Original Article

Effects of resistant starch supplementation on oxidative stress and inflammation biomarkers: A systematic review and meta-analysis of randomized controlled trials

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Background and Objectives: Animal experiments showed that resistant starch (RS) had an antioxidant and anti-inflammatory effect. However, clinical studies showed both insignificant and significant effects of RS on inflammation and oxidative stress. The purpose of this work is to conduct a systematic review and meta-analysis of previous randomized controlled trials (RCTs) to investigate these effects. **Methods and Study Design:** A systematic literature search was conducted on Web of Science, Scopus, PubMed and Cochrane electronic databases, which included studies from the earliest date of the database to September 2021. Key inclusion criteria were: RCTs; reporting at least one inflammatory or oxidative stress biomarker as endpoint; more than seven day intervention. Key exclusion criteria were: using a mixture of RS and other functional food ingredients as intervention substance; inappropriate controls. **Results:** A total of 16 RCTs including 706 subjects were included. RS supplementation significantly improved total antioxidant capacity [standard mean difference (SMD) (95% CI): 2.64 (0.34, 4.94), p=0.03], and significantly reduced blood malondialdehyde concentration [SMD (95% CI): -0.55 (-0.94, -0.17), p=0.01]. RS supplementation significantly reduced blood C-reactive protein concentration in type 2 diabetes mellitus (T2DM) patients [SMD (95% CI): -0.35 (-0.65, -0.05), p=0.02]. RS consumption significantly reduced blood interlukin-6 and tumor necrosis factor- concentration if removing one distinct trial. **Conclusions:** RS supplementation may significantly reduce a few oxidative-stress and inflammation biomarkers such as malondialdehyde and C-reactive protein, particularly in T2DM patients. Future work should investigate the optimal dosage of RS supplementation for modulating oxidative stress and inflammation biomarkers related to T2DM.

Key Words: resistant starch, oxidative stress, inflammation, biomarker, meta-analysis, systematic review

INTRODUCTION

Oxidative stress and inflammation play an important role in the pathology of many chronic diseases.[1,2] Oxidative stress refers to the imbalance between oxidation and anti-oxidation in vivo, resulting in the production of a large number of free radicals such as reactive oxygen species (ROS).[1] Excessive ROS may trigger the activation of NF-κB signaling pathway, and induce inflammation.1 Nutritional intervention is an important way to modulate oxidative stress and inflammation.[3,4]

Resistant starch (RS) is a type of indigestible carbohydrate, which can be fermented into short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate. by the microbiota residing in human gastrointestinal tract.[5] Animal experiment showed that RS promoted the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which modulated the expression of endogenous antioxidant enzymes including CuZn-superoxide dismutase, catalase and glutathione peroxidase.[6] In addition, RS promoted the growth of bifidobacteria in the colon.[7]

Bifidobacteria and SCFAs were shown to reduce ROS by previous systematic review.[3] However, clinical results of RS on antioxidant/oxidative-stress biomarkers were inconsistent. Take malondialdehyde (MDA) and uric acid for example, Karimi and Aliasgharzadeh et al found that RS played a significant role in reducing MDA in the study of females with T2DM,[8,9] while no obvious effect of RS on oxidative stress was found in the study of Meng and Eshghi et al.[10,11] Meng et al found that RS had a significant effect on reducing uric acid,[10] while Laffin and Khosroshahi et al showed that RS had no significant effect on reducing uric acid.[12,13] To our knowledge, no syst-

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ematic review and meta-analysis has been conducted to investigate the effects of RS supplementation on antioxidant/oxidative-stress biomarkers.

RS-fermented SCFAs are vital nutrients for the colonic epithelial cells and the regulatory T cell (T-reg).[13] T-reg is important for the regulation of inflammatory response.[14] SCFAs may also enhance intestinal barrier function and counteract lipopolysaccharide-induced inflammation.[15,16] Therefore, RS may play a role in anti-inflammation. The anti-inflammatory effect of RS has been demonstrated in previous animal experiments.[17,18] However, the clinical results are inconsistent. Laffin and Khosroshahi et al showed that RS had a positive anti-inflammatory effect in people with chronic kidney disease.[12,13] Gargari et al also reported that RS played a positive role in the anti-inflammation of 60 females with type 2 diabetes mellitus (T2DM).[4] Conversely, Meng et al showed that there were no obvious changes in inflammatory markers after RS supplementation in patients with early type 2 diabetic nephropathy.[10]

The aim of our study is to conduct a systematic review and meta-analysis of previous randomized controlled trials (RCTs) to assess the effects of RS on antioxidant/oxidative stress and inflammation biomarkers. The endpoints were common biomarkers related to antioxidant/oxidative stress and inflammation including total antioxidant capacity (TAC), superoxide dismutase (SOD), malondialdehyde (MDA), uric acid, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interferon-γ (IFN-γ), interleukin-1β (IL-1β), interleukin-8 (IL-8) and interleukin-10 (IL-10).

