Probiotics and Antimicrobial Proteins (2020) 12:102–111
https://doi.org/10.1007/s12602-018-9500-1

The Effects of Supplementation with Probiotic on Biomarkers of Oxidative Stress in Adult Subjects: a Systematic Review and Meta-analysis of Randomized Trials

Behzad Zamani[1] · Ali Sheikhi[1] · Nazli Namazi[2] · Bagher Larijani[3] · Leila Azadbakht[1,2,4]

Published online: 21 January 2019

Abstract
Previous studies have supposed that probiotic supplementation led to a positive effect on different health outcomes. Furthermore, several studies indicated that probiotics supplementation improved antioxidant status, while some studies did not indicate these effects. Hence, current systematic review and meta-analysis study was conducted to determine the effect of probiotic supplementation on some oxidative stress biomarkers among adult subjects. We searched four electronic databases PubMed, SCOPUS, ISI Web of Science, and the Cochrane Library till November 2017. Clinical trials that compared the effects of probiotic supplementation with the control group were included. A random-effect model was used to pool weighted mean difference (WMD). Finding of 11 included studies ($n = 577$) indicated that probiotic supplementation increased total antioxidant capacity (TAC) (WMD 77.30 mmol/L; 95% confidence interval [CI] 2.60, 152.01; $I^2 = 88.3\%$) and reduced malondialdehyde (MDA) (WMD − 0.31 μmol/L; 95% CI − 0.54, − 0.08; $I^2 = 71.5\%$) significantly compared to the control group. However, its effects on glutathione (GSH) was not significant (WMD = 19.32 μmol/L; 95% CI − 18.70, 57.33; $I^2 = 64.9\%$). The current meta-analysis revealed that probiotic supplementation may result in increasing TAC and lowering MDA, which improve antioxidant status. However, due to high heterogeneity, findings should be interpreted with caution. Further investigations are required to elucidate the effect of supplementation with probiotics on biomarkers of antioxidants.

Keywords Supplementation · Probiotic · Total antioxidant capacity · Malondialdehyde · Glutathione

Introduction

Reactive oxygen species (ROS) is a natural compound built through the normal metabolism of oxygen. Although it acts as a key factor in homeostasis and cell signaling and it is claimed that have a role in killing micro-organism and cancer cells, it may rise up and lead to oxidative stress due to the imbalance between its production and antioxidant capacity [1]. Oxidation is a process in which an electron is given to an oxidizing agent. The result of this reaction is the production of free radicals having unpaired electrons that lead to a chain reaction in which more free radicals including superoxide anion and hydroxyl radical are being released. Oxidative stress is known to have an effect on the progression of chronic diseases like cancer, cardiovascular diseases, and diabetes [2, 3]. Antioxidants are known to play a preventive role against the occurrence of oxidative stress by inhibiting the process of oxidation. Since antioxidants degenerate during this action, there is a perennial need to reload their stores [4]. Oxidative stress could be measured by several oxidative stress markers such as xanthine oxidase (XO), superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA), and total antioxidant capacity (TAC). Recently, the role of probiotics in prevention of oxidative stress has been discussed.

✉ Leila Azadbakht
azadbakhtleila@gmail.com

[1] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P.O. Box: 1416643931, Tehran, Iran

[2] Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[3] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

Probiotics, which are defined as the live microorganism, have been considered to have significant health benefits if consumed in the adequate amount [5]. Probiotics can be of clinical use in chronic diseases such as gastrointestinal disorders, autoimmune illness, obesity, insulin resistance, type 2 diabetes, and non-alcoholic fatty liver disease [6–8]. These effects are conducted due to the elimination of pathogenic microorganism because of a competitive environment formed by probiotics [9]. Furthermore, probiotics have a potential role to improve immune system function [10]. *Lactobacillus* and *Bifidobacterium* are the most commonly used probiotics [11]. It has been reported that probiotics act as a protective agent against oxidative stress by reducing the pH of gut, producing some digestive enzymes and vitamins, producing antibacterial substances such as hydrogen peroxide, diacetyl, acetaldehyde, and lactoperoxidase, suppression of bacterial infections, removal of carcinogens which leads to reduction of cytokine level, high-sensitivity CRP, and superoxide and hydroxyl radicals, and the increase of glutathione peroxidase [12–16].

Some studies indicated positive effects of probiotics on antioxidant status, while others did not show such beneficial effects. Since there is a controversy over this claim, we conducted a systematic review and meta-analysis on trials investigations to evaluate the effects of probiotic supplementation on antioxidant indices, including TAC, MDA, and GSH, to determine whether probiotics have a protective role against oxidative stress or not.

Methods

This meta-analysis and systematic review were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17].

Search Strategy

PubMed, SCOPUS, ISI Web of Science, and Cochrane databases were searched by two investigators independently (BZ, AS) using the following terms in titles and abstracts. The search strategy was as follows: [probiotics OR microflora OR microbiome OR *Lactobacillus* OR *Bifidobacterium*] AND [Oxidative OR malondialdehyde OR MDA OR Superoxide dismutase OR SOD OR glutathione peroxidase OR GPX OR antioxida* OR anti-oxida* OR TAC]. In order to increase the sensitivity of the search, the wild-card term '_' was used. The literature was searched from inception to November 2017 and it was restricted to the English language.

Study Eligibility

To identify qualified studies the following criteria were used: (1) randomized controlled clinical trial (either parallel or cross-over design), (2) adult individuals (over 18 years old), (3) reported antioxidant indices (TAC, MDA, and GSH) in both placebo and treatment groups before and after the intervention, (4) studies in which the patients were treated with probiotics supplementation in comparison to a control group whose participants received placebo or no supplementation at all. Exclusion criteria were as follows: (1) other study design except for clinical trial, (2) animal or in vitro study, (3) conducted on children or adolescent, (4) did not have control group, (5) studied enriched food with probiotic, (6) examined the effect of probiotic supplementation along with other intervention, (7) participants suffering from malignancy diseases such as cancer, and (8) duration of intervention was lower than 2 weeks.

