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Full Length Research Paper

Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus

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The aim of the present study was to evaluate the effects of garlic on fasting blood sugar and HbA1c in patients with type 2 diabetes mellitus. This was a 24 week, single-blind placebo controlled study. The patients (n = 210) with fasting blood sugar above 126 mg/dl were recruited and divided into 7 groups (A, B, C, D, E, F and G), each comprised of 30 patients. Group A, B, C, D, and E were given garlic tablets at doses of 300, 600, 900, 1200, and 1500 mg per day respectively. Group F received metformin while group G received placebo. FBS and HbA1c were measured at week 0, 12 and 24. Present study showed significant decrease in fasting blood sugar and HbA1c in both dose and duration dependent manner. In each garlic treated group, significant reduction in FBS ($p < 0.005$) and HbA1c ($p < 0.005$) were observed when compared with placebo. Highly significant reduction in FBS and improvement in $HbA1_C$ were observed at higher doses of garlic and with increase in the duration of study. Garlic is more effective than placebo and comparable to metformin in reducing fasting blood glucose and may be a valuable addition in the management of diabetic patients.

Key words: Garlic, diabetes mellitus, fasting blood sugar, $HbA1_C$, complementary therapy.

INTRODUCTION

Diabetes mellitus is a group of diseases characterized by high blood glucose levels resulting from defects in insulin secretion, insulin action, or both. Abnormalities in the metabolism of carbohydrate, protein, and fat are also present (Defronzo, 1997). The prevalence of type 2 diabetes is increasing globally (Zimmet et al., 2001; Mokdad et al., 2001). It is anticipated that by the year 2025 over 75% of all people with diabetes will belong to the developing countries. In Pakistan, no of patients afflicted with diabetes are estimated to increase from 4.3 million in 1995 to 14.5 million in 2025 (Shera et al., 2007).

Despite the availability of medication for management of diabetes, the interest in alternative traditional remedies is increasing (Pari and Umamaheswari, 2000). The use of natural substances has become more extensive over the past few years, motivated certainly by the faith that they may have fewer side effects as compared to pharmaceuticals and by their effortless accessibility to the populace without prescriptions or visits to the health providers (Ashraf et al., 2005). Many natural substances have shown the potential to condense number of cardiovascular risk factors including diabetes mellitus (Marles and Farnsworth, 1995; Alarcon-Aguilara, 1998). Garlic and various forms of extracts prepared from it represent an example of such natural substances (Steiner and Li, 2001).

Garlic is known to possess a number of biologically active compounds having anticoagulant (Fukao et al., 2007), antioxidant (Banerjee et al., 2003; Lee et al., 2009), antihyperlipidemic (Gupta and Porter, 2001) and antihypertensive effects (Verma et al., 2008).

Antidiabetic potential of garlic has been reported in many previous trials conducted in animal models (Marles

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and Farnsworth, 1995; Alarcon-Aguilara et al., 1998; Banerjee and Maulik, 2002; Anwar and Meki, 2003; Liu et al., 2005; Liu et al., 2006; Eidia et al., 2006; Jelodar et al., 2005; Lee et al., 2009).

Garlic principle active agent appears to be allicin, a sulfur-containing compound that with its breakdown products gives garlic its characteristic odour (Elkayam et al., 2003). Allicin is formed enzymatically from an odourless precursor, alliin, when garlic cloves are mechanically disrupted (Alpers, 2009). The probable mechanism underlying garlic hypoglycemic effects most likely is increased insulin secretion and sensitivity (Birdee and Yeh, 2010). Despite that the antidiabetic potential of garlic has been confirmed in animal studies, scientific evidence from human studies is lacking (Liu et al., 2007). Most of the clinical studies have observed the effects of garlic on blood glucose in normal healthy individuals but not in diabetic patients, leaving no doubt that the role of garlic in the management of diabetic patients still needs to be confirmed. However, bearing in mind that garlic has been an essential part of our diet for centuries, it is taken for granted that garlic is safe in a wide range of doses. Few non-specific adverse effects were reported in clinical studies using garlic and its preparations and frequently consist of gastrointestinal discomfort and nausea. Allergic contact dermatitis has been reported in people with occupational exposure to garlic. There have also been infrequent reports of allergic conjunctivitis, rhinitis, bloating, headache, dizziness, profuse sweating and bronchospasm occurring in response to garlic inhalation or ingestion. Rarely ingestion of fresh garlic and garlic powder was reported to have synergistic effects with anticoagulants or platelet aggregation inhibitors increasing risk of haemorrhage (Banerjee and Maulik, 2002). Thus comprehensive clinical studies in diabetic patients are justified to confirm the efficacy and possible role of garlic in the management of diabetic patients (Thomson et al., 2007).

