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Effect of *Vitex agnus-castus* and *Salvia officinalis* Extracts on Serum Lipids in Postmenopausal Women: An Randomized Clinical Trial

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Abstract

Objectives: This study aimed to investigate the effect of *Vitex agnus-castus* (VAC), and *Salvia officinalis* extracts on serum lipids in postmenopausal women referred to the Bone Densitometry Center, Namazi Hospital, Shiraz, Iran.

Materials and Methods: This randomized clinical trial was conducted on 89 postmenopausal women in 2016 using random permuted blocks with a block size of 3 in the three groups, including the VAC group (3.2-4.8 mg/q8h), *S. officinalis* group (100 mg/q8h), and placebo group for three months. Women were finally compared in terms of low-density lipoprotein, triglycerides (TG), and high-density lipoprotein before and after the intervention. Data were analyzed using SPSS-16 software. Descriptive statistical tests and paired *t* test were used to compare the groups.

Results: A significant decrease in serum cholesterol, low-density lipoprotein, and triglycerides levels and also increase in mean serum high-density lipoprotein levels were observed in VAC and *S. officinalis* groups before and after the intervention ($P = 0.0001$). In comparison, no significant change was observed in serum level of any lipoproteins in the placebo group.

Conclusions: Considering the decrease in the level of cholesterol, low-density lipoprotein, triglycerides, and increased high-density lipoprotein after using VAC and *S. officinalis* in this study, these herbs can be proposed as blood lipid-lowering agents in postmenopausal women.

Keywords: *Vitex agnus-castus*, *Salvia officinalis*, Lipoproteins, LDL, HDL, Triglycerides, Lipids, Postmenopausal, Women

Introduction

Menopause is a sign of passing from fertility to infertility. In this period, symptoms such as hot flashes, night sweats, sleep disturbances, lack of concentration and memory loss, loss of bone mass, vaginal atrophy, increased risk of cardiovascular diseases, anxiety, and depression occur in the long term (1-4). Estrogen is involved in regulating serum lipid metabolism and breast cancer. The administration of estrogen on serum lipid is mainly expressed through its attachment to the estrogen receptor alpha isoform and occurs in most tissues (5). During menopause, lipid metabolism and blood pressure change due to decreased estrogen levels. In this period, the distribution of body lipid changes from the environmental distribution to the central allocation. Also, levels of total cholesterol, low-density lipoprotein (LDL), triglycerides (TG), lipoprotein (a), and high-density lipoprotein (HDL) are reduced. Moreover, metabolic syndrome, hypertension, abdominal obesity, insulin resistance, and dyslipidemia increase during menopause (6). Epidemiologic studies have shown that hormone replacement therapy or estrogen plus progesterone therapy using conjugated estrogens/medroxyprogesterone in menopause women decrease menopausal symptoms, the risk of coronary artery disease and adiponectin concentrations in coronary heart disease (7-9). Considering the side effects of hormone therapy (10,10) and the use of complementary medicine in the treatment of women diseases (12-17), the main chemical properties of *Vitex agnus-castus* (VAC) phytoestrogens appear to guarantee cardiovascular health after menopause with the support of vascular nitric oxide activity, maintaining the vascular endothelial function, preventing atherosclerosis, and reducing cholesterol and TG levels (18). However, despite the many effects of VAC (19, 20), little is known about its impact on the liver's lipid metabolism and oxidation state, especially in postmenopausal women. Most studies have examined the effects of liver lipid metabolism on ovariectomized rats (21).