Data Extraction

Based on pre-defined data extraction sheet, the following data were extracted from eligible studies: (1) first author's name, (2) year of publication, (3) country in which the study was conducted, (4) study design, (5) number of participants in the probiotic and placebo group, (6) dosage, (7) treatment duration, (8) age, (9) gender, (10) body mass index (BMI) of participants, and (11) mean and standard deviation of antioxidant indices at baseline and at the end of study. When our interest data were not reported in the papers, we contacted the authors via email to obtain missing data. Data extraction was performed by two reviewers independently (BZ, AS). Any disagreement in all processes of the systematic review was solved by discussion (LA). When measurements were repeated more than two times, only data at the baseline and at the end of the study were extracted. Moreover, if more than one paper on the same population was published, we only included paper with larger sample size and longer duration of the intervention.

Assessments of Risk Bias and Publication Bias

To examine the methodological quality of the included studies, the Jadad score [18] was used independently by two researchers (BZ, AS). This checklist includes five questions and the score of 0 or 1 are given to each one of the following questions: (i) randomization, (ii) appropriate method for randomization, (iii) double-blinding, (iv) appropriate method for double-blinding, and (v) description dropouts and withdrawals. According to this scale, the overall score of a study ranges between 0 and 5, and the ones that obtain more than median (three) are considered as high quality. Risk bias for the included studies also were examined using criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The assessment included seven items: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome

report, and other sources of bias. We applied Egger regression test to examine publication bias statistically. The present study was supported by Tehran University of Medical Sciences (grant number : 97-03-161-40572).

Data Synthesis and Statistical Analysis

All data from included studies were extracted as mean difference (MD) and standard deviation (SD) in both treatment and control groups. Mean and SD imputed using the median and range in some studies [17]. In addition, if standard error of the mean (SEM) has been presented instead of the standard deviation, we calculated SD using following formula: $SD = SEM \times \sqrt{n}$ (n is the number of participants in each group). Furthermore, the random-effects model (Dersimonian-Liard) were used to examine the MD of the effect of probiotic supplementation on the oxidative stress biomarkers. To examine heterogeneity between studies, Cochran's Q test at the level of significance of $P < 0.1$ and in order to indicate the value of heterogeneity, I^2 index were used. To determine the source of heterogeneity, predefined subgroups were performed based on following criteria: (1) age ($< 50, \geq 50$), (2) duration (≤ 8, > 8 weeks), and (3) sex. Sensitivity analysis was performed to establish the effect of individual study on the pooled mean difference. Egger regression test was applied to investigate publication bias statistically. Stata software version 12 (Stata Corp., College Station, Texas, USA) was used to analyze and $P < 0.05$ was considered as significant.

Results

Study Selection

Figure 1 shows processes of study selection for the current meta-analysis. We found 5633 articles in preliminary search of electronic databases and one study from reference lists. After excluding duplicates (n = 945), 4689 publication remained for screening. Based on title and abstract, 4637 publications were excluded. In the full-text screening step, 55 articles were evaluated and 44 of them were excluded. Reasons for excluding studies were as follow: probiotic fortified foods ($n = 14$), mixed intervention ($n = 13$), did not have control group ($n = 3$), did not report biomarkers of oxidative stress ($n = 11$), critical condition ($n = 1$), and did not have nesessary data ($n = 2$). When necessary data had not reported, we asked the authors through emails in three reasonable interval periods. Finally, 11 eligible articles were included in the present study [20–30].

Systematic Review

Overall, 577 individuals participated in the included studies. Seven studies considered both genders [20–22, 24, 26, 29, 30], while the other included studies recruited only women [23, 25, 27, 28]. The mean age of participants varied from 27.1 to 62.6. In all studies, except one that supplementation was along with dietary intervention in both intervention and control groups [28], were not applied another intervention. Most of the included studies in this review used two types of *Bifidobacterium* and *Lactobacillus* probiotic supplements with single or multiple strains. Dosage of probiotic supplement ranged from 10^8 to 10^{10} CFU/day. The period of intervention ranged from 6 to 12 weeks. Most of the participants were overweight or obese (BMI ranged from 25.4 to 31.7 kg/m^2). Participants of the studies were as follow: type 2 diabetes [20, 21], rheumatoid arthritis [26], diabetic hemodialysis [24], pregnant women [23], gestational diabetes [23], depressive disorder [22], obesity women [28], multiple sclerosis [29], and diabetic foot ulcer [30]. Probiotic supplement administered in two forms: capsule [20–27, 29, 30] and sachet [28] (Table 1).

Among these studies, TAC and MDA were reported in nine and GSH in eight studies. Of the nine studies that measured TAC, eight studies used the ferric-reducing antioxidant power (FRAP) method and one used Randox kit. All of the studies used the thiobarbituric acid and Beutler methods to measured MDA and GSH, respectively. Furthermore, some studies reported additional indices such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx). Since the numbers of the studies which reported the mentioned indices were not enough to make the requirements, they were not involved in this meta-analysis.

Risk Bias and Publication Bias

All studies except one [21] had high quality (total score > 3). All 11 studies applied randomized placebo-control trial design and described the methods of randomization. Ten studies had 'double-blind design and one study [21] reported single-blind design. Enough information about blinding was given in nine studies. Only one study did not report dropouts and their reasons [21]. Judgments of authors on each risk of bias item for all of the included studies were presented in Table 2. Egger's test did not show any publication bias for TAC ($P = 0.36$), while the presence of publication bias was affirmed by Egger's test ($P = 0.01$) for MDA. To correct the effect size, we used the trim and fill method. However, no study was added. We also identified slight publication bias statistically by Egger's test ($P = 0.02$) for GSH. Three studies were imputed after using trim and fill analysis. However, results remained insignificant (− 5.93; 95% CI − 45.66, 33.79; $p = 0.77$).

