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Prebiotics, Prosynbiotics and Synbiotics: Can They Reduce Plasma Oxidative Stress Parameters? A Systematic Review

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Abstract This study assessed the effectiveness of presybiotics, prosybiotics and synbiotics on reducing serum oxidative stress parameters. PubMed/Medline, Ovid, Google Scholar, ISI Web of Science and SCOPUS were searched up to September 2016. English language randomized clinical trials reporting the effect of presybiotics, prosybiotics or synbiotic interventions on serum oxidative stress parameters in human adults were included. Twenty-one randomized clinical trials met the inclusion criteria for systematic review. Two studies investigated prebiotics, four studies synbiotics and fifteen studies probiotics. According to our systematic review, prebiotic could decrease malondialdehyde and increase superoxidative dismutase, but evidence is not enough. In comparison with fructo-oligosaccharide, inulin is much more useful for oxidative stress reduction. Using probiotics with dairy products could reduce oxidative stress significantly, but probiotic in form of supplementation did not have any effect on oxidative stress. There is limited but supportive evidence that presybiotics, prosybiotics and synbiotics are effective for reducing oxidative stress parameters. Further randomized clinical trials with longer duration of intervention especially on population with increased oxidative stress are needed to provide more definitive results before any recommendation for clinical use of these interventions.

Keywords Prebiotics · Probiotics · Synbiotics · Oxidative stress · Systematic review

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Introduction

Pathophysiological and physiological conditions, foreign compound metabolism and radiation are caused by human organisms being exposed to reactive oxygen species (ROS) [1]. The production of free radicals or ROS in these conditions is a normal process. ROS has many physiological roles in cellular signalling and can destroy pathogens [2]. The enhancement of ROS production with the failure of anti-oxidant enzyme activity and endogenous and nutritional anti-oxidants leads to oxidative stress [3]. Some chronic diseases such as coronary heart diseases, cancer, diabetes mellitus, neurodegenerative diseases and cataract and the mechanisms of ageing may be because of oxidative stress [4]. Excessive ROS could attack the cellular proteins, lipids and nucleic acids leading to cellular dysfunction including loss of energy metabolism, altered cell signalling and cell cycle control, genetic mutations, altered cellular transport mechanisms and overall decreased biological activity, immune activation and inflammation. These changes lead to initiation of pathogenic milieu and development of several chronic diseases such as diabetes, cancer and cardiovascular disease [5]. New evidence indicates that diabetic and cardiovascular patient imbalance between prooxidant/anti-oxidant processes exists with an increase in ROS. The overproduction of ROS diminishes the expression of the anti-oxidant enzymes [6]. Therefore, improving the endogenous anti-oxidant system by anti-oxidative supplementation appears worthwhile.

According to meta-analysis and systematic reviews, using anti-oxidants can affect the health status of subjects with chronic disease; for example, using vitamin E can reduce myocardial infarction [6], HbA1c and fasting insulin compared with controls among diabetic patients with low baseline vitamin E status [7]; astaxanthin as an anti-oxidant also can reduce glucose and lipid profile [8]. According to another meta-analysis article result, prolonged anti-oxidant vitamin could be effective in improving endothelial function in non-obese T2DM subjects [9].

Meta-analysis and systematic reviews revealed that natural anti-oxidant can decrease oxidative stress parameters. One meta-analysis study indicated that natural juice with potential anti-oxidant activity could reduce malondialdehyde (MDA) significantly [10]; another meta-analysis on haemodialysis patients revealed that vitamin E could decrease serum thiobarbituric acid-reacting substances (TBARS) [11].

New evidence indicated that useful gut microbial (probiotics) can decrease nuclear factor kappa B (NF-κB) production, which can mediate the transcription of a large number of inflammatory genes such as TNF-α. NF-κB activation can create a cycle between inflammation and oxidative stress, because the enhancement of inflammatory mediators can increase oxidative stress production [12]. Therefore, the blocking of NF-κB by prebiotics results in the downregulation of TNF-α and oxidative stress production [13]. Prebiotics and synbiotics may stimulate the growth and activity of these probiotics. A dietary prebiotic consists of selectively fermented ingredients that results in the enhancement of the gastrointestinal microbial [14], and synbiotic is a product that contains both probiotics and prebiotics. Beside anti-oxidant activity, one systematic review article revealed that prosybiotics, presybiotics and synbiotics can decrease fat mass, insulin resistance and plasma lipid, carbohydrate metabolism and fasting blood glucose. Some probiotics and synbiotics improve the liver and metabolic parameters in patients with non-alcoholic fatty liver (NAFLD) [15].

