J Appl Biotechnol Rep. 2021 December;8(4):326-331

Journal of
Applied Biotechnology Reports

doi 10.30491/JABR.2020.117863

Review Article

The Effect of Probiotic Supplements on Oxidative Stress in Various Diseases: A Systematic Review

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Received October 23, 2019; **Accepted** February 26, 2020; **Online Published** October 12, 2020

Abstract

Introduction: Recently, the consumption of probiotics to decrease Oxidative Stress (OS) has been recommended. The present study aimed to assess the effect of probiotics on OS in various diseases as well as in different models in a systematic review study.

Materials and Methods: Articles were searched through scientific sources such as PubMed, MEDLINE, Wiley, EMBASE, ISI Web of Knowledge and Scopus by two review authors independently. The keywords that applied to search these articles included: Probiotics, OS, Stresses, Oxidative and Stress. Results were then combined and reviewed regarding the type of study, type of disease/participants and outcomes.

Results: In order to conduct this study, 19 eligible studies were investigated. The results showed that various probiotics supplements could improve OS parameters in pregnant women, patients with type 2 diabetics, Diabetic Kidney Disease (DKD) type 2, gestational diabetes mellitus, and the aging process, inflammatory factors in petrochemical workers, acute necrotizing pancreatitis, and polycystic ovary syndrome. However, no significant effect was reported on the oxidative status in patients with Rheumatoid Arthritis.

Conclusions: Probiotics supplements could improve OS biomarkers in various diseases. There are still some controversies about these methods and types of probiotics supplementations. It is recommended that more studies should be conducted for a better decision.

Keywords: Probiotics Supplements, Oxidative Stress

Citation: Mahmoudi S, Ghane MR, Goodarzi H, Faraji M, Shahjooie F, Javadzadeh HR. The Effect of Probiotic Supplements on Oxidative Stress in Various Diseases: A Systematic Review. J Appl Biotechnol Rep. 2021;8(4):326-331. doi:10.30491/JABR.2020.117863

Introduction

Recently, OS has been prevalent in various disease groups and OS related to as inequality between prooxidants and antioxidants.[1-5] Raise in OS is broadly considered as a mechanism included in developing cancer, diabetes, Parkinson's illness, Alzheimer, heart illness, neurological and psychiatric disorders. Furthermore, some studies have revealed an increase in the risk of melanoma, bladder and prostate carcinoma and pulmonary mesothelioma in petrochemical workers.[2-4]

Several procedures to decrease OS have been recommended including the consumption of antioxidants particularly vitamins A, C, and E, carotenoids, polyphenols as well as eating vegetables and fruits.[3-8] Also, the consumption of probiotics in order to decrease OS has been introduced. Probiotics are microorganisms that are supposed to produce health advantages for creatures when used. However, there are some controversies about the effectiveness of different probiotics as well as various diseases on OS. The effects of probiotics have been evaluated in pregnant women, patients with type two diabetes mellitus and the inflammatory factors of subjects.[8-13]

The purpose of this study was to review studies about the effect of probiotics on OS in various diseases in order to support clinicians and patients to have a better knowledge of these methods and determining a better healing option. An extremely standardized evidence-based review can be one of the best references for clinicians to choose their therapy program.

Materials and Methods

We searched records through scientific sources such as PubMed, MEDLINE, Wiley, EMBASE, ISI Web of Knowledge and Scopus by two review authors independently. The keywords that applied to search these articles included: probiotics, OS, stresses, oxidative and stress. Two researchers independently assessed titles and abstracts. After excluding irrelevant records, all the full text of studies were included. Then, results were combined and reviewed regarding the type of study, type of disease/participants and outcomes (Figure 1).

Results

Our search initially retrieved 158 studies published in September 2018. However, 132 papers were eliminated because of duplication between databases. Then, 26 studies were included for primary screening. Upon screening titles

and abstracts, 19 studies were identified for full-text review.