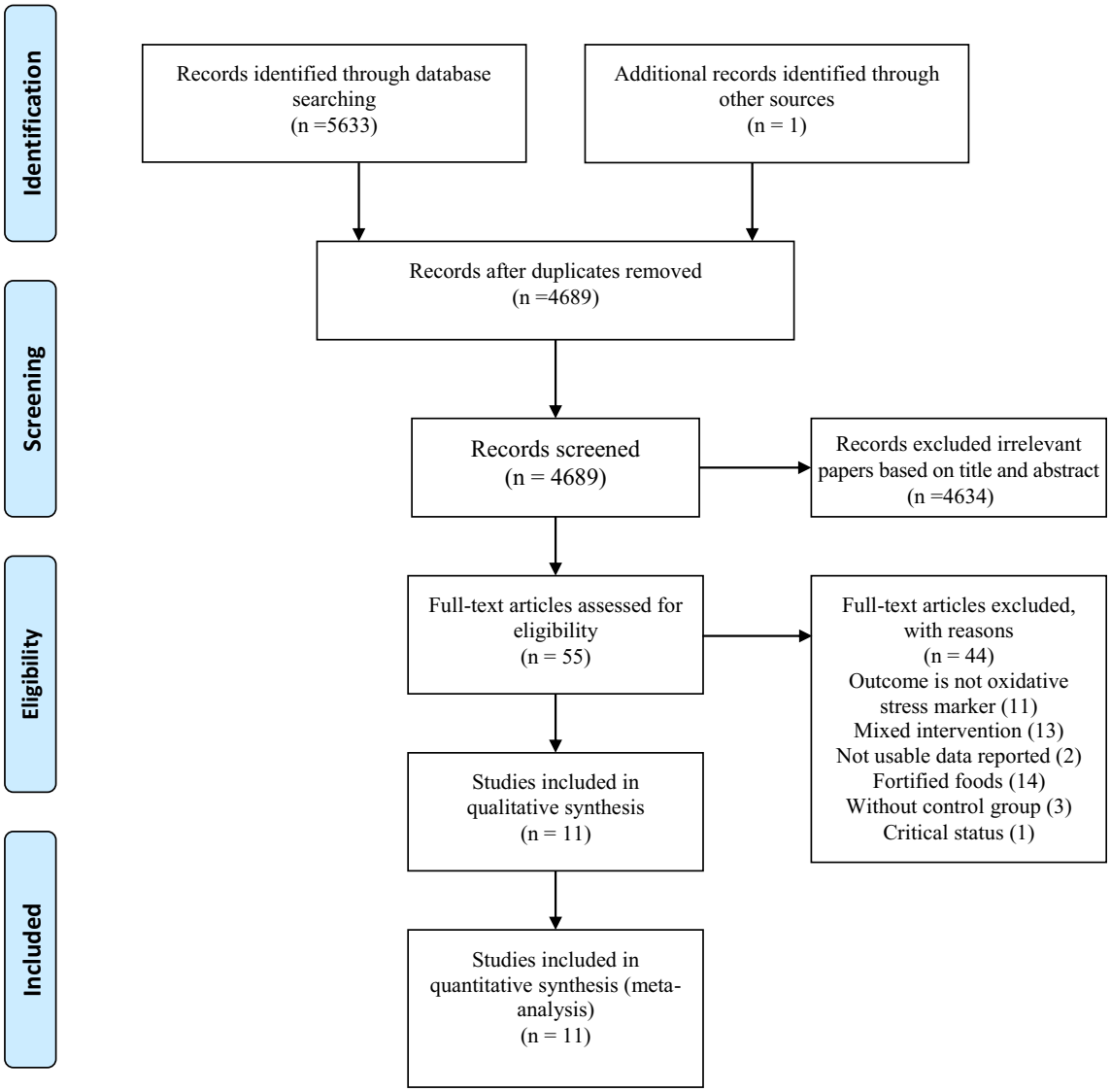

Fig. 1 PRISMA flow diagram of study selection

Meta-Analysis

Total Antioxidant Capacity

Among nine studies that evaluated the effect of probiotics supplements on the TAC, eight entered in the meta-analysis. Overall increased of TAC was 77.30 mmol/L (95% confidence interval [CI] = 2.60 to 152.01; $p = 0.04$) more in probiotic supplement than that in control group (Fig. 2). There was high significant heterogeneity between included studies ($I^2 = 88.3\%$; $p < 0.001$). Furthermore, we conducted subgroup analysis to examine the effect of age (< 50, ≥ 50 years), duration (≥ 8, > 8 weeks), and sex (both sex, female) on TAC. Subgroup analysis of mentioned parameters did not show between-study heterogeneity (Table 3).

We performed a sensitivity analysis to determine the effect of each study on the overall mean difference. There was one study with different BMI (> 30 kg/m^2) and dosage (> 10^{10} CFU/day). The sensitivity analysis indicated that this trial had no significant effect on overall effect size.

