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The effect of Sumac (*Rhus coriaria L.*) supplementation on glycemic indices: A systematic review and meta-analysis of controlled clinical trials

Mohsen Mohit [1,*], Mehran nouri[1,*], Mehnoosh samadi[2, 3], Yasaman Nouri[4], Neda Heidarzadeh-Esfahani [2], Kamesh Venkatakrishnan[5], Cyrus Jalili [6#]

[1]-Student Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Science, Shiraz University of Medical Sciences, Shiraz, Iran

[2]- Department of Nutritional Sciences, School of Nutritional Sciences and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran

[3]-Research Center for Environmental Determinants of Health (RCEDH), School of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran.

[4-]Student Research Committee, Lorestan University of Medical Sciences, Korramabad, Iran

[5]- School of Nutrition, Chung Shan Medical University, Taichung City, Taiwan, ROC

[6]- Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[*]**Co-first Author:** Mohsen Mohit and Mehran Nouri equally contributed to this work.

[#]**Corresponding Author:**

Cyrus Jalili
Medical Biology Research Center, Health Technology Institute

Kermanshah University of Medical Sciences

Kermanshah

Iran

Email address: cjalili@yahoo.com

Highlights

- We examined the effects of sumac supplementation on glycemic indices in adults.
- Sumac did not have any significant effects on glycemic indices.
- More high-quality RCTs with longer duration are needed to further clarify the effects of sumac on blood glucose control, especially among patients with diabetes.

Abstract

Background & aims: *Rhus coriaria L.* (Sumac) is a popular spice/herb with several biological functions owing to its antioxidant and insulin-like activities. Many clinical trials have indicated the potent anti-diabetic property of sumac but the results on few glycemic indices were inconclusive. Hence, this systematic review and meta-analysis were aimed to investigate sumac supplementation effect on glycemic indices.

Methods: Systematically searched was performed by two independent reviewers using online databases including: PubMed, Scopus, web of science, EMBASE from inception until November 2020. Data were pooled using a random-effects model and weighted mean difference (WMD) with 95% confidence intervals (CI).

Results: A total of 6 potentially relevant clinical trials met the inclusion criteria with total of 278 participants. Random-effects meta-analysis suggested no significant effects on the levels of fasting blood glucose [-7.08 mg/dl, 95% CI: -14.85 to 0.70, P = 0.07, I^2 = 59.8%], glycosylated hemoglobin (HbA1c) [-0.48 %, 95% CI: −1.01 to -0.04, P = 0.07, I^2 = 0.0%], homeostatic model assessment for insulin resistance (HOMA-IR) [-0.97, 95% CI: -1.96 to 0.02, P = 0.05, I^2 = 83.8%], and insulin [-2.94 Hedges' g, 95% CI: -6.67 to 0.80, P = 0.12, I^2 = 83.1%] following supplementation with sumac powder.

Conclusion: This meta-analysis showed no significant effects on any glycemic indices following supplementation with sumac powder.

Key Words: Sumac, *Rhus coriaria*, Glycemic indices, Systematic review, Meta-analysis

Introduction

Diabetes is a chronic metabolic disorder caused mainly due to dramatic changes in lifestyle[1, 2] and it is estimated to reach over 300 million cases in both the developed and developing countries by the year 2030 according to the report of the World Health Organization[3-6]. Poor insulin sensitivity is a major factor in the pathogenesis of type 2 diabetes[7]. Recent, studies demonstrated the protective effect of complementary and alternative medicine such as some spices and herbs on handling high blood glucose levels in human and animal models[8, 9]. *Rhus coriaria L.* known as "sumac" is a shrub from the species Anacardiaceae and genus Rhus[10]. Sumac has been used for centuries as spice/herb in the Middle East, Mediterranean regions, and United State including Spain, Southern Italy, Turkey, Iran, and Afghanistan[11, 12]. Sumac is responsible for powerful biological activity including antioxidant, hypoglycemic, anti-inflammatory, cytotoxic, and antithrombin[10, 13, 14]. The above-mentioned biological properties of sumac are due to the presence of various bioactive phyto-components like phenolic acids (gallic acid) and flavonoids (quercetin, kaempferol)[10, 15]. The blood glucose-lowering potential of sumac has been illustrated previously in multiple *in vitro* and *in vivo* animal and human studies[16-20]. Sumac polyphenols display insulin-like properties and have beneficial effects on increasing insulin sensitivity and inhibiting oxidative stress[20]. Nevertheless, the hypoglycemic evidence (anti-diabetic effect) of sumac in various RCTs is inconsistent, and also the correlation between the sumac consumption and various glycemic indices like fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), insulin level, and insulin resistance are not yet explored.

