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Original article

Effects of dietary garlic supplements on serum lipid profiles, LDL oxidation and weight gain in Western diet-fed rats

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Summary. *Background/Objective:* Garlic (*Allium sativum)* has beneficial effects on hypercholesterolemia associated with cardiovascular disease. However, some studies have failed to support the favorable effect of garlic on blood lipid levels. This study was designed to investigate the effect of garlic intake on serum lipids, lipoprotein profiles, low-density lipoprotein (LDL) oxidation and weight gain in rats fed a Western-style diet containing high proportions of fat, cholesterol and refined sugars. *Methods:* A total of 32 male *Wistar* rats were divided into four groups and fed one of the following diets for 14 weeks: chow diet (normal control group), Western diet (Western diet control group, WDC) and Western diet including 5% (WD-5G) or 10% garlic (WD-10G). *Results:* The Western diet significantly increased total cholesterol, LDL cholesterol, non-high-density lipoprotein (non-HDL) cholesterol, atherogenic index and LDL/HDL ratio, and lowered HDL, in comparison to the normal control group. LDL oxidation was increased by the Western diet, and greater differences were observed in group WD-5G vs. group WD-10G. Total cholesterol, LDL cholesterol and non-HDL cholesterol were significantly higher in group WD-10G than in group WDC. Weight gain was significantly lower in both garlic supplementation groups. *Conclusion:* Our data do not support the beneficial effects of garlic on serum LDL oxidation and lipid profile in rats fed a Western diet. Dietary pattern may be an important factor that influences the atheroprotective properties of garlic.

Key words: garlic, body weight, atherogenesis, lipoproteins, oxidized low density lipoprotein, rats

Introduction

Atherosclerosis-related diseases are a major cause of mortality worldwide, especially in developed countries (1). Dyslipidemia is characterized by increased blood levels of total or low-density lipoprotein (LDL) cholesterol and triacylglycerols (TAG), or decreased high-density lipoprotein (HDL) cholesterol levels, and is a risk factor for atherosclerosis. Oxidized LDL, but not native LDL, promotes vascular dysfunction by exerting direct cytotoxicity on endothelial cells, increasing the chemotactic properties of monocytes, transforming macrophages into foam cells, and enhancing the proliferation of endothelial cells, monocytes and muscle cells (2). The Western-style diet frequently contains excessive saturated and trans fatty acids and added sugars, which result in a high glycemic load (3). This foments a proatherogenic blood profile characterized by elevated TAG and small-dense LDLs, while reducing HDL cholesterol and thereby increasing the risk of cardiovascular disease (CVD) (4).

Many patients are turning to alternatives to pharmacotherapy to manage their lipid levels (5). Garlic (Allium sativum) is currently one of the most intensively researched ingredients in herbal medicines, and is the second most widely used complementary therapy for heart disease (1). Epidemiologic studies show an inverse correlation between garlic consumption and progression of CVD (6, 7). Garlic has been shown to inhibit enzymes involved in lipid synthesis, decrease platelet aggregation and prevent the lipid peroxidation of oxidized erythrocytes and LDL. In addition, garlic enhances antioxidant status and inhibits angiotensin-converting enzyme (8). These findings have been further tested in some clinical trials (9, 10).

Sulfur compounds, including allicin, appear to be the active components in the root bulb of the garlic plant (11). Lee et al have shown these compounds to have modest but significant lipid-lowering effects and antiplatelet activity (12), and another *in vitro* study demonstrated that garlic compounds can suppress LDL oxidation (13). A small-scale human study supported the ability of garlic supplementation to increase the resistance of plasma LDL to copper-induced oxidation. Suppressed LDL oxidation may be one of the mechanisms that accounts for the beneficial effects of garlic on cardiovascular health (14).

Hoewer, numerous animal and human trials have reported that garlic treatment does not affect plasma lipids (15-20). Studies in pigs and rats found that garlic had no effect that could be interpreted as interfering with atherosclerotic lesions (21). Van Doom et al. showed that 12 weeks of treatment with garlic powder had no lipid-lowering effect in a normolipidemic population with known risk factors for CVD (22). Randomized clinical trials in which the participants had moderate hypercholestrolemia confirmed that garlic therapy had no effect on plasma lipoproteins (23, 24). These conflicting data may be due to differences among studied in the animal models, garlic preparations, garlic-derived materials, the study sample (normolipidemic vs. hyperlipidemic), cholesterol feeding (25) and probably dietary pattern.