Table 1 shows studies' characteristics regarding the authors' name (year), the type of study, type of disease/participants and outcomes. We reviewed studies about the evaluation of the effect of probiotics on OS based on animal, humans and in vitro studies in various diseases.

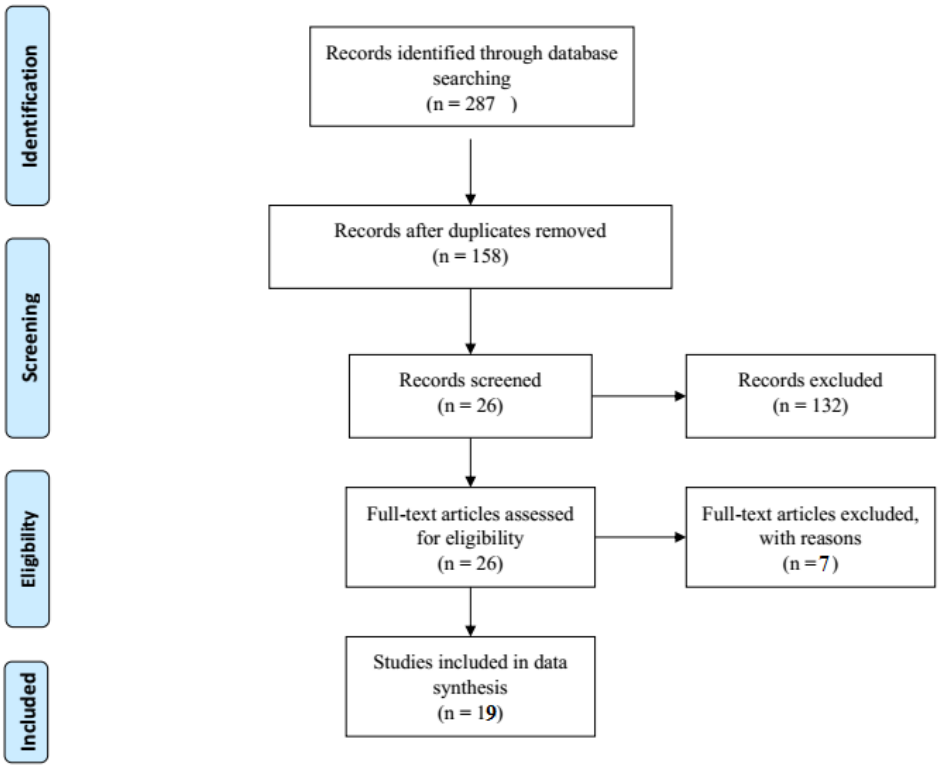

Figure 1. PRISMA Flow Diagram

Animal Studies

Robles-Vera et al. (2018) evaluated the effect of probiotic *Lactobacillus fermentum* CECT5716 (LC40) on the reduction of hypertension in rats with chronic Nitric Oxide (NO) synthase inhibition. They randomly divided the rats into four different groups and followed up for four weeks: 1) vehicle plus L-NAME (50 mg/100 ml in drinking water); 2) vehicle (control); 3) LC40 plus L-NAME; and 4) LC40 (10^9 colony-forming units/day by gavage). The gut dysbiosis increased with L-NAME, mostly by a reduced *Bifidobacterium* content and increased *Fimicutes/Bacteroidetes* (F/B) ratio, decreased Treg in Mesenteric Lymph Nodes (MLN) and raised Th17 cells, increased reactive oxygen species, decreased aortic endothelium-dependent relaxant response to acetylcholine, and hypertension. The LC40 prohibited gut dysbiosis, chiefly by changing the Th17/Treg equilibrium in MLN, inflammation, and vascular OS, which enhanced faintly endothelial dysfunction but did not prevent the increase of L-NAME-induced hypertension. They concluded that chronic LC40 treatment decreased the initial events of atherosclerosis development, including pro-inflammatory status and vascular OS, as an outcome of inhibition of gut dysbiosis.[1]

