

The Link Between the Gut Microbiome and Mental Health Disorders

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DECLARATION

I certify that the whole of this work is the result of my individual effort, and that all sources have been acknowledged.

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Date: 03/10/2024

DECLARATION

I am satisfied that this work is the result of the Student's effort.

Signed (Lecturer)

Date

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Abstract

The relationship between the gut microbiome and mental health has recently gained considerable recognition in research. The gut microbiome describes a complex ecosystem consisting of trillions of micro-organisms living mainly in the gut, serving several essential functions, including supporting overall health and well-being. The World Health Organization describes mental well-being as an individual's ability to acquire their potential, work productively, build meaningful relationships with others, and contribute to their community. In the past decade, there has been a global increase in individuals suffering from mental health conditions. The World Health Organization (WHO) (2023) reports that there are approximately 350 million people affected by Major Depressive Disorder (MDD) and other mental health conditions globally. There is some current evidence that dietary practice and lifestyle factors influence the gut-brain axis and, in turn, contribute to the development and management of mental disorders, such as anxiety and depression. The present review explores the brain-gut axis and associated interventions, such as diet and supplementation, and the role of serotonin, tryptophan, and vagus nerve stimulation (VNS) in bringing positive outcomes to those suffering from mental health disorders. It also examines how a healthy microbiome is crucial for well-being and positive mental health outcomes. A review of current and essential literature (1997 - 2024) was conducted to evaluate the current knowledge of brain-gut-microbiota interactions as related to anxiety and depression. The initial screening of the papers included reading the abstracts to assess the contents using the keywords (*brain-gut axis, gut microbiome and mental health*). Findings identified that diets that increase tryptophan consumption and raise serotonin levels seem to be effective in alleviating depression symptoms. There is also evidence that mental health conditions are affected by the Mediterranean diet, Tryptophan diet, Ketogenic diet, and Western Diet, with the Mediterranean Diet being most potent in treating mental health disorders. In addition, probiotic supplementation has the potential to be a helpful treatment intervention for alleviating depression symptoms. The current study supports the efficacy of dietary strategies and supplementation in the management of anxiety and depression. These findings could provide a helpful mechanism for

health practitioners to help individuals in managing their mental health conditions. Future research would be required to determine the specific outcomes in the general and clinical population.

Section 1: Introduction

Over the past decade, the relationship between the gut microbiome and human health has been increasingly recognised in neuroscience research and the media (Jandhyala, 2015; Frankel and Warren, 2023; Harvard Medical School, 2023; Cassano and Otto, 2023). The gut microbiome contributes over 150 times more genetic information than the human genome (Krga and Glibetic, 2022). Additionally, the gut microbiota plays a crucial role in human health, with gut bacteria serving several vital functions, such as fermentation of nutrients, resistance against pathogens and supporting the immune system (Krga and Glibetic, 2022). Further, it has been noted that gut microbes are integral to the interaction between gut reactions, human behaviour, and mental health disorders such as anxiety and depression (Ochoa-Repáraz and Kasper, 2016; Firth *et al.*, 2020; Quigley, 2020).

Depression is considered a chronic mental health disorder that is the leading cause of disability worldwide (World Health Organization, 2017). The World Health Organization (WHO) (2023) reports that there are approximately 350 million people affected by Major Depressive Disorder (MDD) and other mental health conditions. Within the last ten years, the relationship between the microbiome and mental health has gained considerable interest, with preliminary studies suggesting a clear link between the microbiome and chronic health disorders (Jandhyala, 2015). The gastrointestinal (GI) tract has previously been described as simply a digestive organ; however, new research has begun uncovering the underlying mechanism of the impact of the gut microbiota, the gut barrier integrity on the brain and behaviour, and how mental health disorders are associated with negative alterations in the gut microbiome (Ochoa-Repáraz and Kasper, 2016; Lee and Kim, 2021). Further, research has also begun to show significant differences in the composition of the gut microbiota in patients with mental health disorders compared with healthy individuals (Jandhyala, 2015).

The human microbiome is a general term that describes a complex ecosystem

consisting of trillions of micro-organisms that live mainly in our gut (Marchesi and Ravel, 2015; Ogunrinola *et al.*, 2020). It is well-acknowledged that a healthy functioning microbiome is crucial for overall well-being and positive health outcomes (Jandhyala, 2015). Additionally, the term microbiota describes the diverse community of species within the gut, including bacteria, bacteriophages, viruses, fungi, protozoa, and archaea (Marchesi and Ravel, 2015; Leeming *et al.*, 2019; Shanahan, Ghosh and O'Toole, 2020; Vitetta, 2020). However, both terms are often used interchangeably in neuroscience (Marchesi and Ravel, 2015; Shanahan, Ghosh and O'Toole, 2020). In recent years, research has proposed how the gut microbiota affects several brain and behaviour functions, including mood and behaviour dysregulation (Mohajeri *et al.*, 2018). The physical mechanism through which the microbiome interacts with the brain involves intricate connections through bidirectional signalling through the gut-brain axis (Ochoa-Repáraz and Kasper, 2016; Leeming *et al.*, 2019; Firth *et al.*, 2020). Further, dysregulation of the brain-gut axis has been shown to cause gut dysbiosis, leading to potential inflammation in the intestines, causing alterations in the stress responses in the body, potentially contributing to the development of mental health conditions (Kim and Camilleri, 2000; Lee *et al.*, 2020; Shoubridge *et al.*, 2022).

The present literature review draws together evidence regarding the link between the brain-gut axis, dietary patterns, supplementation, and the impact on mental health. The link between microbiota and mental health disorders will also be examined. Furthermore, this could help determine how and when interventions, such as diet and supplementation, could help bring positive health outcomes to those suffering from mental health disorders, thus improving mental health in the general population. It also looks at the role of serotonin, tryptophan, and the vagus nerve and their contribution to improved mental health.

Aims and objectives.

This review will examine current literature, exploring the link between the gut microbiome and its potential link to mental health disorders. The role of the brain-gut axis and its link to the vagus nerve will also be explored. Moreover, the link between mood, serotonin and tryptophan levels will be investigated. Further, it will also examine how specific diets can support a healthy functioning microbiome and, in turn, have positive effects on mental health symptoms. Furthermore, the role of probiotics will be examined as a potential treatment intervention for mental health disorders. Therefore, the main aim is to understand the complex ways in which what we eat influences our brain, mood, and microbiome. The review evaluates relevant papers from 1997 onwards, looking at this new and emerging research in neuroscience.

Objectives

The four key objectives are:

1. To examine the link between the gut microbiome and levels of serotonin (mood levels).
2. To evaluate the connection between the gut microbiome and anxiety and depression
3. To critically evaluate the emerging biology of gut-brain communication and the role of the vagus nerve
4. To critically consider research and practice relating to how diet can improve symptoms of anxiety and depression.

Section 2: Method

A literature review was conducted to evaluate the current knowledge of brain-gut-microbiota interactions as related to anxiety and depression. An initial search of the University of Wales Trinity Saint David (UWTSD) library site, PubMed, Wiley Online, and Google Scholar was conducted. Published peer-reviewed text articles published between 1997 and 2024 were selected and used for this narrative review. The restriction of dates is due to the emerging pace of scientific research in nutrition. Articles were unrestricted to English and included articles from other countries and nationalities if the English translation was available. The initial screening of the papers included reading the abstracts to evaluate the contents using the keywords and to identify the relevance of the evidence.

Studies were deemed eligible for inclusion if they met the following inclusion criteria:

- Articles published between 1997-2024.
- Original peer-reviewed articles
- Available in the English language,
- Investigating the link between gut microbiome and MH
- Quantitative, qualitative, and mixed methodology articles

Studies were deemed ineligible for inclusion if they met the following exclusion criteria:

- Abstract only.
- Websites and media sources
- Articles published before 1997.

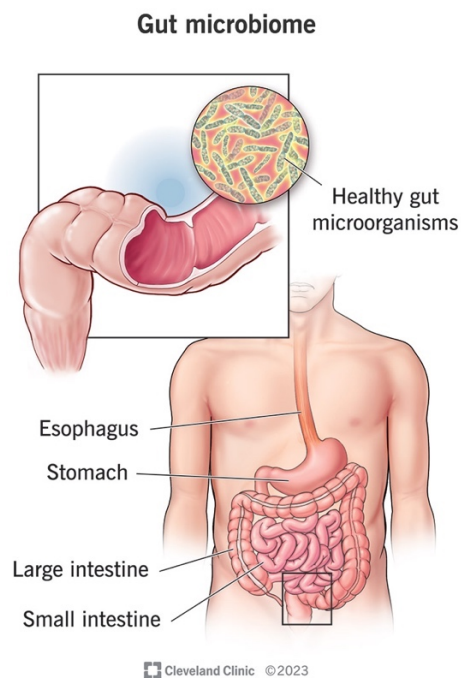
Keywords and combinations of keywords for the searches were: *brain-gut axis; gut microbiome and gastrointestinal (GI) microbiome; gut microbes, nutrition; mental health, mood, anxiety, depression, serotonin, tryptophan, vagus nerve and behaviour.*

Section 3: Discussion

Section 3.1: Digestion

The gut microbiota resembles a complex and diverse microbial community crucial in human health and chronic health conditions (Gomaa, 2020; Leeming *et al.*, 2021). These microbial communities within the GI tract (figure 1) change throughout our lives due to many factors, including diet, chronic health conditions and medical treatments (Gerber, 2014). Moreover, this complex ecosystem contains billions of microbial cells fundamental to human health (Gerber, 2014; Gomaa, 2020; Leeming *et al.*, 2021). The microbiome is linked to immunity, nutrition absorption, metabolism, and digestion (Gomaa, 2020). Digestion involves numerous distinguishing processes that change food into absorbable nutrients that support the human body (Gomaa, 2020; Leeming *et al.*, 2021). The digestive system comprises the GI tract, liver, pancreas, and gallbladder, joined from a long extended tube originating from the mouth down to the anus (Gomaa, 2020; Leeming *et al.*, 2021). Mackie, Mulet-Cabero and Torcello-Gómez (2020) explain how digestion starts in the mouth, where food is chewed, mixed with saliva, and broken down into carbohydrates. It then travels down the oesophagus to the stomach, where enzymes and acids digest and break down fats, proteins, and carbohydrates. Bile helps with further digestion in the small intestine, allowing nutrients to be absorbed (Mackie, Mulet-Cabero and Torcello-Gómez, 2020). Finally, any remaining waste moves to the large intestine for water absorption, forming faeces expelled during defecation (Mackie, Mulet-Cabero and Torcello-Gómez, 2020; Sensoy, 2021).

Figure 1 – Human Microbiome



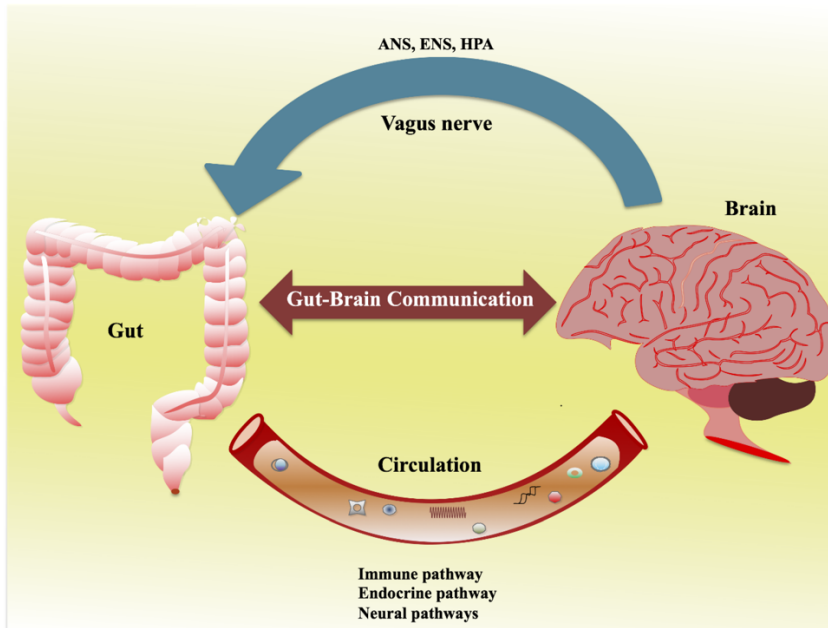
Section 3.2: The microbiome

The human microbiome is a general term that describes a complex system consisting of trillions of micro-organisms that live mainly in our gut (Ogunrinola *et al.* (2020). The microbiota comprises a diverse community of approximately 500-1000 types of species, including bacteria, bacteriophages, viruses, fungi, protozoa, and archaea, known collectively as the microbiota (Gilbert *et al.*, 2018). The microbiota is generally responsible for metabolising dietary elements into bioactive food components (Gomaa, 2020). The microbial species within the microbiome are known to synthesise neurotransmitters but also regulate mood, digestion, and emotions (Kim and Camilleri, 2000; Lee *et al.*, 2020; Shoubridge *et al.*, 2022). The physical mechanism through which the microbiome interacts with the brain involves intricate connections through bidirectional signalling through the gut-brain axis (Kim and Camilleri, 2000; Lee *et al.*, 2020; Shoubridge *et al.*, 2022). Amon and Sanderson (2017) note how the human microbiome has a vast number of functions in the body, including immunity, defence against pathogens, and the production of short-chain

fatty acids, which are crucial in supporting energy metabolism and the production of vitamins in the body (Amon and Sanderson, 2017).

In recent years, microbiome research has begun to examine how this complex ecosystem impacts mental health disorders (Kim and Camilleri, 2000; Lee *et al.*, 2020; Shoubridge *et al.*, 2022). Further, how various factors, such as stress, poor mental health, and an unhealthy diet, can all alter the microbiome's composition, leading to dysbiosis, a state of imbalance related to chronic health conditions (Wang, *et al.*, 2016). Over the past decade, advances in microbiome technology have allowed research to evolve, creating a better understanding of the complex interactions of the microbiota. These species reside within the gut, and how they are linked to human health and disease through the brain-gut axis.

Figure 2 - Brain-Gut Axis



Section 3.3: The role of the brain-gut axis and vagus nerve

The brain-gut axis (figure 2), often referred to as the bidirectional communication system linked to the gut and central nervous system, comprises the spinal cord, the central nervous system (CNS) and the enteric nervous system (ENS), which is a complex network of neurons that regulate the function of the GI tract (Kim and Camilleri, 2000; Appleton, 2018; Lucas, 2018; Lee *et al.*, 2020). Gerber, (2014) notes around 69 million neurons reside in the spinal cord, often called the highway of interaction between the body and the brain (Gerber, 2014). The brain-gut axis communication operates through specific pathways in the body, including hormonal signalling, immune system function and neural connections (Kim and Camilleri, 2000; Appleton, 2018; Lucas, 2018; Lee *et al.*, 2020). In recent years, scientific research has suggested how the brain-gut axis affects various brain and behaviour functions, including mood and behaviour dysregulation (Mohajeri *et al.*, 2018). Past research has defined how dysregulation of the brain-gut axis can cause gut dysbiosis, potentially leading to increased inflammation in the intestines and, in turn, altering stress responses in the body (Kim and Camilleri, 2000; Lee *et al.*, 2020;

Shoubridge *et al.*, 2022). Thus, potentially contributing to the development of mental health conditions such as anxiety and depression (Kim and Camilleri, 2000; Lee *et al.*, 2020; Shoubridge *et al.*, 2022). Understanding these complex communications between the brain, gut, and microbiome is crucial for developing effective treatments for improving mental health symptoms (Cryan and O'Mahony, 2011).

The vagus nerve (VN), the tenth cranial nerve or 'wandering nerve', extends from its origin in the brainstem through the neck and the thorax down to the abdomen (Breit *et al.*, 2018). The VN symbolises a key component in the nervous system, controlling several bodily functions, including mood, emotion, and food digestion (George *et al.*, 2008; Kim, 2016; Breit *et al.*, 2018; Tan *et al.*, 2022). Interestingly, the VN comprises 20% "efferent" fibres sending signals from the brain to the body and 80% "afferent" or sensory fibres carrying information from the body to the brain (Breit *et al.*, 2018). Research suggests gut bacteria has a beneficial effect on mood and anxiety, partly by affecting the activity of the vagus nerve (Breit *et al.*, 2018; Tan *et al.*, 2022). The stimulus of vagal afferent fibres in the intestines has been shown to influence systems in the brain stem directly, which play crucial roles in mental health conditions such as depression and anxiety disorders (George *et al.*, 2008; Kim, 2016; Breit *et al.*, 2018; Tan *et al.*, 2022).

Treatments that target the VN increase vagal tone, and, in turn, help manage symptoms of anxiety and depression (Sackeim, 2001; George *et al.*, 2008; Kim, 2016; Tan *et al.*, 2022). New emerging interventions, such as vagus nerve stimulation (VNS) (Sackeim, 2001; George *et al.*, 2008; Breit *et al.*, 2018), are now used to treat and support mental health disorders. VNS therapy is a treatment where a slight electrical pulse is directed through an inserted neurostimulator to a bipolar lead attached to the left vagus nerve (Schlaepfer *et al.*, 2008). Although VNS treatment has been shown in past studies to have advantages, the exact mechanism by which VNS treatment influences symptoms of depression is still not fully understood (Schlaepfer *et al.*, 2008). One study conducted by Sackeim (2001) examined the treatment of VNS in a total of 60 patients who suffered from major depressive disorder. The results found a considerable proportion of adult patients with major depressive symptoms responded positively to VNS. Also, 30–37% of individuals showed substantial medical improvement after treatment. Another study

by Aaronson *et al.* (2013) examined 331 patients through a double-blind, randomised comparison of VNS. All patients were randomised to one of three dose groups: the study results did not show significant differences between the treatment groups in antidepressant efficacy. Although the effect sizes were limited, statistically significant decreases in mean depression scores were observed in all three VNS cohorts. The findings of this study are in line with previous studies demonstrating clear positive outcomes in the use of VNS in the treatment of depression (Sackeim 2001; George *et al.*, 2008; Val-Laillet *et al.*, 2010; de Lartigue, 2016; Kim, 2016; Tan *et al.*, 2022).

Another study conducted by Tan *et al.* (2022) examined the role of VNS as an adjunct to other antidepressant treatments in patients with treatment resistance and mental health disorders, in a total of 205 patients over 12 months. Findings from the study revealed significant reductions in symptoms of depression after the trial had ended. Further, it was found that 30 participants experienced a worsening of depression and received hospitalisation. The outcomes of this trial therefore propose that 12 months of VNS is related to antidepressant effects. However, the longer-term improvements in this study could have resulted from a naturally occurring improvement in depression. Moreover, given the treatment-resistant nature of the sample, such a cause-and-effect looks improbable (Tan *et al.*, 2022). One further study by Rush *et al.* (2005) examined a chronically ill, treatment-resistant depressed population. This 10-week, acute, randomized, controlled, masked trial compared adjunctive VNS with sham treatment in 235 outpatients with major depressive disorder. In this study, they tested VNS treatment for severe depression in a group of patients who were very difficult to treat. Despite previous treatment, the trial did not show clear benefits of VNS over a placebo. Both groups had similar rates of side effects. While there was a slight improvement in depression scores with active VNS compared to the placebo, it was not statistically significant. This suggests either VNS might not work for this group or that the study had flaws in its design, the people it included, or how the treatment was given (Rush *et al.*, 2005).

One further study conducted by Rush *et al.* (2000) evaluated the effectiveness of VNS in patients with treatment-resistant depression. A total of 38 patients were enrolled in the study, with 30 receiving implants. The study found seven of the ten responders attained or remained in remission as of the most recent follow-up visit.

However, a limitation of this study was that there needed to be a control group to compare. Without a controlled placebo group, concluding the effectiveness of VNS in patients with depressive symptoms is difficult. Further, due to the small sample size and limited response rate, the generalisability of the findings is limited.

The treatment of VNS seems to be a promising intervention in the treatment of depression. Further research on the treatment of VNS offers hope for improving treatments for mental health disorders such as anxiety and depression. Further randomised controlled trials are required to confirm the mechanisms by which VNS affects the brain-gut axis; further developments will provide alternative therapies for those who have not responded well to traditional treatments such as hospitalisation and antidepressants. Furthermore, this research has the potential to reduce anxiety and depressive symptoms through the relationships between the biome and hormones such as serotonin that, in turn, promote well-being for individuals suffering from mental health conditions.

Section 3.4

The Role of Serotonin

Serotonin or 5-Hydroxytryptamine is often referred to as the feel-good hormone due to its ability to contribute to feelings of happiness and well-being (Kim and Camilleri, 2000; Banskota, Ghia and Khan, 2019; Lee *et al.*, 2020). Research has shown an estimated 95% of serotonin is found in the GI tract, and only 5% is found in the brain, which indicates its significant role in digestion and its link to the microbiome (Kim and Camilleri, 2000; Lee *et al.*, 2020). Moreover, the microbes that live within the GI tract produce neurotransmitters, such as serotonin, which can affect mood regulation (Cryan and O'Mahony, 2011; Appleton, 2018). Research suggests this intricate system plays a vital role in the brain-gut axis (Cryan and O'Mahony, 2011; Appleton, 2018). Furthermore, the microbiome is known for synthesising and releasing serotonin alongside the endogenous production of gamma-aminobutyric acid (GABA) within the GI tract, which is crucial in regulating mood, emotions, and feelings of happiness (O'Mahony *et al.*, 2015; Shoubridge *et al.*, 2022).

Over the past few decades, developments have been made in understanding serotonin's role in controlling mood and behaviour as well as playing a vital role in communication between the gut and brain (Kim and Camilleri, 2000; Young and Leyton, 2002; Merens *et al.*, 2007; Lee *et al.*, 2020). Moreover, it has been shown how serotonin is related to regulating hunger, the sleep-wake cycle, and the body's stress response, all of which can significantly impact mood, behaviour, and mental health (Ruhé, Mason, and Schene, 2007; Merens *et al.*, 2007; Lindseth *et al.*, 2015; Lee *et al.*, 2020).

In recent years, mental health symptoms, such as low mood, depression, and anxiety, have been associated with altered neurotransmitter signals, specifically in serotonin levels, due to fluctuations in the gut microbiome and leading to changes in serotonin production and tryptophan levels (Kim and Camilleri, 2000; Kim, 2000; Ruhé, Mason, and Schene, 2007; Merens *et al.*, 2007; Lindseth *et al.*, 2015; Lee *et al.*, 2020). Consequently, disturbances in serotonin and tryptophan function can

suggestively influence the onset of chronic mental health disorders (Young and Leyton, 2002; Merens *et al.*, 2007). However, evidence suggests that increasing serotonin levels in the body can promote feelings of well-being and, in turn, reduce mental health symptoms.

Tryptophan is an essential amino acid and a precursor for serotonin synthesis (Kim and Camilleri, 2000; Kim, 2000; Young and Leyton, 2002; Hensler, 2010; Banskota, Ghia and Khan, 2019; Lee *et al.*, 2020). Increasing tryptophan levels has been shown to increase serotonin levels as much as double while decreasing tryptophan availability can cause a substantial decline in serotonin synthesis (Kim and Camilleri, 2000; Kim, 2000; Young and Leyton, 2002; Banskota, Ghia and Khan, 2019; Lee *et al.*, 2020). Tryptophan supplementation is believed to increase serotonin synthesis and in turn, improve mood levels (Hensler, 2010). Further, dysregulation of this system can often contribute to various mental health disorders, such as anxiety and depression, thus highlighting the importance of understanding the role of tryptophan and serotonin's mechanism in mental health.

In one study conducted by Booij *et al.* (2005), fourteen depressed patients were selected and received randomised doses of either 100g or 25g of tryptophan each day. It was theorised that acute tryptophan depletion (ATD) would improve symptoms in patients treated with antidepressants and would have no effect on patients who receive other treatments. The results of the study proposed that patients who received high-dose ATD experienced improved depressive symptoms, while no effects were shown in patients receiving other depression treatments (Booij *et al.*, 2005). Furthermore, although the study has positive patient outcomes, it also had several limitations. Firstly, patients had been taking antidepressant medication for an extended time, which could have interfered with the results of the study. Moreover, the sample size was small and difficult to generalise. Moreover, no further support or assessments for improvement were done outside the first 24 hours of the study.

Another study by Smith, Fairburn and Cowen (1997) conducted a double-blind crossover study in a total of fifteen women who had suffered recurring events of significant depression and were no longer on drug treatment. Patients received two

amino acid drinks; one contained tryptophan, and the other did not. The findings presented that after drinking the tryptophan-free mixture, ten of the fifteen women experienced temporary yet significant depressive symptoms. Further, no changes in mood were found after taking the tryptophan mixture (Smith, Fairburn and Cowen, 1997). Although this study demonstrated valuable insights into the potential benefits of tryptophan depletion on depressive symptoms, it does have several limitations. Firstly, the small-scale sample of 15 women limits the generalisability of the results. Further, the study was only focused on women; therefore, it may not apply to the general population. Additionally, the study examined the short-term effects of consuming the mixtures closely but did not examine the long-term effects of tryptophan depletion on depressive symptoms.

The mechanisms by which the gut microbiota regulates tryptophan metabolism are still unclear. Limited studies have shown that increasing tryptophan consumption can potentially raise serotonin levels and, in turn, alleviate depression symptoms (Booij *et al.*, 2005). However, the effectiveness of this treatment can vary among individuals. Future studies examining this will be crucial in understanding the mechanism by which the microbiota-brain interactions correlate with optimal brain function and mental health.

3.5 Diets

The association between diet and mental health has been a topic of interest in recent years (Bremner *et al.*, 2020). Epidemiological studies have begun to analyse the role of dietary patterns in helping prevent and treat mental health disorders (Sánchez-Villegas *et al.*, 2019). Poor nutritional patterns have previously been suggested to disrupt the intricate signalling in the microbiome and, in turn, precipitate changes in gut permeability and inflammation, linking to mental health disturbances (Lucas, 2018; Shoubridge *et al.*, 2022). This section explores the Mediterranean-based diet, tryptophan diet, ketogenic diet, and Western diet, assessing their link to the microbiome and alleviating or worsening mental health symptoms.

3.5.1 Mediterranean-based diet

A growing body of research has established an association between the treatment of symptoms of depression and the Mediterranean diet (MD). The MD is now considered one of the healthiest dietary patterns in the world (Opie *et al.*, 2017; Sánchez-Villegas *et al.*, 2019; Firth *et al.*, 2020; Quigley, 2020; Shoubridge *et al.*, 2022). The American Gut Study (Quigley, 2020), the most extensive published study to date on the human microbiome, found that people who regularly consumed a Mediterranean-style diet and who ate more than 30 different types of plant foods each week, such as fruits, vegetables, grains, legumes, nuts, and seeds had a significantly more diverse microbiome than those eating ten or fewer different plants. Moreover, adhering to an MD, associated with fibre-rich plant-based foods, olive oil, fish, poultry, dairy, and only occasional red meat, is associated with a reduced risk of depression (Firth *et al.*, 2020). The link between the microbiome and nutritional patterns, such as the MD, highlights the complex relationship between nutrition and gut health and has been associated with various positive effects on the microbiome and, in turn, mental health symptoms (Opie *et al.* 2017; Sánchez-Villegas *et al.* 2019; Shoubridge *et al.*, 2022).

The SMILES trial is the most extensive study in the world, conducted by Jackal *et al.* (2018), to examine the influence of the MD on individuals suffering from depression. The trial consisted of 166 participants in two control groups; group 1 was on an MD, and group 2 received counselling sessions (social support). The outcomes of the SMILES trial signified those individuals who followed an MD experienced substantial improvement in depressive symptoms compared to those who received social support alone. Moreover, after 12 weeks, a higher number of participants in the dietary intervention group achieved remission from depression compared to the social support group. Additionally, the dietary intervention group showed better reductions in depression scores throughout the study.

Additionally, a survey conducted by Opie *et al.* (2017) also reported significant improvements in depressive symptoms in 56 patients after 12 weeks of a dietary intervention with an MD in comparison to a social intervention. Since then, another study conducted by Sánchez-Villegas *et al.* (2019) examined the MD supplemented with extra virgin olive oil or nuts to prevent the risk of relapse in depression, and its findings were in line with the previous studies. This study found a 40% risk reduction of depression compared to extreme quintiles of MD adherence (Sánchez-Villegas *et al.*, 2019). Another study in line with these findings was conducted by Cabrera-Suárez *et al.* (2023) in a 2-year multicentre, randomised, single-blinded trial. The PREDIDEP study aimed to improve adherence to the MD in patients recovering from depression. The study included 52 men and 144 women between 18 and 86 years old. The findings indicated that after the study, the MD group improved mental health symptoms compared to the control group (usual clinical care only). However, the results obtained in the study might not apply to the general population due to the study being based on patients with depression (Cabrera-Suárez *et al.* 2023).

3.5.2 *The ketogenic diet*

The ketogenic diet (KD) is a well-recognised diet high in fat, moderate in protein, and low in carbohydrates (Brietzke *et al.*, 2018; Tillery *et al.*, 2021). The KD has recently been studied in relation to several health outcomes, including neurological disorders. (Brietzke *et al.*, 2018; Tillery *et al.*, 2021). The KD provides nutrients such as fatty acids, which have been revealed to alter the microbiota composition positively and, in turn, improve symptoms of depression in some populations (Cucuzzella *et al.*, 2017; Grabowska *et al.*, 2024). A self-reported uncontrolled study of low carbohydrate diets in 1580 patients reported considerable improvements in mood and anxiety and a reduction in antidepressant use after 12 months (Cucuzzella *et al.*, 2017). The outcomes of this study show that implementing a KD may have advantageous effects on mood and anxiety, as well as potentially reducing the need for antidepressant medication over 12 months (Cucuzzella *et al.*, 2017). Further, dietary interventions, such as the KD, could play a potential role in managing mental health conditions. However, it is necessary to note that further controlled trials are required to confirm these findings and clarify the mechanisms underlying the observed effects.

Further, a survey conducted by Tillery *et al.* (2021) reported the effects of KD on a 65-year-old female with a 26-year history of depression. The study was carried out over 12 weeks, with the participant consuming 65% fat, 25% protein, and 10% carbohydrates daily. The patient's symptoms improved significantly after the study, and her daily medication was reduced by 75%. Whilst this study appears to have dramatic results, due to it being based on one participant, it provides only a limited understanding of the mechanisms by which the KD affects the microbiota and, in turn, symptoms of depression in the broader population (Tillery *et al.*, 2021)

3.5.3 Tryptophan diet.

Foods high in tryptophan have been shown to increase serotonin levels in the body (Lindseth *et al.*, 2015). In recent years, the tryptophan diet (TD) has been examined for its possible influence on mental health disorders, mainly due to its role as a precursor to serotonin synthesis (Booij *et al.*, 2005; Lindseth *et al.*, 2015). Increasing tryptophan intake has been previously linked to improvements in mood, reduction in anxiety symptoms, and lessening of depressive symptoms (Booij *et al.*, 2005; Lindseth *et al.*, 2015). However, individual reactions to dietary interventions, including those targeting tryptophan intake, can vary due to genetics, nutritional patterns, gut health, and lifestyle factors (Booij *et al.*, 2005; Lindseth *et al.*, 2015). One randomised crossover study conducted by Lindseth *et al.* (2015) investigated the changes in symptoms of anxiety, depression, and mood in twenty-five adults over four days, with 1 group consuming a diet high and the other low in tryptophan. (Watson, Clark, and Tellegen, 1988). The results of this study showed that individuals who consumed higher levels of tryptophan ($> 10\text{mg/kg}$ body weight) had significantly lower levels of anxiety and depressive symptoms compared to those who consumed lower levels ($< 5\text{ mg/kg}$ body weight/). These discoveries signify that dietary tryptophan can positively affect serotonin levels in the brain and, in turn, reduce symptoms of anxiety and depression. These findings are in line with Booij *et al.*'s (2005) study, where tryptophan whey-rich protein foods were compared to a placebo in twenty-three recovered depressed patients and twenty matched controls. The results signified a considerable improvement in mood levels in the tryptophan group compared to the placebo. Furthermore, it was found patients who had previously experienced depression in the past suffered from adverse mood changes when tryptophan was depleted (Booij *et al.*, 2005).

3.5.4 *The Western diet.*

The Western diet (WD) has been a topic of interest in recent years (Vicente Javier Clemente-Suárez *et al.*, 2023). The WD dietary pattern is often considered high in processed and refined foods, saturated fats, fried foods, added sugars, and low intakes of fruits, vegetables, whole grains, and lean proteins (Vicente Javier Clemente-Suárez *et al.*, 2023). The WD has been associated with various adverse health outcomes in recent years, including mental health disorders (López-Taboada, González-Pardo and Conejo, 2020). A growing body of research between the WD and alterations in the composition and diversity of the gut microbiota has now been recognised (López-Taboada, González-Pardo and Conejo, 2020). One study conducted by Akbaraly *et al.* (2009) examined associations between two different dietary patterns in 3486 participants split into two groups: 1) a diet rich in whole foods such as fruits, vegetables, whole grains, legumes, and fish, and 2) processed foods high in processed meat, fried foods, and sugary desserts. The results from the study showed that the whole food dietary pattern was associated with lower levels of depression and the processed food pattern with a higher likelihood of depression (Akbaraly *et al.*, 2009). Further, a systematic review and analysis conducted by Wu, Chen and Belcastro (2020) showed that healthy dietary patterns and higher intakes of vegetables, fruits, legumes/ beans, and fish were associated with a reduced risk of depression in older adults. Additionally, a study by Hecht *et al.* (2022) found a representative sample of American adults who reported higher intakes of ultra-processed foods in their diet had statistically significant increases in adverse mental health symptoms (Hecht *et al.*, 2022).

Furthermore, after reviewing all four diets, it is evident that the MD stands out as the most beneficial in treating mental health disorders. Several scientific studies highlight the role the MD has on mental health due to being high in nutrient-dense foods, which are associated with a reduced risk of developing mental health conditions (Opie *et al.* 2017; Jackal *et al.*; 2018; Sánchez-Villegas *et al.* 2019). The MD also emphasises foods high in antioxidants, omega-3 fatty acids, and other crucial nutrients which support cognitive health and mood regulation (Opie *et al.* 2017; Jackal *et al.* 2018; Sánchez-Villegas *et al.* 2019). In contrast, diets high in saturated fats and ultra-processed foods, such as the WD, have been linked to increased inflammation and oxidative stress, worsening symptoms of anxiety and depression (López-Taboada, González-Pardo and Conejo, 2020). Further, whilst there is evidence suggesting a potential link between TD and improvements in mental health disorders, research is limited. Moreover, the TD provides promising signs of supporting mental health, although it seems to lack the complete nutrient profile of the MD. Further randomised controlled trials are needed to understand the mechanisms involved fully and to determine the effectiveness of a TD as a standalone treatment for mental health disorders.

In terms of the KD, although the exact mechanisms underlying the relationship between the KD and the brain-gut axis are still being examined, dietary interventions have positively affected neurological and gastrointestinal health by influencing the bidirectional communication between the brain and the gut. Whilst the KD's potential impact on mental health remains largely unknown, with limited data available, future research is imperative to clarify its effects on mental health outcomes, including the possible benefits or risks for individuals with anxiety and depression (López-Taboada, González-Pardo and Conejo, 2020).

3.5.5 Probiotics

The previous section evaluated current evidence on diets that affect the microbiome and are considered prebiotic foods that support microbiome diversity. Oral probiotics, a formulation of live beneficial microorganisms, introduce new bacterial species directly into the gut and have been shown to have potential therapeutic effects on mental health symptoms (Steenbergen *et al.*, 2015; Akkasheh *et al.*, 2016; Park *et al.*, 2018). It has been reported that gut probiotics play a significant role in the bidirectional communication between the gut and the brain (Huang, Wang and Hu, 2016). In recent decades, there has been emerging interest in the link between mental health disorders, the gut microbiome, and the likely positive effects of using probiotic treatments (Akkasheh *et al.*, 2016; Park *et al.*, 2018). Research in probiotic supplementation has found that live microorganisms in the GI tract exert several health benefits when ingested in adequate amounts (Messaoudi *et al.*, 2011; Akkasheh *et al.*, 2016; Park *et al.*, 2018). Research suggests that using probiotic supplementation may be a potential antidepressant treatment option for individuals with depressive disorder due to it altering the composition of the gut microbiome, with preclinical studies now demonstrating how the use of probiotics can positively change behaviour, enhance mood, and symptoms of depression (Wallace and Milev, 2017).

Schaub *et al.*'s (2022) trial was the earliest randomised controlled trial to establish whether short-term, high-dose supplementation of probiotics lessens symptoms of depression in clinically depressed patients. For four weeks, 47 participants were allocated to two study groups, a probiotic group and a placebo group, and tested at three different time points before, directly after, and again four weeks after the intervention. Findings indicated an improvement in depressive symptoms after four weeks of daily, high-dose probiotic supplementation. Further, it was reported that the probiotics group experienced a remission rate of 55% compared to 40% in the placebo group (Schaub *et al.*, 2022). Another study in line with these findings was conducted by Akkasheh *et al.* (2016), which examined the effects of probiotic supplementation on symptoms of depression. A total of 40 patients took part in the study over an 8-week randomised, double-blind, placebo-controlled trial. The results

of the study indicated that individuals receiving probiotic treatment had considerably lower depression scores compared to the placebo group (Akkasheh *et al.*, 2016).

Another study by Steenbergen *et al.* (2015) investigated the effect of probiotic supplementation on cognitive reactivity to sad mood. Participants received a 4-week supplementation intervention of either probiotics or placebo. The study showed that the probiotic intervention group experienced reduced aggressive and ruminative thoughts in response to sad moods. Another study in line with these findings was conducted by Wallace and Milev (2021). This 8-week open-label exploratory study with 10 participants examined the effect of probiotic supplementation on individuals with depression. The findings signified a noticeable improvement in overall mood, anxiety, and depressive symptoms after eight weeks. However, as a small-scale study, further research using larger sample sizes is essential to validate these findings and understand their broader implications (Wallace and Milev, 2021).

Another clinical trial in line with these findings was conducted by Kim *et al.* (2020). The study was a randomised, double-blind, placebo-controlled, multicentre clinical trial that ran for 12 weeks and examined the influence of probiotic supplementation on 63 participants. During the trial period, participants consumed probiotic supplementation twice daily for 12 consecutive weeks. Results found that after 12 weeks, whilst the stress scores were increased in the placebo group, they dramatically decreased in the probiotics group. Further, the study found probiotics promoted cognitive and mental health due to altered gut microbial composition in older adults (Kim *et al.*, 2020).

In contrast, a more recent meta-analysis by Ng *et al.* (2018) examined probiotic use on symptoms of low mood. Their study reported that probiotic supplementation had an overall insignificant effect on depressive symptoms. In addition, a double-blind, randomised, placebo-controlled trial in two probiotic strain treatments for symptoms of depression reported that neither of these probiotic formulations was effective in treating low mood (Romijn *et al.*, 2017). Similarly, Chung *et al.* (2014) implemented a 12-week, double-blind, randomised controlled trial with healthy individuals aged between 60- 75 years old. The study's results showed no significant improvement in the geriatric depression scale. Further, Rao *et al.* (2009) conducted a study with 35

patients receiving a probiotic or placebo twice daily for two months. Depression and anxiety symptoms were assessed pre- and post-study, with results showing that while consumption of the probiotic improved anxiety scores, it did not affect depression symptoms.

Additionally, Chahwan *et al.* (2019) examined the efficacy of probiotic supplementation in reducing symptoms of depression in adults. Seventy-one participants were assigned to either a probiotic or placebo group, which consumed probiotics daily for over eight weeks. The study showed the probiotic group did not demonstrate more significant levels of reduction in depressive symptoms than the placebo group (Chahwan *et al.*, 2019). These findings indicate that the use of probiotic supplementation alone is not an effective treatment option for reducing depressive symptoms, with any positive effect equal to the placebo. Similarly, a trial by Kazemi *et al.* (2019) investigated whether probiotics and prebiotics improved mood, stress, and anxiety in 81 participants. Participants were allocated into three groups for eight weeks: probiotic, prebiotic and placebo. The study results concluded that no significant correlations were found between participants' depressive symptoms and using probiotics and prebiotics and supplementation (Kazemi *et al.*, 2019).

In summary, evidence suggests that probiotic supplementation is a beneficial treatment intervention for alleviating depression symptoms. Whilst previous trials have produced positive outcomes concerning probiotic supplementation, additional trials have reported no significant difference. Therefore, to validate these conclusions, further double-blind, randomised controlled trials involving larger samples that can be validated and generalised upon are essential to assess their effectiveness comprehensively. This would also increase understanding regarding the positive benefits of probiotic supplementation in lessening symptoms of depression.

3.6 Study Limitations

Upon conducting this narrative review, several limitations were observed. Firstly, Minimal data exists on the long-term effects of VNS treatment as an intervention for depression. Most studies conducted had no control group, making comparison results difficult. Moreover, without a controlled trial, there is limited evidence obtainable on the placebo group, making concluding the efficiency of VNS in patients with depressive symptoms challenging. Further, due to small sample sizes and limited response rates, the generalisability of the findings could be improved. Further, there are a minimal number of studies examining the link between ATD and lessening symptoms of depression. A further limitation was that participants were suffering from long-term depression and taking antidepressants to relieve symptoms during the trials. Therefore, stopping this treatment would not be medically safe or ethical. Thus, this created a variable that could have skewed the results, meaning validity could not be ensured. This is because it is not clear whether it was the antidepressant medication, the ATD intervention, or both acting together that helped participants feel the improvements in their mental health.

