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Effect of Probiotic Supplementation on Cognitive Function and Gut-Brain Axis Modulation in Females with Mild Depression.

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Faculty of Medicine, Cairo University Postgraduate Research Protocol

(Please read carefully provided guidance documents for a comprehensive understanding and proper formulation of your thesis protocol and required forms)

1. Study

a- Proposed Study Title: Effect of Probiotic Supplementation on Cognitive Function and Gut-Brain Axis Modulation in Females with Mild Depression.
b- Degree: MD of family medicine
c- Date of Registration of MSc or MD: October 2025

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4. **Scientific committee approval**
(Was it scientifically approved by the department?) Yes

Date of approval: 2/3/2026

5. **Background and Rationale:** (Describe the research question and justification for undertaking the study explaining the aspects of novelty in the study)

Depression poses a significant global public health challenge. It is widely recognized as one of the leading causes of disability worldwide, and projections suggest that it may become the first leading contributor to the global burden of disease by 2030. Women are reported to be 2-3 times more likely than men to develop depression. The prevalence of depression tends to increase with age, reaching its highest levels among individuals aged 50–59 years. **(Christl et al., 2025)**

Emerging evidence suggests a bidirectional relationship between depression and cognitive impairment, as both conditions appear to share several underlying pathophysiological mechanisms. Therefore, screening for cognitive impairment in individuals with depression may help identify those at increased risk of progression to dementia and assist in guiding clinical management and follow-up. **(Federman et al., 2024)**

There has been increasing interest in the role of the gut microbiome in mental health, particularly in relation to cognition and depression through the gut–brain axis. This bidirectional communication occurs through several pathways, including the vagal nerve, microbial metabolites, neurotransmitter production, and immune interactions. **(Rathore et al., 2025)**

Dysbiosis of the gut microbiota may contribute to the development of an inflammatory state, impaired neurogenesis, and increased vulnerability to the onset and progression of mental disorders. Therefore, targeting the gut microbiota may represent a promising approach for the prevention and treatment of mental disorders. **(Xiong et al., 2023)**

Notably, the microbial ecosystem is dynamic, it undergoes substantial remodeling across the lifespan. Both advancing age and hormonal fluctuations particularly those occurring during the menopausal transition have been shown to alter microbial composition and diversity. **(Aznou et al., 2025)**

Probiotics modulate the gut-brain axis through neurotransmitter production, modulation of inflammation, and enhancement of vagal tone and intestinal barrier integrity. However, the variability in outcomes suggests that not all Lactobacillus strains exert the

same effects, underscoring the need for more targeted and systematic investigations. Employing probiotics of this genus as a therapeutic intervention in mental health raises several questions that must be addressed**. (Fernández-Rodríguez et al., 2025)**

Although, several studies have explored the role of probiotics in improving cognitive function in depressive patient, results and mechanisms remain inconsistent.

For instance, a randomized double-blind trial investigating Lactobacillus plantarum in patients with major depressive disorder reported no significant improvement in depressive symptoms and no significant changes in inflammatory markers, including high sensitivity C-reactive protein (hs-CRP). Moreover, participants were receiving concurrent antidepressant therapy, which may have masked the independent effects of probiotic supplementation. **(Lin et al., 2024)**

A study found that after 8 weeks, patients with major depressive disorder receiving selective serotonin reuptake inhibitor (SSRI) treatment showed improvements in attention, processing speed, and verbal learning and memory in the probiotic intervention group. Nevertheless, no significant changes were observed in other tests of processing speed or executive functions, nor were there significant improvements in depressive symptoms or hs-CRP levels**. (Rudzki et al., 2019)**

Moreover, a meta-analysis on multi species probiotic supplementation in patients with depression receiving treatment reported moderate improvements in some cognitive domains but negligible effects on depressive symptoms. Future studies should explore the mechanisms of specific probiotic strains to enable the development of more targeted and effective interventions. It should also be noted that the use of a fixed-effects model, despite potential heterogeneity in diagnostic tools, dosages, and intervention durations, may affect the interpretation of pooled results. **(He et al., 2023)**