Hence, the current study was designed to investigate a comprehensive systematic review and meta-Analysis on the effect of sumac supplementation on various glycemic indices.

Methods

The present systematic review and meta-analysis were performed under the Preferred Reporting Items for systematic reviews and Meta-Analyses (PRISMA) statement[21].

Data sources and search strategy

PubMed, Scopus, web of science, EMBASE databases were systematically searched to November 2020. The search was not restricted to any filters. The following key words was used to search: (sumac [Title/Abstract] OR "Rhus coriaria"[Title/Abstract] OR sumach[Title/Abstract]) AND (Cross-over [Title/Abstract] OR RCT [Title/Abstract] OR placebo [Title/Abstract] OR intervention [Title/Abstract] OR randomized [Title/Abstract] OR randomi* [Title/Abstract] OR trial [Title/Abstract] OR control* [Title/Abstract] OR Parallel [Title/Abstract] OR supplement* [Title/Abstract] OR blind [Title/Abstract]). A manual search in the reference lists of selected studies and Google Scholar was also conducted to identify additional studies.

Inclusion and exclusion criteria

Documents imported into endnote and two researchers were screened independently (M. M and M. N). To identify the eligible randomized controlled trials(RCTs), studies that met the following characteristics included: a) a clinical trial with parallel or cross-over design, b) reported a change at least one of the glycemic indexes (FBG, HbA1C, insulin levels, homeostatic model assessment for insulin resistance [HOMA-IR]) as primary or secondary outcomes, c) performed in participants who 18 years and older. Other types of articles such as animal studies, review articles, conference papers, brief reports, and letter to editor were excluded. Studies with short duration of follow-up (<2 weeks), trials without sufficient data and studies with duplicate data were also excluded. Any different opinions between the two investigators was settled by panel discussion.

Data extraction and quality assessment

According to the following characteristics, data were extracted from articles: the first author's name, publish year, country, design of the study, sample size, health status, mean age, type of administration, duration of intervention, and dosage. Data extraction was performed by (M. M and M.N). Disagreements were resolved after being presented in the team group.

The Jadad scale was used for the assessment of the quality of articles. According to the following characters, articles were evaluated: 1) randomization, 2) blinding, 3) withdrawal and dropouts 4) randomization method 5) blinding methods. Scores between 0-2 and 3-5 were assigned as low and high quality, respectively.

Statistical analysis

Mean change and standard deviation (SD) for FBG, serum insulin, HbA1c, and HOMA-IR were essential to approximate the overall effect of the intervention. If only SD for the baseline and final values was provided, SD for the net changes was assigned based on the Follmann method [22] using a correlation coefficient of 0.5. In order to be confident that our meta-analysis is not affected by the particular correlation coefficient (R = 0.5), all analyses were described by applying the correlation coefficient of 0.2 and 0.8. The random-effects model was employed to calculate weighted mean differences (WMDs) with 95% confidence intervals (CIs) for FBG, serum insulin, HbA1c, and HOMA-IR. Between-study heterogeneity was estimated by I-squared (I^2) statistic. A pre-planned subgroup analysis according to study duration, sumac dosage, baseline BMI was done to explain the effects of sumac on selected outcomes. Sensitivity analysis evaluated the proportion of each study in overall effect. In order to assess publication bias, Begg's rank correlation and Egger's regression asymmetry tests were employed. Statistical analysis was carried out by STATA 11 software (Stata Corp, College Station, Texas, USA). A P value of < 0.05 was considered statistically significant in this trial unless otherwise specified.

Results

Study selection

Out of 544 papers identified in the above-mentioned databases and 2 records through other sources, 538 articles were excluded for duplication, title, and abstract screening. Then, only 6 articles were included (eligible) for this systematic review and meta-analysis[18, 23-27]. The study selection process is demonstrated in **Figure 1**.

Study characteristics

The characteristics of the eligible studies are summarized in table 1. The studies sample size was between 20 and 80 participants. The design of 5 trials was parallel[18, 24-27], and one was cross-over[23]. The duration of follow-up was 6 to 12 weeks. Eligible studies were conducted in type 2 diabetes mellitus (T2DM)[18, 24, 25], dyslipidemia[23], and obese and overweight subjects[26, 27]. Two studied investigated sumac at a dose of 1 g/day[23, 26], one study at a dose of 2 g/day[27], two studies at a dose of 3 g/day[18, 25], and one study at a dose of 6 g/day[24].

