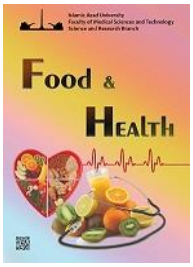

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Positive effects of garlic on insulin resistance and other indices of glucose metabolism: A systematic review of clinical trials

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ABSTRACT

Insulin resistance (IR) causes various metabolic disorders depending on the individual's genetic background. It can be detected up to 10-15 years before a person develops type 2 diabetes mellitus. The prevalence of diabetes is projected to increase from 8.4% in 2017 to 9.9% in 2045. Garlic has been used as herbal medicine. It has various biological effects such as anti-inflammatory, anti-diabetic, and antioxidants. The present study aims to investigate the impact of garlic on IR and other indices of glucose metabolism. Electronic databases including PubMed, Google Scholar, ScienceDirect, Science Information Database (SID), and publisher databases such as Elsevier, SpringerLink, and Wiley Online Library were searched till February 2022. Search terms involved "garlic" OR "Allium sativum" OR "alliin" OR "allicin" in combination with "fasting blood glucose" OR "fasting plasma glucose" OR "fasting blood sugar" OR "insulin resistance" OR "fasting insulin" OR "homeostasis assessment model" OR "HOMA" AND "polycystic ovary syndrome" OR "diabetes mellitus" OR "type 2 diabetes mellitus" OR "metabolic syndrome" OR "nonalcoholic fatty liver disease" OR "cardiovascular diseases". After reviewing the databases mentioned seven articles were identified for this review. Totally, 459 participants including 228 women and 231 men, enrolled in the trials. Assessing the findings of these articles indicates that garlic has a positive effect on IR, plasma insulin, and fasting glucose. The hypoglycemic action of garlic is related to its sulfur-containing compounds which directly or indirectly stimulate insulin secretion. Also, allicin in garlic can combine with endogenous thiol-containing molecules which can release insulin from inactivation.

1. Introduction

Insulin resistance (IR) causes various metabolic disorders depending on the individual's genetic background and the impact on tissues, generally the liver, adipose tissue, and muscle. IR can be detected up to 10-15 years before a person develops type 2 diabetes mellitus (T2DM), and in addition to adults, children are also affected by this (1, 2). The prevalence of diabetes is projected to increase from 8.4% in 2017 to 9.9% in 2045 among the population aged 18 to 99. The global diabetes healthcare spending in this age range is estimated at $958 billion by 2045 (3). Some complications following IR include microvascular diseases (nephropathy, retinopathy, and peripheral neuropathy), cardiac microvascular disease (cardiomyopathy, angina, and coronary artery spasm), central nervous system disorders (gait instability, dementia, and mood disturbance), loss of visual acuity, and chronic renal failure. These findings have placed obstacles in the way of healthcare systems in the USA that are continuously searching for methods to treat complications caused by IR (1). People with a lack of physical activity and excessive calorie intake are at a higher risk of developing most metabolic diseases (4). Obesity itself increases the risk of metabolic disorders, specifically IR (5). Factors that actively contribute to IR are categorized as acquired, hereditary and mixed. The acquired category is known to be the main cause of IR with the greatest impact on a large number of people. Some examples of the acquired category are having a diet that consists of nutrient imbalances