Yadav et al. (2018) examined the effects of probiotic bacteria *Lactobacillus fermentum* MTCC for decreasing cholesterol in rats fed with cholesterol-enriched diet. They divided the rats into three groups: 1) control group (SD); 2) fed cholesterol-enriched diet along with L. fermentum MTCC; 3) fed cholesterol-enriched diet (CED) for 90 days. They demonstrated that the levels of anti-oxidative enzyme activities such as superoxide dismutase, catalase, and glutathione peroxidase in the kidney and liver decreased in the CED group compared to the SD group. Hence, this study recommended probiotic supplementation can be improved to suppress the OS created by overload of cholesterol by rising the anti-oxidative enzyme activities in the liver and kidney.[2]

Aluwong et al. (2015) assigned the effects of vitamin C (Vit-C) and probiotic therapy on OS, hyperglycemia, and dyslipidemia in alloxan-induced diabetic rats. The animals were divided into six groups based on received regimens for four weeks: (a) Normal saline; (b) alloxan (c) alloxan + insulin; (d) alloxan + probiotic; (e) alloxan + Vit-C; (f) alloxan + probiotic + Vit-C. The Probiotic + Vit-C regimen significantly reduced blood glucose levels in the diabetic treated group, compared with the untreated diabetic group. The Probiotic + Vit-C regimen decreased serum malondialdehyde level, in kidneys and brain, but improved the activity of

