

PSYCHOTROPIC PROPERTIES OF PROBIOTICS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Even though psychological disorders can be treated with various methods, one of the emerging concepts is psychobiotics. Psychobiotics are the probiotics that have psychotropic properties in it, and these probiotics proved with the proper administration could provide physiological and psychological benefits to healthy individuals. In past years, many interventions have been conducted to identify these effects using human and animal samples. Thus, the objective of this review is to summarise current human studies conducted to investigate the effect of probiotics on psychological conditions

Materials and Methods: A literature search was conducted using different databases includes Scopus, Pub Med, Web of Science, Science direct, and Google scholar referring to the past 15 years. 526 studies have been extracted and after removing duplicates and studies that do not meet the inclusion criteria, twenty-two studies were selected to document in the present review from 2004 to 2018.

Result: Majority of these studies have revealed the effect of probiotics for improving the psychological disorders such as anxiety, stress, and depression with the significant difference between experiment and placebo groups. Thus, some studies showed no significant difference between groups. This may be due to different dosages, probiotic strains, intervention duration used in the studies.

Conclusion: Daily probiotic supplementation can positively affect psychological conditions among different populations.

Keywords: Anxiety, stress, probiotics, psychobiotics

1.0 Introduction

Depression, stress, anxiety, sleeping, and mood disorders, are commonly experienced by different populations, especially those with hectic lifestyles. It is evident that 20% of the world population is suffering from a major depressive disorder for at least once in their lifetime (Abhari & Hosseini, 2018). Microbiota-gut-brain axis was revealed many years during the last decade (Foster & McVey Neufeld, 2013) and the complex bi-directional relationship between the gastrointestinal tract and the brain is still subjected to research. Many studies have shown that gut microbiota could directly affect the psychophysiological conditions of the human (e.g., Akkasheh et al., 2016; Messaoudi et al., 2011; Mohammadi et al., 2016).

Due to the poor dietary intake, antibiotic usage, and medical treatments, the gastrointestinal tract may experience dysbiosis or the discrepancies of the gut microbiota, which could lead to many psychological disorders such as stress and depression. Probiotics are a promising approach to improve these conditions. According to Abhari and Hosseini (2018), as well as Kane and Kinzel (2018), the gut can influence the brain in different ways. One such influence is through the probiotics' ability to secrete neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin and catecholamines that are capable of inhibiting the transmission of nerve impulses in the central nervous system (CNS). Secondly, the probiotics have an ability to correct the dysfunctional hypothalamic–pituitary–adrenal axis (HPA axis). When in stressful conditions, the HPA axis gets activated and causes adrenal glands to secrete cortisol. The probiotics can alter this dysfunction and helps to improve stress. Furthermore, probiotics can act as anti-inflammatory agents. When inflammation occurs, those transmitters send impulses to the brain through the vagus nerve causing anxiety, stress, and depression but probiotics are capable of minimizing the inflammations, thereby improving the immune functions (Abhari & Hosseini, 2018).

Psychobiotics are the probiotics that have psychotropic properties, and most of the lactobacillus and bifidobacterium strains can be considered as psychobiotics. Many studies have been conducted over a decade using human and animal samples to investigate the effect of psychobiotics over psychological disorders such as anxiety, stress, mood, and depression. The objective of this systematic review is to analyse the studies that have been conducted over 15 years to determine the effect of psychobiotics on psychological conditions.

2.0 Materials and Methods

Text Studies were gathered from various online databases such as Scopus, Pub Med, Web of Science, Science direct and Google scholar. Literature searches were conducted using keywords such as probiotics, psychobiotics, Lactobacillus, Bifidobacterium, anxiety, stress, depression, and psychology as keywords. Records were obtained from 2003 to September 2018 representing the past 15 years, and after deleting the duplicates, all the studies were screened to match the inclusion criteria.

Eligible studies for the present review were: (1) full research articles published in English, (2) Randomized double-blind placebo-controlled interventions (3) administrated daily probiotic supplementation, (4) measured psychological parameters using questionnaires/ self-reported inventories, (5) only human studies were considered, thus excluding all animal studies, (6) studies that included supplementations other than probiotics were excluded and (7) studies that measured psychological responses using only physiological methods were also excluded from the present review. After screening all the studies only 22 studies were matched to be included in the present review.

