Garlic (Allium sativum L.) Efficacy as an Adjuvant Therapy for Type 2 Diabetes Mellitus: A Scoping Review

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Abstract. Type 2 Diabetes Mellitus (T2DM) is a chronic disease with increasing prevalence worldwide and causing many threatening life complications. Various alternative therapies continue to be developed to control blood sugar level in T2DM, including from tradisional plants. Garlic (Allium sativum L.) is a traditional plant that is easily obtained at relatively low cost. Many preclinical and clinical studies have shown the capability of Allium sativum L. to inhibit T2DM pathophysiology. This scoping review was aimed to know the efficacy of Allium sativum L. as adjuvant therapy for T2DM patients. Articles used for this review were original articles about Allium sativum L. adjuvant intervention for T2DM patients, published in 2011–2021, and in English or Indonesian language. Databases used were EBSCO, Google Scholar, PubMed, ScienceDirect, ProQuest, Taylor & Francis Online, Ovid, Springer Link, Portal Garuda, OneSearch, and Neliti, with Boolean search. The articles in the search results were selected by PRISMA-ScR. Selected articles were extracted, pointed, then synthesized to answer the review goal. Review process from six selected articles have shown that administration of 500–900 mg/day Allium sativum L. combined with metformin for 12- or 24-weeks improved blood glucose, ADA, hs-CRP, and lipid profile significantly. However, intervention of Allium sativum L. in less than 12 weeks, did not improve the result significantly. Enteric-coated and odorless tablet preparation of Allium sativum L. is recommended to prevent digestive disturbances from Allium sativum L. This scoping review showed that administration of 500–900 mg/day Allium sativum L. for 12 or 24 weeks, showed efficacy for T2DM as an adjuvant therapy with still considering patient clinical conditions and adverse events that may be occurred.

Keywords: efficacy · Allium sativum L. · adjuvant therapy · T2DM

1 Introduction

Diabetes Mellitus (DM) is a severe chronic disease with increasing prevalence worldwide. Type 2 DM (T2DM) is diabetes with the highest prevalence globally, in almost

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90% in 2019. In 2045, the world's prevalence of DM approximately increases to 700 million people or by 51% from 2019 [1]. The clinical complications of T2DM, including macroangiopathy, microangiopathy, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemia (HHS), reduce the quality of human resources, social and occupational disabilities, and economic growth. Those also can increase health costs [2]. Moreover, the increased prevalence of DM (77%) is more common in countries with low and middle income per capita [3].

Combination therapy for T2DM is useful in inhibiting the pathogenesis of T2DM but it can exacerbate the side effects of T2DM therapy, especially for T2DM patients with high HbA1c levels. The most significant risk of side effects from administering a combination of antidiabetic drugs is hypoglycemia, which can cause cardiovascular complications [4]. The combination of antidiabetic therapy also causes problems for T2DM patients with limited economic status. In 2018, about 8.5% of T2DM patients in Indonesia were irregularly taking antidiabetic drugs due to unaffordability of those drugs and in 2.1% of T2DM patients were due to unavailability of those drugs in health care facilities [5].

These conditions causes an increase in the use of herbal medicines [6]. The World Health Organization (WHO) stated that traditional and herbal medicines can maintain public health, including chronic diseases such as T2DM. In this regard, WHO also supports various efforts to improve traditional and herbal medicines' safety and efficacy [7].

For many centuries, garlic (Allium sativum L.) is often used as a cooking spice, traditional therapy, and herbal therapy [8]. Allium sativum L. is capable of increasing insulin sensitivity [9], lowering fasting blood glucose, total cholesterol, triglycerides, and Low-Density Lipoprotein (LDL) accompanied by an increase in High-Density Lipoprotein (HDL) [10], as a prebiotic in increasing intestinal microbiota to reduce hyperglycemia [11], suppressing inflammatory cytokines and oxidative stress that occur due to increased blood glucose and increasing lipolysis in the body [8], reducing fructosamine and HbA1c levels [12], and inhibiting the albumin glycation reaction [13]. In addition, recent studies have also proven the similarity properties between Allium sativum L. and resveratrol in increasing insulin secretion from pancreatic β cells [14]. Therefore, Allium sativum L. has benefit potentials for T2DM adjuvant therapy. Adjuvant therapy is used as a companion to the primary therapy of disease [15].

In its potential as adjuvant therapy for T2DM patients, Allium sativum L. is known to synergize with glibenclamide in reducing hyperglycemia in a streptozocin-induced mouse model [16]. On administration of Allium sativum L. without any other drug combination, Allium sativum L. can reduce blood glucose levels in the alloxan-induced rat model [17]. In addition, Allium sativum L. can also increase the peak level (C max) of metformin in plasma in a mouse model [18]. Based on these findings, further studies are needed to find out more about the efficacy of Allium sativum L. as adjuvant therapy for T2DM patients. This scoping review is conducted to give information regarding the efficacy of Allium sativum L. as cost-effective adjuvant therapy in T2DM patients.

2 Method

2.1 Article Criteria

The articles reviewed in this study are peer-reviewed or grey literature original articles on Allium sativum L. as adjuvant therapy for T2DM, with Randomized Controlled Trial (RCT) or non-Randomized Controlled Trial (non-RCT) research method, published in 2011-2021, and in English or Indonesian.

2.2 Databased Used in the Study

The databases used in this review were EBSCO, Google Scholar, PubMed, ScienceDirect, ProQuest, Taylor & Francis Online, Ovid, Springer Link, Portal Garuda, OneSearch, and Neliti.

2.3 Searching Strategy

The searching strategy in this scoping review used combination of keywords as listed in Table 1.

