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Sumac as a novel adjunctive treatment in hypertension: A randomized, double-blind, placebo-controlled clinical trial

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Background: Sumac (*Rhus coriaria* L., Anacardiaceae) is a medicinal plant traditionally used for the treatment of cardiovascular disorders. This study was designed to evaluate the effects of sumac fruits in hypertensive patients. **Material and Methods:** A randomized, double-blind, placebo-controlled clinical trial was conducted on 80 hypertensive patients who were receiving captopril (25 mg/day). The patients were randomly divided into 2 groups: the first group received *R. coriaria* fruit capsules (500 mg twice a day) and captopril (25 mg once a day), and the second one received placebo capsules (500 mg starch twice a day) and captopril (25 mg once a day), for 8 weeks. Blood pressure (BP) and body weight index (BMI) in all patients were determined every week. Phytochemical analysis of *R. coriaria* fruits was performed by using HPLC–DAD/QTOF-MS for analysing its phenolic compounds. **Results:** Data indicated that hypertension was decreased significantly in *R. coriaria* group compared to baseline and placebo groups after 8 weeks, but BMI was not demonstrated a marked change in comparison with baseline and placebo groups. Moreover, the most abundant phenolic compounds identified in *R. coriaria* fruits were luteolin, apigenin, and quercetin flavonoids. **Discussion:** This finding suggests that *R. coriaria* fruits could be used as an effective natural remedy for management of hypertension. Since flavonoids were the main chemical constituents of this plant, its antihypertensive activity could be attributed to such compounds.

Keywords: *Rhus coriaria* L., Sumac, Anacardiaceae, blood pressure, body mass index, flavonoids,

Introduction

Hypertension (HTN: Blood pressure above 140/90 mmHg) is one of the most important medical problems worldwide [1]. It is the most common, readily identifiable and reversible risk factor for stroke, myocardial infarction, congestive heart failure (CHF), renal failure, atrial fibrillation, aortic dissection, and coronary and peripheral arterial diseases [2, 3]. The global burden of HTN is increasing due to escalating obesity, population aging and urbanization in developed and developing countries [4]. Prevention and treatment of obesity, avoidance of high sodium chloride intake, appropriate amounts of aerobic physical activity, adequate dietary and calcium intakes, limiting alcohol consumption and avoiding cigarette smoking are appropriate strategies to reduce cardiovascular disease risk, morbidity and mortality due to HTN [5]. The sympathetic nervous system overactivity [6] and increase in norepinephrine cause hypertrophy of cardiac and vascular cells and stimulate renin release [7]. So, renal, hormonal and vascular mechanisms are involved and conspire in a myriad of ways to produce HTN. Over time, endothelial dysfunction, neuro-hormonal activation, vascular inflammation and elevated Blood pressure (BP) cause re-modelling of both small and large arteries which further perpetuates HTN. As a result, apart from life style modification, most patients need multiple antihypertensive drugs of different classes to overcome multiple mechanisms suspected to have a role in inducing their HTN. Initiation of drug therapy is recommended for individuals with systolic BP above 140 mmHg or diastolic BP more than 90 mmHg when re-measured at least three times over at least four weeks. However, if the level of BP is very high (> 180/110 mmHg) or symptomatic end organ damage is manifested at first presentation; medication should be started before the definite diagnosis is established. The degree of benefit derived from antihypertensive agents is related to the magnitude of the BP reduction [8]. Lowering systolic BP by 10-12 mmHg and diastolic BP by 5-6 mmHg confers relative risk reductions of 35-40% for stroke and 12-16% for coronary heart disease (CHD) within five years of initiating treatment [9]. The optimal goal of antihypertensive therapy in patients with 60 years old or older, who do not have diabetes or chronic kidney disease, is <150/90 mmHg; and in patients with 18 to 59 years old without major comorbidities, is <140/90 mmHg [10]. Control is enhanced when access to health care is readily available, frequent contact with the same physician is maintained, and physician performance is monitored [11]. The side effects of antihypertensive drugs such as dizziness, dehydration, constipation and drowsiness have a pivotal role in discontinuation of therapy [12]. In recent years, herbal remedies such as saffron, celery, hawthorn and garlic are used for management of hypertension [13]. *Rhus coriaria* L., commonly called tanner's sumac is a member of

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Anacardiaceae family. Beneficial effects of sumac on cardiovascular diseases are reported [14, 15]. However, clinical antihypertensive activity of *R. coriaria* has not been investigated yet. The aim of the present work was to investigate the efficacy of sumac fruits in management of hypertension, as well as analysing its chemical components. Our results clarify the efficacy of this medicinal plant on clinical BP. So, the results of this study introduce this plant as a promising herbal antihypertensive agent.

