

Influence of Probiotics on Depressive Disorders

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Depressive disorders have a major impact on occupational health and are costly to the economy and the healthcare system. Probiotics are live, non-pathogenic micro-organisms that, when ingested in adequate amounts, can colonize the intestinal tract and confer health benefits on the patient. Numerous studies have described the potential usefulness of certain probiotic strains in the treatment and prevention of depressive disorders, with differing results.

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1. Introduction

The World Health Organization (WHO) assembly proposes to develop national policies and action plans and to create institutional competencies for occupational health, ensuring, in collaboration with other relevant national health programmes, mental health ^[1]. According to the International Labour Organization (ILO), work helps to maintain good health as long as the worker's physical and mental capacities are not overtaxed ^[2].

Research shows that health interventions in the workplace can reduce sickness-related absenteeism by 27% and the cost of healthcare for companies by 26% ^[4]. Globally, 12,000 million working days are estimated to be lost each year due to depression and anxiety, at a cost of USD 1 billion per year in productivity loss. Related health problems in this area cause a loss of GDP (gross domestic product) of between 4 and 6% in most countries. In 2019, an estimated 15% of working-age adults suffered from a mental disorder ^[1], and the ILO has established a number of occupational illnesses, including mental and behavioural disorders ^[3].

2. Depressive Disorders

According to the International Classification of Diseases (ICD) ^[4], depressive disorders are characterised by a persistent mood of sadness, irritability and lack of interest in daily activities, with a loss of pleasure accompanied by other cognitive, behavioural or neurovegetative symptoms that significantly affect the individual's ability to function. Depression can be long-lasting or recurring and considerably impair a person's ability to work, study or to cope with everyday life. In its most severe form, depression can lead to suicide ^{[5][6][7]}. Depressive disorders represent one of the leading causes of disability in the world, affecting 6.8% of the adult population, with a higher prevalence in women than in men ^[8]. During the COVID-19 pandemic, 23% of frontline healthcare workers suffered from

depression and anxiety, and 39% suffered from insomnia. These professions are prone to depressive disorders, with an increased risk of suicide worldwide [9].

Psychological treatment is the first line against depressive disorders. This can be combined with antidepressants in cases of moderate and severe disorders. Effective psychological treatment may include behavioural activation, cognitive behavioural therapy, interpersonal psychotherapy and problem resolution treatment. While the most commonly used pharmacological treatments are serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants [10][11][12][13], it should be borne in mind that all antidepressant drugs have a latency period of response, which can vary between two and four weeks, until the 5-HT_{1A} receptor (serotonin receptor subtype located in presynaptic and postsynaptic regions) becomes desensitised. During this period, the patient, in addition to not noticing significant improvement, will perceive the possible side effects of the medication, which adds frustration, mistrust and possible non-adherence to the treatment [11][14]. Moreover, in most patients, the response to treatment is suboptimal, so that the dose has to be increased or combined with other antidepressants, further aggravating adverse symptomatology [15]. This insufficient response to antidepressants in a certain number of cases suggests that alternative or complementary medication, in addition to faster clinical response treatments, should be sought [16].

3. Microbiota

Microbiota are the set of microorganisms (bacteria, fungi, archaea, viruses and parasites) that reside in our body, which, in turn, can be differentiated into commensals, mutualists and pathogens [17][18]. Microbial communities can be found throughout the human body, the most complex and dense being the one inhabiting the digestive tract and, specifically, the large intestine (gut microbiota). It plays numerous roles in our organism, particularly the maturation and development of the central nervous system (CNS), as well as immune response development and modulation. It is referred to as the “second brain” of humans because of its regulatory effect on the central nervous system through neural, chemical and immune pathways [11][19][20]. Studies of the gut–brain axis (GBA) through the vagus nerve have provided essential insights into the healthy regulation of the hypothalamic–pituitary–adrenal axis (HPA), neuromodulation and neuronal plasticity [21]. This axis forms a network that includes the gastrointestinal tract, the enteric nervous system and the brain [20]. This gut microbiota play an essential role in the regulation of immune, endocrine and metabolic functions. Bacterial metabolites from this microbiota include the short chain fatty acids (SCFAs), made from fermentation of dietary fibre in the gut. Other enzymes and metabolites, such as tryptophan metabolites, gamma-aminobutyric acid (GABA), serotonin, dopamine, norepinephrine, acetylcholine and many neuropeptides, are produced by the microbiota present in the gut [16][19].

