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Original article

Effects of probiotics and synbiotic supplementation on antioxidant status: A meta-analysis of randomized clinical trials

Hanieh Roshan [a], Ehsan Ghaedi [b, c, **], Jamal Rahmani [a], Meisam Barati [a], Marziyeh Najafi [a], Mehraneh Karimzedeh [d], Omid Nikpayam [e, *]

[a] Clinical Nutrition and Dietetics Department, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[c] Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[d] Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Biochemistry and Diet Therapy, Nutrition Research Center, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

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SUMMARY

Background and aim: Oxidative stress implicated in the pathogenesis of several diseases. Anti-oxidative characteristics of probiotics reported previously. Thus, we aimed to critically investigate the effectiveness of probiotics and synbiotics supplementation on antioxidant biomarkers.

Methods: A comprehensive search of Scopus and Medline was performed up to November 2017. All randomized controlled trials (RCT) which evaluate the effect of probiotics or synbiotics on superoxide dismutase (SOD) activity, total antioxidant capacity (TAC) and glutathione (GSH) levels were included. Weighted mean difference (WMD) were pooled using random effect model.

Results: Sixteen eligible RCTs with 915 participants were included in present study. Findings showed that probiotics could significantly increase GSH level compared to the control groups ((WMD): 132.36, 95% CI: 27.76, 236.95, P = 0.01). Because of considerable heterogeneity among included the studies, subgroup analyses were conducted. Subgroup analysis revealed that GSH level significantly increased in non-diabetic individuals; the effect size was not significant in diabetic patients. Furthermore, probiotics and synbiotics showed no significant effect on TAC level (WMD: 0.04, 95% CI: −0.07, 0.15, P: 0.50) and SOD activity (WMD: 0.04, 95% CI: −0.06, 0.13, P = 0.43).

Conclusion: Probiotics and synbiotics supplementation improve GSH as a biomarkers of antioxidant status in the body. However, additional studies needed for concluding about TAC and SOD activity.

1. Introduction

Probiotics as well-known supplements reached considerable popularity around the world [1]. Probiotics are live microorganisms which should administered in sufficient quantities to exert favorable health effects for the host [2]. Two well-documented groups of these microorganisms are strains of Lactobacillus and Bifidobacterium [3]. Probiotics could be added to usual diet as a dietary supplement or food enrichment [4]. Health benefits contributed to the probiotics comprising increasing pathogens in the intestine, enabling immune response through different T-helper cell reactions, lowering blood cholesterol and reducing intensity and duration of respiratory tract infections [5–7]. The beneficial effects of probiotics reported in different diseases [1]. Previous clinical studies showed probiotics efficacy for improving insulin resistance, lipid profile inflammation and oxidative stress [8].

* Corresponding author. Department of Biochemistry and Diet Therapy, Nutrition Research Center, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, 5166614711, Iran.
** Corresponding author. Department of Cellular and Molecular Nutrition, School of Nutrition Sciences and Dietetics, Tehran University of Medical Sciences, Poorsina Street, Enghelab Avenue, PO Box: 14155-6446, Tehran, Iran. Fax: +982188974462.
E-mail addresses: ehsanghaedi073@gmail.com (E. Ghaedi), nikpayamomid@gmail.com (O. Nikpayam).

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Body in the normal state maintains a balance between pro-oxidants and antioxidants [9]. Any factor which interrupts this balance in which existence of oxidants are more than the scavenging capacity of antioxidants, could result in oxidative stress [10]. The reactive oxygen and nitrogen species (RONS) are the main oxidants which are constantly produced in body [9]. Reactive oxygen species (ROS) present in different chemical forms such as superoxide, hydroxyl radicals and hydrogen peroxide [11]. Moreover, ROS plays a critical role in cell proliferation, growth, apoptosis and inflammatory reactions [12]. Antioxidants could be endogenous such as superoxide dismutase (SOD), catalase (CAT), peroxidase, glutathione (GSH) and peroxiredoxin or exogenous like vitamin E and vitamin C [13] that the role of oxidative stress in the pathogenesis of diabetes [14], atherosclerosis [15], inflammation [16], Alzheimer [17], cancer [18] and metabolic syndrome [19] discussed previously.

Improving the antioxidant capacity of human body are one of health benefits of probiotics; probiotics reported to increase plasma total GSH level [20,21], SOD activity [22,23] and total antioxidant capacity (TAC) [23–25]. Decreased oxidized low density lipoprotein cholesterol (Ox-LDL), 8-isoprostanes, glutathione redox ratio [26] and malondialdehyde (MDA) concentration [24,25] have been reported following probiotic administration. However, in some studies probiotics did not have any effect on CAT [23,27] and TAC levels [8,20,21,27], SOD activity [27,28] or GSH level [8]. Additionally, in some trials probiotics did not influence MDA concentration [23,27,29].

