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Review Article

You Can't Buy Happiness, But You Can Have a Healthy Gut: Therapeutic Effects for Depression via the Gut-Brain Axis

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Abstract

The World Health Organization states that Major Depressive Disorder (MDD) is a leading cause of disability, affecting about 300 million people worldwide, and is expected to be the leading burden of disease by 2030. Pharmacological therapy for depression is only effective for 74% of patients. The ineffectiveness of therapy, in addition to the overprescribing of antidepressants, has pushed research to explore the gut-brain-microbiota axis and evaluate it as a therapeutic option when addressing mental health. We have conducted a review of the PubMed databases focusing on the past decade, with consideration to the physiological make-up of depression, serotonin, gut-brain axis, and the pros and cons associated with them. We also considered the influence of the COVID-19 and its long-term effects associated with depression and gut microbiome. Studies have established how unhealthy microbiota results in lower serotonin levels, which are seen in patients with MDD. Similarly, research has uncovered various bacteria, hormonal influences, target pathways, and lifestyle changes, which have been shown to improve the health of the gut, increase serotonin levels, and provide an overall positive influence on the patient's wellbeing. Gaining further understanding of the gut's microbiome and effects of treatment, such as bacteriophage therapy, will help clarify the role of the gut in MDD and allow researchers to optimize the gut's overall health with the goal of providing a more comprehensive, effective treatment for patients affected by MDD. As research continues and understanding of how the gut communicates with the brain comes to fruition, treatment of MDD will stand a higher chance of yielding healthy guts and happy people.

Keywords: *Happiness; Healthy Gut; Depression; Gut-Brain Axis*

Introduction

The World Health Organization (WHO) states that depression is a leading cause of disability, affecting about 300 million people worldwide, and the trend is increasing [1]. It has been hypothesized that a gut-brain connection exists. Recently, there has been an increased interest in the influence of intestinal microbiota on mental health [2]. Intestinal microbiota may influence the brain mainly through the vagus nerve by humoral and neural means of the gut-brain axis [3].

Depression is a common, chronic health condition, and it imposes a substantial burden of disability globally [4]. The World Health Organization reported that depression is the fourth-ranked burden of global disease, with predictions of becoming the leading burden in 2030 [5].

As a result, efforts are being made to understand depression in a wider context, extending further than merely to neuro-biochemical changes. Moreover, pharmacological therapy for depression is only effective for 74%, even in combinations [1]. As a result, the ineffectiveness of combination therapy, together with the overprescribing of antidepressants, raises the need for alternate therapeutic approaches [6].

Since 95% of serotonin is produced in the gut, and varying levels of serotonin have been analyzed in people with depression, scientists suggest that a healthy gut may be instrumental to improving people's quality of life [8]. In particular, the microbiota-gut-brain axis is of particular interest as it is a rather modernized idea in which scientists have found there is communication between the gut and the brain [9]. As research progresses and uncovers the impact of the gut's microbiome on the overall health of a person both physically and mentally, a balancing act between biological systems becomes evident. When one part falls out of balance, effects are felt throughout the entire body and can manifest themselves as disorders, such as Major Depressive Disorder [10]. Common treatment pinpoints serotonin and other antidepressant medication as main mediators in relief of depressive symptoms [11]. However, scientists now recognize that there are many factors that may be able to be targeted and have more immediate, resounding therapeutic results on people who suffer from Major Depressive Disorder. In order to evaluate the gut-brain axis as a central factor, a preliminary assessment of the current literature on depression and serotonin will be followed by a discussion of their interface with the gut microbiome. The presentation of multiple studies and several metabolic pathways will weigh into the analysis of the pros and cons of this relationship. This review paper focuses on the association between serotonin in the gut and its interaction with depression and whether this interaction offers a new approach to treating people with depression.

Depression

Major Depressive Disorder (MDD) affects about 20% of the world's population and is one of the leading disabilities in people in the United States [7]. The main brain regions and systems implicated in depression are the subcortical limbic brain regions (amygdala, hippocampus, and dorsomedial thalamus) and prefrontal cortex, dorsal and ventral anterior cingulate cortex, and orbital frontal cortex and insula [7].