METHODS

Search strategy

Three project members (JL, XQ and ZS) independently conducted the literature search. Any dispute was resolved by group discussion. The literature search was conducted on the Web of Science, Scopus, PubMed and Cochrane electronic databases, which retrieved publications from the earliest date of the database to September 2021. The search terms were: ("inflammation" OR "pentraxin 3" OR "acute phase protein" OR "C reactive protein" OR "CRP" OR "cytokine" OR "interleukin" OR "tumor necrosis factor" OR "TNF" OR "matrix metalloproteinase" OR "MMPs" OR "selectins" OR "e-selectin" OR "p-selectin" OR "L-selectin" OR "intercellular adhesion molecule-1" OR "ICAM-1"OR "monocyte chemotactic protein" OR "MCP-1" OR "oxidative stress" OR "malondialdehyde" OR "propanedial" OR "malonyldialdehyde" OR "F2 isoprostane" OR "total antioxidant capacity" OR "superoxide dismutase" OR "SOD" OR "8-hydroxy-2-deoxyguanosine" OR "thiobarbituric acid reactive substances" OR "TBARS" OR "glutathione peroxidase" OR "malonaldehyde" OR "malonylaldehyde" OR "MDA" OR "isoprostane") AND ("Resistant Starch"). We referenced previous literature for these common oxidative stress and inflammatory biomarkers.[1,2]

Eligibility criteria

Inclusion criteria were: (1) RCTs; (2) reporting at least one inflammatory or oxidative stress biomarker as endpoint; (3) more than seven-day intervention. Exclusion criteria were: (1) review articles; (2) animal or in vitro studies; (3) inappropriate control; (4) RS mixed with other nutrients as intervention substance.

Data extraction and quality assessment

Two project members (BM and JL) collated and checked qualified studies, and extracted the following information：(1) year of publication; (2) first author' s name; (3) country; (4) number of participants in the control group and intervention group; (5) gender and age; (6) body mass index (BMI); (7) intervention substance and placebo form; (8) intervention period; (9) health status; (10) study design; (11) biomarkers of antioxidant or oxidative stress (including uric acid, MDA, SOD, and TAC) or inflammatory (including CRP, TNF-α, IL-6, IFN-γ, IL-1β, IL-8, IL-10). Any dispute is settled through group discussion. Necessary clarifications were obtained by contacting with the authors of the studies.

Jadad scale was used to evaluate the quality of qualified studies, which included items related to randomization, blinding and withdraw/dropout statement (1-3 points for low quality, 4-5 points for high quality).[19] Begg's rank correlation and Egger's linear regression were used to assess potential publication bias.[20,21] Sensitivity analysis was conducted by removing one study at a time and recalculating the pooling effect.

Statistical analysis

The mean difference of the net changes between the intervention group and the control group was taken as the effect size for each parameter. The standard deviation (SD) of the net change was calculated using the following formula:

$$SD=\sqrt{[SD_{pre\text{-}treatment}^2 + SD_{post\text{-}treatment}^2 - (2 \times R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]}$$

assuming a R (correlation coefficient) of 0.5. Statistical analysis was performed using the Stata software (version 11.0, from statacorp LLC). A p value of less than 0.05 was considered statistically significant. When parameters were measured in the same way, effect size was represented by weighted mean difference (WMD). When measurement methods were different, effect size was expressed by standard mean difference (SMD). Study heterogeneity was tested by the Cochrane's Q-test and quantified by the I^2 statistics, in which $I^2 \geq 50\%$ represented substantial heterogeneity.[22]

RESULTS

The flow diagram of the literature retrieval process is shown in Figure 1. 2872 eligible studies were retrieved from the Web of Science, Scopus, PubMed and Cochrane electronic databases based on the inclusion criteria. 1579 were included after removing duplicates. 1551 were excluded after reviewing titles and abstracts. The remaining 28 studies were reviewed for full texts, of which 9 studies lacked information for relevant parameters and 4 studies had a short intervention period (less than seven-day intervention). As a result, a total of 15 studies were included. The study by Alfa et al. investigated two populations including middle-aged and elderly subjects,[23] which were treated as two trials. Thus a total of 16 randomized con-

