

Retracted Evidence and Emerging Insights: A Meta-Analytic Reassessment of the Probiotics Supplementation as an Adjunctive Therapy in Relapsing-Remitting Multiple Sclerosis

Reza Mosaddeghi-Heris^{1*}, Niloufar Pourakbar^{2*}, Niloofar Taheri³, Mahnaz Talebi¹, Sarvin Sanaie^{4*}, Amirreza Naseri^{2,4,5*}

¹Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran

²Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

³Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA

⁴Research Center for Integrative Medicine in Aging, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

⁵Research Center for Evidence-Based Medicine, Iranian EBM Centre: A Joanna Briggs Institute (JBI) Center of Excellence, Tabriz University of Medical Sciences, Tabriz, Iran

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The gut-brain axis has become a crucial area of study in multiple sclerosis (MS) research¹, and dysbiosis in the intestinal microbiota has been linked to the disease through immune modulation, inflammation, and blood-brain barrier integrity.² Theoretically, probiotics, which are live microbial supplements with anti-inflammatory and immunomodulatory effects,³ might help restore microbial balance and reduce MS symptoms. Multiple published systematic reviews shed light on the antidepressive effects of probiotics in MS, in addition to the impacts on the level of disability based on the expanded disability status scale (EDSS)⁴⁻⁶; however, the reliability of evidence in this area has been affected due to recent retraction of one of the included studies, due to concerns about data integrity.⁷ In addition, recently published studies in this field,^{8,9} highlight the need for a prompt re-evaluation of the clinical evidence on the effects of probiotics supplementation on depressive symptoms and level of disability in RRMS patients, which constitutes the objective of the current study.

Randomized placebo-controlled trials assessing the effects of probiotics supplementation on depressive symptoms and/or level of disability in patients with MS, published in English, were eligible for inclusion; therefore, clinical studies with observational designs, animal studies, review articles, single-case studies, non-English papers, and conference abstracts were not included. Risk of bias assessments were performed using the Cochrane risk of

bias tool (RoB2).¹⁰ Quality assessment and data extraction were performed by two independent researchers. Quantitative syntheses were conducted using the means and standard deviations of changes in the scores, extracted or calculated from the pre-post values, using the third version of the Comprehensive Meta-Analysis software (CMA3). Random-effect model analysis was applied to all meta-analyses, considering the clinical variability between the studies regarding the type of probiotics, which might have different effects,¹¹ treatment dose and duration, and eligibility criteria. Statistical heterogeneity was assessed using the I² statistic, with values above 75% considered indicative of considerable heterogeneity. The level of significance was set at <0.05, and pooled effect sizes were reported with 95% confidence intervals (CIs). Standardized mean differences (SMDs) were calculated to allow comparison across studies using different outcome measures. Certainty of evidence is graded based on the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.¹²

Four studies assessed the effects of probiotics supplementation on patients with MS (Table 1). All of the studies were judged as high risk of bias. Regarding the depressive symptoms in relapsing-remitting MS (RRMS) patients, based on the Beck Depression Inventory-II (BDI-II), probiotics supplementation was not associated with significant improvement based on three studies^{8,13,14} (SMD:-2.03; 95%CI: -4.79 to 0.73, *P*=0.15; I²=97.4%).

***Corresponding Author:** Sarvin Sanaie, Email: sarvin_so2000@yahoo.com and Amirreza Naseri, Email: Amirx2eza@gmail.com

^{*}These authors contribute equally as first co-authors.

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Table 1. The characteristics of the studies on the effects of probiotics supplementation on depressive symptoms and disability in patients with multiple sclerosis.

Study	Final sample size	Probiotics supplementation details	Key inclusion criteria	Key exclusion criteria
Naseri et al. 2025 ⁸	60	7-strain + prebiotic (Lactocare®), BID for 4-months	RRMS (2017 MacDonald criteria), EDSS <4	Relapse in the last three months, diagnosed depression
Rahimlou et al. 2022 ¹⁴	65	14-strain (Protexin®), BID for 6-months	RRMS (2005 MacDonald criteria), EDSS ≤4.5	Acute or severe phase, using omega-3 or other antioxidant supplements, history or presence of severe depression
Motlagh Asghari et al. 2023 ⁹	40	Saccharomyces boulardii (BioDigest®), OD for 4-months	RRMS (2010 MacDonald criteria), EDSS ≤4.5	Relapse in the last three months, smoking
Salami et al. 2019 ¹³	48	6-strain (Lactobacilli and Bifidobacteria), OD for 4-months	RRMS (MacDonald criteria), EDSS ≤4.5	Relapse in the last one month

RRMS: relapsing-remitting multiple sclerosis; EDSS: expanded disability status scale

Adding the study using the depression subscale of the General Health Questionnaire (GHQ),⁹ did not affect the significance (SMD: -0.38; 95%CI: -0.24 to 0.99, $P=0.23$; $I^2=97.9\%$). The Meta-analysis focused on disability progression in RRMS patients, based on the EDSS in three studies,^{8,13,14} shed light on the significant benefits (SMD: -3.91; 95%CI: -6.66 to -1.16, $P=0.005$; $I^2=97.6\%$), however, sensitivity analysis with excluding the outlier,¹³ made the results non-significant (SMD: -0.75, 95% CI: -1.61 to 0.11, $P=0.088$; $I^2=81.8\%$). The certainty of evidence for both outcomes was graded as low, considering the high risk of bias and inconsistency.

In addition to the small sample sizes and limited number of the included studies as the main limitations of evidence, the generalizability of the findings is also questionable, as all of the included studies were conducted in Iran. Focusing solely on RRMS also limits the knowledge about progressive forms of MS. In conclusion, while the updated analyses lessen the excitement about the effects of probiotics supplementation on depressive symptoms in patients with RRMS, they still tentatively support the idea of influencing disability, calling for cautious optimism. Contrary to the previously published meta-analyses,^{4,6} non-significant results in our quantitative syntheses represent an example of how invalid data can influence the conclusions of meta-analyses, which are considered the highest level of evidence and may substantially influence the clinical guidelines and practice. In some cases, even the recently published meta-analysis,⁶ cannot be considered current evidence,¹⁵ which sheds light on the need for timely updating the systematic reviews and post-publication evaluation of these studies.

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Authors' Contribution

Conceptualization: Reza Mosaddeghi-Heris, Niloufar Pourakbar, Niloofar Taheri, Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Formal analysis: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Funding acquisition: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Investigation: Reza Mosaddeghi-Heris, Niloufar Pourakbar, Niloofar Taheri
 Methodology: Reza Mosaddeghi-Heris, Niloufar Pourakbar, Niloofar Taheri, Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Project administration: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri

Supervision: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Validation: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Visualization: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri
 Writing–original draft: Reza Mosaddeghi-Heris, Niloufar Pourakbar, Niloofar Taheri
 Writing–review & editing: Mahnaz Talebi, Sarvin Sanaie, Amirreza Naseri

Cometing Interests

None declared.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Ethical Approval

Not applicable.

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