Many factors have been investigated to figure out pathological reasons for depression. For example, the basal ganglia is implicated in terms of motor control and movement, which is closely related to the dopaminergic reward system [12]. People with MDD are diagnosed with having decreased desire to perform actions throughout the day. Of particular interest, scientists have identified how there seems to exist a connection between the microbiome in the gut and depression [12]. Via the interaction of the listed brain regions, the microbiome has been shown to play an effect in the HPA axis and immune system (Figure 1) [12]. More specifically, higher levels of serotonin in the corticolimbic regions of the brain have revealed decreased anxiety-like behaviors [12]. Furthermore, the presence of a larger colony of microbiota in the gut is linked with increased levels of serotonin [12].

Due to lack of certainty of the exact onset of MDD, proposed treatments for depression range from nonpharmacologic to pharmacologic treatments. Some of the nonpharmacologic treatments include psychotherapy, complementary and alternative medicine, exercise, and pharmacotherapy [11]. In contrast, some of the pharmacologic treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, or trazadone [11]. Based off of a comparison review of these methods, clinicians surmised that the best treatment for MDD was either cognitive behavioral therapy or antidepressants [11].

One specific type of treatment considering the health of the gut and its association with MDD is the introduction of different types of probiotic bacteria. Some effective probiotic bacteria are *Bifidobacteria infantis* and *Lactobacillus,* which revealed improvements in the central HPA axis and monoaminergic activity [10]. Considering the depressive cycle, significant results were seen in higher serotonin levels, which suggest that the bacteria may contribute to alleviating depressive features in people [14].

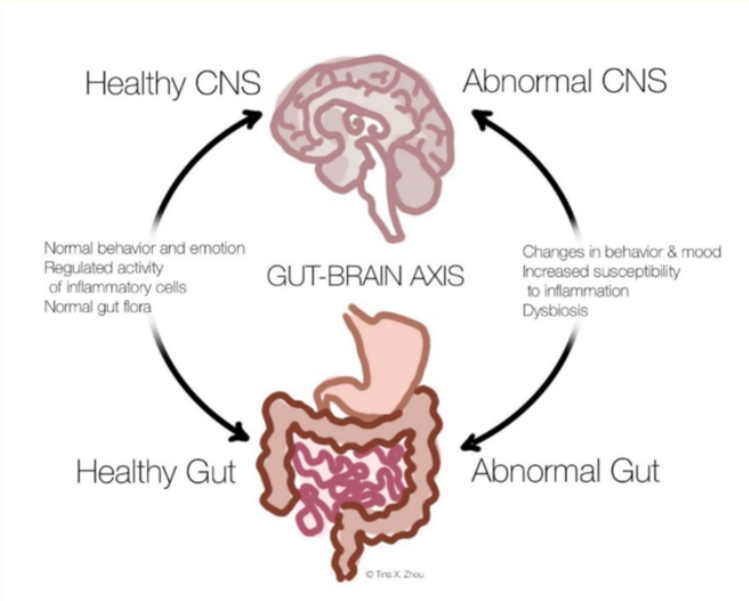

Figure 1: *The associated behaviors and physiological characteristics of a healthy gut versus an abnormal gut and the CNS (central nervous system) [13].*

Serotonin

In the scenario of serotonin being implicated in MDD, the monoamine hypothesis states that monoamines, such as serotonin, norepinephrine, and dopamine are lower in people diagnosed with MDD [15]. Due to this hypothesis, many antidepressant medications have been aimed at addressing this issue. However, results show that effects are not seen until about 2 - 4 weeks into taking the medication, further supporting the possibility that identifying another form of treatment is necessary [15].

In regular physiological terms, serotonin is synthesized in the gut and brain. The enteroendocrine cells make up the majority of hormonal tissue [8]. Enterochromaffin cells are a subset of these cells, which specialize in synthesizing 90 - 95% of the serotonin in the body [8]. Serotonin comes from the precursor, tryptophan, which enters the body's circulation via one's diet after absorption into the gut [8]. Tryptophan is converted to 5-hydroxytryptophan (5-HT) and can be localized to either the brain or the enteric nervous system [16].