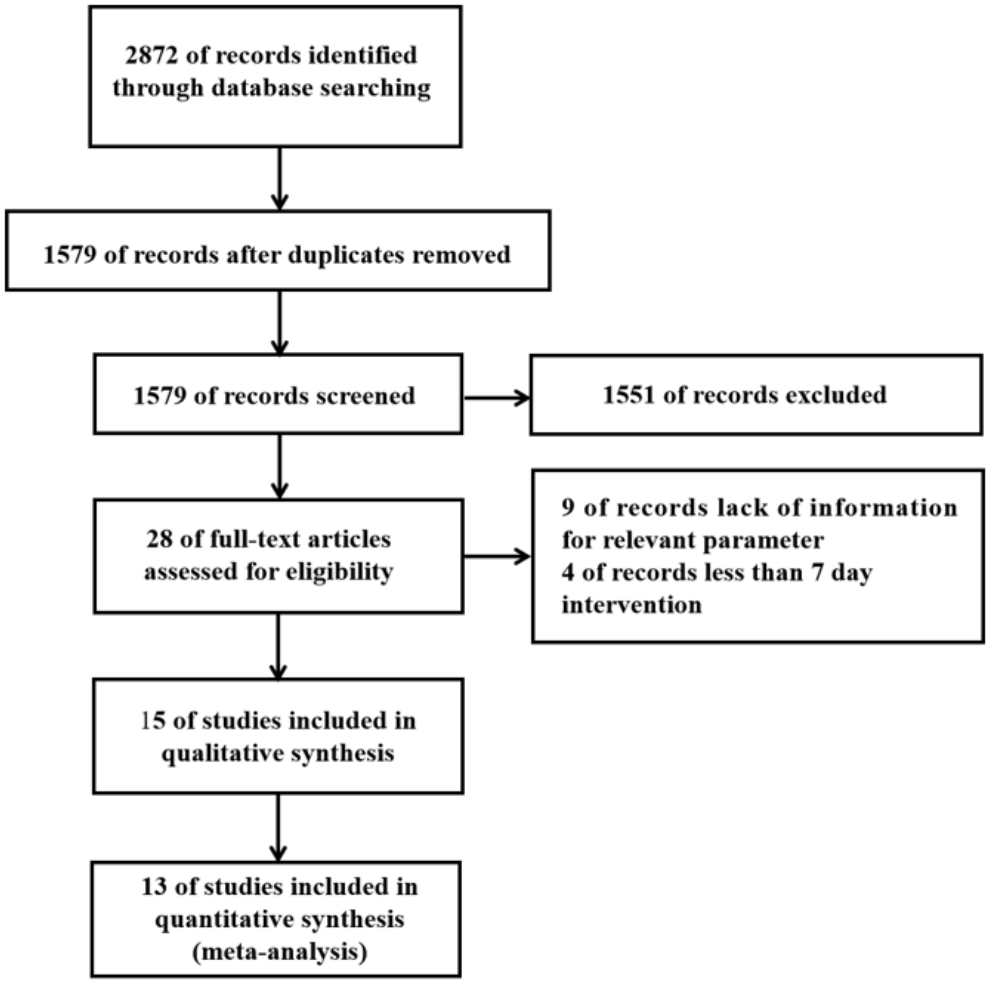

Figure 1. Flow diagram of the literature selection process.

trolled trials involving 706 patients were included in the current systematic review and meta-analysis.

Study characteristics

The characteristics of the included trials were shown in Table 1. Nine trials were conducted in Asia, six in America and one in Africa. The number of participants ranged from 17 to 70. The supplementary dosage of RS ranged from 6 g/d to 27 g/d, and the intervention duration ranged from four to twelve weeks. Two trials had healthy people as participants, six had T2DM, three had end stage renal disease, two had chronic kidney disease and three had people with potential health risks (like overweight or risks for T2DM). Three trials focused on women. The quality of the included trials was moderate, as indicated by the Jadad scores ranging from 3 to 5.

Effect on antioxidant/oxidative-stress biomarkers

RS supplementation significantly improved TAC [SMD (95% CI): 2.64 (0.34, 4.94), p=0.03] (Figure 2) based on a meta-analysis of three trials. RS supplementation tended to improve SOD activity [SMD (95% CI): 0.20 (-0.10, 0.51), p=0.19] (Figure 3) based on a meta-analysis of three trials. RS supplementation significantly reduced the blood MDA concentration [SMD (95% CI): -0.55 (-0.94, -0.17), p=0.01] (Figure 4) based on a meta-analysis of six trials. The effects of RS supplementation on uric acid were not significant [SMD (95% CI): 0.13 (-0.13, 0.38), p=0.32] (Figure 5) based on a meta-analysis of five trials. Limited trials reported the effects of RS supplementation on other antioxidant/oxidative-stress biomarkers. Esgalhado et al. reported a null effect of RS supplementation on protein carbonyl [MD (95% CI): -0.20 (-0.58, 0.18), p=0.30].[24] Karimi et al indicated that RS supplementation significantly improved the activity of glutathione peroxidase [MD (95% CI): 2.50 (0.69, 4.31), p=0.01], and had a null effect on catalase activity [MD (95% CI): -2.45 (-11.8, 6.93), p=0.61].[8]

Effect on inflammation biomarkers

RS supplementation significantly reduced the blood CRP concentration in T2DM patients [SMD (95% CI): -0.35 (-0.65, -0.05), p=0.02] with a zero heterogeneity (Figure 6) based on a meta-analysis of three trials. The effects of RS supplementation on the blood CRP concentrations in non T2DM and overall population were not significant. RS supplementation significantly reduced blood IL-6 concentration [SMD (95% CI): -0.90 (-1.36, -0.45), p<0.01] (Figure 7) based on a meta-analysis of three trials and TNF-α concentrations [SMD (95% CI): -0.55 (-1.02, -0.09), p=0.02] (Figure 8) based on a meta-analysis of four trials both in non-T2DM subjects.

For the other inflammatory indicators, Farhangi et al reported the effects of RS supplementation on IFN-γ. A significant effect of RS was observed on IFN-γ (mean