The aim of the present study was to evaluate the effect of crushed raw garlic on the levels of serum lipids, LDL oxidation and their concomitant effects on body weight in rats fed a Western-style diet (WD).

Materials and methods

Animals

Male *Wistar* rats (mean body weight 208 ± 27 g) were purchased from the Institute Pasteur (Tehran, Iran). The rats (n = 32) were randomly divided into four groups of 8 animals each, and were fed one of the following diets: chow diet (normal control group, C), Western diet (Western diet control group, WDC), or a modification of TestDiet 5TJT, i.e. WDC supplemented with 5% (WD-5G) or 10% crushed raw garlic (WD-10G). Food and water were provided ad libitum throughout the acclimation and experimental periods. The animals were acclimatized to the animal room conditions and were maintained at 22°C ± 2°C with a 12-h light/dark cycle for 14 weeks. Body weight was recorded once a week, and the amount of food eaten and were measured every 2 days. Feeding efficiency was calculated as body-weight gain (g)/energy intake (kcal).

All experiments were designed in accordance with the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication, No. 86-23, revised 1996) and approved by the Animal Experimentation Ethics Committee of Hamadan University of Medical Sciences, Iran.

Diets

The Western diet was designed according to the standard high-cholesterol (%1) Western diet diet (TestDiet 5TJT). First, dry powder was mixed slowly for 15 min with an electric mixer (Dito Electrolux, France). Garlic was purchased at a local grocery shop, and peeled raw garlic cloves were crushed in a blender for 10 min. Subsequently, fatty oils and an appropriate amount of fresh crushed garlic were added to the powder mixture and mixed for 15 min. To avoid auto-oxidation of the fat components, the food was stored at 4°C.

The chow diet was formulated to provide adequate growth in rats according to the manufacturer's information, and consisted of 21% crude protein, 5.5% crude fiber, 4.5-5.1% crude fat, 0.5% NaCl, 0.7% mineral mixture (manganese, zinc, iron, copper, cobalt and selenium) and vitamins (B2, B1, K, E, D3, A), with a

Table 1. Nutrient profile of the diets

	Groups			
	Chow diet (C)	**Western diet control (WDC)**	**Western diet 5% garlic (WD-5G)**	**Western diet 10% garlic (WD-10G)**
Macronutrients				
Calories from				
Protein (%)	33.9	33.9	14.96	14.27
Carbohydrate (%)	52.6	52.6	42.81	42.46
Fat (%)	13.5	13.5	42.23	43.27
Ingredients				
(per 1000 g of diet)	(g)	(g)	(g)	(g)
Chow diet	1000	677	627	577
Sucrose	0	173	173	173
Milk fat (anhydrous)	0	83	83	83
Hydrogenated vegetable oils	0	40.5	40.5	40.5
Soybean oil	0	8.5	8.5	8.5
Cholesterol[1]	0	10	10	10
Sodium cholate[1]	0	8	8	8
Garlic	0	0	50	100

[1] *Sigma Aldrich*

total energy of 2547 kcal./kg diet (Rodent Diet, Javaneh, Khorasan, Iran). The nutrient profile and ingredients of the diets are shown in Table 1.

Serum preparation and laboratory tests

After 14 weeks of feeding with the control and experimental diets, the rats were deprived of food and water for 12 h, and then anesthetized with 75 to 100 mg/kg intraperitoneal ketamine (Rotex Media, Germany). The heart, liver and fat pads were removed and weighed. The liver index was calculated as liver weight/body weight × 100. Blood samples were taken from the superior vena cava, allowed to clot for 2 h at room temperature, and then centrifuged in a cooled centrifuge for 20 min. Each serum sample was transferred to special microtubes and stored at –80°C. Triacylglycerols were measured with the glycerol-3-phosphate oxidase method using a commercial kit (Pars Azmoon, Iran). Total cholesterol was measured with the cholesterol oxidase method (Pars Azmoon). Serum HDL- and LDL-cholesterol levels were measured with standard enzymatic techniques (Pars Azmoon). The atherogenic index (AI) was calculated as (total cholesterol – HDL)/HDL (25). Serum LDL oxidation was measured with an ELISA method using a commercial kit (Life Sciences Advanced Technologies Co., UK).

