International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

ORIGINAL ARTICLE

The Effect of Sumac Powder (*Rhus Coriaria L*) on Homocysteine and High-Sensitivity C-Reactive Protein in Patients with Type 2 Diabetes Mellitus

Azadeh Nadjarzadeh[1], Mohammad Reza Fattahi[1], Fatemeh Moghtaderi[1], Alireza Vahidi[2], Salimeh Hajiahmadi[1], Mohammad Ali Mohsenpour[1*]

1. Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Herbal Medicine Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ARTICLE INFO

Keywords:
Sumac
Rhus Coriaria
Homocysteine
C-reactive protein
Diabetes mellitus

**Corresponding author:*
Mohammad Ali Mohsenpour, PhD;
Nutrition and Food Security Research Center
Shahid Sadoughi University of Medical Sciences,
Yazd, Iran.
Tel: +98-9173019134
Email: mohammadali.mohsenpour@gmail.com
Received: October 3, 2023
Revised: January 27, 2024
Accepted: February 4, 2024

ABSTRACT

Background: High-sensitivity C-reactive protein (hs-CRP), and homocysteine increase along with inflammation in type 2 diabetes mellitus (T2DM). The antioxidant properties of sumac might affect homocysteine and hs-CRP levels. We aimed to examine the effects of sumac powder (*Rhus Coriaria L*) on homocysteine and hs-CRP in patients with T2DM.

Methods: In a single-blinded, randomized controlled clinical trial, conducted in Ardekan city, Yazd, Iran; 60 patients with T2DM were randomly divided into 2 groups to consume either low-fat yogurt alone in the control group or along with 6 (2×3 grams) grams of sumac powder daily in the intervention group, for 3 months. Fasting blood samples were used to analyze the fasting blood sugar (FBS), serum homocysteine, and hs-CRP at the baseline and after 90 days. *P* values <0.05 were considered statistically significant.

Results: Fifty-eight individuals (intervention n=30, control n=28) with a mean age of 52.30±7.05 years in the intervention, and 51.61±7.07 years in the control group, finished the study. No significant differences were seen for FBS (p=0.94) and homocysteine (p=0.69) changes between the groups; but hs-CRP changes were significantly different between the groups (p=0.03).

Conclusion: Daily consumption of sumac powder for 3 months may not have a reducing effect on FBS and serum homocysteine. This is while sumac may prevent increment of hs-CRP in patients with T2DM.

Please cite this article as: Nadjarzadeh A, Fattahi MR, Moghtaderi F, Vahidi AR, Hajiahmadi S, Mohsenpour MA. The Effect of Sumac Powder (*Rhus Coriaria L*) on Homocysteine and High-Sensitivity C-Reactive Protein in Patients with Type 2 Diabetes Mellitus. Int J Nutr Sci. 2024;9(1):71-79. doi: 10.30476/IJNS.2024.100116.1268.

Introduction

Sumac, under the scientific name of *Rhus coriaria L* belongs to the Anacardiaceae family, is a reputed plant-derived substance widely consumed for medicinal goals (1). Its plants grow in temperate and tropical regions like Mediterranean areas (2). In addition to its usual usage as a condiment, appetizer, and souring agent (1), it has anti-inflammatory (3), antioxidant(4),andanti-dyslipidemia(5)effects.These properties are related to its 191 chemical compounds (1) such as phenolic acids and flavonoids, including gallic acid (GA) (6), as potent antioxidants (7).

In addition, tannins as an antioxidant (2), are known to have anti-carcinogenic effects (7). Other compounds with potent health benefits are methyl gallate, kaempferol, and quercetin (6).

Sumac is traditionally used in the type 2 diabetes mellitus (T2DM) (8), which is highly prevalent in Iran (9, 10). T2DM is accompanied by increasing atherosclerosis-related risk factors such as lipid peroxidation, oxidative stress (11), hypertension (HTN), lowering of high-density lipoprotein-cholesterol (HDL), increased serum triglycerides, small, dense LDL cholesterols; and obesity. Consequently, diabetes intensifies atherosclerosis risk (12). Since atherosclerosis is an inflammatory process (13), it is suggested that sumac can protect cells from lipid peroxidation (2). Thus, according to the anti-inflammatory properties of sumac, it may reduce the risk of atherosclerosis.

Some inflammatory markers are used as predictors for coronary risk evaluation (14). High-sensitivity C-reactive protein (hs-CRP) concentration is a predictor of atherosclerotic activity (15). It is also known to be a good factor for the identification of the causes which lead to atherosclerosis (15). Moreover, homocysteine can be named as another important predictor of heart diseases (14, 16). According to studies, raised serum homocysteine is independently accompanied by atherosclerosis (16). This is while, T2DM related factors including insulin level, malondialdehyde, paraoxonase 1, and hs-CRP have decreased after treatments with sumac (17).