2.4 Articles Selection Process

The article selection process was carried out based on inclusion-exclusion criteria. The inclusion criteria were the article's characteristics, the study subject, and the study object. Inclusion criteria in terms of the characteristics of the selected articles involve peer-reviewed or grey literature original articles with RCT or non-RCT research methods,

Table 1. Keyword combinations used in the article searching process

Database	Keyword combinations used
PubMed	"Allium sativum" AND "Diabetes Mellitus type 2"
Google Scholar, EBSCO, ProQuest, ScienceDirect, Taylor & Francis Online, Ovid, and Springer Link	"Allium sativum" AND "Diabetes Mellitus type 2" AND "human" AND "randomized controlled trial"
Portal Garuda, OneSearch, and Neliti	"Allium sativum" "Diabetes Mellitus type 2"

Notes:

a. In adding more search results, the word "Diabetes Mellitus type 2" is replaced with "DM type 2", "Type 2 Diabetes Mellitus", "Noninsulin Dependent Diabetes Mellitus", "T2DM" then "NIDDM", while for "Allium sativum" is replaced with "garlic" in subsequent searches.
b. In subsequent searches, the word "randomized controlled trial" is replaced with "nonrandomized controlled trial" to search articles with non-RCT research methods.
c. In searching Indonesian articles using Google Scholar, without the word "human", the use of the word "Diabetes Mellitus type 2" is replaced with "Diabetes Mellitus tipe 2", "DM tipe 2", "Noninsulin Dependent Diabetes Mellitus", "T2DM" then "NIDDM", while for "Allium sativum" is replaced with "bawang putih" in subsequent searches.
d. In adding more search results through Indonesian databases (Portal Garuda, OneSearch, and Neliti), the word "Diabetes Mellitus tipe 2" is replaced with "DM tipe 2", "Noninsulin Dependent Diabetes Mellitus", "T2DM" then "NIDDM", while for "Allium sativum" is replaced with "bawang putih" in subsequent searches.

articles in English or Indonesian, and articles that have been published or written in the period 2011–2021. Regarding the subjects studied, the inclusion criteria selected were all patients with T2DM, both in terms of age, gender, presence or absence of comorbidities, and the presence or absence of complications experienced. As for the object being studied, the inclusion criteria selected were Allium sativum L. which was intervened as adjuvant therapy for T2DM. In this case, all dosage forms of Allium sativum L. used in research and studies that only examined certain content of Allium sativum L. were also included.

From articles that meet the inclusion criteria, the exclusion criteria are identic articles, articles that cannot be accessed in full text with abstracts that do not explain detailed research methods and results, and selected abstracts that cannot be accessed. Articles that contain study subjects that are not having T2DM clearly, articles containing research on the effect of the combination of Allium sativum L. with other herbal medicines on T2DM, but not precisely discussing the effect of Allium sativum L. on T2DM, and articles that were discussing species other than Allium sativum L. from search results with the keyword "garlic," were also excluded.

The article selection process was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extensions for Scoping Review (PRISMA-ScR), which consists of several stages: (a) Identification, a process from entering a combination of keywords in the database until it is obtained the number of articles in the database that match the keyword combination, including the specified inclusion criteria; (b) Screening, a process of removing identical articles so that only one article is selected to be entered into the next stage; (c) Eligibility, a process for removing inaccessible articles: and (d) Inclusion, a process for selecting articles to be reviewed based on the inclusion and exclusion criteria that have been set [19].

2.5 Data Extraction

The data extraction process is carried out manually for each article reviewed. The articles reviewed are emphasized on the methods, results, and conclusions. Apart from these sections and the gaps in each of the reviewed studies are used as additional information.

2.6 Data Item

The data item is a process of reviewing the results of data extraction for each article to identify the variables analyzed according to the variables determined in this study, namely: (a) the form of Allium sativum L. used; (b) partial content of selected Allium sativum L.; (c) the dose of Allium sativum L. administered; (d) duration of intervention; (e) glucose and HbA1c post-test results; (f) Allium sativum L. interaction with standard antidiabetic drugs and other therapies that were given; (g) comparison of the Allium sativum L. effect on standard antidiabetic drugs and other therapies that were given; (h) clinical changes in T2DM patients; (i) Allium sativum L. side effects; and (j) other parameters used to test the efficacy of Allium sativum L. against T2DM patients.

2.7 Data Synthesis

Data synthesis was carried out by comparing the extracted data, data items findings from each article, and counting the number of articles with similar results. The comparison results, similar results, and additional information obtained are then connected and sorted in a conical manner according to the research objectives to answer the research problem formulation. The data synthesis results were then developed to form a review study that discussed the efficacy of Allium sativum L. as adjuvant therapy for T2DM patients.

3 Result and Discussion

3.1 Articles Selection Results

Six articles were finally reviewed from the selection process. All articles are in English and have full-text access. From these articles, two articles are grey literature. Figure 1 displayed the searching process flow for articles reviewed based on PRISMA-ScR.

3.2 Studies Characteristic

Characteristic of studies included in the analysis is listed in Table 2.