It seems that these discrepancies are due to the protocol, duration of intervention and various dosages or strains of the administered probiotics. In order to clarify the anti-oxidative impacts of probiotics, we aimed to include all randomized controlled trials (RCT) on this topic. Such evidence could produce the evidence with greater clarity for efficacy of probiotics and synbiotics as an antioxidant agent against oxidative imbalance.

2. Methods

2.1. Search strategy

This meta-analysis was conducted according to the 2009 guideline of preferred reporting items for systematic reviews and meta-analysis statement (PRISMA) (www.prisma-statement.org.) [30]. All articles were identified by searching Scopus (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) in English language in order to detect all the relevant published trials up to November 2017. The search keywords consisted of: “probiotic” OR “symbiotic” OR “oxidative stress” OR “glutathione” OR “total antioxidant capacity” OR “superoxide dismutase” OR “GSH” OR “TAC” OR “SOD”. Initially, no restriction was imposed for detecting human studies or clinical trials in order to explore all the relevant researches. Afterwards, the studies which met our inclusion criteria were selected following examining title and abstract of the articles.

2.2. Study selection and eligibility criteria

All RCTs which evaluated the effect of probiotics or synbiotics on the biomarkers of antioxidant status (TAC, SOD and GSH) were included. All studies which met the inclusion criteria were included in present study. Inclusion criteria comprising [1]: were in adults (>18 years old) [2] conducted as RCT [3]; investigated the impact of probiotic and synbiotics on biomarkers of antioxidant status (we also included the studies that supplemented another agent in combination with probiotics in both intervention and control groups) [4]; presented data of interest on TAC, SOD and GSH in both intervention and placebo groups; and [5] administered probiotics or synbiotics for at least one week. The title and abstract of all articles which were identified by searching were screened by two authors independently and the articles which did not have eligibility for analysis were excluded. Exclusion criteria were [1] using a mixture of probiotic or synbiotics with other substance only in intervention group and not in control group [2]; non-RCT trials or trial without a control group. [3]; duplicate studies with same population [4]; animal studies. We eliminated the articles which were cross-sectional, review, animal studies and the articles which did not have sufficient information about SOD activity, TAC and GSH level at baseline and at the end of the trial.

2.3. Data extraction

Full texts of the all articles were scrutinized and the following data were extracted from eligible studies: first author name, year of publication, study design, the country of study, number of participants in each group, age, gender, dose of supplement, strain of bacteria, type of supplement, duration of intervention, disease type and the probiotics impacts on SOD activity, TAC and GSH level.

2.4. Statistical analysis

All statistical analyses were performed using STATA software version 12 (STATA Crop, College Station, Texas). The effect of probiotics and synbiotics supplementation on antioxidant status were evaluated by means of the following factors: SOD activity, TAC and GSH level. Standard deviations (SD) of mean differences that were not mentioned were calculated by the following formula: SD^2 change $= SD^2$ baseline $+ SD^2$ final $-$ ($2 \times$ correlation coefficient $\times$ SD baseline $\times$ SD final) assuming that the correlation coefficient (R) was 0.5 [31]. To avoid publication bias, wide search among the published papers was conducted; publication bias also evaluated visually by funnel plots and statistically by Egger's regression test and Begg's test [32]. We estimated the heterogeneity of articles by *I*-squared (I^2) statistic. Furthermore, a random-effects model was applied if heterogeneity was more than %50 to calculate the pooled weight mean difference (WMD). To detect the source of heterogeneity, all analyses were conducted by pre-defined subgroups. Sex, dose of supplement, type of bacteria and disease type were the pre-defined subgroups.

3. Result

Initially, 1784 articles were detected by electronic literature review. Following extracting the duplicate records, 1737 articles were appraised by screening their title and abstract. Out of the 1737 articles, 1690 records which were not eligible were excluded. Subsequently, full texts of the 47 eligible studies were examined and 31 articles which did not have sufficient data were excluded. Eventually, sixteen studies which met our inclusion criteria were included in present meta-analysis. These sixteen trials consisted of 915 participants with 459 subjects in the treatment groups and 457 individuals in the control groups. The PRISMA flowchart of study selection procedure is illustrated in Supplemental Fig. 1.

