Bulletin of Pharmacy Practice
Content Available at www.lapinpress.com ISSN (O): 3139-9444
(An online peer reviewed Referred Journal)
Research Article
OPEN ACCESS

# EVALUATE THE EFFECTIVENESS OF PROBIOTICS AS AN ADJUNCT THERAPY IN REDUCING DEPRESSIVE AND ANXIETY SYMPTOMS IN PATIENTS DIAGNOSED WITH DEPRESSION USING A RANDOMISED CONTROLLED TRIAL DESIGN

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**Article History:** Received: 11 Sep 2026, Revised: 27 Oct 2026, Accepted: 18 Nov 2026

**Abstract: Background:** Depression, also known as Major Depressive Disorder (MDD), is a common and serious mental health condition characterised by persistent feelings of sadness, loss of interest, and a decline in emotional and physical functioning. **Aim and objectives:** To evaluate the effectiveness of probiotics as an adjunct therapy in reducing depressive and anxiety symptoms in patients diagnosed with depression using a randomised controlled trial design. To assess the effect of probiotic supplementation on the severity of anxiety symptoms compared to standard treatment alone. **Methodology:** A prospective, Randomized, Controlled, interventional. Patient diagnosed with depression with or without anxiety symptoms, attending the psychiatry department. **Results:** A total of 120 patients were included in the study. The study population was divided into two major groups. Age-wise distribution indicates that middle-aged adults (31-50 years) constitute the largest affected group, accounting for more than 40% of cases. A notable proportion of elderly patients (<60 years) also suggests increased vulnerability in later life. Younger age groups (<20 years) showed comparatively lower prevalence. **Discussion:** Most cases were observed in the 30-60 years age group, indicating that psychiatric disorders such as anxiety and depression are more common in middle - aged adults. **Conclusion:** Overall, the results of the study suggest that probiotics can serve as a beneficial adjunct therapy in the treatment of both anxiety and depression. The addition of probiotics to conventional pharmacological treatment may enhance therapeutic effectiveness and accelerate symptom improvement.

***Keywords:*** *Major Depressive Disorder, anxiety disorders, probiotics.*

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## 1. INTRODUCTION

**Definition:** Depression, also known as Major Depressive Disorder (MDD), is a common and serious mental health condition characterised by persistent feelings of sadness, loss of interest, and a decline in emotional and physical functioning. Depression is a multifactorial mood disorder involving dysregulation of neurotransmitters (such as serotonin, norepinephrine, and dopamine) and characterised by long-lasting emotional distress, cognitive impairment, and functional decline [1-2].

**Epidemiology**

**Global prevalence**

- According to the World Health Organisation (WHO):
- Around 280-300 million people globally suffer from depression.
- It affects approximately 3.5% to 5% of the global population.
- Depression is a leading cause of disability worldwide and a major contributor to years lived with disability (YLDs) [3].

**Incidence**

- Annual incidence rates range from 2% to7%, depending on the population and region.
- Higher incidence is observed in:
- Urban populations
- Individuals with chronic illnesses.
- People are exposed to psychosocial stress [4-5].

**Age – wise Distribution**

Most commonly affects individuals aged 18-44 years.

- Increasing prevalence in:
- Adolescents (due to social, academic, and digital stressors)
- Elderly population (due to isolation, comorbidities).

**Gender -wise Distribution**

- Depression is more common in females than in males:
- Females: Males ratio 2:1
- Reasons include: Hormonal fluctuations, Psychosocial stressors, Greater reporting and diagnosis in females.

**Geographical Variation**

- Higher prevalence in:
- Low – and middle – income countries (LMICs)
- Conflict – affected regions

**In India:**

- Estimated prevalence:4%-5%
- Lifetime prevalence:5%-15%
- Rapid urbanisation and socioeconomic stress contribute significantly [6-9].

