

A placebo control double blind study of effects of atorvastatin + allium hirtifolium on carotid intima media thickness

Seyed Ali Mousavi¹, Ahmad Chitsaz², Suzan Rahimi³,
Mustafa Ghanadian⁴, Gholamreza Askari⁵, Fariborz Khorvash⁶

ABSTRACT

Objectives: Different medications have been developed to treat atherosclerosis. Allium hirtifolium (shallot) has different therapeutic properties such as antioxidant effects which make it a possible effective agent in treatment of atherosclerosis. This investigation was designed to see whether or not adding allium hirtifolium to the routine treatment with atorvastatin can have more beneficial effects.

Methodology: Fifty participants having common carotid artery intima media thickness (CCIMT) more than 0.80mm were randomly allocated to two equal treatment groups of atorvastatin (40mg daily) + placebo (2 capsules a day) and atorvastatin (40mg daily) + shallot (500mg capsules twice a day). Patients were treated for nine months, and then, CCIMT was rechecked. Pre and post treatment CCIMT was compared between and within groups.

Results: Despite no significant difference between two groups in pre-treatment CCIMT ($p:0.79$), post treatment CCIMT was significantly lower in case group (0.830 ± 0.05 mm Vs. 0.851 ± 0.04 , $p:0.04$). Post-treatment CCIMT was significantly lower than pre-treatment values in both case and control groups ($p < 0.0001$ and 0.03 respectively).

Conclusion: This study showed that atorvastatin plus placebo and atorvastatin plus allium hirtifolium both reduced CCIMT significantly. However, this CCIMT reduction was significantly more in patients treated with allium hirtifolium plus atorvastatin. However, further studies are required to re-evaluate these findings in larger sample size and to determine whether taking shallot alone will produce such effects on CCIMT or not.

KEY WORDS: Atherosclerosis, Shallots, Statin, Atorvastatin.

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1. Seyed Ali Mousavi,
Professor of Neurology,
 2. Ahmad Chitsaz,
Associate Professor of Neurology,
 3. Suzan Rahimi,
Resident of Neurology,
 4. Mustafa Ghanadian,
Department of Pharmacognosy,
School of Pharmacy & Pharmaceutical Science,
 5. Gholamreza Askari,
Assistant Professor of Clinical Nutrition,
 6. Fariborz Khorvash,
Assistant Professor of Neurology,
- 1-3,6: Isfahan Neurosciences Research Center,
1-6: Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence:

Fariborz Khorvash,
Assistant Professor of Neurology,
E-mail: fkhorvash@med.mui.ac.ir

INTRODUCTION

The combination of lipoprotein deposition into the arterial intima and oxidative modification of lipids is the main component of a complex phenomenon known as atherosclerosis.^{1,2} Atherosclerosis increases the risk of development of hypertension and cardiovascular diseases by narrowing or occluding arteries;³ therefore, it is considered as the major cause of death and premature disability.⁴ For this reason, different therapeutic modalities and medications have been developed to treat hyperlipidemia which is the most important contributing factor in atherosclerosis.⁴ Statins are effective therapeutic agents which have been used

to treat dyslipidemia, reduce carotid intima media thickness (an important index of atherosclerosis progression in clinical research)^{5,6} and consequently, reduce the risk of cardiovascular morbidity and mortality.⁷ In addition to pharmaceutical medications, several herbal medications have been prescribed for years as lipid lowering agent.^{4,8} Medicinal plants are prescribed either alone or in combination with other drugs. Garlic or *Allium sativum* is a member of "Alliaceae family", and has a long history of herbal usage.⁸