While there is no direct path in which serotonin synthesized in the gut is able to affect or interact with serotonin in the brain due to the blood brain barrier, the gut microbiota has been identified as a point of modulation. Microbiota in the gut interacts with its localized serotonin, which will impact the immune system [17]. This is possible because immune cells such as lymphocytes, mast cells, dendritic cells, and monocytes have serotonin receptors, which can impact immune system activation and depression [17]. The changes in the immune system are then sensed in the brain and may influence the overall affect of a person.

One study experimented with germ-free rodents (organisms without a microbiome) and found that they had decreased serotonin levels [18]. However, when a new microbiome was introduced into the organism's system, serotonin levels increased, which showed that the microbiome could induce changes in serotonin levels [18]. This finding supplements the idea that there are neuro-immune interactions in the GI tract, which will ultimately have a lasting effect on the brain due to the immune system [19].

Regarding serotonin synthesis in the brain, some of its primary functions are to control mood, reward, anger, memory, sexuality, and attention [20]. Furthermore, modulation of different serotonin receptors in the brain will affect multiple behaviors. This makes it so that many serotonin-targeting drugs will cause a widespread change and multiple behaviors may be altered, since it is difficult to target the receptors for one specific behavior [20].

Expanding on the point of serotonin-targeted drugs, the main focus for how serotonin is used is in SSRIs [21]. SSRIs keep serotonin in the synaptic clefts for longer periods of time to counter the depressive effects associated with low serotonin levels in MDD [21]. However, as mentioned earlier, many anti-depressant medications do not have immediate effects, so it takes SSRIs several weeks to act before the patient is able to see results [15]. In addition, SSRIs are known to have side effects, because as serotonin and its receptors are mainly localized in the gut, SSRIs may also act on the gastrointestinal serotonin receptors, which will result in excessive peristaltic action and contractions of the tract that can lead to gastrointestinal-related diseases [20].

Gut-brain axis

Researchers have investigated the interaction between depression and serotonin from the gut and come up with the "gut-brain axis" [22]. The axis is a two-way system in which the brain and gut communicate [22]. In terms of how the gut-brain axis relates to MDD, several points must be considered. Firstly, serotonin in the brain is the primary regulator of mood and cognition [22]. The gut-brain axis relates emotion and cognition to control and function of the gut [22]. Although serotonin from the enteric nervous system cannot directly enter the central nervous system, it can act through interactions with sympathetic and parasympathetic projections to the vagus nerve, which can deliver messages to and from the brain (Figure 2) [22]. In a study in which the researchers performed a vagotomy on a mouse being given *Lactobacillus rhamnosus,* they found that there was no decrease in depressive-like symptoms, which also supported the key finding that the vagus nerve is critical in the gut-brain axis [22]. When the same experiment was performed on a mouse with an intact vagus nerve, depressive-like symptoms decreased, which showed how the gut microbiota modulated this system [22]. Furthermore, the previously discussed neuro-immune system is identified as a form of humeral signaling by using bacterial factors, cytokines, and hormones, which has been found to impact depressive symptoms too [12,22].

Another key player in the gut-brain axis is brain-derived neurotrophic factor (BDNF). BDNF is related to the neuroplasticity in the brain, and more specifically, the morphological development of serotonergic neurons [25]. Due to BDNF's ability to influence growth of serotonergic neurons and dendrites, it has been targeted as a point of interest when considering antidepressant treatments for patients [25]. Varying BDNF levels have been found to have a correlation with microbiota, and therefore, be an indicator of gut dysfunction [26]. Just as serotonin is regulated independently in the brain versus the gut, so are BDNF levels [26]. In fact, a study found that increased BDNF levels associated with the gut resulted in irritable bowel syndrome [27]. Ultimately, low BDNF levels are strongly indicative of low serotonin levels and the possible onset of depressive-like symptoms [27].

Pros and cons of the gut-brain axis

When exploring the gut-brain axis (brain, gut, microbiome, serotonergic pathways) and looking at its interactions with MDD to identify any form of therapy or relief, every component and its overall effect must be evaluated [28].