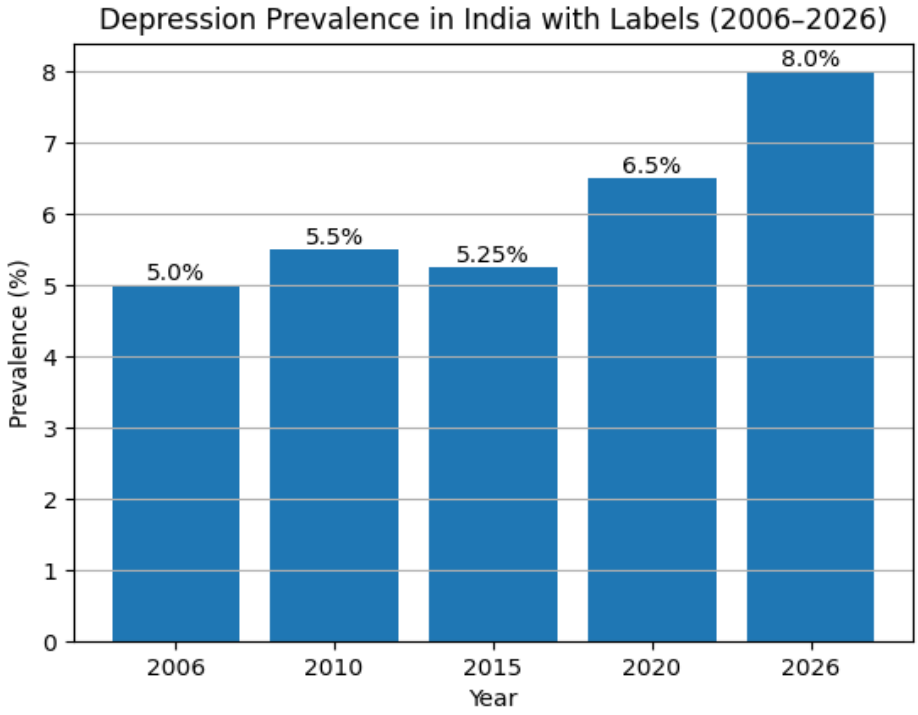



Figure 01: Depression prevalence in India

**TYPES**

1. **Major Depressive Disorder (MDD):** A mood disorder characterised by persistent depressed mood or loss of interest, lasting for at least 2 weeks, along with cognitive and physical symptoms.
   **Explanation:** patients experience sadness, anhedonia, fatigue, sleep and sometimes suicidal thoughts. Symptoms significantly impair daily functioning [10].
2. **Persistent Depressive Disorder (Dysthymia**): A chronic form of depression with milder symptoms lasting at least 2 years (1 year in children/adolescents).
   **Explanation:** though symptoms are less severe than MDD, they are long- lasting and include low mood, low self-esteem, hopelessness, and reduced energy, leading to long-term functional impairment [11].
3. **Bipolar Depression (Depressive episodes in bipolar disorder):** A depression episode occurring as part of bipolar disorder, where periods of depression alternate with mania or hypomania.
   **Explanation:** depressive symptoms resemble MDD but occur in an individual with a history of manic/hypomanic episodes. Proper diagnosis is crucial as antidepressants alone may worsen the illness.
4. **Seasonal affective disorder (SAD):** A type of depression that occurs seasonally, most commonly during winter months, and remits in spring or summer [12].
   **Explanation:** reduced sunlight affects circadian rhythm, melatonin, and serotonin levels, leading to symptoms such as low mood, hypersomnia, increased appetite, and weight gain.

