REVIEW ARTICLE

The relationship of depression, gut microbiota and colorectal cancer: A negative cycle

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ABSTRACT

It has been reported that gut microbiota play an important role in the development of colorectal cancer (CRC), and emerging evidence suggests that disturbances in the gut microbiome may also impact the central nervous system through the microbiome-gut-brain axis (MGBA). This review aimed to explore the potential connections between CRC, depression, and gut microbiota, in order to identify new clinical strategies for alleviating depressive symptoms. We utilized data from the 2005–2016 Continuous National Health and Nutrition Examination Survey (NHANES) provided by the Centers for Disease Control and Prevention (CDC), specifically using the Depression Screener Questionnaire (DPQ), which includes nine items scored from "0" (not at all) to "3" (nearly every day). We extracted the proportion of CRC patients who scored "3" on each item and calculated their percentage relative to the total number of participants for each year. This analysis generated bar graphs and tables summarizing the prevalence of depressive symptoms. Results showed that the most frequently reported symptoms were related to neurological dysfunction, such as persistent fatigue and abnormal sleep patterns, which indirectly support the existence of gut-brain interactions. In conclusion, our findings highlight a potential link between intestinal microbiota imbalance, CRC, and depression, suggesting that the gut microbiome may play a significant role in the onset or progression of depression and could serve as a novel target for the treatment of mental health disorders.

Key words: colorectal cancer, depression, gut microbiota

SYSTEMATIC REVIEW REGISTRATION

Cancer has always been a major influencing factor of human health, and the mortality rate of colon cancer ranks among the top. Although the relevant mechanisms have not been clearly determined, a large number of studies have confirmed that the microorganisms in the human gut have a certain influence on the occurrence and development of colorectal cancer (CRC).

Research has found that several factors affecting the gut microbiota, such as obesity, frequent smoking, and excessive drinking, are believed to have a close relationship with the development of colon cancer (Zhang *et al.*, 2021).

Some specific gut bacteria have been confirmed to be associated with cancer as well (Liu *et al.*, 2021b). At the same time, compared to healthy individual, the diversity and abundance of bacteria those living in CRC patient's

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intestine were significantly reduced, while the numbers of Firmicutes and Bacteroidetes were significantly increased (Silva *et al.*, 2021).

Thousands of smallest and simplest of creatures, known as gut microbiota, inhabiting animal's digestive tract and coexisting with the host. Under normal environment, gut microbiota and host are both essential entities for each other, in other words, they have a symbiotic relationship, but once the balance of their living environment is disrupted, the imbalance can lead to some gastrointestinal diseases, for instance, enteritis and even cancer (Quaglio *et al.*, 2022). The toxins and metabolites produced by the dysregulated microbiota can damage intestinal epithelial cells, causing inflammation and cancer to persist.

The birth of the concept of "microbiome-gut-brain axis"(MGBA) (Foster & McVey Neufeld, 2013) and the continuous deepening of collaborative research have opened a new door for people's understanding of the human body, more and more people believed that the gut is indispensable for the second brain of humans. Form this regard, a lot of research' results of animal experiments are far ahead. For example, in one experiment, when mice underwent fecal microbiota transplantation (FMT) surgery to reconstruct their gut microbiota, their behavior patterns underwent significant changes (Lyte *et al.*, 2006).

Although the specific mechanism is not yet clear, the research achievements from now to see we can indicate that not the nervous system of human body can affect microorganisms those inhabit in digestive system, especially the intestines, but this latter can reverse the former as well. That is to say, the MGBA is bidirectional.

As a result, scientists have gradually shifted their focus to the gut microbiota, attempting to find new directions for treating mental illnesses such as depression.

The psychological pressure brought about by cancer and the chronic stress response directly or indirectly caused by the body may both increase the incidence of depression in patients during treatment and even after recovery.

This review revolved around the possible connections between colon cancer, depression, and gut microbiota.

INTRODUCTION

There are a lot of people suffering from CRC around the world. In recent years, CRC is considered to be the third most common malignancy and the second most deadly cancer, its incidence rate is 10% of the global cancer, and 9.4% of cancer deaths (Fras *et al.*, 1967). In the past decade, advances in early diagnosis, chemotherapy, surgery, and radiation therapy have significantly increased survival rates for CRC patients. However, as these survival rates improve, new challenges have emerged, notably the tendency of cancer patients to experience depression during or after treatment.