Although, herbal therapy has shown promising effects in the treatments of metabolic disorders including Spirulina (18) and *M. officinalis* supplementation (19), it can ameliorate hyperlipidemia, amend BMI and blood pressure status (20), and improve insulin level (21). As there are few studies investigating the effect of sumac on hs-CRP, and no study to assess the effect of homocysteine; we planned to investigate the effect of sumac on oxidative predictors of atherosclerosis like hs-CRP and homocysteine among T2DM patients.

Materials and Methods

The present single-blinded, parallel-randomized, controlled clinical trial was designed to investigate the effect of sumac powder on blood levels of hs-CRP and homocysteine in T2DM patients. The protocol of the study was in accordance to Helsinki declaration and was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (ID: 17/1/171485). The protocol of study was registered prospectively in the Iranian Registry of Clinical Trials (IRCT, www.irct.ir) under the registration ID of IRCT2014050410826N9. Eligible individuals with T2DM were patients who referred to the diabetes center of Ardakan city (Mehr Clinic), Yazd province, Iran, after being informed about the study and signed the informed consent form to participate and enter the study. Participants were eligible if they (i) were aged 30-60 years, (ii) had been suffering from diabetes for at least 3 years, (iii) were not professional athletes, (iv) did not suffer from liver, biliary and renal disorders, (v) had no history of using antioxidant drugs and supplements for at least 3 months before the study, (vi) were not pregnant or in lactation period, (vii) were nonsmoker and nondrinker, and finally (viii) were not using insulin to control diabetes. Participants were excluded if any of the following conditions occurred during the study period including (i) using sumac less than 80% of allocated, (ii) obligation to change the dosage or type of drugs or to use insulin or any kind of antioxidants, (iii) occurrence of pregnancy, (iv) diagnosed with liver, biliary or renal diseases, and finally (v) unwillingness to continue cooperation with the study.

With consideration of homocysteine as primary outcome, study power at the level of 80%, α=0.05, and the attrition rate of 10%, 30 participants were estimated as the minimum sample size required for each group (22). Eligible volunteers were randomly assigned into two groups (intervention or control) using computerized generated block random number table (1:1). The allocation remained blind using sealed envelopes, prepared by a person out of the study, and until the beginning of the study. Due to the need for high amount of placebo, we were not able to blind the participants in the placebo group. After allocating participants to two groups, the demographic data form was completed by each participant. Participants in both groups were asked to consume low-fat yogurt (0.5% fat) with their lunch and dinner (twice a day) from the same brand, Porana (Yazd, Iran). Individuals in the intervention group received 3 grams of sumac powder added to their yogurt 2 times per day (totally, 6 grams per day) for 3 months, while the participants in the control group did not consume sumac powder. Sumac powder was provided from valid herbal medicine centers and was approved by a member of the pharmacognosy center of Shahid Sadoughi University of Medical Sciences; while packed in 3 grams sachets.

At the beginning of the study, 90 sachets were given to the participants of the intervention group to use in the first half of the study period (45 days). Phone calls were applied to ensure the consumption of powder and any possible side effects. After passing the first 45 days of the intervention, the

participants of the intervention group were invited to receive their second quota (other 90 sachets) for the remained half of the study. Participants were asked to bring back the sumac sachets, which were not consumed, on the day 45 and 90, from the first and second quota, respectively. Adherence to the study protocol was assessed by counting the unconsumed sachets brought back by participants. Thus, those who had consumed less than 80% of the amount of given sumac, they were excluded from the study. Participants were requested not to change their diabetic diet, physical activity level, lifestyle, and drug dosages too. They were asked to visit the physicians collaborating in our study by presenting their designed membership cards. Physicians were also wanted not to alter patients' drugs or related dosages unless it was necessary.

Weight was measured in the lightest possible clothing status, utilizing the Seca scale (Hamburg, Germany) with an accuracy of 100 grams. Stadiometer was employed to measure height with the accuracy of 0.5 cm in a standing position without shoes or hat, while the participant's head, shoulder blades, buttocks, and heels had touched the wall. BMI was computed using the standard formula [weight (kg) divided by the height squared (m^2)]. A 3-day (2 week days and one week end) 24-hour food record was applied to estimate the intake of energy, macronutrients, and micronutrients at baseline and at the end of the study. Records were analyzed using the 4th version of the nutritionist computer program (Nutritionist IV). Participants were demanded to maintain their physical activity level during the study. For assessments, the international physical activity questionnaire (IPAQ) was used at the baseline and the end of the study (23) and participants were followed for 90 days. A 10 mL venous blood was taken on the 90th day after 10-12 hours of overnight fasting at the beginning and the end of the study to determine serum FBS, homocysteine, and hs-CRP. In order to reduce the errors, all the biochemical tests were done by the same laboratory.