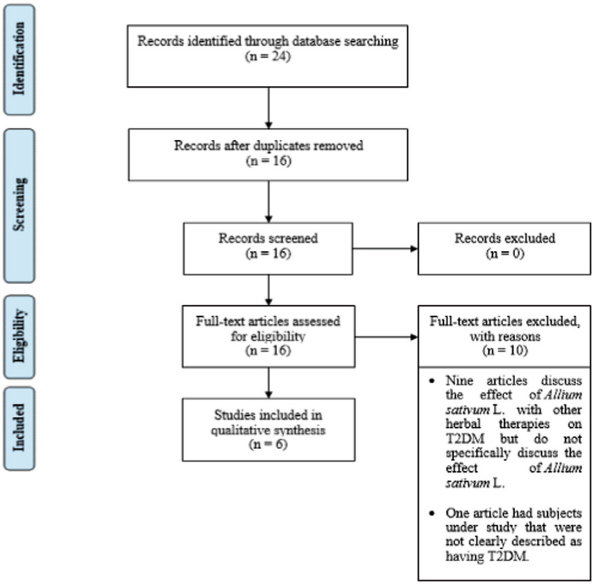

Fig. 1. The searching process of articles based on PRISMA-ScR

Table 2. Characteristic of studies included

Authors	Study design	*Allium sativum* L. intervention (I)	Comparation (C)	Intervention duration (weeks)	Total Participants	
					I	C
Kumar et al. (2013)	non-RCT; quasi-experimental; parallel	Metformin 500 mg 2–3 times a day with Allium *sativum* L. tablet 250 mg twice a day	Metformin 500 mg 2–3 times a day	12	30	30
Shoshi & Akter et al. (2017)	RCT; simple random sampling; parallel	Metformin 1000 mg a day with Allium *sativum* L. capsule 250 mg twice a day	Metformin 1000 mg a day	12	30	30
Ashraf et al. (2011b)	Non-RCT; parallel; single-blind; placebo-controlled study	Metformin 500 mg twice a day with Allium *sativum* L. tablet 300 mg three times a day	Metformin 500 mg twice a day with placebo 300 mg three times a day	24	30	30
Dafriani et al. (2020)	Non-RCT; quasi-experimental; parallel	Any standard antidiabetic medication that the patient has currently used with Allium *sativum* L. three cloves a day	Any standard antidiabetic medication that the patient has currently used	2	10	10

(*continued*)

Table 2. (*continued*)

Authors	Study design	*Allium sativum* L. intervention (I)	Comparation (C)	Intervention duration (weeks)	Total Participants	
					I	C
Mansouri et al. (2018)	RCT; parallel	Single therapy oral antidiabetic drug with Allium *sativum* L powder 300 mg three times a day	Single therapy of standard antidiabetic drugs + *Cuminum cyminum* L. seed extract 100 mg 2 times a day (C1); Single therapy of standard antidiabetic drugs + placebo (C2)	8	25	25 (C1) 25 (C2)
Atkin et al. (2016)	RCT; cross-over; double blind; wash-out period	Any current therapy with AGE 1200 mg once a day	Any current therapy with placebo	4 (for intervention and wash-out)	26	26

4 Discussion

4.1 Result Findings

4.1.1 Participant's Characteristics

The selecting participant criteria from each article reviewed in this scoping review have differences in demographics and inclusion-exclusion criteria. The average age of the participants in six studies were between 40–60 years. In addition to T2DM, participants were also known to have obesity and dyslipidemia [20, 21] or hypertension [22, 23] comorbidity. These data strengthen the need for T2DM routine screening in groups that have a high risk of T2DM, such as hypertension, obesity, or people over 45 years old [2].

The participants generally came from four countries in South Asia (Bangladesh, India, Iran, Pakistan), one country in Southeast Asia (Indonesia), and one country in Northern Europe (United Kingdom) based on six selected articles review. It has shown that studies regarding the efficacy of Allium sativum L. as adjuvant therapy for T2DM patients are still few and generally limited to the Caucasoid and Mongoloid races. Thus, it is necessary to study the efficacy of Allium sativum L. with a broader range of participants, such as the Negroid race in the African region, so that the standard dose of Allium sativum L. supplementation can be determined to avoid the Allium sativum L. toxicity [24].

Aside from the participant demographic aspect, five of the six articles reviewed did not include participants with heart, liver, or kidney disorders [20, 23, 25-27]. It may

be due to the absence of clinical trials examining the efficacy of Allium sativum L. in patients with these disorders.

Mansouri et al. conducted research that did not exclude T2DM patients with heart problems. However, there is no report of T2DM patients who had heart problems from that study results. From the two articles reviewed, Allium sativum L. is known to improve lipid profile and blood pressure in T2DM patients [21, 22]. Further research is needed to determine the efficacy of Allium sativum L. in T2DM patients with heart problems. In addition, several reviewed articles excluded T2DM participants who were taking warfarin or had a history of persistent bleeding [21, 23, 25, 26]. Although research conducted by Ashraf et al. and Mansouri et al. did not exclude these criteria, both studies did not report any patients with T2DM who have bleeding or taking warfarin.

Previous studies have shown that Allium sativum L affects parameters in hemostasis. In a preclinical test on mice to determine the interaction of Allium sativum L. with warfarin, Allium sativum L. administration significantly slowed clotting time compared to the warfarin-only group [28]. In a clinical trial study, the intervention of Allium sativum L. in patients taking warfarin therapy found that Allium sativum L. can inhibit platelet aggregation and, together with warfarin, increase bleeding. In addition, administration of Allium sativum L. with warfarin for eight weeks causes hematuria [29].

Given these conditions, Ge et al. suggested that Allium sativum L., should not be given to T2DM patients who are taking warfarin or other anticoagulants. In this concern, administration of Allium sativum L. should also not be administered to patients with bleeding and conditions associated with bleeding, such as thrombocytopenia, impaired coagulation factors, hemorrhagic stroke, postoperative recovery, and patients with surgery plans [21, 25].

