Clinical Trials on Role of Garlic (*Allium sativum*) in Managing Diabetes: Systematic Review

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ABSTRACT

Diabetes is one of the most common diseases in advanced countries, and modern life plays a big part in it. Type 1 diabetes is related to problems with the function of the pancreas, and type 2 is related to the inefficient ability of insulin receptors.

Like any other disease, both prevention and treatment of diabetes are noticeable. Different treatment methods must be taken for a diabetic patient according to the type and stage of the disease, such as drugs, insulin, etc. Regarding the belief that natural sources can play a good role in treating disorders and leave fewer drawbacks, much research has been done on herbal medicines to find the appropriate ones for treating or even preventing them. Among all of the herbal medicines, garlic (*Allium sativum*) affects diabetes in a good way.

It was observed that raw garlic or some medicinal form of it can lower glucose levels in the blood and have a good effect on diabetes. Not only glucose levels but also some other elements in our blood, such as LDL and HDL, can be affected by garlic.

Keywords: *Allium sativum*, Garlic, Diabetes, Insulin

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ABBREVIATIONS

DM: Diabetes Mellitus; ASCVD: Atherosclerotic Cardiovascular Disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoproteins; FBS: Fasting Blood Sugar; PPG: Post-prandial Glucose

BACKGROUND

A form of bulbous flowering plant belonging to the genus *Allium* is garlic (*Allium sativum*) (Ashraf R, *et al.*, 2011). It is members of the onion family include the Welsh onion, Chinese onion, shallot, and leek (Wang J, *et al.*, 2017). It features a one-meter-tall, upright flowering stem (three feet). The leaf-cutting edge has a sharp zenith, is level, straight, and roughly 1.25-2.5 cm (0.5-1.0 inch) wide. The plant might deliver pink to purple blossoms from July to September in the Northern Hemisphere.

In moderate regions, garlic is easy to develop and might be harvested all year round (Ashraf R, *et al.*, 2005). Different soil types and pH levels are suitable for growing garlic. However, it performs best in soils with high levels of natural matter fixation (Hutchins E, *et al.*, 2020). Central Asia is where garlic started, then extended to different areas of the world. Garlic is presently developed all over the world (Mikaili P, *et al.*, 2013). Since ancient times, individuals have used garlic as a medication to cure numerous disorders, from cancers to coronary disease, inflammation, and common colds (Banerjee SK and Maulik SK, 2022; Mahdizadeh S, *et al.*, 2015). Sanskrit employed it five thousand years ago, and Chinese medicine did so three thousand years ago (Hosseini A and Hosseinzadeh H, 2015).

Diabetes Mellitus is a category of metabolic illnesses characterized by persistently elevated blood sugar levels (American Diabetes Association, 2005). Diabetes is caused by either insufficient pancreatic insulin production or an improper cell response to produce insulin (Gardner DG and Shoback DM, 2017). As per the International Diabetes Federation, 1 in every 11 people aged 20 to 79 years had diabetes overall in 2015. By 2040, specialists anticipate that the number of individuals with DM will ascend from 415 to 642, with the best increments happening in population moving from low to center levels (Zheng Y, *et al.*, 2018). Diabetes entanglements incorporate microvascular, macro-vascular, and neuropathic challenges. Nephropathy, retinopathy, neuropathy, and Atherosclerotic Cardiovascular Disease (ASCVD) events are among the microvascular and macro-vascular entanglements that fluctuates contingent upon the seriousness and length of uncontrolled diabetes, particularly assuming it is joined by different intensifications like dyslipidemia and hypertension (Yamazaki D, *et al.*, 2018). In 2016, Diabetes Mellitus was the seventh most common cause of mortality in the United States (Heron MP, 2018), and it is also the main reason for limb amputations in USA. These outcomes are mostly attributable to the vasculopathy and neuropathy that are part of DM (Forbes JM and Cooper ME, 2013).