5. **Postpartum (postnatal) Depression**: A depressive disorder that develops within weeks to months after childbirth.
   **Explanation:** It is associated with hormonal changes, emotional stress, and sleep deprivation. Symptoms include sadness, anxiety, guilt, poor bonding with the baby, and, in severe cases, suicidal thoughts.
6. **Premenstrual Dysphoric Disorder (PMDD):** A severe mood disorder related to the menstrual cycle, occurring during the luteal phase and resolving after menstruation.
   **Explanation:** symptoms include marked irritability, depression, anxiety, and functional impairment, which are significantly more severe than premenstrual syndrome (PMS).
7. **Atypical Depression:** A subtype of depression characterised by mood reactivity and reversed vegetative symptoms.
   **Explanation:** patients show improvement in mood, positive events, increased sleep, increased appetite, weight gain, leaden paralysis, and sensitivity to rejection.
8. **Melancholic Depression (major depressive episode with melancholic features):** A severe subtype of major depressive disorder marked by loss of pleasure and lack of mood reactivity.
   **Explanation:** Features included early- morning awakening, psychomotor retardation or agitation, significant weight loss, excessive guilt, and profound anhedonia.
9. **Psychotic Depression (major depressive disorder with psychotic features):** A major depressive episode accompanied by psychotic symptoms such as delusions or hallucinations.
   **Explanation:** psychotic features are often mood–congruent (e.g., guilt, nihilism, poverty). This is a severe condition requiring urgent treatment.
10. **Catatonic Depression:** A form of depression associated with catatonic features, involving marked psychomotor disturbance.
    **Explanation:** Patients may exhibit stupor, mutism, rigidity, negativism, posturing, or excessive purposeless activity. It is a medical emergency if untreated [13-16].

## ROLE OF PROBIOTICS IN GUT-BRAIN-MICROBIOTA

Probiotics influence brain activity in depression and anxiety by restoring the balance of gut microbiota and strengthening gut barrier integrity. A healthy gut microbiome enhances the production of key neurotransmitters such as serotonin, GABA, and dopamine, which are essential for mood regulation and stress control. At the same time, probiotics reduce gut permeability and lower the release of proinflammatory cytokines like **IL-6, TNF-ALPHA**, and CRP, thereby decreasing systemic and neuroinflammation. Through modulation of gut – brain – microbiota communication pathway, including the Vagus nerve, immune system, and the **hypothalamic- pituitary – adrenal (HPA)axis**, probiotics help regulate stress hormone levels such as cortisol. These combined effects lead to improved brain function, enhanced neuroplasticity, and better emotional regulation, ultimately resulting in a reduction in symptoms of depression and anxiety [17].

In addition, probiotics support the synthesis of **short-chain fatty acids (SCFAs)** such as butyrate, propionate, and acetate, which play an important role in maintaining intestinal health and influencing brain signalling. These metabolites help reduce oxidative stress and protect neurons from damage. Probiotics also improve gut barrier function, preventing harmful toxins and pathogens from entering the bloodstream and affecting brain health [18-19]. Certain probiotic strains, such as ***Lactobacillus* and *Bifidobacterium***, are known to produce neuroactive compounds that positively affect mood and cognitive function [201-21]. Furthermore, probiotics help maintain microbial diversity in the gut, which is associated with better mental resilience and emotional stability [22]. By regulating immune responses and reducing chronic inflammation, probiotics contribute to improved psychological well-being. These combined effects lead to improved brain function, enhanced neuroplasticity, and better emotional regulation, ultimately resulting in a reduction in symptoms of depression and anxiety [23-26].

## AIM AND OBJECTIVES

**Aim:** To evaluate the effectiveness of probiotics as an adjunct therapy in reducing depressive and anxiety symptoms in patients diagnosed with depression using a randomised controlled trial design.

**Objectives**

- To assess the effect of probiotic supplementation on the severity of anxiety symptoms compared to standard treatment alone.
- To assess the effect of probiotic supplementation on the severity of depression symptoms compared to standard treatment.
- To compare the overall clinical improvement between the probiotic group and the control group.
- To evaluate the safety and tolerability of probiotics when used as an adjunct to antidepressant therapy.
- To assess the changes in quality-of-life following probiotic supplementation.
- To determine the time to symptomatic improvement in both study groups.
- To explore the role of the gut-brain axis in modulating depressive and anxious symptomatology.