Beyond the physiological pathways between the brain and gut, the microbiome is fundamental to someone's wellbeing. Many studies have been conducted to check the effectiveness and necessity of a healthy microbiome. A group of researchers removed the gut microbiome from one set of rodents, placed them in a stressful environment, and measured their behavioral responses [29]. The study found that the rodents without the gut microbiomes had a more extreme, less recoverable stress-induced response than rodents who kept their microbiomes [29]. In a similar study, the researchers acknowledged how the gut microbiome is influential in brain development, so they focused on adult mice to see what effects would be incurred by their lack of microbiomes [30]. Results showed low spatial memory, in-

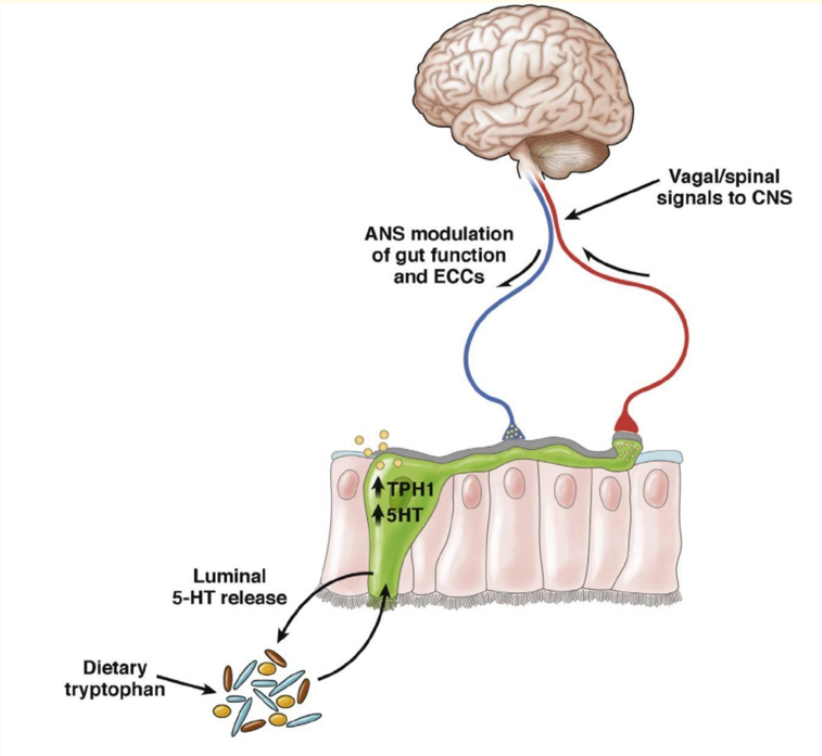

Figure 2: *The interaction of the gut-brain axis and the vagal connection between the serotonin produced in the gut and the central nervous system [23]. TPH1 (tryptophan hydroxylase 1) is depicted in this diagram, because TPH1 is the specific enzyme used in serotonin synthesis in enterochromaffin cells and periphery systems [24]. TPH2 (tryptophan hydroxylase 2) is specific to serotonin synthesis in the central nervous system and enteric neurons [24]. While TPH1 and TPH2 are similar, TPH2 has been implicated as having a more central role in affecting stress response, and ultimately, depression [24]. This figure has been modified from its original format [23].*

creased depressive-like behaviors, less visceral activity, and low levels of serotonin [30]. Together, these experiments propose how one form of therapeutic targeting may be in maintaining one's gut microbiome and screening for the health of MDD patients' GI tract. By doing so, modulation of serotonin in the enteric nervous system may be restored, which will revamp the gut-brain axis.

Paralleling the necessity to ensure patients have a healthy microbiome, recent research has zeroed in on fecal matter transplantations. While transplantations have been mainly analyzed in terms of therapeutic value, one group of researchers considered if the gut microbiota of an unhealthy organism could induce neurobehavioral changes representing this transplantation [31]. The transplanted microbiota had decreased diversity and richness [31]. After the fecal matter was orally given to a mouse without a microbiota, depressive-like symptoms and changes in tryptophan metabolism were recorded [31]. This finding highlights the gut's microbiota as a strong proponent in the advancement of depression. Nourishing one's body with a diverse, rich microbiome could not only result in successful treatment, but possibly prevention of depression.