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with high usage of sodium, glucose, and lipid toxicity, adipose tissue dysfunction, and aging. Lifestyle changes that include increasing physical activity as well as following a balanced diet with restricted calories and carbohydrates to increase insulin demand are recommended to improve IR. The use of medications can also be considered as an alternative solution to improve the circumstances (1). Garlic with the scientific name of *Allium sativum* L. has been used as an herbal medicine in several nations for centuries. It has various biological effects such as anti-inflammatory, anti-diabetic, cardiovascular protective, anti-obesity, and antioxidants. Bioactive compounds with therapeutic properties of garlic include allicin, alliin, ajoene, diallyl sulfide, diallyl disulfide, and S-allyl cysteine (SAC) (6, 7). Maeda et al. (8) have shown that in a mouse model of IR, aged garlic can have a positive effect on IR. Also, Saravanan et al. (9) explained that the administration of SAC to streptozotocin (STZ) diabetic rats has an anti-hyperglycemic effect. They hypothesized that SAC is responsible for increasing the activity of beta cells of the islets of Langerhans to potentiate insulin secretion and can exert its anti-diabetic effect by inhibiting hepatic gluconeogenesis. Moreover, the activity of glucose-6-phosphatase, which increases in the condition of insulin deficiency, decreased in the STZ-induced diabetic rats treated with SAC due to a reduction in serum glucose level. However, recent randomized control trials show the contradictory effect of garlic on indicators of glycemic control (10-16). Due to different suggested outcomes by these articles, the possibility of garlic being effective as a complementary herbal medication in improving glycemic control is unclear. Hence, this systematic review aims to investigate the impact of garlic on IR and other indices of glucose metabolism to prevent complications of diabetes mellitus.

2. Method

This systematic review has followed the PRISMA guidelines (17). Electronic databases including PubMed, Google Scholar, ScienceDirect, Science Information Database (SID), and publisher databases such as Elsevier, SpringerLink, and Wiley Online Library were searched till February 2022. References of all included articles were also screened for any proper studies. Search terms involved “garlic” OR “allium sativum” OR “alliin” OR “allicin” in combination with “fasting blood glucose” OR “fasting plasma glucose” OR “fasting blood sugar” OR “insulin resistance” OR “fasting insulin” OR “homeostasis assessment model” OR “HOMA” AND “polycystic ovary syndrome” OR “diabetes mellitus” OR “type 2 diabetes mellitus” OR “metabolic syndrome” OR “nonalcoholic fatty liver disease” OR “cardiovascular diseases”. After screening the titles and abstracts of the obtained articles, the articles which were included in this review follow these eligible: 1. English or Farsi full-text or any translation to these languages 2. RCTs (both parallel and cross-over) 3. reporting the related outcome of glycemic control. Cell culture and animal studies were excluded in this review and the full text of relevant studies was carefully examined. The following data was extracted in each article: first author, year of publication, study design, age range, number and gender of participants, condition of health, duration, countries, and amount of garlic supplementation.

3. Result

After reviewing the mentioned databases, 407 articles were obtained and reduced to 372 by removing duplicates. The number of articles obtained is as follows: 49 from PubMed, 100 from Google Scholar, 133 from ScienceDirect, 1 from SID, 32 from SpringerLink, and 92 from Wiley Online Library. 367 articles that were not eligible were excluded. 291 of these articles were irrelevant, 36 of them were not RCT, 23 of them were not provided our primary outcome, and 15 of them were animal studies. Eventually, seven articles were identified for review (Fig. 1). The study designs included: 1 double-blind, randomized, placebo-controlled, cross-over trial; 6 randomized, double-blind, placebo-controlled, parallel trials. Totally, 459 participants including 228 women and 231 men, enrolled in the trials. The age range of participants was from 18 to 75 years. The lowest number of participants was reported in the study of Atkin et al. (13) (26 participants) and the highest number was found in the study of Wlosinka et al. (14) (93 participants). The duration of intervention was varying from 28 days to 3 months. The lowest dose of garlic given on a daily basis is related to Aalami-Harandi et al. (12) by 401mg and the highest prescribed dose is related to Wloskina et al. (14) by 2400mg (Table 1).

3.1. Insulin resistance

Three articles out of five selected articles reported that their treatment method showed a significant reduction in the HOMA-IR index compared to the control group. In this case, the P-value reported by Sangouni et al. (10, 11) and Parham et al. (16) was less than 0.001. The duration of intervention in all these studies was 12 weeks or more. On the other hand, Aalami-Harandi et al. (12) and Atkin et al. (13) did not find any significant changes in their treatment and control group.