Current evidence on Lactobacillus plantarum suggests improvement in local gut inflammatory markers, such as reduced fecal calprotectin. However, most clinical trials report no significant reduction in hs-CRP, indicating a lack of consistent effect on systemic inflammation. These inconsistent findings prevent definitive conclusions regarding its role in modulating hs-CRP and highlight the need for further well-designed, adequately powered studies. **(Lazou-Ahrén et al., 2024)**

Although, the gut microbiome is linked to the function of the vagal nerve, data on the link between vagal nerve function and gut microbiota in humans are limited.

A study was conducted demonstrating that a multi-species probiotic supplement can significantly influence vagal nerve (VN) function and gut microbiome composition in

patients with major depression indicating that adding probiotics to standard therapy may help restore microbiota balance, enhance VN function, and improve sleep quality, although sustained long-term use may be necessary. The authors highlighted the need for further research to investigate the effects of targeted psychobiotics on VN function in psychiatric disorders and how these effects evolve over time**. (Mörkl et al., 2025)**

Addressing these research gaps is essential to advance our understanding of the specific effects of individual species within the genus, as well as the mechanisms underlying these effects in response to different interventions, as well as to there is an urgent need to develop innovative and more efficacious therapeutic strategies capable of simultaneously targeting the emotional and cognitive facets of depression.

Therefore, this triple-blind, randomized placebo-controlled trial aims to assess the efficacy of a 12-week probiotic intervention on cognitive function, depressive symptoms, and gut-brain axis related parameters in Egyptian women aged 50-64 years with mild depressive symptoms. By integrating validated psychological assessments with objective measures of systemic inflammation (hs-CRP) and ANS function (smartphone-based HRV).

- Study question:
  In Egyptian women aged 50–64 years, does 12-week single strain probiotic supplementation compared with placebo improve cognitive function and depressive symptoms through modulation of the gut–brain axis?

- Study hypothesis:

  We hypothesize that 12-week supplementation with a single strain probiotic will be superior to placebo in:
  (1) improving cognitive function (measured by MoCA-B) (2) reducing depressive symptom severity (measured by BDI-II), (3) reducing systemic inflammation (measured by hs-CRP), and (4) enhancing autonomic function (measured by HRV) in Egyptian women aged 50-64 years with mild depressive symptoms.

6. Objectives: (describe specific objectives or hypotheses behind the study)

Primary Objectives:

- To evaluate the effect of a 12-week daily probiotic supplementation on cognitive function, as measured by the change in Montreal Cognitive Assessment – Basic (MoCA-B) total score.
- To evaluate the effect of a 12-week daily probiotic supplementation on the severity of depressive symptoms, as measured by the change in Beck Depression Inventory-II (BDI-II) total score.

Secondary Objectives:

- To assess the effect of a 12-week daily probiotic single strain supplementation on autonomic nervous system function, measured by changes in Heart Rate Variability (HRV) parameter (obtained via the Welltory smartphone application).
- To measure the effect on systemic inflammation via change in serum high-sensitivity C-reactive protein (hs-CRP) level.

7. Study Design:

A- Nature of the study

- Prospective study ■
- Retrospective study □

B- Design of the study: (Please insert √ in front of the suitable design)

1-	Case series	
2-	Qualitative	
3-	Survey	
4-	Cross sectional analytic	
5-	Case-control	
6-	Cohort (Longitudinal)	
7-	Randomized Clinical Trial	
8-	Non-randomized clinical trial	
9-	Animal study	
10-	Cellular study	

- **Other study design:** ■

  Please describe: A Triple-Blind, Randomized, Placebo-Controlled Trial

8. Study Methods

- **Population of study:**

  The study population will consist of 80 eligible Egyptian women aged 50–64 years with mild depressive symptoms, recruited from the Family Medicine outpatient clinics, who will meet the inclusion criteria and provide written informed consent. They will be randomly assigned in a 1:1 ratio to either the probiotic intervention group or the placebo control group (40 participants per group).