Kolmogorov-Smirnov test was used to evaluate the normality of data. For the skewed data, the logarithm of non-normal data was used in the analysis. Independent sample t-test and paired t-test were utilized to compare differences between the groups and within the group, respectively. Mean changes between groups were analyzed employing the independent sample t-test. All the statistical analysis was done using SPSS software (Version 16, Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Results

Figure 1 demonstrates the study procedure. One hundred and ten T2DM patients were assessed for eligibility; among them, 35 did not meet the inclusion criteria, 12 were not willing to participate in the study, and 3 stated other reasons not to enter the study. Fifty-eight out of 60 patients completed the investigation (Intervention n=30 and control group n=28).

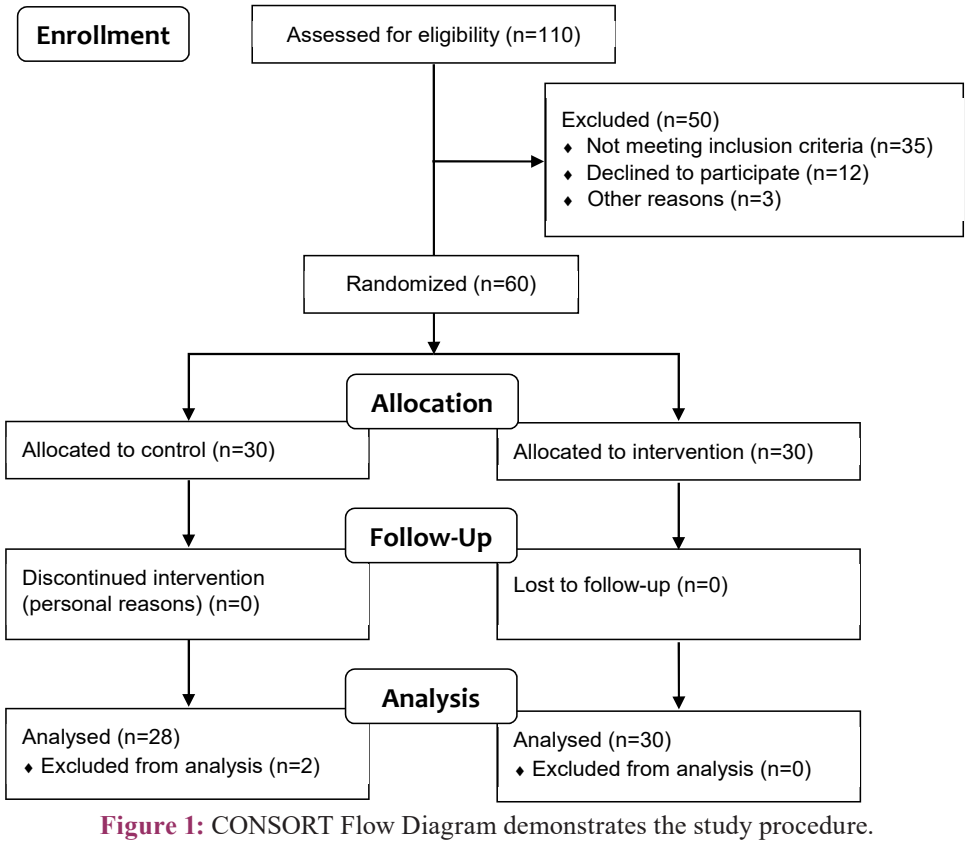

Figure 1: CONSORT Flow Diagram demonstrates the study procedure.

The mean±SD for age was 52.30±7.05 years in the intervention, and 51.61±7.07 years in the control group. Age was not statistically different between the groups at the beginning of the study (p=0.9). The mean for BMI was not significantly different between the groups (p=0.9). Baseline characteristics were shown in Table 1.

Dietary assessment analysis did not reveal any statistically significant changes within the group for energy intake (p=0.3 and 0.06 in intervention and control groups, respectively). During the study, no significant alterations were seen between groups for dietary intake components including energy (p=0.14), consumption of carbohydrates (p=0.95), fats (p=0.66), and proteins (p=0.93). Table 2 compares the energy, carbohydrate, fat, and protein between groups. The distribution of participants for the intensity of physical activity was not statistically significantly between the groups (p=0.8). Table 3 shows results for physical activity before and after the study for the intervention and control groups.