The VAC is native to Europe, the Mediterranean, and Asian countries. Two iridoid glycosides called genocide and combine obtained from its ripe and dried fruits containing

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Key Messages

- *Vitex agnus-castus* and *Salvia officinalis* extracts effectively reduced low-density lipoprotein cholesterol and triglycerides and increased high-density lipoprotein cholesterol compared to the placebo group.
- Due to the nativeness and availability of these plants in our country, and the lack of reports of side effects in this study, it is probably a good option, along with hormone therapy for postmenopausal women.

flavonoids and some essential oils. Flavonoids are other than phytoestrogens (22). *Salvia officinalis* contains tannins, phenolic acids, and flavonoids. Flavonoids are among the phytoestrogens. It originally belongs to the 90-1200 meters' heights in Japan and China (23). Studies showed that flavonoids play an antioxidant role that may reduce oxidized LDL cholesterol and, on the other hand, inhibit platelet aggregation, improve endothelial function, and they also have an anti-inflammatory function (24,25). Different medications such as VAC and *S. officinalis* have phytoestrogen properties and are recommended to treat menopausal symptoms (26, 27).

There is no study conducted on the effect of VAC and *S. officinalis* on lipids in postmenopausal women in Iran. Besides, that existing conducted studies on the effects of these two herbs are more related to the physical and mental symptoms, and also considering the WHO recommendations regarding the focus on complementary medicine. The purpose of this study was to investigate the effect of VAC and *S. officinalis* extracts on serum lipids in postmenopausal women referring to Bone Densitometry Center, Shiraz, Iran.

Materials and Methods

Study Design and Participants

In this randomized clinical trial, 99 postmenopausal women who were not taking drugs that affected the serum lipids, such as LDL, HDL, and triglycerides referred to the Bone Densitometry Center, Namazi Hospital, Shiraz, Iran from May to August 2016 were enrolled.

All women underwent any hormonal treatments or history of allergic reactions to the drugs or herbal medicines were excluded. The postmenopausal women were defined as; all women who had been menopausal for at least 1 year and not taking steroid hormones.

Interventions

Participants were randomly assigned to three groups using random permuted blocks with a block size of 3. The VAC group received one *Vitex agnus* tablet (Goldaru pharmaceutical Co., Isfahan, Iran), *S. officinalis* group received three Salvigol tablets (Goldaru pharmaceutical Co., Isfahan, Iran), and placebo group received three placebo tablets (made at Shiraz Pharmacy School, Shiraz, Iran) every day for three months. According to the pharmaceutical company pamphlet, each Agnugol coated tablet (VAC) was contained 3.2-4.8 mg of dried extract of VAC fruits standardized based on the presence of 0.42-0.55 mg Aucubin (an iridoid glycoside). And each film-coated Salvigol tablet was contained 100 mg of dried extract of *S. officinalis* standardized based on the presence of 19-25 mg tannins (acid tannic).

Herbal tablets were placed in black envelopes and coded by the researcher's assistant. The researcher was blind to the codes until the end of the study, and participants did not meet each other. Besides, statistical consultant analysis also did not know the intervention and control groups.

Outcomes

The venous blood samples were taken from each participant for measuring the total serum cholesterol, LDL, HDL, and TG before and three months after the interventions. The total serum cholesterol levels of less than 200 mg/dL were considered normal, also the LDL levels <100 mg/dL as the optimal conditions, 100-129 mg/dL; low limit, 130-159 mg/dL; high limit, 160-189 mg/dL; high, and ≥190 mg/dL; very high. The HDL levels <40 mg/dL were considered high risk and ≥60 mg/dL; low risk. Normal TG levels were considered to be 160-40 mg/dL in men and 35-35 mg/dL in women. All outcomes were measured by a biochemical auto-analyzer using the calorimetric method.

Sample Size

The sample size was estimated to be 31 in each group by considering the confidence level of 95%, the power of 80%, based on the study by Filip et al (28), and used the following formula:

$$n_1 = ((z_{(1-\alpha/2)} + z_{(1-\beta)})^2 (\sigma_1^2 + \sigma_2^2)) / d^2$$

$\sigma_1 = 30.51$, $\sigma_2 = 29.7$, $\alpha = 0.05$, $\beta = 0.2$

Finally, with a 5% probability of drop-out, 99 women were enrolled in the study, and 89 completed it.

Data Analysis

Data were analyzed using the statistical package for the social sciences (SPSS) software version 16 (IBM Company Armonk, NY, USA). Descriptive statistical tests, ANOVA, and paired *t* test were uses for comparing the study groups. *P* value < 0.05 was considered as the significant.

