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A systematic review and meta-analysis of the probiotics and synbiotics effects on oxidative stress

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ABSTRACT

We performed a comprehensive search of medical bibliographic databases to identify interventional studies reporting the effect of probiotics (or synbiotics) supplementation on biomarkers of oxidative stress. Twenty seven articles that included 1363 subjects (709 cases and 699 controls) were included to our analyses. Oxidative stress parameters levels, including total antioxidant capacity (TAC) (0.31 mmol/L, 95% CI: 0.13–0.50, P < 0.001), glutathione (GSH) (SMD: 0.44 μmol/L, 95% CI: 0.26–0.62, P < 0.001), superoxide dismutase (SOD) (SMD: 0.48 U/mg, 95% CI: 0.16–0.81, P = 0.004) and nitric oxide (NO) (SMD: 0.57 μmol/L, 95% CI: 0.19–0.94, P = 0.003) were higher in probiotics (or synbiotics) group compared to controls. Moreover, malondialdehyde (MDA) (SMD = −0.45 μmol/L, 95%CI = −0.63 to −0.26, P < 0.001) level was lower than controls. Probiotics and synbiotic supplementation improve antioxidant resistance and increase the amount of antioxidant enzymes in the body.

1. Introduction

Oxidative stress has been described as an imbalance between the generations of reactive oxygen species (ROS), and body antioxidant defense systems which has been associated with many non-communicable diseases such as cardiovascular diseases, cancer, and diabetes (Jones, 2006). Free radicals are produced in large quantities as an inevitable by-product of plenty biochemical operations and in some examples, intentionally, such as in activated some immune cells (neutrophils) (Lushchak, 2014). ROS over production could damage the cellular proteins and protein turn over, as well as damage lipids and nucleic acids that cause cellular dysfunction, including lack of energy metabolism, changed cell signaling and cell cycle regulation, DNA and RNA mutations, cellular transportation defect and overall reduced biological functions and immune system performance (Squier, 2001). Past studies have shown that dietary supplements that have antioxidant properties improve antioxidant defense and inhibit oxidative stress and its consequences in cells and tissues that culminate in diseases(Lobo, Patil, Phatak, & Chandra, 2010; White et al., 2014). A systematic review and recent meta-analysis have shown that supplementation with probiotics by altering intestinal and gastrointestinal flora can significantly reduce the NF-kB nuclear factor. The NF-kB factor plays an important role in the expression of inflammatory factors such as INF-gamma and TNF-a, which is effective in inflammation and oxidative stress (Mazidi, Rezaie, Ferns, & Vatanparast, 2017). Probiotics which are defined as live microorganisms prescribed in adequate amounts can has health advantage to their host. The two most usual types of probiotics are *Lactobacilli* and *Bifidobacteria* (Khani et al., 2012). The use of probiotics as substitute biotherapeutics have been effectively indicated in strengthening immune function(Moro-García et al., 2013), decreasing total cholesterol and LDL cholesterol concentration in plasma(Guo et al., 2011) and lowering blood pressure(Khalesi, Sun, Buys, & Jayasinghe, 2014). The effect of supplementation of probiotics on the reduction of oxidative stress and the improvement of antioxidant in-

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dices has been investigated and confirmed in many interventional studies (Asemi, Zare, Shakeri, Sabihi, & Esmaillzadeh, 2013; Badehnoosh et al., 2017; Bahmani et al., 2016; Hajifaraji et al., 2017). A systematic review also examines the effects of probiotic or synbiotic supplementation on oxidative stress indices, and in the end researchers have concluded that more studies are required in this area (Salehi-Abargouei, Ghiasvand, & Hariri, 2017). However, the effect of probiotics and synbiotics on the antioxidant defense ability of the body was not meta-analyzed. The objective of this systematic review and meta-analysis was to systematically review the evidence that probiotics (or synbiotics) can alter oxidative stress parameters compared to placebo in healthy subjects or patients.

2. Methods

We performed a systematic review and meta-analysis using a pre-specified protocol according to the guidelines of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al., 2015).

2.1. Criteria for considering studies for this review

Original studies were included in our analyses if they met the following criteria (1) being a randomized clinical trial (RCT) in either parallel or cross-over design, (2) investigating the effect of probiotics (or synbiotics) (of any form, including capsule, yogurt and kefir) on plasma/serum activities of stress oxidative indices, (3) presentation of sufficient information on activities of stress oxidative parameters at baseline and at the end of intervention in both probiotics (or synbiotics) and control groups. The studies were excluded if: (1) they had a non-experimental (case studies, case series, cross-sectional, case-control, cohort and other retrospective studies) design, (2) they had a quasi-randomized (non-randomized or uncontrolled) design, (3) we were unable to obtain adequate details of study methodology or results, (4) they were presented only as abstracts with no subsequent full report of findings, on-going clinical studies, review papers, letter to editor and editorials, (5) they were without probiotics genus/strains reported or any prebiotics.

