Effect of Garlic Oil (Allium Sativum) on Glycaemic Control and Lipid Profile in Patients with Type 2 Diabetes Mellitus

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أثر الثوم في السيطرة على نسبة السكر في الدم و مستوى الدهون لدى المرضى المصابين بداء السكري النوع الثاني

الخلاصة : تستخدم الأدوية العشبية على نطاق واسع و هذا يعود إلى سهولة استخدامها و قلة أضرارها الجانبية وكلفتها الزهيدة. لذا تسعى الدراسات الطبية الحديثة وبشكل حثيث لدراسة هكذا ميزات متوفرة في النباتات الطبية التقليدية. يعتبر الثوم احد هذه الأعشاب الأكثر استخداما في الطب التقليدي للعديد من الشعوب لمعالجة داء السكري. يرجع الاستخدام الطبي للثوم إلى ما قبل آلاف السنين. وعند مراجعة الموروث التاريخي نلاحظ مدى الاهتمام الكبير بدور الثوم في تقليل عوامل خطر إصابة الأوعية الدموية القلبية. ولكن ليس هناك حاليا الكثير من الأدلة العلمية لدعم وجود الفعالية العلاجية والعقاقيرية للثوم.

أجريت الدراسة الحالية لتقييم تأثير الثوم على السيطرة الايضية ومظهر الدهون لدى مرضى مصابين بداء السكري النوع الثاني. لقد تم تسجيل ٥٩ مريضا يعانون من داء السكري النوع الثاني واختلال مستوى الدهون في الدم. تم إجراء سجلاً تاريخيا وفحصا سريريا للمرضى .لم يتناول أولئك المرضى أي علاج لمعالجة مرضهم فقط حمية غذائية. تمت مراقبة المرضى لمدة اثني عشر أسبوعا وتم تقسيمهم و بشكل عشوائي إلى مجموعتين. لم يعطى للمجموعة الأولى وهي مؤلفة من ٢٦ مريض أي دواء و صنفت بأنها مجموعة سيطرة. كانت المجموعة الثانية مؤلفة من٣٣ مريضا. خضعت هذه المجموعة للعلاج حيث أعطي المريض ٥٠٠ ملغم من جل الثوم الرقيق المستخلص مرتين في اليوم ولمدة اثني عشر أسبوعا و صنفت بأنها مجموعة معالجة. وصل٥٥ مريض من مجموع ٥٩ اشتركوا في هذه الدراسة بينما انسحب أربعة. أخذت عينات الدم من المرضى في بداية الاختبار وبعد اثني عشر أسبوعا من مراقبة الاختبار لقياس مستوى السكر في الدم الصائم، مستوى السكر بعد ساعتين من الأكل و مستوى الدهون. تم تقييم أيضا وظائف كلا من الكبد و الكلى. توصلت الدراسة إلى النتائج التالية:-

نقص ملحوظ وعالي في كلوكوز الدم الصائم، الكولسترول الكلي والكولسترول واطئ الكثافة ($p<0.01$)وزيادة معنوية في الكولسترول عالي الكثافة($p<0.05$) بينما أحدث كل من مستوى السكر بعد ساعتين من الأكل والكلسيريدات الثلاثية والكولسترول واطئ الكثافة جدا انخفاضا غير معنوي($p>0.05$) في المجموعة المعالجة بالثوم قبل و بعد١٢اسبوعا من المراقبة. علاوة على ذلك سبب استهلاك الثوم انخفاضا معنوياً وعالي في كلوكوز الدم الصائم، مستوى السكر بعد ساعتين من الأكل، الكولسترول الكلي والكولسترول واطئ الكثافة($p<0.01$) ونقص بارز في الكلسيريدات الثلاثية والكولسترول واطئ الكثافة جدا($p<0.05$) بينما اظهر الكولسترول عالي الكثافة زيادة معنوية ($p<0.05$) في نهاية فترة الـ١٢اسبوعا بالمقارنة مع مجموعة السيطرة.

تلخص الدراسة إلى الثوم يحدث تأثيرات ضد زيادة نسبة السكر في الدم وفي إنقاص الدهون وهذا يوصي إلى إن الثوم يمكن أن يستخدم كعقار تكميلي لمعالجة المرضى المصابين بداء السكري اختلال مستوى الدهون في الدم، مانعا لمضاعفات داء السكري.