Meta-analysis results

Effect of sumac on FBG

Overall, six studies (278 participants) evaluated the effect of *sumac* on FBG[18, 23-27] . Pooled effect size indicated no significant effect of sumac on FBG (−7.08 mg/dl, 95% CI [−14.85, 0.70], *P*= 0.07) with significant heterogeneity between studies (I^2 = 59.8%) **(Figure 2)**. Subgroup analysis stratified based on BMI (<30 kg/m^2, ≥30 kg/ m^2), sumac dose (<2 g/day vs. ≥2 g/day) and duration (<12 weeks vs. ≥12 weeks). The subgroup analyses showed that sumac in dose ≥2 and duration ≥12 weeks significantly reduced FBG level (-17.39 mg/dl, 95% CI [-28.87, -5.90], *P*= 0.003 and

−13.47 mg/dl, 95% CI [−23.27, −3.67], *P*= 0.007). Heterogeneity between studies in dose ≥2 and duration ≥12 subgroup analysis was not significant (I^2 = 11.6%, and I^2 = 0.0%, respectively). The subgroup analyses results are provided in Table 2.

Effect of sumac on HbA1c

Overall, three studies (179 participants) evaluated the effect of sumac on HbA1c[18, 24, 27] . Pooled effect size indicated no significant effect of sumac on HbA1c (−0.48 %, 95% CI [−1.01, 0.04], *P*= 0.07) with no significant heterogeneity between studies (I^2 = 0.0%) **(Figure 3)**.

Effect of sumac on insulin level

Overall, four studies (207 participants) evaluated the effect of sumac on insulin level[24-27]. Pooled effect size indicated no significant effect of sumac on insulin level (−2.94 Hedges' g, 95% CI [−6.67, 0.80], *P*= 0.12) with significant heterogeneity between studies (I^2 = 83.1%) **(Figure 4)**. Subgroup analysis stratified based on BMI and duration. The subgroup analyses showed that the sumac in BMI and duration was not significant. The subgroup analyses results are provided in Table 2.

Effect of sumac on HOMA-IR

Overall, four studies (207 participants) evaluated the effect of sumac on HOMA-IR[24-27 24-27]. Pooled effect size indicated no significant effect of sumac on HOMA-IR (−0.97, 95% CI [−1.96, 0.02], *P*= 0.05) with significant heterogeneity between studies (I^2 = 83.8%) **(Figure 5)**. Subgroup analysis stratified based on BMI and duration. The subgroup analyses showed that sumac in BMI ≥30 kg.m^2 and duration <12 weeks significantly reduced HOMA-IR. Heterogeneity between studies in BMI ≥30 kg/m^2 and duration <12 weeks subgroup analysis was not significant (I^2 = 0.0%, and I^2 = 0.0%). The subgroup analyses results are provided in Table 2.

Sensitivity analysis

Sensitivity analysis showed that estimate of FBG was influenced by exclusion Asgary et al. study (−12.39 mg/dl, 95% CI [−24.59, -0.19]), insulin by exclusion Ardakani et al. study (−4.61, 95% CI [−7.47, -1.75]) and HOMA-IR by Kazemi et al. study (−0.35, 95% CI [−0.68, -0.02]), but HbA1c was not influenced by elimination of any study.

Publication bias

The evaluation of the publication bias showed no evidence of bias in studies assessing the effect of *sumac* on FBG ($P = 0.18$, Begg's test; and $P = 0.45$, Egger's test), HbA1c ($P = 0.60$, Begg's test; and $P = 0.34$, Egger's test), insulin ($P = 0.49$, Begg's test; and $P = 0.76$, Egger's test) and HOMA-IR ($P = 0.18$, Begg's test; and $P = 0.82$, Egger's test).

Discussion

T2DM is a multifactorial metabolic chronic disorder characterized by the persistent increase in blood glucose level (hyperglycemia) owing to altered insulin action (insulin resistance)[28]. The major pathophysiological events that contribute to T2DM include impaired insulin function, oxidative stress, in[29]flammation, impaired glucose tolerance (insulin resistance) and which eventually results in altered glucose homeostasis and end up in T2DM [30, 31], [32-36]. Many researchers have started to focus on natural phytochemicals for treating various metabolic disorders especially T2DM, due to cheap and low adverse effects[5-6]. Aforementioned that sumac is of a popular spice rich in various phytocomponents including phenolic acids, anthocyanins, tannins, and flavonoids, such as gallic acid, methyl gallate, kaempferol, and quercetin[15]. Those above-mentioned bioactive phytocompounds of sumac have shown various biological actions like anti-inflammatory, antioxidant, hypoglycemic, hypolipidemic, and antiviral activities[32-35]. The hypoglycemic activity

of sumac has been demonstrated by many researchers using various models (cell line, animal and human)[16-20]. Sumac polyphenols display insulin-like properties along with its antioxidant and anti-inflammatory makes it's a potent contender for regulating blood glucose level[16]. Based on the above data, we compiled all the RCTs based on eligibility criteria and filtered only 6 RCTs, and conducted this comprehensive systematic review and meta-analysis to investigate the impact of sumac supplementation on various glycemic indices like FBG, HbA1c, insulin level, and HOMA-IR. In addition, the subgroup analysis was conducted by checking various influencing factors like dose, intervention period, and BMI status.