- **Study location:** (Please provide where the study will be conducted and from where study participants will be recruited)

  Family Medicine outpatient clinics at Kasr- Alainy teaching hospitals

- **Inclusion criteria:**

  -Females, aged 50-64 years
  -Presence of mild depressive symptoms, defined as a Beck Depression inventory II (BDI-II) total score between 14 and 19 (inclusive) at the screening visit.
  -Ability to give informed consent

- **Exclusion criteria:**

  -Moderate and severe depression (BDI-II score > 19) or active suicidal ideation (assessed by clinical interview).
  -Diagnosis of bipolar disorder, schizophrenia, or other major psychotic disorder.
  Current use of antidepressants, antipsychotics, mood stabilizers, or regular anxiolytics
  -Regular consumption of probiotics, prebiotics, or synbiotic supplements within the past 4 weeks.
  -Use of antibiotics or antifungals within the past 4weeks.
  -Known diagnosis of inflammatory bowel disease, celiac disease, or active irritable bowel syndrome with severe symptoms.
  -History of significant cardiovascular disease (e.g., atrial fibrillation, heart failure, recent MI), uncontrolled hypertension, or type 1 diabetes.
  -Current use of systemic hormone replacement therapy within the last 3 months.

-Known allergy to any component of the probiotic or placebo.
-Severe systemic illness (e.g., uncontrolled diabetes, malignancy, severe hepatic, renal disease or auto-immune diseases).
-CRP more than 10

- **Methodology in details:**
  - Participants will be recruited from the Family Medicine outpatient clinics at Kasr Al-Ainy Faculty of Medicine, Cairo University. Potential candidates will be identified during routine clinic visits.

  - Initial Screening Visit:

All potential participants will undergo a comprehensive screening evaluation conducted by the researcher to determine eligibility. The screening process will be structured as follows:

Step 1: Medical, Psychological, and Gynecological History Taking

A thorough medical history will be obtained, including chronic illnesses, past surgical procedures, and psychiatric history.

Step 2: Medication and Supplement Review

A detailed review of current and recent (past 4 weeks) medication use will be conducted, with particular attention to:
Antidepressants, antipsychotics, mood stabilizers, and anxiolytics.
Hormone replacement therapy (systemic).
Antibiotics or antifungals.
Probiotic, prebiotic, or synbiotic supplements.
Any use of these agents will be documented, and participants will be excluded if they meet the exclusion criteria related to medication/supplement use.

Step 3: Depression Symptom Assessment

Depressive symptoms will be assessed using the validated Arabic version of the Beck Depression Inventory-II (BDI-II) **(Ghareeb, 2000).**
A self-administered questionnaire consisting of 21 items, each rated on a 4-point scale from 0 to 3. The items assess cognitive, affective, and somatic symptoms of depression experienced over the past two weeks.

Total scores range from 0 to 63, with higher scores reflecting more severe depressive symptoms. The following cutoffs are applied:

· 0–13: Minimal depression
· 14–19: Mild depression
· 20–28: Moderate depression
· 29–63: Severe depression

Participants scoring between 14 and 19 (inclusive) on the BDI-II will be considered eligible, corresponding to mild depressive symptoms. Those scoring below 14 or above 19 will be excluded and, if appropriate, referred for further clinical evaluation.

- Step 4: Eligibility Confirmation and Enrollment

  Individuals who meet all inclusion criteria will be fully informed about the study.

  Written informed consent will be obtained from all eligible participants prior to any study-specific procedures.

  Consented participants will then proceed to the baseline assessment visit (Week 0).