3.2. Plasma insulin

Plasma insulin was one of the measured characteristics in three articles out of the selected ones. Two of them (10, 11) claim that insulin levels of treatment groups compared with control groups decreased significantly after consumption of garlic ($p \leq 0.001$). The P-value reported by Aalami-Harandi et al. (12) for the decrease in levels of plasma insulin was 0.09 which they named "A trend toward the significant effect" and in this research, we consider it as insignificancy.

3.3. Fasting glucose

Among six studies that examined the effect of garlic on fasting glucose, three reported positive effects on fasting glucose (11, 14, 16) and the other three could not find any

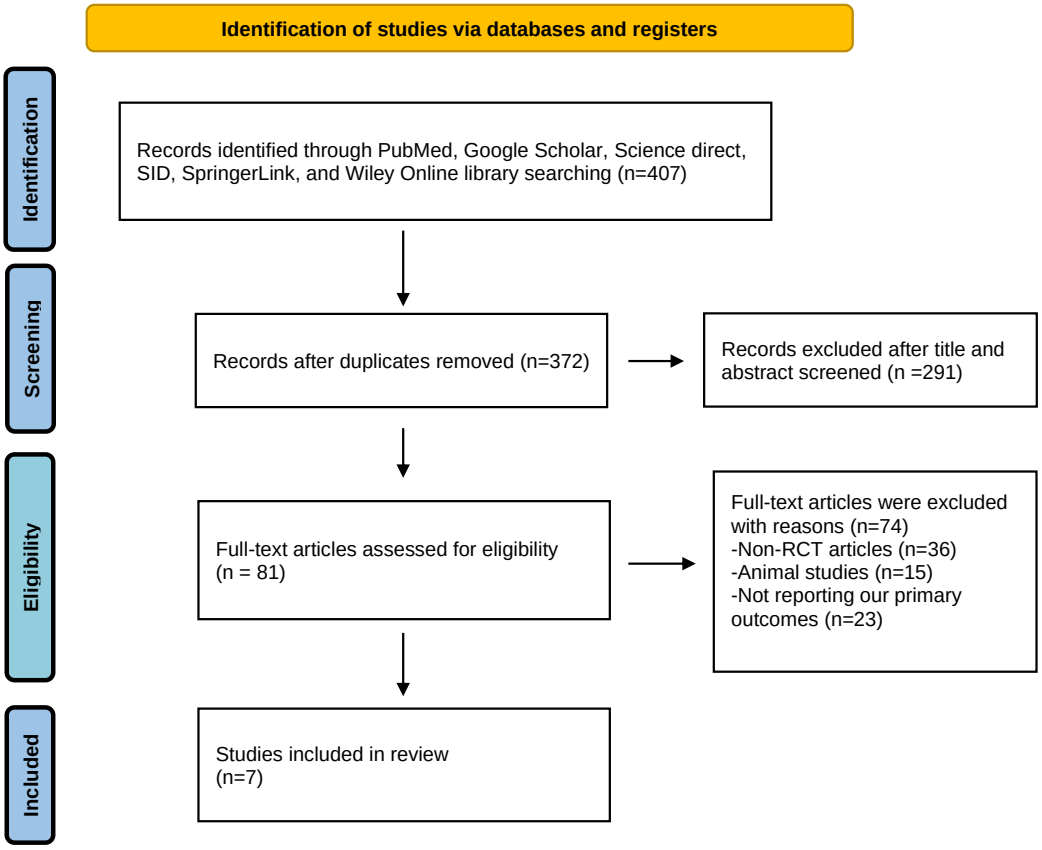

Fig. 1. Flow diagram showing identification of publications.

significance (10, 12, 15). Parham et al. (16) claim that garlic supplementation caused a considerable reducing effect on the level of fasting glucose in patients with T2DM in 12 weeks ($p<0.0001$). Also, Sangouni et al. (11), whose subjects were patients with non-alcoholic fatty liver disease (NAFLD) reported a similarly significant effect ($p=0.01$). Additionally, Wlosinka et al. (14) which has the longest duration and highest dosage of garlic supplementation, reported a significant decrement in fasting glucose levels compared to the placebo group ($p=0.034$).