Results

Out of 95 patients, 80 patients [39 (48.75%) females and 41 (51.25%) male] accomplished this trial. The *R. coriaria* group, included 21 (53.75%) men and 18 (46.25%) women with an average age of 59.76±6.17 years old, and the placebo group included 21 (51.25%) men and 20 (48.75%) women with an average age of 57.52±7.43 years old. The baseline systolic blood pressure/diastolic blood pressure (SBP/DBP) values in *R. coriaria* and placebo groups were 145.34/90.95 mmHg and 143.64/90.51 mmHg, respectively; and the baseline BMI values in *R. coriaria* and placebo groups were 30.83 kg/m^2 and 31.13 kg/m^2, respectively. There were no significant differences between demographic characteristics of the outpatients in these two groups ($P > 0.05$) (Tab 1).

Tab. **1** Baseline characteristics of the outpatients

	Placebo	*R. coriaria*	*P*-value
Sex:			0.46
Male	21	21	
Female	20	18	
Age	57.52 ± 7.43	59.76 ± 6.17	0.33
Weigh	80.61 ± 9.69	81.55 ± 7.40	0.82
BMI	31.13 ± 1.95	30.83 ± 2.21	0.42
SBP	143.64 ± 1.79	145.34 ± 2.08	0.92
DBP	90.51 ± 1.81	90.95 ± 1.97	0.93

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Differences between groups were analysed by ANOVA followed by Tukey's honestly significant difference test.
Values are expressed as mean ± SD.

At the end of week 8, the SBP/DBP values in *R. coriaria* and placebo groups were 115.21/78.33 mmHg and 131.39/81.66 mmHg, respectively; and BMI values were 30.29 kg/m^2 in *R. coriaria* and 30.54 kg/m^2 in placebo group. Also, it was obvious that, *R. coriaria* decreased systolic (Fig 1) and diastolic BP (Fig 2). These results showed a significant decrease in BP level in *R. coriaria* group as compared to the placebo group after 8 weeks ($P < 0.05$) and no significant decrease on BMI in two groups after 8 weeks (Fig 3) ($P >$ 0.05).

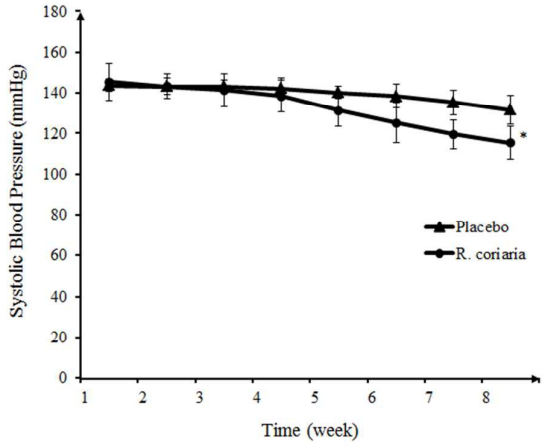

Fig. **1** Decrease in (SBP) Systolic Blood Pressure in response to Sumac in comparison with placebo. Statistical analyses showed a significant difference between sumac and placebo group and baseline. ($P < 0.05$)