2.2. Data sources and study search

Systematic searches of the literature were conducted in the Medline, Embase, Scopus, Web of Science and Cochrane Library up to December 11, 2017 with search terms covering probiotics (or synbiotics) combined with stress oxidative indices, taking into account a wide range of synonyms used for these markers. The search was not restricted by language or year of publication. The search was modified for Web of Science, Embase, Scopus and Cochrane Library using their subject headings instead of the MeSH subject headings. We checked the citation lists of relevant publications, review articles and included studies. We hand searched references of identified selected articles for additional relevant citations. Grey literature was searched as recommended in the current Cochrane Collaboration guidelines, using gray literature databases, and unpublished trials were sought using clinical trials registration databases. Search details are available in Appendix A. The search results of different databases were combined, and duplicates were removed. The search results were reviewed by two independent reviewers (MS and JH) by screening title and abstract, followed by a full text review. Disagreements were settled by discussion or third party opinion (AA).

2.3. Data extraction and quality assessment

Eligible studies were reviewed and the following data were abstracted using a standardized electronic abstraction form, including (1) author's name; (2) year of publication; (3) study location; (4) a clear definition of the study population; (5) baseline characteristics of study participants; (6) probiotics strains, dose, duration of intervention, dosage forms; (7) baseline and endpoint levels of stress oxidative indices. Risk of bias assessment for the included studies were done independently by two reviewers (MS and JH) using criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The assessment included selection bias (method for random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other sources of bias. In addition, sample size calculation and funding declaration associated with each clinical trial were also assessed. Any disagreement was resolved by discussion.

2.4. Statistical analysis

Meta-analysis was conducted using Stata 13.0 software (Stata Corp, College Station, Texas). The effect of probiotics use on oxidative stress parameters was defined as the standardized mean difference (SMD) of oxidative stress parameters changes between the intervention and control groups. A separate random-effect model was constructed for each oxidative stress marker using the DerSimonian–Laird weighting method, which incorporates between-study variability into the calculations. The SDs of the changes of oxidative stress parameters from baseline were calculated using the formula (SD = square root [(SD pre-treatment) 2 + (SD post treatment) 2 − (2R × SD pre-treatment × SD post-treatment)], assuming a correlation coefficient (R) = 0.5), when the studies involved in this meta-analysis did not report them (Berger & Weinstein, 2004; Senn, 1994). Sensitivity analysis, subgroup analysis and meta-regression were also performed. The P-value < 0.05 was considered statistically significant. Additionally, we assessed the probability of publication bias with Begg's funnel plots and Egger's test, with P-value < 0.10 considered representative of statistically significant publication bias. All comparisons were two-tailed, and 95% confidence intervals (CI) were described where applicable.

3. Results

3.1. Literature search

The initial literature search identified 3054 potentially relevant articles: 183 from Pubmed, 1250 from Embase, 741 from Scopus, 502 from Web of Science, 244 from Cochrane Library and 134 from other sources. No unpublished studies were found. 1473 articles were removed due to duplication. By reviewing the title and abstracts of the remaining articles, 1437 studies which were non-relevant to the study objectives were removed. We excluded 95 trials for not reporting relevant data, 5 trials for having experimental design, 4 trials for inappropriate intervention, and 11 trials for not having an RCT design. Eventually, 27 articles that included 1408 subjects (709 cases and 699 controls) were included to our analyses (Fig. 1).

3.2. Summary of study characteristics

Table 1 outlines the main characteristics of all eligible studies. These 27 trials were conducted between 2012 and 2017, of which 14 articles were published after 2015. The trials were conducted in the Iran (23 trials) (Ahmadi et al., 2017; Akbari et al., 2016; Akkasheh et al., 2016; Asemi et al., 2012, 2013; Asemi, Alizadeh, Ahmad, Goli, & Esmaillzadeh, 2016; Asemi, Khorrami-Rad, Alizadeh, Shakeri, & Esmaillzadeh, 2014; Badehnoosh et al., 2017; Bahmani et al., 2016; Ebrahimi-Mameghani, Sanaie, Mahmoodpoor, & Hamishehkar, 2013; Ejtahed et al., 2012; Ekhlasi et al., 2017; Hajifaraji et al., 2017;