3.4. Adverse events

The only reported side effect was indigestion by Atkin et al. (13) in 2 participants. In this case, the kind of treatment was aged garlic extract. Other articles reported no side effects during their treatment.

4. Discussion

In this study, seven articles were reviewed to investigate the relationship between garlic and indicators of glycemic control. Assessing the findings of these articles indicates that garlic has a positive effect on IR, fasting glucose, and plasma insulin in the supplementation group in comparison with the placebo group.

4.1. Effect of garlic on insulin resistance

Five out of seven articles investigated the effect of garlic on IR (10-13, 16). Three of these five studies showed that consumption of garlic reduces IR (10, 11, 16). Therefore, we conclude that the use of garlic leads to a decrease in IR. Liu et al. (18) suggested that the mechanism of garlic's effect to improve IR in diabetic rats is related to the expression of GLUT4 and the improvement of oxidative stress. Ramakrishna and Jailkhani (19) showed that the increase in protein oxidation, lipid peroxidation, and NO levels are complications of diabetes. An increase in total glutathione (GSH) content, GSH peroxidase activity, GSH reductase, and superoxide dismutase (SOD) as well as a decrease in nitrate/nitrite content and lipid peroxidation were seen in diabetic rats treated with garlic oil. The presence of high oxidative stress in skeletal tissues is due to the evaluation of lipid peroxidation and 4-hydroxynonenal levels, which disrupts insulin signaling. Oxidative stress activates the transcription of inflammatory factors that increase pro-inflammatory cytokines and NO levels. Garlic components prevent the production of inflammatory factors such as NO, TNF-α, and IL-1β by inhibiting the activity of NF-κB; therefore, the expression of GLUT4 increases. By the increasing expression of GLUT4, nuclear proteins easily bind to the insulin-responsive element in the GLUT4 promoter, which improves IR (20). However, in

contradiction to our result, Aalami-Harandi et al. (12) and Atkin et al. (13) have not found any significant effect of garlic consumption on IR. Consumption of aged garlic instead of its supplementary form in the study of Atkin et al. (13) and the lowest amount of garlic consumption in the study of Aalami-Harandi et al. (12) can justify this contradiction.

4.2. Effect of garlic on plasma insulin

Three out of seven articles examined the effect of garlic on plasma insulin (10-12). Two of these three studies found that garlic consumption increased plasma insulin (10, 11). Hence, we conclude that the consumption of garlic causes an increase in plasma insulin levels. In line with our findings, several studies on diabetic rats treated with garlic show an increase in plasma insulin (21-24). Incretin hormones stimulate insulin secretion and decrease blood glucose. Dipeptidyl peptidase-4 (DPP-4) as a naturally occurring serine protease is the most important enzyme for the degradation of incretin hormones, especially glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (25, 26). Kalhotra et al. (27) showed that hydroxyl and phenolic functional groups present in garlic extract can inhibit DPP-4 activity in vitro. As a result, the insulinotropic and glucagonostatic effects of incretin hormones are enhanced and lead to delaying gastric emptying and improving the function of pancreatic beta cells. Inhibition of DPP-4 explains the possible mechanism of insulin production and reduction of blood glucose levels. They also demonstrated that garlic extract significantly increases the proliferation of skeletal muscle cells in vitro. Therefore, glucose uptake in skeletal muscle cells increases, and blood glucose level decreases (25, 27). However, in the study of Aalami-Harandi et al. (12) garlic has no significant effect on plasma insulin (p=0.09).

Table 1. Characteristics of included studies.