Table 1. Basic characteristics of the included trials

Year	Author	Country	Participants (control/ intervention)	Gender (F/M)	Mean age (control/ intervention)	BMI (control/ intervention)	Intervention/placebo form	Intervention dosage	Duration	Health status	Outcomes	Jadad score
2018	Alfa#1 [23]	Canada	21/21	24/18	37.0/21.0	NA	RS2 /digestible corn starch in food	21 g/d	12 weeks	Middle-aged people	CRP, IL-10, TNF-α	4
2018	Alfa#2 [23]	Canada	21/21	25/17	75.0/73.0	NA	RS2 /digestible corn starch in food	21 g/d	12 weeks	Elderly people	CRP, IL-10, TNF-α	4
2018	Esgalhado [24]	Brazil	16/15	13/18	53.5/56.0	26.6/26.2	RS2 /manioc flour in cookies	16 g/d	4 weeks	Chronic kidney disease	CRP, IL-6, MDA, protein carbonyl	4
2015	Gargari [4]	Iran	32/28	60/0	49.5/49.6	30.8/31.5	RS2/maltodextrin powder mixed with water	6 g/d	8 weeks	Females with type 2 diabetes	CRP, IL-6, TNF-α	3
2016	Karimi [8]	Iran	28/28	56/0	48.6/49.5	31.0/31.5	RS2/maltodextrin powder mixed with water	6 g/d	8 weeks	Females with type 2 diabetes	CRP, catalase, GSH-Px, MDA, SOD, TAC, UA	3
2019	Khosroshahi [39]	Iran	25/25	29/21	57.9/53.2	23.9/24.4	RS2/waxy corn starch in crackers	12 g/d in the first four weeks and 15 g/d in the next four weeks	8 weeks	End stage renal disease	CRP, TAC, UA	4
2019	Laffin [12]	Iran	9/11	7/13	57.6/53.8	NA	RS2 /wheat flour in biscuits	12 g/d in the first month and 15 g/d the second month	8 weeks	End stage renal disease	IL-6, TNF-α, UA	3
2019	Meng [10]	China	36/34	31/39	61.0/62.9	25.8/26.4	RS2-added lunch and dinner/ common lunch and dinner	17 g/d	12 weeks	Early type 2 diabetic nephropathy	IL-6, MDA, SOD, TNF-α, UA	5
2010	Penn-Marshall [40]	America	17/17	9/8	36.6†	37.7	bread with RS2 or not	7 g/d	6 weeks	At risk for type 2 diabetes	CRP	3
2018	Peterson [14]	America	30/29	39/20	55.0/54.0	35.7/35.5	RS2/AMIOCA® cornstarch in the yogurt	27 g/d	12 weeks	Confirmed prediabetes	TNF-α	3
2015	Ordiz [26]	Malawi	18/18	NA	38.0	NA	RS2 powder mixed with water or not	8.5 g/d	4 weeks	High risk for environmental enteric dysfunction	IL-1β, IL-8	3
2020	Esgalhado [41]	Brazil	16/15	NA	53.5/56.0	26.6/56.0	RS2/manioc flour in cookies	9.6 g/d	4 weeks	Chronic kidney disease	CRP, IL-6, MDA	3
2019	Eshghi [11]	Korea	10/11	8/13	35.0	32.5	RS2/maltodextrin in food	8.1 g/d	4 weeks	Overweight and obese subjects	MDA, SOD, TAC	4

NA: not available; RS2: type 2 resistant starch; CRP: C-reactive protein; IL: interleukin; MDA: malondialdehyde; TNF: tumor necrosis factor; UA: uric acid; SOD: superoxide dismutase; TAC: total antioxidant capacity.; GSH-Px: glutathione peroxidase; IFN: interferon.
†Only the mean age of the total participants was mentioned.

Table 1. Basic characteristics of the included trials (cont.)

Year	Author	Country	Participants (control/ intervention)	Gender (F/M)	Mean age (control/ intervention)	BMI (control/ intervention)	Intervention / placebo form	Intervention dosage	Duration	Health status	Outcomes	Jadad score
2015	Aliasgharzadeh [9]	Iran	25/30	NA	49.6/49.2	30.8/31.8	Resistant dextrin/maltodextrin taken during breakfast and dinner with a cup of water	10 g/d	8 weeks	Females with type 2 diabetes	CRP, IL-6, MDA, TNF-α	4
2017	Farhangi [25]	Iran	25/30	55	49/49	30.8/31.8	Resistant dextrin/Maltodextrin	10g/d	8 weeks	Females with type 2 diabetes	IL-4、IL-10、IL-12、IFN-γ	5
2018	Khosroshahi [13]	Iran	22/22	16/28	60/52	23.3/23.8	RS2/wheat flour prepared as biscuits	12 g/d in the first four weeks and 15 g/d in the next four weeks	8 weeks	End stage renal disease	UA	3

NA: not available; RS2: type 2 resistant starch; CRP: C-reactive protein; IL: interleukin; MDA: malondialdehyde; TNF: tumor necrosis factor; UA: uric acid; SOD: superoxide dismutase; TAC: total antioxidant capacity.; GSH-Px: glutathione peroxidase; IFN: interferon

[†]Only the mean age of the total participants was mentioned.

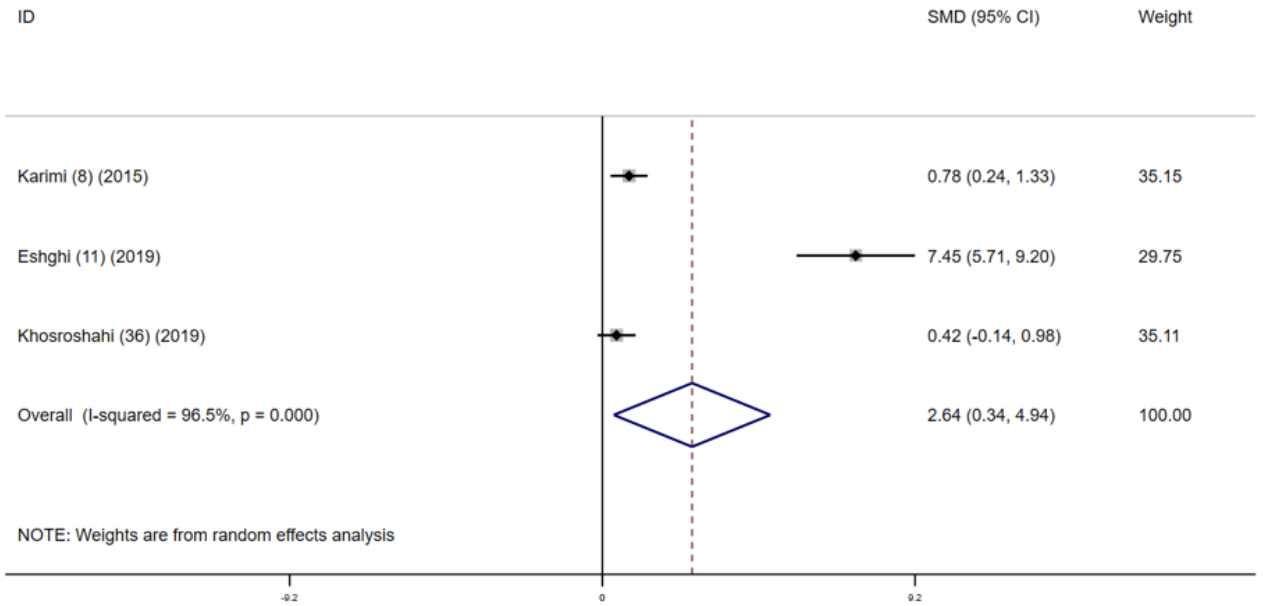

Figure 2. Forest plot of the effects of RS intake on total antioxidant capacity. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test.