As shown in Table 4, FBS insignificantly changed within the group in both groups (p=0.4 and 0.3, for intervention and control groups, respectively), and after the study, no significant change was noticed between the groups (p=0.1).

Table 1: Baseline characteristics of participants demonstrated in intervention and control groups.

Variable		Group		
		Intervention (n=30)	Control (n=28)	*P* value
Gender	Male, n (%)	21 (70)	13 (46.4)	0.6*
	Female, n (%)	9 (30)	15 (53.6)	
Age (years)		52.30±7.05	51.61±7.07	0.9‡
Height (cm)		165.10±8.58	161.54±9.35	0.8‡
Weight (kg)†		78.90±12.19	74.43±9.93	0.7‡
BMI (kg/m^2)†		29.10±5.30	28.65±4.15	0.9‡

All data were reported as mean±SD, otherwise they were mentioned. P<0.05 was considered as significant level. *Chi-square analysis. †Logarithms of data were used for analysis. ‡P was calculated for differences between the groups using indepemdant sample t-test.

Table 2: Energy, carbohydrate, fat, protein, and vitamins E and C intake illustrated at baseline and after the study in intervention and control groups.

Variable	Intervention group (n=30)				Control group (n=28)				*P* value‡	*P* value#
	Before	After	Mean difference	*P* value†	Before	After	Mean difference	*P* value†		
Energy (Kcal)*	2373.83± 923.51	2528.30± 632.08	154.47± 817.71	0.3	2277.14± 831.20	2752.21± 1.41	475.07± 830.49	0.06	0.4	0.14
Carbohydrate (g)*	406.91± 197.32	390.33± 108.72	-16.58± 171.17	0.6	393.39± 156.92	374.28± 126.08	- 19.11± 143.99	0.2	0.6	0.95
Fat (g)*	54.31± 30.50	52.64± 18.98	-1.67± 26.67	0.7	45.95± 18.39	50.36± 22.54	4.41± 20.77	0.3	0.6	0.66
Protein (g)*	82.56± 34.26	79.11± 23.52	-3.45± 30.35	0.3	83.90± 33.42	86.73± 30.29	2.83± 31.97	0.5	0.2	0.93

All data were reported as mean±SD, otherwise they were mentioned. P<0.05 was considered as significant level. *Logarithms of data were used for analysis. †P for difference between baseline and after the study was calculated by paired t-test. ‡P after the study for difference between the groups was calculated utilizing independent sample t-test. #P for mean change between the groups was assessed employing independent sample t-test.

Table 3: Relative abundance of participants for intensity of physical activity shown before and after the study in the intervention and control groups.

Variable	Intervention group (n=30)			Control group (n=28)		
	Before	After	*P* value*	Before	After	*P* value*
Light, n (%)	13 (43.3)	12 (40)	0.8	13 (46.6)	12 (42.8)	0.8
Medium, n (%)	17 (56.6)	18 (60)		15 (53.6)	16 (57.1)	

Results for physical activity intensity were based on records from IPAQ questionnaire completed at the baseline and at the end of the study. *Chi-square test. P<0.05 was considered as significant level.

Table 4: Mean±SD for FBS, high sensitivity C-reactive protein and homocysteine exhibited at the baseline and after the study in the intervention and control groups.

Variable	Intervention group (n=30)				Control group (n=28)				*P* value‡	*P* value#	*P* value††
	Before	After	Mean difference	*P* value†	Before	After	Mean Difference	*P* value†			
FBS* (mg/dL)	177.70± 58.31	172.20± 71.17	-5.5± 65.69	0.4	183.89± 57.69	188.29± 49.45	4.4± 54.04	0.3	0.6	0.1	0.94
Homocysteine* (µmol/L)	18.07± 6.06	25.79± 4.61	7.72± 6.90	<0.001	16.11± 6.48	23.16± 3.65	7.06± 5.78	<0.001	0.2	0.02	0.69
hs-CRP* (mg/L)	1.04± 0.93	1.26± 1.21	0.22± 1.12	0.2	1.65± 2.17	3.08± 4.30	1.43± 2.76	0.001	0.4	0.02	0.03

All data were presented as mean±SD. P<0.05 was considered at significant level. hs-CRP: High sensitivity C-reactive protein. *Logarithms of data were used for analysis. †*P* within the group was calculated utilizing paired t-test. ‡*P* for differences before the study was calculated between the groups employing independent sample t-test. #*P* for difference between groups after the study was determined applying independent sample t-test. ††*P* for mean change between the groups was evaluated using independent sample t-test.