Studies have shown that compared to patients without gastrointestinal symptoms, those with gastrointestinal symptoms often show more clear tendency towards depression, for instance, precipitous decrease in weight because of malabsorption and inexplicable sleep disorders (Yan *et al.*, 2021). This observation has prompted researchers to probe into intricate bridges link gut microbiota to depression, unveiling a critical area of interdisciplinary study.

With the progress of the times, more and more scientists are not only satisfied with animal experiments, but also invest more and more in clinical experiments, and their research results illustrate that ecology and metabolites of gut microbiota can influence the human body through various pathways, such as the MGBA and the immune system, affecting the occurrence, development, and treatment of certain diseases (Knight *et al.*, 2017; Magnúsdóttir *et al.*, 2015; Song *et al.*, 2022).

The human nervous system maintains bi-directional communication with the intestine by transmitting various biological signals, and this bi-directional communication network is called MGBA. This emerging concept links gut microbiota with emotional disorders, including depression and anxiety (Foster & McVey Neufeld, 2013; Grenham *et al.*, 2011; Sandhu *et al.*, 2017; Sharon *et al.*, 2016).

While this network link the microbiota and the MGBA has great explorations in animal experiments, research in humans remains in its early stages. Nonetheless, this emerging paradigm emphasizes the significant position of intestinal tract bacteria from human in a variety of psychological abnormalities such as various mental disorders.

Importantly, the microbiota inhabiting in human gut has also been empirically shown its cricial position of the onset and the promoting effect of processes of CRC. This paper primarily discusses the possible interwoven and complex connections between depression, intestinal tract bacteria from human, and CRC through a review of relevant published studies.

CRC AND GUT MICROBIOTA

There are more than 1000 million microorganisms inhabiting the human digestive tract, scientists call this

complex community as the gut microbiota, coexisting with the host (Gomaa, 2020; Kc *et al*., 2020). It makes great contributions to maintain intestinal homeostasis through various pathways, such as promoting digestion and metabolism, regulating the growth of cells that make up intestinal epithelial to prevent the invasion of pathogenic microorganisms (Belkaid & Naik, 2013; Magnúsdóttir *et al*., 2015; Vaishnava *et al*., 2008), and influencing the human body's immune monitoring of the outside world and itself (Kamada *et al*., 2013; Manfredo Vieira *et al*., 2018).

The ecology of human gut microbiota is intricately linked to this balance. A disruption in this balance can lead to a condition known as microecological imbalance, closely related with the pathological and physiological processes of various human diseases, including CRC (Magnúsdóttir *et al*., 2015).

Advancements in next-generation technology have enabled researchers to investigate and record various indicators of the biological activity of microorganisms during the entire process of starting or/and ending of gastrointestinal diseases. Current research has identified specific microbial communities associated with either preventing or promoting the pathological process of CRC. For instance, certain bacteria produce protein toxins that disrupt environmental homeostasis and promote tumor activity by generating enzyme-active protein toxins, damaging genes of host cells and interfering with various cellular life activities by effecting physiological signaling pathways such as apoptosis and inflammation (Fiorentini *et al*., 2020).

Gut microbiota can have some impacts on CRC risk, and there are various mechanisms related to this, including the maintenance or alteration of inflammatory states, disruption of the DNA in the cells that make up the intestinal epithelium, and the emission of biological signals of carcinogenesis. For example, research point out the dual the contributions made by gut microbiota in both inhibiting and promoting the course of disease during onset and development of tumors (Knight *et al*., 2017). Moreover, gut microbiota significantly impacts the host through the production of metabolites, such as vitamins and metabolic dietary compounds (Magnúsdóttir *et al*., 2015).

Further research underscores the complex and bidirectional relationship between microbiota and cancer. The development of cancer may alter the composition, quantity, and life activities of microbial community, while variations of the microbiota can adjust the development of cancer (Zitvogel *et al*., 2017).

THE BRAIN-GUT-MICROBIOTA SYSTEM AND DEPRESSION

In 1980s, groundbreaking studies discovered biochemical neurological pathways within the endocrine system of digestive tract, indirectly promoted the birth of the MGBA concept. Over following decades, this concept was not only strengthened but also focused people's attention more on the symbiotic microbiota in the human gut and their bidirectional interaction with the brain.

In recent years, the word "brain-gut-microbiota" encompasses more substantial contents than the simple meanings of the axis; a complex network of gut microbiota, systemic endocrine system that is crucial to human health through metabolic activity and chemical signals (Chang *et al*., 2022).

