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Future prospect of garlic usage in clinical practice of hyperlipidemia: A review

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Abstract
Garlic is an important universal dietary and medicinal plant which is being used as food and herbal medicine since ancient times. Hyperlipidemia is a major risk factor in the atherosclerosis and other cardiovascular disease. The medicinal importance of garlic is attributed to its lipids lowering and anti-atherogenic effects. Being important spice in human food, garlic can contribute its lipids lowering and anti –atherogenic effects. So it has been evaluated so far by several clinical trials in hyperlipidemia. Most of the studies on the effect of oral garlic on serum lipids have shown positive results within the low range of hyperlipidemia. The lipids lowering effect of garlic remains for a few months only. So there is need of further planned clinical trials to evaluate its qualitative and quantitative aspect of hypolipidemic effect in clinical practice.

Keywords: Garlic, lipids, lipids lowering, anti-atherogenic, hyperlipidemia

1. Introduction

Garlic is an important dietary and medicinal plant in human history. It is being used as food and medicine since ancient times. It is a member or alliaceae family having botanical name, *Allium sativum*. Due to being enriched with medicinal effects, it had been used in ancient Greece (Hippocrates), Egypt, Rome, India, china and Japan for multiple indications including performance enhancement, pulmonary and digestive complains, abnormal growth, cardiovascular health, emotional health, potency and as an anti- infective agent [1, 2, 3, 4]. In England, garlic was used for toothache, constipation, dropsy and plague [4]. The leading Indian ancient medicinal text, charka -Samhita recommended garlic for the treatment of heart disease and arthritis for over many centuries. It was also used during both world war to prevent gangrene [5]. In course of time, research on garlic began with study of its antibacterial activity in the 1930 with subsequent investigations into cancer inhibition beginning in the late 1940 [5]. Currently in modern medicine, garlic is one of the most widely used herbal compounds in USA with ongoing research in several areas related to cardiovascular health, oncology, infectious disease with encouraging medicinal effects in alleviating hypertension and hyperlipidemia. Garlic is one the most investigated medicinal plants from 1960 to 2007. More than three thousands research papers have been published on the chemical and biological effects of garlic and garlic preparation till date. Hyperlipidemia is a major risk factor in the cardiovascular disease, one of the leading causes of mortality worldwide causing more than 80% of deaths in low and middle income countries [6]. Hyperlipidemia is documented as a major risk factor responsible for the development of atherosclerosis and cardiovascular disease [7]. Atherosclerosis is a complex disease characterized by an excessive inflammatory, fibro fatty and proliferative changes in the arterial wall.
Hyperlipidemia constitutes a major etiological factor for atherosclerosis. The medicinal value of garlic is attributed to its lipid lowering and anti-atherogenic effects. It is claimed to possess beneficial effects for the prevention of various aspects of cardiovascular disease including hypertension and hyperlipidemia [8]. At present, garlic remains widely used herbal product used for the treatment and prevention of cardiovascular disease and cancer. Being important spice in human food, it has been evaluated so far by several clinical trials in hyperlipidemia. Most of the studies examining the effect of oral garlic on serum lipids have shown positive results, whereas some of the studies have shown contradictory results. So this review is focused on the qualitative and quantitative aspect of garlic effect in hyperlipidemia in modern medicine.

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2. Review of Literature

2.1 Chemical Composition of Garlic: Intact garlic cloves contain a few medicinally active chemical compounds. The main chemical constituent of intact garlic is the amino acid "alliin". It is an alkyl derivative of cysteine alkyl sulfoxide, responsible for the typical odors, which may vary from 0.2 – 2% fresh weight. Crushing, chewing, cutting and exposing dehydrated pulverized garlic powder of garlic cloves to water releases the enzyme allinase that acts upon the cystosolic cysteine sulfoxide to form sulfenic acid (R- SOH) which rapidly condenses to form Allicin. It is the main bioactive compound present in garlic. Garlic contains at least 100 sulfur containing compounds basic to medicinal uses. Allicin represents 70-80% of the total thiosulfinates present in garlic. Apart from allicin, other important sulfur containing compounds present in garlic include allyl methyl thio sulfonate,1- propenyl allyl thio sulfonate and γ-1 glutamyl -5-alkyl- L-Cysteine. On an average, a garlic bulb contains upto 0.9% Glutamyl cysteine and upto 1.8% alliin [9].