Abstract

Herbal medicines are widely used because of their convenience, less side effects and low cost, so investigation on such agents from traditional medicinal plants has become more important in present day studies on medical sciences. Garlic is one of the most popular herbs used in the traditional medicine of many cultures for the treatment of diabetes. The medicinal use of garlic dates back to thousands of years. Historically, there has been great interest in the role of garlic in reducing cardiovascular risk factors,

but there was little scientific support of its therapeutic and pharmacologic effectiveness until recently. The present study was conducted to assess the effect of garlic on metabolic control and lipid profile in type 2 diabetic patients. Fifty nine patients with type 2 diabetes mellitus and newly diagnosed dyslipidaemia were enrolled in this study. A full history and complete physical examination was performed. Those patients were not taking any medication for the treatment of their disease a part from dietary modification and they are disease free other than diabetes. Type 2 diabetic patients were followed up for 12weeks and divided randomly into 2 groups. Group I(n=26) no drug was given and designed as diabetic control group . Group II(n=33) underwent treatment with 500mg garlic extract soft gel two times daily for 12 weeks and designated as diabetic treated group . From fifty nine patients participated in this study, fifty five patients reached the end of the study while four patients withdrew (one patient from group I and three patients group II) . Blood samples were drawn from the patients at the beginning and after 12weeks of follow up for testing fasting blood glucose, 2hours postprandial blood sugar and lipid profile including total cholesterol(TC), triglyceride(TG), low density lipoprotein(LDL-C), high density lipoprotein(HDL-C) and very low density lipoprotein(VLDL-C) . Renal and liver functions were also assessed . This study revealed the following results: fasting blood glucose, TC and LDL-C were highly significantly reduced (p<0.01) and HDL-C was significantly increased (p<0.05) while 2hours postprandial blood glucose, triglyceride and VLDL-C show insignificant reduction (p>0.05) in garlic treated group before and after 12weeks of follow up . Furthermore, garlic consumption caused a highly significant reduction (p<0.01) in fasting blood glucose, 2hours postprandial blood sugar, total cholesterol and LDL-C and a significant decrement (p<0.05) in triglyceride and VLDL-C whereas HDL-C revealed a significant increment (p<0.05) at the end of 12weeks in comparison to dyslipidaemic diabetic control group . In conclusion, garlic exerts anti-hyperglyaemic and lipid lowering effects, suggesting that garlic could be used as a supplementary drug for the treatment of patients with diabetes and dyslipidaemia preventing diabetic complications.

Key Words: Type 2 diabetes mellitus, dyslipidaemia and garlic.

Introduction

Diabetes mellitus is a global disease, prevails all over the world, though the prevalence rate differs from country to country[1]. Diabetes, a disorder of carbohydrate metabolism, is characterized by high blood glucose level and glycosuria resulting from dysfunction of pancreatic beta cells and insulin resistance . In advance stages of diabetes, metabolism of protein and lipid is also altered[2]. Many factors like heredity, age, obesity, diet, sex, sedentary life style, socio-economic status and various stresses are involved in the etiology of diabetes mellitus[3]. Patients with type 2 diabetes have a two-fold to four-fold excess risk of coronary artery disease as compared to non-diabetic patients[4] and many of the primary risk factors for coronary artery disease frequently coexisting in this patient population . High blood cholesterol is one of the major modifiable risk factor for coronary heart disease[5,6] . Type 2 diabetes is associated with dyslipidaemia characterized by increased plasma triacylglycerol, reduced HDL cholesterol, and an increased number of small dense LDL particles . This atherogenic lipoprotein profile probably contributes to the very high cardiovascular risk of type 2 diabetic patients[7]. Thus type 2 diabetes mellitus is characterized by premature