- To assess patient treatment adherence and acceptability of probiotic therapy.
- To compare the change in inflammatory markers between the probiotic and control groups.
- To evaluate the effect of probiotics on sleep quality in patients with depression and anxiety.
- To assess the impact of probiotic therapy on cognitive functions such as concentration and memory.
- To determine the influence of probiotics on stress levels as measured by validated stress scales.
- To assess the rate of depressive and anxiety symptoms during the follow-up period.

## METHODOLOGY

**Study Design:** A prospective, Randomized, Controlled, open-label or (double-blind) interventional.

**Study Site:** The study will be conducted in the psychiatry department of a tertiary care teaching hospital during the academic year 2025-2026.

**Study Duration:**

- Study Duration; 6 Months
- Recruitment Period 3 Months
- Intervention and follow-up period 4-8 weeks for participant

**Study Population:** Patient diagnosed with depression with or without anxiety symptoms, attending the psychiatry department

**Sample Size**

- A total of 120 patients will be enrolled and randomly allocated into 2 groups
- Group A (intervention group): 60 patients
- Group B (control group): 60 patients

**Inclusion Criteria**

- Patients aged 15-65 years and above
- Diagnosed with depressive disorder (with or without anxiety)
- Patients receiving stable antidepressant therapy
- Willing to provide written informed consent

**Exclusion Criteria**

- Patients with severe psychiatric illness, e.g., bipolar disorder, schizophrenia
- Patients currently using probiotics or antibiotics
- Patients with gastrointestinal disorders or immunocompromised state
- Pregnant and lactating women
- Patients with substance abuse disorders

**STUDY GROUPS:**

**Group A (INTERVENTION GROUP):** Patients will receive standard antidepressants / anxiolytic therapy plus probiotic supplementation.

**Group B (control Group):** Patients will receive antidepressants / anxiolytic therapy alone

**Methods**

**Study design and site:** This prospective observational, Randomized control study was conducted in a government hospital after obtaining approval from the institutional Ethical Committee (SLVP 2025-2026), Sri Lakshmi Venkateshwara Institute of Pharmaceutical Sciences.

**Study population & consent form preparation:** The total population of this study is 120 patients. A structured informed consent from was prepared in accordance with ethical guidelines. The form included details about the objectives, procedures, confidentiality, and voluntary participation. It was explained to patients in simple language before obtaining their consent.

**Preparation of Assessment Scales:** Standard clinical scales, namely the **Beck Depression Inventory (BDI)** and the **Hamilton Anxiety Rating Scale (HAM-A),** were prepared and used to assess the severity of depression and anxiety among patients.

**Counselling procedure:** Based on the assessment score obtained from BDI and HAM-A scale, appropriate counselling was provided to patients. Counselling focused on improving mental well- being, reducing symptoms, and promoting adherence to treatment.

## RESULTS

The present study, titled "**Randomised control trial probiotics as an Adjunct Therapy to Depression and Anxious Symptomatology",** was conducted to evaluate the therapeutic effect of probiotics when used along with standard pharmacological treatment in patients with depression and anxiety. A total of 120 patients were included in the study. The study population was divided into two major groups:

The study population was divided into two major groups:

- **Anxiety patients – 60**

- **Depression – 60**

Each group was further categorised into two treatment groups:

1. **Single therapy (without probiotics), 30 patients.**
2. **Combination therapy (pharmacological treatment + probiotics) 30 patients.**

Patients were assessed at two different time points:

- **First visit (baseline assessment)**
- **Second visit after 4 weeks of treatment.**

Severity assessment tools used:

- **Hamilton Anxiety Rating Scale (HAM-A)** for anxiety patients.
- **Beck's Depression Inventory (BDI)** for depression patients.

