



The effectiveness of a *Lactobacillus* probiotic on measures of psychosocial health in adults diagnosed with subthreshold depression: a double-blind, randomised, placebo-controlled trial

G. Moschonis¹, K. Sarapis¹, S. Resciniti¹, R. Hall¹, K. Yim¹, M. Tonkovic¹, C. Fitzgerald¹, F. Anixiadis¹, Q. Nhu Dinh², M. Hale³, B. Wright³, M. Pane⁴, C.J. Tuck⁵ and J.R. Biesiekierski^{1,6}

¹Department of Food, Nutrition and Dietetics, La Trobe University, Melbourne, 3086, Australia

²Department of Microbiology, Anatomy, Physiology & Pharmacology, La Trobe University, Melbourne, 3086, Australia

³Department of Psychology, Counselling and Therapy, La Trobe University, Melbourne, 3086, Australia

⁴Probiotal Research, Novara, 28100, Italy

⁵Department of Nursing and Allied Health, Swinburne University, Hawthorn, 3122, Australia

⁶Department of Nutrition, Dietetics and Food, Monash University, Melbourne, 3168, Australia

Depression is the leading cause of disability worldwide⁽¹⁾. The microbiota-gut-brain axis may play a role in the aetiology of depression, and probiotics show promise for improving mood and depressive state⁽²⁾. Further evidence is required to support mechanisms and in high-risk populations, such as those with sub-threshold depression (which may be 2-3 times more prevalent than diagnosed depression)⁽³⁾. The aims were to assess the efficacy of a probiotic compared with placebo in reducing the severity of depressive symptoms in participants with subthreshold depression, and to investigate potential mechanistic markers of inflammatory, antioxidant status and stress response. A double-blind, randomised, placebo-controlled trial was conducted in participants meeting diagnosis of subthreshold depression (DSM-5); aged 18-65 years; ≥ 18.5 kg/m² body mass index; not taking antidepressants, centrally acting medications, probiotics nor antibiotics for at least 6 weeks. The probiotic (4×10^9 AFU/CFU, 2.5 g freeze-dried powder containing *Lactobacillus fermentum* LF16 (DSM26956), *L. rhamnosus* LR06 (DSM21981), *L. plantarum* LP01 (LMG P-21021), *Bifidobacterium longum* BL04 (DSM 23233)) or placebo was taken daily for 3-months. Data was collected at 3 study visits (pre-, mid- (6 weeks), post-intervention). Self-reported questionnaires measured psychological symptoms (Beck Depression Inventory, BDI; Hospital Anxiety Depression Scale, HADS) and quality of life. Blood and salivary samples were collected for biomarkers including cortisol awakening response (CAR). General linear models examined within-group and between-group differences across all time points. Thirty-nine participants completed the study (n = 19 probiotic; n = 20 placebo) using intention-to-treat analysis. The probiotic group decreased in BDI score by -6.5 (95% CI $-12.3; -0.7$) and -7.6 (95% CI $-13.4; -1.8$) at 6 and 12 weeks, respectively. The HADS-A score decreased in the probiotic group by -2.8 (95% CI $-5.2; -0.4$) and -2.7 (95% CI $-5.1; -0.3$) at 6 and 12 weeks, respectively. The HADS-D score decreased in the probiotic group by -3.0 (95% CI $-5.4; -0.7$) and -2.5 ($-4.9; -0.2$) at 6 and 12 weeks of intervention, respectively. No between group differences were found. There were no changes in perceived stress or quality of life scores. The probiotic group had reduced hs-CRP levels (7286.2 ± 1205.8 ng/dL vs. 5976.4 ± 1408.3 ; $P = 0.003$) and increased total glutathione (14.2 ± 8.9 ng/dL vs. 9.3 ± 4.7 ; $P = 0.049$) compared to placebo, post intervention. Lower levels of CAR were found in the probiotic compared to placebo (-0.04 ± 0.17 μ g/dL vs. 0.16 ± 0.25 ; $P = 0.009$). A significant reduction in depressive symptoms and anxiety was observed within the probiotic group only. These results were supported by improvements observed in biomarkers, suggesting probiotics may improve psychological wellbeing in adults experiencing sub-threshold depression, by potential pathways involved in central nervous system homeostasis and inflammation. Future analyses are required to understand changes within the intestinal microbiota and to clarify how their metabolites facilitate emotional processing.

Keywords: probiotics; depression; anxiety; *Lactobacillus*

Ethics Declaration

Yes

Financial Support

This work was supported by Probiotal Spa; and Biome Australia Trading Pty Ltd.

References

1. WHO (2017) Depression and other common mental disorders: Global health estimates. <http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf?ua=1>
2. Goh KK, Liu YW, Kuo PH *et al.* (2019) *Psychiatry Research* **282**, 112568.
3. Marotta A, Sarno E, Del Casale A *et al.* (2019) *Front Psychiatry* **10**, 164.