Revisiting the discussion of pharmacologic versus non-pharmacologic treatment for MDD, one point that may be overlooked is that the gut's microbiome is made up of thousands of tiny microorganisms that live inside of each human, which means humans have the ability to cater and care for their environment [11,32]. This concept can be applied by honing in on several ways in which humans can offer the most optimal environment to their respective microbiomes by modifying dietary intake or implementing certain lifestyle practices. Some dietary fibers commonly found in whole grains are called "microbiota-accessible carbohydrates" (MAC), which have been tagged as the centerpiece to a thriving microbiome [33]. However, as society evolves, so do diets. There has been a trend toward higher fat and protein intake in the population, which are two known causes to upset the gut's environment [33]. Researchers have sought to understand this change in diet and pinpointed how people tend to eat less at home, where they are able to nourish themselves appropriately. Instead they eat out, where the food is often filled with additives that do not cater to a healthy gut microbiome [33].

In regards to lifestyle changes, people have shifted from a relatively dirtier environment to a cleaner one [33]. This change can be seen through something as simple as the movement from working outside to inside. In addition, less babies are being born vaginally, so they are not privy to bacteria from their mothers that inhabit their gut as they exit the vaginal canal [33,34]. Nowadays, there is also a strong focus on meeting public health standards, so everything is cleaned. In regards to personal hygiene, some people excessively implement cleaning practices, such as over-washing their hands or brushing their teeth incessantly [33]. As a result, people are no longer being exposed to bacteria that will support a healthy gut microbiome, so they lack the ability to fight off infections and are more susceptible to diseases and disorders [33].

Further on the point of serotonergic pathways, as the mediator of the central and enteric nervous systems, maintaining serotonin levels in the body is imperative in the human body. Any dysfunction associated with serotonin may result in issues related to mood, as in MDD, or intestinal problems [20,35]. A group of researchers explored the significance of the serotonergic synthesis pathway by comparing mice with a mutation in the rate-limiting enzyme, tryptophan hydroxylase 2, in 5-HT biosynthesis to mice without the mutation [35]. Their study revealed how the mutated mouse's GI tract had growth abnormalities, which they traced back to lower levels of synthesized serotonin being the cause of its variants [35]. When the researchers supplemented the mutated mice with serotonin, the mice's GI tracts were restored [35]. They proposed that their results offer a linkage between constipation and offsets of mood [35]. While treatments, such as SSRIs, have been introduced to patients, reorienting the focus on increasing serotonin levels specifically in the enteric nervous system may be game-changing in identifying a way to improve gut functioning, and therefore, improve quality of life in patients with MDD [21,35].

With serotonin as the main target, its importance in the gut-brain axis and how it relates to MDD is elucidated by studies performed on its precursor, tryptophan. As tryptophan is an amino acid that is normally ingested, it can only make its way into the brain via a specific transporter due to the blood brain barrier [36]. It is then converted into serotonin via its enzyme, tryptophan hydroxylase 2 in the brain [36]. In a study comparing germ-free mice to mice with bacteria in their system, the researchers manipulated the levels of tryptophan present in each mouse type and observed changes in behavior [36]. Their results demonstrated that the germ-free mice, without any other manipulation, showed decreased depressive symptoms compared to the other models [36]. However, when tryptophan levels were depleted in each model, the germ-free model showed the most significant negative change in response [36]. This finding suggested that there is a buffer or therapeutic relief in the other models, which were not germ-free, since they were better equipped to offset the change in response to varying tryptophan levels. Not only are tryptophan levels vital to maintain, but this study also purports how the presence of the gut microbiota can modulate tryptophan, and have an overall impact on serotonin levels.