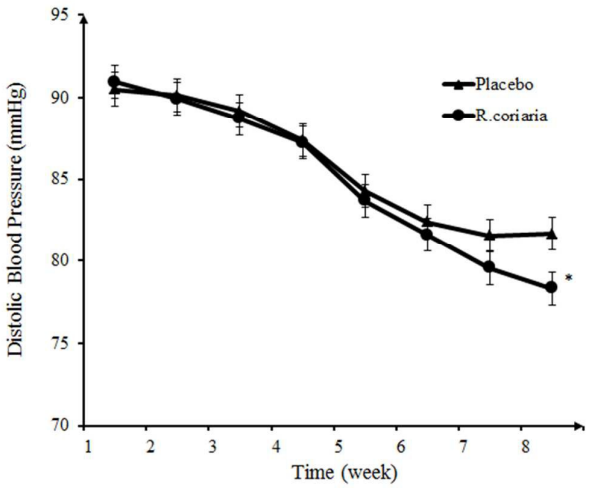

Fig. **2** Decrease in Diastolic Blood Pressure (DBP) in response to Sumac in comparison with placebo. Statistical analyses showed a significant difference between sumac and placebo group and baseline. ($P < 0.05$)

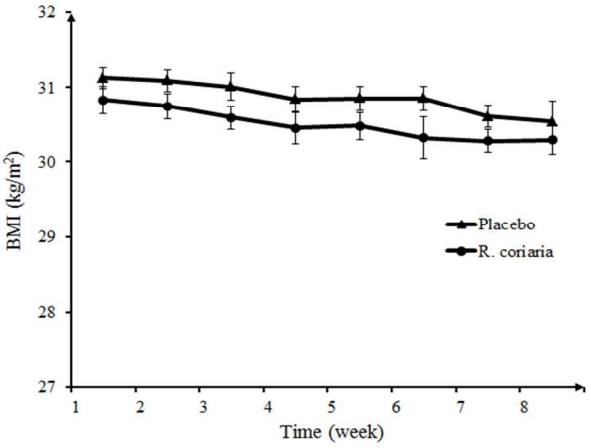

Fig. 3 Body Mass Index (BMI) in response to Sumac in comparison with placebo group. Statistical analyses showed no significant difference between Sumac and placebo group, as well as baseline ($P < 0.05$)

There was a significant reduction in SBP and DBP after 8 weeks of *R. coriaria* administration when compared with baseline. However, such an effect was not observed in the placebo group ($P > 0.05$) (Tab 2).

Tab. 2 BMI, SBP and DBP reduction obtained with the *R. coriaria* compared with placebo in patients during 8 weeks

	Placebo	*R. coriaria*	*P*-value
BMI	0.59 ± 2.45	0.54 ± 3.12	0.71
SBP	12.25 ± 6.12	30.13 ± 4.45*	0.03
DBP	8.85 ± 3.54	12.62 ± 3.81*	0.04

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values are expressed as mean ± SD
*$P < 0.05$, when compared between groups.

Clinical complications were determined as any unwanted effects that occurred from the time of informed consent until one month after the last treatment dose. No serious adverse effects were reported or observed during this trial, except for the *R. coriaria* group in which a patient reported drowsiness. Among the patients who could not accomplish this study there were no reports of any side effects, and most of them left due to missing the follow up. In placebo group two patients reported insomnia and headache. All groups were well matched, and no statistically significant differences were observed among groups on the frequency of side effects (Tab 3).

Tab. 3 Frequency of reported adverse effects among the three study groups.

	R. coriaria group	Placebo group	*P*-value
Weakness	1	0	1.61
Drowsiness	0	0	1.00
Insomnia	0	1	1.83
Headache	0	1	1.00

The Fisher's exact test was applied for analysis of side effects in both groups

In this study the efficacy and tolerability of *R. coriaria* fruit extracts combined with captopril in improving BP and decreasing BMI was investigated. The results showed that *R. coriaria* significantly decreased BP in hypertensive patients compared to the baseline and group received only captopril after 8 weeks (Tab 4). Therefore, *R. coriaria* may serve as an effective complementary therapy along with conventional antihypertensive agents for reducing hypertension.

Tab. 4 Characteristics of randomized subjects before and after 8 weeks.

