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Editorial

Manifold effects of Probiotics on Inflammation, Cognition, Dementia , Depression and Anxiety : A Traditional/Narrative Review - Possible choice of Non-pharmacological therapy at the level of primary care?

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Introduction

Probiotics are microorganisms that can be included in the diet or taken as supplements. They are widely accessible and available at low cost to various populations all over the world. This study aims to gather both supporting and contradicting information from previous studies and additionally discuss the harmful effects of probiotics. Probiotics may offer essential early intervention to lessen the severity of inflammation, cognitive decline, and mood problems by modifying the gut-brain axis in the body. They work on multiple systems, so it is necessary to thoroughly investigate their effects and efficacy through randomized control trials in order to develop therapeutic, affordable, and widely accessible alternative treatment options from them for some of the most prevalent health problems. A thorough search was performed on various databases (PubMed, ScienceDirect, and Google Scholar) using keywords and nineteen studies that fit the inclusion/exclusion criteria were deemed relevant.

Databases used: PubMed, PubMed central, Google scholar

Keywords: Probiotics, Inflammatory markers, OXIDATIVE STRESS, HUMAN MICROBIOME, Nervous System Diseases/diet therapy,Probiotics/therapeutic use, Microbiota/immunology, Alzheimer's disease, Anxiety.

Introduction & Background

"The most famous doctors cure by altering the diet and lifestyle of their patients and by using other substances"-Hippocrates. The natural healing force within us is the most significant in improving our health. Our medicine should be our food and our food should be our medicine [1].

It has been observed that the affected brains appear to be inflamed and glial cells act on these areas of inflammation by removing debris and plaque. However in the process, the glial cells liberate more harmful Aβ, further adding to plaque formation, which attracts more accurate glial cells and the cycle continues [25]. Tamtaji conducted a meta-analysis study that suggests that taking probiotics by patients with neurological disorders had beneficial effects on CRP, MDA, insulin, HOMA-IR(Homeostatic Model Assessment for Insulin Resistance), triglycerides, VLDL-cholesterol(Very low density cholesterol) and HDL-cholesterol levels(High density cholesterol), as thereby significantly impacting the lipid metabolism [26].

Additionally, few lactic acid bacteria (LAB) strains produce the vitamin cobalamin complex (vitamin B12), which has a direct association to AD as seen in various studies that showed lower B12 levels in AD individuals. Studies have shown that myelin related genes are regulated by microbiome and this marks their importance at the level of genomic function [24]. Since the gut microbiota is vital concerning inflammation and metabolic diseases that directly relate to AD pathogenesis, it is crucial to consider and study the effects of probiotics on disease occurrence and progression [24-26].

Studies contraindicating the effects of probiotics on cognition and dementia-

Meta-analysis of randomized control trials (RCT) and a systematic review by Jenifer F Krüger et al., data from 3 RCTs involving 161 Alzheimer's disease patients who received Lactobacillus and Bifidobacterium strains revealed no beneficial impact of probiotic supplementation on cognitive function.

Probiotics are live microorganisms and can be consumed either as supplements or in the diet. In 2001, the World Health Organization (WHO) stated that as live microorganisms, probiotics lead to health benefits for the host [2]. Cheese and fermented products have been prevalent since the Greeks, Romans, and ancient civilizations encouraged their consumption [2]. Among the various probiotic bacteria, Lactobacillus sp. and Bifidobacterium sp. have extensive effects. There has been an increase in the number of reports that have emphasized the benefits of using probiotics for human health and well-being when used in defined quantities consistently [2-4].

Over the last few decades, a vast deal of scientific literature hypothesized the antioxidant effect of probiotics in humans [3-4]. Studies have shown that age-associated inflammation, which challenges the health status of the geriatric population, is directly related to the gut microbiota [5]. The gut microbiota has played a vital role in metabolic diseases, including brain health [6]. This review attempts to comprehend and examine the impact that probiotics play in the treatment of mental illness. Among the primary causes of impairment around the world, these disorders are the most prevalent. Traditional pharmacotherapeutics have varied responses or adverse side effects. Recent studies have revealed a dense bi-directional communication in the human body named the gut-brain axis. Experimental investigations have shown a connection between disturbed intestinal microbiota and psychiatric diseases, opening the door to the development of new treatments with fewer side effects [7].