Contrary to this, a study conducted by Atkin et al. did not report the effect of Allium sativum L. for four weeks in T2DM patients taking aspirin. Another clinical trial using Aged Garlic Extract (AGE) 1200 mg daily for 12 weeks in uncontrolled hypertensive patients who were also taking warfarin or aspirin besides standard antihypertensives, did not show any bleeding symptoms during the intervention [30]. Thus, it is necessary to conduct further research on the use of Allium sativum L. in T2DM patients who are taking anticoagulants.

The exclusion criteria were also obtained from pregnant or lactating women based on the three articles reviewed [20-22]. Other articles did not exclude these criteria, but there were no reports of pregnant or breastfeeding participants. So far, there have been no studies discussing the efficacy of Allium sativum L. in T2DM patients who are pregnant or breastfeeding.

In an RCT study, the intervention of Allium sativum L. tablets 400 mg per day for nine weeks in pregnant women who are at risk for preeclampsia can reduce high sensitivity C-Reactive Protein (hs-CRP) and increase reduced glutathione (GSH) significantly. However, there is a trend of decreasing fasting blood glucose and increasing QUICKI [31]. Another RCT study in pregnant women with prediabetes showed that Allium sativum L. tablets 400 mg per day for eight weeks reduced fasting blood glucose significantly at the end of the intervention [32].

So far, no side effects have been found from the Allium sativum L. given in breastfeeding mothers. In a cross-sectional study, the use of Allium sativum L. in breastfeeding

mothers is known to facilitate and improve the quality of breast milk [33]. Nevertheless, in some cases, it is known to cause colic in breastfed infants [34].

Therefore, dose considerations should be considered to avoid possible side effects. Further studies about the efficacy of Allium sativum L. in pregnant or lactating women with T2DM are also required.

Other exclusion criteria were also obtained from selected articles, such as excluding participants with diseases other than T2DM [23], unable to speak [22], having psychological disorders [22], having thyroid disorders [26], having diabetes infection [26], had a history of Allium sativum L. hypersensitivity [20, 21], and had a history of DKA [21]. However, other articles do not exclude each of the above criteria.

4.1.2 Parameter Tests for Determining the Efficacy of Allium Sativum L. Against T2DM

This scoping review results showed that random blood glucose, fasting blood glucose, postprandial blood glucose, and HbA1c are often parameters to determine the efficacy of Allium sativum L. on T2DM [20-23, 23, 25, 26]. Other related parameters are insulin resistance test using Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and fructosamine test [25].

Fructosamine is a glycated serum protein that is less used as a glycemic control parameter than other parameters [35]. Glycated albumin is a type of fructosamine that is widely used in glycemic control tests. Fructosamine examination is inexpensive, simple, and the presence of erythrocyte disorders does not compromise its sensitivity, so fructosamine examination is often used in countries with low per capita income and areas with high anemia prevalence [36].

Another parameter in this scoping review is hs-CRP as an inflammatory parameter [21, 25]. High Hs-CRP is known to be found in T2DM patients with uncontrolled treatment or already having vascular complications. Hence many studies use this parameter as a predictor of T2DM complications [21]. Besides hs-CRP, the study conducted by Kumar et al. also examined Adenosine Deaminase (ADA). The increase of these enzymes can inhibit insulin sensitivity in the tissues [21].

A study conducted by Atkin et al. also included examination of antioxidant activity parameters such as Total Antioxidant Status (TAOS) level, reduced glutathione per oxidized glutathione (GSH/GSSG) ratio, and Lipid Hydroxy peroxide Plasma (LHP) level. In addition, endothelial function examination of the brachial arteries was also performed with a digital photoplethysmography. An increase in LHP level accompanied by a decrease in GSH/GSSG ratio and TAOS level indicates oxidative stress [25]. Oxidative stress increased levels of proinflammatory cytokines in the blood, and endothelial dysfunction suggests a disturbance of either macroangiopathy or microangiopathy in T2DM [8].

Some of the articles reviewed also included lipid profile parameters [20, 21, 25] and blood pressure [22, 25] in their examination. It does because obesity, dyslipidemia, and hypertension are T2DM comorbid diseases that can worsen the clinical symptoms of T2DM patients [21, 22].

Apart from the parameters above, a study conducted by Atkin et al. also measured the urinary albumin/creatinine ratio. It aimed to investigate further the effect of Allium

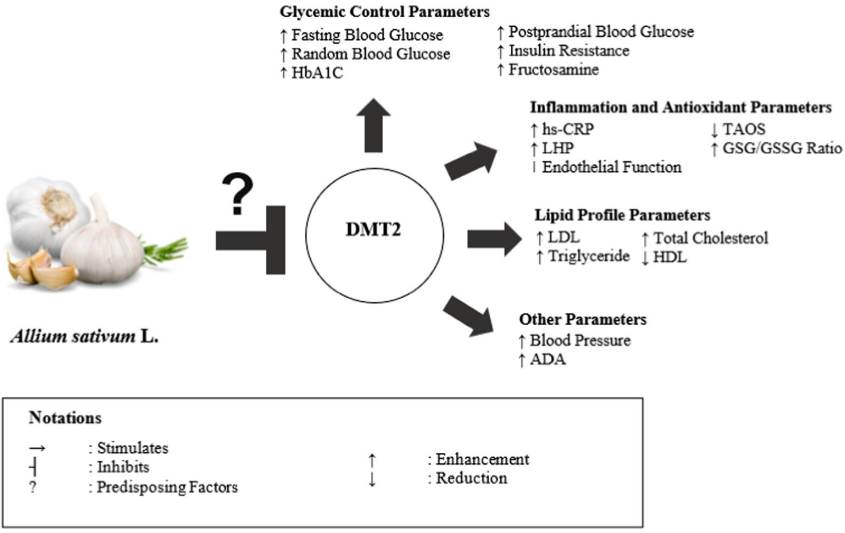

Fig. 2. Theoretical schematic of Allium sativum L. effects on the parameters examined from the six reviewed articles

sativum L. on the kidneys [25]. It is also in line with other studies showing Allium sativum L. can maintain creatinine levels within normal limits [37], but it can increase creatinine levels when overdose [38].