Variable	Placebo	*R. coriaria*	*P*-value
BMI (kg/m²)			0.31
Week 0	31.13 ± 1.95	30.83 ± 1.84	
Week 8	30.54 ± 1.14	30.29 ± 1.48	
SBP (mmHg)			0.03
Week 0	143.64 ± 1.79	145.34 ± 2.08	
Week 8	131.39 ± 2.75	115.21 ± 2.89*	
DBP (mmHg)			0.04
Week 0	90.51 1.81	90.95 ± 1.97	
Week 8	81.66 1.81	78.33 ± 1.97*	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values are expressed as mean ± SD
*$P < 0.05$, when compared with baseline data

According to HPLC–DAD/QTOF-MS analyses, 191 compounds in *R. coriaria* along with their retention times (tR), mass of each phytochemical, as well as the MS/MS fragment ions used in the characterization process were identified. The HPLC analyses showed that apigenin, luteolin and quercetin were the most abundant compounds in *R. coriaria* fruits (Fig 4, Tab 5).

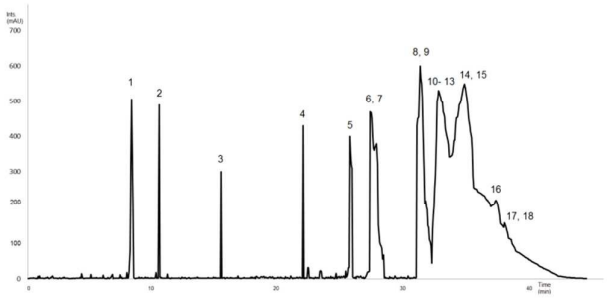

Fig. 4 HPLC analyses and base peak chromatograms (BPC) of UV at 280 nm, for the hydro-methanol extract of *R. coriaria* fruits

Tab. 5 Chemical compositions detected and characterised in *R. coriaria* fruits by HPLC–DAD/QTOF-MS

Peak	Tentative assignment	tR(min.)	[M+H]+(m/z)	[M−H]−(m/z)	Error (ppm)	mSigma	Molecular formula
1	Galloylhexose II	9.10	–	331.0669	0.6	14. 9	$C_{13}H_{16}O_{10}$
2	Digalloyl-hexoside II	11.91	–	483.0773	1.3	1.8	$C_{20}H_{20}O_{14}$
3	Tri-galloyl-hexoside III	19.07	637.1100	635.0882	1.2	2.1	$C_{27}H_{24}O_{18}$
4	Benzoic acid, 3,4,5– trihydroxy-2-oxo-1,3-propanediyl ester	25.15	–	393.0449	3.7	46.8	$C_{17}H_{14}O_{11}$
5	Dihydroxybenzoic acetate-digallate I	28.14	–	544.9894	5.2	43.9	$C_{24}H_{18}O_{15}$
6	Dihydroxybenzoic acetate-digallate III	29.60	–	546.0121	3	37.5	$C_{24}H_{18}O_{15}$
7	Apigenin glucuronide	29.89	445.0245	446.0312	−1.2	143.2	$C_{21}H_{20}O_{11}$
8	Galloyl-valoneic acid bilactone	31.10	623.1457	621.0412	−2.2	26.7	$C_{22}H_{22}O_{21}$
9	Quercetin-rhamnose malic acid I	31.18	564.8637	563.1127	3.7	4.1	$C_{25}H_{24}O_{15}$
10	Quercetin I	32.14	–	302.0119	2.8	13.0	$C_{15}H_{10}O_7$
11	Quercetin-hexose malic acid IV	32.18	581.1312	–	1.0	46.1	$C_{25}H_{24}O_{16}$
12	Isorhamentin hexosemalic acid	33.57	594.9197	–	−12.6	49.2	$C_{26}H_{26}O_{16}$
13	Kaempferol rhamnosemalic acid	33.81	–	548.1168	6.0	31.5	$C_{25}H_{24}O_{14}$
14	Quercitrin O-gallate	34.75	–	599.1019	5.1	26.1	$C_{28}H_{24}O_{15}$
15	Isorhamnetin hexoside IV	34.80	–	477.1021	5.4	14.5	$C_{22}H_{22}O_{12}$
16	Di-benzopyranofuranacetic acid deriv.	35.30	515.0526	–	7.0	50.9	$C_{23}H_{16}O_{14}$
17	Luteolin	36.32	286.8776	285.0348	−5.4	6.9	$C_{15}H_{10}O_6$
18	Quercetin II	36.58	303.0486	301.2481	0.5	2.4	$C_{15}H_{10}O_7$