Allicin, a sulfur-containing molecule that together with its breakdown products gives garlic its distinctive smell, appears to be the main active ingredient in garlic. When garlic cloves are mechanically broken, an odorless precursor called alliin is converted into allicin *via* an enzyme *(Figure 1)*. Specific extraction techniques can affect the amount of allicin produced because the alliin content of natural garlic can vary by up to a fold of 10. Formulation of garlic supplements could therefore be a critical factor. To reduce cardiovascular risk factors, a dried garlic powder tablet standardized to contain 1.3 percent alliin and 0.6 percent allicin has been sold over the counter in Germany (Jain AK, *et al.*, 1993). A supplement with several proven therapeutic properties is called Aged Garlic Extract (AGE). Supplementing with garlic has been proven to benefit cardiovascular health by reducing total cholesterol levels (Sobenin IA, *et al.*, 2008), blood pressure (Ried K, *et al.*, 2013), and oxidative DNA damage in essential hypertension (Dhawan V and Jain S, 2005). Additionally, AGE has been demonstrated to enhance vascular function, slow the development of coronary atherosclerosis, and have positive effects on oxidative biomarkers (Budoff MJ, *et al.*, 2009; Budoff MJ, *et al.*, 2004).
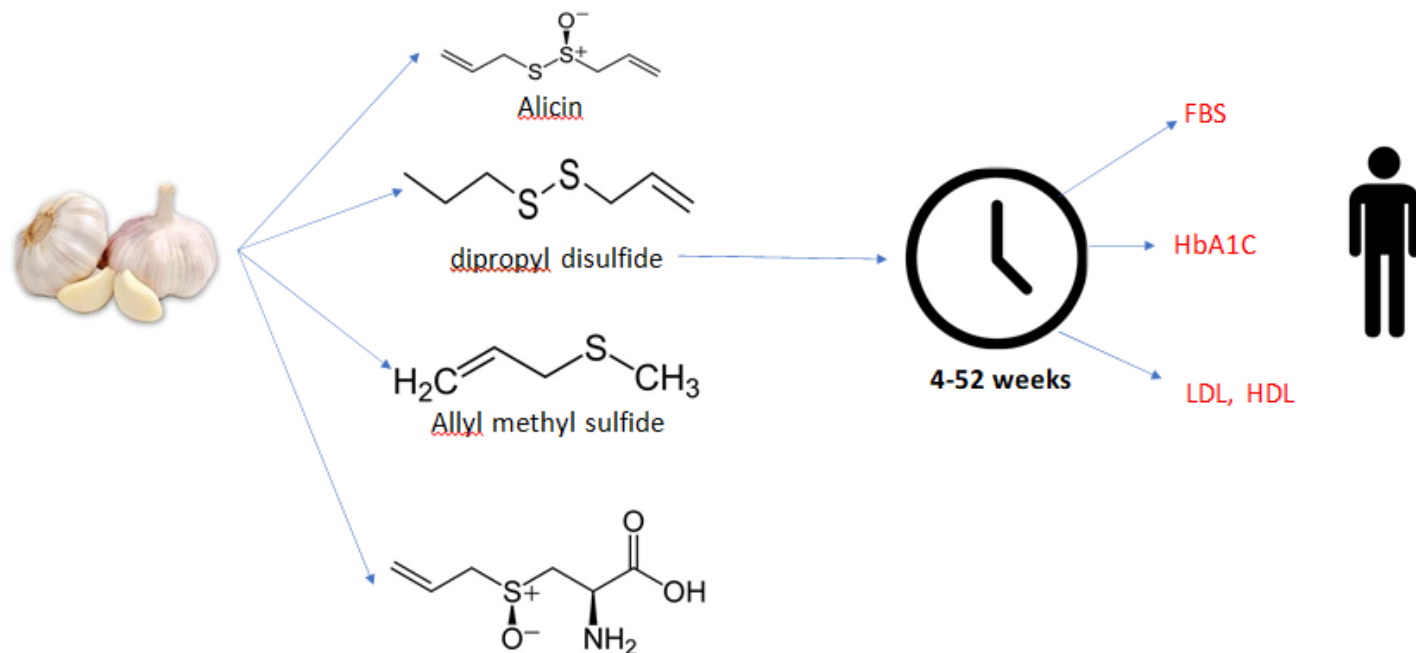
Figure 1: *Allium sativum* effects on diabetes type 2

Despite extensive animal research on garlic's anti-diabetic properties, there is no evidence of its effectiveness in human investigations (Liu CT, *et al.*, 2007). Garlic has been shown to affect blood glucose levels in the majority of clinical investigations, but not in diabetic patients, proving that further research is still needed to determine its role in the treatment of diabetic patients. However, given that garlic has been a crucial component of the human diet for generations, it is assumed that garlic is safe in a variety of amounts. In clinical research utilizing garlic and its preparations, there were few non-specific side effects observed, which typically include nausea and gastrointestinal pain. People exposed to garlic at work have been known to develop allergic contact dermatitis. Infrequent reports of allergic reactions to garlic inhalation or ingestion have also included allergic conjunctivitis, rhinitis, bloating, headache, dizziness, excessive perspiration, and bronchospasm. It has rarely been observed that consuming raw garlic or garlic powder together with anticoagulants or platelet aggregation inhibitors can increase the risk of hemorrhage (Banerjee SK and Maulik SK, 2022). Therefore, extensive clinical research on diabetic patients is warranted to examine the effectiveness and potential applications of garlic in the treatment of diabetic patients (Thomson M, *et al.*, 2007).

Based on these studies, we decided to conduct a systematic review to discuss the role of garlic in diabetes control.

Objective

The objective of the study is to assess the effects of garlic and its extracts on diabetes management. To evaluate this point, we need to analyze and realize how garlic affects the pancreatic secretion of insulin from beta-cells, the release of bound insulin or enhancement of insulin sensitivity, and the transportation of blood glucose to the peripheral tissues. To study these points, we have to analyze related studies based on their results. The conclusion of our study will bring to light regarding the efficacy of garlic in managing diabetes and may offer additional treatment to improve the lives of diabetic patients.

MATERIALS AND METHODS

Search strategies and information sources

In proportion to PRISMA (Preferred Reporting Items for Systematic Re-

views and Meta-Analysis), the review will be carried out on garlic and the effects of its lead compound on diabetes management. Three investigators will carry out this review. All studies on garlic and its role in diabetes management and mechanism of action will be provided. From initiation until the end of July 2021, libraries such as Cochrane, Scopus, Web of Science, Embace, MEDLINE, Scholar, and ProQuest will be consulted using relevant MeSH keywords and equal terms to determine related studies from initiation until the end of July 2021. The research strategy will be based on the following design: ("Garlic" OR "*Allium sativum*" OR "Garlic components") AND ("Diabetes" OR "Diabetes Mellitus" OR "Insulin-Dependent Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "Diabetes Type 2" OR "Adult-Onset Diabetes Mellitus" OR "Adult-Onset Diabetes"). We will also look for preprinted searches for relevant studies. References and articles that quote related articles will be manually searched for other studies. Any related studies published as a part of our investigation will be reviewed and, if necessary, added to the article. In the case of imprecise or missing data, we will contact the relevant authors of the study. The software Endnote 20.0.1 will be used to arrange the included articles.

Eligibility criteria

Inclusion criteria: All publicized clinical trial research involving peer-reviewed and preprint research examining the effect of garlic and its extracts on the management of diabetes in any population until the end of July 2021 will be competent for inclusion. Only English publications will be included. All studies that use garlic itself and its products or lead compounds will be included. There will be no age or gender limitations.

Exclusion criteria: Case reports, case series, perspectives, and editorials will be excluded as there is often limited evidence in these types of studies. Systematic reviews and scope reviews will not be included, but references to other relevant studies will be sought.

Screening and selection techniques

Two investigators will individually review the title and summary of all relevant studies to evaluate the relevant research. Once duplicate studies have been removed, full copies of the relevant studies will be reviewed by the

two researchers mentioned, and the relevance of each study will be verified. The modified Jadad scale or the Oxford Quality Assessment System will be used to assess the quality of the studies. Studies that score at least three marks will be included. If a disagreement arises, the discussion will resolve the issue and, if necessary, a third investigator will make the decision.

Data collection and data items

Two researchers will individually evaluate the probity of publications and extract the following information: The first writer's name; Date of publishing; Population and sample size of each study; Kind of interference and doses used in each study; The period of each study; Study pattern; and outcome of each study. The results of the studies will be assessed based on blood sugar levels, HbA1c, cholesterol, LDL, triglycerides, and HDL.

Data synthesis

Studies obtained through research strategy will be screened, and studies qualified after orientation with eligibility criteria will be included. All relevant information about garlic and its effect on diabetes will be exploited. Based on population and treatment parameters, as well as study design, studies will be grouped. So, to choose the best product and, if it's possible, the best therapy regimen, we will analyze and assess several studies, their findings, and final reports. The mechanism of action will also be described based on the papers that are presented as well as additional sources like animal and human studies.

Quality and risk of bias assessment

By using the modified Jadad scale, the quality of the exams will be measured. Studies that achieve a grade of 3 or more will be considered qualified. We will gather them and review all relevant research to ensure that all available information is used. References, cited papers, including studies, and all associated papers will be reviewed. Throughout the research,

members will consult and discuss taking into account all dimensions and perspectives, the final decision will be made.

Potential limitations

We will not consider non-English-speaking papers since we have restricted the language of some studies, which may have limited the material available. Our knowledge might not be full because we won't always be able to access all the materials we require. We might be unable to perform a meta-analysis to draw more appropriate conclusions from the results given the lack of data available.

RESULTS

According to the studies listed below, garlic can significantly lower glucose levels and result in dyslipidemia in a diabetic person. The research involved 365 patients in total, and 360 of them completed the examinations. The age range of the patients is thirty to seventy-five. The patients were all diabetic. The three studies' major objective is to investigate the medicinal effects of garlic on blood glucose levels. One of the studies, however, focuses on the garlic impact on left ventricular myocardial mass. In these analysis three most important variables are blood glucose, LDL level, and HDL level. Three single-blind studies and one double-blind trial were carried out.

In three studies, the effect of consuming different types of garlic was compared with not using the medical types of garlic (Ashraf R, *et al.*, 2011; Wang J, *et al.*, 2017). But in one study, the difference between garlic consumers and metformin consumers was compared (Rizwan AM, *et al.*, 2011). The duration of the studies is 1, 3, and 6 months, and the longest one is 1 year. Different doses are given to the participants-2400 mg of Aged Garlic Extract per day, 300 mg twice a day in tablet form, and 300, 600, 900, 1200, 1500 mg per day for a different group of the study: (1 clove=1.2 g) once orally daily (Mirunalini S, *et al.*, 2011; Ashraf R, *et al.*, 2005; Hutchins E, *et al.*, 2020) *(Table 1)*.

Table 1: Characteristics of trials included in the systematic review

Author (publication year)	Sample size (Male: Female)	Mean age (y)	Intervention	Dose of intervention (gram per day)	Duration	Health status of participations
Hutchins E, *et al.*, 2020	(39:26)	59	Aged garlic extract	305 g	52 weeks	Increased left ventricular myocardial mass
Ashraf R, *et al.*, 2005	(32:38)	59	Garlic tablet	600 mg	12 weeks	Type 2 diabetic patients
Ashraf R, *et al.*, 2011	(107:73)	45	Garlic tablet/ metformin	300, 600, 900, 1200, 1500 mg	24 weeks	Type 2 diabetic mellitus
Mirunalini S, *et al.*, 2011	20	50	Raw garlic clove	3.6 g	4 weeks	Type 2 diabetic patients

DISCUSSION

This study's major goal is to determine whether or not garlic has a substantial impact on type 2 diabetes patients' blood sugar levels in particular. In other studies, different forms of garlic were utilized, such as raw and powder form and both of them were helpful. It is thought that only medical forms of garlic can affect patients. Although numerous clinical trials have demonstrated that garlic has beneficial effects on hyperlipidemia, atherosclerosis, thrombosis, hypertension, and diabetes (Jabbari A, *et al.*, 2005; Stevinson C, *et al.*, 2000; Sun YE, *et al.*, 2018; Touhidi M and Rahbani M, 2001), several unfavorable studies (Gardner CD, *et al.*, 2001; Peleg A, *et al.*, 2003; Superko HR and Krauss RM, 2000; Tanamai J, *et al.*, 2004; Turner B, *et al.*, 2004) have called into question regarding garlic's effectiveness, particularly its ability to lower cholesterol. All of our data comes from trials done with human models, but in some other studies, trials were done with animal models, and the results were the same ineffectiveness of garlic in decreasing blood sugar levels (Iweala EE, *et al.*, 2005; Khayatnouri M, *et al.*, 2011).