3.1. Study characteristics

Main characteristics of the sixteen studies which were included in this meta-analysis is outlined in Table 1. All of the studies were published in Iran except for two studies which were published in Brazil [28] and Malaysia [22]. In addition, all of the studies were issued between 2012 and 2017. One study was cross-over [33] and the rest of the studies were parallel design. Mean age in the

Table 1
Characteristics of the included randomized clinical trials.

Author	Country	Year	Participants (n) In/C	Mean Age (yr) In/C	Probiotics	Total Dose (10^7 CFU)	Forms	Study Duration (week)	Study Population	Study design	Outcome
Gomes, A. C.	Brazil	2017	21/23	From 20 to 59	L.A-14, L.C-11, LL-23, B.B-06, BL-4	2000	4 mix Pro. Sachets p/d	8	Healthy subjects	RCT	SOD/GPx
Vaghef-Mehrabany, E.	Iran	2016	22/24	41.1/44.2	L.C.	10	Pro. or placebo Capsules	8	Rheumatoid arthritis	RCT	SOD/GPx/TAC
Hariri, M.	Malaysia	2015	20/20	From 32 to 68	L.P. (strain A7)	400	200 ml/d Pro. or Con. soy milk	8	Type 2 diabetes	RCT	SOD
Hanie S. Ejtahed	Iran	2012	30/30	51/50.87	L.A (strain La5), B.L. (strain Bb12)	398	300 g/d Pro. or Con. yogurt	8	Type 2 diabetes	RCT	SOD/GPx/TAC
Karamali, M.	Iran	2017	30/28	27.2/26.2	L.A. strain T.16, L.C. strain T.2, B.B. strain T1	600	Syn. or placebo capsules (with 800 mg inulin)	6	Gestational diabetes	RCT	GSH/TAC
Jamilian, M.	Iran	2016	30/30	27.1/28.4	L.A., L.C., L.B	600	Pro. or placebo capsules	12	Healthy subjects	RCT	GSH/TAC
Bahmani, F.	Iran	2016	27/27	52/53.4	L.S.	10	120 g/d Pro., Syn. (with inulin) or control bread	8	Type 2 diabetes	RCT	GSH/TAC
Akkasheh, G.	Iran	2016	20/20	38.3/36.2	L.A, L.C, B.B.	600	Pro. or placebo capsules	8	Major depressive disorder	RCT	GSH/TAC
Taghizadeh M.	Iran	2013	26/26	29/26.9	L.S.	18	Syn. (with 0.72 g inulin) (2 times/d in 9portions) or control food	9	Pregnant women	RCT	GSH/TAC
Asemi Z.	Iran	2014	62/62	53.1/58	L.S.	27	Syn. (with 1.08 g inulin) (9 g 3times/d) or control food	6	Type 2 diabetes	Cross-over RCT	GSH/TAC
Asemi Z.	Iran	2012	37/33	25.7/24.2	L.A. (strain LA5), B.L (strain BB12)	200	200 g/d Pro. or Con. yogurt	9	Pregnant women	RCT	GSH/TAC
Asemi Z.	Iran	2013	27/27	50.51/52.59	L.A, L.C, L.R, L.B, B.br, B.lon., S.T.	1070	Pro. or placebo capsules	8	Type 2 diabetes	RCT	GSH/TAC
Soleimani A.	Iran	2016	30/30	54/59.4	L.A, L.C, B.B	600	Pro. or placebo capsules	12	Diabetic hemodialysis patients	RCT	TAC
Badehnoosh B.	Iran	2017	30/30	28.8/27.8	L.A, L.C, B.B	600	Pro. or placebo capsules	6	Gestational diabetes	RCT	TAC
Ebrahimi Mameghani M.	Iran	2013	20/20	33.6/35.6	L.C., L.P, L.A, L.D, B.lon., B.br., B.i., S.S.	90	2 sachets/d of Pro. or placebo	1	Critically ill patients	RCT	TAC
Zamani B.	Iran	2017	27/27	49.3/49.5	L.A, L.C. B.B	600	Syn. or placebo capsules	8	Rheumatoid arthritis	RCT	TAC

In= Intervention groups, C = control groups, Pro. = probiotic, Con. = conventional, Syn. = synbiotic, p/d = per day, RCT = Randomized clinical trial, L. = Lactobacillus, L.C. = Lactobacillus. casei, L.P. = Lactobacillus. Plantarum, L.A. = L.acidophilus, L.D. = L. delbrueckiisubsp.bulgaricus, L.L = Lactococcus.lactis, L.S. = Lactobacillus sporogenes, L.R. = L. rhamnosus, L.B. = L. bulgaricus, B. = Bifidobacterium, B.lon. = B.longum, B.br. = B. breve, B.i. = B.infantis, B.B. = B.bifidum, B.L = B.lactis, S.T. = Streptococcus thermophilus. S.S. = Streptococcus salivarius.