Many studies have reported the effect of prebiotics, probiotics and synbiotics on oxidative stress [16–20]. Several intervention studies showed some protective effects [16, 19, 21], while others did not [20, 22, 23]. Nevertheless, according to our search of various databases, no systematic review or meta-analysis tried to evaluate the effect of prebiotics, probiotics and synbiotics on these outcomes. Therefore, we conducted a systematic review to explore a comprehensive summary about the effect of probiotics and synbiotics on oxidative stress.

Materials and Methods

A systematic search was conducted up to September 2016, using PubMed, ISI Web of Science, Scopus and Google scholar database using a combination of two categories of MeSH and non-MeSH terms including (1) 'Glutathione Reductase', 'Reductase, Glutathione', 'Glutathione Peroxidase', 'Peroxidase Glutathione', 'Superoxide Dismutase', 'Dismutase Superoxide', 'Oxidative Stress', 'Stress Oxidative', 'Stress, Oxidative', 'Total Antioxidant Capacity', 'catalase', 'Oxygen Radical Absorbance Capacity', 'Oxygen Radical Absorbance Capacity', 'ORAC', 'Total Radical Trapping Antioxidant Parameter', 'TEAC', 'Ferric reducing antioxidant power', 'FRAP', '2,2-Diphenyl-1-picrylhydrazyl' and 'DPPH' and (2) 'probiotics', 'prebiotics', 'synbiotics', 'Saccharomyces', 'Lactobacillus', 'Bifidobacterium', '*Escherichia coli*', 'fructo-oligosaccharide', 'fructooligosaccharide', 'galacto-oligosaccharide', 'galactooligosaccharide', 'inulin', 'lactulose', 'FOS', 'GOS', 'Oligofructose', 'Saccharomyces', 'Lactobacillus', 'Bifidobacterium', '*Escherichia coli*' and 'fructo-oligosaccharide'. The search strategy has been designed in accordance to database orientation such as Boolean operators (AND and OR), quotation mark, parenthesis and asterisk. We used quotation marks for looking up the exact terms or expressions, parenthesis for searching a group of search terms or combining two search group terms and asterisks for searching all words derived from one keyword. After searching all online databases, the results were exported to the reference manager software Endnote, version X6 (Thomson Reuters, NY, USA).

Title and/or abstract of all relevant published articles were separately screened by two authors (MH and ASA). Moreover, we checked the reference lists of all related articles in order to find further relevant studies. Discrepancies were resolved by discussion with RG.

Inclusion Criteria

We included studies in our review if they met the following criteria: (1) were published as original article, (2) were randomized controlled trial (RCT) in design, (3) were conducted on adult humans aged 18 years or more, (4) used probiotic and prebiotic or symbiotic for intervention, (5) assessed any marker of oxidative stress as the outcome variable and (6) no other diet or supplement used in intervention or control group. We contacted authors by email to ask for additional explanation if there was any potentially eligible article with unclear data.

Exclusion Criteria

Full texts of included articles were separately read by two authors (MH and ASA). Among resting trials, we have excluded those studies that have at least one of the following criteria: (1) the data had not been clearly mentioned, (2) studies without clear inclusion and exclusion criteria and (3) subjects received other food or food supplement with prebiotic, probiotics and synbiotics.

Data Extraction

Two reviewers extracted the following data from an eligible article: the last name of the first author; publication year; study location; sample size in each group; patients' characteristics such as gender, age and disease; composition of synbiotics, prebiotics and probiotics; and the dose used for intervention and placebo group and treatment duration. The authors were consulted again if there was any disagreement between the extracted data. We contacted the corresponding author for requesting information that was absent [24]. In one study by Songisepp et al., two different populations participated as intervention group, one group used 150 ml fermented goat milk and the other three probiotic capsules; therefore, we included their results as two separate studies in our systematic review [24].

Quality Assessment

A five-point Jadad score was used to assess the quality of the selected studies. The possible minimum score for inclusion of every article in our review was one point (one point for randomization) and the maximum score was five points (one point for double-blinding explanation, one point for allocation concealment explanation, one point for point for withdrawal explanation, one point for follow-up completeness) [25].

Results

We identified 8026 articles through database search. After removing duplicate articles, 5674 articles remained. By reading titles and abstracts, 5648 papers were removed and 32 full-text articles were further assessed for eligibility [6, 16–24, 26–47]. After considering the exclusion criteria, 21 RCTs were included in the current systematic review [6, 16–20, 22–24, 26, 28–30, 35, 36, 40–43, 45, 46]. The study selection process is illustrated in Fig. 1.