Given the ability of many probiotics to function as vehicles for the release of neuroactive compounds, such as classical neurotransmitters, they can be used as an adjunct therapy in the management of neurological disorders. For example, certain strains of *Lactobacillus* and *Bifidobacterium* secrete GABA, the main inhibitory neurotransmitter in the brain that regulates affective states, and increases levels of tryptophan, a precursor of serotonin, which suggests it is an antidepressant. The potential of some strains of *Lactobacillus* to produce

acetylcholine, an essential neurotransmitter in several cognitive processes, such as learning and memory, means that they should be included as clear potential adjuvant treatment, as psychobiotics [16].

Alterations in the gut microbiota, or dysbiosis, lead to a variety of diseases, such as inflammatory bowel disease, coeliac disease, metabolic syndrome, diabetes mellitus, colon cancer, as well as autism spectrum disorder, anxiety and neurodegenerative diseases [20][21]. This dysbiosis, due to increased permeability of the gut microbiota, induces decreased SCFA (short chain fatty acid) synthesis, HPA dysregulation and hypersensitivity of the vagus nerve, which predisposes one to depression [20][21] and, in some cases, to the progression or worsening of major depressive disorders (MDDs) [21].

4. Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits on the patient [22]. Recently, the International Scientific Association for Probiotics and Prebiotics [23] established a consensus document with a set of criteria for which microorganisms present in consumer products should be considered as probiotics:

- The microorganism in question must have been scientifically demonstrated to be a safe species that is supported by sufficient evidence of overall beneficial effect in humans.
- Evidence of its viability as a microorganism in human studies must be available.

Several studies [24][25] have proposed the concept of psychobiotics for probiotic bacteria, which, when consumed in adequate amounts, have a beneficial effect on mental health. The mechanisms of action by which bacteria exert their psychobiotic potential have not been fully elucidated. However, it has been found that these bacteria provide their benefits via the enteric nervous system or by stimulating the immune system. In addition, they affect psychophysiological markers of depression and anxiety. This can occur in three different ways: firstly, by affecting the stress response of the HPA axis and reducing systemic inflammation; secondly, through a direct effect on the immune system; and, thirdly, through the secretion of molecules, such as neurotransmitters, proteins and SCFAs [26][27].

Other studies link the intake of probiotics to the prevention and treatment of depression. The work of Bagga et al. [28] examined the clinical relevance of the gut–brain axis with the administration of a multi-species probiotic formulation for four weeks and associated it with changes in brain activation patterns in response to emotional memory tasks and emotional decision making, which were also accompanied by subtle changes in the gut microbiome profile. Akkasheh et al. [29] found that probiotic intake decreased depressive symptomatology as well as oxidative stress levels. In a study by Pirbaglou et al. 2016 [30], an improvement in immune function was observed in those taking probiotics, increasing the number of Natural Killer cells and lymphocytes. This said intake improved the bacterial composition of the gastrointestinal tract and, thus, behaviour and mental health. However,

despite these previous works, a review by Vaghef-Mehrabany et al. [31] concluded that current studies are not sufficient to support or reject the antidepressant effects of probiotics.

The different studies on the subject and the differing results obtained only reinforce the belief that not all probiotics are valid, and that it is important to select probiotic strains that can influence the altered physiological processes of the illness targeted by the probiotic product in question [32]. What is important is that the selection of particular strains is based on objective criteria, preclinical studies or plausible hypotheses as to why a specific strain was selected instead of another. In this way, and with the support of clinical studies on the benefit of specific probiotics in specific pathologies, probiotic products can make a significant contribution to the health of the population and, thus, generate cost savings for health systems.

According to the WHO action plan, the loss of economic production due to mental disorders will amount to EUR 16.3 billion between 2011 and 2030. Depression alone accounts for 4.3% of the global burden of illnesses and is one of the leading causes of disability worldwide [33]. Therefore, new treatment options, such as probiotics, could help treat those affected by the illness and contribute to improving the mental health of the general population.

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