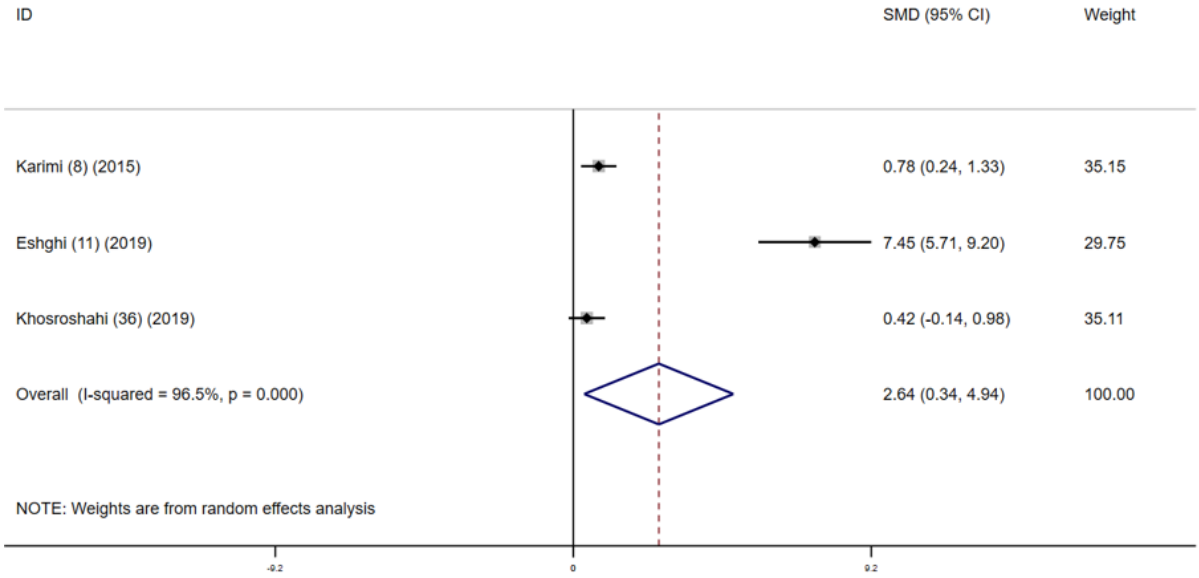

Figure 3. Forest plot of the effects of RS intake on superoxide dismutase. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test.

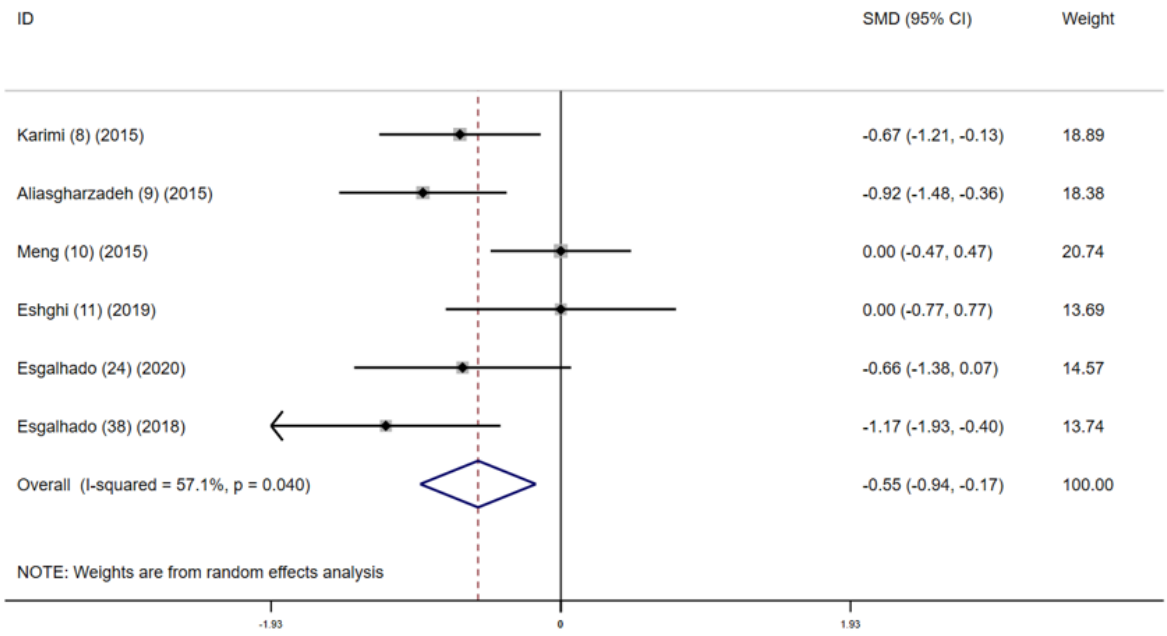

Figure 4. Forest plot of the effects of RS intake on malondialdehyde. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test.

difference: -0.6 pg/mL, $p<0.05$).[25] Ordiz et al reported null effects of RS supplementation on IL-1β ($p=0.05$) and IL-8 ($p=0.23$).[26] Alfa et al investigated the effects of RS on IL-10, and reported null effects,[23] while a significant enhancing effect on IL-10 (mean difference: 2.6 pg/mL, $p<0.05$) was reported in Farhangi et al.[25]