Main characteristics and outcomes of the 21 included trials are shown in Table 1. Included RCTs were published between 2003 and 2016, of which 18 articles were published after 2010 [6, 16–20, 22, 23, 26, 29, 35, 36, 40–43, 45, 46]. Totally, 15 articles were done in Asia [6, 16–20, 23, 26, 29, 35, 36, 40–42, 46] and four articles in Europe [22, 24, 28, 30], one study in Australia [43] and one article in Brazil [45]. Sample size of included articles ranged from 21 to 124 participants, and intervention period ranged from 1 to 9 weeks. The prebiotics administered were mostly inulin and lactitol with doses ranging from 10 to 45 g per day. The synbiotics administered consisted of a combination of inulin or fructo-oligosaccharide and *Lactobacillus sporogenes* species. The maximum dose for inulin in synbiotic trials was 8.4 g per day, and for bacteria, it was 47 billion colony-forming units (CFU) per day. Probiotics

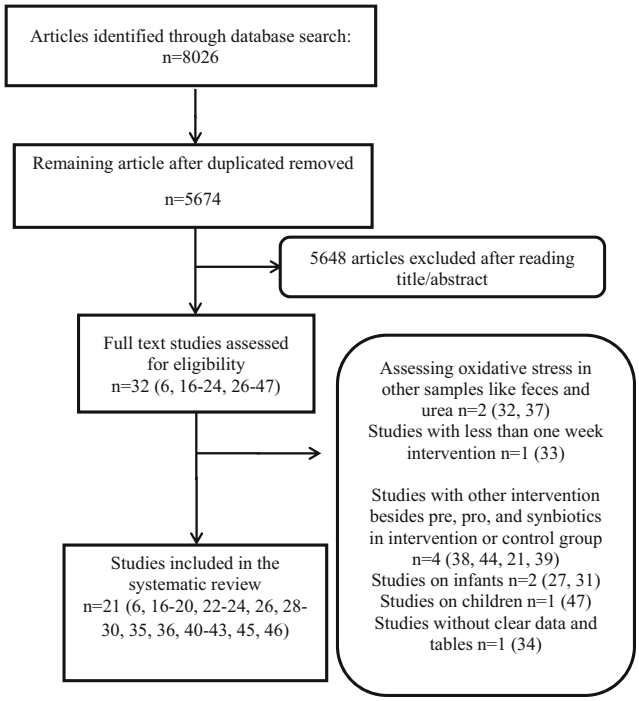

Fig. 1 Study selection process

administered were mostly different species of *Lactobacillus*, and minimum doses were 6×10^6 CFU/day.

Prebiotics Two trials used prebiotic as intervention [35]. Baseline and final values of superoxide dismutase and malondialdehyde (MDA) in one trial [18] and in other trial the effect on superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), MDA and total anti-oxidant capacity (TAC) were assessed [35]. In a trial on patients with chronic viral hepatitis, patients took lactitol 15 to 45 g/day for defecation one to three times a day. After 3 weeks, lactitol significantly reduced serum MDA and increased SOD [18]. In another trial conducted by Pourghassem Gargari B et al. [35], 10 g high-performance inulin was used as prebiotics for 8 weeks in women with type 2 diabetes. In this study, inulin reduced glycaemic parameters and serum MDA and SOD levels; however, the effects on GPx and CAT were not significant.

Synbiotics Four trials assessed the effect of synbiotic intake [17, 36, 40, 43] (n = 189) on serum F2-isoprostanes, GPx, MDA, CAT, glutathione (GSH) and TAC levels. One double-blind randomized cross-over trial by Asemi Z et al. on 62 diabetic patients showed a significant reduction on serum insulin and uric acid; a significant rise in serum GSH but no significant effect was shown on TAC levels [17]. In this study, patients with type 2 diabetes took 2×10^7 CFU/day *L. sporogenes* as probiotic and 1.08 g/day inulin as prebiotics for 6 weeks. In another trial, pregnant women received 18×10^7 CFU/day *L. sporogenes* and 0.72 g/day inulin for 9 weeks. Their results indicated a significant increase in GSH

Table 1 Randomized controlled trial studies eligible to include in the systematic review

