on the formation of modified atherogenic LDL, including oxidized LDL, glycosylated LDL or desialylated LDL [64]. Garlic components and derivatives were shown to inhibit sialidase activity in blood plasma [65–66]. Therefore, treatment with garlic-based preparations may decrease the pool of highly atherogenic modified LDL and therefore alleviate cholesterol deposition in the arterial wall. Finally, inflammation is known to play a key role in atherosclerotic process. It was shown that activation of the inflammatory pathway was a primary cellular response to modified LDL, probably preceding changes in lipid metabolism [67]. Garlic constituents are known to inhibit inflammation signaling, including TNF, IL-1-beta, ICAM-1 and HLA-DR expression and secretion [62, 68]. Therefore, they may have a beneficial effect at the arterial wall cells level.

One of the earliest clinical studies assessing the effect of

garlic preparations in arteriosclerosis patients was the randomized, double-blind, placebo-controlled clinical trial published in 1999 [69]. In this study, measurement of plaque volume by B-mode ultrasound demonstrated attenuated growth (by 5%–18%), and even a slight regression of plaques during the 48-months follow-up period in patients receiving high-dose garlic powder. Our group conducted a double-blind placebo-controlled study to estimate the effect of time-released garlic powder tablets (Allicor) on the progression of carotid atherosclerosis in 211 asymptomatic men aged 40–74 years. The primary outcome was the rate of atherosclerosis progression measured by B-mode ultrasonography as the increase in carotid intima-media thickness (cIMT). After 12-months follow-up, a decrease of cIMT by 0.028 mm was observed in Allicor-treated group, while in placebo group, there was a moderate progression at the rate of 0.014 mm ($P = 0.002$ for the difference) [70]. In the 24-month extension of this study, the mean rate of cIMT decrease in Allicor-treated group was 0.022 mm per year, which was significantly different from the placebo group, in which there was a moderate but statistically significant progression of 0.015 mm per year at the overall mean baseline cIMT of 0.931 mm. Within Allicor-treated group, cIMT significant reduction was observed in 47% of study participants versus 30% in the placebo group. Further significant cIMT increase was registered in 32% study participants in Allicor-treated group versus 47% in the placebo group [61]. However, the observed decrease in LDL-cholesterol, increase in HDL-cholesterol, and decrease in systolic blood pressure did not correlate with cIMT dynamics. Another garlic-based preparation enriched with phytoestrogens from grape seeds, hop cones and green tea leaves (Karinat) was studied in a 12-months randomized double-blinded placebo-controlled clinical trial in asymptomatic postmenopausal women, and the primary endpoint was the annual rate of changes in cIMT [71]. Study participants treated with garlic preparation did not show a significant change in cIMT, while in the placebo group, an increase of the mean cIMT of more than 0.100 mm per year was observed. Garlic powder tablets as supplementary to conventional medical treatment were evaluated in a randomized placebo-controlled study performed in patients with coronary heart disease [72]. In this study, a 0.009 mm reduction of cIMT was observed after 3 months of follow-up in the study group, while in the placebo group, an 0.040 mm cIMT increase was observed. Total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, apo-A1 and apo-B did not differ between the two groups.

Conclusion

Accurate evaluation of anti-atherosclerotic potential of garlic and its preparations is challenging due to the moderate associated effects combined with high heterogeneity of studies in terms of patients' populations, dosages and medicinal forms of garlic-containing substances and concomitant treatments. Moreover, great variety in the outcomes of conducted

clinical trials may be explained in part by the pleiotropic effects of garlic that are often difficult to determine. So far, evidence of beneficial effects of garlic on different aspects of cardiovascular disorders, such as hyperlipidemia or hypertension, remained insufficient for drawing precise recommendations, although the consensus remained favorable of garlic use. Introduction of imaging methods that allowed to measure asymptomatic atherosclerosis progression and evaluate the direct effects of garlic on atherosclerosis yielded some encouraging results. Together, the accumulated knowledge supports the use of garlic preparations as a complement therapy for patients with atherosclerosis and as prevention measure.

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