intervention and control group were 40 and 40.9 years respectively [8,20,21,23–25,27,33–39]. Mean duration of the interventions were 7.8 weeks and dose of the probiotics used in these studies were between 10×10^7 and 2000×10^7 colony-forming units (CFU). Dosage and species of the probiotic bacteria and their administered form (supplement or food) differed between the studies. From all the recorded trials, two of them had administered probiotics in sachet from [28,38], eight studies in supplemental form [20,21,24,25,27,34,36,39] and six studies as a food [8,22,23,33,35,37]. Out of all the trials, five studies had used synbiotics (3 studies in food forms [33,35,37] and 2 studies in supplemental form [34,36]). The other eleven trials included in the meta-analysis had administered probiotics [8,20–25,27,28,38,39].

3.2. Findings form meta-analysis

There was heterogeneity between the studies considering the effects of the probiotics on SOD activity (I^2: %66.3, P heterogeneity = 0.03), GSH (I^2: %98.2, P heterogeneity = 0.001) and TAC level (I^2: %86, P heterogeneity = 0.001).

Also, data from eight studies with 512 participants was investigated to discover the effect of the probiotics administration on GSH level. Pooled effect size revealed a significant increase of GSH level after probiotics supplementation compared to the control group (WMD: 132.36 μmol/l, 95% CI: 27.76, 236.95, P = 0.01) (Fig. 1).

Furthermore, eleven studies from all the recorded trials with 580 participants were considered for evaluating the efficacy of probiotics supplementation on TAC level. Pooled effect size on TAC level (Fig. 2) indicated no significant influence of the probiotics administration on TAC level (WMD: 0.04 mmol/l, 95% CI: −0.07, 0.15, P: 0.50).

Data from four studies with 189 participants were used to appraise the probiotics impacts on SOD activity (Supplemental Fig. 2). Findings indicated no significant effect of probiotics and synbiotics supplementation on SOD activity compared with the control group (WMD: 0.04 U/g Hb, 95% CI: −0.06, 0.13, P = 0.43).

3.3. Subgroup analyses

Subgroup analyses were conducted to find out potential source of heterogeneity between the studies. Sex, dose of bacteria, kind of bacteria and type of disease had the most heterogeneity among the subgroups. The results of the subgroup analyses of the included studies on SOD activity, TAC and GSH level are shown in Table 2.

Regarding SOD activity, females (I^2: %83, P heterogeneity < 0.001) and non-diabetics subjects (I^2: %83, P heterogeneity < 0.001) were potential source of heterogeneity for SOD. After subgroup analyses, the effects of the probiotics on SOD activity were not significant in none of the subgroups performed based on sex, dose, type of strains and disease (Table 2).