Combining six eligible limited clinical trials, we demonstrated that sumac did not show any significant effect on FBG level, HbA1c, insulin level, and HOMA-IR. However, the subgroup analysis showed a significant reduction in FBG level in RCTs with an intervention duration ≥12 weeks and at a dose≥2 g/day. Moreover, the subgroup analyses also revealed that sumac supplementation has significantly lowered insulin resistance in BMI≥30 kg/m^2 subjects and sumac intervention for duration<12 weeks. Previously, Fatahi Ardakani and his coworkers, showed that consumption of 6 grams of sumac powder could considerably reduce the serum fasting insulin and insulin resistance in diabetic patients without altering any glycemic indices[24]. However, the study conducted by Shidfar et al. indicated a significant decrease in serum glucose and HbA1c after intervention with 3 grams of sumac powder daily for 3 months as compared with baseline[18]. Likewise, few animal studies also showed that treatment with sumac extract could significantly reduce the blood glucose level in diabetic rats[37,25]. The results of Chakraborty et al. study showed that sumac (rich in gallic acid) is a potent antioxidant that protects against oxidative DNA-damage[38] and we also concord the above statement that sumac could lower the oxidative stress and thus improve insulin production and thus maintain glucose homeostasis. Moreover, the subgroup

analysis indicated that sumac intervention has significantly lowered the insulin resistance in BMI≥30 kg/m^2 subjects as sumac lower the oxidative stress as well as lower cholesterol absorption and utilization, which results in lower visceral fat. Overall, sumac supplementation would improve insulin function as well as maintain overall health status of diabetic subjects owing to its insulin like activity, antioxidant, anti-obesity, hypolipidemic and anti-inflammatory activities.

Some of the proposed mechanism underlying hypolipidemic or anti-diabetic activity of sumac includes, a significant regulation of various proteins involved in SIRT1, PI3K/Akt and AMPK signaling pathway and thus enhance the insulin activity as well as enhance glucose utilization and thereby lower the insulin resistance[39-41]. Also, sumac has few flavonoids and phenolic acid which might help in lowering oxidative stress and inflammation thus protect the function of beta cells of the pancreas and thus improve insulin production and enhance glucose uptake[40-41]. Furthermore, quercetin and gallic acids of sumac are reported to inhibit intestinal glucose absorption in various rat models[39, 40]. Giancarlo and his colleagues demonstrated that the extract of sumac showed hypoglycemic activity by inhibiting the alpha-amylase activity[41]. The results of this systemic review and meta-analysis (including 6 RCTs) are inconsistent and insignificant due to different duration, doses, intervention period, types of study (double-blind or cross-over study), number of participants, and other inclusion criteria for each RCTs. However, the subgroup analysis hinted a significant reduction in few glycemic indices based on few characteristic factors like duration, doses, and BMI.

This meta-analysis has several limitations that must be taken into account when interpreting its findings. First, the number of articles in this meta-analysis was insufficient to reach definitive conclusions and certainly indicates the need for further clinical trials in this field. Second, all the trials included in this study were conducted among Iranian participants, so the results may not be

generalizable to those of other ethnic origins. Third, the majority of trials did not account for differences in lifestyle (physical activity, diet, sleep, smoking, etc.), which may contribute to glycemic control. In addition, we did not register the protocol of the current study on PROSPERO registry system due to the delay in processing the submitted protocols for studies outside the UK. This lack of registration might be a source of bias for this review. Finally, after sumac consumption, the accurate concentration that appeared in the blood is not specified, because the trials did not assess the bioavailability of sumac.

Conclusion

The current systematic review and meta-analysis including 6 RCTs demonstrated no significant effect of sumac on various glycemic indices like FBG level, HbA1c, insulin level, and insulin resistance. However, the subgroup analysis showed a significant reduction in FBG level (duration ≥12 weeks and at a dose≥2 g/day) and insulin resistance (BMI≥30 kg/m2 and duration<12 weeks). Future prospective studies are required to check in-depth effect of sumac on various glycemic indices and their related parameters.

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Conflict of interest

We declare no conflict of interest.