Table 1. Studies' Characteristics

Authors' name (Year)	Type of study	Type of disease/participants	Type of probiotics	Outcomes
Robles-Vera et al (2018)[1]	Animal	Hypertension in rats that have chronic nitric oxide (NO) synthase inhibition	*Lactobacillus fermentum* CECT5716 (LC40)	Decrease initially events of atherosclerosis development, including pro-inflammatory status and vascular oxidative stress, as an outcome of inhibition of gut dysbiosis
Yadav et al (2018)[2]	Animal	Hyper cholesterol in rat	*Lactobacillus fermentum* MTCC	Suppress the oxidative stress created by overload of cholesterol by rising the anti-oxidative enzyme activities in the liver and kidney
Aluwong et al (2015)[7]	Animal	Hyperglycaemia, and dyslipidaemia in alloxan-induced diabetic rats	Vitamin C (Vit-C) and probiotic	Vit-C and probiotic may be more efficient than Vit-C alone, in oxidative stress, ameliorating hyperglycaemia, and dyslipidaemia in alloxan-induced diabetic rats
Mohammadi Sartang et al (2015)[10]	Animal	Diabetic	Probiotic soymilk fortified with omega-3	Decreased malondialdehyde (MDA) level comparison to the diabtic group
Bouhafs et al. (2015)[11]	Animal	Endosulfan in pregnant rats	*L. plantarum BJ0021*	BJ0021 reduced apoptosis and might perform a protecting function in decreasing toxicity of endosulfan in pregnant rats
Pandey et al. (2015)[13]	Animal	DMH-induced systemic oxidative injury and modified neurotransmitter status in rat brain	PQQ-producing probiotic *E. coli* CFR 16	Improved
Kaushal et al. (2012)[15]	Animal	Aging in mice	Probiotic Dahi including *Lactobacillus acidophilus* and *Bifidobacterium bifidum*	Possible nutraceutical intervention to combat oxidative stress and molecular modifications correlated with aging
Castex et al. (2010)[14]	Animal	Infection level and/or an improvement of the antioxidant status of the shrimps	*L. stylirostris* and probiotic *Pediococcus acidilactici*	Reduction of the infection level
Hajifaraji et al. (2017)[3]	Humans	Women with gestational diabetes mellitus	*Streptococcus Thermophilus* STY-31, *Lactobacillus acidophilus* LA-5, *delbrueckii* bulgaricus LBY-27, *Bifidobacterium* BB-12, and *Lactobacillus*	Improve oxidative stress biomarkers and several inflammations
Karamali et al. (2018)[4]	Humans	Inflammation, and hormonal profiles in women with polycystic ovary syndrome	Probiotic supplementation	Valuable effects on SHBG, total testosterone, mFG scores, TAC and MDA levels, hs-CRP, but did not affect other metabolic profiles
Miraghajani et al. (2017)[5]	Humans	Diabetic kidney disease type 2	Soy milk	Improve several oxidative stress factors
Badehnoosh et al. (2017)[6]	Humans	Pregnancy results in gestational diabetes	*Lactobacillus casei, Lactobacillus acidophilus*, and *Bifidobacterium bifidum*	Reduction fasting plasma glucose, plasma malondialdehyde (MDA) concentrations, MDA/TAC ratio, and serum high-sensitivity C-reactive protein (hs-CRP) compared with the placebo group.
Hariri et al. (2015)[8]	Humans	Type II diabetic patients	Soy milk*, Lactobacillus plantarumA7*	Increased antioxidant status in type II diabetic patients; so that they reported that probiotic soy milk is a potential agent for diabetes management
Vaghef-Mehrabany et al. (2016)[12]	Humans	Women with Rheumatoid Arthritis	Probiotic supplementation such as a daily capsule containing 10(8) colony forming units (CFUs) of Lactobacillus casei 01 (L. casei 01)	No significant impact of L. casei 01 supplementation was recognized on the oxidative status of patients with Rheumatoid Arthritis
Mohammadi et al. (2015)[16]	Humans	Inflammatory factors in petrochemical workers	Probiotic yogurt or multispecies probiotic capsule	Profitable outcomes on biomarkers of oxidative stress
Asemi et al. (2013)[17]	Humans	Metabolic characterizations, high-sensitivity C-reactive protein (hs-CRP), and oxidative stress in type two diabetes cases	Multispecies probiotic appendices	Increase in FPG and resulted in a reduction in serum hs-CRP and a rise in plasma total antioxidant capacity and total glutathione
Asemi et al. (2012)[19]	Humans	Pregnant women	Probiotic yogurt	Raised levels of erythrocyte GR as respect to the traditional yogurt, but could not influence other indices of oxidative stress the use of probiotic yogurt
Romanin et al. (2015)[9]	In vitro	Anti-inflammatory ability	*Kluyveromyces marxianus* CIDCA 8154	The *Caenorhabditis elegans* model used for show ability to change oxidative stress *in vivo.* They demonstrated that *K. marxianus* CIDCA 8154 can manage the cellular oxidative stress and intestinal inflammation

Continue

Akyol et al. (2003)[18]	In vitro	Pancreatic infections	Probiotic *Saccharomyces boulardii* (25 mg/d orally q.d.), group II received meropenem (60 mg/kg intraperitoneally b.i.d.), group III received ciprofloxacin (40 mg/kg intraperitoneally b.i.d.)	MDA levels reduced and SOD levels rose

antioxidant enzymes. They concluded that Vit-C and probiotic may be more efficient than Vit-C alone, in OS, ameliorating hyperglycemia, and dyslipidemia in alloxan-induced diabetic rats.[7]

Mohammadi Sartang et al. (2015) evaluated the effects of probiotic soymilk fortified with omega-3 in diabetic rats. They divided 65 rats into five groups (13 animals per group). They reported that three products considerably decreased the malondialdehyde (MDA) level compared to the diabetic group.[10] Bouhafs et al. (2015) revealed that the performance of *L. Plantarum* BJ0021 reduced apoptosis and might perform a protecting function in decreasing the toxicity of endosulfan in pregnant rats.[11] Pandey et al. (2015) showed the antioxidant effectiveness of PQQ-producing probiotic *E. coli* CFR 16 on DMH-induced systemic oxidative injury and modified the neurotransmitter status in the rat brain.[13] Castex et al. (2010) confirmed that bacterial infection leads to OS in L. stylirostris and showed an advantageous effect of probiotic *Pediococcus acidilactici*, recommending both a competitive elimination outcome leading to a reduction of the infection level and/or an improvement of the antioxidant status of the shrimps.[14] Kaushal et al. (2012) recommended that probiotic Dahi including *Lactobacillus acidophilus* and *Bifidobacterium bifidum* can be utilized as a possible nutraceutical intervention to combat OS and molecular modifications correlated with aging in mice.[15]