Publication bias and sensitivity analysis

No publication bias was observed for the effects of RS supplementation as follows: for TAC, SOD, MDA, uric acid, CRP, IL-6 and TNF-α, which was assessed by combinations of funnel plot, Begg' and Egger's test (Figure A1-A7). The sensitivity analysis results were as follows: for TAC, the omission of the trial by Karimi et al[8] or Khosroshahi et al[13] would make the effects insignificant; for TNF-α and IL-6, the omission of the trial by Meng et al would lead to a significant reducing effect of RS on TNF-α [SMD (95% CI): -0.58 (-0.82, -0.34), $p<0.01$] with a low heterogeneity ($I^2=19.1\%$), and IL-6 [SMD (95% CI): -0.71 (-1.00, -0.42), $p<0.01$] with a low heterogeneity ($I^2=0$) in overall participants.10 The effects of RS on SOD, MDA, uric acid and CRP were stable.

DISCUSSION

To our knowledge, the current work is the first systematic review and meta-analysis for the effect of RS on antioxidant/oxidative-stress biomarkers. RS supplementation significantly improved TAC, and significantly reduced blood MDA concentration. For inflammation, RS supplementation significantly reduced the blood CRP con-

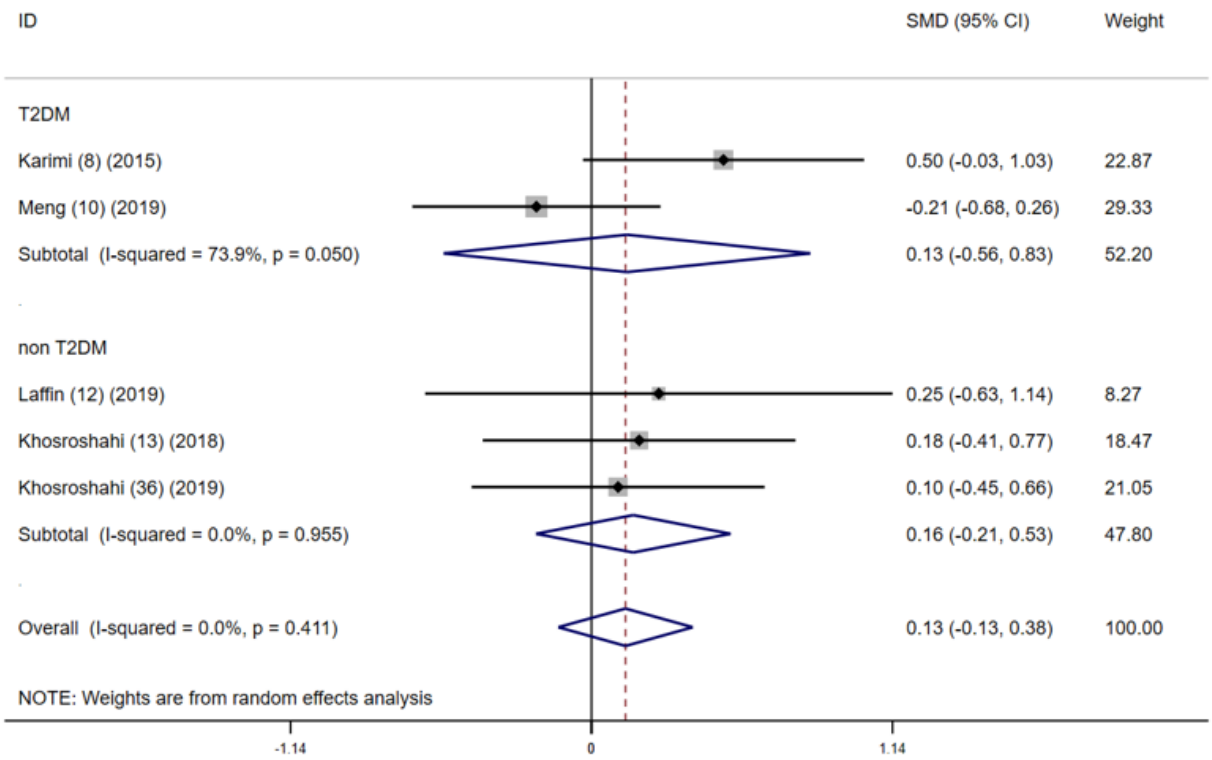

Figure 5. Forest plot of the effects of RS intake on uric acid. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test