Probiotic supplementation can have a dual advantage in improving antioxidant indices and reducing oxidative stress in the body [3-4]. Probiotic supplementation works by improving antioxidant resistance and elevating the number of antioxidant enzymes in the body [8-9]. As suggested by ongoing analyses, they can control the symptoms associated with cognition and digestion in patients with Alzheimer's disease and Parkinson's disease by reducing inflammation and improving lipid metabolism [10-12]. The two mental illnesses that affect people the most frequently are depression and anxiety disorders.

Epidemiology of depression and anxiety -

According to estimates from the World Health Organization (WHO), the prevalence of depression in the world's population was estimated to be 280 million, and 301 million people have an anxiety disorder in 2019 [13].

Probiotic supplementation, however, enhanced insulin resistance, very-low-density lipoprotein cholesterol, plasma lipids, and malondialdehyde levels [27].

1.4 Effects of probiotics on anxiety and depression-

Depression clinically exhibits with signs of poor mood and loss of interest, commonly accompanied by shame, hopelessness, a decrease in appetite, and insomnia. Anxiety is a feeling that is frequently accompanied by tension, concern, fear, and clinical symptoms including trembling, palpitations, digestive problems, shortness of breath, and circulatory difficulties without any apparent objective causation or significant stressors.

Future studies should focus on probiotics' anxiolytic and antidepressant effects in phenotypically homogeneous populations. The concept of the gut microbiota-brain axis provides a novel therapeutic target for the treatment and/or prevention of mood and anxiety disorders by modulation of the gut microbiota [7].

Studies supporting the use of probiotics for anxiety and depression-

Probiotics may be used as adjuvant therapies for mood or emotional disorders as they can lower depressive symptoms [15]. Probiotics like Lactobacillus may regulate the balance of the intestinal flora and play an active role in preventing and treating depression by inhibiting Toll like receptor 4 (TLR4) signaling [28].

A meta-analysis of RCTs was done to assess the multiple effects of probiotic supplementation on mental health (mood disorders like depression and anxiety), biomarkers of inflammation, and oxidative stress in patients with psychiatric disorders. Overall, the current meta-analysis demonstrated that taking probiotics by patients with psychiatric disorders significantly reduced the Hamilton Depression Rating Scale (HAMD). Results also showed that it had beneficial effects on HAMD, CRP, IL-10, and MDA levels [29].

The studies discussed above, discovered favorable outcomes for at least one of the items [7,15,28-29]. We came to the conclusion that the anti-inflammatory impact of probiotics, in particular, had promising effects on the treatment of anxiety and depression symptoms. To support such findings, though, larger and more stringent double-blind randomized clinical trials are required [30].

Given its extensive prevalence, anxiety affects one in nine people around the world and is the sixth most prevalent illness globally [14-15]. The emerging concept of a gut microbiota-brain axis from ongoing research and clinical trials may provide a novel therapeutic target for the treatment and prevention of mood and anxiety disorders by modulating the gut microbiota [6]. The established pathways of communication include the immune system, the enteric nervous system (ENS), the autonomic nervous system (ANS) and the neuroendocrine system [16]. The disease severity and time of administration of probiotics play an effective role compared to dosing or formulation [17]. The figure below (Figure 1) demonstrates the multi-system effects of gut microbiota. Bidirectional communication between gut microbiota and various listed components of the gut-brain axis can alter the homeostasis and thus contribute to the disease [16].

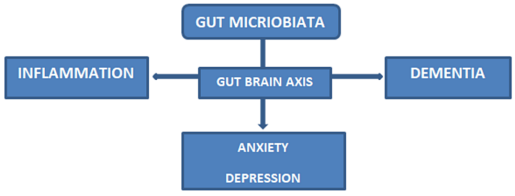

Figure 1: Association of gut Microbiota with multiple systems (Original figure by the author).