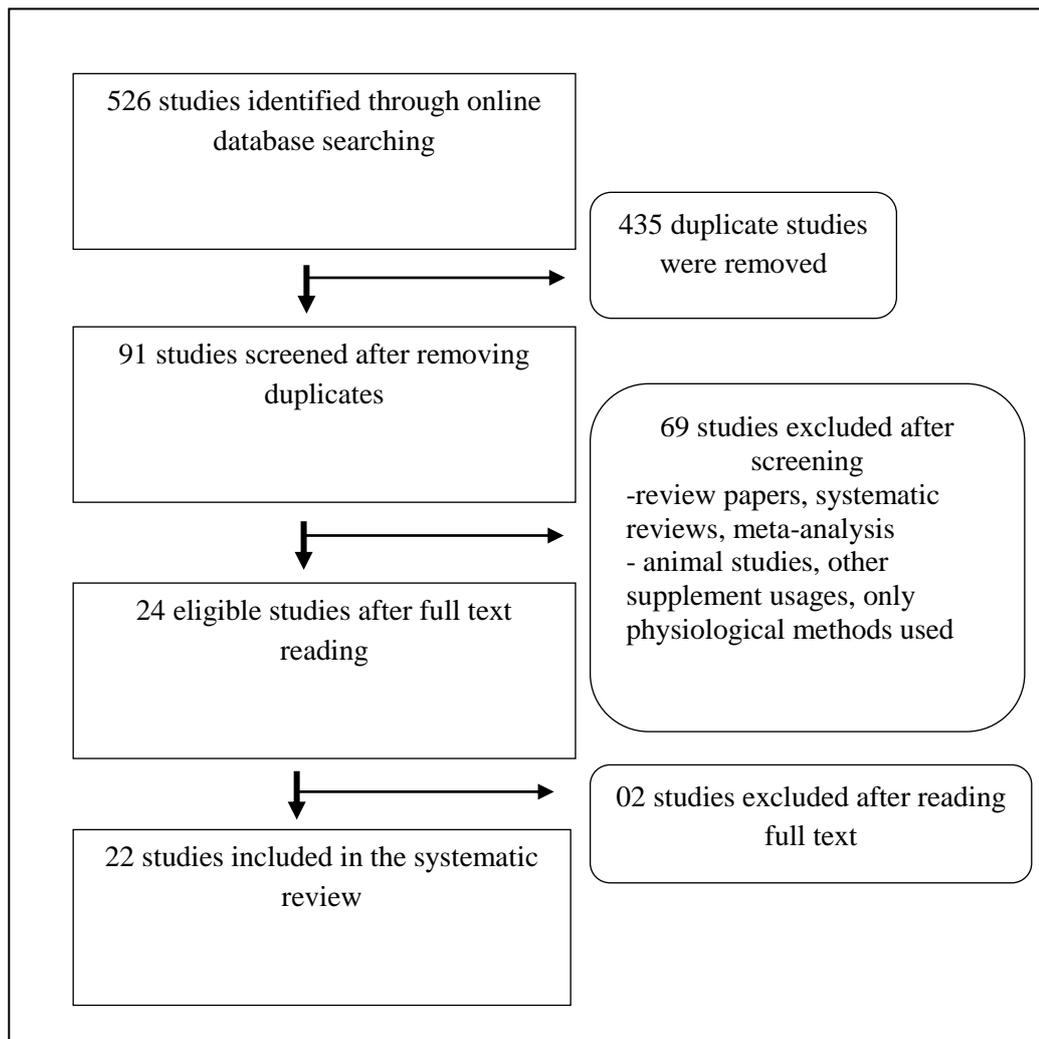


Figure 1: PRISMA flow chart indicating the literature search and inclusion of the studies

3.0 Result and Discussion

In the present review, all the studies have used a similar method: Pre and post-intervention of daily probiotic administration with a placebo group could be found in all the studies except for the studies conducted by the Allen et al. (2016) and Sawada et al. (2017). Apart from these two studies all the other studies used similar intervention method. These two studies used a

slightly different method using two groups of medical students; one group had undergone probiotic treatment and another group the placebo treatment for four weeks and spent three weeks for the washout period and crossover the treatment for another four weeks. Allen et al. (2016), used 22 healthy volunteers who received the placebo treatment for four weeks, followed by probiotic treatment for another four weeks.