Malondialdehyde

This meta-analysis was executed in nine studies. Pooled mean difference for effects of probiotic supplementation on MDA compared to the placebo group was − 0.31 μmol/L (95% CI − 0.54, − 0.08) with high heterogeneity ($I^2 = 71.5\%$; $p < 0.001$) (Fig. 3). A sensitivity analysis was carried out to evaluate the effect of each study on the overall mean difference. None of the included studies had a significant effect on the overall studies. To identify the source of heterogeneity, we conducted subgroup analysis according to age (< 50, ≥ 50 years), duration (≥ 8, > 8 weeks), and sex (both sex, female). Duration of intervention > 8 weeks compared to ≤

Table 1 General characteristics of included studies

Code	Author (year)	Country	Study design	Sample size in intervention group	Sample size in control group	Population study (sex)	Age (years)	BMI (kg/m^2)	Duration (weeks)	Probiotic type	Daily dose (CFU)	Jadad score
1	Asemi, Z. (2013)	Iran	R,DB,PC	27	27	Type 2 diabetes (F/M)	50.51	31.61	8	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus.rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophilus*	3.92×10^{10}	4
2	Mazloom, Z. (2013)	Iran	R,SB,PC	16	18	Type 2 diabetes (F/M)	55.4	27.97	6	*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus bifidum*, *Lactobacillus casei*	1.2×10^{10}	2
3	Akkasheh, G. (2016)	Iran	R,DB,PC	20	20	Depressive disorder (F/M)	38.3	27.6	8	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*	3×10^9	5
4	Jamilian, M. (2016)	Iran	R,DB,PC	30	30	Pregnant women (F)	27.1	25.6	12	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*	3×10^9	5
5	Soleimani, A. (2016)	Iran	R,DB,PC	30	30	Diabetic hemodialysis (F/M)	54	25.5	12	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bifidum*	3×10^9	5
6	Vaghef-Mehrabany, E. (2016)	Iran	R,DB,PC	22	24	Rheumatoid arthritis (F)	41.14	27.7	8	*Lactobacillus casei*	1×10^8	5
7	Zamani, B. (2016)	Iran	R,DB,PC	30	30	Rheumatoid arthritis (F/M)	52.2	29.2	8	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*	3×10^9	5
8	Badehnoosh, B. (2017)	Iran	R,DB,PC	30	30	Gestational diabetes (F)	28.8	28.3	6	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*	3×10^9	5
9	Gomes, Ac. (2017)	Brazil	R,DB,PC	21	22	Obesity (F)	40	31.7	8	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactococcus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*	2×10^{10}	5
10	Kouchaki, E. (2017)	Iran	R,DB,PC	30	30	Multiple sclerosis (F/M)	34.4	25.4	12	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Lactobacillus fermentum*	4×10^9	5
11	Mohseni, S. (2017)	Iran	R,DB,PC	30	30	Diabetic foot ulcer (F/M)	62.6	26.4	12	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Lactobacillus fermentum*	4×10^9	5

DB double-blinded, SB single-blind, PC placebo-control, R randomized, F female, M male

Table 2 Risk of bias for the included studies, assessed according to the Cochrane Risk of Bias Tool

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other Sources of bias	Overall quality
Asemi, Z. (2013)	L	U	L	L	L	L	L	Good
Mazloom, Z. (2013)	L	L	H	H	U	L	L	
Akkasheh, G. (2016)	L	L	L	L	L	L	L	Good
Jamilian, M. (2016)	L	L	L	L	H	L	L	Good
Soleimani, A. (2016)	L	L	L	L	U	L	L	Good
Vaghef-Mehrabany, E. (2016)	L	L	L	L	U	L	L	Good
Zamani, B. (2016)	L	L	L	L	L	L	L	Good
Badehnoosh, B. (2017)	L	L	L	L	U	L	L	Good
Gomes, Ac. (2017)	L	L	L	L	H	L	L	Good
Kouchaki, E. (2017)	L	L	L	L	L	L	L	Good
Mohseni, S. (2017)	L	L	L	L	L	L	L	Good

L low risk of bias, H high risk of bias, U unclear risk of bias

8 weeks and age ≥ 50 years compared to > 50 years results in a higher reduction in MDA, while these parameters were not described between-study heterogeneity. Moreover, analysis based on sex indicated that subgroup of studies with both sexes result in significant reduction in MDA (− 0.45 μmol/L; 95% CI − 0.77, − 0.13; $I^2 = 67.9\%$; $p = 0.014$) compared to females (− 0.11; 95% CI − 0.37, 0.15; $I^2 = 37.9\%$; $p = 0.185$) (Table 3).

Glutathione

Eight clinical trials reported the effect of probiotic supplementation on GSH levels. A pooled mean change in GSH was found to be insignificant (WMD = 19.32 μmol/L; 95% CI − 18.70 to 57.33; $I^2 = 64.9\%$; $p = 0.006$ for heterogeneity) (Fig. 4). To identify the effect of each study and the source of heterogeneity on overall effect size, sensitivity analysis and subgroup analysis were conducted. Based on results of sensitivity analysis, the overall effect size did not depend on a specific study. The subgroup analysis based on age (< 50, ≥ 50 years), duration (≥ 8, > 8 weeks), and sex (both sex, female) were not a potential source of heterogeneity for GSH (Table 3).

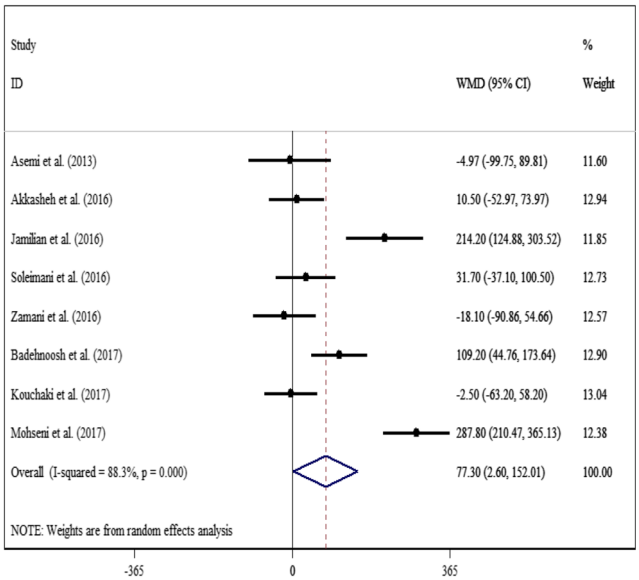

Fig. 2 Forest plot indicating pooled mean difference and 95% confidence intervals for the effect of probiotic supplementation on tota antioxidant capaity (TAC) levels

Discussion

Our meta-analysis demonstrated that probiotic supplementation induces a slightly significant increase in TAC level and slight significant reduction in MDA level, while it did not affect GSH level significantly.