Results

Initially, 99 post menopause women were eligible to enter the study (33/each group). Out of them, three women in the VAC group, 2 in the *S. officinalis* group, and 5 in the placebo group were excluded due to the lack of regular use of herbal and placebo pills and dissatisfaction to continue participating in the study. Finally, the data of 89 participants in three groups were analyzed (Figure 1). The demographic characteristics of participants were not significantly different in terms of age, education, and

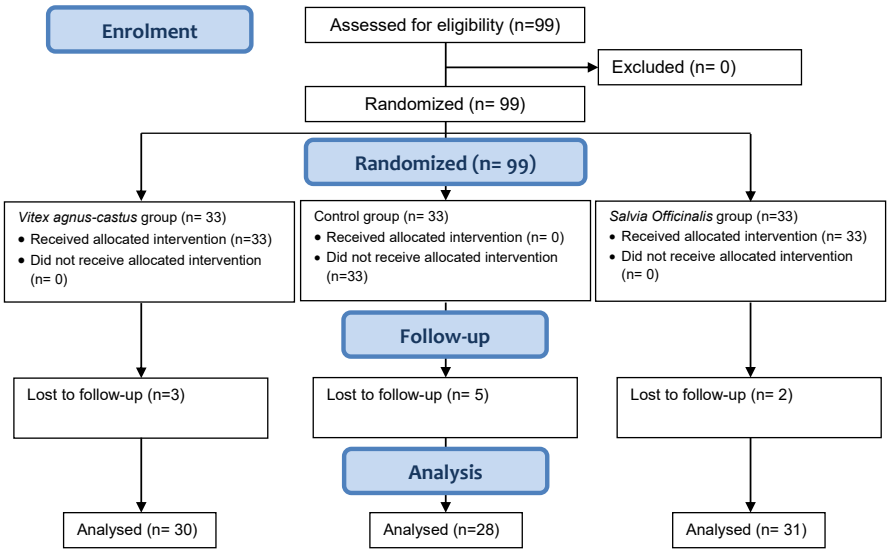

Figure 1. The Study CONSORT Flowchart.

housing status. The mean age of the participants was 55.83 ± 3.63. There were no statistical differences in age, menopausal age, menopausal period, body mass index (BMI), and duration of the marriage between the three groups (Table 1).

There were significant differences in cholesterol levels before and after intervention in the VAC and *S. officinalis* groups ($P=0.0001$). This difference was not significant in the placebo group ($P=0.56$; Table 2).

There was a significant difference in the mean of LDL and TG before and after the intervention in the two intervention groups. In contrast, in the placebo group, it was not significant. There was also a statistically significant difference in HDL levels before and after the intervention in the VAC and *S. officinalis* groups ($P=0.0001$; Tables 2 and 3).

Discussion

This study aimed to investigate the effect of the VAC and *S. officinalis* extracts on serum lipids in postmenopausal women. Our results showed that VAC and *S. officinalis* extracts significantly decreased cholesterol, TG, and LDL and increased HDL compared with the placebo group. In line with our results, some studies showed that *Salvia Officinalis* reduces the total cholesterol, LDL, and TG and increases HDL (29-31). Koubaa-Ghorbel et al evaluated the effects of antioxidant activity of *S. officinalis* essential oil and its protective effect on estrogen deficiency in ovarian rats. The results showed that *S. officinalis* leaves, as an important source of antioxidants, can prevent obesity and oxidative damage to the liver and uterus due to estrogen deficiency (32). In addition, total cholesterol, TG, LDL, and VLDL significantly reduced in hyperlipidemic rats in