As previous clinical trials have cast doubt on the proposed hypoglycemic effects of garlic and there is no previous trial showing the effects or benefits of garlic at different doses on blood glucose in patients with diabetes and also keeping in mind the incidence of diabetes that is quite high in Pakistan and a wide spread belief among general public that garlic has beneficial effects on various cardiovascular risk factors, we designed a study to evaluate the hypoglycemic effects of garlic in patients with type 2 diabetes mellitus in comparison with the standard antidiabetic agent metformin and placebo.

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MATERIALS AND METHOD

This was a 24 week, single-blind study, conducted simultaneously in different primary health care centers in Karachi, Pakistan in cooperation with registered medical practioners. Research protocol has been approved by Board of advanced studies and Research of the University of Karachi.

Patients with previously diagnosed type 2 diabetes mellitus (n = 210) were enrolled after taking informed and written consent and were divided randomly into 7 groups: A, B, C, D, E, F and G, each comprised of 30 patients. Patients in group A, B, C, D and E were given garlic tablets at the dose of 300, 600, 900, 1200 and 1500 mg per day in divided doses respectively for 24 weeks. Group F was given tablet metformin 500 mg twice daily for 24 weeks while patients in Group G were given placebo.

Prior to enrollment we conducted a screening examination in which inclusion and exclusion criteria were evaluated, informed and written consent was taken from each study participant. All the patients were seen at fortnightly interval. Fasting blood sugar and HbA1c were measured at week 0, week 12 and week 24 of study. At each visit, patients were queried about drug compliance and side effects of drugs. Diet control consisted of asking subjects at recruitment to keep to their usual diet throughout the study and especially not to alter their garlic or onion intake. Patients were also motivated to keep their nutritional plan, physical activity and general life style as constant as possible throughout the study period. The patients were advised to avoid taking any other medication during the study period without informing the study physician.

Blood samples were drawn from each patient on the morning of week 0, week 12 and week 24. Blood was drawn by venepuncture with the help of a sterile plastic disposable syringe under aseptic measures. Blood glucose was determined by the enzymatic colorimetric method. Glycated hemoglobin (HbAlc) was estimated by Fast Ion-Exchange Resin Separation Method.

All patients in groups A, B, C, D, E, F and G were selected according to following criteria.

Inclusion criteria

Patients with diagnosed type 2 diabetes mellitus of either sex with fasting blood sugar levels above 126 mg/dl. Patients aged between 25 to 70 years.

Exclusion criteria

The patients were excluded from the study if they are, known to have history of allergy to garlic, pregnant or lactating women, patients with type 1 diabetes mellitus, patients having history of myocardial infarction, coronary artery bypass grafting, established coronary artery disease, unstable angina, clinically manifest heart failure, patients with history of liver disease and impaired renal function and if they are known to have any other concurrent medical illness.

Results are presented as means ± SEM. The paired, two tailed Student t test was performed to compare measurements of FBS and HbA1C at different durations of therapy. Statistical significance was defined as $p < 0.05$.

RESULTS

The demographic characteristics of the study population are shown in Table 1. The patients were male (60%) and females (40%). The mean age was 40 years in garlic treated group and 50 years in metformin treated group (range 25 to 70 years) (Table 1). Fasting blood glucose and HbA1C were measured at week 0 and week 12 and week 24 (Tables 2 and 3, Figure 1and 2).

A total of 210 patients were initially enrolled in the study. 195 patients were associated throughout the study

Table 1. Demographic data of Garlic and standard group.