FBS modification happened during the study period between groups but not significantly (p=0.94). During the study, serum homocysteine level increased in both groups (mean difference±SD in intervention=7.72±6.90 (p<0.001), and for control=7.06±5.78 (p<0.001)); however the mean difference was not significant between the groups (p=0.69). The hs-CRP in intervention group showed a rise, but the increment was not statistically significant (mean difference±SD=0.22±1.12, p=0.2); while, the increment was significant in the control group (mean difference±SD=1.43±2.76, p=0.001). In addition, the mean change for hs-CRP between the groups was statistically significantly (p=0.03). Also after the study, homocysteine and hs-CRP levels were different between the groups (p=0.02). Possible side effects were checked using phone calls during the study and at the end of the study, no side effects were reported by participants.

Discussion

Our results indicated that daily consumption of sumac powder in the amount of 6 grams in patients with T2DM significantly raised homocysteine, but the mean difference between using and not using sumac was not significant (p=0.69). The hs-CRP level increased in the control group in comparison to the intervention group revealing that sumac could prevent the rise in hs-CRP. Also, the mean differences between the groups showed a beneficial effect of sumac on hs-CRP. Rahideh *et al.* similarly investigated the effect of sumac powder on malondialdehyde, paraoxonase 1, and hs-CRP (17) and noticed a reducing effect of sumac on hs-CRP, which is in line with our finding. There are differences between our works that might slightly affect the results including use of lactose as a placebo in their work and consuming yogurt with sumac in our study. The strength of Rahideh *et al.*'s work (17) can be use of higher amounts of sumac powder. In our study, we used 6 grams per day of sumac, while in their research, 3 grams per day were consumed.

Sumac similar to other usual condiments is rich in antioxidants and is widely used in eastern countries. Laboratory analysis showed that GA is an active substance of sumac (6). In a clinical trial done by Ferk *et al.*, 8 rats were fed by 0.02 g/kg body weight/day of sumac and 0.2 mg/kg body weight/day of GA for 3 days. A possible powerful protective effect for GA against ROS-induced DNA damage was observed (24). The imbalance between ROS and antioxidants suggested that it can lead to oxidative stress and triggers diseases such as diabetes. Consequently, the imbalance of ROS can cause vascular and neurodegenerative disorders related to diabetes. These effects are due to ROS damages and a change in DNA signaling (25). As GA is found in sumac, sumac might prevent the increment of ROS and its effect on T2DM (6). The results of Chacraborty *et al.*'s study revealed a protective effect of sumac against DNA damage. It was proposed that GA may be responsible for these properties of sumac. Substances exist in sumac such as tannin and GA (26). Tannic acid extracted from *Rhus chinensis Mill* by improving antioxidants was demonstrated to clear the O-2 glycoprotein (7).

In the study of shidfar *et al.* by using total antioxidant capacity (TAC), the antioxidant properties of sumac were illustrated. In this study, in comparison with baseline, TAC significantly increased (p<0.0001), and also the difference between the groups was significant (p<0.05) (27). Moreover, a probable hypoglycemic effect of sumac might be

due to regulating insulin secretion or action (28). Lack of placebo and blinding the participants in our investigation can be the possible cause of these discrepancies between studies. In addition, presenting lactose as a placebo can affect the results of the above-mentioned study. Mirhadi *et al.* investigated the effect of sumac powder on blood glucose in rats revealing a significant increment in blood glucose ($p<0.05$). In this study, the dosage of sumac was 0.5 g/kg body weight of rats, while this high dosage can cause a rise in blood glucose (29) due to the effect on the pancreas beta cells' function. We also observed some increases in blood glucose, although it was not significant. Differences in doses of sumac and its safe dose can explain the differences in the findings. On the other hand, an investigation by Giancarlo *et al.* exhibited that alcoholic extract of sumac fruit can lead to a reduction in blood glucose by suppression of the alpha-amylase enzyme, suggesting this effect to be due to the existence of flavonoids in sumac (30). Bringing these findings together, considering the hypoglycemic effect of quercetin, the hypoglycemic effect of sumac extract can be related to the presence of this compound based on increasing insulin sensitivity (31).

Polyphenol compounds existing in sumac were shown to have beneficial effects on T2DM by lowering the digestion of starch via suppressing α-amylase and α- glucosidase. Moreover, these compounds can protect β-cells of the pancreas from the damaging effects of high blood glucose (6). Also, they may inhibit series of reactions on proteins called glycation and thus, forming glycated products (31). It was demonstrated that polyphenols extracted from plants can prevent chronic diseases caused by inflammation such as diabetes (32). From other points of view, numerous studies reported that the aggregation of the immigration of smooth muscle cells plays an important role in the pathogenesis of the obstructive vascular disease (33, 34). Antioxidants can also prevent atherosclerosis (35, 36). Tannin and its derivatives were mentioned as vigorous antioxidants to inhibit the immigration of smooth muscle cells (37). Sumac is a rich source of tannin and use of pure tannin extracted from sumac was shown to cause a 62% reduction in the immigration of smooth muscle cells (38).