Although there have been multiple kinds of research regarding the benefits of probiotics, there has not been a correlative study emphasizing the various intertwined multi-system effects. Thus, this traditional review aims to assess and co-relate the impact of probiotic supplementation on inflammation and metabolic diseases, including brain health such as dementia, anxiety and depression in adults using the information available from the previous studies. Pooling data regarding the same would help the clinicians educate people on how minor changes in dietary supplementation daily for prolonged intervals can have significant health benefits.

Review

Search strategy -

Detailed research was conducted using the keywords mentioned in Table 1 to recognize the studies analyzing and assessing the multisystem effects of probiotics on inflammation, cognition, depression, and anxiety using the MeSH strategy (Medical Subject Headings) with

1.5 A study supporting the relation between multi-organ effects and possible reasons-

Probiotic Lactobacillus fermentum strain JDFM216 has shown to improve cognitive behavior and mediate immune response with gut microbiota. Taken together, L. fermentum JDFM216 could modulate the gut microbiota and enhance cognition, physiological behavior, and immunity [6].

1.6 Possible adverse effects of using probiotics therapeutically-

The increase in the usage of probiotics in both public and healthcare backgrounds makes it vital for clinicians to understand the risks and benefits of probiotic treatment. Majority of available probiotics in the market are broadly categorized to be safe but there have been concerns with probiotic use in specific populations. In the food processing industry, the use of probiotics has been historical with an accomplished safety record [31,32].

According to a 2002 report jointly by the WHO and the Food and Agriculture Organization (FAO) of the United Nations, "probiotics may theoretically be responsible for four types of side effects: Systemic infections. Deleterious metabolic activities. Excessive immune stimulation in susceptible individuals. Gene transfer" [33]. The various studied risk factors contributing to probiotic sepsis have been summarized in Table 2 below [34-35].

Table 1: Proposed risk factors for probiotic sepsis

MAJOR RISK FACTORS	MINOR RISK FACTORS
Immunocompromised patients (on chemotherapy/AIDS/organ transplant)	Central venous catheter
Premature infants	Mucosal barrier disturbance or increased adherence of the bacteria*.
Malnutrition (chronic illness)	Use of broad spectrum antibiotics simultaneously.
Malignancy (leukemia)	Cardiac valve abnormalities

PubMed as the primary database. PubMed Central and Google Scholar were used as additional databases. The difficulties associated with adopting probiotics as therapy options have also been covered in length in this study, in addition to its primary objective. Although papers published before 2000 weren't included, all the publications under examination were selected without regard to study type, including conventional reviews, systematic reviews, clinical trials, case-control studies , and cohort studies. Studies included articles with humans >40 years of age and were not refined based on gender or ethnicity. Both human and animal studies were considered. There were no demographic limitations in the search. Up until April 2022, every article that was selected was in the English language.

The sample characteristics from each of the studies have slight variations. All nineteen studies assessed both male and female genders, with some explicitly focusing on adults of age 40+ years. The discrepancies regarding the effects of probiotics in terms of gender and age have not been understood very well.

Discussion

1.0 Introduction to probiotics

The term probiotics refers to the products consisting of living organisms or their products. Probiotics are available as various products such as medicinal products (live biotherapeutic products for human use), medical devices, probiotic foods (foods, food ingredients, dietary supplements or food for particular medical purposes), directly fed microorganisms (for animal use) and designer probiotics (genetically modified probiotics) [18].

Dietary supplements in general, do not have to undergo approval or premarket review by the Food and Drug Administration (FDA), in the United States. Biological products are the products which are marketed exclusively for either preventing or treating a disease. They are not required to be approved or reviewed by the FDA [18].

1.1 Consumption of probiotics

The most challenging job for physicians and patients is to choose the fitting probiotic for determined needs. Currently, in the United States and most other countries, there is inadequate support regarding the data and supervision on probiotic usage [19].

AIDS: Acquired Immunodeficiency Syndrome.*Adherence to the intestinal mucosa can also increase bacterial translocation and virulence. **Paradoxically, the most severely ill patients are the ones who mainly benefit from the use of probiotics, but this population is also at the highest risk of developing adverse effects. Therefore, physicians selecting probiotics for treatment should carefully consider the risks and benefits of their use and closely monitor the patient's condition after administering them. [35,36]

Furthermore, increasing commercial interest in exploiting probiotics' proposed multiple health benefits has contributed to this particular market sector's rapid growth and expansion.