For analysis, the patients were further evaluated based on:

- Age distribution
- Gender distribution
- Severity scores at first visit
- Severity scores at second visit

The severity of depression was assessed using the **Beck Depression Inventory (BDI)** and anxiety using the **Hamilton Anxiety Rating Scale (HAM-A).**

Table 01: Age-Wise Distribution of Depression

| SR. NO | AGE | NO. OF PATIENTS | PERCENTAGE |
|---|---|---|---|
| 1 | 15-20 | 4 | 6.7% |
| 2 | 21-30 | 10 | 16.7% |
| 3 | 31-40 | 14 | 23.3% |
| 4 | 41-50 | 12 | 20% |
| 5 | 51-60 | 9 | 15% |
| 6 | >60 | 11 | 18.3% |
| | **Total** | **60** | **100%** |
| | | **M= 43.13** | |

**Gender – wise distribution of depression**

The study population of 60 patients shows a higher prevalence of depression among females (70%) compared to males (30%).

Table 02: Gender – Wise Distribution of Depression

| S.NO | Gender | No. of patients | Percentage |
|---|---|---|---|
| 1 | Male | 18 | 30% |
| 2 | Female | 42 | 70% |
| | **TOTAL** | **60** | **100%** |

**Treatment type:**

Each group was further categorised into two treatment groups:

1. **Single therapy (Standard therapy)- 30 patients.**
2. **Combination therapy (Pharmacological treatment + Probiotics)- 30 patients.**

Based on the above data in single therapy (30 patients with depression assessed using **Beck's depression inventory score at the 1st visit and 2nd visit**), the severity distribution and percentage were calculated.

Table 03: Severity-wise Distribution- (Depression- single Therapy 1st visit & 2nd visit)

| S.NO | Severity level | 1st visit no. of patients | 1st visit (%) | 2ndvisit no. of patients | 2nd visit (%) |
|---|---|---|---|---|---|
| 1 | No depression | 0 | 0% | 1 | 3.3% |
| 2 | mild depression | 3 | 10% | 3 | 10% |
| 3 | moderate depression | 17 | 56.7% | 24 | 80% |
| 4 | severe depression | 10 | 33.3% | 2 | 6.7% |
| | **total** | **30** | **100%** | **30** | **100%** |

Table 04: Severity-wise distribution (depression combination therapy with probiotics 1st visit & 2nd visit)

| S.no | Severity level | 1st visit (n=30) | 1st visit (%) | 2nd visit (n=30) | 2nd visit (%) | Improvement Rate |
|---|---|---|---|---|---|---|
| 1 | No depression | 0 | 0% | 12 | 40% | Increased |
| 2 | Mild | 5 | 16.7% | 13 | 43.3% | Decreased |
| 3 | Moderate | 8 | 26.7% | 5 | 16.7% | Completely reduced |
| 4 | Severe | 17 | 56.6% | 0 | 0% | Major improvement |
| | **Total** | 30 | 100% | 30 | 100% | - |

Table 05: Severity-Wise Distribution after 4 Weeks of Treatment (2nd visit)

| S.No | Severity level | Single therapy (2nd visit n=30) | Single therapy (%) | Combination therapy (2nd visit n=30) | Combination (%) |
|---|---|---|---|---|---|
| 1 | No depression | 1 | 3.3% | 12 | 40% |
| 2 | Mild | 3 | 10% | 13 | 43.3% |
| 3 | Moderate | 24 | 80% | 5 | 16.7% |
| 4 | Severe | 2 | 6.7% | 0 | 0% |
| | Total | 30 | 100% | 30 | 100% |

- In the baseline visit, severe depression was higher in the combination therapy group (56.6%) compared to the single therapy group (33.3%).
- After treatment, severe depression was eliminated in the combination therapy group, where as 6.7% of patients remained severe in the single therapy group.
- Complete remission in no depression) was observed in 40% of patients receiving Probiotics adjunct therapy, compared to only 3.3% in single therapy.
- A large proportion of patients in the single therapy group remained in the moderate category (80%), while many patients in the combination therapy group improved to mild to no depression.