	Placebo treated group	Garlic treated group	Metformin treated group
Men	15	90	17
Women	15	60	13
Age (years)	45 ± 4.58	40 ± 5.04	50 ± 5.80
Body weight (Kg)	69.1 ± 7.58	68.2 ± 10.45	65.4 ± 9.80
Height (cm)	166.4 ± 6.58	165.2 ± 8.81	167.60 ± 9.20
Average duration of type 2 diabetes mellitus	3 years	3 years	2.5 years
Co-morbid disease	None	None	None

Table 2. Effect of different doses of Garlic in comparison with Placebo and Metformin on fasting blood sugar from week 0 to week 12 and week 24.

Group according to dose	Fasting blood sugar (mg/dl)		
	Week 0	Week 12	Week 24
(Group A) Garlic 300 mg	127 ± 0.334 (n = 30)	126 ± 0.360** (n = 27)	125 ± 0.379** (n = 27)
(Group B) Garlic 600 mg	128 ± 0.311 (n = 30)	127 ± 0.369** (n = 27)	126 ± 0.446** (n = 27)
(Group C) Garlic 900 mg	128 ± 0.263 (n = 30)	126 ± 0.274** (n = 27)	124 ± 0.289** (n = 27)
(Group D) Garlic 1200 mg	128 ± 0.315 (n = 30)	125 ± 0.264** (n = 27)	123 ± 0.263** (n = 27)
(Group E) Garlic 1500 mg	129 ± 0.223 (n = 30)	126 ± 0.213** (n = 27)	123 ± 0.225** (n = 27)
(Group F) Metformin 500 mg	125 ± 1.246 (n = 30)	119 ± 1.243** (n = 27)	118 ± 1.045** (n = 27)
(Group G) Placebo	127 ± 0.192 (n = 30)	129 ± 0.241** (n = 27)	131 ± 0.363** (n = 27)

Data are presented as mean ± standard error. Asterisk denotes significant p values. * Significant $p < 0.05$ ** Highly significant $p < 0.005$.

Table 3. Changes in HbA1C with Garlic, Metformin and Placebo from week 0 to week 12 and week 24.

Group	Blood levels of $HbA1_C$ (%)			
	Week 0	Week 12	Week 24	Mean difference
Group A (300 mg dose of garlic)	6.59 ± 0.044	6.26 ± 0.044**	6.02 ± 0.048**	- 0.57
Group B (600 mg dose of garlic)	6.52 ± 0.055	6.33 ± 0.064	6.06 ± 0.054**	- 0.46
Group C (900 mg dose of garlic)	6.60 ± 0.055	6.31 ± 0.053*	6.03 ± 0.054**	- 0.57
Group D (1200 mg dose of garlic)	6.53 ± 0.056	6.26 ± 0.045	6 ± 0.053**	- 0.53
Group E (1500 mg dose of garlic)	6. 73 ± 0.035	6.32 ± 0.041**	5.97 ± 0.032**	- 0.76
Group F (Metformin 500 mg)	6.64 ± 0.044	6.26 ± 0.036**	6.21 ± 0.042**	- 0.43
Placebo	6.31 ± 0.036	6.37 ± 0.035	6.40 ± 0.049	+ 0.09

* Significant $p < 0.05$, ** Highly significant $p < 0.005$, (-) indicates decrease in mean HbA1C from week 0 to week 24. (+) indicates increase in mean HbA1C from week 0 to week 24.

and completed the protocol till week 24. Out of the dropped 15 patients, 3 patients were dropped from metformin treated group, 2 patients due to vague abdominal discomforts and refused to continue the protocol while 1 patient complained of weight loss and did not come for follow up after 12 weeks. The remaining patients were dropped from different garlic treated groups, 8 patients did not come for follow-up due to unknown reasons, 4 patients refused to give the blood samples for biochemical analysis so were forbidden to continue the study. 3 patients were dropped in the garlic treated group with 1500 mg, who reported heart burn in the first week of study and refused to take any further treatment. During this study, every possible attempt has been made to keep the number of patients as much as to provide a valid statistical data.