Table 1. The Demographic Characteristics of Study Participants

Variables		VAC Group (n=30)	*Salvia Officinalis* Group (n=31)	Placebo Group (n=28)	*P* Value
Age (y)		55.6±4.6	55.6±3.7	56.3±3	0.292[a]
BMI (kg/m²)		26.5±3.2	28.3±4.7	28.5±4.6	1.524[a]
Menopausal age (y)		46.6±7.3	48.6±5.9	47.8±6	0.409[a]
Menopausal period (y)		8.8±7.9	6.6±7.1	8.5±6.3	0.612[a]
Duration of the marriage (y)		34.7±8.7	36.8±4.1	38.9±5.8	0.069[a]
Education	Illiterate	5 (16.7)	6 (19.4)	4 (14.3)	0.783[b]
	Primary	15 (40)	12 (38.7)	13 (46.4)	
	Secondary	5 (16.7)	4 (12.9)	4 (14.3)	
	Diploma	4 (13.3)	8 (25.8)	5 (17.8)	
	University	4 (13.3)	1 (3.2)	1 (7.1)	
Occupation	Employed	4 (13.3)	2 (6.5)	3 (7.4)	0.604[b]
	Housewife	26 (86.7)	29 (93.5)	25 (92.6	
Housing status	Personal	20 (66.7)	28 (90.3)	24 (85.7)	0.082[b]
	Rent	10 (33.3)	3 (9.7)	4 (14.3)	

VAC: *Vitex Agnus-Castus*, BMI: Body mass index.
All data presented as mean ± SD.
[a] One-way ANOVA test; [b] Chi-Square test.

Table 2. Comparison of Mean Cholesterol, Triglyceride, LDL, and HDL in Study Groups Before and After Intervention

Variables	Time	VAC Group (n=30)	*Salvia Officinalis* Group (n=31)	Placebo Group (n=28)
Cholesterol	Before intervention	229.35±43.74	220.10±38.68	208.39±41.67
	After intervention	209.65±45.83	194.57±37.97	210.36±41.39
P value[a]		0.0001	0.0001	0.569
LDL	Before intervention	112.26±26.20	108.37±26.67	110.14±28.57
	After intervention	91.55±29.72	89.30±24.53	110.75±29.09
P value[a]		0.0001	0.0001	0.21
Triglyceride	Before intervention	169.00±66.52	182.57±73.54	141.11±57.33
	After intervention	142.52±64.89	156.73±72.26	149.29±56.03
P value[a]		0.0001	0.0001	0.139
HDL	Before intervention	48.94±8.68	49.87±12.10	49.00±11.67
	After intervention	54.77±9.06	54.33±11.39	48.39±10.97
P value[a]		0.0001	0.0001	0.159

VAC: *Vitex Agnus-Castus*, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.
All data presented as mean ± SD.
[a] Paired *t* test.

Table 3. Comparison of Changes in Mean Cholesterol, Triglyceride LDL, and HDL in Three Study Groups

Variables	VAC Group (n=30)	*Salvia Officinalis* Group (n=31)	Placebo Group (n=28)	*P* Value*
Cholesterol	19.70±17.51 (13.28-26.13)	25.53±22.99 (16.94-34.11)	1.96±18.02 (-8.95-5.02)	0.0001
LDL	30.70±15.05 (15.02-26.39)	19.06±22.05 (10.64-27.49)	-0.60±2.49 (-1.57-0.36)	0.0001
Triglyceride	26.48±24.59 (17.46-35.50)	25.83±27.30 (15.63-36.03)	8.17±28.35 (2.81-19.17)	0.0001
HDL	5.83±4,58 (-7.51- -4.15)	4.46±4.28 (-60.6- -2.86)	0.60±2.21 (-0.25-1.46)	0.0001

VAC: *Vitex Agnus-Castus*, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.
All data presented as mean ± SD (95% confidence interval).
[a] Paired *t* test.

a study by Kianbakht and colleagues after treatment with VAC extract, which may be due to the high activity in the ability to inhibit free radicals (33)

Our study showed that, after the intervention, these two herbs significantly caused a decrease in LDL cholesterol and TG and increased HDL- cholesterol compared to the control group.