Discussion

In many hypertensive patients, keeping BP in an optimal range is difficult and prescribing several drugs from different pharmacological classes of antihypertensive agents with high dosage is frequently needed. Increasing the number and dosage of drugs in 24 hours enhances the possibility of developing medical side effects but reduces patient's compliances. As a result, discontinuation of treatment is not far-fetched. Currently, introduction of some adjunctive therapies, such as herbal drugs and exercise, seems reasonable. Furthermore, optimizing the modifiable cardiovascular risk factors (i.e. high BMI and low physical activity) is important and should be taken into account.

The results from phytochemical analysis demonstrated that the most abundant constituents of *R. coriaria* were polyphenolic compounds including hydrolysable tannins, flavonoids and anthocyanins. This analysis is almost in accordance with our previous analysis on a sample of *R. coriaria* collected from different place. However a new compound, Benzoic acid, 3,4,5– trihydroxy-2-oxo-1,3- propanediyl ester, was identified in the present study. Other investigations have indicated that sumac is highly rich in cyanidin and galloyl-galactose and anthocyanin derivatives [16, 17]. A number of studies have shown that flavonoids such as quercetin can play important roles in decreasing BP [18, 19]. The potential of quercetin as an effective vasodilator has been indicated [20]. In addition, reductions in systolic, diastolic and mean arterial pressures were observed in stage 1 hypertensive patients after a high dose quercetin treatment in a randomized, double-blind, placebo-controlled, crossover study [21]. Apigenin, another flavonoid in *R. coriaria*, showed antihypertensive activity in spontaneously hypertensive rats via up-regulating the expression of angiotensin-converting enzyme 2 in kidney [22]. Renin is a crucial enzyme in the renin-angiotensin system, and its inhibition is considered as a useful approach to the treatment of hypertension. Gallic acid as another main phenolic compound of *R. coriaria* has exhibited inhibitory effect on renin. It seems that galloyl moiety and ortho-trihydroxy phenyl structures are favorable for the renin-inhibitory activity [23].

Oxidative stress, due to the accumulation of free radicals, may play an important role in pathogenesis of cardiovascular diseases like hypertension [24]. Oxidative stress stimulates the proliferation and hypertrophy of vascular smooth muscle and collagen deposition which lead to narrowing of the vascular lumen caused by thickening of the vascular media [25]. Also, increased oxidative stress can damage the endothelium and increase vascular contractile activity [26]. All these effects can explain how oxidative stress can be a cause of hypertension. So, treatment with antioxidant components is suggested for improving BP [27]. As mentioned the *R. coriaria* is highly rich in antioxidative phenolic components, such as tannins and flavonoids [28]. Thus, adjunctive therapy with *R. coriaria* can provide further protection as it contains powerful antioxidants and plays an important role in preventing free radical-induced damage in vessels endothelium [29].

The effect of flavonoid intake on body weight and BMI is already investigated [30]. Indeed, beneficial antioxidant effects can modulate BMI [31]. Also it is observed that a source of flavonoid (green tea) can reduce body weight and body fat in overweight individuals [32]. Additionally, animal studies have shown an anti-obesity effect for flavonoids, through mechanisms such as fatty acid catabolism or intervention on glucose uptake [33]. However in our study *R. coriaria* as a reach source of flavonoids could not decrease BMI in patients after 8 weeks of administration. Adverse effects such as vertigo, flashing, insomnia and headache have been reported previously in administration of antihypertensive drugs [34]. Our findings indicated that *R. coriaria* did not have serious side effects in administered dose, although more investigations are needed. Moreover,

Long term studies with larger sample size is recommended for better understanding of the *R. coriaria* effects on BP and BMI is being recommended.

Experimental

Plant Material

Sumac (*R. coriaria* L.) fruits with voucher specimen No.21121 were obtained from the Shahid Beheshti University of Medical Sciences, Teharn, Iran (Identified by Prof. Dr. Valiollah Mozafarian). The samples were transferred to the lab, dried at 70 °C for 24 hours and stored at 5 °C until used.