3.1 Probiotic Supplementation

Most studies have employed the commercially available probiotic supplementations in the form of drinks, sticks, shots, or capsules. Even though there are different probiotic strains, Bifidobacterium and Lactobacillus strains are commonly used in commercial production, and these two strain are known to have psychotropic properties (Abhari & Hosseini, 2018). Misra and Mohanty (2017) identified the multiple effects of these two strains as psychobiotics. For example, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus fermentum*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, *Lactobacillus bulgaricus*, *Lactobacillus plantarum*, *Lactobacillus salvarius* were the lactobacillus strains were used in reviewed studies whereas bifidobacterium strains which included *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium lactis*, *Bifidobacterium breve*. Other than these two main strains, *Streptococcus thermophilus* were used in some studies (Marcos et al., 2004; Simrén et al., 2010) and *Clostridium butyricum* (Yang et al., 2016).

Although the probiotic strain can affect the outcome of the investigation, none of the studies confirmed which strain was the most effective probiotic strain to improve the psychological conditions. Recently, researchers such as Kelly et al. (2017), Östlund-lagerström et al. (2016), Pinto-sanchez et al. (2018), Sawada et al. (2017), Slykerman et al. (2017), and Takada et al. (2016) used one probiotic strain, while some of the researchers namely Akkasheh et al. (2016), Kouchaki et al. (2017), Simrén et al. (2010), and Steenbergen, Sellaro, van Hemert, Bosch, & Colzato (2015) focused on combinations of strains.

3.2 Dosage

Even though the dosage had an effect on the outcomes of the reviewed research, the minimal dosage required in order to see a significant effect of probiotics is yet unknown (Minelli & Benini, 2008). However, as Minelli and Benini (2008) mentioned that a probiotics dose of $1 \times 10^{7-9}$ CFU/ mg per day is effective on humans for daily consumption. All the researchers reviewed had used probiotic dosages within this range in their studies.

3.3 Intervention Duration

Intervention duration is another parameter that can affect the outcomes of the studies. However, evidence suggested the minimum duration of intervention that showed a significant effect of the probiotic treatment is scarce. Some researchers such as Kouchaki et al. (2017) and Slykerman et al. (2017) conducted twelve weeks of experiments, while Allen et al. (2016) and Steenbergen et al. (2015) focused on a four weeks intervention trial. Although the treatment durations are different, the results revealed that probiotic treatment significantly improved the psychological conditions of the participants.

Most of the randomised double-blind placebo-controlled studies were conducted as eight weeks interventions. However, Yang et al. (2016) conducted a study using 20 laryngeal cancer patients and daily probiotic intervention of two weeks duration before their surgery to examine its effect on anxiety using the Hamilton anxiety scale and serum cortisol. The study found that patients in the probiotic group showed a significant reduction in anxiety and cortisol levels compared to the placebo group. A similar study was conducted by Kouchaki et al. (2017), employing 60 multiple sclerosis patients over 12 weeks of daily probiotic intervention to measure their stress, anxiety, and depression. The result revealed that the probiotic group was able to significantly decrease the scores of depressions, anxiety stress scale (DASS), and becks anxiety inventory (BAI).

Another study conducted by the Slykerman et al. (2017), assessed pregnant women who were in their 14th to 16th week of pregnancy, and this study conducted over 12 months. The researchers found that postnatal stress and depression were significantly lowered in the probiotic group.