Statistical analysis

The data are reported as the mean ± standard deviation (SD). One-way analysis of variance ANOVA (LSD multiple range method) was used to detect associations in the results among different groups of animals. All statistical analyses were done with SPSS v. 16.0 software (SPSS, Inc., Chicago, IL, USA). P values of 0.05 or less were considered statistically significant.

Results and Discussion

The lipid profiles in the four groups of rats are shown in Table 2. The levels of total cholesterol, LDL, non-HDL cholesterol, AI and LDL/HDL ratio were significantly higher and HDL was significantly lower in rats fed the Western diet than in the normal control group. Total cholesterol level in groups WD-5G and WD-10G, and LDL and non-HDL cholesterol in group WD-10G, were significantly higher than in group WDC. TAG level did not differ significantly among the four groups. The effect of garlic on lipid profiles has been investigated in several clinical trials and summarized in numerous metaanalyses (18, 19, 27). Many clinical trials (10, 11, 28) showed a positive effect of garlic in almost all cardiovascular conditions;

Table 2. Serum lipid profiles, atherogenic index and LDL/HDL level after 14 weeks in rats in different groups[a,b]

	TAG Cholesterol (mg/dl)	Total Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)	Non-HDL index (mg/dL)	Atherogenic	LDL/HDL
Normal control chow diet, C)	66.29 ± 18.33	68.94 ± 7.40	39.94 ± 2.69	17.45 ± 2.63	29.0 ± 6.45	0.73 ± 0.16	0.44 ± 0.07
Western diet control (WDC)	63.88 ± 17.97	134.94 ± 32.28**	21.63 ± 6.02***	76.33 ± 18.14**	113.15 ± 31.53***	5.75 ± 2.46**	3.78 ± 1.23**
5% Garlic (WD-5G)	72.00 ± 20.77	178.40 ± 31.58$^{***¥}$	25.25 ± 9.53***	105.50 ± 23.90***	153.15 ± 31.04 ***	7.35 ± 4.90***	5.15 ± 3.68***
10% Garlic (WD-10G)	65.00 ± 21.20	211.06 ± 42.70$^{***¥¥}$	27.90 ± 6.65**	131.96 ± 29.05$^{***¥¥}$	182.72 ± 41.74$^{***¥¥}$	6.73 ± 2.13***	4.87 ± 1.50***

[a]C, normal control group fed the chow diet; WDC, control group fed the Western diet; WD-5G, group fed the Western diet containing 5% garlic; WD-10G, group fed the Western diet containing 10% garlic. [b]All values are means ± SD of 8 rats/diet. **P < 0.01, ***P < 0.001 versus normal control; $^{¥}$P < 0.05, $^{¥¥}$P < 0.01 versus Western diet control

however, a number of negative studies have recently cast doubt on the efficacy of garlic, in particular regarding its cholesterol lowering effect (18, 23, 29, 30). In a metaanalysis of 13 trials, garlic therapy did not produce any statistically significant reduction in the serum level of total cholesterol, LDL-cholesterol, triglycerides or apolipoprotein B, and there was no difference between garlic and the placebo in the effect on HDL-cholesterol level (29). Some *in vivo* clinical studies showed that garlic had no cholesterol-lowering effect (All references in 31). Similarly, in animal models that used feeding with a Western diet, garlic supplementation for 28 weeks did not affect plasma lipids or anti-atherosclerotic properties (25). Santo and colleagues, in a similar study, observed that garlic-derived sulfur-rich compounds or consuming garlic powder for 8 weeks had no consistent effect on lipoprotein profiles (32). The major difference among the studies lies in the type of animal diet. With reference to the results of the present study, future research should investigate the role of garlic combined with refined sugars and saturated lipid diets in hyperlipidemia. Hence, dietary patterns may be a mechanistic explanation for the differences in response to garlic among rats in these studies.

Western diet we used here affected LDL oxidation level, which was significantly higher in group WD-5G than in normal control rats. Unlike 5% garlic (group WD-5G), 10% garlic (group WD-10G) did not lead to a significant increase in LDL oxidation (Fig. 1).

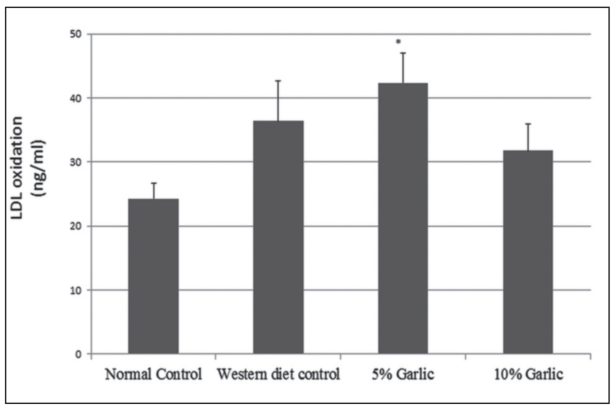

Figure 1. Serum LDL oxidation level in rats fed the chow diet (normal control), Western diet (Western diet control), Western diet containing 5% garlic (5% garlic) or Western diet containing 10% garlic (10% garlic). Rats were randomly divided into four groups of 8 animals each and fed the diet for 14 weeks. Data are presented as the mean ± SD of 8 rats. **P* < 0.05 versus normal control.

Several short-term *in vitro* studies have demonstrated that garlic compounds can suppress LDL oxidation (33). Orekhov and Grunwald suggested that the four organosulfur compounds derived from garlic are potent agents that protect LDL against oxidation (34). A few small-scale human studies support the ability of garlic supplementation to increase the resistance of plasma LDL to oxidation (35, 36). Ide and Lau showed that preincubation of endothelial cells with the extract of S-allylcysteine prevented membrane damage, loss

Table 3. Body weight, weight gain, food intake, energy intake and feeding efficiency after 14 weeks in rats in different groups[a, b]

	Body weight (g)		Weight gain (g)	Food intake (g/rat/day)	Total energy intake (kcal/rat/day)	Feeding efficiency (g/kcal)
	Final	Initial				
Normal control (chow diet, C)	216.8 ± 14.4	333.5 ± 49.6	116.8 ± 49.9	19.59 ± 1.18	48.44 ± 2.91	2.45 ± 1.05
Western diet control (WDC)	205.5 ± 31.1	357.9 ± 11.1	152.4 ± 33.5*	18.59 ± 0.03**	69.05 ± 0.13***	2.25 ± 0.49
5% Garlic (WD-5G)	206.8 ± 33.3	315.4 ± 38.5¥	108.6 ± 15.5¥	17.68 ± 0.51***¥	64.68 ± 1.86***	1.72 ± 0.26**
10% Garlic (WD-10G)	204.2 ± 30.6	307.2 ± 31.7¥	103.0 ± 13.8¥¥¥	17.03 ± 0.66***¥¥¥	61.61 ± 2.37***	1.71 ± 0.29**

*[a]C, normal control group fed the chow diet; WDC, control group fed the Western diet; WD-5G, group fed the Western diet containing 5% garlic; WD-10G, group fed the Western diet containing 10% garlic. [b]All values are means ± SD of 8 rats/diet. *P < 0.05, **P < 0.01, ***P < 0.001 versus normal control; ¥P<0.05, ¥¥¥P<0.001 versus Western diet control*

of cell viability and lipid peroxidation (37). Another study, however, found that garlic had no demonstrable effect on either the susceptibility or resistance of LDL to oxidation (38). The reason for this discrepancy may be the use of unrealistically high concentrations of garlic-derived materials in the *in vitro* studies, while the *in vivo* dose of garlic in the diet was lower.

All animals that received dietary garlic supplementation gained significantly less body weight than the Western diet control group (Table 3). In rats fed the Western diet, body weight increased more than in control animals fed a chow diet and rats fed the Western diet supplemented with garlic (Table 3 and Fig. 2). The lowest body weight was seen in the group fed the Western diet containing 10% garlic. However, the levels of total energy intake did not differ significantly among groups WDC, WD-5G and WD-10G. Dietary treatment with 5% or 10% garlic led to significantly lower feeding efficiency compared to the normal control group (Table 3). Garlic supplementation also resulted in smaller gains in body weight independently of total energy intake, and associated with decreased feeding efficiency. Experimental studies by Santo et al. (25) and Lee et al. (39) yielded similar results. Moreover, Elkayam and colleague observed lower body weights in rats fed allicin, an active compound from garlic (40). The disposal of fatty acids and energy via feces can at least partly explain why garlic-based substances induced weight reduction (25, 41). Another reason may be the downregulation of adipogenic gene expression in adipose depots together with the up-regulation of the expression of uncoupling proteins in brown adipose tissue and metabolically active tissues and organs for fat oxidation (41, 42). Lee et al. suggested that the anti-obesity effects of garlic were probably mediated via activation of AMP-activated protein kinase (AMPK), which increases thermogenesis and decreases the expression of multiple genes involved in

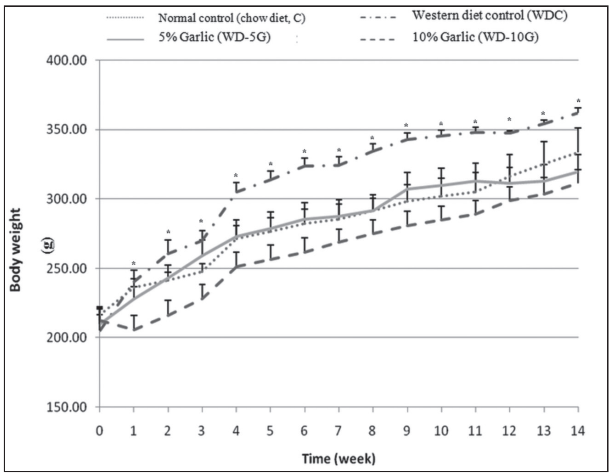

Figure 2. Body weight gain in male *Wistar* rats during 14 weeks of feeding with chow diet (normal control, C), Western diet (Western diet control, WDC), Western diet containing 5% garlic (WD-5G) or Western diet containing 10% garlic (WD-10G). Rats were randomly divided into four groups of 8 animals each for 14 weeks. The rats were given free access to tap water and diets, and were weighed at the end of every week. Data are presented as the mean ± SEM of 8 rats in each group. *P < 0.05 WDC versus WD-10G

Table 4. Liver weight, liver index, heart weight and body fat weight after 14 weeks in rats in different groups[a,b]

	Liver weight (g)	Liver index %	Heart weight (g)	Fat pad weight(g)		Total epididymal and retroperitoneal pad fat (g)
				Epididymal	Retroperitoneal	
Normal control (chow diet, C)	10.18 ± 1.84	3.04 ± 0.15	1.13 ± 0.15	2.93 ± 1.09	2.07 ± 0.74	5.00 ± 1.65
Western diet control (WDC)	20.95 ± 2.80***	5.86 ± 0.78***	1.18 ± 0.11	3.66 ± 1.27	3.00 ± 1.91	6.66 ± 3.16
5% Garlic (WD-5G)	17.58 ± 1.55$^{***¥¥}$	5.66 ± 0.88***	1.05 ± 0.14	3.28 ± 1.11	2.74 ± 1.09	6.02 ± 1.88
10% Garlic (WD-10G)	18.86 ± 2.40***	6.18 ± 0.87***	1.17 ± 0.16	3.45 ± 0.84	2.83 ± 1.03	6.28 ± 1.55

[a]*C, normal control group fed the chow diet; WDC, control group fed the Western diet; WD-5G, group fed the Western diet containing 5% garlic; WD-10G, group fed the Western diet containing 10% garlic.* [b]*All values are means ± SD of 8 rats/diet.* ****P < 0.001 versus normal control;* $^{¥¥}$*P < 0.01 versus Western diet control*

adipogenesis (39). Taken together, these results suggest that adding garlic to the daily diet may be effective in weight management and preventing obesity.

As detailed in Table 4, liver weight and liver index increased significantly in all three experimental groups compared to the normal control group. Heart, epididymis and retroperitoneal fat pad weights were higher in rats fed with WD, especially WDC. However, the differences were not significant. Previous studies showed that a Western diet can induce fatty liver via the fructokinase-dependent pathway (43). Together, these results suggest that the effect of a Western diet on increased fat accumulation in the liver favors the development of mitochondrial dysfunction and metabolic syndrome (44), and garlic supplements did not prevent these changes in the absence of dietary correction.

Conclusion

The present study investigated the anti-atherosclerotic effects of raw crushed garlic in rats fed a Western diet. Dietary supplementation with garlic had no beneficial effects on serum TAG or the increased serum total cholesterol, LDL and non-HDL cholesterol in rats fed a Western diet. Serum levels of HDL, AI and LDL/ HDL were not affected by garlic. We also observed smaller gains in body weight in rats fed a Western diet supplemented with 5% or 10% crushed garlic. Dietary patterns may play an important role in the difference in response to garlic in different groups of rats in this study.

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Conflict of interest

The authors have declared that there is no conflict of interest.

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