2.2 Garlic Prepration: Garlic has been clinically studied with its different preparations. Now-a-days it is commercially available in different forms such as raw garlic, aged garlic extract (AGE), garlic oil and garlic powder. Aged garlic extract (AGE) is a widely studied garlic preparation. Sliced raw garlic is stored in 15-20% of ethanol for 20 months. This process of storage leads to alteration in chemical composition of garlic extract thereby the odorous harsh and irritating compounds in garlic are converted naturally into stable and safe sulfur compounds with substantial loss of allicin activity and increased activity of new compounds like s-allyl cysteine (SAC), s-allyl mercaptocysteine, allixin and selenin which are stable, highly bioavailable and significantly antioxidant [10] Another recently identified antioxidant compound of AGE is N-alpha-(1-deoxy-D- Fructose-1-yl)-L-arginine (Fru-Arg) which is not present in raw or heat treated garlic [11]. Another important preparation of garlic is garlic oil. It is produced as a result of distillation process of raw garlic. Garlic essential oil is obtained by steam distillation of garlic. The essential oil content of garlic cloves is 0.2-0.5% and consists of a variety of sulfides, such as diallyl disulphide (DADS, 26%) and diallyl trisulfide (DATS 19%) [12, 13]. All the water soluble contents including allicin are completely eliminated from the oil. Oil macerates were originally developed for use as condiments. Oil macerate products are made of encapsulated mixtures of whole garlic cloves ground into vegetable oil. This preparations contains allicin decomposed compounds such as dithiins, ajoene and sulfides, residual amounts of alliin and other constituents in garlic [14]. Ether extracted garlic oil (essential oil) contains nine times as much of the vinyl-dithiins (5.7mg/gm) and allyl sulfides (1.4 mg/gm) and four times as much of the ajoenes (0.4 mg/gm) [9]. A typical commercial preparation of garlic contains diallyl disulfide (DADS, 26%), diallyl tri-sulfide (DATS-19%), allyl methyl trisulfide (15%), diallyl methyl disulfide (13%), diallyl tetrasulfide (8%), and allyl methyl tetrasulfide (6%).

Next preparation of garlic is garlic powder. Garlic powder is primarily used as a flavoring agent for condiments and processed foods. Garlic cloves are sliced or crushed, dried and grounded into powder. The composition of garlic powder is the same as that of raw garlic. However the proportion and amount of various constituents differ significantly, that is, average content of alliin present in garlic is 0.8%, however raw garlic contains around 3.7 mg/gm of alliin [14]. The allinase

activity of garlic powder is identical to that of fresh garlic. Dehydration of garlic above 60 ^{0}C temperature causes inactivation of allinase enzyme.

2.3 Pharmacological Action: Based upon human study, the active principle of garlic for hypolipidemia is reportedly the essential oil which contains a combination of sulfur containing compounds mainly, allyl propyl disulphide and diallyl disulphide**[15]** Garlic lipid lowering effect may occur via inhibition of HMG-CoA reductase or other enzymes possibly by diallyl di-and trisulphide components of garlic [16- 18]. Other suggested mechanisms includes increased loss of bile salts in faeces and mobilization of tissue lipids into circulation as garlic has a profound effect on postprandial hyperlipidemia [19-20]. Wild garlic (*allium urinum*) has shown effect similar to domestic garlic (*Alliums sativum*) in decreasing hepatocyte cholesterol synthesis in-vitro. Aged garlic extract and its constituents have been shown to inhibit Cu^{2+} induced oxidative modification of low density lipoprotein [21] Aged garlic extract and its constituents S-allyl cystine have been found to protect vascular endothelial cells from injuries caused by oxidized LDL [22]. Animal and human cell lines have demonstrated reduction in vascular tissue lipids, fatty streak formation and atherosclerotic plaque effect [23-26]. The mechanism of an action may include reduction of lipoprotein oxidation as demonstrated in- vitro [27-28] and *in vivo* [29], possibly due to organosulfur compounds in garlic [30]. However, this hypothesis has been in dispute based upon a six month trial in moderately hypercholesteromic volunteers which failed to demonstrate any effects of garlic supplementation on lipoprotein oxidation [31].