A growing number of evidence from related research tell us the responsible information exchange network between human gut microbiota and the central nervous system significant to depression-like phenotypes. Rodents displaying stress induced a tendency towards depression have shown along with changes in the metabolites of gut microbiota, certain host behaviors may also exhibit slight changes and made serotonin (5-HT) levels of brain a change (Li *et al*., 2019; Wu *et al*., 2020), Conversely, some research has demonstrated that the management of specific microbiota and metabolic products of them could either induce or alleviate depression behaviors, suggesting MGBA has a regulatory two-way effect on depression.

A recent proteomics analysis on depressive mouse model, caused by FMT from depressed suffers, scientists found obvious protein changes in the serum, brain, liver, and digestive tract (Liu *et al*., 2021b). These protein profiles driven by microbiota changes in human organs tissues were predicted particularly important for metabolic regulation and the response of inflammatory immune, potentially leading to depression *via* the MGBA (Liu *et al*., 2021b).

Furthermore, other research tell us that stress significantly affects the MGBA regulation. Notably, research has identified several peripheral target organs sensitive to the stress stimulation, including the lower gastrointestinal tract (Binder & Nemeroff, 2010; Collins, 2001; Stengel & Taché, 2009; Taché & Bonaz, 2007). When the body suffers stress, the hypothalamus, the pituitary and the adrenal secrete hormones and other biological signals to activate the central nervous system, while building a communication network with the intestinal nervous system through the sympathetic and parasympathetic pathways, thereby forming the MGBA

(Carabotti *et al.*, 2015). The autonomic nervous system (ANS) conveys incoming signals from the gut through the sympathetic and parasympathetic limbs to the central nervous system (CNS) through the gut, spinal cord, and vagus pathways, and directs outgoing signals for back and forth communication between the CNS and the digestive tract wall (Carabotti *et al.*, 2015).

This communication involving MGBA components, CNS, the hypothalamic pituitary adrenal(HPA), ANS, and the enteric nervous system (ENS), through neural, immune, and endocrine mediators, connects the brain's neural emotional and cognitive control centers with various certain regulatory ways on the intestines, such as regulation of the efficiency of material exchange in the intestine and alimentary canal local immunity (Carabotti *et al.*, 2015).

Moreover, HPA activation under excessive stress can elevate cortisol levels, disrupting BGA and the gastrointestinal immune system. This disruption may lead to impaired digestion and absorption of food, intestinal mucosa inflammation, and sustained high cortisol levels, further impairing the immune system. Chronic inflammation can ultimately lead to an immune system breakdown and intestinal microbiota imbalance (Gao *et al.*, 2018), contributing to increased intestinal wall permeability and motility disorders, which are known to exacerbate inflammation (Chang *et al.*, 2014; Eutamene *et al.*, 2007; Lyte *et al.*, 2006; Sun *et al.*, 2013 Xu *et al.*, 2014). Such intestinal inflammation is closely linked to colon cancer; for instance, inflammatory bowel disease (IBD) is considered a pusher of CRC (Keller *et al* ., 2019; Mattar *et al.*, 2011; Shalapour & Karin, 2015; Zisman & Rubin, 2008). Changes in the colonic immune microenvironment, such as accelerated angiogenesis, cell proliferation, and increased tumor cell invasiveness, can drive the development and progression of cancer (Shalapour & Karin, 2015).

This evidence enhances our findings of the complex interactions of the "two brains", one up and one down, providing strong support for the MGBA's contributions for depression (Jiang *et al.*, 2015; Naseribafrouei *et al.*, 2014; Park *et al.*, 2013; Tillmann *et al.*, 2019; Yang *et al.*, 2020; Zheng *et al.*, 2020).

GUT MICROBIOTA AND DEPRESSION

Depression is not only the most prevalent spiritual disorder but also the principal pathogeny of disability all around the world (Beurel *et al.*, 2020). Although extensive research, there are a lot of unknown answers to the pathophysiological mechanisms underlying depression. However, an increasing body of evidences from studies discovered that based on the MGBA, the gut microbiota's metabolites from basic metabolism under different situations can have multiple impacts on pathology and physiology of depression, implicating various systems in the human body, such as immune systems. .