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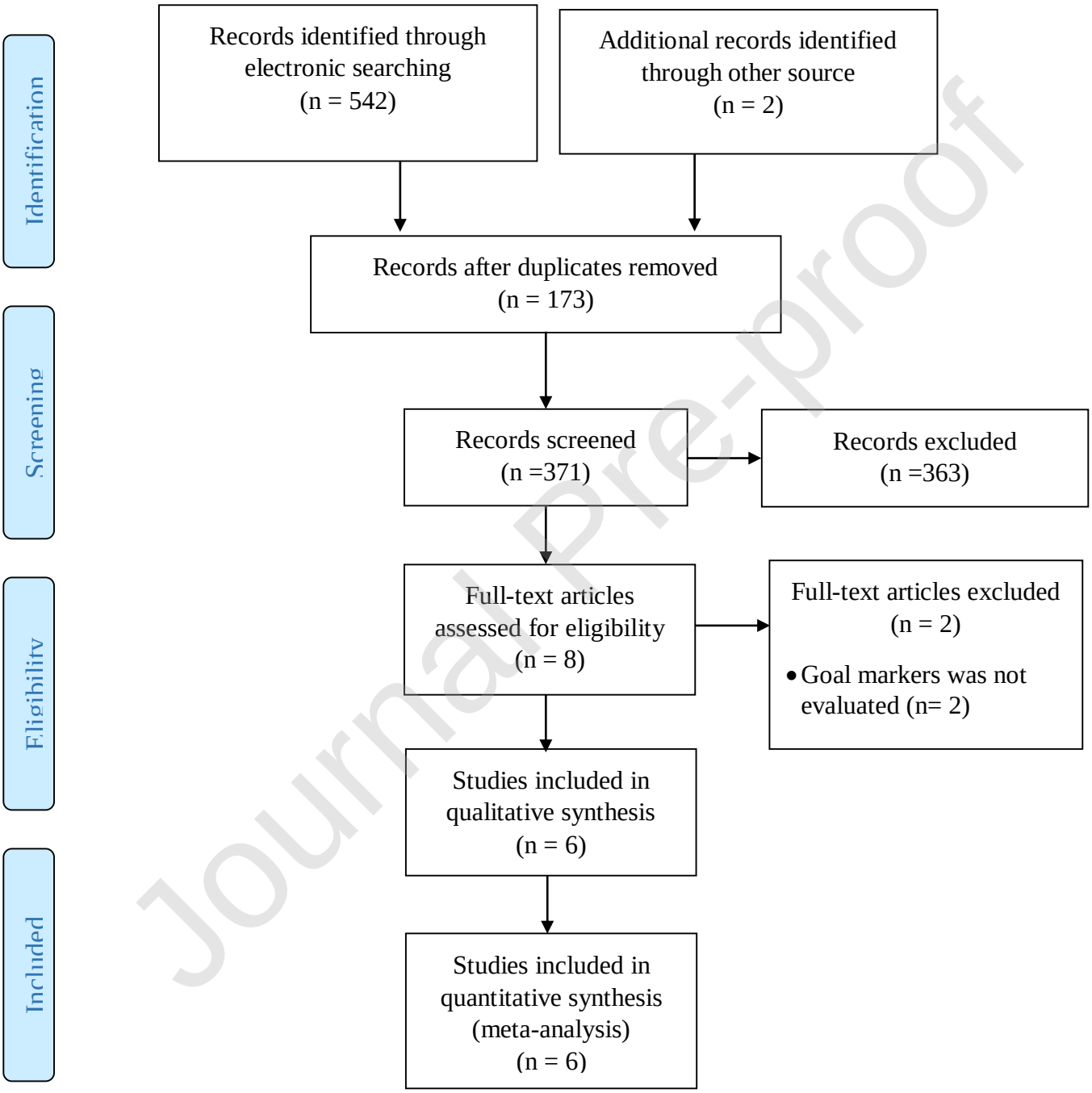

Figure 1. Flow diagram of data selection process.