The selection of parameters from the six reviewed articles is consistent with the results generated by the clinical progression of T2DM. From the previous theories, Allium sativum L. can increase insulin sensitivity [9], reduce fasting blood glucose, and improve lipid profile [10], as an antioxidant to inhibit T2DM complications [8], and reduce HbA1c and fructosamine levels [12]. Therefore, using the parameters measured by the six reviewed articles strengthens those theories concerning the efficacy of Allium sativum L. as adjuvant T2DM therapy, as shown in Fig. 2.

4.1.3 The Association Between Dosage Form, Strength, Dosage, and Duration of Allium Sativum L. Interventions with Parameters Analyzed

The dosage form, strength, and dose of Allium sativum L. did not improve the parameters used in the included articles. The duration of intervention is a significant determinant factor for the parameters analyzed. The adminstration of Allium sativum L. 300 mg three times a day for eight weeks significantly improved blood pressure in T2DM patients [22]. Meanwhile, the intervention of Allium sativum L. 250 mg twice daily for 12 weeks significantly improved lipid profiles and significantly, also reduced random blood glucose, fasting blood glucose, postprandial glucose, ADA, and hs-CRP [21, 26].

Regarding the HbA1c parameter, there were no significant decrease in HbA1c level in administration of Allium sativum L. for four weeks [25] or 12 weeks [21, 26]. Another study investigated about the intervention of 300–1200 mg per day Allium sativum L. tablets alone without oral antidiabetic drugs for 24 weeks significantly reduced HbA1c. In the control group, administration of 500 mg metformin per day for 24 weeks significantly

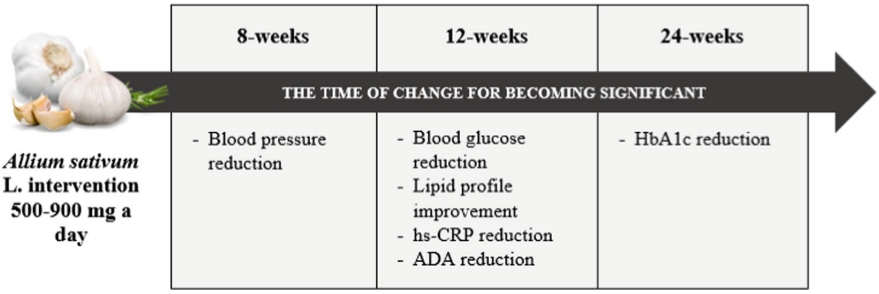

Fig. 3. The relationship between dose and duration of Allium sativum L. intervention on the parameters analyzed

reduced HbA1c [39]. These findings suggested that the combination of Allium sativum L. with metformin for 24 weeks might significantly reduce HbA1c, but it needs further investigation.

Regarding parameters of fructosamine, insulin resistance, endothelial function, TAOS, GSH/GSSG ratio, and LHP, there were no significant changes were found from the articles reviewed [25]. However, the previous theory showed that Allium sativum L. can play a role as an antioxidant, increase insulin sensitivity, and reduce fructosamine levels [8, 9, 12]. Therefore, an elaboration of the intervention duration of Allium sativum L. on testing these parameters is needed in further research.

Figure 3 shows the relationship between dose and duration of Allium sativum L. intervention on the improvement of the parameters analyzed. The intervention of Allium sativum L. 250–900 mg per day for eight weeks significantly reduced blood pressure [22]. The 12-week intervention significantly decreased blood glucose, improved lipid profile, decreased hs-CRP, and decreased ADA [21, 26]. Meanwhile, the intervention for 24 weeks gave significant results in decreasing HbA1c [39].

4.1.4 The Effects of Allium Sativum L. Interaction with Standard Antidiabetic Treatments and Other Treatments Used

Metformin is one of the first-line T2DM drugs often used due to inexpensiveness, affordability, and fewer side effects [21]. The intervention of Allium sativum L. did not interfere with the pharmacokinetics of metformin during the study [20, 22, 25]. Allium sativum L. with metformin reduced blood glucose levels and improved lipid profiles [20, 21, 26]. There were also no reports of the interaction of Allium sativum L. with the oral antidiabetic drug used during the study. Allium sativum L. also reported had no interactions with other standard therapies taking by participants, including ACE-I, statins, and aspirin [25].

In the use of Allium sativum L. with insulin therapy, so far, there have been no clinical trials examining the combination of insulin therapy with Allium sativum L. in T2DM patients. In preclinical RCT trials, administration of Allium sativum L. paste 250 mg/kg BW for eight weeks significantly increased insulin sensitivity in rats induced by a fructose diet [40]. Therefore, the efficacy of the combination of Allium sativum

L. with insulin therapy in T2DM in both preclinical and clinical trials is needed in the development of further research by considering the possible risk of hypoglycemia.

Besides pharmacological management, healthy lifestyle modifications like applying the Mediterranean diet or Dietary Approach to Stop Hypertension (DASH), reducing foods containing saturated fatty acids, and doing light-moderate intensity physical activity for 3–5 days per week are also needed for T2DM patients [2]. In the Allium sativum L. intervention during the study, there was no interaction between Allium sativum L. and healthy lifestyle modifications made by the participants [22, 25].