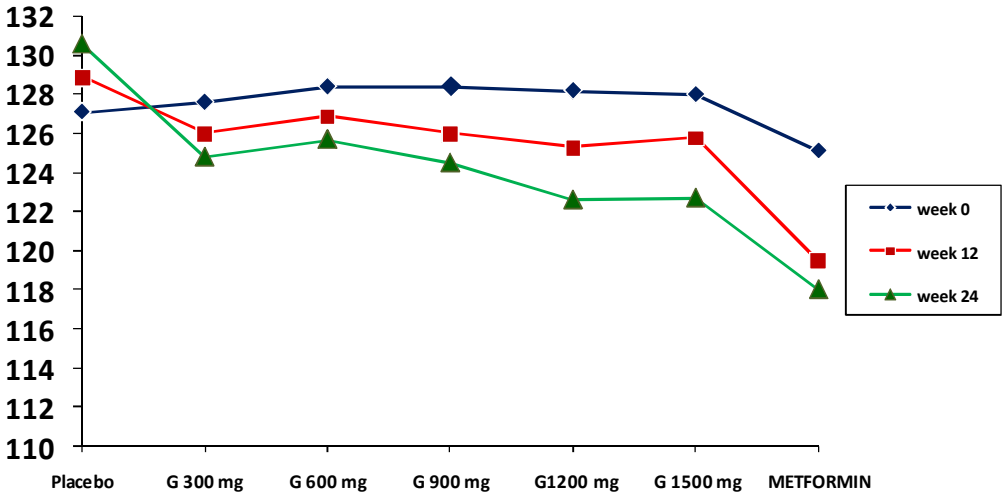

Figure 1. Changes in mean FBS at different doses of Garlic in comparison with Placebo and Metformin from week 0 to week 12 and week 24.

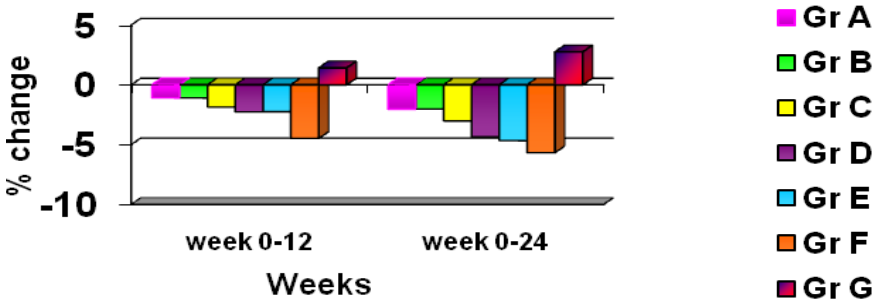

Figure 2. Percentage changes in FBS from week 0 to week 12 and from week 0 to week 24. Gr A = Garlic 300 mg, Gr B = Garlic 600 mg, Gr C = Garlic 900 mg, Gr D = Garlic 1200 mg, Gr E = Garlic 1500 mg, Gr F = Metformin, Gr G = Placebo. The (-) sign denote decrease in percentage.

The result in the present study showed significant decrease in fasting blood sugar and HbA1C in both dose dependent and duration dependent manner when compared with placebo and standard antidiabetic agent metformin. The fasting blood sugar (FBS) was reduced from 127.4 ± 0.334 at baseline from week 0 to 126.0 ± 0.360 ($p < 0.05$) at week 12 and to 124.8 ± 0.378 ($p < 0.001$) at week 24 in group. A patient who have been given garlic at a dose of 300 mg daily. In group B, at a dose of 600 mg the reduction in FBS was found to be almost equivalent with that in group A with a decrease from baseline value of 128.3 ± 0.311 at week 0 to 126.9 ± 0.369 ($p < 0.05$) at week 12 and 125.7 ± 0.446 ($p < 0.001$). In group C, patients were given garlic at a dose of 900 mg and the FBS was found to be reduced from 128.4 ± 0.263 at the baseline from week 0 to 126.0 ± 0.274 ($p < 0.001$) at week 12 and 124.5 ± 0.289 at week 24 ($p < 0.001$). In group D, the dose of garlic given was 1200 mg/day. The reduction in FBS from baseline value of 128.2 ± 0.315 at week 0 to 125.3 ± 0.264 ($p < 0.001$) at week 12 and to 122.6 ± 0.263 ($p < 0.001$) was found to be highly significant when compared to group A and B at week 12. Group E patients were given the highest dose of garlic in the present study. The FBS decrease in this group was highly significant from 128.7 ± 0.223 at week 0 125.8 ± 0.213 ($p < 0.001$) and to 122.7 ± 0.225 at week 24 ($p < 0.001$). Group F patients were given metformin at a dose of 500 mg twice daily. In this group the FBS at week 0 was 125.1 ± 1.157, which was reduced to 119.5 ± 1.243 at week 12 ($p < 0.05$) and to 118.0 ± 1.045 at week 24 ($p < 0.001$). In comparison significant increase change in the FBS was observed in patients with placebo with the mean increase of 4 mg/dl ($P < 0.005$) Table 2, Figure 1 and 2. The HbA1C percentage was also found to be improved in all the groups treated either by garlic or metformin as compared to placebo. In group A, HbA1C at