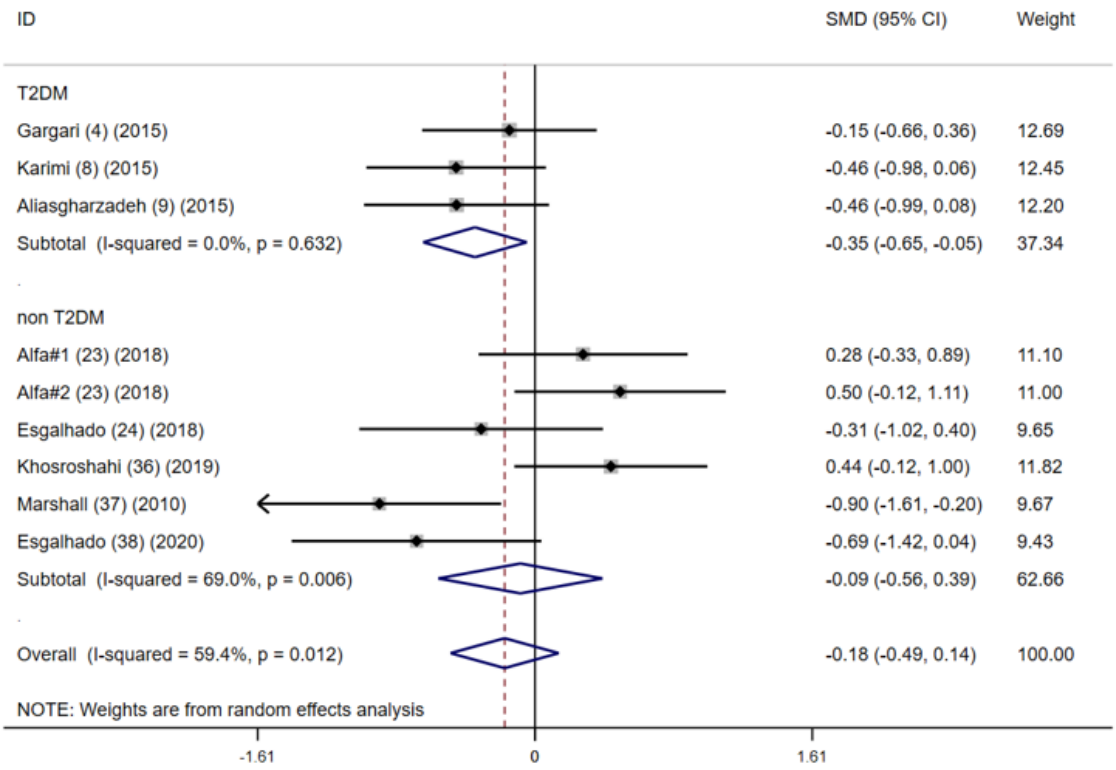

Figure 6. Forest plot of the effects of RS intake on C-reactive protein. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test

centration in T2DM patients. RS supplementation also significantly reduced blood IL-6 and TNF-α concentration if removing one distinct trial.

Previous animal studies indicated that RS supplementation significantly improved the activity of endogenous antioxidant enzymes including SOD, glutathione peroxidase (GSH-Px) and catalase, and enhanced TAC.[5,27,28] In addition, RS supplementation significantly reduced oxidative stress biomarkers like MDA.[27,28] The current work showed consistent results in clinical trials. RS supplemen-

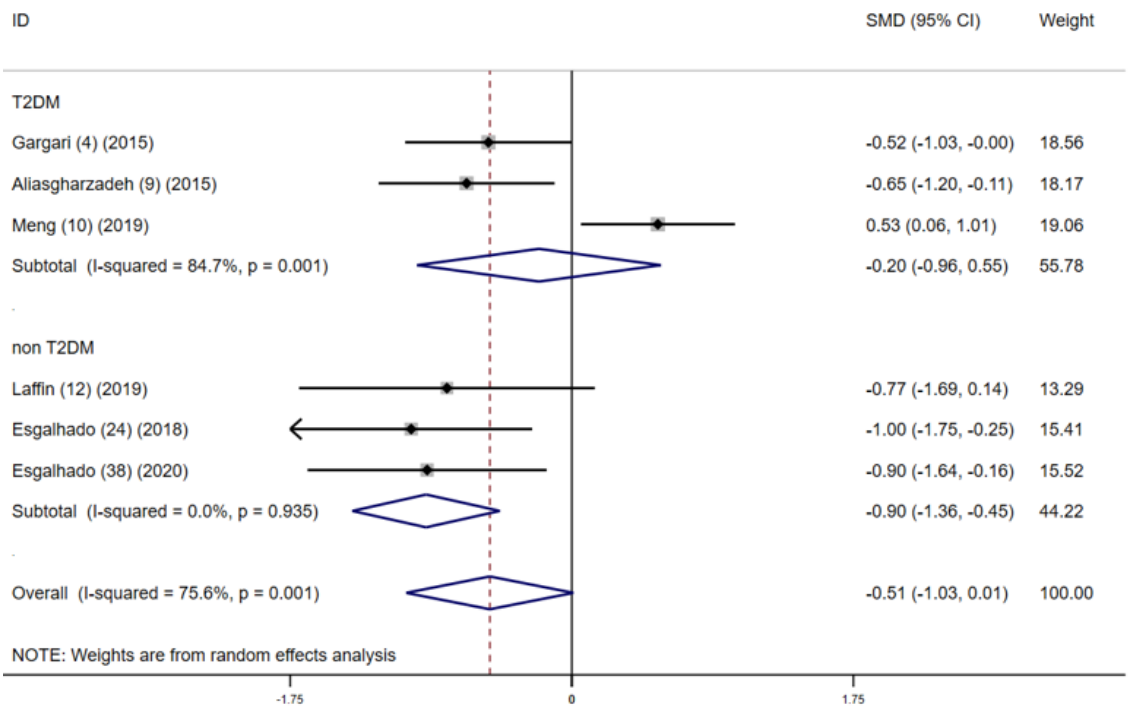

Figure 7. Forest plot of the effects of RS intake on interlukin-6. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test