Oxidative stress is associated with insulin resistance [31] and chronic diseases such as diabetes, cardiovascular diseases, and cancers [32, 33]. There are several studies that have evaluated the effect of probiotic supplementation on the oxidative status. In line with our finding, Heshmati et al. concluded that probiotics increased and decreased the serum levels of TAC and MDA, respectively. Furthermore, they found that probiotics increased the serum level of GSH, while we did not find a significant association between probiotic supplementation and GSH levels. One possible reason is including symbiotic and fortified foods, in Heshmati et al.'s study, while we considered supplements only [34]. Similar to our results, a clinical trial by Mohammadi et al. indicated that probiotic intake, whether as yogurt or capsule, results in improvement of serum biomarkers of oxidative stress level in petrochemical workers [35]. Moreover, a systematic review by Mishra et al. suggested that probiotic consumption has a positive effect on

Table 3 Subgroup analyses of probiotics supplementation on level of TAC, MDA, and GSH

	TAC				MDA				GSH			
	N	MD (95%CI)	I^2 (%)	*P* heterogeneity	*N*	MD (95%CI)	I^2 (%)	*P* heterogeneity	*N*	MD (95%CI)	I^2 (%)	*P* heterogeneity
Sex												
Both sex	6	50.30 (−37.70, 138.30)	89	< 0.001	5	−0.45 (−0.77, −0.13)	67	0.014	6	18.29 (−34.98, 71.57)	69.8	0.005
Female	2	156.95 (54.48, 259.44)	71	0.062	4	−0.11 (−0.37, 0.15)	37	0.185	2	30.21 (−4.44, 64.87)	0.0	0.558
Duration												
≤ 8 weeks	4	27.12 (−33.43, 87.68)	64	0.039	5	−0.16 (−0.40, 0.09)	52	0.076	4	55.31 (−6.15, 116.78)	55.3	0.082
> 8 weeks	4	130.86 (−8.14, 269.86)	93	< 0.001	4	−0.44 (−0.78, −0.10)	63	0.041	4	−5.94 (−48.26, 36.39)	60.2	0.057
Age												
< 50 years	4	78.68 (−9.57, 166.93)	85	< 0.001	5	−0.17 (−0.40, 0.06)	54	0.068	4	19.27 (−40.14, 78.68)	79.9	0.002
≥ 50 years	4	74.46 (−66.39, 215.31)	92	< 0.001	4	−0.58 (−1.06, −0.10)	75	0.006	4	19.20 (−30.04, 68.44)	35.6	0.198

TAC total antioxidant capacity, MDA malondialdehyde, GSH glutathione, MD mean difference, CI confidence interval

oxidative damage reduction and antioxidant enzyme, as well as it is a proper approach to promote dietary antioxidant content [36]. On the other hand, Aqaeinezhad et al. failed to find the notable effect of probiotic supplementation on serum level of MDA and TAC in rheumatoid arthritis patients [37]. An earlier meta-analysis by Samah et al. showed that probiotic supplementation did not have antioxidative effects in individuals with type 2 diabetes [38].

Although numerous studies were performed to evaluate the effect of probiotic intake on health outcome, the cause of it has not been yet proven, which may be due to antioxidant properties of probiotics [39]. To evaluate the influence of age, sex, and duration on the meta-analysis results, subgroup analyses

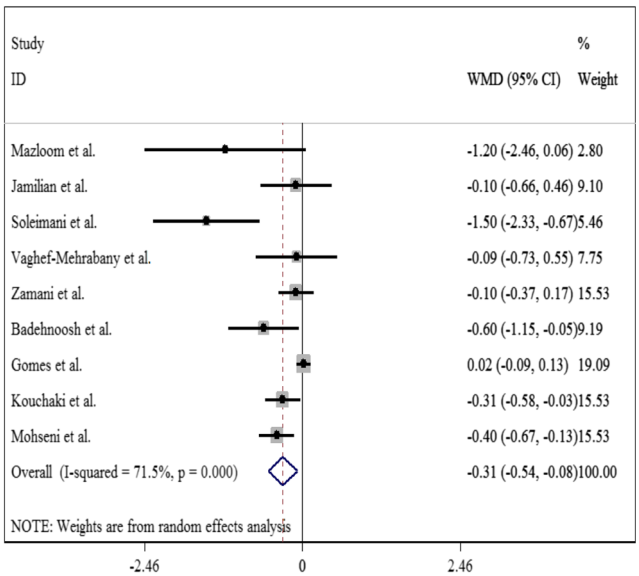

Fig. 3 Forest plot indicating pooled mean difference and 95% confidence intervals for the effect of probiotic supplementation on malondialdehyde (MDA) levels