Compared to patients, studies on depression and bipolar disorder have identified a distinct the components that make up the gut microbiota in healthy individuals (Zheng *et al.*, 2020), indicating that patients' gut microbiota have a more abnormal composition than that of healthy controls. For instance, microbial changes in patients with depression not only vary but also typically show an increased presence of latent damaging and inflammatory bacteria, for instance, Proteus contrasts with the usually abundant and symbiotic bacteria found in healthy controls (Aizawa *et al.*, 2016; Jiang *et al.*, 2015; Kelly *et al.*, 2016; Naseribafrouei *et al.*, 2014; Valles-Colomer *et al.*, 2019; Zheng *et al.*, 2016). In patients suffer from generalized mental disorder, although few anomalies were observed, symbiotic bacteria also showed a similar decrease (Jiang *et al.*, 2018). The absence of a definitive "gut microbiota profile" for depression or anxiety could stem from methodological differences in evaluating multiple physiological indicators of gut microbiota, as well as individual variations in microorganisms that coexist with humans (Neufeld *et al.*, 2011).

Research into depression and anxiety encompasses (1) exploring the close connection between diet and mentality and (2) investigating the impact of gastrointestinal symbiotic microbiota on impacts of nerves and behaviorgut, a field known as the MGBA. It has been demonstrated that patients' daily diets and symbiotic microbiota in their gut significantly influence emotions and behaviors, with dietary intervention can effectively improve the patient's gastrointestinal tract health (Oriach *et al.*, 2016).

The interaction between gastrointestinal symbiotic microbiota and brain function occurs through multiple pathways, notably involving immune regulation, neuroendocrine, and vagal pathways. Recent studies have shown that there has been a continuously increasing focus on the position and contribution in neurological diseases of symbiotic microbiota, especially those residing in the gut.

Clinical research has revealed that the origin of depression is accompanied by changes and imbalances in various hormones, including hormones that can be managed by gut microbiota to regulate the reproductive system, nervous system, and stress response. This modulation may cause certain impact on depression through the MGBA.

Recent studies point out that interventions based on the patient's daily diet, such as vitamin D, omega-fatty acids, iron, and fiber which can effectively lessen or prevent some common negative emotions of perinatal mothers, such as low mood and anxiety, though their efficacy is significantly influenced by the gut microbiota (Song *et al* ., 2022).

Notably, there are significant differences in the gut microbiota characteristics between patients with depression and healthy individuals (Kurina, 2001; Naseribafrouei *et al*., 2014). For example, analysis of the gut microbiota from nearly 2000 volunteers revealed that individuals with depression had lower levels of Coprococcus and Dialister bacteria, whereas those with a higher quality of life possessed a greater abundance of fecal and Faecalibacterium microbiota (Valles-Colomer *et al*., 2019). This evidence strongly supports a correlation between gut microbiota and depression.

Moreover, existing research indicates that most patients with intestinal inflammation exhibit cognitive and emotional disorders (Kurina, 2001). Clinical studies *in vivo* have also shown that gastrointestinal inflammation can modify the central nervous system, leading to anxiety-like behaviors (Bercik *et al*., 2010; Lyte *et al*., 1998), with anxiety and stress recognized as primary triggers of depression.

Animal-based medical research has demonstrated that depressive symptoms can be spread through FMT. In one study, mice treated with fecal microbiota from depressed suffer exhibited more depressive symptoms than those treated with healthy fecal microbiota (Zheng *et al*., 2016). Similarly, Kelly found that rats receiving fecal microbiota from depressed suffers displayed significant pleasure deficits and anxiety-like behaviors, along with tryptophan metabolic disorders, changes not observed in recipients of healthy fecal microbiota (Kelly *et al*., 2016).

These findings underline the strong correlation between gut microbiota and depression. Despite compelling evidence linking microbiota to emotional behaviors, the mechanisms and clinical significance remain to be fully understood (Bear *et al*., 2020).

DEPRESSION AND CRC

Social and clinical surveys indicate that patients with depression are significantly more susceptible to certain diseases, such as cardiovascular diseases, cancer, and diabetes, which shortens their lifespan compared to healthy individuals (Benros *et al*., 2013; Bortolato *et al*., 2017; Windle & Windle, 2013). Furthermore, not only are individuals with depression more prone to these diseases, but the effectiveness of treatments for these conditions is also often compromised (Katon, 2011). In recent years, the incidence rate and mortality rate of depression have increased year by year, imposing a substantial economic burden on society.