3.4 Sample variation

These studies mainly focused on the different populations, and the highest number of studies targeted healthy volunteers, (Allen et al., 2016; Kelly et al., 2017; Romijn, Rucklidge, Kuijer, & Frampton, 2017), medical students who are vulnerable to stress due to examinations (Kato-Kataoka et al., 2016; Sawada et al., 2017; Takada et al., 2016) and older adults (Chung, Jin, Cui, & Sik, 2014; Östlund-lagerström et al., 2016). Some researchers targeted patients with major depressive disorders (Akkasheh et al., 2016), irritable bowel syndrome (Pinto-sanchez et al., 2018; Simrén et al., 2010) and chronic fatigue syndrome (Rao et al., 2009) to better understand the effects of probiotics in improving psychophysiological conditions.

3.5. Psychological Disorders

Stress, anxiety, depression, sleep, cognitive, and mood disorders are the most common psychological parameters that have been addressed in the reviewed studies. Self-reported questionnaires were used to abstract the data, and very few studies had employed physiological parameters such as hormone-like cortisol and brain wave activities to include psychological conditions together with the data gathered from questionnaires.

3.6 Research Instruments

Psychological responses were measured using validated questionnaires which included the Becks Anxiety Inventory (Kelly et al., 2017; Rao et al., 2009; Steenbergen et al., 2015), Becks Depression Inventory (Akkasheh et al., 2016; Allen et al., 2016 ; Kelly et al., 2017; Kouchaki et al., 2017), State-Trait Anxiety Inventory (Kelly et al., 2017; Pinto-sanchez et al., 2018; Sawada et al., 2017; Slykerman et al., 2017; Takada et al., 2016), Perceived Stress Scale (Allen et al., 2016; Diop, Guillou, & Durand, 2008; Messaoudi et al., 2011; Östlund-lagerström et al., 2016), Depression Anxiety Stress Scale (Kouchaki et al., 2017; Mohammadi et al., 2016; Romijn et al., 2017), Pittsburgh Sleep Quality Index (Kelly et al., 2017; Kato-Kataoka et al., 2016; Sawada et al., 2017), Self-rating Depression Scale (Kato-Kataoka et al., 2016; Sawada et al., 2017), Hospital Anxiety and Depression Scale (Pinto-Sanchez et al.,

2017; Sawada et al., 2017), Depression Rating Scale (Messaoudi et al., 2011; Östlund-lagerström et al., 2016), Inventory of Depressive Symptomatology (Romijn et al., 2017), Edinburgh Postnatal Depression Scale (Slykerman et al., 2017), Hamilton Anxiety Scale (Yang et al., 2016), Revised Leiden index of depression sensitivity scale (Steenbergen et al., 2015), Geriatric depression scale-short form (Chung et al., 2014) and Profile of Mood States (Sashihara et al., 2013). These questionnaires were used by researchers to obtain psychological responses. Most researchers used more than one questionnaire to obtain different psychological responses.

Some researchers such as Kato-Kataoka et al. (2016), Nishimura, Ohkawara, Tetsuka, & Kawasaki (2015), Sawada et al. (2017), Takada et al. (2016), Yang et al. (2016), and Marcos et al., (2004) used serum cortisol as a physiological stress indicator. Apart from the psychological and physiological tools mentioned above, Kelly et al. (2017) used electroencephalography to measure the changes in brain wave activities of 29 healthy males caused by daily probiotic supplementation. Table 1 presents a summary of the studies conducted to investigate the effect of probiotics on the psychological responses of the subjects.

Table 1. Summarised review of the effect of probiotics on psychological responses