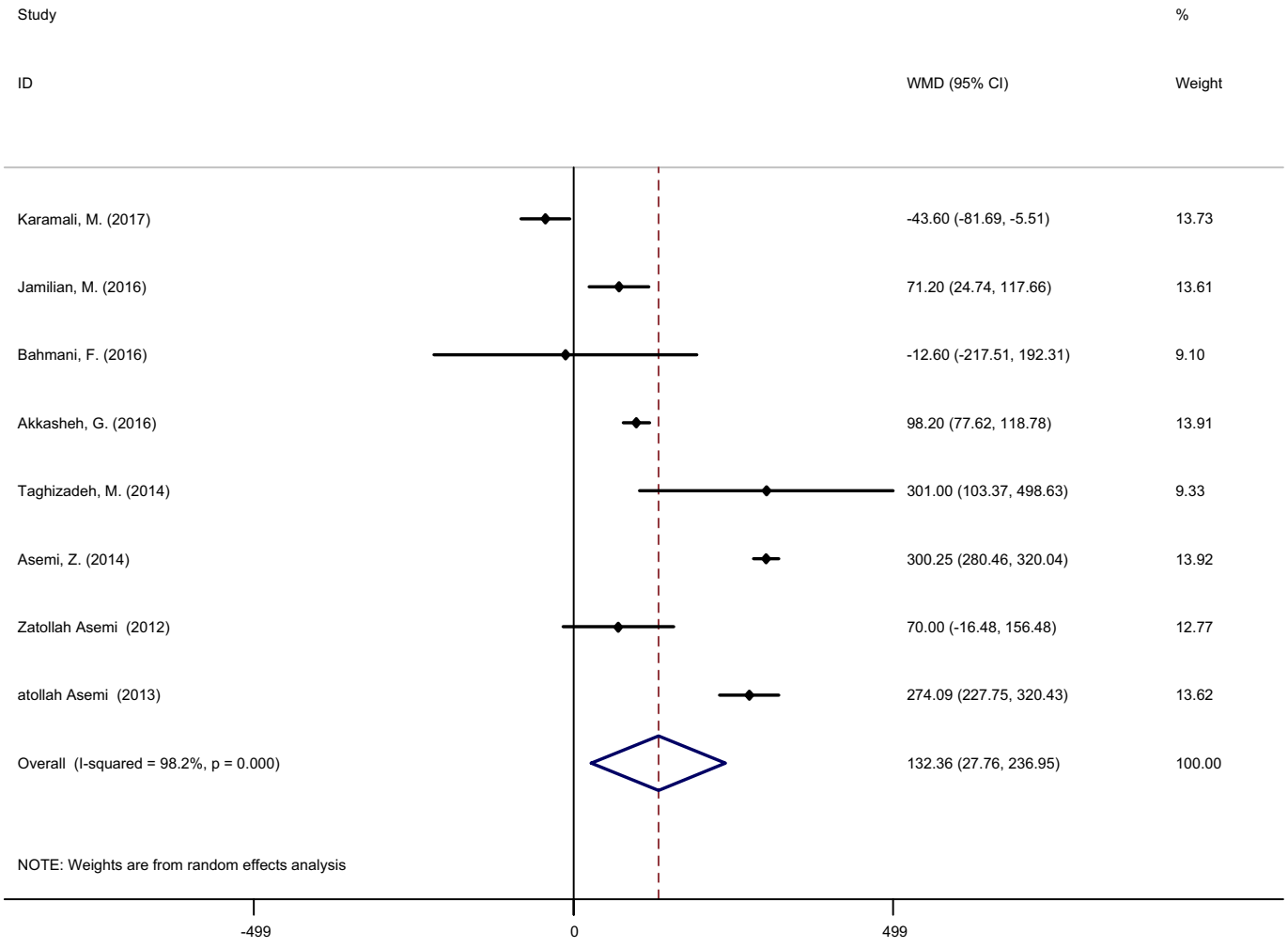

Fig. 1. Forest plot of the studies indicating the probiotics effects on GSH level.