Table 06: Severity–wise distribution of anxiety (combination therapy 1st& 2nd visit)

| S. No | Severity level | First visit (n) | First visit (%) | Next visit (n) | Next visit (%) | Improvement rate |
|---|---|---|---|---|---|---|
| 1 | No anxiety | 0 | 0% | 5 | 16.6% | New recovery cases |
| 2 | mild | 1 | 3.3% | 17 | 56.7% | Large increase in mild cases |
| 3 | moderate | 7 | 23.3% | 8 | 26.7% | Slight increase |
| 4 | severe | 22 | 73.3% | 0 | 0% | Completely reduced |
| | total | 30 | 100% | 30 | 100% | Significant improvement |

The severity-wise analysis of anxiety patients receiving combination therapy with probiotics shows a marked improvement between the first and follow-up visits.

- During the first visit, the majority of patients (73.3%) were categorised as severe anxiety, while only 3.3% had mild anxiety'
- After treatment, there was a substantial reduction in severity.
- Severe anxiety cases completely disappeared in the next visit.
- Mild anxiety cases increased significantly to 56.7%, indicating symptom Improvement.
- Five patients (16.6%) reported no anxiety symptoms, showing full clinical response.
- Overall, the findings suggest that combination therapy, including probiotics alongside pharmacological treatment, leads to considerable improvement in anxiety severity.

## DISCUSSION

### Randomised Controlled Trial: "Probiotics as an Adjunct Therapy for Depression and Anxiety Symptomatology"

### Study Settings and Duration

The present prospective observational study was conducted in a tertiary care hospital over a period of six months to evaluate the role of probiotics as an adjunct therapy in patients with anxiety and depression. A total of 120 patients diagnosed with anxiety and depressive disorders were included in the study. The study population was divided into two major groups: 60 patients with anxiety disorders and 60 patients with depressive disorders [27-28]. Each group was further categorised into two treatment groups, consisting of 30 patients receiving single therapy (pharmacological

treatment without probiotics) and 30 patients receiving combination therapy (pharmacological treatment along with probiotics). Patients were assessed at two different time points: the first visit (baseline assessment) and the second visit after four weeks of treatment. The Hamilton Anxiety Rating Scale (HAM-A) was used to assess the severity of anxiety symptoms, while Beck's Depression Inventory (BDI) was used to evaluate the severity of depressive symptoms [29]. The study aimed to compare clinical improvement between patients receiving single pharmacological therapy and those receiving combination therapy with probiotics [30].

**Demographic Characteristics of the Study Population**

The present study included 120 patients, of whom 60 were diagnosed with anxiety disorders and 60 with depressive disorders. The age of the study population ranged from 18 to 80 years, with most cases observed in the 30–60-year age group, indicating a higher representation of middle-aged adults among patients with psychiatric disorders such as anxiety and depression [31-32]. This may be associated with various factors, including occupational stress, financial pressure, family responsibilities and lifestyle changes. The gender distribution showed a slightly higher prevalence among females than males. This observation is consistent with previous epidemiological studies suggesting that women may be more vulnerable to anxiety and depressive disorders due to hormonal changes, psychosocial stressors and emotional sensitivity P [33].

**Depression Patients**

**First Visit Severity (Baseline Assessment)**

During the first visit, the severity of depressive symptoms was evaluated using Beck's Depression Inventory (BDI). The baseline results showed that most patients were categorised as having moderate to severe depression, while only a small proportion presented with mild depression. Common symptoms reported by patients included persistent sadness, loss of interest in daily activities, fatigue, sleep disturbances, reduced appetite and impaired concentration. These findings indicate that depression is often diagnosed at a later stage, when symptoms become sufficiently severe to interfere with daily activities and overall quality of life [34].

**Second Visit (After Four Weeks)**

After four weeks of treatment, the follow-up assessment showed noticeable improvements in depressive symptoms among patients receiving both single and combination therapies.

**Single Therapy Group (Without Probiotics):** Patients receiving antidepressant therapy alone, including medications such as sertraline, escitalopram, fluoxetine and amitriptyline, showed a gradual reduction in BDI scores. The second-visit results indicated that several patients improved from severe to moderate depression, while some patients shifted from moderate to mild depression. However, some patients continued to experience moderate depressive symptoms, suggesting that antidepressant therapy alone may require a longer treatment duration to achieve complete remission [35-39].