Authors (year)	Sample	Research groups	Treatment and dosage	Duration	Psychological and physiological measure	Effects of probiotic treatment
Kelly et al. (2017)	N=29 (Healthy male adults)	Probiotic group =14 Placebo group = 15	<i>Lactobacillus Rhamnosus</i> 1x10 ⁹ CFU <i>capsule</i>	8 weeks	EEG Beck Depression Inventory/ Beck Anxiety Inventory/ Perceived Stress Scale/ State/Trait Anxiety Inventory Symptom Checklist-90/ Pittsburgh sleep quality index	No significant changes in mood, stress, anxiety and EEG.
Kouchaki et al. (2017)	N= 60 (Multiple sclerosis patients)	Probiotic group = 30 Placebo group= 30	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Bifidobacterium bifidum</i> and <i>Lactobacillus fermentum</i> (2x10 ⁹ CFU/g) <i>capsule</i>	12 weeks	Beck Depression Inventory/ Depression Anxiety and Stress Scale	Probiotic treatment significantly decreased the BDI and DASS scores compared to the placebo group.
Sawada et al. (2017)	N= not specified (Male Medical students under pressure)	Probiotic group and placebo groups underwent treatments for 4 weeks and then 3 weeks washout period and crossover treatment for another 4 weeks	<i>Lactobacillus gasseri</i> - 1x10 ¹⁰ CFU /g (2.5 g) <i>powder</i>	4 weeks	General Health Questionnaire/ Self-rating Depression Scale/ Hospital Anxiety and Depression Scale/ State-Trait Anxiety Inventory/ Pittsburgh Sleep Quality Index/ Salivary cortisol	Significant improvement in anxiety, depression, and sleep in the probiotic group in each phase.

Research	Sample	Research groups	Treatment and Dosage	Duration	Psychological and physiological measure	Result
Romijn, Rucklidge, Kuijer, & Frampton (2017)	N=69 (Healthy Volunteers)	Probiotic group =33 Placebo group =36	<i>Lactobacillus helveticus</i> and <i>Bifidobacterium longum</i> - 3×10 ⁹ CFU/per 1.5 g sachet	8 weeks	Montgomery-Åsberg Depression Rating Scale/ Inventory of Depressive Symptomatology/ Depression Anxiety and Stress Scale	Anxiety and depression scores decreased but not significantly in the probiotic group compared to the placebo group.
Slykerman et al. (2017)	N= 423 (Pregnant women in 14 to 16 weeks of pregnancy)	Probiotics group =212 Placebo group =211	<i>Lactobacillus rhamnosus</i> at a dose of 6×10 ⁹ CFU	12 months	Edinburgh Postnatal Depression Scale/ State-Trait Anxiety Inventory	Significantly lower symptoms of anxiety and depression showed by the probiotic group.
Pinto-Sanchez et al. (2017)	N= 44 (Patients with IBS)	Probiotics group =22 Placebo group =22	<i>Bifidobacterium longum</i>	6 weeks	Hospital Anxiety and Depression State-Trait Anxiety Inventory	Probiotic treatment significantly reduced the depression scores but not the anxiety scores.
Kato-Kataoka et al. (2016)	N= 51 (Medical Students)	Probiotic group =26 Placebo group = 25	<i>Lactobacillus casei</i> Shirota - 1.0×10 ⁹ CFU/ml	8 weeks	State-Trait Anxiety Inventory/ Hospital Anxiety and Depression Scale/ Self-rating Depression Scale/ Pittsburgh Sleep Quality Index/ Salivary cortisol	Probiotic treatment showed a decrement in salivary cortisol and STAI scores compared to the placebo group but results are not statistically significant.

Research	Sample	Research groups	Treatment and Dosage	Duration	Psychological and physiological measure	Result
Akkasheh et al. (2016)	N=40 (Major depressive disorder)	Control group = 20 Probiotic group = 20	<i>Lactobacillus acidophilus</i> – 2×10^9 CFU/g <i>Lactobacillus casei</i> – 2×10^9 CFU /g <i>Bifidobacterium bifidum</i> – 2×10^9 CFU/g	8 weeks	Beck Depression Inventory	A significant decrease in Beck Depression Inventory scores in the treatment group
Takada et al. (2016)	N= 140 (Medical students in examination stress)	Probiotic group=70 Placebo group=70	<i>Lactobacillus casei</i> Shirota - 1×10^9 CFU/ml	8 weeks	State-Trait Anxiety Index/ Salivary cortisol levels	Anxiety index and cortisol levels were significantly increased in both groups on the day before exam; STAI scores between groups were not significantly different.
Mohammadi et al. (2016)	N=70 (Petrochemical workers)	Probiotic yogurt + placebo capsule= 25 Probiotic capsule + yogurt =25 Yogurt + placebo capsule= 20	<u>Probiotic yogurt</u> – <i>L. acidophilus</i> , <i>Bifidobacterium lactis</i> - 1×10^7 CFU <u>Conventional yogurt</u> - <i>Streptococcus thermophilus</i> and <i>L. bulgaricus</i> <u>Probiotic capsule</u> - <i>L. casei</i> 3×10^3 CFU, <i>L. acidophilus</i> 3×10^7 CFU, <i>L. rhamnosus</i> 7×10^9 CFU, <i>L. bulgaricus</i> - 5×10^8 CFU, <i>Bifidobacterium breve</i>	6 weeks	General health questionnaire/ Depression Anxiety and Stress scale	Significant improvement in general health and anxiety in probiotic capsule group and probiotic yogurt group.