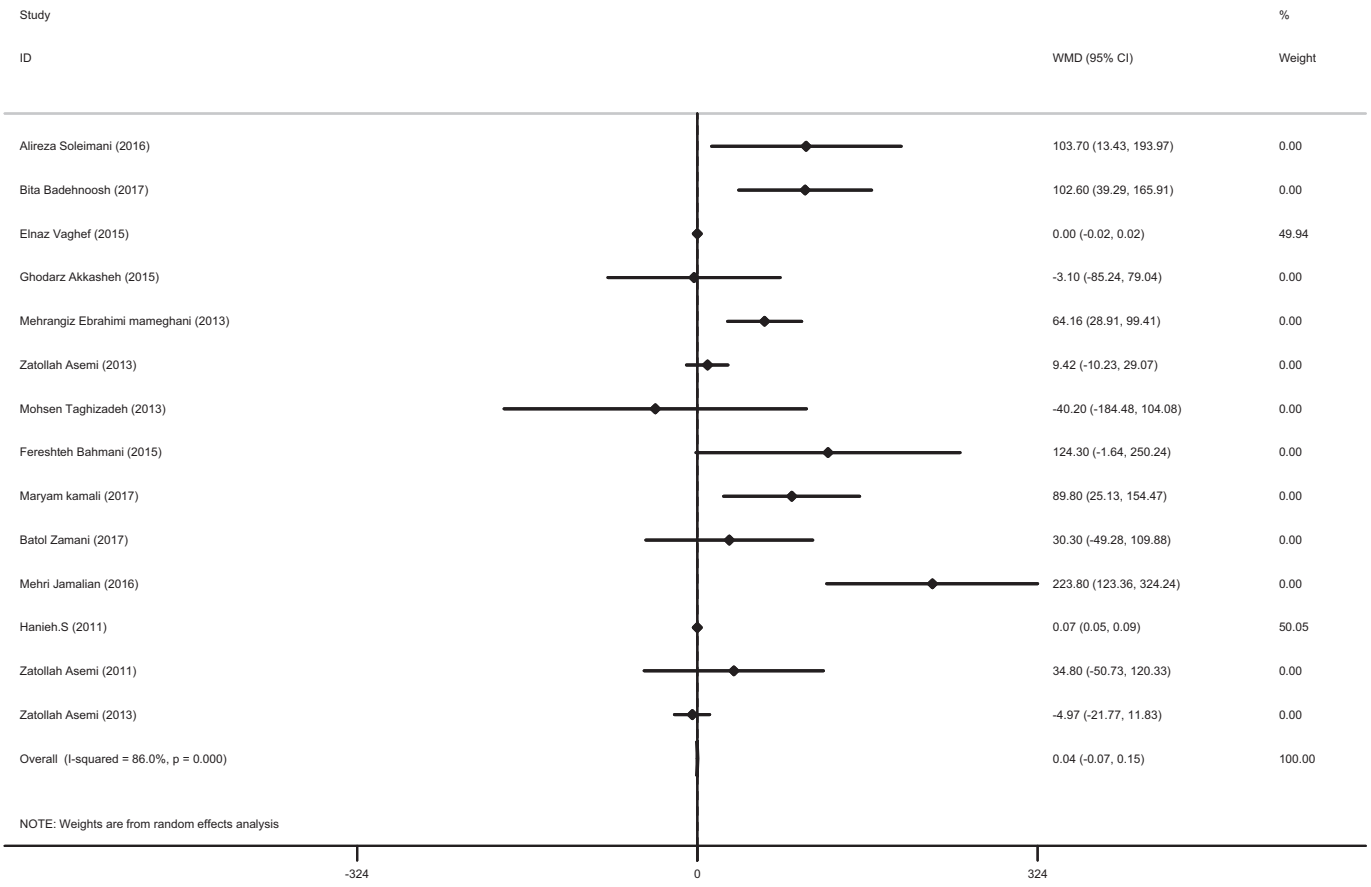

Fig. 2. Forest plot of the studies indicating the probiotics effects on TAC level.

For GSH level, all of the subgroups except for non-diabetics produced heterogeneity. Subgroup analysis revealed that, GSH level in non-diabetic individuals had a consistent and significant increase (WMD: 92.70 μmol/l, 95% CI: 54.38, 131.02, P < 0.001); however, its increment in the diabetic patients was not significant. (WMD: 138.05 μmol/l, 95% CI: −55.58, 331.68, P: 0.16). GSH alterations in other subgroups were not significant due to existence of high heterogeneity (Table 2).

Table 2
Results of subgroup analysis of the included randomized controlled trials in meta-analysis of probiotics on SOD, GSH and TAC.

Variables		sex		dose		bacteria		Type of disease		Pregnancy	
		Female	Both	$<25*10^9$	$\geq 25*10^9$	lactobacillus	mixed	Diabetics	Non-Diabetics	Pregnant	Non-pregnant
SOD											
No. of comparison		2	2	2	2	2	2	2	2	–	–
WMD		0.25	0.07	0.007	0.28	0.007	0.28	0.25	0.07	–	–
95% CI	Lower	−0.97	−0.06	−0.02	−0.47	−0.02	−0.47	−0.97	−0.06	–	–
	Higher	1.47	0.22	0.04	1.03	0.04	1.03	1.47	0.22	–	–
p value		0.67	0.30	0.68	0.46	0.68	0.46	0.67	0.30	–	–
I^2 (%)		37	0.83	0.18	0.16	0.18	0.16	37	0.83	–	–
p-heterogeneity		0.20	<0.001	0.26	0.27	0.26	0.27	0.20	<0.001	–	–
GSH											
No. of comparison		4	4	3	5	3	5	4	4	3	5
WMD		66.37	183.52	260.36	71.22	213.87	94.9	138.05	92.70	78.576	159.878
95% CI	Lower	−28.32	48.78	191.41	−3.11	37.39	0.08	−55.58	54.38	−67.261	42.587
	Higher	161.07	318.26	329.31	145.55	390.35	188.09	331.68	131.02	224.413	277.168
p value		0.17	0.008	<0.001	0.06	0.01	0.05	0.16	<0.001	0.291	0.008
I^2 (%)		87	98	79	91	77	96	98	46	87.3	98.3
p-heterogeneity		0.001	<0.001	0.008	<0.001	0.01	<0.001	<0.001	0.13	<0.001	<0.001
TAC											
No. of comparison		6	8	5	9	4	10	7	7	5	9
WMD		69.08	16.57	0.03	62.24	48.70	4.28	24.63	42.54	89.767	0.036
95% CI	Lower	3.29	−1.20	−0.03	17.09	20.91	−10.89	3.24	−3.58	24.674	−0.049
	Higher	134.87	34.35	0.10	107.39	76.49	19.46	46.01	88.66	154.860	0.120
p value		0.04	0.06	0.33	0.007	0.001	0.58	0.02	0.07	0.007	0.407
I2 (%)		86	69	89	82	83	39	78	82	65.7	85.5
p-heterogeneity		<0.001	0.002	<0.001	<0.001	<0.01	0.17	<0.001	<0.001	0.020	<0.001