4.1.5 Allium Sativum L. Adverse Events

The most common side effect of Allium sativum L. is a gastric disorder. On administration of Allium sativum L. tablets at a dose of 300 mg three times a day for 24 weeks, one participant experienced heartburn [20]. On administration of Allium sativum L. extract 1200 mg per day for four weeks, two participants experienced gastric discomfort and were finally excluded from the study [25].

The results of a literature study conducted by Ashraf et al. found that odorless breathing, nausea, vomiting, diarrhea, and Allium sativum L. allergy were some possible side effects when using excess Allium sativum L. Other side effects that have been reported are colic in infants and bleeding [29, 34]. These finding was consistent with study report by Ried et al., that the intervention of encapsulated AGE 1200 mg for 12 weeks in 50 uncontrolled hypertensive patients caused an increase in gastric acid (8%), bowel movements frequency escalation (3%), diarrhea (7%), and frequent belching (5%) [30]. These gastrointestinal side effects require the use of enteric-coated and odorless tablet preparation Allium sativum L. to reduce its side effects on the digestive system (20). Allium sativum L. with 500–900 mg dose per day for 12 or 24 weeks is also known to minimize side effects while increasing the efficacy of Allium sativum L. against T2DM [20, 21, 26, 38].

Allium sativum L. should not be given to T2DM patients who are taking warfarin or are in a bleeding disorder. That is to prevent the risk of worsening bleeding that may occur [29].

In addition, the use of Allium sativum L. should be considered in patients with liver and kidney disorders. Because of the six articles reviewed, there have been no reports of T2DM participants with liver or kidney disorders. In a preclinical RCT trial, the intervention of 1 ml (63 mg/kg BW) of 300 mg Allium sativum L. tablet dissolved in 40 ml of 0.9% NaCl for four weeks in a mouse model induced by orally sodium fluoride (NaF) compared with a control group was found to maintain levels of Creatine Kinase-MB (CKMB), cardiac Troponin I (cTnI), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) within normal limits. In the control group, these four parameters increased significantly [41].

Another study showed that, the administration of Allium sativum L. extract 100–200 mg/kg BW for 21 days in alloxan-induced rat model was able to maintain plasma creatinine, urea, ALT, and AST levels within normal limits compared to the control group [37]. However, toxicity profile of Allium sativum L. extract in a dose more than 400 mg/kg BW for 38 days in rats, showed that there was a significant increase in AST, ALT, and serum creatinine [38]. Therefore, to know more about the efficacy of Allium

sativum L. in T2DM patients with kidney or liver disorders, it is necessary to consider the safety limit when choosing the dosage.

4.2 Limitations of Review

Studies related to the efficacy of Allium sativum L. as adjuvant therapy for T2DM patients were minimal, thus the participant demographic and the standard drugs combined with Allium sativum L. were still lacking. Therefore, further research by multiplying those two variations is needed to determine the efficacy of Allium sativum L. as adjuvant T2DM therapy in depth.

Besides the effectiveness of keywords usage, expanding reference sources by increasing the number of databases is also needed. It can be helpful when the articles selected to the included stage of PRISMA Sc-R are few. The small number of articles can cause the resulting data synthesis less in-depth.

5 Conclusion

The efficacy of Allium sativum L. as adjuvant therapy in T2DM patients depends on its dosage form, strength, dosage, and duration. Administration of Allium sativum L. at a dose of 250–900 mg per day and metformin for 12 weeks or 24 weeks can significantly reduce random blood glucose, fasting blood glucose, postprandial glucose, hs-CRP, and ADA with significant improvement in lipid profile.

In terms of side effects, administration of Allium sativum L. 500 mg per day in tablet or capsule form was not reported to cause side effects on digestive system disorders compared to giving doses of more than 900 mg per day or extract dosage forms. Allium sativum L. in enteric-coated and odorless tablet preparation is recommended to reduce the side effects.

In addition, Allium sativum L. usage as adjuvant therapy in T2DM patients needs to be considered according to the patient's clinical condition. The use of Allium sativum L. is not recommended in conjunction with warfarin or when the patient is undergoing a bleeding-related disease.

5.1 Recommendations

Further studies related to the efficacy of Allium sativum L. on T2DM are needed, especially for these conditions: under varied population demographics, use of antidiabetic agent other than metformin, longer intervention duration, also in subjects with heart, kidney, or liver disorders, and in pregnant or lactating women.

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Author's Contribution. HA designed the study, collected and analyzed data, also drafted the manuscript. IM contributed to analysis and interpretation of the findings, review the manuscript, and as a correspondence author.