Research	Sample	Research groups	Treatment and Dosage	Duration	Psychological and physiological measure	Result
			2×10 ¹⁰ CFU, <i>B. longum</i> 1×10 ⁹ cfu, <i>S. thermophilus</i> 3×10 ⁸ CFU /g, and 100 mg			
Östlund-lagerström et al. (2016)	N= 290 (Older adults)	Probiotic group= 125 Placebo group= 124	<i>Lactobacillus reuteri</i> - 1 × 10 ⁸ CFU	12 weeks	Hospital anxiety and depression scale/ Perceived stress scale	Stress was decreased with the treatment but not significant.
Yang et al. (2016)	N= 20 (Laryngeal cancer Patients before surgery)	Probiotic group= 10 Control group =10	<i>Clostridium butyricum</i> ; 420 mg/capsule	2 weeks	Hamilton Anxiety Scale Serum Cortisol	Cortisol level, heart rate, and anxiety significantly decreased in the probiotic group compared to the control group
Allen et al. (2016)	N= 22 (Healthy Volunteers)	Placebo for 4 weeks Probiotics for 4 weeks	<i>Bifidobacterium longum</i> 1714 strain 1×10 ⁹ CFU	4 weeks	Beck Depression Inventory/ Perceived Stress Scale/ State-Trait Anxiety Inventory/ EEG	Stress and anxiety significantly reduced in treatment group; the treatment improved memory significantly
Steenbergen, Sellaro, van Hemert, Bosch, & Colzato (2015)	N=40 (Healthy participants)	Probiotics group = 20 Placebo group =20	<i>Bifidobacterium bifidum</i> , <i>Bifidobacterium lactis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus brevis</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus salivarius</i> , and <i>Lactococcus lactis</i>	4 weeks	Revised Leiden index of depression sensitivity scale/ Beck Depression Inventory-II/ Beck Anxiety Inventory	A significant reduction in a sad mood compared to the placebo group. BAI, BDI scores decreased but not significant.

Mixed - 2.5×10^9 CFU/g

Research	Sample	Research groups	Treatment and Dosage	Duration	Psychological and physiological measure	Result
Chung, Jin, Cui, & Sik (2014)	N=36 (Older Adults)	Probiotic group (500g) = 10 Probiotic group (1000g) = 7 Probiotic group (2000g) = 9 Placebo group = 10	<i>Lactobacillus helveticus</i>	12 weeks	Cognitive tests/ perceived stress scale/ Geriatric depression scale-short form/ Brain-derived neurotrophic factor/ Blood viscosity (WBV)	No significant differences between groups in PSS, GDS-SF, WBV
Sashihara et al. (2013)	N = 44 (Collegiate Athletes)	Probiotic group = 15 Probiotic + alpha-lactalbumin group = 15 Placebo group = 14	<i>Lactobacillus gasseri</i> – 1.5g per day	4 weeks	Profile of Mood States Blood samples	Probiotic treatment significantly reduced anxiety
Messaoudi et al. (2011)	N=55 (Healthy volunteers)	Probiotic group=26 Placebo group=29	<i>Lactobacillus helveticus</i> and <i>Bifidobacterium longum</i> - 3×10^9 CFU/stick	4 weeks	Hopkins Symptom Checklist/ Hospital Anxiety and Depression Scale/ Perceived Stress Scale/ Coping Checklist and 24 h urinary free cortisol	Probiotics treatment significantly improved depression and anxiety scores compared to control.
Simrén et al. (2010)	N= 74 (Irritable Bowel Syndrome)	Probiotic group= 37 Placebo group = 37	<i>Lactobacillus bulgaricus</i> and <i>Streptococcus thermophilus</i> with <i>Lactobacillus paracasei</i> , <i>Lactobacillus</i>	8 weeks	Hospital Anxiety and Depression	Both groups improved their anxiety scores during the treatment but no significant difference between groups.