Furthermore, in terms of TAC level, all of the subgroups except for mixed bacteria in the bacteria subgroup had generated heterogeneity. TAC changes in the subgroups were not significant due to the substantial heterogeneity existence (Table 2).

3.4. Publication bias

Funnel plots and statistical tests of Begg's and Egger's were performed to detect whether publication bias occurred for all of the included studies. Funnel plot of SOD activity is illustrated in Supplemental Fig. 3. According to the shape of the funnel plot, studies did not reveal any asymmetric distribution in terms of the effect size of probiotics on SOD activity. Moreover, no publication bias was discovered among the studies on SOD (Begg's P = 0.68 and Egger's P = 0.49).

Also, the funnel plot for GSH level is depicted in Supplemental Fig. 3. The shape of the funnel plot of studies does not demonstrate any asymmetric distribution considering the effect size of the probiotics on GSH level. In addition, there was not any publication bias between the clinical trials investigating the probiotics impacts on GSH level statistically (Begg's P = 0.80 and Egger's P = 0.56).

Furthermore, Supplemental Fig. 3 showed the funnel plot for TAC level. No asymmetric distribution of the effect size of probiotics administration on TAC level was discovered. Also, no publication bias was found among studies investigating TAC level statistically (Begg's P = 0.87 and Egger's P = 0.08).

4. Discussion

The present meta-analysis was carried out to evaluate the effect of probiotics and synbiotics on SOD activity, TAC and GSH level as biomarkers of antioxidant status. To the best of our knowledge, this is the first meta-analysis investigating this topic. This meta-analysis of sixteen clinical trials demonstrated that probiotics and synbiotics could significantly increase GSH level. Nevertheless, no significant effect was found in terms of SOD activity and TAC level following the probiotics supplementation.

In present meta-analysis, we showed that probiotics could significantly increase GSH level compared with the control groups. Also, it was demonstrated that GSH level increased significantly in non-diabetic individuals; however, pooled effect size did not showed significant effect in diabetic patients Specific strains of the probiotics reported to be beneficial for increasing glutathione-s-transferase, glutathione reductase, glutathione peroxidase, SOD and CAT activities [24]. Probiotics reported to increase GSH level through induction of its synthesis or its secretion [27]. In particular, specific strains such as *L. fermentum*, *Lactobacillus reuteri*, *Bifidobacterium* and *Lactococcus* strains reported to be capable of releasing GSH from other tissues [8]. GSH as the most important antioxidant biomarker, is an indispensable endogenous antioxidant which regulates intracellular redox homeostasis in body [35]. GSH molecule has a sulfhydryl (SH) group on its cysteinyl component which contributes to its electron-donating properties. While the electrons are lost, two oxidized molecules get dimerized to generate glutathione disulfide (GSSG). Glutathione disulfide reductase catalyzes GSH recycling by means of reducing equivalents from nicotinamide adenine dinucleotide phosphate (NADPH) to reproduce 2 GSHs from GSSG [40]. The increase in GSH level following probiotics supplementation could be explained by inducing production of short chain fatty acids (SCFAs) in the colon particularly butyrate. In fact butyrate could induce NADPH production for GSH synthesis [33,35]. In addition, this finding might be due to elevated glutamate-cysteine-

Table 3
Different methods employed to measure biomarkers of antioxidant status.