It contains antioxidant compounds, increases nitric oxide production and decreases level of inflammatory cytokines.⁹ Having these useful properties, garlic has several beneficial effects including anticarcinogenic action,¹⁰⁻¹² antimicrobial and antifungal effects⁴ and cardiovascular protective effects.¹³⁻¹⁵ As regards to the cardiovascular protective effects, it can reduce serum cholesterol levels, inhibit cholesterol biosynthesis, suppress LDL oxidation, lower plasma fibrinogen and increase fibrinolytic activity.⁹ *Allium hirtifolium* or "Iranian shallot" is another member of Alliaceae family which has been reported to be similar to garlic.¹⁶ It has been reported that *Allium hirtifolium* has antioxidant properties¹⁷ and anticancer¹⁸ and immune system regulating effects.¹⁹ However, unlike garlic, there is limited information regarding its therapeutic effects. Based on the above mentioned properties, it is felt that *Allium hirtifolium* may have lipid lowering effects, and hence, it can be prescribed as a treatment for atherosclerosis. In light of the above, this investigation was designed to answer the question of whether or not adding *allium hirtifolium* to the routine treatment with statins can have more beneficial effects.

METHODOLOGY

Study population and design: After approval of the study by the ethic committee of Isfahan University of Medical Sciences and obtaining informed consent, this double blind, randomized, placebo-controlled clinical trial was performed on patients who were referred to neurology outpatient clinic of Al-zahra Hospital, Isfahan, Iran, between September 2011 and August 2012. All participants underwent carotid artery Doppler ultrasound, and those with bilateral common carotid intima media thickness (CCIMT) more than 0.8 mm entered the study. Exclusion criteria were smoking, pregnancy, stenotic lesions of the carotid artery, severe internal disorders (i.e. functional disorders of the heart, circulatory system, liver, kidney and lung;

decompensated heart failure, severe arrhythmias, acute myocardial infarction (less than 6 months ago), chronic obstructive pulmonary diseases, asthma, systolic blood pressure more than 180 mmHg or less than 110 mmHg, portal hypertension, renal failure (creatinine more than 2.0 mg/dl) and simultaneous treatment with other lipid lowering agents, aspirin, naftidrofuryl, pentoxifyllin, omega-3-fatty acid, calcium antagonists, oral antithrombotic agents.²⁰ Moreover, patients who did not take their medications regularly were excluded.

According to aforementioned criteria, 50 patients initially entered the study. First, Doppler ultrasound examinations of both common carotid arteries were performed using a 7.5 MHz transducer (Ultramark 9 from ATL) to measure mean of right and left CIMT. All ultrasound examinations were carried out by a single experienced neurologist who was unaware of patients' group. Intima and media lines were identified as two echogenic bright lines in the vessel wall. The distance between the main edge of the first to the main edge of the second lines was considered as carotid IMT. All measurements were repeated two times. Then, subjects were randomly allocated into two equal groups of case (atorvastatin + *allium hirtifolium*) and control (atorvastatin + placebo). All participants received atorvastatin 40 mg produced by Amin Pharmaceutical Company, Iran. Six patients developed adverse effects during the study, and therefore, terminated the treatment. These subjects were replaced with 6 new participants, and finally, 50 patients completed the study. The two groups were matched for baseline characteristics (age, sexual distribution and pre-treatment CCIMT). Patients of case group were started on atorvastatin 40mg daily and *allium hirtifolium* capsule 500mg twice a day. For the control group, *allium hirtifolium* capsule was replaced with placebo (identical-looking capsule containing cornstarch). Each participant was followed for 9 months, and they were asked to report any adverse effect during the investigation.

Nine months after the start of this study, patients were checked for post-treatment mean of right and left CIMT.

Persian shallot capsule preparation: The bulbs of *Allium hirtifolium* Boiss. (Persian shallot) which is a wild onion species known as "Musir" in Persia, were collected in the June of 2012 from ChaharMahal and Bakhteyari province located in the center of the mountain chains of Zagros mountains in Iran. It was identified by Dr. Ghanadian specialized in pharmacognosy at the Isfahan Pharmaceutical

Sciences Research Center, in Isfahan, Iran. The bulbs of shallot were shade dried at room temperature (20-22°C) and based on quercetinaglycone as one of the *Allium hirtifolium* constituents, capsules were prepared from 500 mg standardized dry powder substance.^{17,21}