Moreover, tryptophan has two main pathways where it can be metabolized: the serotonin pathway and the kynurenine pathway [10]. While the focus has been on how serotonin is synthesized and used, 90% of tryptophan will be directed to the kynurenine pathway (Figure 3) [10]. Scientists have discovered a precarious loop in which levels of tryptophan, gut microbiota, and kynurenine all modulate each other. However, if the system falls out of balance and the kynurenine pathway hijacks the available tryptophan stores, studies have shown

a potential link to the onset of depressive-like symptoms [10]. In fact, IDO1, the rate-limiting enzyme of the kynurenine pathway, has a trade-off relationship with the gut microbiota in that each can activate or suppress the activity of the other [10]. Instances in which IDO1 have contributed to the death of some of the microbiota have also occurred [10]. In situations of stress, or inflammation as mediated by pro-inflammatory cytokines, the body can upregulate this pathway and inhibit serotonin synthesis. If chronically triggered, this event can result in an overall depressive state of the person [33]. Acknowledging and understanding this second pathway for tryptophan proposes another method in which treatment for MDD can be addressed. By identifying the pathway, it becomes possible to target and manipulate in order to have tryptophan favor the serotonin pathway over the kynurenine pathway in the case of a patient with MDD.

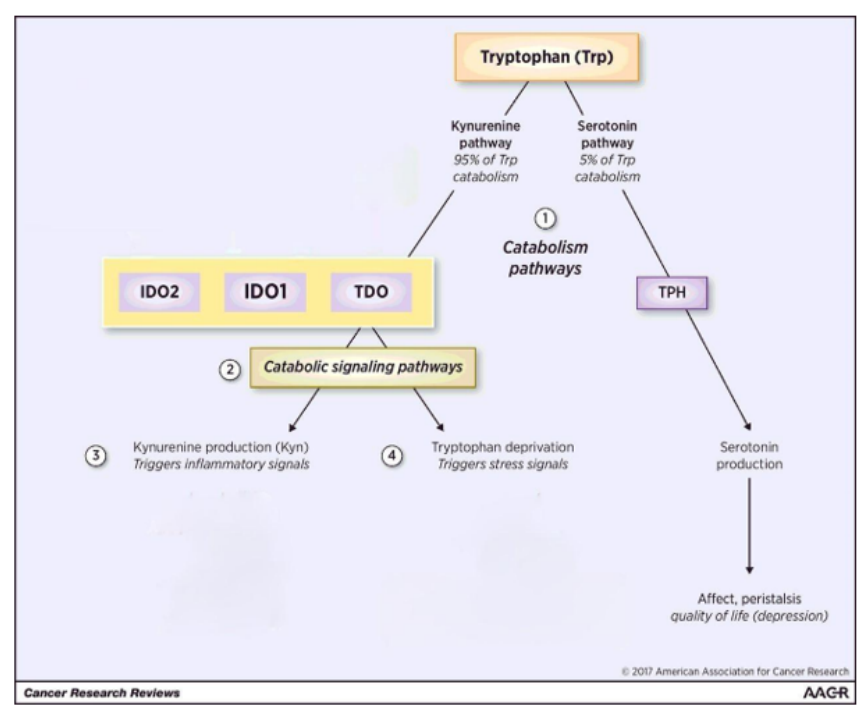

Figure 3: *Two catabolic pathways dietary tryptophan can follow and their overall effects [37]. While one study stated that 90% of tryptophan is shunted to the kynurenine pathway, another study alleged 95% of tryptophan is shunted [10,37]. Due to biological variation, it is reasonable to conclude that 90 - 95% of tryptophan is directed to the kynurenine pathway [10,37]. This figure has been modified from its original format [37].*

Although there is strong evidence subsidizing how if the body's serotonin levels are replenished, all will be well, there remains the possibility of having too much serotonin and its potential side effects. Specifically looking at excessively high serotonin levels in the bowels, scientists have found that people can get irritable bowel syndrome associated with this increase [20]. As more serotonin from the gut interacts with serotonin receptors in the enteric nervous system, there is the chance of activating vagal afferent signals to the vomiting center [20].