First author (year), country	Subjects and gender	Age	Study design	Duration (weeks)	Intervention	Control	Subjects	Jadad score	Results
Chen C (2013), China [18]	M/F = 60	35	RCT	3	Prebiotic: lactitol ranged from 15 to 45 g/day	Standard medical treatment	Patients with chronic viral hepatitis	2	SOD increased significantly, MDA decreased significantly
Pourghassem Gargari B (2013), Iran [35]	F 49	20–65[a]	Triple-blind RCT	8	Prebiotics: 10 g high-performance inulin	10 g maltodextrin	Patient with type 2 Diabetes	3	SOD and TAC increased significantly and MDA significantly decreased.
Taghizadeh M (2013), Iran [36]	F 52	18–35	Double-blinded RCT	9	Synbiotics: 18×10^7 CFU *L. sporogenes* and 0.72 g inulin each day.	Substance without probiotic bacteria and prebiotic	Pregnant women	2	GSH significantly increased
Rossi M (2016), Australia [43]	M 21, F 35	69 ± 10[b]	Double-blinded cross over RCT	6	Synbiotics: fructo-oligosaccharides and galacto-oligosaccharides powder and the probiotic capsule including 45 billion CFU of nine different strains across the *Lactobacillus*, *Bifidobacteria* and *Streptococcus* genera	Maltodextrin powder and capsule	Patients with chronic Kidney disease	3	F2-isoprostanes and GPx did not change significantly
Asemi Z (2013), Iran [17]	M 38, F 86	53.1 ± 8.7	Double-blinded cross over RCT	6	Synbiotics: 2×10^7 CFU *L. Sporogenes* and 1.08 g inulin each day	Same substance without probiotic bacteria and prebiotic inulin	Type 2 diabetic patients	2	GSH increased significantly
Bahmani F (2015), Iran [40]		35–70	Double-blinded RCT	8	Group A: 120 g/day synbiotic bread containing *Lactobacillus* sporogenes (1×10^8 CFU) and 0.07 g inulin per 1 g; group B: probiotic bread containing *Lactobacillus* sporogenes (1×10^8 CFU) 120 g/day	Control bread	Patients with type 2 diabetes	3	Synbiotic bread decreased MDA significantly, but TAC, CAT and GSH did not change
Kullisaar T (2005), Estonia [30]	F = 16, M = 5	35–65	RCT	3	Probiotics: fermented goats' milk (150 g/day) with *Lactobacilli* = 3×10^{11} CFU	Goats' milk group (150 g/day)	Healthy subjects	2	TAA increased significantly
Asemi Z (2012), Iran [16]	F 70	18–30	Double-blinded RCT	9	Probiotics: 200 g yogurt with a total 1×10^7 CFU of two strains lactobacilli	200 g conventional yogurt	Pregnant women	2	GR increased significantly
Ebrahimi-Mameghani M (2013), Iran [20]	M 27, F 13	33.6 ± 5.5	Double-blinded RCT	1	Probiotics: 2 sachets probiotics. Each sachet of probiotics contained 900 billion viable lyophilized bacteria consisting of 4 strains of *Lactobacillus* and 3 strains of *Bifidobacterium*	Not mention	patients admitted to the intensive care unit	1	Oxidative stress parameters did not change significantly
Ejtahed HS (2012), Iran [19]	M 23, F 37		Double-blinded RCT	6	Probiotics: 300 g/day probiotic yogurt enriched with *B. lactis* Bb12 7×10^6 and		Patients with T2 diabetes	2	

Table 1 (continued)

First author (year), country	Subjects and gender	Age	Study design	Duration (weeks)	Intervention	Control	Subjects	Jadad score	Results
		51.0 ± 7.-32			*L. acidophilus La5* 6×10^6	300 g/day conventional yogurts			SOD, GPX and TAS increased significantly, and MDA decreased significantly
Valentini L (2014), Germany [22]	F 33, M 29	70.1 ± 3.9	Open-label RCT	8	Probiotics: two capsules VSL#3 per day containing 112 lyophilized bacteria and web-based dietary advice	Web-based dietary advice	Healthy aged individuals	3	Oxidative stress parameters did not change significantly
Mazloom Z (2013), Iran [23]	F 26, M 8	51.8 ± 10-.2	Single-blinded RCT	6	Probiotics: 1500-mg probiotic capsules twice daily	1000 mg magnesium stearate twice daily	Patients with T2 diabetes	2	Oxidative stress parameters did not change significantly
Asemi Z (2013), Iran [26]	F 38, M 16	53.0 ± 8.7	Double-blinded RCT	8	*Probiotic*: *L. acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. rhamnosus* (1.5×10 9 CFU), *L. bulgaricus* (2×10^8 CFU), *Bifidobacterium breve* (2×10^{10} CFU), *B. longum* (7×10^9 CFU), *Streptococcus thermophilus* (1.5×10^9 CFU) and 100 mg fructo-oligosaccharide with lactose as carrier substances	The same substance without bacteria	Patients with T2 diabetes	1	GSH increase significantly
Kang Y. M (2011), Korea [29]	M 48	52.4 ± 7.8	Double-blinded RCT	4	Probiotics: fermented sea tangle by *Lactobacillus brevis* BJ20	Mixing of 311 mg lactose, 32 mg cellulose and 7 mg magnesium stearate	Healthy volunteer	2	MDA decreased significantly, and catalase and SOD increased significantly
Songisepp E (2005), Stonia [24]	F 17 M 5	35–60	Open RCT	3	Probiotics: 150 ml fermented goat milk with 11.2 to 11.8 log CFU per person	Same dose of fresh goat milk	Healthy volunteers	3	TAA and TAS increase significantly
Songisepp E (2005), Stonia [24]	F 9, M 15	40–60	Double-blinded RCT	3	Probiotics: *L. fermentum* ME 9.2 log CFU/day	Identical capsules without the probiotic strain	Healthy volunteers	3	TAA and TAS increase significantly
Fabian E (2008), Austria [28]	F 33	22–29	RCT	4	Probiotics: probiotic yogurt containing *Lactobacillus* (3.6×10^8 CFU/g).	Conventional yogurt	Healthy women	2	Flavin adenine dinucleotide (FAD) decreased significantly flavin mononucleotide (FMN), and free riboflavin increased significantly.
Akkasheh G. (2016), Iran [6]	F 34, M 6	20–55	RCT	8	Probiotics: *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus casei*	Same capsule containing starch	Major depressive disorder	3	Glutathione decreased significantly, and total anti-oxidant capacity did not change.