accelerated atherosclerosis development leading to invalidization and high mortality in this category of patients[8]. Hyperglycaemia, a characteristic feature of diabetes, predispose to vascular complications[9]. So, proper metabolic control of hyperglycemia and dyslipidemia is needed to prevent late complications of diabetes[10]. Non pharmacological intervention (dietary and lifestyle modification) are first line therapy and are used with pharmacological therapy when necessary[11]. Lipid lowering drugs used for treating high-risk persons include 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, statins . None of these pharmacological options are free of adverse effects and some have been associated with potential carcinogenicity. A harmless yet effective therapy for lowering cholesterol levels would therefore be of considerable interest[12]. There has been an increasing recognition that certain natural substances have the potential to reduce the detrimental effect of a number of cardiovascular risk factors. The use of natural substances has become more widespread over the past few years, driven undoubtedly by the belief that natural substances may have fewer side effects than do pharmaceuticals .Garlic is an example of such natural substances that have been claimed to possess beneficial effects for the presentation of various aspects of cardiovascular disease[13,14] . Garlic (Allium sativum) is a member of the Liliaceae family is one of the most popular herbs used worldwide[15] . Actually, garlic contains a variety of effective compounds that exhibit anticoagulant (anti-thrombotic)[16] , antioxidant[17], antibiotic[18], hypocholesterolaemic and hypoglycaemic as well as hypotensive activities[19,20]. Garlic flavor is due to the formation of organosulfur compounds when the main odorless precursor, alliin, is converted by the enzyme alliinase. This occurs at low rates unless the garlic cloves are crushed or damaged. The main compound formed by this reaction is a thiosulfinate, allicin, the compound responsible for the characteristic odor and flavor of fresh garlic. Allicin is considered the most important biologically active compound in garlic, a safe compound which contributes heavily to the health benefits of garlic since it decomposes to other sulfur containing molecules (thiosulfonates and disulfides) which have purported activity in the human and model systems under investigation[21,14] . The alliin content of natural garlic may vary 10-fold, the quantity of allicin released can be influenced by specific extraction methods[14]. Most of the studies showed that garlic can reduce blood glucose levels in diabetic mice, rats and rabbits[22]. Augusti consistently showed that garlic had a potential to reduce the diabetic condition in rats almost to the same extent as did glibenclamide and insulin [23]. Though many clinical trials showed a positive effect of garlic on hyperlipidemia[24,25] however a number of negative studies[26,13] have cast doubt on the efficacy of garlic specially its cholesterol lowering effect . In humans, the hypoglycaemic effect of garlic is not well studied while many reporters have shown a significant effect of garlic on blood glucose in normal individuals but not in diabetic patients. Thus the role of garlic on blood sugar in diabetes in humans is yet to be confirmed[14] . As previous clinical trials have cast doubt on the proposed lipid lowering effects of garlic and there is no previous trial showing the effects or benefits of garlic on hyperlipidemia in patients with diabetes and also keeping in mind the incidence of hyperlipidemia that is quite high in Iraq and a wide spread belief among general public that garlic has beneficial effects on cardiovascular system, we designed a study to evaluate the hypolipidemic and hypoglycaemic effects of garlic in patients with type 2 diabetes mellitus .

Patients, material and methods

A total of fifty nine patients (mean age: 42.33±2.78 years; 32 men and 27 women) with type 2 diabetes mellitus (mean fasting blood glucose 9.34±0.52mmol/l), with a mean duration of diabetes from the time of diagnosis was 2.96±1.30 years and a newly diagnosed dyslipidaemia (mean LDL-C level 4.71±0.17mmol/l) were participated in this study. The patients were selected randomly from diabetics attending Al-Najaf Center for Researches and Treatment of Diabetes Mellitus and Endocrine Glands in Directorate of Al-Sadr Teaching Medical City in Al-Najaf Governorate in the period between 1st June to 1st Dec. 2010. These patients underwent full history and complete physical examination. The patients were previously diagnosed according to World Health Organization of diabetes as fasting blood glucose ≥7.0mmo/l or 2 hours post load plasma glucose ≥11.1mmol/l . A verbal consent were taken from each participant and the study was approved by Kufa Medical College Ethical Committee . Patients with the following criteria were excluded from the study: history of allergy to garlic, pregnant or lactating women, history of myocardial infarction, proven coronary artery disease, unstable angina, those with bleeding disorder or taking anticoagulant, hepatic dysfunction and impaired renal function[27] . Those patients were not taking any medication for the treatment of their disease a part from dietary modification and they are disease free other than diabetes . According to the design of the study, type 2 diabetic patients were followed up for 12weeks and divided randomly into 2 groups . Group I(n=26) no drug was given and designed as diabetic control group . Group II(n=33)underwent treatment with 500mg odorless garlic extract soft gel (Erlic® Vitane Pharmaceuticals Inc., Costa Mesa 92626-5918. California, USA) two times daily preferably with meals for 12 weeks[28] and served as diabetic treated group . The patients were put on diet regimen and followed every four weeks during the time of the study in order to make sure that they were using the medication properly and to supply the drug to the patients . Four ml of venous blood specimen were drawn from each patients enrolled in this study in the laboratory department of Al-Sadr Medical City before and after 12weeks of follow up following at least 12-14 hours over night fast between 8:30-10:00 a.m. for determination of fasting blood glucose and lipid profile . Then the patients allowed to eat and 2 hours after 1ml of blood specimen were taken for calculation of 2hrs postprandial blood glucose. Renal and hepatic functions were also assessed. The blood was put in plain tubes and allowed to clot at 37C$^{°}$ for 10mints and the serum sample prepared following centrifugation at 3000 rpm for 15mints and then analyzed for determination of blood tests . blood glucose was measured by procedure supplied by Biolabo company France kit[29]. Total cholesterol, Triglyceride and HDL-C were calculated according to procedures supplied by BioMerieux company France kits[30].Serum LDL-C and VLDL-C were calculated according to the Friedwald equation:

LDL-C= Total cholesterol – (HDL-C + VLDL-C). VLDL-C= Triglyceride/ 2.2[31].

Statistical analysis: The data were expressed as mean± Standard deviation. Paired t-test was used to compare the difference between pre and post treatment of each group . Independent t-test was used to compare the difference between diabetic treated and control groups . Statistical analysis were done by using computer program(SPSS)version 10. In all tests P value <0.05 was considered to be statistically significant.

Result

Baseline demographic and biochemical characteristics of diabetic treated and control groups. From fifty nine patients included in this study, fifty five patients completed the test while four patients withdrew (one patient from group I and three patients group II) because of GIT upset and for unknown reason. There was no statistical significant difference (p>0.05) in the baseline demographic and biochemical characteristics regarding the age, sex, duration, body mass index(BMI), fasting blood glucose, 2 hours postprandial blood glucose, total cholesterol, triglyceride, HDL-C, LDL-C and VLDL - C. Table-1.

Table-1: Baseline demographic and biochemical characteristics of treated and control diabetic groups.

Parameters	Diabetic control n=25	Garlic n=30
Age years	42.24±2.6814	42.4±2.8959
Sex(male/female)	14/11	17/13
Duration years	2.96±1.2069	2.9667±1.406
BMI	27.3±0.71	27.4±0.64
FBS mmo/l	9.3119±0.516	9.361±0.5272
2hrs pp mmol/l	16.9282±1.9972	15.9794±3.3111
TC mmol/l	6.792±0.1571	6.772±0.1606
TG mmo/l	2.8596±7.071	2.8485±6.370
HDL-C mmol/l	0.7708±6.178	0.7701±6.662
LDL-C mmol/l	4.7215±0.1541	4.7028±0.1769
VLDL-C mmol/l	1.2998±3.215	1.2947±2.896

P>0.05 .
Values are expressed as mean±SD.

Effect of garlic (500mg) two times daily on glycaemic control and lipid profile at the beginning and after 12 weeks of follow up and changes in dyslipidaemic diabetic control.

Fasting blood glucose, total cholesterol and LDL-C were highly significantly reduced (p<0.01) and HDL-C was significantly increased (p<0.05) while 2hours postprandial blood glucose, triglyceride and VLDL-C show insignificant reduction (p>0.05) in garlic treated group . Furthermore, there were insignificant changes (p>0.05) in fasting blood glucose, 2hours postprandial, total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C in dyslipidaemic diabetic control group . Table-2 .

Table-2: Biochemical parameters at the start and after 12wks of treatment with garlic (500mg) two times daily and changes in dyslipidaemic diabetic control group.

Parameters	Diabetic control n=25		Garlic n=30	
	Before treatment	After Treatment	Before treatment	After treatment
FBS(mmol/l)	9.3199±0.5159	9.4809±0.6894[*]	9.3610±0.5272	8.0416±0.3575[***]
2hs pp(mmol/l)	16.9282±1.9972	17.0114±2.0471[*]	15.9794±3.3111	14.8471±2.9714[*]
TC(mmol / l)	6.7920±0.1571	6.7413±0.2195[*]	6.7720±0.1606	5.9993±0.1689[***]
TG(mmol / l)	2.8596±7.0710	2.8815±6.6900[*]	2.8485±6.3700	2.8428±5.7700[*]
HDL(mmol /l)	0.7708±6.1780	0.7697±6.7920[*]	0.7701±6.6620	0.8064±5.5150[**]
LDL(mmol /l)	4.7215±0.1541	4.6618±0.2300[*]	4.7028±0.1769	3.9009±0.1793[***]
VLDL(mmol/l)	1.2998±3.2150	1.3097±3.0420[*]	1.2947±2.8960	1.2920±2.6070[*]

[*]P>0.05 .N.S .
[**]P<0.05 .
[***]P<0.01 .
Values are given as mean±SD.