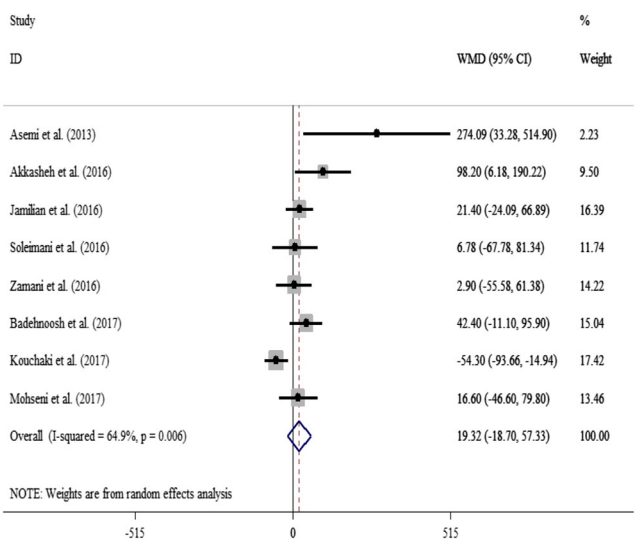

Fig. 4 Forest plot indicating pooled mean difference and 95% confidence intervals for the effect of probiotic supplementation on glutathione (GSH) levels

were conducted. However, none of the mentioned variables result in a significant effect on TAC level. Subgroup analysis according to sex showed that probiotic supplementation led to significant reduction in MDA level in both sex subgroups, while did not decrease MDA level significantly in females. It may be interpreted by the fact that probiotic supplementation has more beneficial effects in men rather than women. However, population studies of men are needed to determine these effects. In our meta-analysis, supplementation with probiotics did not affect GSH level. There was high heterogeneity between studies, which source of heterogeneity was not identified after stratifications based on predefined criteria in most subgroups. A possibility is that heterogeneity is due to other variables such as limited studies, health condition, sample size, and baseline characteristics. Most of the included studies used multistrain probiotic except one which used only lactobacilli casei strain. Although overall meta-analysis demonstrated that probiotic supplementation decreased serum level of MDA and increased TAC, in the study by Vaghef-Mehrabany et al., the level of MDA and TAC did not alter after the intervention [25]. Consistent with our results, Chapman et al. concluded that supplementation with multistrain probiotic showed more beneficial effect than single strain [40]. Also, most of the included studies used a narrow range of probiotic dosages (10^9 CFU/day) except two studies which dosage of supplementation was 10^{10} CFU/day. However, the biomarkers of TAC, GSH, and MDA changed significantly in the aforementioned studies and some studies suggested that greater dosage of probiotics led to greater therapeutic effect [41]. After excluding, the pooled mean difference did not change significantly. Due to limited studies, we could not perform subgroup analysis to clarify the effect of different dosage.

Antioxidants effects of probiotics are exemplified by several mechanisms. Some studies suggested that probiotics could improve absorption of polyphenols in the intestine. Some polyphenols are inactive as glycosylated, which could not be absorbed in the upper part of gastrointestinal system. When these compounds are transformed into the large intestine, they will be decomposed by probiotics and then polyphenols will convert to their active form and become absorbable [42]. Probiotics can produce some of vitamins B group [43], which have antioxidant properties [44]. Also, probiotic can decrease pathogenic bacteria via competitive behavior, which consequently reduces endotoxins. High level of endotoxins can stimulate secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) [45, 46]. Furthermore, probiotics have an important role in scavenging superoxide and hydroxyl radicals [47]. Probiotics modulate production of short-chain fatty acids [48], which via inhibiting production of pro-inflammatory and upregulation of antioxidant enzyme improve inflammation and oxidative stress status [49]. Some bioactive peptides are generated by probiotics, which have antioxidant and radical scavenging activities [50, 51]. The serum level of MDA is correlated to oxidation of lipids in body. Several studies illustrated that probiotics could alter lipid profile. Thus, the reduction effect of probiotics on MDA may be due to improvement of lipid profile.

It is necessary to present some limitations in this meta-analysis. The number of studies and population of studies were relatively small, which undermine the results of the studies. Most of the included studies were conducted in Iran; hence, the results could not be applied to other populations. Because of the similarity in the BMI of the subjects and dosages of probiotic supplementations, the subgroup analysis could not be executed based on these two variables. Furthermore, there was high heterogeneity between studies, which may be due to health status. The requirement for further investigation is felt by supplementation of probiotics according to specific health status and particular strain of probiotic.

Conclusion

Overall, the finding of this meta-analysis suggested that probiotic supplementation may improve oxidative stress condition, which could lead to beneficial effects in prevention of some chronic diseases. However, the results should be interpreted with great caution because of high heterogeneity. Future investigations are required with larger sample size, different doses, and strains of probiotics, and healthy condition to evaluate the effect of probiotic supplementation on oxidative stress biomarkers.

Funding The present study was supported by Tehran University of Medical Sciences (grant number : 97-03-161-40572).

Compliance with Ethical Standards

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

References

1. Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD (2004) Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India 52: 794–804
2. Ceriello A, Motz E (2004) Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 24(5):816–823. https://doi.org/10.1161/01.atv.0000122852.22604.78