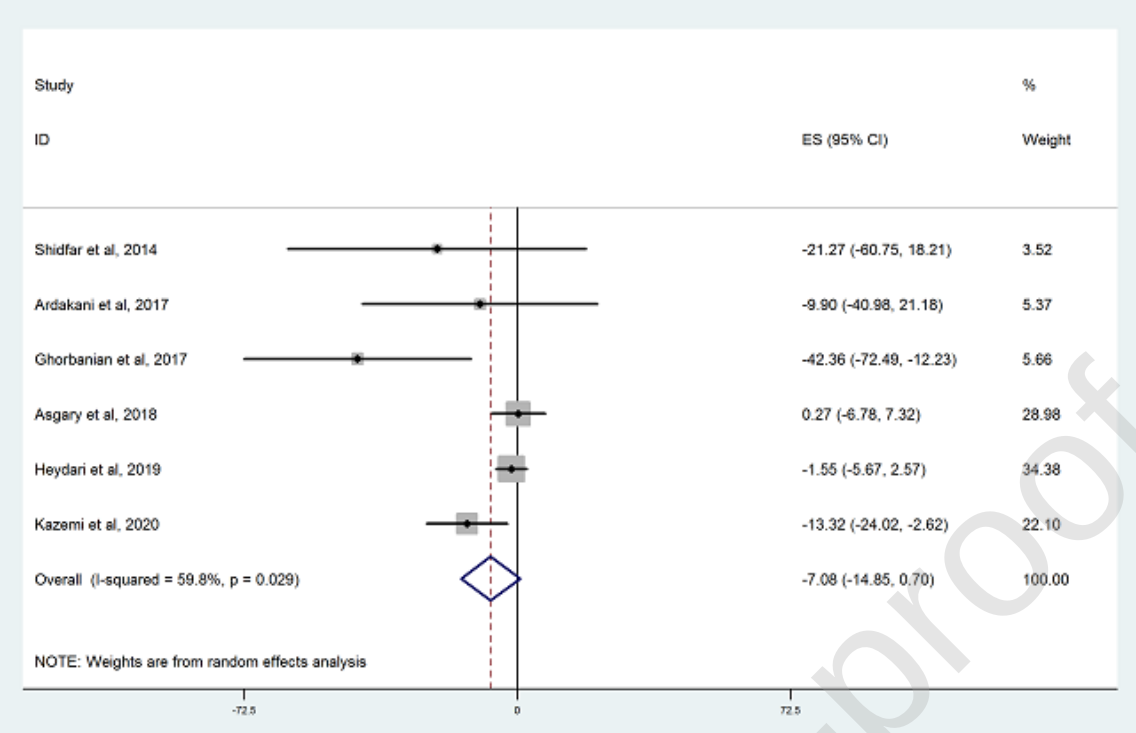

Figure 2. The effect of sumac powder on FBG.

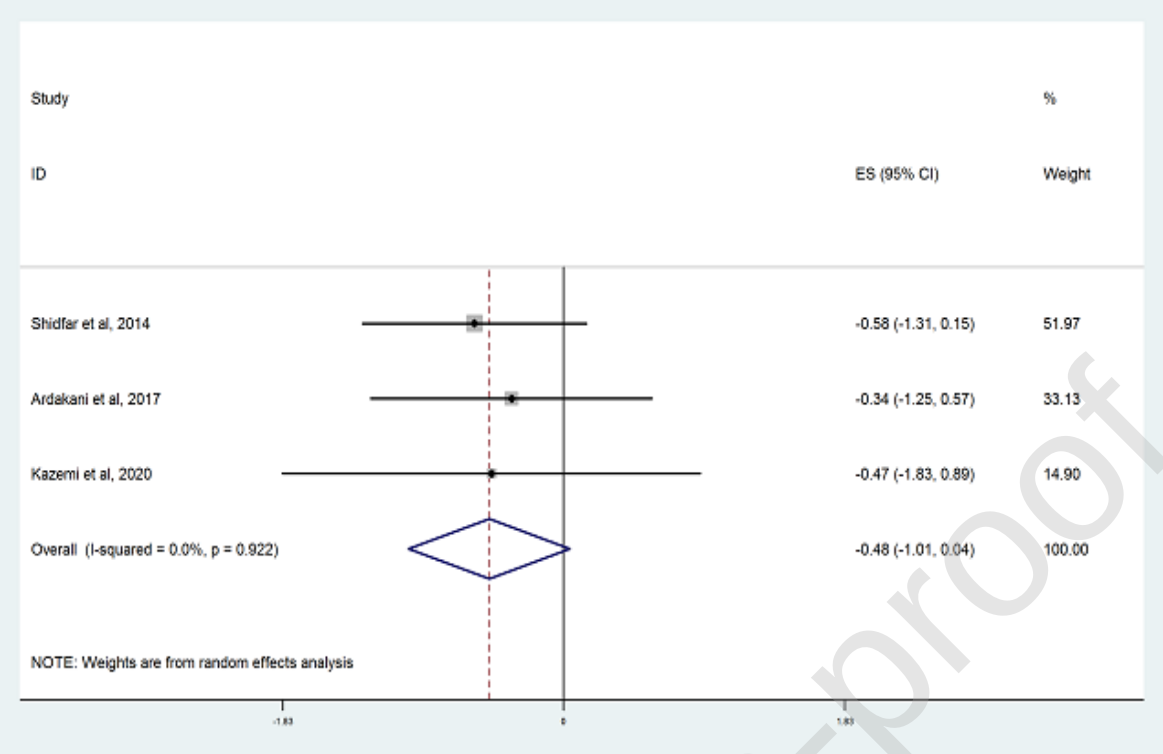

Figure 3. The effect of sumac powder on HbA1c.