2.4 Mechanism of Action of Garlic in Hyperlipidemia
Several mechanisms of garlic as hypolipidemic action has been proposed. The possible mechanism of action of garlic are (i) depressed activity of hepatic lipogenesis and cholesterolegenic enzyme such as malic enzyme, fatty acid synthetase, glucose 6 –phosphate dehydrogenase and 3-hydroxy,3-methyl glutaryl CoA (HMG-CoA) reductase [32]. (ii) Inhanced excreation of acidic and neutral steroid into bile after garlic feeding [16] and increased loss of bile salt in faeces and mobilization of tissue lipid into circulation as garlic has a profound effect in post- prandial hyperlipidemia [33]. (iii) Suppressed LDL oxidation by garlic preparation, especially by aged garlic extract (AGE) and aqueous garlic extract [34], thus having anti-atherogenic effect. [19, 35]. Allicin present in garlic has been identified as the active compound responsible for anti-atherosclerotic effects. Recent in-vitro studies revealed that water soluble organosulfur compounds especially S-allyl cysteine (SAC) present in aged garlic extract and diallyl-disulphide (DADS) present in garlic oil are also potent inhibitors of cholesterol synthesis [32, 36]. Aged garlic extract and its constituents S-allyl cysteine have been found to protect vascular endothelial cell against injury caused by oxidized LDL [22]. (iv) Garlic is a potential stimulant of lipase enzyme thereby, decreasing blood triglyceride level [37-39].

2.5 Garlic Dosage
Medicinal effects of garlic have been studied mostly with oral garlic preparation. Administration of 600 to 1200 mg daily of non-enteric coated dehydrated garlic powder in three divided doses standardized to 1.3% allicin content has been studied in multiple clinical trials of hyperlipidemia, peripheral vascular disease and hyper tension [30. 40, 41]. 2.1g. of garlic powder daily

for three months has been used [42]. Enteric coated garlic powder tablet equivalent to 300 to 400 mg of garlic twice daily has been used. Garlic supplements equivalent to an average sized garlic clove, 6 days of every weeks for six months has been used. [43-44]. Safety or efficacy of garlic supplement has not been established in children aged less than eighteen year [45].

2.6 Adverse Effects of Garlic Use
A review of 45 randomized trials and 73 studies of garlic use found limited information relating to adverse effects [46]. Common side effects of oral and intravenous garlic use are malodorous breath, body odour, nausea, vomiting, flatulence, weight loss, facial flushing, tachycardia, dizziness, insomnia and allergic reactions [16, 32]. Based on human studies, administration of intravenous garlic more than one month causes liver, kidney and bone marrow damage [32]. In addition to side effects, there are certain contraindications of garlic supplementation as mention below-
1. Bleeding disorder [19, 35] 2. Thyroid dysfunction [19] 3. Diabetes Mellitus or Patients on hypoglycemic drugs [32]. 4. Patients on antihypertensive drug [32, 37] 5. Patients on vasodilator [38] 6. Patients on fish oil containing Eicosopentanoic acid (EPA). [39] and Peptic ulcer disease [47].

Table 1: Studies Showing Hypolipidemic Action of Garlic

Study	Type	Target	Duration of Treatment	Dose	Case/control	Outcome
Mader,(1990) [48]	Randomized placebo-controlled	Hyperlipidemic	12 Weeks	800 mg garlic powder	130/131	Dec in T.chol level-12% TG level-17%
Gadkari and joshi,(1991) [47]	Randomized control trial	Normal individuals	2 months	10 gm of raw garlic	25/25	Dec T.chol, increase clotting time, and fibrinolytic activity
Rotzsch et al., (1994) [49]	Ranomized,Placebo -controlled, double- blind trial	Healthy individuals with low HDL	6 Weeks	900 mg garlic powder	12/12	Dec TG levels and increase HDL, levels
Saradeth et al., (1994) [50]	Randomized double–blind study, placebo –controlled trial	Healthy individuals with normal lipid levels	15 Week	600 mg dried garlic powder	34/34	T. chol dec from 223to 214mg/dl TG dec from 124 to 118 mg/dl
Steiner et al., (1996) [51]	Double-blind crossover trial lipidmic	Hyperlipidemic	11 months	7.2g aged garlic	20/21	Dec.T chol 6.1%, dec LDL 4%, systolic BP 5.5% dec, and modest dec in diastolic Bp noticed
Satitvipawee et al., (2003) [52]	Randomized double–blind, placebo –controlled trial	Hyperlipidemic	4 Weeks/12 weeks	Garlic extract	70/70	No dec in T.chol, dL, TG, and HDL levels noticed
Mahmoodi et al., (2006) [53]	Clinical trial	Hyperlipidemic	42 days	Raw garlic 5gm twice daily	30	Dec T. chol, dec LDL, dec TG, increase HDL levels Reversed after stopping of garlic
Sobenin et al., (2008) [54]	Double blinded placebo controlled	Hyperlipidemic	12 Weeks	Allicor (600mg daily)	21/21	T. chol 7.6% dec, LDL 11.8%, and HDL inc 11.5%