Humans' Studies

Hajifaraji et al. (2017) evaluated the effect of probiotic supplementation on OS biomarkers and inflammation in women with Gestational Diabetes Mellitus (GDM). They studied 64 pregnant women with GDM in a clinical trial, and randomly examined them to receive a probiotic including four bacterial strains of *Streptococcus thermophilus* STY-31, *Lactobacillus acidophilus* LA-5, *delbrueckii* bulgaricus LBY-27, *Bifidobacterium* BB-12, and *Lactobacillus* for eight following weeks. The results demonstrated improving tumor necrosis factor-α and high-sensitivity C-reactive protein levels in the probiotic group. On the other hand, the serum interleukin-6 levels reduced in both groups following the intervention. Erythrocyte glutathione peroxidase, glutathione reductase, and malondialdehyde levels enhanced considerably when using probiotics. They concluded that probiotics including bacterial strains of *Streptococcus Thermophilus* STY31, *Lactobacillus acidophilus* LA5, *Lactobacillus delbrueckii* subsp. bulgaricus LBY-27, *Bifidobacterium* BB-12, and *Lactobacillus* can improve OS biomarkers and several inflammations in women with GDM.[3]

Karamali et al. (2018) assessed the effects of probiotic supplementation on the biomarkers of OS and inflammation, and hormonal profiles in women with Polycystic Ovary Syndrome (PCOS). These 60 women (18-40 years) with PCOS were divided into two groups to receive either probiotics or placebo (n = 30 each group) for 12 weeks. The results after 12 weeks intervention demonstrated the fact that probiotic supplementation considerably improved plasma Total Antioxidant Capacity (TAC) (p = 0.04) and serum Sex Hormone-Binding Globulin (SHBG) (p<0.001), modified Ferriman-Gallwey (mF-G) scores (p<0.001), decreased serum total testosterone (p = 0.03), plasma MDA concentrations (p<0.001), and serum high-sensitivity C-reactive protein (p<0.001). Ultimately, they concluded that probiotic supplementation of PCOS women for 12 weeks have valuable effects on SHBG, total testosterone, mFG scores, TAC and MDA levels, hs-CRP, but did not affect other metabolic profiles.[4]

Miraghajani et al. (2017) evaluated the effects of probiotic soymilk utilization on OS biomarkers in DKD type 2 patients. They examined 48 patients using diet probiotic soymilk (200 ml/day) for eight weeks of intervention. They demonstrated that probiotic soymilk groups had an upper mean value of reduced glutathione (GSH) compared with the placebo group. The oxidized glutathione levels constantly and considerably decreased compared to the control group. In addition, the activity levels of antioxidant enzymes significantly increased. They concluded that probiotic soymilk consumption can improve several OS factors in DKD patients. They recommended that advanced studies should be carried out with consideration of personality differences.[5]

Badehnoosh et al. (2017) evaluated the effects of probiotic supplementation on OS, biomarkers of inflammation, and pregnancy results in Gestational Diabetes (GDM). Sixty subjects with GDM enrolled in this study. Patients were divided into two groups including a placebo group (n = 30) and receiving a probiotic capsule containing *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum* group (n = 30) for 6 weeks. The results demonstrated that probiotic supplementation considerably reduces fasting plasma glucose (p = 0.01), plasma MDA concentrations (p = 0.03), MDA/TAC ratio (p = 0.004), and serum high-sensitivity C-

reactive protein (hs-CRP) (p<0.001) compared with the placebo group. Also, TAC levels significantly rose (p = 0.002) in probiotic supplementation.[6]