Kianbakht and colleagues showed that *S. officinalis* extract causes a decrease in LDL and TG and increased HDL (29). Liu and others (2016) showed that *S. officinalis* extract causes a reduction in LDL, total cholesterol, and TG and an increase in HDL (30). Kwok and co-workers showed that *S. officinalis* causes a decrease in LDL and total cholesterol levels and increases the thickness of the carotid intima (31). The stories of LDL, cholesterol (6.92), and total cholesterol (5.85) decreased significantly in the intervention group compared to the control group (cholesterol [3.42] and total cholesterol [3.21]). A Study about the effects of *S. officinalis* essential oil on hyperlipidemic rats was showed the beneficial impact of *S. officinalis* essential oil in managing these disorders without causing side effects. More than one synthetic drug reduces essential fats and improves antioxidant status (32). In addition, total cholesterol, TG, LDL, and VLDL significantly reduced in hyperlipidemic rats in a study by Kianbakht and colleagues after treatment with VAC extract of Agnus castus, which may be due to the high activity in the ability to inhibit free radicals (33).

Two iridoid glycosides named agonose and akubin are obtained from the dried ripe fruits of vitex containing flavonoids and essential oils. Flavonoids are compounds of phytoestrogens (34). Some combinations of this plant include tannins, phenolic acids, and flavonoids, among which are compounds of phytoestrogens (35). A study also showed that flavonoids have phytoestrogenic properties. Estrogen reduces blood cholesterol, and that is why postmenopausal women are prone to hyperlipidemia (36). In a study show that polypeptides, steroids, and flavonoids present in herbs may have lipid-lowering effects (37). Possible mechanisms of lipid-lowering effects of flavonoids reduce the activity of enzymes involved in cholesterol acyltransferase of liver cells (responsible for cholesterol esterification and its storage) (38,39). Flavonoids also have antioxidant properties (40) and hence can collect hydroxyl and superoxide radicals and prevent lipid peroxidation (41). The positive effect of antioxidants has also been reported with radical free-oxygen inhibition in laboratory animals to decrease lipid glucose level (42,43). Another mechanism noted by researchers is that herbs and antioxidants cause a reduction in lipids by stimulating cholesterol secretion through bile and an increase in cholesterol excretion by feces. They may also inhibit the enzymes and proteins involved in lipid and lipoprotein metabolism, and in this way, they will reduce

serum lipids (44-46).

Finally, it is noteworthy that herbal complexes with medicinal properties can be used in health conditions for prevention or treatment. VAC with phytoestrogenic properties may support vascular nitric oxide activity, prevent atherosclerosis and reduce cholesterol and TG levels.

Limitations of the Study

One of the limitations of this study was the possible negligence of the participants in the correct use of the pills. To solve this problem, the addresses and telephone numbers of the participants were recorded at the beginning of the study, and the researcher contacted them every week during the intervention to warn them about the accurate and timely use of the pills. However, if a participant did not follow the intervention protocol for any reason, she would be excluded from the study. Another limitation of the present study was the duration of the study. Due to the long-term effect of medicinal plants, it is recommended to design other studies with a larger sample size and more extended period (6 to 12 months) to investigate the impact of these plants on menopausal complications better and more accurately.

Conclusions

Considering the decrease in cholesterol, LDL, TG, and increased HDL level after using VAC and *S. officinalis* in this study, it concluded that these herbs could be proposed as blood lipid-lowering agents in postmenopausal women. VAC and *S. officinalis* contain several chemical compounds. It is suggested to isolate their components and investigate the active compounds in similar studies. Moreover, further studies are required on the intracellular signaling pathway better to understand the effect of these plants on lipid profiles.

Authors' Contribution

MA, AZ and ME designed the study and conducted the research. MA, ME, and MRS monitored, evaluated, and analyzed the result of the study. Further, MA, MJ reviewed the article. All authors approved the final manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This research was carried out in Namazi Hospital after obtaining approval from the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.SUMS.REC.1394.209). Also, the study proposal was registered on the Iranian Registry of Clinical Trials website (identifier: IRCT2016041613940N4; https://www.irct.ir/trial/13658). After signing an informed consent form, eligible women were included in the study. Then, participants were reassured that their information would be confidential and that no names would be mentioned.

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