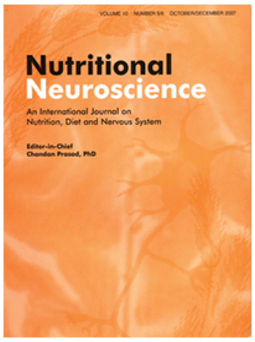

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Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety

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Mental disorders including depression and anxiety are often comorbid with gut problems, suggesting a bidirectional relationship between mental health and gut function. Several mechanisms might explain this comorbidity, such as inflammation and immune activation; intestinal permeability; perturbations in the hypothalamic–pituitary–adrenal axis; neurotransmitter/neuropeptide dysregulation; dietary deficiencies; and disturbed gut microbiome composition. The potential of modulating the microbiome–gut–brain axis, and subsequently mental health, through the use of functional foods, is an emerging and novel topic of interest. Fermented foods are considered functional foods due to their putative health benefits. The process of microbial fermentation converts food substrates into more nutritionally and functionally rich products, resulting in functional microorganisms (probiotics), substrates that enhance proliferation of beneficial bacteria in the gut (prebiotics), and bioactive components (biogenics). These functional ingredients act biologically in the gastrointestinal tract and have the ability to modify the gut microbiota, influence translocation of endotoxins and subsequent immune activation, and promote host nutrition. This narrative review explores the theoretical potential of the functional components present in fermented foods to alter gut physiology and to impact the biological mechanisms thought to underpin depression and anxiety. Pre-clinical studies indicate the benefits of fermented foods in relieving perturbed gut function and for animal models of depression and anxiety. However, in humans, the literature relating to the relevance of fermented food for treating or preventing depression and anxiety is sparse, heterogeneous and has significant limitations. This review identifies a critical research gap for further evaluation of fermented foods in the management of depression anxiety in humans.

Keywords: fermented foods, gut health, probiotics, prebiotics, biogenics, depression, anxiety

Introduction

Unipolar depression is a highly prevalent condition, affecting 6.2% of 18–85-year-olds in Australia.[1] It is a leading cause of disability-adjusted life years (DALYs) globally and in Australia.[2] Anxiety disorders are even more prevalent than depression, with 14.4% of Australians aged 18–85 experiencing an anxiety disorder within the past 12 months.[1] The aetiology of major depressive disorder and anxiety-related disorders remain complex and inconclusive. However, there is robust evidence linking various gut microbiome-related biological pathways to the aetiology of depression, in particular.[3] These include the inflammatory hypothesis [e.g. elevations in C-reactive protein (CRP) and inflammatory cytokines, and oxidative and nitrosative stress]; 'leaky gut' hypothesis; the hypothalamic–pituitary–adrenal (HPA) axis (e.g. cortisol perturbations); neurotransmitter/neuropeptide imbalances (e.g. dopamine, serotonin, gamma-aminobutyric acid (GABA), brain-derived neurotrophic factor (BDNF), and other systems); and certain nutritional deficiencies (e.g. omega-3, tyramine, and vitamins).[4–8]

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Conventional pharmacological treatments for depression and anxiety do not work for all individuals.[9] Given the substantial burden arising from the common mental disorders, the development of new, accessible treatments for depression and anxiety that can augment existing treatment practices would be beneficial to the economy, healthcare system, and individuals. Diet is of particular interest as it may play a role in influencing the risk for mental health conditions.[10] For instance, high-quality diets including the Mediterranean diet are protective against depression,[11] while poor quality diets such as the western diet are associated with an increased risk of depression.[12] Fermented foods are an important component of many traditional diets, including the Mediterranean diet, and these have recently gained attention due to their putative health benefits.[10]

Fermentation is a biochemical process involving microorganisms being deliberately added to foods, or occurring naturally in foods. Due to the fermentation process, fermented foods (such as sauerkraut, kimchi, miso, soy sauce, tempeh, kombucha, kefir, cheese and yoghurt), contain three main functional components that may be present in varying amounts: functional microorganisms (probiotics), prebiotics, and biogenics – metabolites that make fermented foods functionally active.[13,14] Some or all of these components can: influence the gut microbiome composition and function;[15] alter macronutrient breakdown and absorption;[16] change gut permeability;[17] and stimulate immune cells in the gut.[18,19] Fermented foods have also been reported to have direct anti-inflammatory,[20] immunomodulatory,[21,22] and brain modulatory[23] effects. For this reason, fermented foods may have the potential to modify depression and anxiety by altering the underlying pathways involved in the aetiology of these common mental disorders.

The aim of this review is to outline specific features of fermented food and their impact on neural mechanisms that could potentially be utilized as preventive or treatment strategies in depression and anxiety. We firstly provide an overview of fermentation processes and the functional properties of fermented foods. We then discuss how these functional properties may influence some of the hypothesized gut-related biological mechanisms underpinning anxiety and depression. We then review the clinical evidence describing the relationships between fermented food consumption and depression or anxiety-related symptoms in humans. We conducted a broad literature search via Ovid Medline, search terms included 'Depression' or 'Depressive' or 'anxiety' or 'neurotic*' or 'stress' or 'fermented' or 'gut barrier' or 'gut inflammation' and 'gut microbiota'. All articles were reviewed for relevance and the included studies are listed in Table 1. Finally, we discuss the possible implications for clinical practice and give recommendations for future research.

The fermentation process

The fermentation of foods begins with the introduction of bacteria or yeast to initiate the fermentation process[24] (see Fig. 1.). The microbes then transform an initial food substrate into a complex end-product that is biochemically and physiologically different to the initial substrate.[25] Fermentation is a slow, anaerobic exothermic reaction whereby organic molecules are broken down into simple molecules by microbial enzymes.[26] The two main types of fermenting processes are alcoholic and lactic acid fermentation.[27,28] The production of lactic acid from glucose[27] can be further subdivided to homolactic and heterolactic fermentation, depending on the pathways hexoses (monosaccharides with six carbon atoms) are metabolized.[29] In homolactic fermentation, the pyruvate molecule is catabolized to lactic acid, and in heterolactic fermentation a mixture of other, non-lactic acid, by-products are generated.[30] The microbes that undertake lactic acid fermentation are termed lactic acid bacteria (LAB). The LAB group includes genera such as *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, *Bifidobacterium*, and *Leuconostoc*.[31] LAB are used to produce various products such as cheese, butter, yogurt, kefir, sauerkraut, pickles, fermented fruits and vegetables, soy sauce, sourdough bread, and fermented cereals.[32] Alcoholic fermentation is heterolactic and involves the action of yeast, *Saccharomyces*, on the food substrate. In the absence of oxygen, the yeast and bacteria transform sugars into ethanol and CO_2. This process is central to the manufacturing of bread, beer and wine.[33]

Functional components of fermented foods

The three main functional components of fermented foods are functional microorganisms (probiotics), prebiotics, and biogenics.[13] The functional microorganisms present can exert antimicrobial, antioxidant and probiotic effects.[25] 'Probiotics', by definition, refers to microorganisms that might confer health benefit[34] when administrated in adequate quantities.[35] Many of the LAB, such as *Lactobacilli* and *Bifidobacteria*, have putative probiotic effects.[25,34] Fermented food consumption can inoculate the gut with beneficial probiotics, if the microbial cultures are available in sufficient concentrations and are in a viable state.[36] Two recent randomized controlled trials support the efficacy of probiotics for reducing symptoms of mental disorders.[37,38] The probiotics present in fermented foods may confer other benefits relevant to mental health, such as improved colonic health; immunomodulatory benefits; reductions in allergy responses and

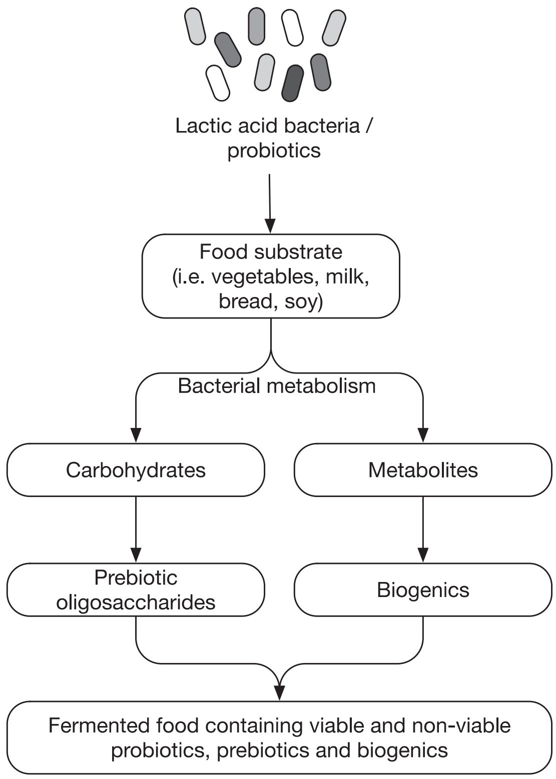

Figure 1 Production of fermented foods. Fermented food contains probiotics, biogenics (functional metabolites), and prebiotics. The fermentation process is initiated by the addition of lactic acid bacteria to a food substrate. The Lactic acid bacteria are predominantly probiotics, their metabolic action on the food substrates produces prebiotic oligosaccharides and bacterial metabolites that are categorized as biogenics (for example, vitamins and neurotransmitters).

vitamin synthesis;[39,40] and production of neurotransmitters.[41] Even non-viable probiotics that have lost their ability to colonize the colon may still be bioactive; gamma-irradiated probiotics have been shown to have anti-inflammatory properties via their DNA in a murine model of colitis.[42]

Fermented foods also contain varying amounts of prebiotics. Prebiotics are non-digestible foods that act as substrates for the bacteria and thereby stimulate growth or activity of beneficial bacteria in the colon.[43] During the process of food fermentation, many prebiotic oligosaccharides are formed[44] and these may promote the survival and growth of beneficial bacteria in the gastrointestinal tract.[45]

Fermented foods also contain biogenics, which alter the nutritional value of the food in comparison to the unfermented substrate. Biogenics are biochemical components derived through microbial metabolism and they contain numerous direct health benefits that are not essentially mediated through gut microbiota.[46] For instance, vitamins, lacto-try-peptides, bacteriocins and immunopotentiators are produced during the process of fermentation and these are considered biogenics.[47] In addition, some of the bacterial metabolites (biogenics) also demonstrate immunostimulating[47] and neuroactive properties. For instance, gamma-aminobutyric acid (GABA) is a neurotransmitter and abundantly found in fermented foods.[48] Thus, biogenics may make fermented foods functionally active, even if live microorganisms are no longer present at the time of consumption.[46]

Hypothesized mechanisms underpinning potential modification of mental disorders by fermented foods

There is evidence linking various gut-related biological pathways and mechanisms to the aetiology of depressive and anxiety disorders.[3] Many of these are related to the gut, such as inflammation associated with increased intestinal permeability,[49] microbial dysbiosis,[50] HPA axis dysfunction,[51] neuroactive substances[52] and dietary deficiencies.[53] The functional properties of fermented foods may modulate depression and anxiety through their action on some of these pathways linked to depression and anxiety (Fig. 2).

Inflammation in anxiety and depression

Systemic inflammation is implicated in the aetiology of depression.[54,55] Major depressive disorder and anxiety-related conditions are associated with elevated levels of markers of inflammation[56–58] as well as immune dysfunction.[59,60] Inflammation is the body's response to injury or infection[61] and involves the influx of immune cells and release of specific inflammatory cytokines (e.g. IL-1b, IL-6, TNF-α). At a cellular level, the inflammatory response is driven by activation of nuclear factor kappa B (NF-κB) and increased transcription of pro-inflammatory molecules.[62] Pro-inflammatory cytokines activate the HPA axis, perturb serotonin metabolism, and are involved in neuroprogression,[63,64] and these are relevant to depression and anxiety. There is extensive evidence to support inflammation as a driver of depression risk. For example, exogenous cytokine infusions can cause depressive symptoms in humans;[65] a substantial proportion of people given interferon for the treatment of hepatitis C develop major depression.[66] Observational data also support systemic inflammation as a risk factor for major depressive disorders.[67]

Systemic inflammation may be induced through impairments to the gut barrier.[49,68] Under normal healthy conditions, the intestinal mucosa act as a shield preventing bacteria and endotoxins from reaching the blood stream.[69] However, factors such as intestinal inflammation associated with gut disease, poor quality low-fibre diets,[70] high alcohol consumption,[71] high-fat diets[72] and other factors that injure mucosal cells in the gut[73,74] result in increased permeability of

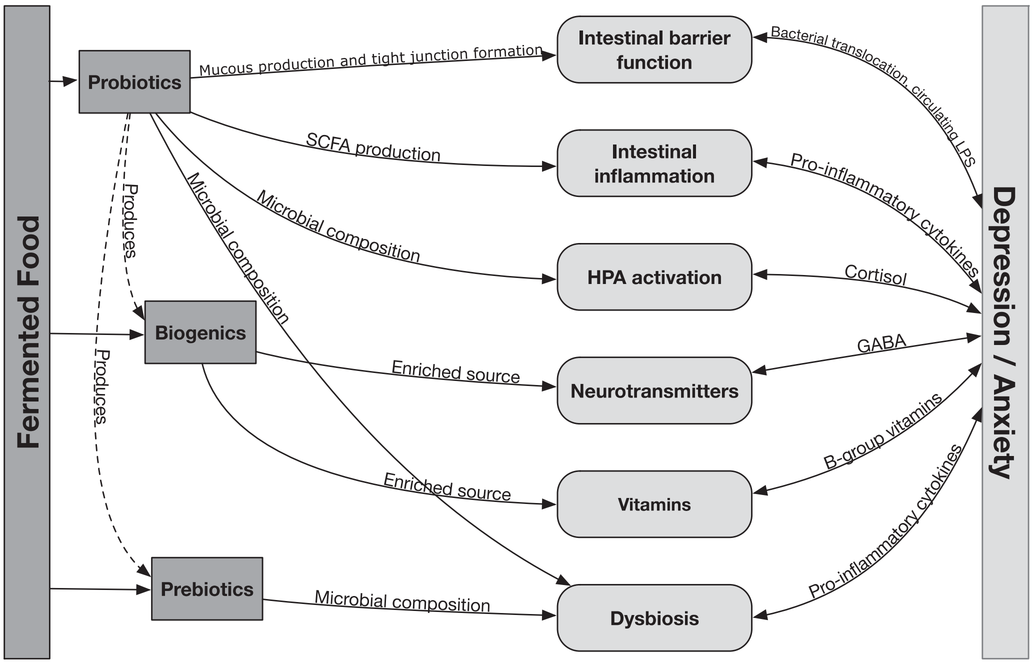

Figure 2 Interaction between the functional components of fermented food and the hypothesized biological mechanisms influencing mental health.The dark grey rectangular boxes are the functional components of fermented foods. The arrows from each functional component to the hypothesized biological mechanisms influencing mental health (rounded rectangular boxes) indicate a benefit or restoration. The double-headed arrows denote bidirectional relationships between the hypothesized biological mechanisms and depression and/ or anxiety.

the gut lining. Interestingly, similar factors drive permeability of the blood brain barrier.[75] Translocation of Lipopolysaccharide (LPS) is facilitated through greater intestinal permeability.[49] LPS is an endotoxic, cell wall component of gram-negative bacteria. It activates the innate immune system via toll-like receptors (TLR) and initiates pro-inflammatory cytokine production.[49] Translocated LPS promotes chronic neuroinflammation by the production of brain TNF-α, as brain microglia are triggered to increase pro-inflammatory cytokine production.[76]

Influence of fermented foods on inflammation

Although inflammation is associated with depression,[54,55] direct evidence for fermented foods alleviating inflammation in depressed patients is lacking. The current evidence focuses on gastrointestinal (GI) disorders;[77,78] these are often comorbid with depressive and anxiety symptoms and associated with increased levels of inflammation.[79,80] Indeed, a meta-analysis found that antidepressants were effective in treating functional GI disorders.[81] Fermented food reduces inflammation in GI disorders.[77,78] Fermented foods are postulated to modify inflammation by reducing pro- circulating inflammatory cytokines,[78] producing short-chain fatty acids (SCFA),[77] and improving the gut barrier functions that are relevant to both GI and mental disorders.[82]

A study published in 2005 showed that malted milk containing *L. salivarius* or *B. infantis* was able to reduce the pro-inflammatory cytokine levels in IBS patients compared to the baseline, following ingestion for 8 weeks. This study showed a normalized ratio of anti-inflammatory to pro-inflammatory cytokines levels as a response to treatment with the fermented food product.[78] Another study showed that fermented milk containing *L. paracasei* was effective in reducing the cell death caused by pro-inflammatory cytokines (IFN-γ/TNF-α) in vitro in Caco-2 cell lines.[83]

SCFA are major metabolic end products (acetate, propionate, and butyrate) of gut microbial fermentation.[84] Fermented foods are a potential source of SCFA, given that they are a product of microbial fermentation. However, robust data on the type and concentrations of SCFAs in fermented foods are currently lacking in the literature. SCFAs influence immune function and inflammatory responses via cellular receptors. Butyrate may attenuate inflammation via several pathways; it enhances intestinal barrier integrity[85] thereby limiting the translocation of intestinal contents, and inhibiting NF-κB activation.[55] In addition, butyrate has the potential to modulate inflammation by repressing LPS and cytokine-induced pro-inflammation (TNF-α, IL-6 and NO).[86] A study showed that when humans with IBS symptoms consumed fermented milk products containing dairy starters and *B. animalis*, the severity of IBS symptoms reduced compared to the controls. Moreover, the study demonstrated that patients with IBS who consumed fermented dairy had higher levels of butyrate-producing bacteria and SCFA concentrations in faeces.[77] This suggests that fermented foods may dampen inflammation by favouring the growth of butyrate-producers in the gut along with increasing the production of butyrate and total SCFA concentrations.

Insults to the gut barrier contribute towards systemic inflammation.[87] The probiotics, prebiotics and biogenics in fermented foods collectively contribute to replenishing the gut barrier by enhancing gut epithelial function[88] and mucous production, and enhancing tight junction and barrier integrity.[89] Most of the evidence relating to the potential of fermented food to influence gut barrier functions and mucosal immunity are derived from animal models.[82,90] Mice fed fermented milk containing probiotics showed an increased number of goblet cells compared to the control group.[88] The intestinal goblet cells are vital to maintain barrier integrity and this study suggests the capacity of the fermented milk to strengthen the gut epithelia by augmenting the barrier functions.[91] Concordantly, another mouse study investigated the effects of *B. lactis* present in fermented milk on intestinal barrier integrity.[82] This study showed that *B. lactis* counteracted increased intestinal permeability by restoring the function of tight junction protein such as occludin and junctional adhesion molecule-A expression to control levels in rats subjected to partial resistant stress.[82] Moreover, when probiotic strains (*L. paracasei* subsp. *paracasei* G15 and *L. casei* G14) extracted from traditional Chinese Yak yogurt were administered to mice with type 2 diabetes for 6-weeks,[92] the mice showed reduced intestinal mucosal permeability, lower levels of circulating LPS and inflammatory cytokines, and improved epithelial barrier function, compared to control mice.

In addition to this, some studies showed the potential of bioactive components in fermented foods to modulate gut barrier functions.[17,93] For instance, a study that compared the effect of Fermented Yupingfeng polysaccharide (a supplement used for treating inflammatory diseases) against unfermented Yupingfeng showed that the fermented product was more effective in maintaining barrier integrity and functionality in the rabbit gut.[17] Fermented Yupingfeng altered the gut barrier integrity by upregulating the expression of tight junction proteins, zonula occludens 1, claudin mRNA in the jejunum and ileum. Woo *et al.*[93] demonstrated the potential of a fermented soy bean and barley mixture, which are sources of isoflavonoids and β-glucan,[94,95] to affect gut barrier function. The fermented mix reduced the epithelial barrier dysfunction by increasing the tight junction protein levels in colonic tissues, thus preventing bacterial translocation to mesenteric lymph nodes.

These data suggest that fermented food have the potential to modulate inflammation. Although they are not direct evidence for the efficacy of fermented foods in reducing inflammation linked to depression, these findings demonstrate that fermented foods affect pathways that influence inflammation.

Gut microbiota dysbiosis in anxiety and depression-like behaviour

Dysbiosis is a condition where the host microbiota are disturbed compared to healthy subjects, and can be categorized by a loss of beneficial microbes, expansion of pathobionts and loss of diversity.[96] Microbial dysbiosis has been linked to mental disorders.[97] In humans, the links between symptomatology, bacterial diversity, bacterial species and their function in depression remain unclear. However compositional differences have been noted between those with depression and healthy controls.[50,98] Specifically, differences between the levels of Actinobacteria, Bacteroides, Firmicutes,[99–101] *Lactobacillus and Bifidobacterium*,[98] the *Prevotellaceae* family and the *Prevotella* genus[102] have been observed between those with clinical depression and non-depressed controls.

Extensive pre-clinical evidence demonstrates that intestinal microbiota influence anxiety-like behaviours,[103–105] and that depression-like behaviours can be modulated by microbial manipulation through probiotics[106,107] antibiotics[108,109] or by human faecal transplant.[50] For instance, germ-free mice raised without commensal bacteria, developed depression-like behaviours when faecal microbiota were transplanted from the patients with the major depressive disorder.[50]

Influence of fermented foods on gut microbiota

There is some evidence indicating the potential of fermented foods to modulate the composition of the gut microbiota. An animal study demonstrated that administration of fermented barley and soybean increased the proportion of *Lactobacilli* and *Bacteroides,* in mice with IBD.[93] In addition, the fermented food dampened inflammation and improved intestinal barrier integrity, as discussed above.[93] Fermented foods have also been reported to alter human gut microbiota composition. Viega *et al.*[77] demonstrated that fermented milk reduced the abundance of a *B. wadsworthia,* a pathogenic species associated with inflammation, and increased the abundance of butyrate-producing bacterial species. Another study showed that fermented milk containing *L. casei* increased the abundance of *Lactobacillus* and *Bifidobacteria* in stools, both of which are considered beneficial probiotics.[15] Also, a randomized controlled trial demonstrated that fermented Kimchi altered gut microbiota composition and reduced the Firmicutes/ Bacteroidetes ratio compared to a control group consuming fresh Kimchi.[110] These trials support the efficacy of fermented foods in modulating the composition of the gut microbiota.

HPA axis dysfunction in anxiety and depression

The biological response to stress is mediated through the HPA axis via the actions of the central nervous system and the endocrine system. Exaggerated HPA axis responses have also been linked with the aetiology of depression and anxiety disorders.[51] Perturbations in cortisol levels and other adrenal hormones are associated with activation of the sympathetic ('fight or flight') response, and activation of the emotional centres of the brain, such as the amygdala and hippocampus. This is understood to underlie the physiological and cognitive symptoms observed in many anxiety disorders.[51]

Increased concentration of serum cortisol is seen in those with depression and anxiety due to the activation of the HPA axis.[111] As previously discussed, depression and anxiety conditions are also often accompanied with increased pro-inflammatory cytokines in circulation,[112–114] and these cytokines can disrupt the gut barrier leading to gut permeability and increased bacterial translocation leading to immune and neuronal cells activation, thereby facilitating HPA axis activation.[115–117]

There is also evidence that the HPA axis is influenced by the intestinal microbiota and factors released by the bacteria. Intestinal dysbiosis is associated with HPA axis activation and, conversely, stress is also associated with changes in gut microbiota.[8,118,119] For example, infants of mothers with high cumulative stress scores during pregnancy had high abundances of pathogenic *Proteobacteria* strains and a reduced abundance of Lactic acid bacteria and *Bifidobacteria* compared to those born to mothers with lower stress scores.[120]

Influence of fermented foods on the HPA axis

While there is evidence that fermented foods have the potential to restore gut barrier function,[83] which in turn may influence the HPA axis, there are currently no studies directly assessing the capacity of fermented food to influence HPA axis activity. However, there are data demonstrating that probiotic administration attenuates HPA axis activation. Michael *et al.,* investigated the anxiolytic effects of a probiotic formulation containing *L. helveticus* R0052 and *B. longum* in rats and human volunteers[121] and showed that the probiotic formulation reduced anxiety-like behaviour in rats, mitigated psychological distress, and reduced urine free cortisol levels in volunteers.[121] This may be a direct effect of the probiotic strains rather than fermented foods. However, given that probiotics are the main component of fermented foods and some probiotics have the capacity to modulate the HPA axis, fermented food consumption may also have the potential to modulate HPA activity and the stress response. This warrants investigation, but if efficacious may have implications for the treatment of depression and anxiety disorders.

Altered concentrations of neuroactive substances in depression and anxiety

Animal and human evidence demonstrates the involvement of neurotransmitters, such as gamma-aminobutyric acid (GABA), in the aetiology of depression and anxiety. For example, depression is associated with reduced GABAergic action, while treatment with antidepressants can improve GABAergic function.[52] The gut microbiome synthesizes various neuroactive substances including GABA, norepinephrine, serotonin and dopamine, Brain-derived Neurotrophic Factor (BDNF), and ammonium. For instance, *Lactobacillus* produce acetylcholine and GABA; *Bifidobacterium* species produce GABA; and *Escherichia* produces norepinephrine, serotonin and dopamine.[41] These factors are hypothesized to act locally on the enteric nervous system to influence brain activity via the vagus nerve.[106] However, currently, it is unclear as to whether these neurotransmitters are actually absorbed through the gut into the blood stream to exert influences beyond the enteric nervous system, including on the central nervous system.[55]

Influence of fermented foods on neuroactive substances

Live cultures (probiotics) present in fermented food can synthesize GABA.[122,123] Many strains of the LAB are capable of producing GABA and are already considered a safe and natural way to enhance the bioavailability of GABA in food products.[124] Fermented food products such as yogurt,[48] soy milk[125] and cheese[126] have recently been modified to indirectly increase GABA by incorporating the bacteria that produce it. Attempts have also been made to understand the effect of dietary GABA on the brain. Mabunga *et al.*[127] designed a study to investigate the effects on sleep in mice using dietary GABA derived from fermented rice germ. The study found that GABA ingestion was protective against caffeine-induced sleep disturbance. However, it was unclear whether the effect was mediated by a local impact on the intestine or changes to blood and/or the CNS. Other animal experiments have endeavoured to study the effect of GABA present in fermented foods in improving depressive and anxiety-like behaviours.[128–130] For example, a fermented product with a full dose of GABA significantly decreased immobility time in a forced swimming test, indicating that a fermented food intervention reduced depressive-like behaviours, and possibly enhanced the bioavailability of GABA.[128] Likewise, Daglia *et al*. compared two tea products rich in GABA, 'Green GABA' (non-fermented) and 'Oolong GABA' (fermented), in a post-stroke depression model of 60 mice.[130] Depressive and anxiety-like behaviours were assessed through the forced swim test and a tail suspension test respectively. The study reported that consumption of the fermented GABA-rich tea product attenuated depression-like behaviours compared to the non-fermented tea product. Fermented red ginseng was also shown to be superior in reducing depressive-like behaviours compared to non-fermented red ginseng hydrolysed by malted barley, unaltered red ginseng, or fluoxetine when fed to rats over a 2-week period.[129] These examples demonstrate the potential of biogenic neuroactive substances to influence depressive-like behaviours in animals.

Altered B-group vitamin levels in depression and anxiety

Humans are unable to synthesize many of the vitamins required for cellular metabolism and depend on extrinsic sources from the diet. Diets deficient in folate or vitamin B12 are associated with depression, particularly in older adults.[53,131] However, certain gut microbiota also synthesize vitamins, particularly the B-group vitamins and vitamin K. It is estimated that the microbiota synthesize a large proportion of the daily reference intakes (37% for folate, 31% for cobalamin (B12), and 86% for pyridoxine).[132] However, vitamin synthesis may be limited in those with gut dysbiosis.[60] This may be relevant in a depressed population, given depression is potentially linked with gut dysbiosis.

Influence of fermented foods on B-group vitamin levels

The microorganisms in fermented foods produce a range of B-group vitamins, including riboflavin (B2), niacin (B3), pyridoxine (B6) and folate.[13] Susanna *et al.*[133] showed that yeast fermentation significantly increased the folate content in the process of sourdough fermentation of rye. Additionally, riboflavin (B2) producing strains have been extracted from fermented milk products.[134] This, taken together with the alterations to microbial composition, may increase B-group vitamin synthesis.

Observational evidence relating fermented foods with depression and anxiety in humans

Only two observational studies were identified that reported the relationship between fermented foods and mental health. In a birth-cohort study of 9030 women, no significant association was observed between fermented food consumption and psychological distress in pregnancy.[135] This study used the Kessler 6-item scale (K6), which is a basic screening tool for mental illness, but is not diagnostic.[136] In a cross-sectional study of 710 students, Hilimire *et al.* reported that exercise frequency, neuroticism and fermented food consumption was associated with social anxiety.[137] For those who had higher neuroticism on personality testing, higher fermented food intake was associated with lower social anxiety. The relationship between fermented food and mental health, however, remains unclear due to the limited number of studies, the possibility of reverse causality and differing populations investigated.[135,137]

Direct evidence for fermented foods in modulating depression and anxiety in humans

Studies specifically investigating the influence of fermented food interventions on depression and anxiety are limited and vary widely in methodology. Tillisch *et al.*[23] evaluated the impact of a fermented milk product on functional brain imaging in non-depressed women. The authors conducted a randomized controlled trial, in which 23 healthy women were randomized to either the four-week consumption of a fermented milk product containing a combination of probiotics (*Bifidobacterium animalis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis*) ($n = 12$), or a non-fermented milk product control ($n = 11$). Participants underwent functional magnetic resonance imaging before and after the intervention. An emotional faces attention task and resting brain activity were measured, with multivariate and region of interest analyses performed. This study found that four-week intake of the fermented milk product by healthy women affected affective, viscerosensory and somatosensory cortices of the brain.[23] This study demonstrated brain changes in the emotional and pain centres of the brain following a fermented food intervention. However, in interpreting these findings, the small sample size and the possibility of Type 1 error needs to be taken into account. In 93 non-depressed postmenopausal women, two week's administration of fermented ginseng improved cognitive depressive symptoms (but not somatic depressive symptoms) on the Beck Depression Inventory (BDI) compared to a placebo.[138]

The potential for fermented foods to modulate mood and anxiety has also been evaluated in medical populations.[139,140] Jiang *et al*. observed an improvement in depression and anxiety following daily consumption of fermented red ginseng for 60 days in those receiving chemotherapy for Small Cell Lung Cancer (SCLC), compared to treatment as usual.[139] However, given that there was no non-fermented ginseng comparator, it is unclear whether this effect was due to fermentation or other properties of the ginseng. In contrast, Simren *et al.*[140] did not observe any significant change in depressive symptoms following an 8-week administration of a fermented milk product in patients with Irritable Bowel Syndrome (IBS). It should be noted that these studies also suffered from methodological limitations. It was unknown whether study participants were depressed or had an anxiety disorder at baseline, as this was not evaluated. Furthermore, mental health outcomes were not a primary outcome measure of either of these studies. Whilst it is not possible to draw any definitive clinical implications from these studies, they suggest the potential for fermented foods to improve depressive and anxiety symptoms in medical populations.

Three studies investigated physical symptoms of stress, and the potential for fermented foods to modify these.[23,141,142] Baseline depression or anxiety was not documented in any of the studies, however, all three found that fermented food interventions had significant anti-stress effects compared to non-fermented control products.[23,141,142] Each of these studies used different measures to evaluate stress. Kato-kataoka *et al*. evaluated physical symptoms associated with stress through a double-blind placebo-controlled pilot study in medical students preparing for their exams.[141] Twenty-four students were randomized to an eight-week trial of a fermented milk product containing *Lactobacillus casei* strain Shirota, and 23 were randomized to a placebo.[141] The study found that the fermented milk intervention prevented the onset of physical symptoms in medical students under academic examination stress. Similarly, Takada *et al*. investigated the effects of fermented milk containing the probiotic *Lactobacillus casei* Shirota on psychological and physiological stress responses.[142] In students under exam-stress conditions, the fermented milk reduced stress-induced physical symptoms. However, there were no significant changes in anxiety levels, or cortisol levels in the intervention group compared with the placebo group.[142]

The studies identified in this review were sparse and suffered from methodological weaknesses and heterogeneity. Thus, whilst it is not possible to draw any clinical conclusions from these studies, the results suggest that fermented foods may act to modulate mood and anxiety pathways and moderate the experience of stress-related physical symptoms or pain.

Safety of fermented foods

Fermented foods have been widely consumed for thousands of years throughout Asia,[27] although to our knowledge there are no comprehensive studies that have assessed the safety of fermented foods, particularly for special populations such as the medically ill, elderly, children and pregnant women. Fermented foods do contain some non-nutritive components, such as biogenic amines, which are by-products produced through microbial metabolism of amino acids; these amines are particularly found in sauerkraut, fish products, cheese, wine, beer, dry sausages, etc.[25] Ingestion of excessive amount of these biogenic amines have been reported to be associated with changes in gastrointestinal functions (digestion), nausea, headaches, respiratory problems and change in blood pressure, and potentially interact with monoamine oxidase inhibitor antidepressants.[143] Due to this, many countries and international food regulating bodies have established safe concentrations of detectable biogenic amines in food.[144] There is a lack of human trials examining the safety of fermented foods. In a murine model, kefir exacerbated the disease severity of *Clostridium difficile* infection.[145] Further data on safe daily intakes of biogenic amines present in fermented foods would be needed prior to widespread recommendations for the use of fermented foods.

Quantitative nutritional measurements required for determining the daily dosage of fermented foods are lacking. Fermented foods contain probiotics, prebiotics and biogenics, but the concentrations of these are typically not detailed. Even the number of colony forming units (CFU), a measure of viable probiotic bacterial counts, at the time of consumption would likely vary depending on the product, processing technique and storage conditions. This makes it difficult to compare products. Further investigation is needed to determine the viable counts of probiotics present in fermented food products available on the market. This sort of information is necessary for clinicians and dieticians to recommend fermented food products to patients as an adjunctive treatment strategy in many pathophysiological conditions.

Implications for clinical practice and further research

The body of evidence evaluating the efficacy of fermented food interventions for the treatment of depression and anxiety suffers from limitations, including wide heterogeneity due to differing study characteristics, and with few demonstrating robust methodology for evaluating mental health outcomes. Furthermore, many of the studies had small samples sizes and were not designed to answer the clinical question of whether fermented foods may be a potential treatment for depression or anxiety. In addition, the fermented foods used in existing studies, along with their constituent ingredients and properties, varied widely; as such, the data are too limited to draw any conclusions about each food separately or as an aggregate. Finally, there is inadequate safety data available to be able to sufficiently advise patients through a risk-

Table 1 Human studies investigating fermented foods, depression and anxiety

Study	Study design	Participants	Intervention	Outcome measures	Results
Takashi *et al* 2016 [135]	Birth-cohort study	9030 pregnant women	NA	Fermented food consumption measured by FFQ, correlated with psychological distress measured by Kessler 6-item psychological distress in T2 and T3 of pregnancy	There was no correlation between increased fermented food consumption and K6 > 13
Hilimire *et al* 2015 [137]	Cross-sectional study	710 psychology students	NA	Fermented food consumption measured by FFQ, SPAI-23 to measure social anxiety and neuroticism	Exercise frequency, neuroticism and fermented food consumption predicted social anxiety
Lee *et al* 2014 [138]	Double-blind placebo-controlled RCT	93 non-depressed postmenopausal women	2-week fermented ginseng consumption ($n = 49$) Placebo, edible starch ($n = 44$)	BDI pre- and post-intervention (secondary outcome measure)	Cognitive depressive symptoms (but not somatic depressive symptoms) were improved in the intervention group compared to the placebo group
Jiang *et al* 2017 [139]	Non-blinded RCT	60 chemotherapy patients with NSCLC	Fermented red ginseng plus chemotherapy ($n = 34$) Chemotherapy only ($n = 26$)	SRAS and SRDS scores (both secondary outcomes)	Significant improvements in depressive and anxiety scales in the intervention group compared to the control group
Tillisch *et al* 2013 [23]	Double-blind placebo-controlled RCT	23 healthy, non-depressed women	4-week consumption fermented milk plus probiotic ($n = 12$) Non-fermented milk control ($n = 11$)	fMRI pre- and post-intervention, and an emotional faces task measuring resting brain activity. Multivariate region of interest analyses performed	The intervention affected affective, viscerosensory and somatosensory cortices of the brain
Simren *et al* 2010 [140]	Double-blind placebo-controlled RCT	74 patients with IBS	An 8-week intervention with a fermented milk product containing *Lactobacillus paracasei*, ssp. Paracasei F19, *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 (n = 37) Placebo, acidified milk without bacteria ($n = 37$)	HADS pre- and post-intervention (secondary outcome)	No significant change seen in HADS from baseline to post intervention
Kato-Kataoka *et al* 2016 [141]	Double-blind placebo-controlled pilot study	47 Medical students under exam stress	An 8-week intervention with fermented milk product ($n = 24$) Placebo milk product ($n = 23$)	Abdominal and URTI symptoms, psychophysical state, salivary cortisol, faecal serotonin, and plasma L-tryptophan	The placebo group reported greater physical symptoms and anxiety one day before the exam and had significantly increased L-tryptophan and salivary cortisol levels The intervention group had significantly higher faecal serotonin 2-weeks after the exam
Takada *et al* 2016 [142]	Double-blind placebo-controlled RCT	140 medical students under exam stress	An 8-week intervention with *Lactobacillus casei* prior to a high-stakes exam ($n = 70$) Placebo unfermented milk product ($n = 70$)	Salivary cortisol, HPI, GHQ, STAI	No significant changes in STAI or salivary cortisol levels in intervention group compared with control. However, the intervention group experienced significantly decreased stress-related physical symptoms compared with the control group

Note: BDI, Beck Depression Inventory; FFQ, Food frequency questionnaire; fMRI, Functional MRI; HADS, Hospital Anxiety and Depression Scale; HADS, Hospital Anxiety and Depression Scale; K6, Kessler 6 item scale; NA, not applicable; RCT, Randomized Control Trial; SPAI-23, Social Phobia and Anxiety Index; SRAS, Self-Rating Anxiety Scale; SRDS, Self-Rating Depression Scale; T2, Second trimester; T3, Third trimester; URTI, Upper respiratory tract infection; HPI, Health Practice Index; GHQ, General Health Questionnaire score; STAI, State-Trait Anxiety Index; FFQ, Food Frequency Questionnaire; BDI, Beck Depression Inventory; fMRI: Functional Magnetic Resonance Imaging.

benefit analysis of the potential advantages against possible risks of fermented foods, particularly in the case of the special populations listed above.

Thus, there is currently insufficient evidence around both efficacy and safety to be able to recommend the use of fermented foods as an adjunctive treatment for depression or anxiety. Fermented foods, however, do appear to influence many of the mechanistic pathways relating to depression and anxiety. The promising pilot level data nevertheless suggest that larger randomized controlled trial studies are warranted to determine the efficacy and safety of using fermented foods for symptom management or prevention.

Conclusions

Probiotics, prebiotic and biogenics constitute the functional properties of fermented foods and these may act upon some of the biological mechanisms underpinning anxiety and depression. Fermented foods hold promise as a dietary intervention due to their theoretical potential to modify the gut microbiota and improve the integrity of the intestinal barrier. However, the body of literature relating to the relevance of fermented food for treating or preventing depression and anxiety as a whole is sparse, heterogeneous and has significant limitations. Moreover, the lack of data relating to safety, dosage or intake upper limits warrants caution. This review identifies a critical research gap and calls for high-quality studies investigating the impact of fermented foods on depression and anxiety in humans. Fermented foods may have potential as a treatment strategy for depression or anxiety but further research in this field is greatly needed.

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