**Combination Therapy Group (With Probiotics):** Patients treated with antidepressants along with probiotics demonstrated greater improvement compared with those receiving single pharmacological therapy. At the second visit, several patients improved to mild depression, some achieved a status indicating the absence of depression, and a significant reduction in the number of moderate and severe depression cases was observed [40-42]. These findings support the hypothesis that gut microbiota may play an important role in mood regulation through the gut–brain axis. Probiotics may contribute to improvements in depressive symptoms through several mechanisms, including restoration of healthy gut microbiota, reduction of neuroinflammation, modulation of the hypothalamic–pituitary–adrenal (HPA) axis and increased production or regulation of serotonin and other neurotransmitters [43-46].

**Anxiety Disorder Patients**

**First Visit Severity (Baseline Assessment)**

During the first visit, the severity of anxiety symptoms was assessed using the Hamilton Anxiety Rating Scale (HAM-A). The baseline results indicated that the majority of patients presented with moderate to severe anxiety, while only a small proportion showed mild anxiety symptoms [47]. This suggests that many patients seek medical attention only after their symptoms have significantly worsened and begun to affect their daily functioning. Common symptoms observed among patients with anxiety disorders included excessive worry, restlessness, irritability, sleep disturbances and difficulty concentrating [48].

**Second Visit (After Four Weeks of Treatment)**

After four weeks of treatment, patients were reassessed to evaluate the clinical outcomes of the prescribed therapies.

**Single Therapy Group (Without Probiotics):** Patients receiving single pharmacological therapy, including medications such as sertraline, escitalopram, fluoxetine and combinations involving clonazepam, were evaluated for changes in their anxiety symptoms using the HAM-A scale [49]. The follow-up assessment was intended to determine the extent of symptom improvement following pharmacological treatment alone and to compare these outcomes with those observed in patients receiving combination therapy with probiotics.

## CONCLUSION

The study findings demonstrated that both anxiety and depression patients showed improvement after treatment, as evidenced by a reduction in HAM-A and BDI scores at the second visit. However, patients receiving combination therapy with probiotics exhibited greater clinical improvement than those receiving pharmacological therapy alone. A larger

proportion of patients in the combination therapy group shifted from severe and moderate categories to mild or no depression, indicating better therapeutic outcomes. The improved response observed in the probiotic group may be explained by the interaction between gut microbiota and the central nervous system through the gut- brain axis. Probiotics help restore healthy intestinal microbiota and regulate neurotransmitter production. Reduce inflammation and modulate the stress response, which may contribute to improvement in psychological symptoms. Overall, the results of the study suggest that probiotics can serve as a beneficial adjunct therapy in the treatment of both anxiety and depression. The addition of probiotics to conventional pharmacological treatment may enhance therapeutic effectiveness and accelerate symptom improvement. Therefore, the present study supports the concept that modulation of gut microbiota plays an important role in mental health management, and probiotics may be considered a safe and effective supportive strategy in the treatment of depressive and anxiety disorders. Further large–scale clinical studies with longer follow- up duration are recommended to confirm these findings and to establish standardised guidelines for the use of probiotics in psychiatric practice.

**FUNDING**
Nil

**ACKNOWLEDGEMENT**
Not Declared.

**CONFLICT OF INTEREST**
Nil

**INFORMED CONSENT**
Written informed consent was obtained from all participants before enrolment. The purpose and procedures of the study were explained, and confidentiality was maintained. Participation was voluntary, and participants were allowed to withdraw at any time without affecting their medical care.

**ETHICAL STATEMENT**
The study was conducted at a government hospital after obtaining approval from the Institutional Ethics Committee (IEC), under reference number SLVP 2025–2026. All ethical guidelines for research involving human participants were followed.

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