A study done by Ahmadi *et al.* revealed that pomegranate peel extract, a rich source of tannin, can considerably reduce the formation of atherosclerosis rate and lead to early repair of endothelial damage (39). These findings displayed that the tannin in sumac could prevent atherosclerosis (38) denoting to the reason of discrepancy in the present study with others. The participants of the present study were older than other studies as the mean age of participants in the intervention group was 52.30±7.05 years and in the control group was 51.61±7.07 (17). On the other hand, participants of our study suffered from diabetes for 7.8 years in the intervention and 7.6 years in the control group (data were not shown). If this intervention was done on new cases of diabetes or even pre-diabetics, it might show a positive effect. The considerable point is a few studies regarding the antidiabetic and antioxidant effects of sumac, especially in humans. Most of the studies have been done on experimental animals (26, 29, 40). The conditions of the laboratory environment were highly controlled and the development of disease in animals was artificial revealing the need for more trials in human beings.

There were limitations in our study. In our work, we intended to use a placebo in the control group to increase the quality of the trial. However, due to the high number of capsules needed for 6 grams of sumac or placebo, it was not feasible, so it can be considered as the limitation of our study. Also, we were not able to blind our study. Our participants were suffering from diabetes for a long period, which might affect our results. We used a higher dosage of sumac in comparison to a similar study done by Rahideh *et al.* (17) and also, for the first time, we assessed the effect of sumac powder on homocysteine in T2DM patients. According to the lack of studies that investigated the effect of sumac in T2DM, it is recommended further studies with higher sample sizes, different dosages, and trial periods, assessing different oxidant factors, controlling possible confounders, and including younger participants to be conducted. Also, it can be useful to include pre-diabetic patients or T2DM patients who have no struggle with T2DM for a long time.

Conclusion

This study showed that daily consumption of sumac powder for 3 months may not have a reducing effect on fasting serum homocysteine in patients with T2DM. This is while, 6 grams of sumac per day for 3 months could inhibit increase in hs-CRP level of individuals with T2DM.

Acknowledgement

The research executive team would like to warmly thank all the participants and the staff of the Diabetes Center of Ardakan City (Mehr Clinic), Yazd province, Iran. We also have to thank the Research Council of Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran for the scientific and financial support of the present study. All

procedures performed in studies involving human participants were in accordance with the Helsinki Declaration and study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (ID: 17/1/171485). The study was registered prospectively in the Iranian Registry of Clinical Trials (IRCT, www.irct.ir) under the registration ID of IRCT2014050410826N9. All participants signed an informed consent form prior to enrollment.

Authors' Contribution

AN, MRF, AV, and MAM conceptualized and designed the study. MRF, FM, and SH performed the study. AN, MRF, and MAM wrote the first manuscript draft and all authors revised and approved the final manuscript.

Conflict of Interest

None declared

References

1 Rayne S, Mazza G. Biological activities of extracts from sumac (Rhus spp.): a review. *Plant Foods Hum Nutr*. 2007;62:165-75. DOI:10.1007/s11130-007-0058-4. PMID:17909971.

2 Pourahmad J, Eskandari MR, Shakibaei R, et al. A search for hepatoprotective activity of aqueous extract of Rhus coriaria L. against oxidative stress cytotoxicity. *Food Chem Toxicol*. 2010;48:854-8. DOI:10.1016/j.fct.2009.12.021. PMID:20036300.

3 Hariri N, Darafshi Ghahroudi S, Jahangiri S, et al. The beneficial effects of sumac (Rhus coriaria L.) supplementation along with restricted calorie diet on anthropometric indices, oxidative stress, and inflammation in overweight or obese women with depression: A randomized clinical trial. *Phytother Res*. 2020;34:3041-51. DOI:10.1002/ptr.6737. PMID:32940404.

4 Alsamri H, Athamneh K, Pintus G, et al. Pharmacological and antioxidant activities of Rhus coriaria L.(Sumac). *Antioxidants*. 2021;10:73. DOI:10.3390/antiox10010073. PMID:33430013.

5 Akbari-Fakhrabadi M, Heshmati J, Sepidarkish M, et al. Effect of sumac (Rhus Coriaria) on blood lipids: A systematic review and meta-analysis. *Complement Ther Med*. 2018;40:8-12. DOI:10.1016/j.ctim.2018.07.001. PMID:30219474.

6 Shabana MM, El Sayed AM, Yousif MF, et al. Bioactive constituents from Harpephyllum caffrum Bernh. and Rhus coriaria L. *Pharmacogn Mag*. 2011;7:298-306. DOI:10.4103/0973-1296.90410. PMID:22262932.