Table 1 (continued)

First author (year), country	Subjects and gender	Age	Study design	Duration (weeks)	Intervention	Control	Subjects	Jadad score	Results
					(2×10^9 CFU/g) and *Bifidobacterium bifidum* (2×10^9 CFU/g)				
Mohammadi A.A. (2015), Iran [42]	F/M 35	20–60	Double-blinded RCT	6	Probiotics: first group: capsules containing *Actobacillus casei* 3×10^3, *L. acidophilus* 3×10^7, *Lactobacillus rhamnosus* 7×10^9, *Lactobacillus bulgaricus* 5×10^8, *Bifidobacterium breve* 2×10^{10}, *Bifidobacterium longum* 1×10^9 and *Streptococcus thermophilus* 3×10^8 CFU/g. Second group: 100 g/day probiotic yoghurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* with a total of min 1×10^7 CFU.	100 g/day conventional yogurt	Petrochemical workers	2	Probiotic capsule decreased plasma PC, and isoprostaglandin probiotic yogurt decreased. Plasma protein carbonyl 8-oxoguanine levels did not change in any groups
Tonucci L. B (2015), Brazil [45]	M 16, F 19	35–60	Double-blinded RCT	6	Probiotics: 120 g/day fermented milk containing *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 (10^9 CFU/day, each)	120 g/day of conventional fermented goat	Type 2 diabetes	4	F2-isoprostane and TAS plasma levels did not change significantly
Vaghef-mehrabani M (2016), Iran [46]	F 46	Not mention	Double-blinded RCT	8	Probiotic: 10^8 CFUs of *Lactobacillus casei* 01	Identical capsules containing maltodextrin	Rheumatoid arthritis patients	3	SOD activity decreased in probiotic group, but MDA, TAC, CAT and GPx activity did not change.
Hariri M (2015), Iran [41]	F 21, M19	35–68	Double-blinded RCT	8	Probiotics: 200 ml/day of probiotic soy milk containing 10^7 *Lactobacillus plantarum* A7	conventional soy milk	Type II diabetic patients	3	8-OHdG decreased significantly, and SOD increased significantly.

F female, *M* male

[a] Range

[b] Mean ± SD

levels, while the effect on TAC levels and health status parameters such as lipid profile were not significant [36]. In other double-blind randomized cross-over trial on patients with chronic kidney disease, fructo-oligosaccharide and galacto-oligosaccharides were used as prebiotic and 45 billion CFU/day of nine different strains across the *Lactobacillus*, *Bifidobacteria* and *Streptococcus* genera as probiotics. Their result showed that synbiotic intervention for 6 weeks cannot change F2-isoprostanes, GPx and other health parameters significantly [43]. Bhamani et al. have done one clinical trial on patients with type 2 diabetes. In this study, patients were divided into three groups: group A received synbiotic bread containing 1×10^8 CFU *L. sporogenes* and 0.07 g inulin per g, group B took probiotic capsules containing *L. sporogenes* (1×10^8 CFU), and group C took conventional bread for 8 weeks. Anti-oxidant parameters and liver enzymes were measured before and after intervention. Their results indicated that synbiotic bread decreased MDA significantly, but TAC, CAT, GSH and liver enzyme did not change [40].