Both innate and acquired immune mechanisms are essential for humans to fend off external harm. Sensitization of the immune system can give rise to inflammatory reactions, characterized by redness, swelling, fever, pain, and other symptoms. These reactions involve the coordination of various immune cells and mechanisms to counter foreign substances, thus maintaining internal environmental homeostasis. However, dysfunction in these processes is often linked to diseases, with growing evidence pointing to a connection with mental illnesses such as depression (Murphy & Weaver, 2017).

Research on mice has demonstrated that intestinal infections or chemically induced colitis can lead to behaviors typically associated with anxiety, such as reduced exploration (Lyte *et al*., 2006) and significant behavioral inhibition (Bercik *et al*., 2010; Lyte *et al*., 1998).

Psychological stress, a major contributor to depression, can also manifest acute symptoms. Studies suggest that abnormal levels of cytokines in patients suffering mental disorders, such as schizophrenia, might increase the propensity for common immune pathways post-treatment (Goldsmith *et al*., 2016).

This suggests that psychiatric patients with acute symptoms may experience an acute inflammatory state, aligning with the observed increase in inflammatory markers and response after psychological stress in healthy individuals. These inflammatory factors are also implicated in the development of depression (Maes *et al*., 1998; Miller & Raison, 2015; Miller & Raison, 2016).

Furthermore, experiments based on mouse models examine the effect of stress can make contributions to tumor development revealed that stress-induced adrenaline can accelerate the proliferation and metastasis of CRC (Zhou *et al*., 2022). The combination of the inflammatory response triggered by pro-inflammatory factors and the chronic stress experienced by patients with depression could potentially initiate and accelerate the development of colon cancer (Baritaki *et al*., 2019; Shah & Itzkowitz, 2022).

Depression is commonly comorbid with cancer, affecting more than 10% of cancer patients. The fear associated with cancer is profound in both daily life and clinical settings, where the diagnosis of cancer often brings more distress than other diseases (Mishel *et al*.,

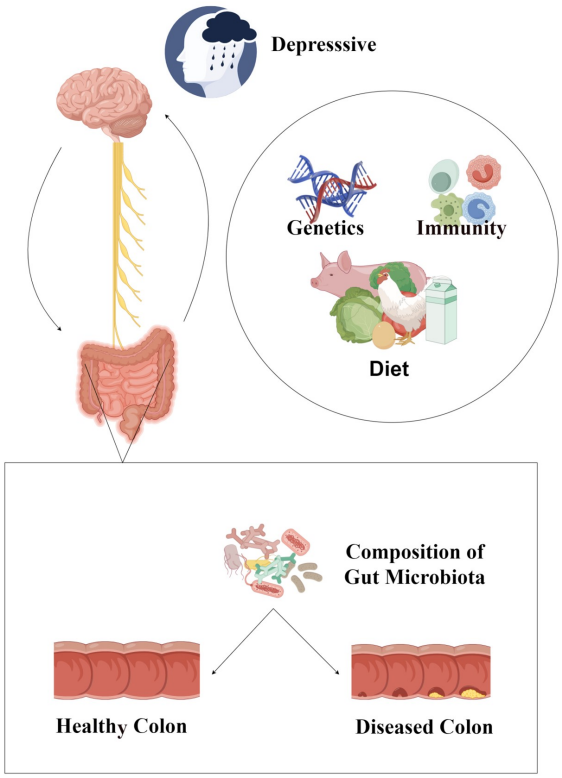

Figure 1. Interplay between depression, gut microbiota and colorectal cancer.

1984). Cancer patients frequently endure significant mental anguish during their treatment and daily lives, leading to depression or anxiety (Linden *et al.*, 2012), with the coexistence of these states being common (Brintzenhofe-Szoc *et al.*, 2009).

Pain is a prevalent symptom among cancer patients (Sheinfeld Sheinfeld Gorin *et al.*, 2012), arising from cancer cell metastasis to bones, soft tissue infiltration, or nerve compression by tumors. Additionally, cancer treatments like chemotherapy and radiation can cause acute inflammatory pain conditions such as mucositis, dermatitis, or enteritis (Bray *et al.*, 2016; Harb *et al.*, 2014). Pain may persist as a sequela even after recovery.

The presence of metastases and cancer-related pain is linked to increased depression levels (Ciaramella & Poli, 2001). The clear mechanism between the level of the cushion of the patient and the incidence of depression is not clear, but its strong correlation has been confirmed, with depression occurring in more than 30% of patients experiencing high levels of pain compared to less than 15% in those with minimal suffering (Spiegel *et al.*, 1994). This suggests suffering as a potential factor which may cause mental and psychological disorders.