week 0 was 6.585 ± 0.044. It was found to reduced to 6.256 ± 0.044 ($p < 0.001$) at week 12 and to 6.019 ± 0.048 ($p < 0.001$) at week 24. In group B, HbA1c was reduced from 6.519 ± 0.055 at week 0 to 6.330 ± 0.064 at week 12 and 6.063 ± 0.054 ($p < 0.001$) at week 24. This decrease was statistically insignificant when compared from week 0 to week 12 but was found to be statistically significant when compared from week to week 24. In group C reduction in HbA1C was significant from baseline value of 6.596 ± 0.055 at week 0 to 6.307 ± 0.053 ($p < 0.05$) at week 12 and highly significant to 6.033 ± 0.054 ($p < 0.001$) at week 24. In group D, the HbA1C was reduced from baseline value of 6.530 ± 0.056 to 6.256 ± 0.045 ($p < 0.05$) and 5.996 ± 0.052 ($p < 0.001$) at week 12 and 24 respectively. Group E patients showed highest improvement in HbA1C with a reduction from baseline value of 6.726 ± 0.035 at week 0 to 6.332 ± 0.041 at week 12 ($p < 0.001$) and 5.974 ± 0.032 ($p < 0.001$) at week 24. Metformin treated group F also showed similar reduction like group E with a decrease in HBA1C value of 6.637 ± 0.044 at baseline to 6.259 ± 0.036 ($p < 0.001$) at week 12 and to 6.207 ± 0.042 ($p < 0.001$) at week 24. In comparison no significant change in HbA1C was observed in patients who were given placebo.

DISCUSSION

The present study monitored effects of garlic in comparison with placebo and a standard antidiabetic agent ‘metformin’ on fasting blood sugar and HbA1c in patients with type 2 diabetes mellitus with respect to its ability to provoke a decrease in fasting blood sugar at different doses and to find out the time taken for this decrease. FBS and HbA1C were measured at week 0, week 12 and week 24. The results observed in the present study demonstrated significant decrease in fasting blood glucose and improvement in serum HBA1C when compared from week 0 to week 12 and week 24. Garlic was found to be effective in improving the glycemic control at all doses. Exceedingly significant changes observed at the higher doses of 900, 1200 and 1500 mg as compared to when garlic was administered at a dose of 300 or 600 mg. The improvement in glycemic control was found to be more when compared with placebo and equivalent when compared with standard antidiabetic agent metformin. Highly significant reduction in both fasting blood sugar and HbA1C is observed at week 24 in all the groups treated with garlic and metformin with comparable efficacy as compared to placebo which showed no significant change in FBS and HbA1C.

The present study is unique from previous clinical trials as this is the first time that effects of garlic were observed in a dose dependent and duration dependent manner in patients with type 2 diabetes mellitus. The changes in fasting blood sugar and HbA1C observed in the present study are consistent with the observations from previous preclinical and clinical trials. Many of the trials evaluating the hypoglycemic effects of garlic were done in animal models. Garlic was reported to be effective in reducing blood glucose in streptozocin-induced as well as alloxan-induced diabetic rats and mice (Mathew and Augusti, 1973; Swanston-Flatt et al., 1990; Kasuga et al., 1999; Ohaeri, 2001). It was also reported that ingestion of garlic juice and aqueous garlic extracts resulted in better utilization of glucose in glucose tolerance test performed in diabetic animal models (Jain and Vyas, 1973; Jain and Vyas, 1975; Jalal et al., 2007). Two of the previous studies reported that allicin, a sulfur containing amino acid in garlic has a potential to reduce diabetic condition in rat almost to the same extent as did glibenclamide and insulin (Sheela and Augusti, 1992; Sheela et al., 1995).