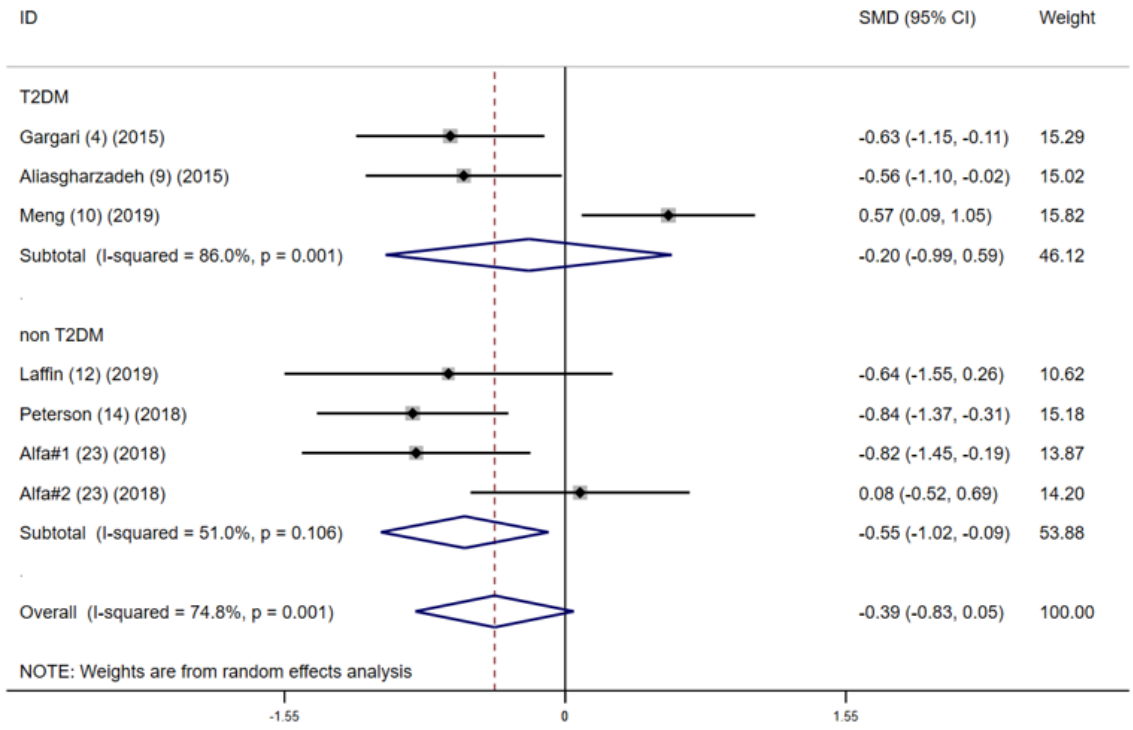

Figure 8. Forest plot of the effects of RS intake on tumor necrosis factor-α. The results were obtained using a random-effects model. The diamond represents the estimated pooling effect, the horizontal line represents the 95% confidence interval of each individual test, and the gray bar represents the weight percentage of each individual test

tation likely reduce oxidative stress. RS may promote the expression of endogenous antioxidant enzymes through mediating the Nrf2 pathway.[5] In addition, gut microbiota is known to affect host health.[29] RS can promote the growth of bifidobacteria, which was shown to increase GSH and decrease a few oxidative stress biomarkers in a systematic review of clinical trials.[7]

Nutritional intervention is an important method to modulate inflammation and related chronic diseases.[4,30,31] Elevated CRP is a strong predictor for T2DM and cardiovascular diseases.[2,32,33] Our meta-analysis showed that RS supplementation was especially useful for suppressing CRP in T2DM patients, indicating that RS supplementation may be beneficial for T2DM. CRP is produced by hepatocytes under the control of cytokines such as IL-6,

IL-1, TNF-α and IFN-γ. RS is fermented into SCFAs in digestive tract. SCFAs may reduce the release of inflammatory cytokines, such as IL-6, TNF-α and IFN-γ, which consequently reduces the CRP production.[34,35]

Halajzadeh et al. conducted a meta-analysis for the effect of RS on CRP in patients with metabolic syndrome and related disorders, and reported a null effect [WMD (95% CI): -0.40 (-1.56, 0.77)].[36] Vahdat et al performed a meta-analysis of CRP for all populations and reported similar results as of this study [WMD (95% CI): -0.21 (-1.06, 0.63), p=0.61] of this study,[37] however they did not perform a subgroup analysis to reveal the suppressing effect of RS supplementation on CRP in T2DM patients.

It is well established that inflammation in adipose tissue, as indicated by elevated TNF-α, triggers insulin resistance. The current meta-analysis suggested that RS significantly reduced TNF-α in non-T2DM subjects, but not in T2DM patients. However, our sensitivity analysis showed that the removal of the study by Meng et al. would make the effects of RS supplementation on TNF-α significant in T2DM patients [SMD (95% CI): -0.60 (-0.97, -0.22), p=0.002].[10] Halajzadeh et al reported a significant reduction effect of RS on TNF-α for patients with metabolic syndrome [WMD (95% Cl): -2.02 (-3.14, -0.90)].[36]

IL-6 is also a known predictor for T2DM.[2,32,38] Our meta-analysis indicated a significantly reduction effect of RS on IL-6 in non-T2DM subjects, but not in T2DM patients. In sensitivity analysis, we found that again the removal of the results by Meng et al[10] would make the reduction effects significant in T2DM patients [SMD (95% CI): -0.58 (-0.96, -0.21), p<0.01]. Halajzadeh et al reported a null effect of RS supplementation on IL-6 for patients with metabolic syndrome.[36]

The following limitations should be acknowledged. First, the number of available trials for a few biomarkers was relatively small, which may lead to a lower statistical power. Second, the various dosage and intervention duration may partially contribute to the high heterogeneity.

Conclusion

RS supplementation may reduce the blood concentrations of a few oxidative stress and inflammation biomarkers such as MDA and CRP, particularly in T2DM patients. Future work should investigate the optimal dosage of RS supplementation for modulating oxidative stress and inflammation biomarkers related to T2DM.

AUTHOR DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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