  -Step5: we will inform all the patients about their condition, explain it clearly, and discuss the management plan. All patients will be advised to contact us immediately if any warning signs occur (suicidal thoughts, worsening of symptoms, psychotic features like hallucinations or delusions)

- Baseline Assessment visit (Week 0)

At baseline, all enrolled participants will undergo comprehensive assessment including:

1. Collection of socio-demographic data using updated Socio-demographic status (SES) scale:

Detailed data was assessed according to the scale developed by **Fahmy et al., (2015)**, which measured different domains includes (education and cultural domain, family, economic and occupational domain) with a total score of 48. A score was assigned for each item and the total score was calculated and the socioeconomic level was classified into low, medium and high levels depending on the quartiles of the score calculated, which is low < 40, middle 40-70 and high ≥ 70.

2. Anthropometric measurements (weight, height, BMI)

3. Cognitive function

The Montreal Cognitive Assessment – Basic, Arabic version (MoCA-B-A) is a culturally adapted and validated screening tool for detecting mild and major neurocognitive disorders among Arabic-speaking populations, including illiterate and low-educated individuals. It preserves the multidomain structure of the original MoCA while replacing literacy-dependent items with culturally appropriate non-verbal tasks. The total score ranges from 0 to 30, with higher scores indicating better cognitive function. Validation studies in Egypt demonstrated excellent reliability (Cronbach's alpha ≈ 0.91) and strong diagnostic accuracy. For identifying mild neurocognitive disorder, a cut-off of 21/22 achieved sensitivity of 92.5% and specificity of 98.2%, while a cut-off of 16/17 was optimal for detecting major neurocognitive disorder (dementia), with sensitivity of 90.7% and specificity of 97.4%. These findings support the use of MoCA-B-A as a reliable tool in both clinical and research settings. (**Saleh et al., 2019**).

4. HRV Measurement Methodology Camera-Based

- Position:

Measurements will be performed after a 10-minute resting period in the sitting position.

- Device:

HRV will be measured using a smartphone-based photoplethysmography application (Welltory), operated by the assessor.

- Duration:

Short-term HRV recording will be conducted over a 5-minute period.

- Environment:

Measurements will be carried out in a quiet, temperature-controlled room, and all assessments will be performed at the same time of day.

HRV has demonstrated good validity and reliability in reflecting autonomic nervous system regulation **(Moya-Ramon et al., 2022)**

- Reduced HRV has been consistently associated with depressive symptoms and psychological stress

5- Collection of venous blood samples for measurement of high sensitivity C-reactive protein(hs-CRP)

- Measurement: enzyme-linked immunosorbent assay (ELISA)
- Sample: venous blood (8-12 hour fast)
- Units: mg/L
- Categories: Low risk (<1.0), Average risk (1.0-3.0), High risk (>3.0)

6. Randomization, Allocation and Blinding

Participants will be randomly allocated in a 1:1 ratio to the probiotic or placebo group.

A computer-generated random allocation sequence will be created using a permuted block design with variable block sizes of 4 and 6 (http://www.randomization.com/)

The envelope containing code will be kept exclusively by an independent research assistant (a colleague from the Family Medicine Department) who is not involved in participant recruitment, intervention administration, outcome assessment, or data analysis.

Blinding:

This study employs a triple-blind design:
-Participant blinding: Both the probiotic and placebo capsules are identical in appearance, size, color, and packaging. Participants will remain unaware of their group assignment throughout the study.
-Assessor blinding: involving in screening, administering questionnaires (BDI-II, MoCA-B, etc.), and measuring outcomes (HRV, hs-CRP) will be blinded to group allocation.
-Statistician blinding: The dataset provided to the statistician for final analysis will be coded (Group A vs. Group B), with the code key held securely by the assistant researcher until the analysis is complete.

Emergency unblinding

Emergency unblinding will be permitted only in the case of a serious adverse event where knowledge of the treatment assignment is essential for participant management. The assessor will document the reason for unblinding, and the participant will be withdrawn from further study participation if unblinding occurs.

- Intervention Phase (Weeks 1-12)

The pharmacist will prepare the study capsules by dividing them into two groups, labeled A and B. Each box contained only capsules corresponding to its assigned group. Participants were provided with the box matching their group allocation (i.e., participants in group A received box A). Prior to distribution, all boxes were verified by the study team to ensure that they

contained the correct capsules, maintaining blinding and ensuring accurate delivery of the intervention.