Study design

A randomized, parallel-group, double-blind, and placebo-controlled clinical trial was conducted on 80 hypertensive patients in the Arad Hospital, Tehran, Iran, from September to January 2014 with code of ethics No.93776 (approval date: 2014 August). During 8 weeks after, 80 patients (aged from 30 to 65 years old) with uncontrolled HTN stages [stage 1 (SBP: 140-159 and DBP: 90-99 mmHg), stage 2 (SBP: 160 – 179 and DBP: 100-109 mmHg) or stage 3 (SBP: 180 and DBP: 110) that in their medical history during the last 6 months, were receiving just captopril as an antihypertensive therapy were enrolled in our study. This study was done in accordance with the Declaration of Helsinki. Patients who had SBP more than 180 mmHg at the time of selection, documented secondary HTN, congestive heart failure, moderate to severe valvular heart disease, recent history of myocardial infarction (MI ≤ 6 months), chronic renal failure, as well as alcohol consumers and pregnant patients were excluded. Informed consent was obtained from all participants before the study began. All patients were assessed weekly for 8 weeks, and data were recorded at baseline and after every week. Parameters collected at baseline were BP, age, sex, weight, height and marital status.

Interventions

All participants were divided randomly in two groups. Each group contained 40 patients. In the sumac group, patients received captopril (25 mg/day once a day, before breakfast) plus *R. coriaria* powder capsules [1000 mg/day: 500 mg BID (twice a day), one capsule before lunch and one before dinner] and patients in the placebo group received captopril (25 mg/day once a day, before breakfast) plus placebo capsules (1000 mg/day starch: 500 mg BID, one capsule before lunch and one before dinner) as an adjunctive therapy for 8 weeks. *R. coriaria* and placebo capsules were prepared in the same way. They were similar in shape, color, size and order. All capsules were prepared by a pharmacist and packed in the same container with a code number. Thus, participants and investigators were all blind to the treatment group assignments. Participants were not permitted to receive any other antihypertensive drugs during the study time. All patients were checked regularly and their compliance and medication adherence were estimated through checking with the patient and his/her care taker along with a pill count at each visit.

Measurement of BP

Standard BP was assessed by trained research nurses with a random-zero sphygmomanometer in accordance with American Heart Association protocols [35]. Due to measurement bias at each visit, controlling of BP was performed with the same nurse and sphygmomanometer and from. Before assessing BP, the patients were asked to seat comfortably with the left arm supported and positioned at the level of the heart and the back resting against a chair. The measurement time was under the morning fasting condition (12±2 h after the last drug ingestion). The patients rested at least five minutes and avoided caffeine or smoke within 30 minutes preceding the measurement. The cuff size (12×22 for small-size adults, 16×30 for medium-size adults and 16×42 for large-size adults) was encircled the left arm which lowered edge of its position in 2.5 cm above the antecubital space. Inflated the bladder quickly to a pressure 20 mmHg above SBP, was recognized by the disappearance of radial pulse and then deflated it 3mmHg/s. BP was recorded the korotkoff phase 1 (appearance) and phase 5 (disappearance) as SBP and DBP, respectively. On each occasion, at least three measurements were applied, separated by 10 minute intervals. If data showed variations of more than 5 mmHg, an additional measurement was applied until two of them were close and the highest BP was recorded.

Ascertainment of BMI

BMI (body mass index) is a person's weight in kilograms divided by the square of height in meters. BMI was calculated in the baseline and in the last follow up session by the same trained nurses.