Hariri et al. (2015) examined the impacts of probiotic soymilk on OS in type 2 diabetic patients. The 40 patients (35–68 years) were divided into two groups (experimental group (200 ml/day of probiotic soymilk [*Lactobacillus plantarum* A7]), and control group (200 ml/day of soymilk) for eight weeks. They reported a considerable boost in superoxide dismutase (SOD) activity in the probiotic soymilk group (p = 0.01). They concluded that the use of probiotic soymilk increased the antioxidant status in type 2 diabetic patients. They reported that probiotic soy milk is a potential agent for diabetes management.[8]

In a randomized double-blind clinical trial study, Vaghef-Mehrabany et al. (2016) assessed the influence of probiotic supplementation such as a daily capsule containing 10 Colony Forming Units (CFUs) of *Lactobacillus casei* 01 on OS in women with Rheumatoid Arthritis. They reported no significant impact of *L. casei* 01 supplementation on the oxidative status of patients with Rheumatoid Arthritis.[12]

In a randomized, double-blind, placebo-controlled trial study in petrochemical workers, Mohammadi et al. (2015) revealed that the use of probiotic yogurt or multispecies probiotic capsules had profitable outcomes on the biomarkers of OS.[16]

Asemi et al. (2013) evaluated the influences of multispecies probiotic appendices on metabolic characterizations, high-sensitivity C-reactive protein (hs-CRP), and OS in type two diabetes cases. They showed an increase in FPG and resulted in a reduction in serum hs-CRP and a rise in plasma total antioxidant capacity and total glutathione. Also, in a randomized controlled clinical trial study, Asemi et al. (2012) showed raised levels of erythrocyte GR as respect to the traditional yogurt.[17]

In Vitro Studies

Romanin et al. (2015) evaluated the anti-inflammatory ability of *Kluyveromyces marxianus* CIDCA 8154 in different models. They reported that pretreatment of epithelial cells with yeast decrease the concentration of intracellular reactive oxygen species. The model of yeast-treated animals showed a decrease in the levels of circulating interleukin 6 (p < 0.05) and histopathological score (p < 0.05). The *Caenorhabditis elegans* model was used to show the ability to change OS *in vivo*. They demonstrated that *K. marxianus* CIDCA 8154 can manage cellular OS and intestinal inflammation.[9]

Akyol et al. (2003) assessed the influence of antibiotic and probiotic treatment on secondary pancreatic infections and OS parameters in acute necrotizing pancreatitis. They determined that MDA levels reduced and SOD levels rose.[18]

Conclusion

The results showed that various probiotics supplements could improve OS parameters in pregnant women, patients with type 2 diabetics, DKD type 2, gestational diabetes mellitus, and aging process, inflammatory factors in petrochemical workers, acute necrotizing pancreatitis, and polycystic ovary syndrome. No significant effect was reported on the oxidative status of patients with Rheumatoid Arthritis. So far, several methods have been suggested in order to decrease OS. However, recent studies have introduced probiotic supplements to decrease OS. There are still some controversies about these methods. Therefore, it is recommended that advanced studies should be conducted for a better decision.

Acknowledgment

The authors would like to thank the staff of the Trauma Research Center, Baqiyatallah University of Medical Sciences for their kind cooperation with the researchers of this study.

Authors' Contributions

Concept and design: SM and HRJ; Data gathering: SM, MRG, HG, MF, FS, and HRJ; Data analysis: SM, MRG, HG, MF, FS, and HRJ; preparing draft and confirming of final version: SM, MRG, HG, MF, FS, and HRJ.

Conflict of Interest Disclosures

The authors declare that they have no conflicts interest.

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