References

1. International Diabetes Federation, IDF Diabetes Atlas, 9th ed. Brussels: International Diabetes Federation, 2019.
2. S. A. Soelistijo et al., Guidelines on the Management and Prevention of Adult Type 2 Diabetes Mellitus in Indonesia. Jakarta, 2019.
3. E. Standl, K. Khunti, T. B. Hansen, and O. Schnell, "The global epidemics of diabetes in the 21st century: Current situation and perspectives," Eur. J. Prev. Cardiol., vol. 26, no. 2_suppl, pp. 7–14, 2019, doi: https://doi.org/10.1177/2047487319881021.
4. R. C. Sihotang, R. Ramadhani, and D. L. Tahapary, "Efikasi dan Keamanan Obat Anti Diabetik Oral pada Pasien Diabetes Melitus Tipe 2 dengan Penyakit Ginjal Kronik," J. Penyakit Dalam Indones., vol. 5, no. 3, pp. 150–155, 2018, doi: https://doi.org/10.7454/jpdi.v5i3.202.
5. Minisry of Health Republic of Indonesia, Report on Result of National Basic Health Research (RISKESDAS). Jakarta: Minisry of Health, Republic of Indonesia, 2018
6. Ismail, "Faktor Yang Mempengaruhi Keputusan Masyarakat Memilih Obat Tradisional Di Gampong Lam Ujong," Idea Nurs. J., vol. 6, no. 1, pp. 7–14, 2015.
7. Bustanussalam, "Pemanfaataan Obat Tradisional (Herbal) sebagai Obat Alternatif," BioTrends, vol. 7, no. 1, pp. 20–25, 2016.
8. S. Ourouadi, H. Moumene, N. Zaki, A.-A. Boulli, A. Ouatmane, and A. Hasib, "Garlic (Allium Sativum): A Source of Multiple Nutraceutical and Functional Components (Review)," vol. 7, p. 13, 2016.
9. R. Padiya, T. N. Khatua, P. K. Bagul, M. Kuncha, and S. K. Banerjee, "Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats," Funct. Foods Connect. Between Nutr. Heal. Food Sci., pp. 315–332, 2013, doi: https://doi.org/10.1201/b16307.
10. N. Najafi and S. J. Masoumi, "The Effect of Garlic (Allium Sativum) Supplementation in Patients with Type 2 Diabetes Mellitus : A Systematic Review," Int. J. Nutr. Sci., vol. 3, no. 1, pp. 7–11, 2018.
11. B. Zhai et al., "Hypoglycemic and hypolipidemic effect of S-allyl-cysteine sulfoxide (alliin) in DIO mice," Sci. Rep., vol. 8, no. 1, pp. 1–7, 2018, doi: https://doi.org/10.1038/s41598-018-21421-x.
12. A. Shang et al., "Bioactive compounds and biological functions of garlic (allium sativum L.)," Foods, vol. 8, no. 7, pp. 1–31, 2019, doi: https://doi.org/10.3390/foods8070246.
13. E. Sovia et al., "Aktivitas Inhibisi Ekstrak Bawang Putih dan S-metil sistein terhadap Reaksi Glikasi Albumin secara In Vitro Inhibition Activity of Garlic Extract and S-methyl Cysteine against the Reaction of the In Vitro Albumin Glication," J. Kedokt. Maranatha, vol. 10, no. 2, pp. 98–109, 2011.
14. G. Kaur et al., "Garlic and resveratrol attenuate diabetic complications, loss of β-cells, pancreatic and hepatic oxidative stress in streptozotocin-induced diabetic rats," Front. Pharmacol., vol. 7, no. OCT, pp. 1–15, 2016, doi: https://doi.org/10.3389/fphar.2016.00360.
15. L. Wulandari, C. H. N. Prihharsanti, and Y. W. Prajoko, "Peran Radioterapi Eksterna Tambahan terhadap Penderita Kanker Payudara Stadium Lokal-Lanjut : Studi terhadap Angka Harapan Hidup Dua Tahun," Universitas Diponegoro, 2012.
16. T. Poonam, G. P. Prakash, and L. V. Kumar, "Influence of Allium sativum extract on the hypoglycemic activity of glibenclamide: an approach to possible herb-drug interaction," Drug Metab. Pers. Ther., vol. 8, no. 4, 2013, doi: https://doi.org/10.1515/dmdi-2013-0031.
17. B. P. Cahya, C. Mambo, and M. P. Wowor, "Uji Efek Ekstrak Umbi Bawang Putih (Allium sativum L.) terhadap Kadar Glukosa Darah Tikus Wistar (Rattus norvegicus) yang Diinduksi Aloksan," J. e-Biomedik, vol. 3, no. 1, 2015, doi: https://doi.org/10.35790/ebm.3.1.2015.6615.