3. Sosa V, Moline T, Somoza R, Paciucci R, Kondoh H, ME LL (2013) Oxidative stress and cancer: an overview. Ageing Res Rev 12(1):376–390. https://doi.org/10.1016/j.arr.2012.10.004
4. Halliwell B, Gutteridge JM (1990) The antioxidants of human extracellular fluids. Arch Biochem Biophys 280(1):1–8
5. Mazidi M, Rezaie P, Kengne AP, Mobarhan MG, Ferns GA (2016) Gut microbiome and metabolic syndrome. Diabetes Metab Syndr 10(2 Suppl 1):S150–S157. https://doi.org/10.1016/j.dsx.2016.01.024
6. Zuccotti GV, Meneghin F, Raimondi C, Dilillo D, Agostoni C, Riva E, Giovannini M (2008) Probiotics in clinical practice: an overview. J Int Med Res 36:1A–53A. https://doi.org/10.1177/14732300080360s101
7. Alipour B, Homayouni-Rad A, Vaghef-Mehrabany E, Sharif SK, Vaghef-Mehrabany L, Asghari-Jafarabadi M, Nakhjavani MR, Mohtadi-Nia J (2014) Effects of *Lactobacillus casei* supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: a randomized double-blind clinical trial. Int J Rheum Dis 17(5):519–527. https://doi.org/10.1111/1756-185x.12333
8. Saez-Lara MJ, Robles-Sanchez C, Ruiz-Ojeda FJ, Plaza-Diaz J, Gil A (2016) Effects of probiotics and synbiotics on obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease: a review of human clinical trials. Int J Mol Sci 17 (6). doi: https://doi.org/10.3390/ijms17060928
9. Mishra V, Prasad DN (2005) Application of in vitro methods for selection of *Lactobacillus casei* strains as potential probiotics. Int J Food Microbiol 103(1):109–115. https://doi.org/10.1016/j.ijfoodmicro.2004.10.047
10. Moro-Garcia MA, Alonso-Arias R, Baltadjieva M, Fernandez Benitez C, Fernandez Barrial MA, Diaz Ruisanchez E, Alonso Santos R, Alvarez Sanchez M, Saavedra Mijan J, Lopez-Larrea C (2013) Oral supplementation with *Lactobacillus delbrueckii subsp. bulgaricus* 8481 enhances systemic immunity in elderly subjects. Age 35(4):1311–1326. https://doi.org/10.1007/s11357-012-9434-6
11. Roberfroid MB (2000) Prebiotics and probiotics: are they functional foods? Am J Clin Nutr 71(6 Suppl):1682S–1687S discussion 1688S–1690S
12. Ouwehand AC, Tölkkö S, Kulmala J, Salminen S, Salminen E (2000) Adhesion of inactivated probiotic strains to intestinal mucus. Lett Appl Microbiol 31(1):82–86. https://doi.org/10.1046/j.1472-765x.2000.00773.x
13. Bergmann RSO, Pereira MA, Veiga SMOM, Schneedorf JM, Oliveira NMS, Fiorini JE (2010) Microbial profile of a kefir sample preparations: grains in natura and lyophilized and fermented suspension. Food Sci Technol 30:1022–1026
14. Holzapfel WH (2002) Appropriate starter culture technologies for small-scale fermentation in developing countries. Int J Food Microbiol 75(3):197–212
15. Peran L, Camuesco D, Comalada M, Nieto A, Concha A, Adrio JL, Olivares M, Xaus J, Zarzuelo A, Galvez J (2006) *Lactobacillus fermentum*, a probiotic capable to release glutathione, prevents colonic inflammation in the TNBS model of rat colitis. Int J Color Dis 21(8):737–746. https://doi.org/10.1007/s00384-005-0773-y
16. Kullisaar T, Zilmer M, Mikelsaar M, Vihalemm T, Annuk H, Kairane C, Kilk A (2002) Two antioxidative strains as promising probiotics. Int J Food Microbiol 72(3):215–224. https://doi.org/10.1016/S0168-1605(01)00674-2
17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1. https://doi.org/10.1186/2046-4053-4-1
18. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17(1):1–12
19. Anderson R, Hay I, Wyk H, Theron A (1983) Ascorbic acid in bronchial asthma. S Afr Med J 63(17):649–652
20. Asemi Z, Zare Z, Shakeri H, Sabihi S, Esmaillzadeh A (2013) Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. Ann Nutr Metab 63(1–2):1–9. https://doi.org/10.1159/000349922
21. Mazloom Z, Yousefinejad A, Dabbaghmanesh MH (2013) Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress, and inflammatory markers in patients with type 2 diabetes: a clinical trial. Iran J Med Sci 38(1):38–43
22. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Memarzadeh M, Asemi Z, Esmaillzadeh A (2016) Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition 32(3):315–320. https://doi.org/10.1016/j.nut.2015.09.003
23. Jamilian M, Bahmani F, Vahedpoor Z, Salmani A, Tajabadi-Ebrahimi M, Jafari P, Hashemi Dizaji S, Asemi Z (2016) Effects of probiotic supplementation on metabolic status in pregnant women: a randomized, double-blind, placebo-controlled trial. Arch Iran Med 19(10):687–692
24. Soleimani A, Zarrati MM, Bahmani F, Taghizadeh M, Ramezani M, Tajabadi-Ebrahimi M, Jafari P, Esmaillzadeh A, Asemi Z (2016) Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. Kidney Int 91:435–442. https://doi.org/10.1016/j.kint.2016.09.040
25. Vaghef-Mehrabany E, Homayouni-Rad A, Alipour B, Sharif S, Vaghef-Mehrabany L, Alipour-Ajiry S (2016) Effects of probiotic supplementation on oxidative stress indices in women with rheumatoid arthritis: a randomized double-blind clinical trial. J Am Coll Nutr 35(4):291–299. https://doi.org/10.1080/07315724.2014.959208
26. Zamani B, Golkar HR, Farshbaf S, Emadi-Baygi M, Tajabadi-Ebrahimi M, Jafari P, Akhavan R, Taghizadeh M, Memarzadeh MR, Asemi Z (2016) Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Int J Rheum Dis 19(9):869–879. https://doi.org/10.1111/1756-185x.12888
27. Badehnoosh B, Karamali M, Zarrati M, Jamilian M, Bahmani F, Tajabadi-Ebrahimi M, Jafari P, Rahmani E, Asemi Z (2017) The effects of probiotic supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in journal of maternal-fetal & neonatal medicine. J Matern Fetal Neonatal Med 31:1128–1136. https://doi.org/10.1080/14767058.2017.1310193
28. Gomes A, Sousa R, Botelho P, Gomes T, Prada P, Mota J (2017) The additional effects of a probiotic mix on abdominal adiposity and antioxidant status: a double-blind, randomized trial. Obesity 25(1):30–38. https://doi.org/10.1002/oby.21671
29. Kouchaki E, Tamtaji OR, Salami M, Bahmani F, Daneshvar Kakhaki R, Akbari E, Tajabadi-Ebrahimi M, Jafari P, Asemi Z (2017) Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Clin Nutr 36(5):1245–1249. https://doi.org/10.1016/j.clnu.2016.08.015
30. Mohseni S, Bayani M, Bahmani F, Tajabadi-Ebrahimi M, Bayani MA, Jafari P, Asemi Z (2017) The effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.2970
31. Paneni F, Costantino S, Cosentino F (2015) Role of oxidative stress in endothelial insulin resistance. World J Diabetes 6(2):326–332. https://doi.org/10.4239/wjd.v6.i2.326
32. White PA, Oliveira RC, Oliveira AP, Serafini MR, Araujo AA, Gelain DP, Moreira JC, Almeida JR, Quintans JS, Quintans-Junior LJ, Santos MR (2014) Antioxidant activity and mechanisms of action of natural compounds isolated from lichens: a systematic

review. Molecules 19(9):14496–14527. https://doi.org/10.3390/molecules190914496
33. Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn Rev 4(8):118–126. https://doi.org/10.4103/0973-7847.70902
34. Heshmati J, Farsi F, Shokri F, Rezaeinejad M, Almasi-Hashiani A, Vesali S, Sepidarkish M (2018) A systematic review and meta-analysis of the probiotics and synbiotics effects on oxidative stress. J Funct Foods 46:66–84
35. Mohammadi AA, Jazayeri S, Khosravi-Darani K, Solati Z, Mohammadpour N, Asemi Z, Adab Z, Djalali M, Tehrani-Doost M, Hosseini M, Eghtesadi S (2015) Effects of probiotics on biomarkers of oxidative stress and inflammatory factors in petrochemical workers: a randomized, double-blind, placebo-controlled trial. Int J Prev Med 6:82. https://doi.org/10.4103/2008-7802.164146
36. Mishra V, Shah C, Mokashe N, Chavan R, Yadav H, Prajapati J (2015) Probiotics as potential antioxidants: a systematic review. J Agric Food Chem 63(14):3615–3626. https://doi.org/10.1021/jf506326t
37. Aqaeinezhad Rudbane SM, Rahmdel S, Abdollahzadeh SM, Zare M, Bazrafshan A, Mazloomi SM (2018) The efficacy of probiotic supplementation in rheumatoid arthritis: a meta-analysis of randomized, controlled trials. Inflammopharmacology 26(1):67–76. https://doi.org/10.1007/s10787-017-0436-y
38. Samah S, Ramasamy K, Lim SM, Neoh CF (2016) Probiotics for the management of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 118:172–182. https://doi.org/10.1016/j.diabres.2016.06.014
39. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V (2012) Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 28(5):539–543. https://doi.org/10.1016/j.nut.2011.08.013
40. Chapman CM, Gibson GR, Rowland I (2011) Health benefits of probiotics: are mixtures more effective than single strains? Eur J Nutr 50(1):1–17. https://doi.org/10.1007/s00394-010-0166-z
41. Fujimori S, Tatsuguchi A, Gudis K, Kishida T, Mitsui K, Ehara A, Kobayashi T, Sekita Y, Seo T, Sakamoto C (2007) High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. J Gastroenterol Hepatol 22(8):1199–1204. https://doi.org/10.1111/j.1440-1746.2006.04535.x
42. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D (2015) Role of the normal gut microbiota. World J Gastroenterol 21(29):8787–8803. https://doi.org/10.3748/wjg.v21.i29.8787
43. Li P, Zhou Q, Gu Q (2016) Complete genome sequence of *Lactobacillus plantarum LZ227*, a potential probiotic strain producing B-group vitamins. J Biotechnol 234:66–70. https://doi.org/10.1016/j.jbiotec.2016.07.020
44. Ashoori M, Saedisomeolia A (2014) Riboflavin (vitamin B(2)) and oxidative stress: a review. Br J Nutr 111(11):1985–1991. https://doi.org/10.1017/s0007114514000178
45. Behnsen J, Deriu E, Sassone-Corsi M, Raffatellu M (2013) Probiotics: properties, examples, and specific applications. Cold Spring Harb Perspect Med 3:a010074. https://doi.org/10.1101/cshperspect.a010074
46. Osman N, Adawi D, Ahrné S, Jeppsson B, Molin G (2007) Endotoxin- and d-galactosamine-induced liver injury improved by the administration of *Lactobacillus, Bifidobacterium* and blueberry. Dig Liver Dis 39(9):849–856. https://doi.org/10.1016/j.dld.2007.06.001
47. Kullisaar T, Zilmer M, Mikelsaar M, Vihalemm T, Annuk H, Kairane C, Kilk A (2002) Two antioxidative lactobacilli strains as promising probiotics. Int J Food Microbiol 72(3):215–224
48. Gargari G, Taverniti V, Balzaretti S, Ferrario C, Gardana C, Simonetti P, Guglielmetti S (2016) Consumption of a *Bifidobacterium bifidum* strain for 4 weeks modulates dominant intestinal bacterial taxa and fecal butyrate in healthy adults. Appl Environ Microbiol 82(19):5850–5859. https://doi.org/10.1128/aem.01753-16
49. Yuan X, Wang L, Bhat OM, Lohner H, Li P-L (2018) Differential effects of short chain fatty acids on endothelial Nlrp3 inflammasome activation and neointima formation: antioxidant action of butyrate. Redox Biol 16:21–31. https://doi.org/10.1016/j.redox.2018.02.007
50. Saiga A, Tanabe S, Nishimura T (2003) Antioxidant activity of peptides obtained from porcine myofibrillar proteins by protease treatment. J Agric Food Chem 51(12):3661–3667. https://doi.org/10.1021/jf021156g
51. Suetsuna K, Ukeda H, Ochi H (2000) Isolation and characterization of free radical scavenging activities peptides derived from casein. J Nutr Biochem 11(3):128–131