Likewise, studies examining the impact of dietary patterns, specifically the TD and KD, could have been more extensive. This gap in the research hindered the understanding of the potential effects of these diets on alleviating mental health symptoms. Further, it limited the capacity to determine their effectiveness in relieving symptoms of depression. Further, the mechanism by which these diets influence positive mood changes, whether through weight loss in patients or through anti-inflammatory mechanisms, still needs to be clarified, making it difficult to conclude with a valid outcome. Moreover, previous trials have produced positive outcomes regarding probiotic supplementation. However, additional trials have reported no significant difference. Therefore, it is difficult to conclude these findings. One main issue was the need for more reliability across the study designs. Factors such as probiotic dosages, strains and treatment durations could have significantly impacted the outcomes observed. Therefore, without standardised protocols, it becomes easier to compare results between studies. Furthermore, several studies included diagnosed clinically depressed patients on antidepressant medication. Thus, the anti-depressants may have influenced mood outcomes, making it difficult to attribute

changes directly to probiotics.

3.7 Future Research

Further research on the role of VNS could develop upon existing research in alleviating symptoms of depression. Examining the mechanisms of VNS and its long-term effects on mental health patients will give valuable insights into its potential therapeutic effects. Further, exploring the efficiency of VNS in combination with other treatment interventions could reveal its role as a treatment intervention. Additionally, future research could further examine the mechanisms by which the potential development of mental health symptoms occurs through alterations in serotonin and tryptophan levels, with a particular focus on conducting further ATD randomised controlled trials using larger sample sizes.

At present, there is limited research looking at specific dietary patterns as a treatment for mental health disorders. Further studies should focus on the intricate connections between diet and mental health, specifically on revealing the mechanisms essential to the therapeutic effects of specific diets. Further, dietary studies and randomised controlled trials looking at the long-term impact on KD, TD and MD could provide additional evidence supporting the role of diet in preventing and managing mental health disorders long-term. Moreover, further research is also needed to underline ultra-processed foods' harmful effects on mental health and validate how diets rich in whole, nutrient-dense foods can be used as a treatment intervention for individuals suffering from mental health disorders.

Additionally, conducting controlled trials within healthcare environments and applying the well-recognised MD as a treatment intervention for mental health patients would not only develop the existing literature but also provide further insight into the effectiveness of this dietary pattern in decreasing symptoms of mental health disorders. Similarly, further trials looking into probiotic supplementation as a treatment intervention for mental health symptoms could involve larger samples that can systematically clarify and validate their efficacy. This would increase understanding regarding the positive benefits of probiotic supplementation in lessening symptoms of depression.

4. Summary

This narrative review examined the current literature, exploring the link between the gut microbiome and mental health disorders. It also investigated the mechanism of the brain-gut axis and its link to the vagus nerve. Further, it examined the function of serotonin and tryptophan in mood regulation. Likewise, it investigated the role of diet and how it can improve or worsen mental health symptoms. Lastly, the role of probiotic supplementation was reviewed as a treatment intervention for managing mental health disorders. Over the past decade, developments in microbiome research have evolved, allowing for an advanced understanding of the intricate interactions of the microbiota via the brain-gut axis and how this links with human mental health and disease. In recent years, there has been a growing body of evidence linking dietary factors to microbiome health, and treatment interventions used to alleviate symptoms of mental health include specific diets (for example, the Mediterranean diet), the use of probiotics, and increasing tryptophan to raise serotonin levels in the body.

It is evident that the MD stands out as the most beneficial in treating mental health disorders. Several scientific studies highlight the role the MD has on mental health due to being high in nutrient-dense foods, which are associated with a reduced risk of developing mental health conditions. The MD also emphasises foods high in antioxidants, omega-3 fatty acids, and other crucial nutrients supporting cognitive health and mood regulation. In contrast, diets high in saturated fats and ultra-processed foods, such as the WD, have been linked to increased inflammation and oxidative stress, worsening symptoms of anxiety and depression. Further, whilst there is evidence suggesting a potential link between TD and improvements in mental health disorders, research is limited. Moreover, the TD provides promising signs of supporting mental health, although it seems to lack the complete nutrient profile of the MD. Maintaining a balanced diet that includes tryptophan-rich foods as part of a healthy lifestyle may contribute to overall well-being and support mental health.

Moreover, further research could examine how specific foods affect tryptophan absorption and metabolism levels. For example, it could study how foods high in fats

or carbohydrates influence tryptophan levels in the body. Further, individualised nutrition interventions could tailor diets to individual needs. An improved understanding of how diet impacts tryptophan levels and its effects on health can be found by examining these possibilities.

However, as the mechanisms by which the gut microbiota regulates tryptophan metabolism are not fully understood, further research is required to understand the associations between foods, dietary practice and nutritional supplementation and these mechanisms. Further randomised controlled trials are needed to understand the mechanisms involved fully and to determine the effectiveness of a TD as a standalone treatment for mental health disorders. Similarly, the exact mechanisms underlying the relationship between the KD and the brain-gut axis are still being examined; dietary interventions have positively affected neurological and gastrointestinal health by influencing the bidirectional communication between the brain and the gut. Whilst the KD's potential impact on mental health remains largely unknown, with limited data available, future research is crucial to clarify its effects on mental health outcomes, including the possible benefits or risks for individuals with anxiety and depression (López-Taboada, González-Pardo and Conejo, 2020). Past studies have generally used tryptophan supplements or depletion techniques to fully understand the impact tryptophan has on mood, depression, and anxiety levels. However, these studies are minimal. Further randomised controlled trials with larger sample sizes are needed to understand the mechanism by which tryptophan levels positively affect mental health symptoms. Emerging evidence supports the use of specific dietary interventions in treating individuals with mental health disorders (Swainson *et al.*, 2023). However, the mechanism by which diets influence positive mood changes, whether through weight loss in patients or through anti-inflammatory mechanisms, remains unclear (Swainson *et al.*, 2023).

To conclude, probiotic supplementation offers potential hope for individuals suffering from mental health disorders such as depression. However, whilst some trials have produced positive outcomes, additional trials have reported no significant difference. Therefore, to validate these conclusions, further double-blind, randomised controlled trials involving larger samples are needed to confirm and generalise these findings,

which is essential to assess their effectiveness comprehensively.

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