18. R. C. Gupta, D. Chang, S. Nammi, A. Bensoussan, K. Bilinski, and B. D. Roufogalis, "Interactions between antidiabetic drugs and herbs: An overview of mechanisms of action and clinical implications," Diabetol. Metab. Syndr., vol. 9, no. 1, pp. 1–12, 2017, doi: https://doi.org/10.1186/s13098-017-0254-9.
19. E. P. Larsen, A. H. Rao, and F. Sasangohar, "Understanding the scope of downtime threats: A scoping review of downtime-focused literature and news media," Health Informatics J., vol. 26, no. 4, pp. 2660–2672, 2020, doi: https://doi.org/10.1177/1460458220918539.
20. R. Ashraf, R. A. Khan, and I. Ashraf, "Garlic (Allium sativum) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients," Pak. J. Pharm. Sci., vol. 24, no. 4, pp. 565–570, 2011.
21. R. Kumar et al., "Antihyperglycemic, antihyperlipidemic, anti-inflammatory and adenosine deaminase–lowering effects of garlic in patients with type 2 diabetes mellitus with obesity," Diabetes, Metab. Syndr. Obes. Targets Ther., vol. 6, pp. 49–56, 2013.
22. A. Mansouri, A. S. Vahed, H. Shahdadi, F. Dashtban, and A. Arbabisarjou, "The effect of garlic and cumin on blood pressure and glycosylated hemoglobin in patients with type 2 diabetes," Bali Med. J., vol. 7, no. 1, p. 156, 2018, doi: https://doi.org/10.15562/bmj.v7i1.849.
23. P. Dafriani, R. Marlinda, E. Arman, and M. Idaman, "Garlic: an alternative in reducing blood glucose on diabetic patients," Int. J. Community Med. Public Heal., vol. 7, no. 6, p. 2078, 2020, doi: https://doi.org/10.18203/2394-6040.ijcmph20202455.
24. K. Alare and T. Alare, "Review of Toxicity of Allicin From Garlic," Open Access J. Toxicol., vol. 4, no. 5, pp. 132–133, 2020, doi: https://doi.org/10.19080/OAJT.2020.04.555647.
25. M. Atkin, D. Laight, and M. H. Cummings, "The effects of garlic extract upon endothelial function, vascular inflammation, oxidative stress and insulin resistance in adults with type 2 diabetes at high cardiovascular risk. A pilot double blind randomized placebo controlled trial," J. Diabetes Complications, vol. 30, no. 4, pp. 723–727, 2016, doi: https://doi.org/10.1016/j.jdiacomp.2016.01.003.
26. M. S. J. Shoshi and H. Akter, "Effects of Garlic (Allium sativum) on Blood Glucose Level in Type 2 Diabetes Mellitus Patients Treated with Metformin," J. Enam Med. Coll., vol. 7, no. 3, pp. 151–155, 2017, doi: https://doi.org/10.3329/jemc.v7i3.34075.
27. V. Kumar, A. K. Abbas, and J. C. Aster, Robbins Basic Pathology, 9th ed. Philadelphia: Elsevier Saunders, 2013.
28. B. Musubika, G. Domínguez Montero, M. Betancourt Valladares, and D. Nkwangu, "Anti-haemostatic effect of combination of allium sativum L. Ethanol extract and warfarin in wistar rats," Rev. Cuba. Plantas Med., vol. 20, no. 3, pp. 301–312, 2015.
29. B. Ge, Z. Zhang, and Z. Zuo, "Updates on the clinical evidenced herb-warfarin interactions," Evidence-based Complement. Altern. Med., vol. 2014, 2014, doi: https://doi.org/10.1155/2014/957362.
30. K. Ried, N. Travica, and A. Sali, "The Effect of Aged Garlic Extract on Blood Pressure and Other Cardiovascular Risk Factors in Uncontrolled Hypertensives : the AGE at Heart Trial," Integr. Blood Press. Contro;, vol. 9, pp. 9–21, 2016.
31. R. Aalami-Harandi, M. Karamali, and Z. Asemi, "The favorable effects of garlic intake on metabolic profiles, hs-CRP, biomarkers of oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia: Randomized, double-blind, placebo-controlled trial," J. Matern. Neonatal Med., vol. 28, no. 17, pp. 2020–2027, 2015, doi: https://doi.org/10.3109/14767058.2014.977248.
32. F. Faroughi, S. M. A. Charandabi, Y. Javadzadeh, and M. Mirghafourvand, "Effects of garlic pill on blood glucose level in borderline gestational diabetes mellitus: A randomized controlled trial," Iran. Red Crescent Med. J., vol. 20, no. 5, 2018, doi: https://doi.org/10.5812/ircmj.60675.

33. M. Kaygusuz, R. Ş. Gümüştakım, C. Kuş, S. İpek, and A. Tok, "TCM use in pregnant women and nursing mothers: A study from Turkey," Complement. Ther. Clin. Pract., vol. 42, 2021, doi: https://doi.org/10.1016/j.ctcp.2020.101300.
34. P. O. Anderson, "Potentially Toxic Foods While Breastfeeding: Garlic, Caffeine, Mushrooms, and More," Breastfeed. Med., vol. 13, no. 10, pp. 642–644, 2018, doi: https://doi.org/10.1089/bfm.2018.0192.
35. J. R. N. Nansseu, J. Fokom-Domgue, J. J. N. Noubiap, E. V. Balti, E. Sobngwi, and A. P. Kengne, "Fructosamine measurement for diabetes mellitus diagnosis and monitoring: A systematic review and meta-analysis protocol," BMJ Open, vol. 5, no. 5, 2015, doi: https://doi.org/10.1136/bmjopen-2015-007689.
36. E. Venos and L. De Koning, "Endocrine markers of diabetes and cardiovascular disease risk," in Endocrine Biomarkers: Clinicians and Clinical Chemists in Partnership, Amsterdam: Elsevier B.V., 2017, pp. 251–299.
37. J. Aprioku and F. Amah-Tariah, "Garlic (Allium sativum L.) Protects Hepatic and Renal Toxicity of Alloxan in Rats," J. Pharm. Res. Int., vol. 17, no. 6, pp. 1–7, 2017, doi: https://doi.org/10.9734/jpri/2017/34909.
38. A. Fowotade, A. Fowotade, B. Enaibe, and G. Avwioro, "Evaluating Toxicity Profile of Garlic (Allium sativum) on the Liver, Kidney and Heart Using Wistar Rat Model," Int. J. Trop. Dis. Heal., vol. 26, no. 2, pp. 1–12, 2017, doi: https://doi.org/10.9734/ijtdh/2017/36282.
39. R. Ashraf, R. A. Khan, and I. Ashraf, "Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus," J. Med. Plants Res., vol. 5, no. 13, pp. 2922–2928, 2011.
40. R. Padiya, T. N. Khatua, P. K. Bagul, M. Kuncha, and S. K. Banerjee, "Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats," Nutr. Metab., vol. 8, no. 1, p. 53, 2011, doi: https://doi.org/10.1186/1743-7075-8-53.
41. E. S. Abdel-Baky and O. N. Abdel-Rahman, "Cardioprotective effects of the garlic (Allium sativum) in sodium fluoride-treated rats," J. Basic Appl. Zool., vol. 81, no. 1, pp. 1–7, 2020, doi: https://doi.org/10.1186/s41936-020-0140-0