Table 2: Studies Showing No Cholesterol Lowering Effect

References	Preparation	Duration	Dose	Outcome
Ziaei et al., 2001 [55]	Garlic powder	3 months	800 mg/day	No change in cholesterol or other lipid parameters
Gardner et al., 2001 [56]	Garlic powder	12 weeks 500,	1000 mg/day	,,
Rahman et al., 2000 [57]	Aged garlic extract	13 weeks	5 ml/day	,,
Superko et al., 2000 [58]	Garlic powder	3 months	900 mg/day	,,
Byrne et al.,1999 [59]	Garlic powder (kwai)	6 months	900 mg/day	,,
McCrindle et al., 1998 [34]	Garlic powder (kwai)	8 weeks	900 mg/day	,,
Berthold et al.,1998 [60]	Steam-distilled garlic oil	12 weeks	10 mg/day	,,
Isaacsohn et al., 1998 [61]	Garlic powder (kwai)	12 weeks	900 mg/day	,,
Simons et al., 1995 [62]	Garlic powder (kwai)	12 weeks	900 mg/day	,,
Luley et al., 1986 [63]	Commercial dried garlic	6 weeks	600 mg/day	,,
Lutomski, 1984 [64]	Commercial garlic preparation	12 weeks	-	,,

3. Discussion
There has been several randomized, double blind, placebo controlled studies on hypocholesterolemic effect of Garlic. Most of them showed modest reduction in total cholesterol Vs placebo over 4-12 weeks with unclear effects after 20 weeks [65, 66]. Whereas some of the studies showed no cholesterol lowering effect of Garlic (TABLE 2). Most studies used non – enteric coated dehydrated Garlic powder tablets. Some studies used Garlic in non- powder form which lowered serum cholesterol and serum triglycerides more significantly than powder form Garlic preparation over 1-3 months [67]. Serum cholesterol and trigycerides lowered by 8% in power form and by 15% in non –powder form [68] Studies using dried Garlic preparation in daily dose of range 600-900 mg showed similar

lipid lowering effect [34]. It was also obsered in various studies that HDL level remained essentially unchanged. [31, 65, 67]. Studies showing Garlic extact treatment in children with hypercholesterolemia showed no significant beneficial effects on lipid level [34]. There is also a preliminary evidence that aged Garlic extract may elicit superior resistance to LDL oxidation and better lipid lowering action than fresh Garlic. It was also observed in various studies that Garlic lowered total cholesterol and triglycerides in the lower range of hypercholesterolemia. Duration of study, dietary control, lifestyle of subjects and methods of study may also have a significant influence on result of studies. Therefore, these findings emphasize the further need for standardization of Garlic preparation in order to to reach a valid conclusion in hypocholesterolemic effect of Garlic. Clinical trials exploring the effects of garlic and its various preparations in hypercholesteromia have demostrated somewhat contradictory results. Diverse composition of sulfur compounds in different garlic preparations might be responsible for above mentioned inconsistent results. Other factors like subject recruitment, duration of study, dietary control, life style of subjects and methods of study may also have a significant influence on result of studies.

4. Conclusion
On the basis of the clinical trials so far done, it can be concluded that hypocholesterolemic effect of garlic is limited in terms of period and efficacy. Long term effects remains unclear to be still further discovered. Therefore, these findings emphasize the further need for standardization of Garlic preparation in order to reach a valid conclusion in lipids lowering effect of Garlic so that it can be used as an effective herbal medicine in clinical practice of hyperlipidemia.

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