Study	SOD	GSH OR GPX	TAC
Gomes, A. C.	Using A Micro-Assay By A Multi-Wavelength Detection Microplate Reader (Biotek, Synergy Ht, Winooski, Vt)	Using A Microassay By A Multiwavelength Detection Microplate Reader (Biotek, Synergy Ht, Winooski, Vt)	–
Vaghef-Mehrabany, E.	Spectrophotometrically Using A Ransod Kit (Randox Laboratories, Crumlin, Uk)	Using The Spectrophotometric Technique And A Ransel Kit (Randox Laboratories, Crumlin, Uk)	Using A Randox Kit (Randox Laboratories, Crumlin, Uk)
Hariri, M.	Using A Biorex Kit Method (Cat No: Bxc0531a, Biorex, Uk)	–	–
Hanie S. Ejtahed	Spectrophotometrically Using A Ransod Kit (Randox Laboratories, Crumlin, Uk)	Using The Spectrophotometric Technique And A Ransel Kit (Randox Laboratories)	Using A Randox Tas Kit (Randox Laboratories)
Karamali, M.	–	Using Spectrophotometric Methods	Using Spectrophotometric Methods
Jamilian, M.	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Bahmani, F.	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Akkasheh, G.	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Taghizadeh M.	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Asemi Z. (2012)	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Asemi Z. (2013)	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Asemi Z. (2014)	–	The Method Of Beutler	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Soleimani A.	–	–	Using The Ferric-Reducing Antioxidant Power Developed By Benzie And Strain
Badehnoosh B.	–	–	The Method Of Ferric Reducing Antioxidant Power (Frap) Developed By Benzie And Strain
Ebrahimi Mameghani M.	–	–	Using An Elisa Kit (Imanox, Immunodiagnostic Ag, Bensheim, Germany)
Zamani B.	–	–	Using The Ferric Reducing Antioxidant Power Method Developed By Benzie & Strain

ligase (GCL) activity and expression which can lead to increased GSH synthesis. Moreover, up-regulated gene expression of interleukine-18 as an anti-inflammatory cytokine by SCFAs [36], suppressed pro-inflammatory cytokines, down-regulated toll-like receptor pathways and genes regulating oxidative stress could be implicated in probiotics effects on GSH level [35]. Metal ion chelation, inhibiting ascorbate autoxidation, reducing free radicals, attenuating Ox-LDL level, diminishing 8-isoprostanes level and GSH redox ratio [23,27,36] considered as possible other antioxidant mechanism of probiotics in the body.

In previous studies, Lactobacillus as a probiotic bacterium has been demonstrated to have the complete glutathione system required for GSH recycling, synthesis and transporting. Lactobacillus reported to have Mn-superoxide dismutase activity [22]. In this meta-analysis, despite the positive results discovered in terms of the probiotics effects on GSH level, no significant effects was detected on SOD activity and TAC level. Limited number of existing clinical trials investigating the probiotics effects on SOD could be the main result. Furthermore, existence of high heterogeneity among the studies in terms of the different strains and dosages of probiotics could be possible other reason. This is due to the fact that the anti-oxidative property of probiotics are extremely strain specific [21] and also if they are administered as a food it could be raised by the anti-oxidative agents present in the administered food.

At last it must be noted that measuring biomarkers of antioxidant and oxidative status are very different. Actually the biomarkers which investigated in present study has the most heterogeneity in literature [41–43]. We tried to represent all methods applied in all studies included in present study (Table 3). But it could be considered as possible limitation; regarding GSH measurement only one study applied different method with other studies [36]. Among fourteen included studies for TAC, only four study applied different method for TAC measurement; additional studies are needed before any firm conclusion could be drawn.

This meta-analysis had some limitations including restricted number of eligible clinical trials particularly for evaluating the probiotics effects on SOD activity. In addition different doses and strains of the administered probiotic, assessment of the probiotics effects in patients with different types of diseases and different duration of the studies and inclusion of studies assessing synbiotics effects, must be acknowledged as possible drawbacks which lead to heterogeneity. Furthermore, two type of supplementation were performed in included studies; probiotic supplementation as supplement and enrichment of regular food with probiotics. However, it must be noted that although most of included studies reported main micronutrient and macronutrient composition of enrolled subjects in intervention and control group, but all of confounding factors could not be controlled. In that case main food groups which can affect gut microbiome like fiber were not statistically significant but other confounding factors exist; therefore, it must be noted as limitation in present study. Furthermore, a high degree of heterogeneity existed between the included studies. Also, due to lack of adequate clinical trials evaluating other oxidative stress biomarkers, other indices of oxidative stress could not be assessed.

To sum up, the present meta-analysis concluded that the probiotics might ameliorate oxidative stress through elevating glutathione level. Nevertheless, no significant effect of the probiotics on superoxide dismutase activity or total antioxidant capacity was found. These results must be prudently interpreted because of the high heterogeneity among the included studies. Other larger and longer clinical trials are required to corroborate the effects of probiotics on oxidative stress before any firm conclusion could be drawn.

Conflicts of interest

All the authors declared that they have no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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Author contribution

O.N., M.K. and J.R. screened and extracted articles. E.G. and M.B. contributed for statistical analysis, H.R. write the primary manuscript, O.N. add comments ad revised article, All the authors approve the manuscript with last edition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.02.003.

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