Statistical Analyses

All data were expressed as mean ± SD. The characteristics of groups at baseline were compared by one-way analyses of variance (ANOVA). The changes in BP and BMI were analysed using one-way repeated measures ANOVA and Tukey's post hoc and their comparison with the baseline data. A *P*-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

Plant Extraction and HPLC analyses

Extraction of phenolic compounds were done according to Abu-Reidah et al [36]. . Briefly, one gram of *R. coriaria* dried fruit was mixed with 16 mL of methanol/H_2O (80:20, v/v) and sonicated for 60 min. Then, the solvent was evaporated under vacuum at 40 °C and the dry remnant was resolved in 0.5 mL of methanol/H_2O (80:20, v/v). The extract was centrifuged and the supernatant was filtered through a in syringe filter (d = 0.2 µm) and stored at 15 °C. Chromatographic analysis of extracts was carried out by an Agilent 1200 series Rapid Resolution Machine through an Agilent Zorbax C18 column (4.6 _ 150 mm, 5 µm). Acetic acid 0.5% v/v and acetonitrile were used as mobile phases A and B, respectively. The gradient program was set as follow: 0 min, 0% B; 20 min, 20% B; 30 min, 30% B; 40 min, 50% B; 50 min, 75% B; 60 min, 100% B; 62 min 0% B. Ultimately, the initial conditions were held for 10 min for re-equilibration. The injection volume and column temperature were 10 µL and 25 °C, respectively. The HPLC system was coupled to a quadrupole time of flight (Bruker Daltonik GmbH, Bremen, Germany) orthogonal accelerated Q-TOF mass spectrometer, fitted out with an electrospray ionization source (ESI). Analyses of parameters were set by negative and positive ion modes, with spectra obtained over a mass range from m/z 50 to 1100.

Conclusions

In this study, administration of *R. coriaria* fruit capsules [1000 (2×500) mg/day] augmented the effects of antihypertensive drugs in hypertensive's patients. Without causing any considerable side effect, *R. coriaria* was shown to be an effective therapeutic adjuvant. Moreover, the effects of sumac could be attributed to flavonoids as the dominant constituents in this plant. However, further research is required to clarify the mechanisms behind these observations.

Acknowledgements

The authors gratefully acknowledge the Vice Chancellor of Research, Tehran University of Medical Sciences for financial supports (grant number No.93776).

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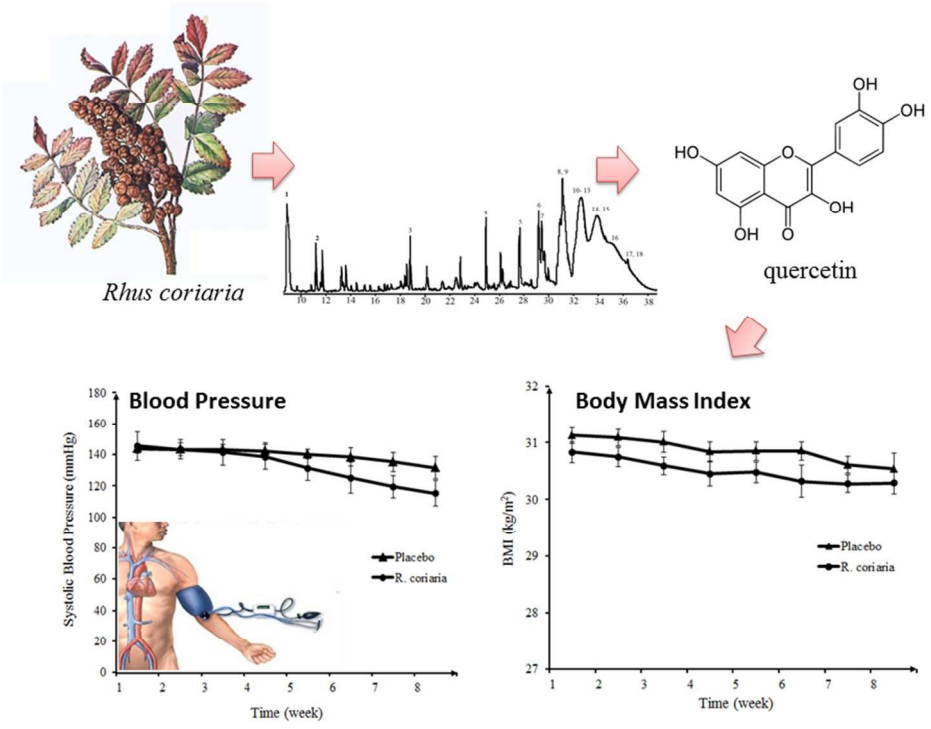

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