All participants will receive one capsule daily, taken orally in the morning with breakfast for 12 weeks

All participants will be advised to maintain their usual diet and lifestyle and to avoid initiating new supplements or medications during the study period,
Adherence will be monitored through weekly follow-up what's app messages ,and monthly capsule count at visits

- Post-Intervention Assessment (Week 12)

  At the end of the intervention period, participants will undergo repeat assessments identical to baseline:
  MoCA-B ,BDI-II
  HRV measurement under standardized resting
  Fasting blood sample collection for hs-CRP

- **Intervention:**

  ■ Therapeutic intervention (please describe):

  The probiotic capsules will consist of single-strain containing Lactobacillus plantarum. Each capsule provides approximately 10 billion colony-forming units (CFU) per capsule, sold in Egyptian markets under brand name Lactogemikan, manufactured by Pescado Pharmaceuticals, Cairo, Egypt, registered with the Egyptian Drug Authority (EDA).

  The placebo capsules, identical in appearance, size, color, and packaging, will contain only inert excipients (starch) and will be manufactured by faculty of pharmacy, Cairo University.

  Participants would be instructed to follow the plan for 12 weeks and to report any dietary changes or adverse effects.

- **Does the research involve?**

  ■ Human participants

Biological samples/Tissues

☐ Identifiable private data/Information

- **Type of consent of study participants:**

■ Written consent

☐ No consent needed (Please justify)

- **Potential risks:**
(Please mention all risks involved even mild ones as pain, discomfort, chance of infection or psychological effects)

1- Time consuming during interview.

2- Discomfort.

3- blood sampling risks

4- rare allergic reactions

- **Confidentiality of data:**

-All personal identifiable data of the patients will be coded by the researcher.
-The only copy of the records will be with the researcher and kept in a safe place.
-The records will be used only for research purposes.

9- Study outcomes:

- **Primary outcomes** (Most important measurable outcomes)

- Change in cognitive function from baseline to week 12, as measured by MoCA-B total score.

-Change in depressive symptom severity from baseline to week 12, as measured by the BDI-II total score.

- **Secondary outcome parameters** (other outcomes to be assessed)

- Change in serum high sensitivity C-reactive protein (hs-CRP) concentration from baseline to week 12.
- Change in heart rate variability (HRV) from baseline to week 12

10- Sample size and technique (number of study subjects included and justification including the clinical and statistical assumptions supporting sample size calculation)

Sample size was calculated by G*power software V3.1.9.6

In a previous study by **Fei Y et al. (2023)**, The mean ± SD change (mean difference from baseline) in MoCA score at 12 weeks was 2.25 ± 2.82 in the probiotic group., compared to 0.30 ± 2.27 in the placebo group. Based on these findings, and assuming a statistical power of 95%, ratio of 1:1 and a significance level of 5%, the estimated sample size required for the present study is **80 participants**, with **40 participants allocated to each group. A**counting for 10% drop out rate, the final required sample size is 88 participants (44 participants per group) to detect a similar statistically significant difference between the two randomized groups.

11- Statistical analysis (Please describe your data analysis plan)

Organization, tabulation, presentation and analysis of data will be performed using SPSS, version 20. Numerical data will present as Mean and Standard deviation (SD) or Median and Interquartile range (IQR). Student t-test and other parametric tests will be used for statistical analysis. Non parametric tests may also be used for statistical analysis if required. Categorical data will be presented as numbers and percentages and the chi-squared test will be used for statistical analysis .The level of significance adopted for this study is $P < 0.05$.

12- Source of funding: (Please include source of funding even if self funding)

- Faculty of Medicine, Cairo Univer ☐
- Other sources ■

Please specify: Probiotic capsules and laboratory investigation→ self-funded

Placebo capsules → Cairo University

13- Time plan:

- When to start (**the start date should be after getting REC approval**)? After protocol approval

- When expected to finish? After one year

- When to publish? One month is required for writing and another one month for publishing

14- References:

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