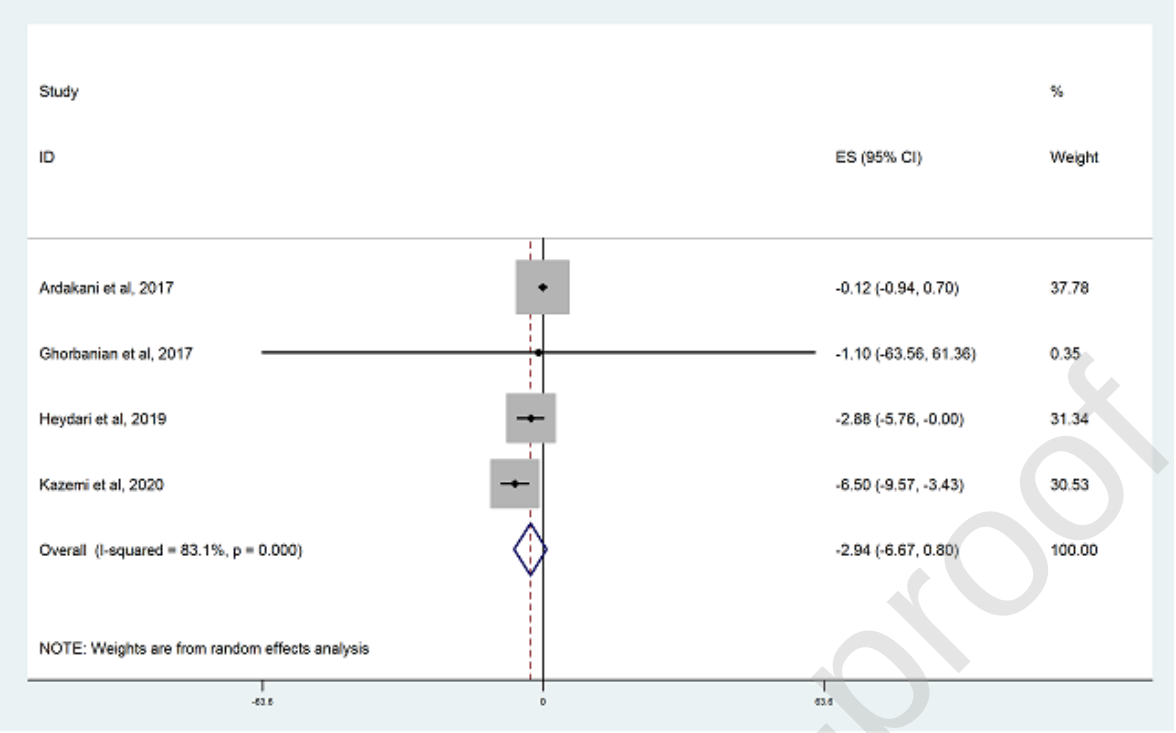

Figure 4. The effect of sumac powder on Insulin.