Standardization of the Persian shallot by the HPLC analysis: HPLC (High-performance liquid chromatographic) analysis was done on a Waters system, equipped with 515 HPLC pump, UV-Visible detector (2487 dual absorbance) operated at 365 nm, and millennium software for the determination of quercetinaglycone. 1g of the dried powders of the *A. hirtifolium* bulbs were mixed thoroughly with 5 mL acetone repeatedly three times. The combined acetone extract containing flavonoid material was filtered and evaporated to 5mL. Then 20 µl of the sample injected three times into a reversed-phase HPLC column (RP-18, 100 mm × 4.6 mm, 5 µm particle size, Waters, USA) using NaH₂PO₄ (0.78 g/L), H₃PO₄ (0.2 mL) in water (pH=2.6) as solvent A and acetonitrile as solvent B with isocratic elution at 40 °C with ratio of 85% A to 15% B at a flow rate of 2 ml/min. A standard calibration curve also in the range of 0.005 to 0.1 mg/mL for quantitative analysis was prepared using different concentrations of quercetin (Sigma Aldrich, USA) as standard material (0.100, 0.025, 0.010, and 0.005 mg/ml). The relationship between the concentration and peak-area was measured using the minimum

square method (R² value). Validation of HPLC Method was calculated as the percent recovery of spiked extract sample with standard quercetin at 0.01 mg/mL concentration.

HPLC Standardization of the Persian shallot: Quercetin peak appeared at a retention time of 14.8 min. By the aid of the millennium processing software, the calibration curve was determined by linear regression in the range of 0.005-0.1 mg/mL. The regression equation was $Y=5.62e+7 X - 2.64e+5$, where X is the concentration of quercetin in sample (mg/mL) with the correlation co-factor (R²) of 0.98 (Fig.1). The percent recovery was 95 % indicating of the accuracy of the method. Then sample obtained from *A. hirtifolium* bulbs was injected and its concentration determined through quercetin calibration curve. Considering each capsule containing 500 mg of the dried powders of the *A. hirtifolium* bulbs, it was standardized to contain 0.016 ± 0.0001 mg quercetinaglycone in each capsule.

Statistical analysis: Data were analyzed by SPSS 16.5 using paired T-test, independent T-test and chi-square. P-values less than 0.05 were considered statistically significant.

RESULTS

Baseline data: The study sample consisted of 27 (54%) men and 23 (46%) women. No significant

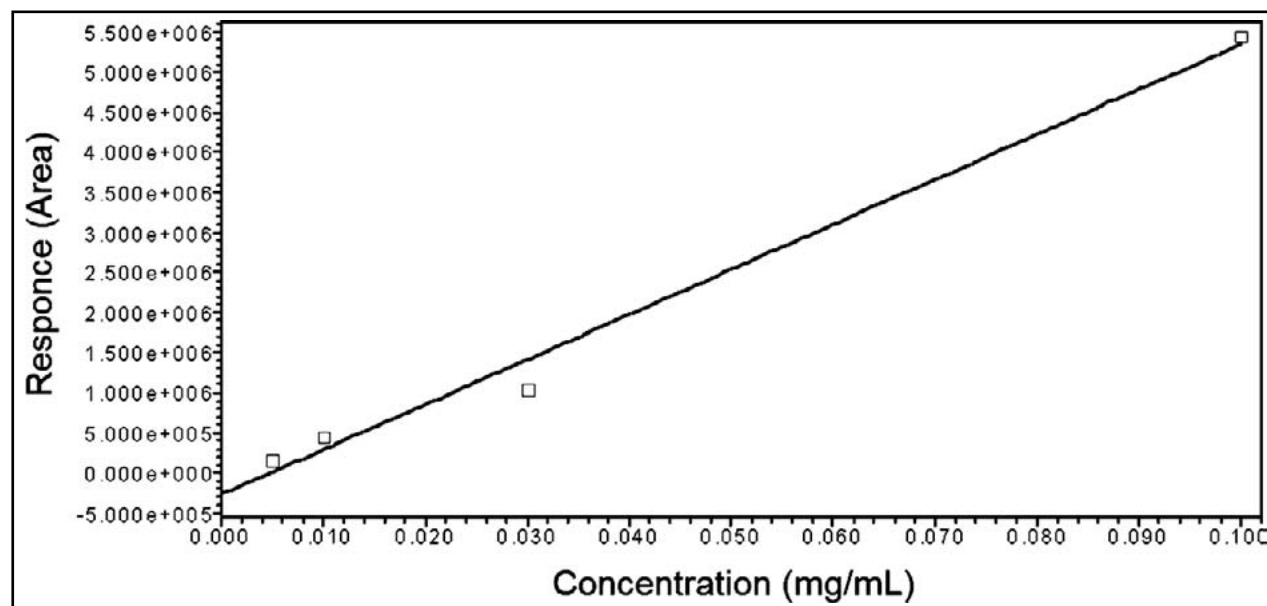


Fig.1: Calibration curve of quercetin using HPLC method in solutions with ionic strength adjusted with 10 mM sodium phosphate buffer (pH 2.6) at 365 nm. Using the millennium processing software, the calibration curve was determined by linear regression in the range of 0.005-0.1 mg/mL. The regression equation was $Y=5.62e+7 X - 2.64e+5$, where X is the concentration of quercetin in sample (mg/mL) with the correlation co-factor (R²) of 0.98.

Table-I: Baseline characteristics of two groups

	Case group (N:25)	Control group (N:25)	Total (N:50)	p-value
Age (year)	66.96±8.35	67.72±10.40	67.34±9.34	0.51
Sex (male/female)	15(60%)/10(40%)	12(48%)/13(52%)	27(54%)/23(46%)	0.28
Pre-treatment CIMT(mm)	0.866±0.10	0.860±0.04	0.863±0.07	0.79

Data are presented as mean±SD, or number (%) N: number of patients

Table-II: Comparison of pre and post treatment CCIMT between and within 2 groups.

	Case group (N:25)	Control group (N:25)	Total (N:50)	p-value
Pre-treatment CCIMT(mm)	0.866±0.10	0.860±0.04	0.863±0.07	0.79
Post-treatment CCIMT(mm)	0.830±0.05	0.851±0.04	0.841±0.05	0.04
p-value	<0.0001	0.03	0.02	

Data are presented as mean±SD N: number of patients

different was found between two groups regarding baseline characteristics (Table-I).

Pre-treatment CCIMT: Mean of right and left common carotid intima media thickness before the treatment.

CCIMT changes: Comparison of pre and post treatment CCIMT showed that after 9 months of treatment, post treatment CCIMT has reduced significantly in both case and control groups. In addition, post-treatment CCIMT of the case group was significantly lower than the control group (Table-II: and Fig.2).

Pre-treatment CCIMT: Mean of right and left common carotid intima media thickness before the treatment.

Post-treatment CCIMT: Mean of right and left common carotid intima media thickness after the treatment.

Adverse effects: Six patients in the case group withdrew from the study due to adverse effects

(abdominal pain (2 cases), nausea and vomiting (2 cases), fever (one case) and skin rash (one case)); however, they were replaced by new subjects to maintain sample size. None of the patients reported adverse effects in the control group.

DISCUSSION

Recently, more people have become interested in use of herbal medications;²² however, herbal medicine needs to be investigated for safety and efficacy using conventional trial methodology.²² This study showed that atorvastatin plus placebo and atorvastatin plus allium hirtifolium both reduced CCIMT significantly. However, this CCIMT reduction was significantly more in patients treated with allium hirtifolium plus atorvastatin. Intima media thickness is considered as an important index and a strong predictor of atherosclerosis progression.^{5,6,23} It is assumed that atherosclerosis has a generalized effect on all arterial vessels rather than affecting an isolated site. Hence, measurement of intima media thickness provides a good estimation of vessel wall structure and enables early detection early treatment of atherosclerotic changes.²⁴

Therefore, our findings imply that allium hirtifolium adds more beneficial effects to the routine therapeutic regimen of atorvastatin in treatment of atherosclerosis. Although several studies have reported benefits with atorvastatin therapy in slowing down the progression of carotid intima media thickness and treatment of atherosclerosis which confirms our finding,²⁵⁻³¹ to our knowledge, it is the first study that investigated effects of allium hirtifolium on CCIMT. Previous studies mostly have investigated biochemical properties of shallot, or performed animal studies, not human clinical

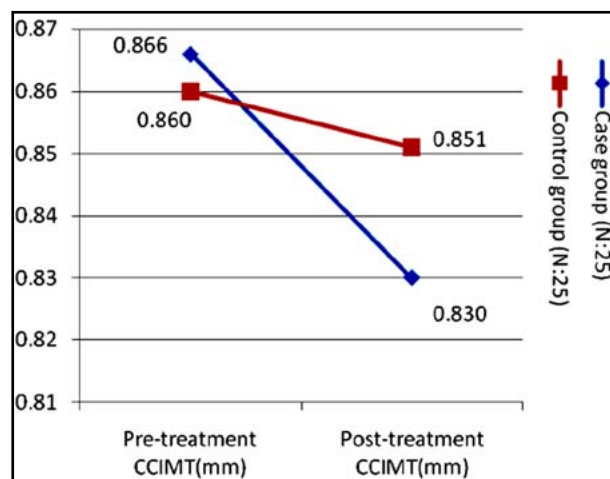


Fig.2: Changes in CCIMT in two groups over the study period.

trials.^{16-19,32,33} In contrast to the limited clinical data that are available for shallot, there are several clinical trials which studied different clinical effects of other plants in the *Allium* genus, including onion and garlic.³² However, given the fact that shallot belongs to the same biological genus as garlic and their similar properties and effects,¹⁶ previous studies on other members of this family can be helpful.

For instance, a randomized, double-blind, placebo-controlled clinical trial performed by Koscielny et.al determined clinical effects of *Allium sativum* on the plaque volumes in both carotid and femoral arteries of 152 probationers by B-mode ultrasound. They concluded that not only garlic has a preventive effect, but also it may have a curative role in arteriosclerosis therapy (plaque regression).²⁰ Another study on animal samples by Lu and colleagues demonstrated that Allicin - a sulfur compounds founded in *Allium* genus- has a significant cholesterol lowering effect, and therefore, provides protection against the onset of atherosclerosis.³ Although our investigation is not a basic study to determine mechanisms of action, these findings raises a question in mind that by which mechanism shallot improves atherosclerosis.

An investigation performed by Leelarungrayub et.al. Demonstrated that shallot has significant antioxidant activity similar to that associated with garlic.¹⁷ Having strong antioxidant and free radical-scavenging properties,¹⁷ it is not surprising to find anti-atherosclerotic effects for shallot. Besides, many other effective compounds such as active sulphur compounds are found in *Allium* genus. It has been suggested that some beneficial effects of shallot may be associated to these compounds.³² Shallot can oxidize the lipid synthesizing enzymes using (-SH) groups of sulphur compounds, and this activity may lead to reduce or inhibit lipid synthesis which is a well-known risk factor for atherosclerosis. In addition, these compounds can inhibit lipid synthesis more by oxidizing Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH during lipid synthesis stages) to Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADP).^{32,34}

Sulphur compounds also induce 7-alpha hydroxylase enzyme. Increased activity of this enzyme leads to further conversion of cholesterol to bile acids.³⁵ According to findings of current study and aforementioned properties of shallot, it seems that adding shallot to atorvastatin can lead to more improvement of atherosclerosis. However, further

studies are required to re-evaluate these findings in larger sample size and to determine whether taking shallot alone will produce such effects on CCIMT or not.

Conflict of Interests: The authors declare no potential conflicts of interest.

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