In the case of a patient suffering from cancer, as the disease progresses, tumor metastasis that infiltrates or compresses the intestinal tract can lead to intestinal obstruction, causing severe abdominal pain. Advanced stages of colon cancer may result in cancer cells spreading to other abdominal locations, causing necrosis and inflammation, which are particularly painful for patients with low tolerance. Moreover, colon cancer can invade surrounding organs, such as the urethra and bladder, leading to additional pain. Metastasis to abdominal lymph nodes can compress the abdominal plexus, causing significant discomfort, and bone metastasis can also result in pain at the affected sites. These scenarios can exacerbate patients' pain levels, thereby increasing their likelihood of suffering from depression.

The sequential relationship between these conditions is not definitively established, but the evidence strongly suggests a bidirectional relationship between depression and cancer (Figure 1).

There are a number of aspects can impact the microorganisms residing in the human gut which has been proven by multiple studies can lead to intestinal disease. Meanwhile, due to the "two-way bridge" links gut and brain, the imbalance of gut microbiota can affect brain through multiple pathways, and such complex relationships are likely to exist in patients with depression.

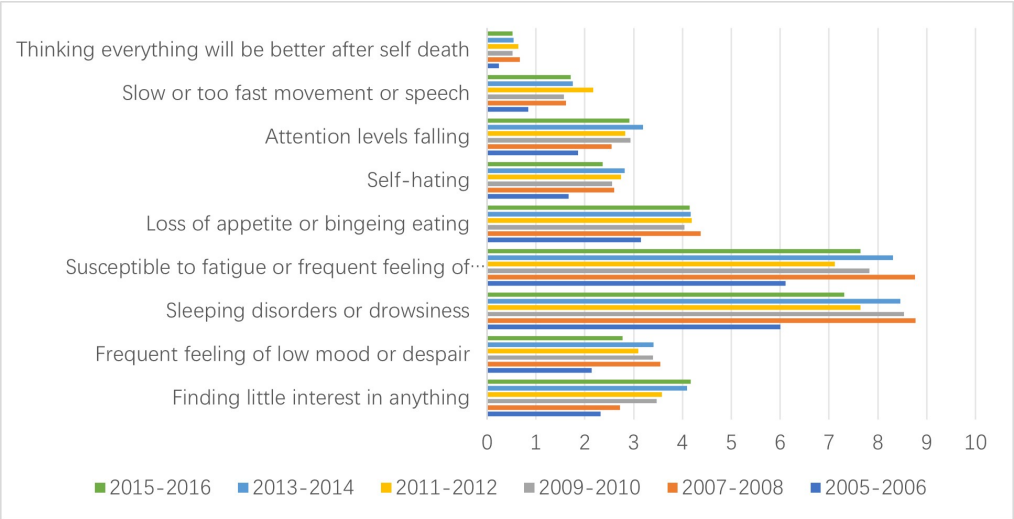

Figure 2. Depressive symptomatology tracking through PHQ-9 instrumentation: A 12-

During 2005 to 2016, the CDC collected data from participants (colon cancer patients) by using a self-reported health questionnaire (PHQ-9) based on nine depression signs and symptoms from the Diagnostic and Statistical Manual of Mental Disorders (4th version,USA) (DSM-IV), which has been proven to be a exact pathway to diagnosing depression.

This questionnaire also known as the Depression Screening Questionnaire (DPQ), scores nine symptom questions from "0"(completely absent) to "3"(almost every day). The graph(Figure. 2) shows the proportion of CRC patients with a score of 3 (almost every day) to the total number of people surveyed that year.

The symptom "Susceptible to fatigue or frequent feeling of fatigue" consistently shows the highest values across all time periods,and the symptom "Thinking everything will be better after self death" consistently shows the lowest values across all time periods. Other highly ranked symptoms include sleeping disorders or drowsiness, loss of appetite or bingeing eating, and attention levels falling. Many symptoms appear to show fluctuations in prevalence across the different time periods, which suggests a possible relationship with broader social conditions.

The consistently high prevalence of fatigue and sleep disturbances could indicate a widespread issue related to stress, lifestyle factors, or underlying health conditions. The trends of the symptoms are mostly even across periods, which may imply that a similar population and conditions have been measured across time. Further research would be needed to explore the underlying causes of the symptom trends. Factors like economic conditions, social trends, healthcare access, and cultural shifts could all play a role.