Research	Sample	Research groups	Treatment and Dosage	Duration	Psychological and physiological measure	Result
			<i>acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12 - 5×10^7 CFU/ml, 200ml twice daily			
Rao et al. (2009)	N=31 (Chronic fatigue syndrome)	Probiotic group=16 Placebo group=15	<i>Lactobacillus casei</i> Shirota - 24 billion colony forming units (CFU)	8 weeks	Beck Depression Inventory/ Beck Anxiety Inventory	Probiotic treatment significantly reduced BAI scores
Diop, Guillou, & Durand (2008)	N=64 (Healthy Volunteers)	Probiotic group = 31 Placebo group = 33	<i>Lactobacillus acidophilus</i> Rosell- 52 and <i>Bifidobacterium longum</i> Rosell-175 (3×10^9 CFU per sachet)	3 weeks	General Health Questionnaire/ Depression Anxiety and Stress Questionnaire/ Perceived Stress Scale/ Dispositional Resilience Scale/ Recovery-Stress Questionnaire	Probiotics group showed significant improvement in stress-induced gastrointestinal symptoms.
Benton, Williams, & Brown (2007)	N=124 (Health volunteers)	Probiotic= not specified Placebo= not specified	<i>Lactobacillus casei</i> Shirota - 6.5×10^9 CFU	3 weeks	Profile of Mood States	Treatment did not change the mood significantly but a decrease in constipation was reported in probiotic group.
Marcos et al. (2004)	N=155 (University students in	Probiotic group= 73 Control group =63	<i>Lactobacillus delbrueckii</i> (<i>Bulgaricus</i>)- 10^7 cfu/ml) <i>Streptococcus salivarius</i>	6 weeks	State-Trait Anxiety Inventory / Salivary Cortisol	Anxiety increased with time for the exam in both groups; treatment

examination
period)

(Thermophilus)- 10⁸ CFU
/ml
Lactobacillus casei- 10⁸
CFU /ml

group showed a
decrement in anxiety but
not significant.

4.0 Conclusion

Daily probiotic supplementation has shown improvement in the participants' level of anxiety, stress, mood, depression, sleep disorders, cognitive disorders in the participants in the numerous studies, proving that the psychotropic properties of the probiotics. Even though these studies used different probiotic streams, dosages, samples, sample sizes, and treatment durations, most studies such as Akkashah et al. (2016), Kouchaki et al. (2017), Sawada et al. (2017), Slykerman et al. (2017) and Yang et al. (2016), revealed an improvement in the treatment groups compared to the controls. However, some studies showed an improvement in psychological conditions of the treatment group, which was not statistically significant when compared with the placebo group (Östlund-lagerström et al., 2016; Pinto-Sanchez et al., 2017; Romijn et al., 2017). Only a few studies have shown no differences between the experimental probiotic group and the placebo group with respect to probiotic supplementation.

It is worth noting that very limited human studies have been conducted in relation to the psychotropic effects of probiotics in the past, but a considerable amount of studies was published during the last three years proving the demands in the research area. There are still many components to verify, such as the best probiotic strain, dosage, and duration, which opens a wide gap to be addressed by future researchers. This review reveals that Psychobiotics can be used as a therapy to improve psychological disorders not only among patients who suffer from mental disorders but among healthy people as well.

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Declaration

Authors declare that there was no conflict of interest.

Author's contribution

CA conducted the literature search, analysed and interpreted the data; MA and GK analysed, interpreted and approved the submitted data; all authors wrote the paper.

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