There is a high scope of market advertising and exploiting the product for benefits. Thorough research has to be done prior, to prevent bad outcomes [36].

1.7 Limitations and challenges faced while using probiotics as therapeutics

A)Probiotic strain specificity-

Studies conducted by Sarah L Young et al., on dendritic cell function variation by Bifidobacterium has shown significant variation among species [37]. For that reason, it is inevitable to examine probiotic efficacy based on further classification by species instead of generalizing within the same species for optimum results.

B)Probiotic treatment schedules-

Multiple factors come into play to determine the count of viable bacteria that can colonize the intestine. These include the probiotic formulation, co-administration of food (which may protect the probiotics from gastric acid), the gastric pH (gastric acid secretion), intestinal motility and prior composition of the intestinal microbiota which vary among individuals [34].

C)Probiotics mechanism of action-

The major hindrance of using probiotics clinically is from the limitations of our understanding regarding their various methods of functioning.

D)Microbiological mechanisms-

A study by Sniffen et al., found adequate proof for 22 dissimilar varieties of probiotics from 249 trials. The results summarized that strain specificity and disease specificity determined the efficacy of probiotics. The determining factors include strain matching as regards to the chosen disease, formulation type and dosage. 15 out of 22 varieties of probiotics had moderate significance in terms of efficacy for a certain disease [19].

1.2 Probiotic's effects on inflammation

Modulation of the gut microbiota, immune system, and enhancement of the epithelial barrier are some advantages of probiotics [20]. Available evidence suggests that probiotic supplementation can significantly increase serum Total antioxidant capacity (TAC), Superoxide dismutase (SOD), Glutathione (GSH) and Nitric oxide (NO). They also reduce malondialdehyde (MDA) levels in adults [3,4].

Studies supporting the use of probiotics to reduce inflammation-

The results from 27 articles seem to conclude that probiotics and synbiotic supplementation improve antioxidant resistance and increase the number of antioxidant enzymes in the body [9].

People from various countries, either with underlying comorbidities or healthy individuals, were given probiotic supplementation. The results suggest that probiotic administration significantly reduces serum C-reactive protein (CRP) [11]. There has been growing evidence suggesting chronic low-grade inflammation (LGI) to be one of the possible mechanisms underlying the aging process. A meta-analysis of 49 articles examined the association of pre-selected interventions on two established biomarkers of inflammation, interleukin-6 (IL-6) and CRP, in middle-aged and older adults with chronic LGI. Results showed a significant small to considerable effect in reducing IL-6 levels, whereas for CRP, a small to medium effect was observed with probiotics [21].

Probiotics and a few of their secreted metabolic products act as ligands for innate immune system receptors. Thereby directly influencing key pro-inflammatory pathways, stimulating the differentiation and activity of critical immune cells (e.g., dendritic cells, T cells) which has been summarized in the Figure 2 below [22] .

It is essential for the probiotics to populate the intestinal tract to be of benefit. It is understood that some probiotic strains remain in the intestinal tract for more than two weeks after administration. This time interval perhaps helps in defending the intestinal mucosa from being colonized by other harmful microbes, by triggering immune response and strengthening mucosal barrier function [34]. Nevertheless, there is no evidence to prove that colonizing intestinal mucosa is mandatory for the beneficial action of probiotics.

E)Immunological mechanisms

The notable therapeutic effects of probiotics is majorly by two mechanisms:
- Epithelial homeostasis of the intestine regulated through toll like receptor (TLR) mediated actions and
- by specific effects from individual strains on certain immune functions [38,39].

Limitations

Although there has been evidence on the benefits of probiotics in terms of improving lipid metabolism, inflammation, mental disorders and their role in dementia, due to variation in microbiota of humans, other co-morbidities and altering efficacy of probiotics, their role as a therapeutic intervention cannot be assured strongly unless more RCT's and clinical trials are conducted. Additionally, the following limitations discussed in the article need to be addressed in future studies to further understand their mechanism of action [34, 37-39].