Probiotics Totally, 15 trials examined the effect of probiotic supplementation on the serum markers of oxidative stress [6, 16, 19, 20, 22–24, 26, 28–30, 41, 42, 45, 46].

In one trial in 2012, pregnant women took yogurt fermented with a total 1×10^7 CFU of two strains of lactobacilli for 9 weeks and its effect was reported on oxidative stress parameters only. Probiotic yogurt in this study could increase GR activity significantly but did not have any effect on other oxidative stress indices [16]. Ebrahimi-Mameghan M in 2013 did a pilot study on 40 patients admitted to intensive care. In this study, the patients received two probiotic sachets containing 900 billion lyophilized bacteria. Using probiotics caused improvement of clinical outcome, but they did not find any significant results on oxidative stress parameters after 1 week [20]. There are five articles on healthy subjects [22, 24, 28–30]. In one study by Kullisaar T, 21 healthy participants received 150 g/day fermented goat milk with 3×10^{11} CFU lactobacilli for 3 weeks. Their results showed that fermented goat milk could improve anti-atherogenicity parameters and increase total anti-oxidant activity (TAA) significantly [30]. In another study, fermented sea tangle on healthy volunteers after 4 weeks decreased MDA significantly and increased CAT and SOD significantly [29]. Songisepp Epp has done two trials on healthy subjects. In one trial, he used 150 ml fermented goat milk with 11.2 to 11.8 log CFU *Lactobacillus fermentum* ME for 3 weeks, while in the other trial, he used *L. fermentum* ME 9.2 log CFU/day as a supplement for 3 weeks. His results showed that in both trials, TAA and TAS increased significantly, serum urine decreased significantly, but GSH did not change [24]. Fabian E et al. had also conducted another trial on healthy women. They fortified yogurt with 3.6×10^8 CFU/g *Lactobacillus*. Healthy women took 100 g/day probiotic yogurt for 2 weeks and 200 g/day for another 2 weeks. Their results indicated that probiotic yogurt decreased flavin adenine dinucleotide (FAD) significantly and increased flavin mononucleotide (FMN) and free riboflavin [28]. Healthy participants in another study received two capsules VSL#3 containing 112 billion lyophilized bacteria per day for 8 weeks. Probiotics could reduce homocysteine, but its effects on oxidative stress were not significant [22]. Four clinical trials were done on patients with type II diabetes [19, 26, 41, 45]. In one study in 2015, diabetic patients took 120 g/day fermented milk by *Lactobacillus acidophilus* La-5 and *Bifidobacterium* (10^9 CFU/day, each) for 6 weeks. Their results after 6 weeks revealed that probiotic milk could not decrease oxidative stress among diabetic patients [45]. Diabetic patients in other double-blinded randomized clinical trials received 300 g/day probiotic yogurt fermented with 7×10^6 CFU *Bifidobacterium lactis* Bb12 and 6×10^6 CFU *L. acidophilus* La5 for 6 weeks. After 6 weeks, it was seen that probiotics improved glycaemic control and lipid profiles. Oxidative stress parameters such as SOD, GPx and TAS increased and MDA decreased significantly [19]. In another double-blinded clinical trial by Hariri M et al., diabetic patients took 200 ml/day probiotic soy milk containing 10^7 CFU *Lactobacillus plantarum* A7. After 8 weeks, SOD activity increased significantly, and 8-oxo 2-deoxyguanosine decreased significantly [41]. In 2013, multispecies probiotics after 8 weeks could decrease fasting blood glucose and increase GSH significantly among patients with type II diabetes [26]. Mohammadi AA et al. had done one clinical trial on petrochemical workers. In this study, intervention groups took multispecies probiotic or 100 g/day probiotic yogurt containing *L. acidophilus* and *B. lactis* with a total of min 1×10^7 CFU. Plasma protein carbonyl 8-oxoguanine and isoprostaglandin levels were measured after 6 weeks as oxidative stress parameters. Probiotic yogurt could decrease plasma protein carbonyl 8-oxoguanine, but isoprostaglandin levels did not change in both probiotic supplement group and probiotic yogurt group [42]. In 2016, females with rheumatoid arthritis took 10^8 CFUs of *Lactobacillus casei* 01 for 8 weeks. Probiotic supplement in this study could decrease SOD activity, but MDA, TAC, CAT and GPx activity did not change [46]. Another trial on patients with major depressive disorder probiotic supplements involving *L. acidophilus* (2×10^9 CFU/g), *L. casei* (2×10^9 CFU/g) and *Bifidobacterium bifidum* (2×10^9 CFU/g) could decrease GSH significantly after 8 weeks, but TAC did not change. In this study, probiotics also improved the Beck Depression Inventory, insulin and homeostasis model assessment of insulin resistance [6].