Although many of the previous trials in animal models showed significant effects of garlic on glycemic control, hypoglycemic effect of garlic in human is not well studied. All human studies (Kiesewetter et al., 1991; Jain et al., 1993; Ali and Thomson, 1995; Bordia et al., 1998; Zhang et al., 2001) apart from two (Afkhami-Ardekani et al., 2006; Sobenin et al., 2008), has showed the effect of garlic on blood glucose level in normal healthy individuals but not in diabetic patients. The present study confirmed the hypoglycemic effects of garlic observed in the two previous clinical trials in patients with type 2 diabetes mellitus. The effects of garlic tablets preparation used in the present study were found to produce the similar changes in the fasting blood glucose. In addition HbA1c was also found to be significantly improved as compared to baseline readings. The present study contradicts with a previous clinical trial of Bordia et al., 1998, that evaluated the effects of garlic on serum glucose and lipids in patients with coronary artery disease and reported no significant change in fasting and 2 h postprandial blood glucose levels. The changes in FBS observed in the our study are in accordance with the previous clinical trial by Li et al., 2000 that reported the marked decrease in blood sugar levels in cases with hyperglycemia.

The precise mechanism of garlic as antidiabetic agent is not unambiguous but in-vivo, (Mathew and Augusti, 1973; Jain, 1973) as well as in vitro (Augusti and Sheela, 1996) studies showed that garlic acts as an insulin secretagogue in diabetic rats. It has also been proposed that antioxidant effect of S-allyl cysteine sulfoxide (isolated product from garlic) may also contribute for its beneficial effect in diabetes (Banerjee et al., 2003). Garlic has been reported to spare insulin from sulphydryl group which is known to inactivate insulin. Garlic allicin can effectively combine with compounds like cysteine and enhance serum insulin (Mathew and Augusti, 1973). It has also been projected that garlic can act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the beta cells or its release from bound insulin (Jain and Vyas, 1975). In addition to the aforementioned proposed mechanisms garlic is also known to prevent the long term complications of diabetes

by inhibiting the formation of advanced glycation end products (AGEs). Advanced glycation end-products are recognized contributors to the pathophysiology of aging and diabetic chronic complications. People with diabetes have higher levels of AGEs than nondiabetic subjects because hyperglycemia and oxidative stress both contribute to their accumulation (Huebschmann et al., 2006). The formation of AGEs occurs at an accelerated rate in patients with diabetes mellitus. AGEs are not only markers but also important causative factors for the pathogenesis of diabetes, cataracts, atherosclerosis, and diabetic nephropathy (Gutiérrez et al., 2010). Compounds having both antiglycation and antioxidant properties are recommended therapeutic preference. It has been suggested that aged garlic extract (AGE) inhibits both the formation of AGEs and glycation-derived free radicals. A key constituent of aged garlic, 'S-Allylcysteine', is an effective antioxidant and can inhibit AGE formation (Ahmad and Ahmed, 2006; Ahmad et al., 2007). Organosulfur compounds derived from garlic, diallyl sulfide, S-ethylcysteine, S-allylcysteine, and N-acetylcysteine, are known to protect LDL against oxidation and glycation and this might be a possible mechanism how garlic protects against cardiovascular disease (Ou et al., 2003). Although garlic is generally considered safe herbal remedy and has been used for many common ailments since ancient times, too much utilization of garlic may cause problems most commonly related to gastrointestinal tract like nausea and diarrhea. Garlic breath and halitosis or bad body odour are also one of the main garlic side effects reported especially when fresh garlic is ingested. Infrequent allergic response is also a known predictable adverse effect (Ackerman et al., 2001). In the present study, garlic did not produce any considerable problem in patients with type 2 diabetes mellitus and only one patient has complained of gastric discomfort, the possible reasons for this good tolerance is most likely to the enteric coated, odourless garlic tablet preparation used in this study.

Conclusion

Garlic was found to reduce fasting blood glucose and HbA1C significantly as compared to metformin and placebo and may be an effective addition in the family of antidiabetic agents. Clinical trials using garlic in combination with different antidiabetic agents are warranted to further explore the benefits of garlic in diabetics

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