Another risk of serotonin is serotonin syndrome. The syndrome is characterized by hyperactivity of the serotonergic pathway, which is induced by antidepressant medications, such as SSRIs, monoamine oxidase inhibitors, and selective norepinephrine reuptake inhibitors

[38]. Disproportionate amounts of serotonin may result in muscular and autonomic abnormalities in the human body, which can lead to death if not addressed [38]. The exact mechanism in which this syndrome acts is not known [38]. However, the principle of the syndrome occurring due to overactivation of serotonin receptors exposes how the lack of specificity of the medications that have been linked to it can be detrimental to one's life.

Gut microbiome, MDD, and COVID-19

Considering the COVID-19 global pandemic, research has discovered that there appears to be a direct interaction between the SARS-CoV-2 RNA virus and the gut [39]. The virus has been detected in stool samples for up to 14 days after having a negative respiratory test for COVID-19 [39]. Furthermore, 17.6% of patients who tested positive for COVID-19 reported gastrointestinal symptoms [39]. Some of the most severe infections were associated with gastrointestinal findings [39]. This is further compounded by the fact that 35% of patients who have recovered from a COVID-19 infection, report continued symptoms of depression that impact various aspects of their lives [40]. Considering all of these points together, the composition of a patient's gut microbiome may have changed during the pandemic and could be contributing to post-COVID-19 symptoms. Further research on long-term effects of COVID-19 are needed.

Discussion

Major Depressive Disorder is a multifactorial disease. The human body is a delicate balance between activating certain systems, inhibiting others, and having just the right amount of hormones and neurotransmitters. The move from the gut-brain axis to the microbiota-gut-brain axis is pivotal in addressing issues affecting patients with this disease, because scientists now realize there is not one mainstream component responsible for people developing MDD, but rather a collection of components in which the microbiota is a key player [9].

Although many of the experiments performed on the gut-brain axis used rodents as test models, the results hold value and provide insight to human etiology of MDD. For example, discovering the importance of the vagus nerve as necessary to communication between the gut and the brain is critical in proving how the make-up of the gut can have an effect on the brain's state [22,41]. In addition, pinpointing how lack of healthy gut flora resulted in depressive-like symptoms in the rodent further validates the redefining of the gut-brain axis to include the microbiota [29,30]. Future studies should shift their research to human models. As the movement toward individualized medicine advances, the discussed interaction of serotonin and the microbiota should be evaluated in patients in order to provide care for people in a faster, more efficient, targeted manner [9]. In doing so, pharmaceutical companies can focus on developing drugs to avoid relapse of MDD symptoms and clinicians can implement nonpharmacological treatments.

Future applications of the findings associated with the gut-brain axis may lead to further research in pathologically-related diseases and open up a plethora of treatment options. In the case of diet, identifying an attainable diet for most people that will promote the survival of healthy, good microbiota may result in improvement in brain functioning and serve as a preventative measure in depression. Many of the research studies investigating the interaction of depression and serotonin disclosed that the pathology of the axis is still being discovered. Once the interaction is fully exploited, research can refocus its attention to mapping out the pathway in individuals and identifying places of dysfunction.

One point of debate is how the majority of studies named the rate-limiting enzyme of the serotonin pathway as tryptophan hydroxylase. Tryptophan hydroxylase is generalized to account for tryptophan hydroxylase 1 (THP1) and tryptophan hydroxylase 2 (THP2) [24]. Figure 2 shows how the enzymes do have differences and are localized to specific tissues, namely peripheral versus central [24]. The majority of current research focuses on THP2 when looking into pharmacological treatment and does not acknowledge THP1. However, the gut and microbiota are key players in depression, so therefore, THP1 which is associated with enterochromaffin cells lining the gut, should be addressed since 95% of the serotonin in the body is made in the gut [8,24]. Considering how studies have established how unhealthy microbiota results in lower serotonin levels, finding a way to upregulate THP1 in the face of a sub-optimal lumen could offer another method of treatment to MDD patients.

Currently, bacteriophage therapy is being explored as a possible form of ridding the body of harmful bacteria in the gut, which will further clarify the role of bacteria in the axis and allow it to function at optimal health [42]. This is just one of the unique forms of therapy made possible by unmasking the interaction of serotonin, microbiome, and MDD. As research continues and understanding of how the gut communicates with the brain comes to fruition, treatment of MDD will stand a higher chance of yielding healthy guts and happy people.

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