Discussion

Our objective in this article was to determine the effects of probiotics, prebiotics or synbiotics (in supplement form or

fortified food) on oxidative stress. Studies that used other food supplements with probiotics, prebiotics or synbiotics were excluded. All included studies evaluated either synbiotics, probiotics or prebiotics' effect in subjects aged 18 years or more. To our knowledge, this is the first systematic review performed to assess the effect of presybiotics, prosybiotics and synbiotics on oxidative parameters.

Studies included in this review were heterogeneous in duration, sample size, intervention, population and inclusion or exclusion criteria, which potentially were the reasons behind conflicting results between articles. It is believed that the beneficial effects of probiotics (hypoglycaemic, anti-inflammatory or anti-oxidative properties) could be highly strain specific. Marteau [6] claimed that the beneficial outcome of probiotic administration could most likely be achieved with the combined use of multiple probiotic strains. Different strains or species seemed to exhibit different mechanisms of action, and how these differences influence the study outcome is yet to be determined in clinical trials. Another important consideration for interpreting the inconsistencies of the study findings is the variety of the study populations. We had five articles on healthy subjects [22, 24, 28–30], two articles on pregnant women [16, 36] and 14 articles on unhealthy subjects [6, 17–20, 23, 26, 35, 40–43, 45, 46]. The heterogeneity of subjects could lead to variation in results, overestimation and bias [48]. Nevertheless, the quality of reporting for the majority of the RCTs was low, lacking adequate information to facilitate understanding of the trial's design, conduct, analysis and interpretation. Most RCTs randomized a small number of participants [23, 24, 28, 30] and did not mention the concealment of their treatment allocation and the steps taken to conceal the sequence of intervention that was assigned. In RCTs, it is vital to make sure that treatment allocation is conducted to eliminate all potential selection bias [49].

Two studies analysed the effects of prebiotic supplementation on oxidative stress index [18, 35]. Both articles reached the same result on MDA and SOD. In one article, on patients with chronic viral [18] hepatitis, 15 to 45 g/day lactitol after 3 weeks significantly reduced serum MDA and increased SOD, while in another trial, among patients with type 2 diabetes [40], 10 g inulin after 8 weeks got the same result for MDA and SOD, but GPx and CAT did not change significantly.

Ferolla SM et al. in their narrative review noted that the numbers of alcohol-producing microbiota in metabolic diseases increased. This elevated serum blood ethanol concentration and led to increased oxidative stress due to alcohol metabolism [50]. In addition to ethanol production, the intestinal bacterial microbiota also produces lipopolysaccharides (LPS) that promote the release of the proinflammatory cytokine from the hepatic and cause mitochondrial oxidative stress [51]. New evidence indicated that the consumption of prebiotics stimulates the growth of probiotics such as *Bifidobacteria* and *Lactobacilli*. *Bifidobacteria* has SOD, and evidence of in vitro studies has proposed that the fermentation of prebiotics by *Bifidobacteria* leads to the elimination of free radicals. Furthermore, lactobacilli resident in gut release *Bifidobacteria* intracellular anti-oxidant by leasing them; therefore, they help to decrease the MDA [52, 53]. Prebiotic fermentation can produce short-chain fatty acids (SCFAs). SCFAs are ligands for the G protein-coupled receptors (GPRs). GPRs can decrease ROS production; furthermore, these receptors are involved in elimination of inappropriate ROS production [54]. Interpreting the effects of prebiotics on oxidative stress is difficult due to the limited number of studies. According to our systematic review, prebiotics can decrease MDA and increase SOD, but the evidence is not enough. Well-designed RCTs with long-term follow-up, using same prebiotic, and duration are needed to establish the effects of prebiotics on oxidative stress.

Four articles reported the effect of synbiotics on oxidative stress parameters, and all but one saw a trend for a decrease in oxidative stress [43]. Rossi M et al. did not find any benefits of synbiotics on oxidative stress, but other studies believe that synbiotics can decrease oxidative stress [17, 36, 40]. Rossi's article was different compared to other articles in prebiotic and probiotic combination. Rossi M has used fructo-oligosaccharides and galacto-oligosaccharides as prebiotics and different strains of *Lactobacillus*, *Bifidobacteria* and *Streptococcus* as probiotics. In another three articles, inulin and *L. sporogenes* were used as prebiotic and probiotic, respectively. According to our systematic review, using inulin with probiotic might be better than fructo-oligosaccharides and galacto-oligosaccharides for oxidative stress reduction, but we need more evidence for this conclusion, because probiotic strains and participants are different between studies. The synbiotics trials included in the systematic review were done among diabetic patients [17, 40] and pregnant women [36]. In these conditions, the concentrations of plasma LPS and proinflammatory cytokines are increased [55, 56]. An increase of these mediators leads to oxidative stress enhancement [51]. Synbiotics by changing microflora composition and reducing LPS concentration could improve gut microflora composition and reduce oxidative stress [57].