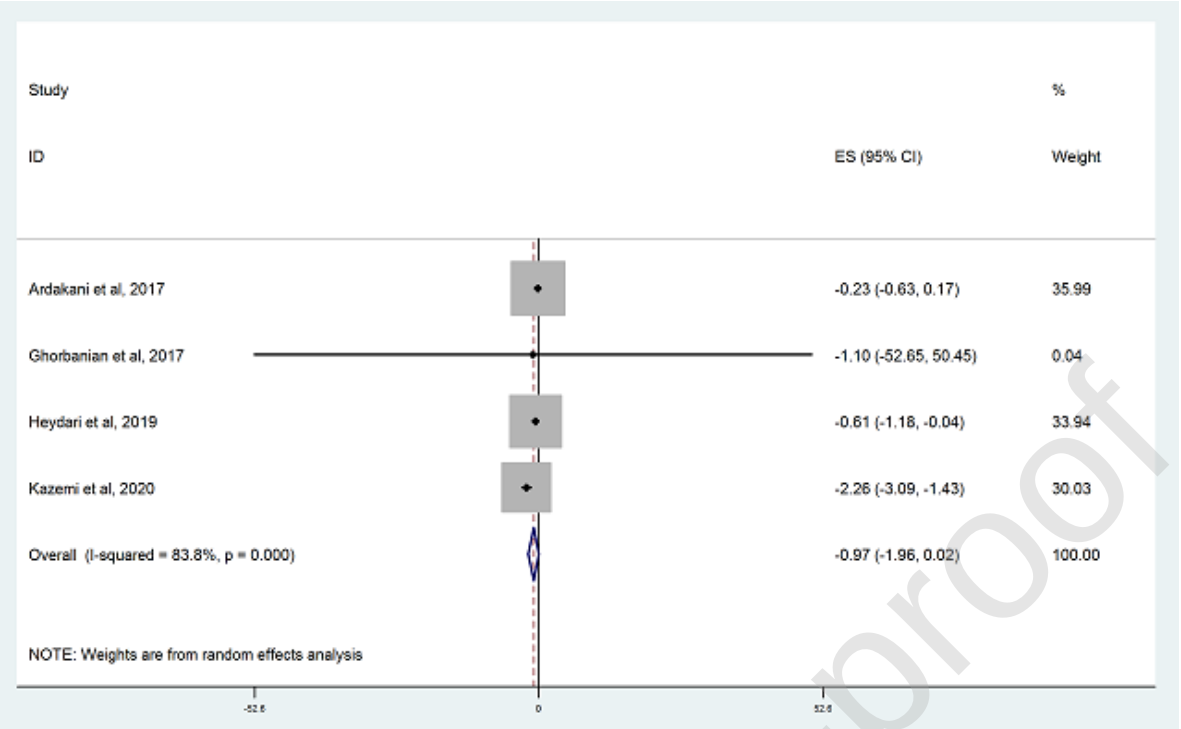

Figure 5. The effect of sumac powder on HOMA-IR.

Table 1. Characteristics of included studies.

First author, year	country	Study design	Participants (Intervention, Control)	Population	Mean age (Intervention, Control)	Mean age	Mean BMI	Type of administration	Duration of intervention	Dosage (g/d)	factors	Quality
Shidfar, 2014	Iran	RCT, Parallel	(22, 19)	Type 2 Diabetic Patients	(46.1, 47.5)	46.74	29.5	Powder	12 weeks	3	FBG, HbA1c	High quality
Ardakani, 2017	Iran	RCT, Parallel	(30, 28)	Type 2 Diabetic Patients	(52.30, 51,61)	51.96	28.88	Powder	12 weeks	6	FBG, HbA1, fasting insulin, HOMA-IR	High quality
Ghorbanian , 2017	Iran	RCT, Parallel	(10, 10)	Type 2 Diabetic woman	(55.4, 57.2)	56.3	32.25	Tablet	10 weeks	3	FBG, fasting insulin, HOMA-IR	Low quality
Asgary, 2018	Iran	RCT, Cross-over	(15, 15)	Dyslipidemia patients	(45.62, 49.26)	47.44	27.58	Capsule	10 weeks	1	FBG	High quality
Heydari, 2019	Iran	RCT, Parallel	(25, 24)	Obese or overweight patients	(45.16, 43.13)	44.16	30.14	Capsule	6 weeks	1	FBG, fasting insulin, HOMA-IR	High quality
Kazemi, 2020	Iran	RCT, Parallel	(40, 40)	Non-alcoholic fatty liver disease	(41.80, 41.40)	41.60	27.61	Capsule	12 weeks	2	FBG, fasting insulin, HOMA-IR, HbA1c	High quality

Abbreviation: RCT; randomized controlled trial, BMI; body mass index, FBG; fasting blood glucose, HOMA-IR; homeostatic model assessment for insulin resistance

Table 2. Subgroup analyses to assess the effect of sumac on glycemic indexes.

Sub-grouped by	No. of trials	Effect size[1]	95% CI	P for effect size	I^2 (%)	P for heterogeneity
FBG						
Baseline BMI						
<30 kg/m^2	4	-6.83	-72.49, -12.23	0.17	42.0	0.159
≥30 kg/m^2	2	-19.11	-58.72, 20.49	0.34	85.5	0.009
Dose						
<2 g/day	2	-1.09	-4.64, 2.47	0.54	0.0	0.662
≥2 g/day	4	-17.39	-28.87, -5.90	0.003	11.6	0.335
Duration						
<12 weeks	3	-4.24	-13.78, 5.30	0.38	72.6	0.026
≥12 weeks	3	-13.47	-72.49, -12.23	0.007	0.0	0.094
Insulin						
Baseline BMI						
<30 kg/m^2	2	-3.13	-9.73, 3.11	0.32	93.5	< 0.001
≥30 kg/m^2	2	-2.88	-5.75, -0.00	0.05	0.0	0.956
Duration						
<12 weeks	2	-2.88	-5.75, -0.0	0.05	0.0	0.956
≥12 weeks	2	-3.13	-9.37, 3.11	0.32	93.5	< 0.001
HOMA-IR						
Baseline BMI						
<30 kg/m^2	2	-1.21	-3.20, 0.78	0.23	94.6	< 0.001
≥30 kg/m^2	2	-0.61	-1.18, -0.04	0.03	0.0	0.985
Duration						
<12 weeks	2	-0.61	-1.18, -0.04	0.03	0.0	0.985
≥12 weeks	2	-1.21	-3.20, 0.78	0.23	94.6	< 0.001

[1]Calculated by Random-effects model

FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance