



Review Article

Available online at www.SciMedJournal.org

SciMedicine Journal

(ISSN: 2704-9833)

Vol. 5, No. 2, June, 2023



Systematic Review on the Effects of Food on Mental Health via Gut Microbiome

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Received 21 March 2023; Revised 23 May 2023; Accepted 26 May 2023; Published 01 June 2023

Abstract

Recent studies have suggested that diet may affect the gut microbiome, subsequently influencing mental health. While several systematic reviews have been done on the effects of diet on mental health via the gut microbiome, there are focused on either specific diets or mental disorders. This systematic review examines the effect of diet and broad-based mental health via the gut microbiome. 21 out of 99 studies published prior to 2023 and listed in PubMed are included. Our analysis suggests that a vegan diet, a Mediterranean-style diet, fiber, probiotics, dietary vitamin D, unpasteurized milk, foods with a low omega-3 to omega-6 ratio, and *Xiao Yan San* may have positive effects on gut microbiome, leading to a positive influence on mental health, while a meat-rich diet, a high-fat diet, high fructose intake, and zinc deficiency may have negative effects on gut microbiome, leading to a negative influence on mental health. Collectively, the effects of diet on mental health via gut microbiome may be explained by the composition of gut microbiome and the metabolites produced by gut microbiome on gut permeability.

Keywords: Mental Health; Gut Microbiome; Diet; Food.

1. Introduction

In recent years, nutrition psychiatry is an emerging field where there is an emphasis on how diet and food choices can affect our mental health [1]. This topic is of great interest due to its potential to open new doors to innovative intervention approaches in mental health care. The brain and the gastrointestinal system, commonly referred to as the gut, are closely connected in a bidirectional relationship known as the “gut-brain-axis” (GBA). The gut can influence mental health and cognition, while the brain can influence one’s intestinal activities [2]. It links the emotional and cognitive centers of the brain with the peripheral intestinal functions of the gut via immune, endocrine, and neural mechanisms [3]. The GBA consists of the central nervous system, the autonomic nervous system, the brain, the spinal cord, the enteric nervous system, and the hypothalamic pituitary adrenal (HPA) axis. Afferent signals driven by the autonomic system arise through the lumen and are transmitted through spinal, vagal, and enteric pathways to the central nervous system. Efferent signals are transmitted from the central nervous system to the intestinal wall. At the same time, the HPA axis responds to stressors of any kind, which leads to the secretion of cortisol, which is a major stress hormone affecting many human organs, such as the digestive tract [4].

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 <http://dx.doi.org/10.28991/SciMedJ-2023-05-02-05>

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Recently, mental health has been at the forefront due to the COVID-19 pandemic, with 40% of US adults showing at least one adverse mental or behavioral condition in 2020 [5]. The relationship between diet to mental health has been suggested [6]. To date, only 4 systematic reviews examining the effects of diet on mental health via gut microbiome have been published and listed in PubMed, which include the effects of plant-based diet [7], diet on psychiatric disorders [8], gut microbiome changes in patients with psychotic and affective disorders [9], and temperament in infant and early childhood development [10]. Hence, no systematic review to date has examined diet and broad-based mental health via the gut microbiome. Therefore, this systematic review seeks to highlight the dynamic relationship between diet, gut microbiome, and mental health.

2. Research Methodology

Search Strategy: A PubMed literature search was undertaken on January 7, 2023, to locate existing studies prior to January 1, 2023, that examine the effects of food on mental health via the gut microbiome. The search terms (diet [tiab] AND gut [tiab] AND microbiome [tiab] AND mental [tiab])* were used.

Inclusion/Exclusion Criteria: PRISMA [11–15] was used as the methodology for inclusion/exclusion. The following exclusion criteria were used: (A) non-English articles; (B) articles without full-text access; (C) secondary research articles including systematic reviews, narrative reviews, and meta-analysis; (D) articles with on-going research; and (E) articles with no findings on the research focus areas (the effects of food on gut microbiome and the influence on mental health). Articles remaining after applying the exclusions were included.

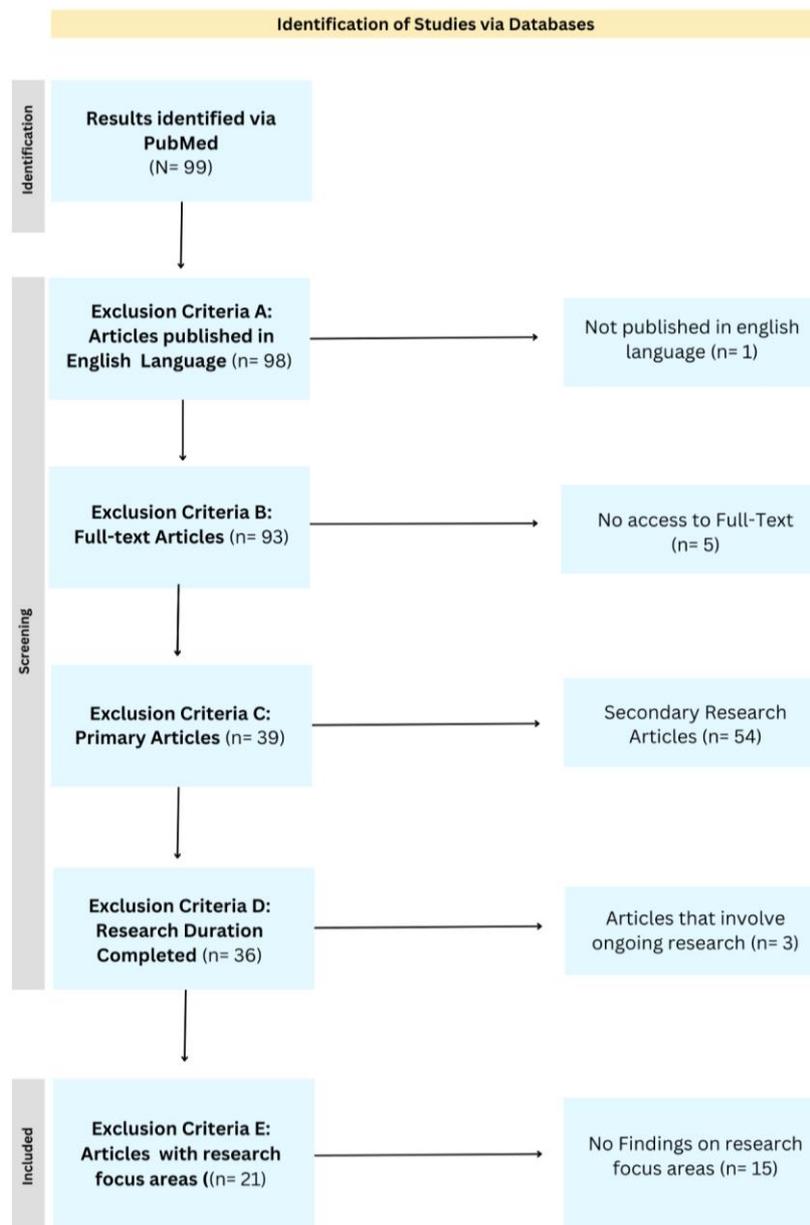


Figure 1. Research process using the PRISMA

*[https://pubmed.ncbi.nlm.nih.gov/?term=diet\[tiab\]+AND+gut\[tiab\]+AND+microbiome\[tiab\]+AND+mental\[tiab\]&filter=dates.1000/1/1-2023/1/1](https://pubmed.ncbi.nlm.nih.gov/?term=diet[tiab]+AND+gut[tiab]+AND+microbiome[tiab]+AND+mental[tiab]&filter=dates.1000/1/1-2023/1/1)

3. Results and Discussion

Analysis of Search Results: A total of 99 literature were retrieved from PubMed (Figure 1) by using the search terms. 98 articles are in English (Criteria A), of which 93 articles had full-text access (Criteria B). Within the full-text articles, 39 articles are primary articles (Criteria C), of which 36 have completed their research duration or have the study results included (Criteria D). Within these articles, 21 have findings on the research focus areas (Criteria E) and are included in this review and can be classified into positive or negative effects (Table 1). However, there are also potential limitations for various studies (Table 2).

Table 1. Thematic classification of studies on the effects of diet on mental health via gut microbiome

Theme	Sub-themes	Number of articles	Percentage
Positive effects of diet on gut microbiome that potentially positively influences mental health	Vegan and Mediterranean style diet	4 [16–19]	19.0 %
	Fibre	4 [20–23]	19.0 %
	Probiotics	3 [24–26]	14.3 %
	Other specific foods	4 [15, 19, 27, 28]	19.0 %
Negative effects of diet on gut microbiome that potentially negatively influences mental health	Meat-rich and High-fat diet	6 [18, 29–33]	28.6 %
	Other specific foods and conditions	2 [34, 35]	9.5 %

Table 2. Limitations of included studies and potential solutions for reducing limitations

Effects	Food	Limitations	Potential solution(s)
Positive effects of diet on gut microbiome that potentially positively influences mental health	Diet [16, 18]	Confounding variables [16].	Future studies may shed light on other variables involved that may affects results.
		Small sample size [18].	A larger sample size is suggested for future studies.
		Reduced compliance by participants that might cause inaccurate results [18].	Reminding participants of crucial steps to comply to and having transparency.
	Fibre [20–23]	Small sample size [20, 22].	A larger sample size is suggested for future studies.
		No causality evaluation experiment that confirms depression to be due to gut microbiome alteration during high dietary fibre intake [21].	Further experiments needed such as antibiotics treatment and/or faecal microbiota transplantation to confirm the causality relationship between gut microbiome alterations and behavioural changes.
		Study subjects are specific in sex, ethnicity and demographic characteristics [22].	Ensuring that generalisations should be made with caution; more research to reflect general population accurately.
		Dietary questionnaire examining diet, microbiome and mood may not be sensitive enough to accurately discern specific mood disorders [23].	In future research, more comprehensive and sensitive measures should be used.
	Probiotics [24–26]	The average used as a representative to measure hippocampal macromolecular baseline might not accurately assess brain function [24].	Standardising measurement procedure to reduce measurement error.
		Study subjects are gender specific [25].	Future research to include both males and females to increase translational value.
		Small sample size, selection bias [26].	A larger sample size and longitudinal design is suggested for future studies.
Other specific foods [19, 27, 28]	Highlights association but not causation [19].	Warrants further future analysis.	
	Confounding variables [27].	Disentangling the impact of different variables during analysis.	
Negative effects of diet on gut microbiome that potentially negatively influences mental health	Diet [18, 29–33]	Study subjects are gender specific [28].	Future research to include both males and females to increase translational value due to gender specific difference in response.
		Confounding variables [29–32].	Future studies may shed light on other variables involved that may affect results.
		Only one behavioural test was used and might not accurately represent depression [29].	Additional tests could be used to define behavioural changes as equivalent to depressive-like behaviour.
		Small sample size [18, 30, 33].	A larger sample size is suggested for future studies
	Reduced compliance by participants that might cause inaccurate results [18].	Reminding participants of crucial steps to comply to and having transparency.	
Others [34]	Study subjects are gender specific [34].	Future research to include both males and females to increase translational value due to possible gender specific differences in response.	

Positive effects of diet on the gut microbiome that potentially positively influence mental health: Various studies find that healthy diets have a positive effect on the gut microbiome. The diversity of the gut microbiome can be affected by diets, which may influence one's mental health [17, 36], leading to potential improvements in mental health [15–27, 29]. A healthy diet commonly refers to the consumption of vegetables, fruits, fish, and whole-diet interventions instead of only examining individual nutrients or foods. This is especially helpful in treating mental health disorders such as depression and anxiety [2, 17]. Fendrich et al. [16] examined the link between the GBA and specific symptoms of severe mental illness, such as schizophrenia, and found that the diets between healthy controls and psychotic groups are different, with the psychotic group consuming more ready-made meals and seafood compared to the healthy controls group. These differences suggest associations between one's diet and mental health disorders.

Positive effects: Vegan diet: Several studies find that the vegan diet is effective in promoting a diverse and healthy gut microbiome, which may lead to an improvement in overall health, including mental health [18]. A vegan diet excludes all types of animals and their by-products [37]. Significantly higher counts of *Bacteroidetes*-related operational taxonomic units are found in vegans as compared to omnivorous participants [38]. Furthermore, nutrients from vegan food take longer to digest, have intact plant cell walls, and have lower bioavailability, all of which allow nutrients to reach lower levels in the gastrointestinal system. This increases nutrient delivery to the gut microbiome, further favoring the growth of beneficial bacteria in the colon [38].

In a four-week randomized controlled trial investigating the effect of a vegan diet and a meat-rich diet on healthy omnivorous participants, *Coprococcus* was reported to be enriched in the vegan diet from 42% at baseline to 81% at the end of the trial. This is compared to the meat-rich diet, where the amount of *Coprococcus* decreased from 69% at baseline to 50% at the end of the trial [18]. *Coprococcus*, which is depleted in those who suffer from depression, may play a supportive role in mental health. However, these differences are highly individual-dependent and not significantly altered by short-term dietary changes. The quality of a vegan diet may be important, as an Australian study surveying 219 vegans suggests that a high-quality vegan diet is associated with decreased symptoms of depression; conversely, a low-quality vegan diet is associated with increased symptoms of depression [39].

Positive effects: Mediterranean style diet: The Mediterranean style diet, consisting of vegetables, whole grains, fruits, and lean protein from fish, poultry, and good fats, has been found to increase diversity in the gut microbiome and is strongly associated with better mental health [19]. There is also evidence suggesting that the Mediterranean diet is more beneficial to brain health as compared to the vegan diet [19, 40]. A Mediterranean-style diet is generally low in animal protein and saturated fat but rich in fiber, antioxidants, monounsaturated fat, and probiotics. Additionally, it has a good balance of omega-3 and omega-6 fatty acids. Evidence suggests significant differences between the gut microbiome of subjects who follow a Western diet model that is high in processed food and low in fiber, as compared to subjects following a Mediterranean-style diet that has high-fiber whole natural foods [41]. Garcia-Mantrana et al. [42] find that subjects with higher adherence to the Mediterranean diet had higher counts of *Bifidobacteria* and short-chain fatty acids in their gut microbiome. In another study, the effects of the Mediterranean-style diet on 67 subjects with depression were investigated for 12 weeks and showed improvements in the depression rating scale of those with depression when compared to the social support control group [40].

Positive effects: Fibre: Dietary fiber is a type of carbohydrate mainly found in vegetables, fruits, whole grains, and legumes that cannot be digested or absorbed by the body. Several studies find that dietary fiber has a significant impact on the gut microbiome and is suggested to be positively correlated with mental health improvements via the GBA [20–23]. When consumed, fiber remains largely undigested until it reaches the large intestine. There, it serves as a microbiota energy source that promotes the growth of beneficial bacteria in the gut and serves as a substrate for short-chain fatty acid synthesis. Moreover, fiber is the primary fuel source for gut bacteria, so they will not feed on the intestinal lining of the gut. Results show a consistency between dietary fiber intake and gut microbiome diversity [20, 20–22]. The growth of bacteria by dietary fibers is highly specific, as it is influenced by the different interactions between the chains of monomers and enzymes [43]. Schnorr et al. [44] report increased microbiome richness and diversity in Hadza hunter-gatherer individuals whose diet is rich in fiber, as compared to urban Italian controls. This shows that fiber intake is associated with a higher faecal abundance of *Bifidobacteria* and *Lactobacillus*, which is found to improve mental state and decrease cortisol levels [20, 45].

During the fermentation of dietary fiber, anaerobic gut bacteria produce short-chain fatty acids, which are highly correlated with depressive-like behaviors. Enhanced short-chain fatty acid production helps to protect gut-barrier function and prevent damage to the synapse structure [21]. One reason for the depressive symptoms is due to “leaky gut” caused by an increase in gut barrier permeability, leading to bacterial toxins entering the bloodstream, which may trigger inflammation in the brain [46]. Hence, short-chain fatty acids, particularly butyrate, directly improve gut barrier integrity, thus reducing the symptoms of “leaky gut” and indirectly improving mental health [47].

Positive effects: Probiotics: Probiotics are live microorganisms that are found in dietary supplements, cultured milk, and fermented food. They are relatively safe and known for their health benefits, such as playing a significant role in altering one's gut microbiome, which impacts the communication between the gut and the brain, thus

influencing mental health [24, 25]. Probiotics usually come in single strains or mixed cultures of two or more strains [24]. The two commonly consumed probiotic genera are *Bifidobacteria* and *Lactobacillus*, which are found to be lesser in the gut flora of depressive patients [48]. A study on 60 overweight but otherwise healthy adults who consumed probiotics containing three strains of *Bifidobacteria* and four strains of *Lactobacillus* in a randomized placebo-controlled trial shows a significant increase in the concentration of these strains in the gut microbiome of these adults as compared to the placebo group [49]. *Bifidobacteria* produces short-chain fatty acids and lactic acids, while *Lactobacillus* produces lactase and lactic acid, thereby promoting gut health and exerting anti-inflammatory effects. Marin et al. [50] investigate the association of *Lactobacillus* and stress-induced despair behaviors and find that chronic stress depletes *Lactobacillus* in the gut microbiome, which has a negative impact on the brain and mental health. *Lactobacillus* diet supplementation is shown to alter the gut microbiome composition and reverse depressive-like behavior [25, 50]. There is also a significant decrease in stress and anxiety levels in a healthy population after four weeks of probiotic supplementation [51]. In addition, a meta-analysis found that the effects of probiotics on people with low levels of depression were more prominent as compared to people with high levels of depression [52]. Nonetheless, the complexity of the microbiome ecosystem suggests that there is a possibility of other changes in the gut barrier lining even without changing the abundance of *Bifidobacteria* and *Lactobacillus* [26].

Positive effects: Other specific foods: Dietary vitamin D, unpasteurized milk, foods with a low omega-3 to omega-6 ratio, and *Xiao Yan San* [15, 19, 27, 28], may also have a positive effect on the gut microbiome. Consuming a sufficient amount of vitamin D helps to regulate the gut microbiome and benefit gut health [53]. Vitamin D is generated through the skin's exposure to sunlight or consumed through a diet or supplement. Vitamin D3 is more easily absorbed by the intestine compared to Vitamin D2 [54]. Foods rich in dietary vitamin D include salmon, egg yolks, mushrooms, and red meat. A lack of dietary vitamin D has been associated with mental illnesses, while extreme vitamin D deficiency is found in patients with acute schizophrenia [27]. Vitamin D heals the gut epithelium, hence maintaining the integrity of the epithelial barrier [55]. A study by Singh et al. [56] on 80 women with vitamin D deficiency demonstrates an increase in gut microbiome diversity, specifically in the *Bacteroides* to *Firmicutes* ratio, with an increase in the amounts of *Bifidobacterium* after Vitamin D supplementation. Despite this, excessive vitamin D consumption may lead to intoxication with symptoms such as confusion, recurrent vomiting, and abdominal pain [57]. Therefore, while vitamin D benefits one's overall health, including mental health, consuming the recommended dosage is crucial.

Unpasteurized milk or raw milk may also have a positive effect on the gut microbiome and mental health [19]. Although bacterial diversity in pasteurized and unpasteurized milk was similar, the lactic acid bacteria present in pasteurized milk would be in a non-viable state [19]. While pasteurization reduces the number of harmful bacteria in the pasteurized milk, which increases shelf life, it also destroys beneficial bacteria such as the *Lactobacillus* species in the process. In this study, 24 healthy participants between the ages of 18 to 65 showed a significant increase in the amount of *Lactobacillus* in their gut microbiome after consuming unpasteurized milk [19]. *Lactobacillus*, which is a beneficial bacteria, has the ability to decrease stress and anxiety levels in healthy subjects and help in anxiety regulation [58, 59].

Consuming a good balance of omega-3 and omega-6 fatty acids may have a positive effect on the gut microbiome. Foods rich in omega-3 include chia seeds, cold-water fatty fish such as salmon and mackerel, while foods rich in omega-6 include soybeans, corn, nuts, and seeds. The Mediterranean-style diet has an adequate balance of omega-3 and omega-6 fatty acids [40]. A study by Reemst et al. [28] shows that mice fed with a diet low in omega-3 to omega-6 ratio have higher amounts of *Clostridia* in their gut microbiome as compared to those fed with a diet high in omega-3 to omega-6 ratio. *Clostridia* is a beneficial bacteria as it is involved in the production of butyrate, a short-chain acid that is vital for good mental health [28].

Xiao Yan San is a traditional Chinese medicine (TCM) formulation consisting of eight herbal medicines widely used to treat anxiety and depression. Yang et al. [15] find that *Xiao Yan San* improves anxiety and depression symptoms in a gut microbiome-dependent manner in mice [15]. The consumption of *Xiao Yan San* affects the gut microbiome composition as there is an increased amount of *Faecalibaculum rodentium*, which produces short-chain fatty acids [60]. This may inhibit inflammation in the brain, potentially leading to reduced anxiety and depression symptoms [15].

Negative effects of diet on the gut microbiome that potentially negatively influence mental health: Conversely, diet may have negative effects on the gut microbiome. Komorniak et al. [30] find that an increase in protein and a decrease in fiber negatively affect the gut microbiome of those who undergo bariatric surgery. Depressive symptoms were developed after an initial significant improvement in mental health, with stool samples found to contain an increased amount of branched-chain fatty acids resulting from the high protein intake. This leads to the formation of metabolites, which inflame the mucosa and affect the intestinal nervous system, causing more symptoms of depression to occur [30]. In particular, meat-rich diets and high-fat diets are found to alter the gut microbiome and affect mental health. Out of the two, there is more evidence suggesting that a high-fat diet is associated with an increased risk of depression [61].

Negative effects: Meat-rich diet: Kohnert et al. [18] define a meat-rich diet as consuming more than 150g of meat per day, which is roughly around the size of your palm. A meat-rich diet is found to increase the amounts of *Roseburia* and *Faecalibacterium* while decreasing the amount of *Coproccoccus* in the gut microbiome of people with depression. A meta-analysis suggested that a meat-rich diet is associated with a moderately high depression risk [62]. Specifically, red meat, such as beef, mutton, and pork, as well as processed meat like sausages, luncheon meat, frankfurters, and corned beef, are correlated with mental and physical fatigue [30].

Negative effects: High-fat diet: Several studies examine the effects on the gut microbiome and mental health of high-fat diets as compared to meat-rich diets [29, 31, 32]. The four major types of fats in foods are saturated fats, trans-fats, monounsaturated fats, and polyunsaturated fats. A typical Western diet is high in trans-fat and saturated fat (commonly known as unhealthy fats) and low in monounsaturated and polyunsaturated fats (commonly known as health-promoting fats or healthy fats) [49]. A high-fat diet generally consists of 60% or more fat, inclusive of saturated fat, monounsaturated fat, and polyunsaturated fat, that is consumed over a sustained period of one month or more [29, 32]. A high-fat diet induces changes to the gut microbiome by disrupting intestinal barrier proteins. This increases intestinal permeability and may impair neurocognitive behavior even in the absence of obesity [32]. For example, a shift in bacteria species in the gut microbiome saw a 5.4-fold decrease in the amounts of *Akkermansia muciniphila*, a generally beneficial bacterium, and a 300 times increase in *Bilophila*, which is harmful to the gut microbiome [32]. These changes were associated with the health of the gut microbiome, although this does not reflect the complexity of the changes [63]. An increase in the amounts of *Faecalibacterium prausnitzii* was found in a diet high in saturated fat. Meanwhile, a diet high in monounsaturated fats found no change in the relative abundance of any beneficial bacteria [49].

Other studies find that a high-fat diet increases the amounts of *Bacteroides* in the gut microbiome and fat-free acids (FFA) being absorbed into the bloodstream [29, 49]. *Bacteroides* digest host mucins due to the low levels of starch present in a high-fat diet. The toxins from *Bacteroides* then decrease messenger ribonucleic acid (mRNA) levels in the epithelial layer that lines the gut microbiome. This causes leaky gut, which results in bacterial toxins entering the peripheral system and increases the levels of adiposity and leptin. When this happens, microglia, a type of immune cell in the central nervous system, is activated and causes inflammation in the brain. As such, behavioral despair is observed in the mice, which mimics negative moods in humans [29].

Negative effects: Other specific foods and conditions: Zinc deficiency and high fructose intake are found to negatively affect the gut microbiome and influence mental health [34, 35]. Zinc is an essential micronutrient that is vital for healthy brain function [64]. Though it is one of the most abundant trace metals in the body, it requires regular consumption as it cannot be stored in large amounts. Foods that contain zinc include beans, nuts, meat, and dairy products [65]. Zinc is a cofactor of several enzymes, whereby intra- and extracellular zinc concentrations affect the gut microbiome [66]. A zinc deficiency, which is prone to occur during pregnancy [67], alters gut physiology and microbiome composition. Additionally, it decreases the overall zinc species diversity and increases leakiness of the gut, which is linked to depression [68]. A study observed that mice on a zinc-deficient diet had gut microbiomes with similar alterations to stress and depressive-like behavior, though not in identical ways [34].

High fructose intake may trigger gut dysbiosis and aggravate depressive-like behavior [35]. Fructose is a monosaccharide naturally found in fruits and forms sucrose when bonded with glucose [69]. In food ingredients, the major source of high fructose is commonly found in corn syrup and condiments such as ketchup, jams, gassy drinks, and candies. Hsu et al. [70] report that high fructose consumption increases the negative impacts of chronic stress in mice, contributing to an increased risk of depression. This is because high fructose intake causes decreased amounts of *Bifidobacterium* and *Lactobacillus* in the gut microbiome. When this happens, there is a reduction in short-chain fatty acids derived from the gut microbiome and a loss in tight junction proteins in the gut. This increases gut permeability, which causes neuroinflammation and promotes depressive-like symptoms [71].

4. Conclusion

This systematic review demonstrates that foods can have either positive or negative effects on the gut microbiome and their subsequent influence on mental health. Our analysis suggests the following may have positive effects on the gut microbiome, leading to a positive influence on mental health: (a) vegan diet, (b) Mediterranean style diet, (c) fiber, (d) probiotics, (e) dietary vitamin D, (f) unpasteurized milk, (g) foods with a low omega-3 to omega-6 ratio, and (h) *Xiao Yan San*; while the following may have negative effects on gut microbiome leading to negative influence on mental health: (a) meat-rich diet, (b) high-fat diet, (c) high fructose intake, and (d) zinc deficiency. Collectively, the effects of diet on mental health via gut microbiome may be explained by the composition of gut microbiome and the metabolites produced by gut microbiome on gut permeability.

5. Declarations

5.1. Author Contributions

Conceptualization, S.L. and M.H.L.; methodology, S.L.; validation, S.K.S., R.T.O., and V.S.D.; investigation, S.L.; data curation, S.L.; writing—original draft preparation, S.L.; writing—review and editing, S.K.S., R.T.O., and V.S.D.; visualization, S.L.; supervision, M.H.L.; project administration, M.H.L. All authors have read and agreed to the published version of the manuscript.

5.2. Data Availability Statement

The data presented in this study are openly available in: https://bit.ly/diet_MH.

5.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

5.4. Institutional Review Board Statement

Not applicable.

5.5. Informed Consent Statement

Not applicable.

5.6. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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