7 Capcarova M, Slamecka J, Abbas K, et al. Effects of dietary inclusion of Rhus coriaria on internal milieu of rabbits. *J Anim Physiol Anim Nutr*. 2012;96:459-65. DOI:10.1111/j.1439-0396.2011.01164.x. PMID:21585564.

8 Hashem-Dabaghian F, Ghods R, Shojaii A, et al. Rhus coriaria L., a new candidate for controlling metabolic syndrome: a systematic review. *J Pharm Pharmacol*. 2022;74:1-12. DOI:10.1093/jpp/rgab120. PMID:34673978.

9 Hosseini SE, Rezaei E, Mehrabani D, et al. Effect of pomegranate juice on lipid profile in streptozotocin-induced diabetic adult male rats. *J Exp Anim Biol*. 2013;2:13-20.

10 Lotfi MH, Saadati H, Afzali M. Prevalence of diabetes in people aged ≥ 30 years: the results of screen-ing program of Yazd Province, Iran, in 2012. *J Res Health Sci*. 2014;14:87-91. PMID:24402857.

11 La Sala L, Prattichizzo F, Ceriello A. The link between diabetes and atherosclerosis. *European journal of preventive cardiology*. 2019;26(2_suppl):15-24. DOI:10.1177/2047487319878373. PMID:31722564.

12 Islam MA, Amin MN, Siddiqui SA, et al. Trans fatty acids and lipid profile: A serious risk factor to cardiovascular disease, cancer and diabetes. *Diabetes Metab Syndr*. 2019;13:1643-7. DOI:10.1016/j.dsx.2019.03.033. PMID:31336535.

13 Montero-Vega MT. The inflammatory process underlying atherosclerosis. *Crit Rev Immunol*. 2012;32:373-462. DOI:10.1615/critrevimmunol.v32.i5.10. PMID:23339672.

14 Sreckovic B, Sreckovic VD, Soldatovic I, et al. Homocysteine is a marker for metabolic syndrome and atherosclerosis. *Diabetes Metab Syndr*. 2017;11:179-82. DOI:10.1016/j.dsx.2016.08.026. PMID:27600468.

15 Calabro P, Golia E, Yeh ET. CRP and the risk of atherosclerotic events. *Seminars in Immunopathol*. 2009;31:79-94. DOI:10.1007/s00281-009-0149-4.

16 Kim JM, Park KY, Shin DW, et al. Relation of serum homocysteine levels to cerebral artery calcification and atherosclerosis. *Atherosclerosis*. 2016;254:200-4. DOI:10.1016/j.atherosclerosis.2016.10.023. PMID:27760401.

17 Rahideh ST, Shidfar F, Khandozi N, et al. The effect of sumac (Rhus coriaria L.) powder on insulin resistance, malondialdehyde, high sensitive C-reactive protein and paraoxonase 1 activity in type 2 diabetic patients. *J Res Med Sci*. 2014;19:933-8. PMID:25538775.

18 Rezaiyan M, Sasani N, Kazemi A, et al. The effect of spirulina sauce on glycemic index,

lipid profile, and oxidative stress in type 2 diabetic patients: A randomized double-blind clinical trial. *Food Sci Nutr*. 2023;11:5199-208. DOI:10.1002/fsn3.3479. PMID:37701187.

19 Jandaghi P, Noroozi M, Ardalani H, et al. Lemon balm: A promising herbal therapy for patients with borderline hyperlipidemia—A randomized double-blind placebo-controlled clinical trial. *Complement Ther Med*. 2016;26:136-40. DOI:10.1016/j.ctim.2016.03.012. PMID:27261994.

20 Ardalani H, Jandaghi P, Meraji A, et al. The Effect of Cynara scolymus on blood pressure and BMI in hypertensive patients: A randomized, double-blind, placebo-controlled, clinical trial. *Complement Med Res*. 2020;27:40-6. DOI:10.1159/000502280. PMID:31484191.

21 Mohsenpour MA, Samadani M, Shahsavani Z, et al. The effect of celery (Apium graveolens) powder on cardiometabolic factors in overweight/obese individuals with type 2 diabetes mellitus: A pilot randomized, double-blinded, placebo-controlled clinical trial. *Food Sci Nutr*. 2023;11:5351-63. DOI:10.1002/fsn3.3493. PMID:37701242.

22 Aghamohammadi V, Gargari BP, Aliasgharzadeh A. Effect of folic acid supplementation on homocysteine, serum total antioxidant capacity, and malondialdehyde in patients with type 2 diabetes mellitus. *J Am Coll Nutr*. 2011;30:210-5. DOI:10.1080/07315724.2011.10719962. PMID:21896879.