Effect of garlic (500mg) two times daily on metabolic control and lipid profile at the last of 12 weeks of follow up in comparison to dyslipidaemic diabetic control group.

There was a highly significant reduction ($p<0.01$) in fasting blood glucose, 2hours postprandial blood glucose, total cholesterol and LDL-C and a significant decrement ($p<0.05$) in triglyceride and VLDL-C whereas HDL-C showed a significant increment ($p<0.05$) in garlic treated group in comparison to dyslipidaemic diabetic control group . Table-3.

Table-3: Effect of garlic (500mg) two times daily on glycaemic control and lipid profile at the end of 12 weeks in comparison to dyslipidaemic diabetic control group.

Parameters	Diabetic control n=25 End of 12wks	Garlic n=30 End of 12wks
FBS(mmol/l)	9.4809±0.6894	8.0416±0.3575[**]
2hs pp(mmol/l)	17.0114±2.0471	14.8471±2.9714[**]
TC(mmol / l)	6.7413±0.2195	5.9993±0.1689[**]
TG(mmol / l)	2.8815±6.6900	2.8428±5.7700[*]
HDL(mmol /l)	0.7697±6.7920	0.8064±5.5150[*]
LDL(mmol /l)	4.6618±0.2300	3.9009±0.1793[**]
VLDL(mmol/l)	1.3097±3.0420	1.2920±2.6070[*]

[**]$P<0.01$.
[*]$P<0.05$.
Values are expressed as mean±SD.

Percentage changes with garlic(500mg) two times daily from week 0 to week 12 on lipid profile in patients with type 2diabetes.
Garlic reduced total cholesterol by (-11.4%), TG by(-0.2%), LDL-C by(-17.05%), VLDL-C by(-0.28%) and increased HDL-C by(+4.7%) Figure-1 .
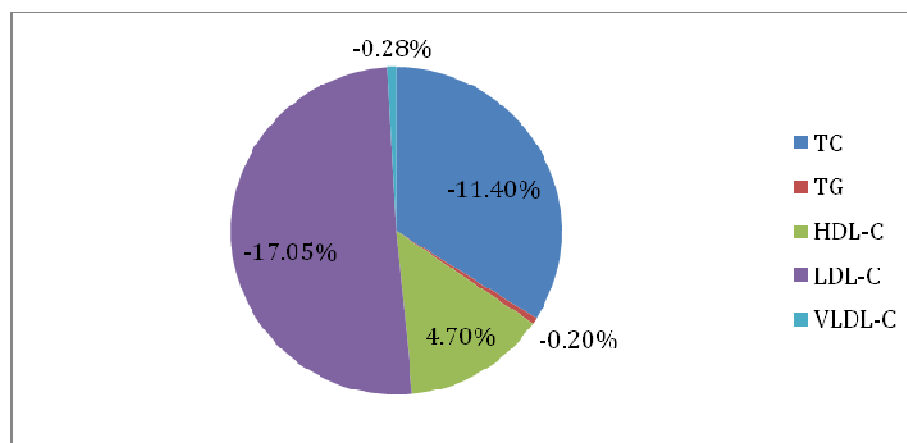

Figure-1: Percentage changes with garlic at the beginning and at the end of study on lipid profile .

Percentage changes with garlic (500mg) two times daily on fasting and 2hours postprandial blood glucose in patients with type 2diabetes from week 0 to week 12.
Garlic reduced fasting blood glucose by (-14%) and 2hours postprandial glucose by(-7%)Figure-2.
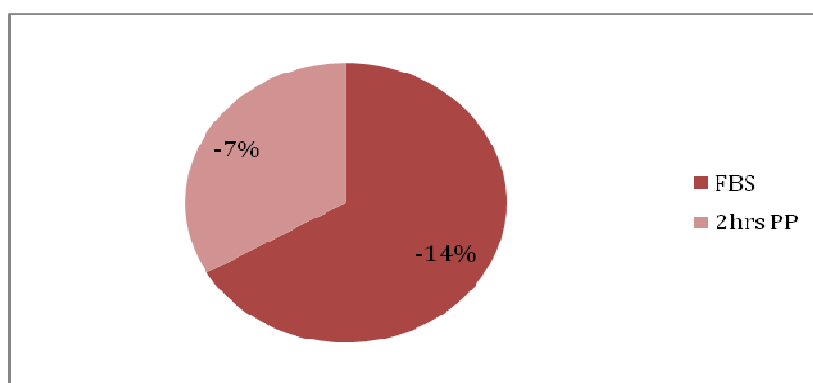
Figure-2: Percentage changes with garlic on fasting and 2hours postprandial blood glucose at the start and at the last of study .