GSH can regulate the intracellular redox homeostasis. GSH increased significantly in two studies [17, 36]. SCFAs produced by synbiotics, in particular butyrate, are responsible for the synthesis of NADPH for GSH production [58]. Another factor might be the enhancement of glutamate cysteine ligase (GCL) by synbiotics [59]. Furthermore, synbiotics' effect on proinflammatory cytokine reduction as well as on downregulation of genes involved in oxidative stress may cause GSH enhancement [51] and explain their useful effect on GSH levels. The lack of effect on TAC, CAT and GSH in a study by Bahmani F may be because of strain and dosage of

probiotics and inulin. According to the review of all databases, there have been no review articles regarding the effect of synbiotics on the oxidative statues. Therefore, we did not have other results for reporting and comparing.

Effect of probiotics on oxidative stress was conflicting. Five studies looking at the effect of probiotics have been conducted on the healthy population, and their results revealed the anti-oxidative effect of probiotics [22, 24, 28–30]. Levels of oxidative parameters are low, and microflora is normal among healthy participants [60]. Therefore, probiotic supplements can fortify their intestine microflora and decrease oxidative stress very easily. In one clinical trial by Valentini et al. [22], probiotics did not have any effect on oxidative stress among healthy subjects. Participants in this study were old. Intestine probiotic is lower, and oxidative stress is higher in old age. Therefore, it might be the reason of non-significant results in their study. Other clinical trials have been conducted among unhealthy participants [6, 19, 20, 23, 26, 41, 42, 45, 46] and pregnant women [16], where oxidative stress is high and intestine microflora is different, respectively. Probiotics in these clinical trials might improve oxidant pathways and decrease free radical production, but its effect on biochemical parameters related to oxidative stress might be non-significant. The effect of probiotics on oxidative stress is also strain specific [61, 62]. The lack of a significant effect on oxidative mediators in included trials may also be explained by the different species and dosage of probiotics used. Studies that use dairy probiotics are more effective in reducing oxidative stress. This may be because of natural anti-oxidant peptides in fermented dairies [63, 64]. Mirmiran P et al. in their narrative review proposed that probiotics in patients with metabolic diseases resulted in favourable metabolic consequences especially reducing oxidative stress in diabetic patients [65]. The result of our systematic review confirms their conclusion.

All 15 probiotic articles used various strains of *Bifidobacteria* and *Lactobacillus* with different treatment durations and doses. Long-term follow-up and well-designed clinical trials using similar probiotic strains, dose and treatment duration are needed to confirm the effects of probiotics on oxidative stress.

For both presybiotics and synbiotics, we could not find a threshold dose required to get effective results because of fewer articles. The most interesting findings of our article are that probiotic in the form of supplementation did not have any effect on oxidative stress, but when scientists used them with other fermentable foods like yogurt or milk, they yielded significant result. Finding the concept of a threshold dose for probiotics is complicated by the different durations of supplementation and using different probiotic species, but it seems that probiotics at a dose of 10^6/day achieve a benefit, and beyond this dose, there is no additive benefit.

According to our result, in these clinical trials, prosybiotics, presybiotics and synbiotics beside anti-oxidative effects can improve health parameters among healthy and unhealthy subjects, especially glycaemic parameters and insulin concentration.

These clinical trials have several common limitations, including short study duration [18, 20, 30], having low baseline of toxins [22, 28–30] and small sample size [24, 30], and authors have not shown the probiotic effect in terms of changes in the gut microbiota composition, that is, the main target for all metabolic benefits through this type of supplementation. In addition, most published papers were from Asia and limited data are available from other countries, particularly from the USA.

The strengths of this review are that in most trials, the subjects were not taking any intervention except presybiotics, prosybiotics and synbiotics, making the results of systematic review more consistent. Despite this, we could not establish a dosage range and duration of intervention to get effective results. The benefit of these interventions, indicated by this systematic review, makes the microflora one of the therapeutic targets in the management of various diseases and health promotion.

Conclusion

We need more new well-designed trials with these types of interventions to show beneficial dose, duration and the composition of supplements to achieve beneficial effects.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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