The component mindful of garlic's ameliorative impacts on PPG and FBS may be expanded to include insulin discharge and affectability (Kumar R, *et al.*, 2013). Garlic can enhance the transportation of blood glucose to the peripheral tissues and, in this manner, induce an affront reaction that upgrades the transformation of the dormant shape of glycogen synthetase to its dynamic frame that comes about in the augmentation of the transformation of blood glucose into glycogen. Garlic can release affront discharge from its bound frame. There is uncertainty about the effectiveness of HbA1c (Emami S, *et al.*, 2017), but it seems that garlic shows a decrease in blood sugar levels and some relevant factors, such as HbA1c. Not only glucose, but garlic also have a positive effect on cholesterol, LDL, triglyceride, and HDL levels and reduce them. The hypoglycemic action of garlic could be due to an increase in the pancreatic secretion of insulin from beta-cells, release of bound insulin, or enhancement of insulin sensitivity (Rizwan AM, *et al.*, 2011). Garlic does have an effect by reducing the glucose in the blood, reducing LDL and cholesterol, and causing dyslipidemia in the patients (Chen K, *et al.*, 2019; Chan WJ, *et al.*, 2020). Both dose and duration are important in the effect of garlic on reducing blood glucose. The treatment with garlic depends on both dose and duration, and longer treatments show better changes.

In clinical research employing garlic and its preparations, there were few non-specific side effects observed, and they typically included nausea and gastrointestinal pain. People who are exposed to garlic at work have been known to develop allergic contact dermatitis. Infrequent reports of allergic reactions to garlic inhalation or ingestion have also included allergic conjunctivitis, rhinitis, bloating, headache, dizziness, excessive perspiration, and bronchospasm. It has rarely been observed that consuming raw garlic or garlic powder together with anticoagulants or platelet aggregation inhibitors can increase the risk of hemorrhage (Liu CT, *et al.*, 2007). Therefore, extensive clinical research on diabetes patients is warranted to support the effectiveness and potential function of garlic in the treatment of diabetic patients (Banerjee SK and Maulik SK, 2022).

In all the studies, BMI, diet, and age of the participants are mentioned as causes of the effect of garlic in diabetic patients with different features. Allicin is one of the most important active ingredient that exist in garlic, and the main effects of garlic in reducing blood sugar depend on it. Studies show that the dosage of garlic is important in the effects of garlic in diabetic patients, and different dosages will cause variable results in quantity (Rizwan AM, *et al.*, 2011). These results come from the trials that occurred with normal garlic, but we also know another type of garlic called black garlic, and it has therapeutic features too (Choi DJ, *et al.*, 2008; Zintchenko A, *et al.*, 2008). Later research on black garlic and its effects on diabetes patients could be a good topic for further research. There are some other known medicinal plants for treating diabetic patients that have sulfur in-

side, and we think that the anti-diabetic effects of these plants relate to sulfur-containing compounds. This fact can help us by scanning more plants and finding appropriate herbs for treating and even preventing diabetes.

CONCLUSION

Diabetes type 2 is a worldwide disease which can lead to blindness and amputation in untreated cases. So the approaches to cure or even preventing the prevalence of this disorder are really important.

Insulin and some drugs such as metformin are some treatments which have vast usage in treating diabetes type 2. Besides these, treatments which have an organic base and have natural resources have always been subjected to attention. Garlic, as a candidate for treating diabetes type 2, is going under review.

DECLARATIONS

Ethical approval and consent to participate

The study was carried out according to the principles stated in the Declaration of Helsinki.

Consent for publication

All authors agreed to submit manuscript.

Availability of data and material

All identified data are available upon reasonable request.

Authors' contributions

Study concept and design: R.F and E.A; Acquisition of data: R.F and M.S; Analysis and interpretation of data: R.F and E.A and A.B; Drafting of the manuscript: R.F and M.S; Critical revision of the manuscript for important intellectual content: E.A and G.M; Statistical analysis: E.A and R.F; Administrative, technical, and material support: E.A; Study supervision: E.A

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