Discussion

Diabetes mellitus is a severe health problem and the prevalence of diabetes keeps increasing markedly due to an aging population, increased urbanization and more sedentary lifestyles[32]. Many traditional plants treatments have been recommended in the alternative system of medicine for treatment of diabetes and garlic is one example of herbals used but most of the evidence for their beneficial effects is anecdotal[33]. Many studies, mostly short term, have investigated the hypoglycaemic and hypolipidaemic effect of garlic. Results were conflicting, ranging from a non-detectable to a statistically significant effect[34,35]. These differences may be attributable to various causes, such as differences in study design (not all were randomized, double-blind placebo-controlled) and in characteristics of the participants (especially with regard to lipid profile, dietary modification, and compliance). Another possible confounder is the type of garlic preparation used (aged garlic extracts, dehydrated powdered garlic, steam-distilled garlic oil), which could yield different amounts of the active compound. It could, also, be that the decreased sample size and biological variation would be behind this[13]. Our study showed significant differences between fasting blood glucose and 2hours postprandial glucose level after garlic consumption in comparison to control group . Moreover, fasting blood glucose significantly lowered and 2hours postprandial blood glucose reduced in-significantly before and after garlic consumption . Our results were in accordance with Igor A. *et al* [8], Eidi A. *et al* [56], Al-Qattan K. *et al* [37] and Mahesar H. *et al* [14]. Contrary findings were reached by Mohammad A. *et al* [2], Jain AK. *et al* [38] and Mansell P. *et al* [28] who concluded that garlic had no effect on blood sugar. Although there are suggestions about the hypoglycaemic effect of garlic, the exact mechanism is unclear . Garlic may act on blood glucose through different mechanisms, the presence of insulin-like substances (flavonoids and allyle propyl disulphide or diallyle disulphide) in garlic and therefore directly reduce blood glucose levels by stimulating glycogenesis and inhibiting gluconeogenesis and glycogenolysis in hepatic and muscle cells[39], stimulation of beta-cells to produce more insulin and others may increase beta-cells in the pancreas by activating regeneration of these cells or due to an increase in the insulin response[40,41]. The fiber of garlic may also interfere with carbohydrate absorption; thereby affecting blood glucose[33]. The present study demonstrated significant differences in lipid profile after garlic consumption in comparison to control group whereas total cholesterol, LDL-C reduced significantly, HDL-C increased significantly and triglyceride with VLDL-C decreased in-significantly at the beginning and at the end of garlic consumption. Our results were coincides with Mansell P. *et al* [28], Siegel *et al* [42], Tohidi M. *et al* [25]. Conflicting results were obtained by Ariela Peleg MA. *et al* [13] , Stevinson C. *et al* [43] and Isaacsohn JL. *et al* [44] who reported that garlic produces in-significant effect on lipid profile . The cholesterol-

lowering effect of garlic is attributed to the bioavailability of allicin and its derivatives[13]. It is also reported that this is due to antioxidant property of the garlic which decrease the free radicals and resulting in lipid oxidation inhibition[19]. The lipid lowering effect of garlic may be due largely to the action of s-allyl cystein (SAC) and di-allyl-di sulfide (DADS) present in garlic . These ingredients are potent inhibitors of mono-oxygenase enzyme. Inhibition of mono-oxygenase enzyme inhibits cholesterol synthesis[45]. The lowering effect of garlic on cholesterol may also be attributed to the fact that garlic increases the excretion of cholesterol . Furthermore, garlic depresses the hepatic activities of lipogenic and cholesterogenic enzymes, such as malic enzyme, fatty acid synthase, glucose 6-phosphate dehydrogenase (G6PD) and hydroxyl methylglutaryl-CoA reductase (HMG-CoA reductase) [46] . Garlic may also suppress LDL-C oxidation[47] and delayed lipid absorption from the GI tract [2]. Based on the results of this study, we conclude that, garlic possesses hypoglycaemic and hypolipidaemic properties and may allow recommending garlic for the treatment of type 2 diabetes mellitus along with dietary regimen and/or oral hypoglycaemic agents to achieve better metabolic control and to a greater extent, could be useful in preventing diabetic complications.

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