Author/ year	Number of participants by gender	County	Age range	Study design	Duration	Treatment group	Control group	Result
Aalami-Harandi et al. 2015 (12)	44 pregnant women at risk for pre-eclampsia	Iran	18-40 years	Double-blind parallel	9 weeks	1 tablet (400 mg garlic and 1 mg allicin) daily	N/A	No significant effect of garlic was found on IR, plasma insulin, and fasting glucose
Sangouni et al. 2020 (11)	31 women 57 men With NAFLD	Iran	33-58 years	Double-blind parallel	12 weeks	4 tablets of garlic (each coated tablet contained 400 mg garlic powder) daily	4 tablets of placebo (each coated tablet contained 400 mg starch) daily	there was a significant decrease in IR, plasma insulin, and fasting glucose
Atkin et al. 2016 (13)	9 women 17 men With T2DM	UK	61±8 years	Double-blind Cross-over	4 weeks with 4 weeks washout period	1200mg of aged garlic extract daily	N/A	It had no significant effect on IR
Sangouni et al. 2021 (10)	30 women 54 men With metabolic syndrome	Iran	34-59 years	Double-blind parallel	3 months	1600 mg of garlic daily	4 placebos (coated tablets containing starch) daily	Improvement of IR, plasma insulin was observed No significant effect was found on fasting glucose
Parham et al. 2020 (16)	16 men 48 women With T2DM	Iran	25-70 years	Double-blind parallel	12 weeks	A capsule that contained 20% of garlic and onion three times a day	A capsule that contained micro-crystalline cellulose and bran three times a day	Garlic effectively reduced fasting glucose and IR
Wlosinka et al. 2020 (33)	61 men 32 women with Framingham risk factor	Sweden	40-75 years	Double-blind parallel	12 months	2400 mg of aged garlic extract daily	A capsule that contained starch	fasting glucose was reduced
Sobenin et al. 2008 (15)	26 men 34 women with T2DM	Russia	34-62 years	Double-blind parallel	28 days	300 mg dehydrated garlic powder twice a day	N/A	No significant effect on fasting glucose was observed

The inconsistent results may be due to the shorter duration (9 weeks) and the lowest amount of garlic consumption in their study compared to other studies that found a positive effect.

4.3. Effect of garlic on fasting glucose

Six out of seven articles examined the effect of garlic on fasting glucose (10-12, 14-16). Three of these six studies reported that consumption of garlic effectively reduced fasting glucose (11, 14, 16). As a result, we conclude that the consumption of garlic possibly plays a role in reducing fasting

glucose. Consistent with our findings, Saravanan et al. (28) showed the anti-hyperglycemic effect of garlic on diabetic rats. This hypoglycemic action of garlic is related to its sulfur-containing compounds, such as SAC, which directly or indirectly stimulate insulin secretion (29). According to the findings of Kim et al. (30), the blood glucose level was significantly reduced in STZ-treated mice treated with SAC. This effect can be attributed to the increase in insulin secretion from the remaining pancreatic beta cells or its release from bound insulin (31). In another study by Saravan et al. (9), they showed that SAC is related to increased activity of liver hexokinase enzyme. Increasing the activity of hexokinase, in return, activates glycolysis. Hence in mice treated with SAC, the restoration of insulin secretion and increased glucose utilization were observed. Also, allicin in garlic can combine with endogenous thiol-containing molecules such as cysteine, glutathione, and serum albumins which can release insulin from inactivation (32). The other three articles have not found a significant relationship between garlic and fasting glucose (10, 12, 15). Two of them had a shorter duration of treatment compared to the articles that saw a positive effect (12, 15). Also, the contradictory result in the article of Sangoniet al. (10) may be due to the fact that the rest of the risk factors of metabolic syndrome have a negative effect on glucose metabolism.

4.4. Limitation

The numbers of human articles that have examined the effect of garlic on IR were limited. Differences in preparation conditions, production process, harvest season, plant species in different countries, and chemical compounds in garlic were found in the studies. The study designs of the articles, such as the duration and the dose given, were also different. Moreover, most of the articles were limited to the geographical area of Iran.

Author contributions

The author's responsibilities were as follows: BA contributed to the study design and supervised. BA, MS, and HG contributed to the manuscript draft; MS and HG contributed to editing the manuscript. All authors read and approved the final manuscript.

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