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Designing probiotic-containing fermented food to improve mental disorders derived from childhood emotional neglect

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Emotional neglect (EN) during childhood is a worldwide problem compromising cognitive functions and mental health. Its scars can be life-lasting and often associated with community violence. Therefore, different approaches are mandatory to reduce its detrimental effects. This review discusses the EN's negative impact on the hypothalamic-pituitary-adrenal axis, its consequences on the immune system, and its subsequent impact on the limbic system. On the other hand, growing evidence shows that gut microbiota affects mental health and vice versa; mental disorders affect microbiota leading to dysbiosis and triggering other metabolic malfunctions. Production of functional fermented foods containing targeted probiotic strains and neuroactive compounds released during fermentation may aid to modulate inflammation via immune processes alleviating anxiety and depressive symptoms and improving cognitive function. Therefore, we propose that tailored probiotic-containing fermented food can improve the mental health of EN victims via immune system modulation.

KEYWORDS

emotional neglect, hypothalamic-pituitary-adrenal axis, probiotics, fermented food, mental health

Introduction

Child abuse (sexual abuse, physical abuse, and emotional abuse) is a problem that lacerates the entire culture and worldwide society. Particularly, negligence is a type of abuse defined as an act of omission by parents or caregivers, which can be harmful to the child (Leeb, 2008) and affects the health, survival, development, and dignity in the context of a relationship of responsibility, trust or power (World Health Organization, 1999). In emotional neglect, caregivers might address physical, academic, or medical needs, however, there exists a lack of psychological (emotional) availability from parents to their children (Stoltenborgh et al., 2013).

Almost 75% of the 6.6 million allegations of child maltreatment have been related to neglectful practices (U.S. Department of Health & Human Services, 2016). The clinical affectations are manifested in different domains of the individual and given the risk it represents to society, the magnitude of this problem is a serious concern, and therefore suitable solutions are still needed.

On the other hand, fermentation is an ancient biotechnology used to enhance the shelf life, nutritional value, and acceptability of food. Part of the microbiome in fermented food may act as probiotics, which are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014). In this sense, probiotics that deliver a benefit to patients suffering from psychiatric illness are classified as psychobiotics (Dinan et al., 2013). Furthermore, fermented food may also contain prebiotics, which are defined as substrates, such as oligosaccharides, that are selectively utilized by host microorganisms conferring a health benefit (Gibson et al., 2017). Additionally, a synbiotic is defined as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" (Swanson et al., 2020). Finally, biogenics are molecules produced by microorganisms that benefit the host, including the neurotransmitters gamma-aminobutyric acid (GABA), tryptophane (a serotonin precursor), and short-chain-fatty-acids (SCFAs) such as butyrate and acetate, neuroactive peptides, and vitamins (Aslam et al., 2020). Recent evidence shows that these fermented food components positively affect the microbiota-gut-brain axis, improving mental health in different mental disorders (Wastyk et al., 2021; Berding and Cryan, 2022). For examples of studies of probiotics on mental disorders see Supplementary Table 1. In this perspective article, we discuss the pathological basis of EN and how anti-inflammatory factors in probiotic fermented food may act as a treatment for the deleterious process of mental disorders in EN victims.

Emotional neglect and mental health

Emotional neglect (EN) is the most common type of abuse (Hildyard and Wolfe, 2002; Stoltenborgh et al., 2013; Cohen et al., 2017), especially when the increase of technology is becoming common in our societies and parents are less emotionally available to their children (Sundqvist et al., 2020; Nabi and Wolfers, 2022; Yang et al., 2023).

Clinical manifestations observed in neglected children are anxious attachment (Egeland and Sroufe, 1981), affectation on their ability to discriminate emotions (Pollak et al., 2000), negative affective reactions to tasks, and less presentation of positive reactions to the Peek-a-boo task (Smyke et al., 2007). Moreover, EN children showed more negative attitudes compared to other types of abuse (Egeland et al., 1983) and worse language development scores compared to the other maltreatment groups (Egeland and Sroufe, 1981). Also, it is registered with internalizing (anxiety disorders and depressive disorders) and externalizing symptoms and disorders like attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder, and conduct disorder (Zeanah et al., 2009) and with depression, and anxiety in adolescents (Hevia-Orozco and Sanz-Martín, 2017).

In adulthood, EN is related to countless affectations like psychiatric conditions such as depression, dysthymia, and social phobia (Spinhoven et al., 2010; Cohen et al., 2017), post-traumatic stress disorder (PTSD) (Grassi-Oliveira and Stein, 2008; Salokangas et al., 2020), as well as an increased risk of the onset of schizophrenia (Cancel et al., 2015), paranoid and avoidant personality (Johnson et al., 2000), having trouble identifying emotional expressions (Maheu et al., 2010) and differentiating them from one another (Kim and Cicchetti, 2009). Concerning cognitive affectations, detrimental effects on language and different cognitive functions have been described (Tarullo et al., 2007; Loman et al., 2009). For a review of psychiatric affectations, the reader is recommended to refer to Bos et al. (2011); and Dozier et al. (2012).

Pathological basis

It has been postulated that the absence or lack of socio-emotional stimulation in the child is a stressful environment. This can be explained through the mechanism described as "serve and return" (National Scientific Council on the Developing Child, 2012). In this experience-expectant social interaction, the caregiver addresses the child's socio-emotional needs through sounds and movements that the caregiver makes to attract the child's attention and allow them to develop emotional, attentional, and cognitive skills. The impossibility of having these expected and significant interactions in children triggers a metabolic response, which influences the development of the stress response system. In the case of lacking social and emotional stimuli, this response is represented by lower levels of cortisol. This happens in opposition to the higher cortisol levels found in other types of maltreatment (Doom et al., 2022).

In the face of a stress response, the activity of the hypothalamus-pituitary-adrenal (HPA) axis increases triggering a series of reactions that involves both the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by the paraventricular nucleus of the hypothalamus (Serra et al., 2005). Those hormones stimulate the anterior pituitary gland to produce a release of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal gland, located at the upper pole of the renal glands, for the final release of cortisol. The activation of the HPA axis derived from cognitive and emotional stressors occurs through the activation of the limbic system, which is in charge of detecting signals with an emotional charge from the environment, involving the participation of brain regions such as the amygdala (Bogdan et al., 2012) and the insula (Kim-Spoon et al., 2021).

Hypercortisolemia is a common finding in depression (Murphy, 1997; Gillespie and Nemeroff, 2005). Conversely, hypocortisolemia has been found in atypical types of depression (Fries et al., 2005). This type of depression is clinically featured by mood reactivity and two or more of the following features: increased appetite or weight gain, hypersomnia, leaden paralysis, and long-standing interpersonal rejection sensitivity (Parker et al., 2002). In the case of EN, hypocortisolemia has also been reported, derived from an affectation both in the corticotropin-releasing system and in the corticotropin-releasing hormone and adrenocorticotropic hormone. This was found in Rhesus monkeys that were separated from their mothers for 3 h per day that exhibit a flattened diurnal cortisol rhythm and a delayed cortisol peak in response to stress (Feng et al., 2011). This same pattern has been found in adolescents raised in shelters where socio-emotional deprivation is high (Koss et al., 2016). In adolescents with a history of institutionalization, it has been found that the normal cortisol peak in the morning (30–45 after waking up) is flattened (Leneman et al., 2018). This response is typical of adolescents under a scheme of parental care neglect but not parental harshness as previously reported (Gunnar and Donzella, 2002; Doom et al., 2022). Thus, neglectful experiences shape how the HPA axis functions and responds to stressors that the child will face in the following years of life (Koss et al., 2016).

Humans, as a social specie, perceive the lack of social stimuli as a stressor. This has been shown in animal models in social isolation in the early stages of life, and the natural response to this type of stressor is an increase in blood cortisol (Cacioppo et al., 2011). However, the continuous increases in glucocorticoids associated with acute stress over time cause the GR receptors found in the immune system to become less responsive to the influence of cortisol, inducing resistance to glucocorticoids, perhaps as a protective mechanism (Fries et al., 2005). Consequently, this causes the immune system activity to be gradually less regulated (Hawkley et al., 2012). The result of this lower sensitization of the immune system to the cortisol effect is the increment of different inflammation biomarkers such as C-reactive protein (CRP), interleukin-6 (IL−6), and tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β), among others (Nobis et al., 2020; Kerr et al., 2021).

Concerning the effect of the immune system on the brain, it has been postulated that some peripheral cytokines, such as IL-1β, IL-6, and TNF-α, may gain access to the central nervous system through active transport or may cross the blood-brain barrier (BBB) (Mapunda et al., 2022). Peripheral cytokines can also reach the central nervous system through their concentration with receptors of afferent vagal fibers, which project to the limbic system through the nucleus of the solitary tract, knowing this immuno-neuronal communication as the neuro-immune circuit (Irwin and Cole, 2011), affecting regions such as the limbic system and the structures that comprise it (Harrison, 2009). In this way, we can establish a link between negligence and affectations in the central nervous system, through alterations in the immune system.

What are the regions affected by EN through damage to the immune system that leads to changes in moods and subsequent psychiatric disorders? One of the main regions affected by EN is the limbic system (Sciarrino et al., 2018). This finding may be closely associated with the impact of some cytokines on these brain regions. For example, in a study carried out by Harrison (2009), the level of IL-6 in the nervous system was increased through the application of typhoid vaccination, and emotionally charged facial expression perception tasks were carried out during the acquisition of functional magnetic resonance imaging, in addition to applying questionnaires on the state of mind. The authors found a decrease in mood 3 hours after the application of the vaccine. Furthermore, these mood findings were related to decreased functional connectivity of the anterior cingulate, amygdala, medial prefrontal cortex, nucleus accumbens, and superior temporal sulcus. This finding confirms previous studies about the impact of the immune system on the structures of the limbic system (Haas and Schauenstein, 1997). It is likely that this lower cortico-limbic connectivity in children with a history of neglect and the subsequent hyperreactivity of the limbic system to emotional stimuli (Inagaki et al., 2012), was behind the psychopathological behaviors described in this population group (Callaghan et al., 2020).

Gut microbiota influence on the CNS

Regarding the analysis of mental health pathophysiology, one of the main agents that have gained importance is the gut-brain axis. A milestone on the gut microbiota (GM) influence on the gut-brain axis and mental health was Zheng et al. (2016) study where they demonstrated that fecal microbiota transplantation (FMT) of subjects with depression into healthy germ-free mice triggered depressive-like symptoms. GM involves a vast diversity of microorganisms, which is defined by the host's diet, medication, and health. Evidence shows that the communication between the gut and the brain is in a bidirectional sense, mental disorders may impact GM diversity and quality, whereas GM diversity plays an important role in maintaining mental health (Jiang et al., 2015; Dinan and Cryan, 2017; Winter et al., 2018). This bidirectional communication has also revealed great avenues of research to find the bases that support alterations in the anatomy and physiology of the brain that affect the behavior or cognition of people (Dinan and Cryan, 2012). Child abuse is not an exception (Callaghan et al., 2020). GM is altered in adult patients with a history of abuse and anxiety scores measured by the Hamilton scale (Zhang et al., 2022). In the same study, variability in the microbiota was found as an important mediator between abuse and depression in these participants (Zhang et al., 2022). Other authors have found similar results in patients with a history of sexual abuse (Chuang et al., 2019).

GM diversity often marks the difference between the health-promoting microbiome and pro-inflammatory dysbiosis (Galley et al., 2023). A systematic review comparing the GM taxa diversity in individuals with anxiety and or depression found that certain disorders are related to the abundance of pro-inflammatory taxa such as *Enterobacteriaceae* and *Desulfovibrio* (Simpson et al., 2021). Moreover, abundance in taxa such as UCG-002, *Ruminococcus_torques_group*, and *Ruminococcus*, were correlated to anxiety and depression symptoms in individuals that suffered stress in confined spaces, as a human anxiety model (Chen et al., 2022). These findings represent a great opportunity to explore new treatment pathways, such as fermented food containing probiotics or synbiotics to restore the GM eubiosis that may lead to alternative treatments for mental disorders.

Discussion

Fermented food (FF) is associated with decreased inflammatory markers and an increase in GM diversity (Wastyk et al., 2021). FF products can be engineered using different approaches to produce probiotic-containing functional food to aid mental disorders in EN victims related to chronic inflammation: (1) enrichment with butyrate-producing probiotic, either directly (Tamanai-Shacoori et al., 2017) or induced by diet (Bach Knudsen et al., 2018; Wastyk et al., 2021), (2) production of neuroactive compounds during fermentation, such as GABA (Cui et al., 2020), and (3) microbiota-targeted composition (Foster et al., 2021; Berding and Cryan, 2022).

SCFAs, such as butyrate, bind to free fatty acid receptors hindering inflammatory response (Rooks and Garrett, 2016). Butyrate regulates the production of cytokines in T-cells through histone deacetylase (HDACs) inhibition acting as an anti-inflammatory and antitumoral agent (Koh et al., 2016). Previous studies have shown that probiotic strains could hinder IL-6 production, a pro-inflammatory cytokine tied to cognitive development in children (Rasmussen et al., 2019), by generating butyrate (Pham et al., 2021). Moreover, evidence shows that the induction of cytokines production by probiotics

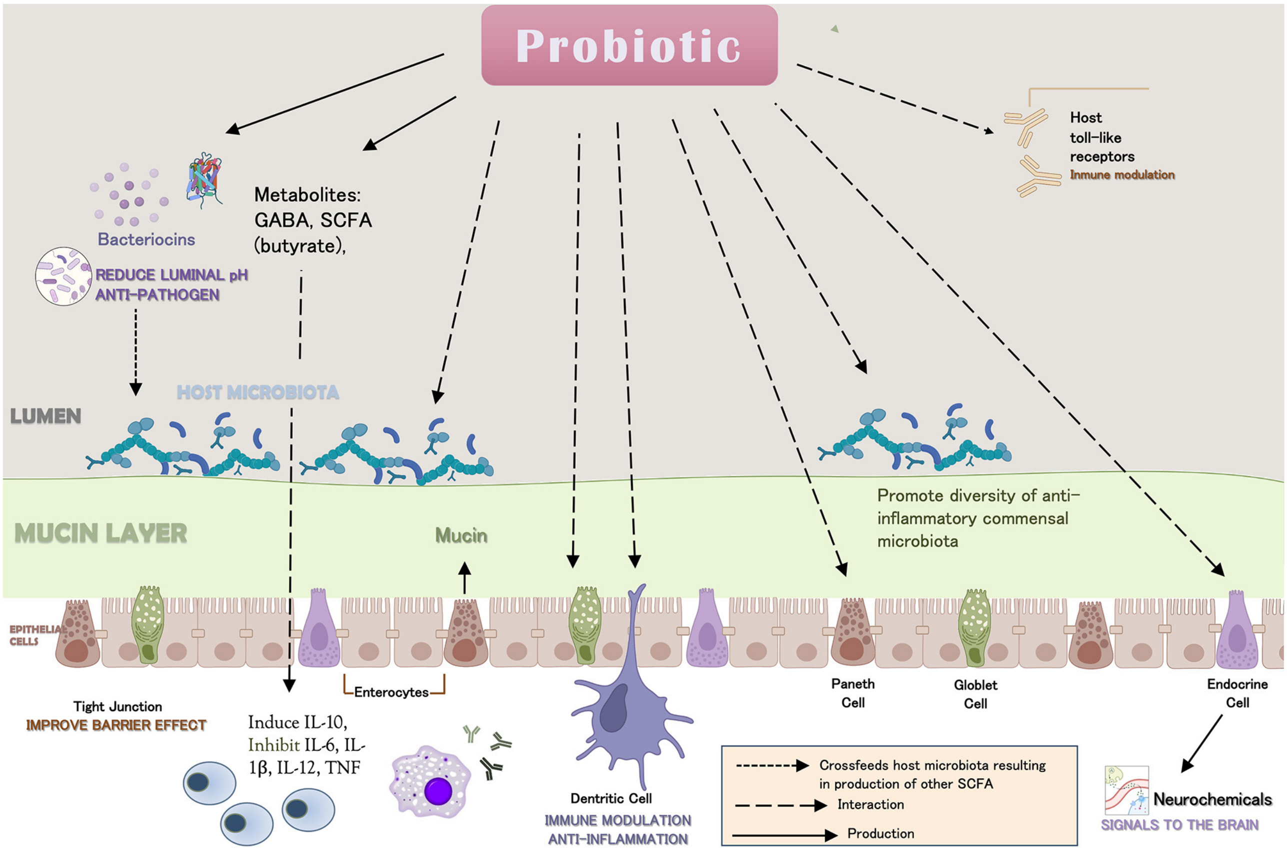

FIGURE 1
Mechanisms described of probiotics modulation on the immune system leading to anti-inflammatory activity.

is strain dependent. For instance, *Bifidobacterium* (*B.*) *infantis* CCUG52486, isolated from elderly subjects, showed a higher increase in the IL-10/IL-12 ratio compared to *Lacticaseibacillus rhamnosus* GG, *Lacticaseibacillus casei* Shirota or *B. longum* SP 07/3 in PBMC (You and Yaqoob, 2012). Although evidence suggests the benefit of butyrate-producing probiotics in mental disorders (Mörkl et al., 2023), more clinical studies are needed to test the efficacy in individuals with EN and their effect on inflammatory biomarkers.

Another anti-inflammatory mechanism of probiotics is their antipathogenic activity. The presence of pathogens can activate microglia inducing inflammation that in turn may lead to CNS cell damage and consequently to neurodegeneration (Rodríguez et al., 2022). Conversely, probiotics attenuate the pro-inflammatory effect of pathogenic bacteria induced by lipoproteins saccharides (LPS) (Vemuri et al., 2017). Their impact on the GM and the subsequent regulation of the immune system to reduce proinflammatory cytokines (Park et al., 2018) are summarized in Figure 1.

GABA can be a mediator to modulate inflammatory processes in EN mental disorders. GABA has been found naturally occurring in ripened cheese and lactic acid bacteria have been isolated with the capability to produce GABA in high yields by optimization of milk fermentation (Gonzalez-Gonzalez et al., 2019; Santos-Espinosa et al., 2020). Additionally, by adding L-monosodium glutamate, GABA production can be optimized by substrate induction during fermentation (Zhuang et al., 2018). Although the capability of peripheral GABA to cross the BBB is still in debate, a study demonstrated that it could regulate cytokine content in CD4+ T cells in peripheral blood (Bhandage et al., 2018). Therefore, the intake of GABA can act as an anti-inflammatory coadjutant in a dose-dependent- manner. Further studies are needed to establish an effective concentration in psychiatric patients.

Probiotics may also intervene in the GM improving microbiota alpha diversity and modulating the immune system improving cognitive function and mental health. For instance, intervention with *Lactobacillus acidophilus* DDS-1 in aging mice modulated the GM increasing levels of SCFA producer *Akkermansia* and *Lactobacillus* spp and lowering levels of mucin degraders *Bacteroides acidifaciens* and *Ruminococcus gnavus* (Vemuri et al., 2019). Besides DDS-1 increased levels of butyrate, downregulating the production of pro-inflammatory cytokines (Vemuri et al., 2019). *Lactiloplantibacillus plantarum* probiotic strains have also shown the capacity to increase *Veillonella*, *Bifidobacterium*, *Akkermansia*, and *Lactobacillus* genus, in human interventions, helping to restore the eubiosis (Echegaray et al., 2023). Moreover, tailored microbiota-targeted therapies based on microbiome-based biomarkers are promising (Foster et al., 2021). However, this approach is still in its cradle. More studies are necessary to associate host phenotypes to the GM that aid to define biomarkers, particularly in mental disorders (Manor et al., 2020).