23 Mohsenpour MA, Mohammadi F, Razmjooei N, et al. Milk kefir drink may not reduce depression in patients with non-alcoholic fatty liver disease: secondary outcome analysis of a randomized, single-blinded, controlled clinical trial. *BMC Nutr*. 2023;9:80. DOI:10.1186/s40795-023-00732-x. PMID:37386551.

24 Ferk F, Chakraborty A, Simic T, et al., editors. Antioxidant and free radical scavenging activities of sumac (Rhus coriaria) and identification of gallic acid as its active principle. BMC Pharmacology; 2007: BioMed Central.

25 Umeno A, Biju V, Yoshida Y. In vivo ROS production and use of oxidative stress-derived biomarkers to detect the onset of diseases such as Alzheimer's disease, Parkinson's disease, and diabetes. *Free Radic Res*. 2017;51:413-27. DOI:10.1080/10715762.2017.1315114. PMID:28372523.

26 Chakraborty A, Ferk F, Simic T, et al. DNA-protective effects of sumach (Rhus coriaria L.), a common spice: results of human and animal studies. *Mutat Res*. 2009;661:10-7. DOI:10.1016/j.mrfmmm.2008.10.009. PMID:19022266.

27 Shidfar F, Rahideh ST, Rajab A, et al. The Effect of Sumac (Rhus coriaria L.)Powder on Serum Glycemic Status, ApoB, ApoA-I and Total Antioxidant Capacity in Type 2 Diabetic Patients. *Iran J Pharm Res*. 2014;13:1249-55. PMID:25587314.

28 Mohammadi S, Montasser Kouhsari S, Monavar Feshani A. Antidiabetic properties of the ethanolic extract of Rhus coriaria fruits in rats. *Daru*. 010;18:270-5. PMID:22615627.

29 Mirhadi K, Daryoush B, Saeid S. Orally administration effect of sumac on blood sugar in rat. *J Advance Environ Biol*. 2011;5:2077-9.

30 Giancarlo S, Rosa LM, Nadjafi F, et al. Hypoglycaemic activity of two spices extracts: Rhus coriaria L. and Bunium persicum Boiss. *Nat Prod Res* 2006;20:882-6. DOI:10.1080/14786410500520186. PMID:16753927.

31 Yan SX, Li X, Sun CD, et al. [Hypoglycemic and hypolipidemic effects of quercetin and its glycosides]. *Zhongguo Zhong Yao Za Zhi*. 2015;40:4560-7. PMID:27141664.

32 Yahfoufi N, Alsadi N, Jambi M, et al. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients*. 2018;10:1618. DOI:10.3390/nu10111618. PMID:30400131.

33 Rudijanto A. The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. *Acta Med Indones*. 2007;39:86-93. PMID:17933075.

34 Doran AC, Meller N, McNamara CA. Role of smooth muscle cells in the initiation and early progression of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2008;28:812-9. DOI:10.1161/ATVBAHA.107.159327. PMID:18276911.

35 Ma A, Qi S, Chen H. Antioxidant therapy for prevention of inflammation, ischemic reperfusion injuries and allograft rejection. *Cardiovasc Hematol Agents Med Chem*. 2008;6:20-43. DOI:10.2174/187152508783329966. PMID:18220719.

36 Siekmeier R, Steffen C, März W. Role of oxidants and antioxidants in atherosclerosis: results of in vitro and in vivo investigations. *J Cardiovasc Pharmacol Ther*. 2007;12:265-82. DOI:10.1177/1074248407299519. PMID:18172221.

37 Harimaya K, Tanaka K, Matsumoto Y, et al. Antioxidants inhibit TNFα-induced motility and invasion of human osteosarcoma cells: possible involvement of NFκB activation. *Clin Exp Metastasis*. 2000;18:121-9. DOI:10.1023/a:1006791723233. PMID:11235987.

38 Zargham H, Zargham R. Tannin extracted from Sumac inhibits vascular smooth muscle cell migration. *Mcgill J Med*. 2008;11:119-23. PMID:19148309.

39 Ahmadi M, Nili N, Haghjooy Javanmard S, et

al. Pomegranate Peel Extract Supplementation Increases the Number of Endothelial Progenitor Cells and Attenuates the Development of Atherosclerosis Plaque. *J Isfahan Med School*. 2012;30.

40 Salimi Z, Eskandary A, Headari R, et al. Antioxidant effect of aqueous extract of sumac (Rhus coriaria L.) in the alloxan-induced diabetic rats. *Indian J Physiol Pharmacol*. 2015;59:87-93. PMID:26571989.