Conclusions

In this article, studies supporting and contradicting the benefits of probiotic supplements in terms of improving mood, reducing anxiety, inflammation, and alleviating cognitive symptoms have been discussed. Most of the studies found positive results without major adverse events. Considering the stated limitations, probiotics may provide the necessary early intervention to slow the development and severity of inflammation, cognitive decline, and mood disorders via modulating the gut-brain axis on multiple organ systems of the body. Due to their action on multiple systems, probiotics' effects and effectiveness must be established through thorough research studies and randomized control trials in order to derive therapeutic, economical, easily available alternative treatment options from them.

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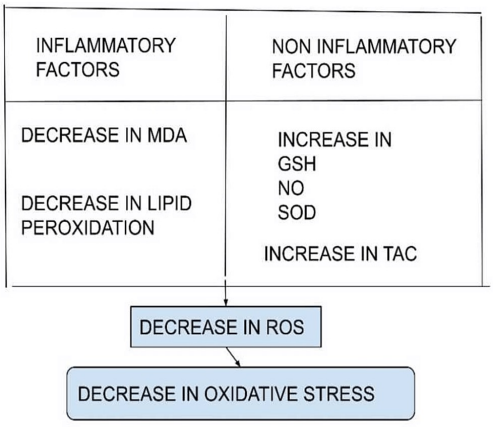

Figure 2: The effect of probiotics on inflammatory and anti inflammatory markers thereby contributing to a total decrease in oxidative stress (Original figure by the author) MDA: Malonaldehyde; GSH: Reduced Glutathione; NO: Nitric oxide; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; ROS: Reactive oxygen species.

They subsequently increase the production of critical regulatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF). TNF-alpha (TNF-alpha) secretion can be downregulated and the production of the anti-inflammatory IL-10 can be upregulated, especially when L. acidophilus and L. casei are present.

This study has shown that probiotic metabolites have beneficial anti-inflammatory and antioxidant properties, acting on intestinal epithelial cells followed by immune cells. However, not all probiotic strains have the same immunomodulatory effect on the host, indicating that the selection of probiotic strains used in nutraceutical formulations requires special consideration [22].

Studies contraindicating the use of probiotics to reduce inflammation-

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The following two studies have shown contrary results on how microbiota-driven therapy affects inflammatory markers in aged people [5],[23].

Ten RCTs involving 689 older adults were analysed (347 individuals placed in the microbiota-driven therapy group and 342 individuals placed in the placebo group). However, the current meta-analysis of the available randomised controlled studies failed to identify any notable advantages of microbiota-driven therapy for reducing inflammatory responses in aged people [5]. Nevertheless, these beneficial effects of decreasing inflammatory markers seem to be marginal compared to drug therapy and a healthy lifestyle and are clinically non-relevant [23].

1.3 Probiotic's effects on dementia, cognition, Alzheimer's, and Parkinson's progression.

Dementia

Dementia is a syndrome that affects memory majorly and cognitive functions to an extent where it makes daily functioning challenging. Most common conditions contributing to dementia, include neurodegenerative disorders [e.g., Alzheimer's disease (AD), Parkinson's disease (PD)], cerebrovascular disease (stroke), brain injury (accidents/trauma), and certain infections (most common being sepsis/meningitis). Among the most prevalent neurodegenerative disorders, AD has been the dominant cause of dementia globally. AD is a significantly debilitating disorder, proceeding from minor memory problems to a complete loss of mental functions and resulting in death eventually.

Studies supporting the effects of probiotics on cognition and dementia

Zhu et al., conducted a meta analysis with findings suggesting that dietary supplementation with probiotics at adequate amounts for twelve weeks or longer improves cognitive function, especially in people with MCI [24]. A double blinded Randomized control trial (RCT) conducted by the Frontiers editorial office showed that Probiotic consumption consistently for 12 weeks positively affects cognitive function and some metabolic statuses in AD patients. Hence, the results of using probiotics depend on the duration of the interval and consistency of intake [24].

There has been evidence suggesting the role of cholesterol metabolism in the brain and Aβ plaques generation in of AD.

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