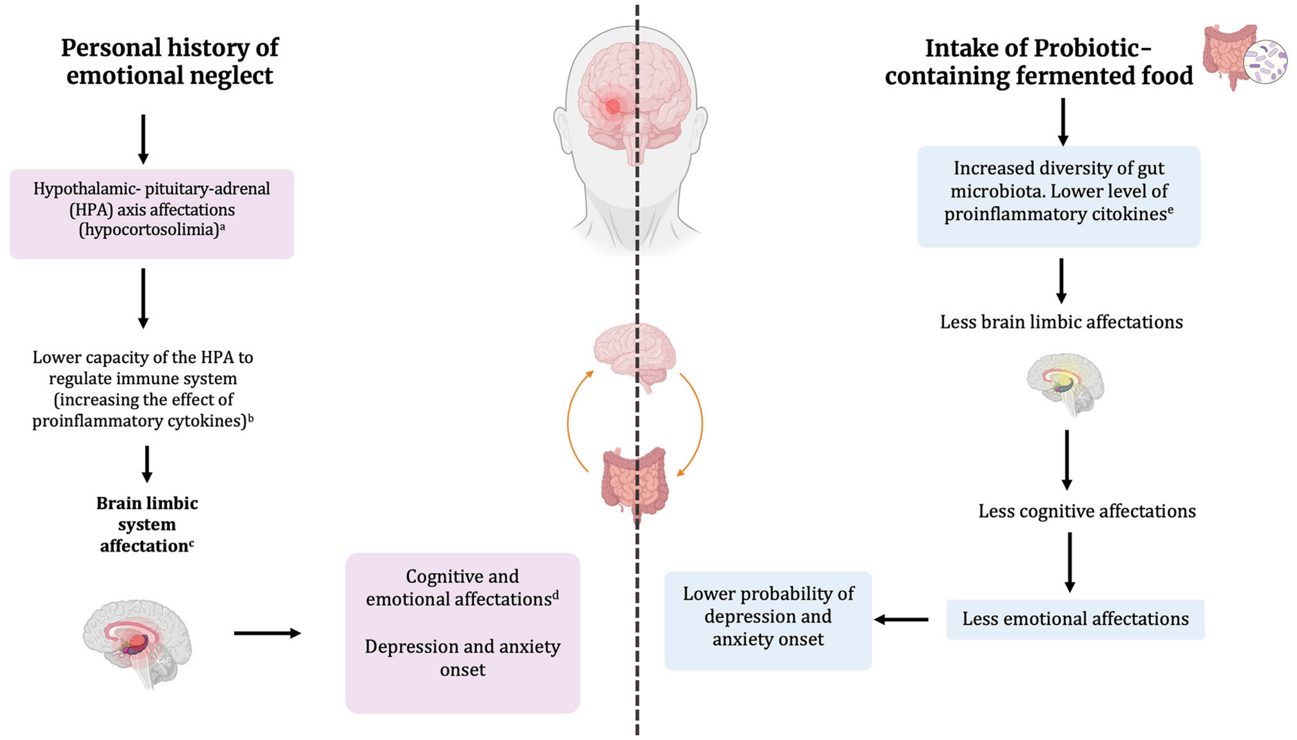

FIGURE 2
Overview of emotional neglect affectations in the HPA axis and the limbic systems are countered by probiotic-containing fermented food intake reducing the probability of depression and anxiety via immune system modulation. (a) Reilly and Gunnar (2019); (b) Elenkov and Chrousos (2002); (c) Harrison (2009); (d) Sciarrino et al. (2018); (e) Simpson et al. (2021).

A systematic review of clinical trials from 2016 to 2022 in patients with depression reports that consumption of probiotics or synbiotics showed improvement with a short margin of effect compared to placebo. However, this was not the case for prebiotics, which did not show a significant difference (Alli et al., 2022). This indicates that prebiotics alone cannot always improve health conditions in patients with dysbiosis, possibly due to the insufficient presence of beneficial microbiota to promote significant changes. Thus, intervention with tailored microbiome composition, including probiotics may improve eubiosis and mental health in individuals (Kang et al., 2014; Dash et al., 2015; Bear et al., 2020; Manor et al., 2020). Finally, cognitive-behavioral interventions will increase the opportunities for synbiotic therapy success. Those types of intervention need to cover the lack of personal stimulation through individual, long - term and affective support, for instance, an after-school program to teach virtues and values to EN children.

In summary, evidence shows that the immune system is affected by the HPA axis disturbed by EN chronic stress. This disturbance has been associated with GM dysbiosis in EN individuals. Due to the bidirectional nature of gut-brain axis communication, this affectation can be reversibly modulated using probiotics' capability to act as an anti-inflammatory agent through the production of bioactive compounds during fermentation. When probiotics are administered in functional FF with a prebiotic matrix as synbiotics, they can improve the GM to achieve a healthier microbiota that aims to regulate the immune system may improve EN symptoms, and reverse its psychosocial detrimental effects, as proposed in Figure 2. Hence, we propose tailored fermented food, such as fermented milk, yogurt, or cheese, containing probiotic strains able to produce SFCAs including butyrate, and/or GABA, as means to promote anti-inflammatory activity that may contribute to other types of intervention, such as cognitive-behavioral therapy, for people with anxiety and depression with antecedents of EN.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsufs.2023.1161153/full#supplementary-material

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