From this graph (Figure 2), we can see that the symptoms of depression in volunteers are most commonly related to neurological abnormalities such as easy to feeling fatigued and abnormal sleep habits and time, which to some extent reflects the close connection that links gut and brain.

POSSIBLE CONNECTION BETWEEN CRC, DEPRESSION AND GUT MICROBIOTA

The gut microbiota is mainly composed of two types of microorganisms, namely beneficial bacteria and harmful bacteria. There is a dynamic balance in the quantity of two types of microorganisms, which collectively maintain the normal physiological functions of the intestine and the human body, and are closely related to the occurrence and development of various diseases.

In an experiment conducted on CRC patients, the results showed significant differences in the number of gut microbiota between the patient group and the healthy controls. The number of beneficial bacteria in the study group was less than that in the control group, while the number of neutral and harmful bacteria was more than that in the control group ($P < 0.05$), indicating a certain correlation between gut microbiota and the incidence of CRC; According to clinical staging, stage I and stage II, There are quantitative differences in the gut microbiota of stage III patients, with fewer beneficial bacteria and more neutral or harmful bacteria compared to stage I. This suggests significant differences in gut microbiota among CRC patients with different disease stages (Shi & Zhai, 2024).

One team found that psychological stress can promote the progress of breast cancer by changing the intestinal

flora through studying the model of sterile mice and antibiotic treated mice. A. Muciniphila and butyrate can be used as microbial biomarkers of stress related breast cancer, while probiotics supplementation and high fiber diet show good intervention potential (Cui *et al.*, 2025).

At the same time, another study suggests that Coprococcus seems to have a pathway related to dopamine metabolism, which is a key brain signal in the onset of depression. The synthesis potential of DOPAC, a metabolite of dopamine in gut microbiota, has also been shown to be associated with higher quality of life indicators in butyrate producing fecal bacteria and fecal cocci (Valles-Colomer *et al.*, 2019).

This side reveals the potential connection between the three, but research currently cannot explain the causal relationship or directionality of the interaction between the microbiota gut brain axis. How gut microbiota interacts with the human central nervous system, and whether it affects or even alters individual behavior or triggers diseases, all need to be tested and discussed in further research in the future.

CONCLUSION

Human intestine serves as a habitat for the vast majority of human microbiota, with current research clearly indicating that these microorganisms are significant of regulating both our physical and mental health through the MGBA (Cenit *et al.*, 2017; Cryan *et al.*, 2019). This regulatory function heavily depends on the balance of the gut microbiota. Destroy this balance can give rise to a number of diseases, such as enteritis, systemic inflammation, colon cancer, and mental illnesses such as depression.

In the case of colon cancer, numerous studies have found out tight associations between its onset and progression and the imbalance of gut microbiota. For instance, changes in metabolites, variations in bacterial species, or the presence of inflammation can significantly affect the development of colon cancer.

Additionally, imbalances in human Intestinal microbiota may negatively impact the brain via the MGBA, potentially increasing the risk of mental health issues. Conversely, abnormal emotional patterns and dietary habits in individuals with mental illnesses can also make impact on the gut microbiota, further affecting intestinal health.

As our understanding of the biological and pathological connections between diet, the gut microbiome, and the MGBA deepens, this finding points out that these insights will lead to substantial shifts in treatment approaches for anxiety, emotional disorders, depression, and colon cancer recovery.

Ongoing human and animal research about the MGBA mechanism continues to shed light on how gut microbiota influences symptoms of negative emotions in humans, among other psychological and neural effects. Dietary interventions are proving to have significant advantages over traditional medication and chemotherapy, offering direct benefits to gut and brain physiology in a gentler, more cost-effective manner, and facilitating indirect benefits through gut microbiota modulation. In the future, dietary interventions hold promise as an attractive and economical alternative or complementary therapy.

The connection between depression and cancer is sophisticated and non-sequential, often presenting as concurrent conditions with varying timelines and numerous clinical challenges. For instance, clinical signs of depression, such as tiredness, poor appetite, weight changes, and cognitive difficulties (Smith, 2015), can be misinterpreted by healthcare providers as cancer symptoms or side effects of cancer treatment. This misinterpretation can lead to underdiagnosis and delays in appropriate treatment.

Moreover, the current gap in definitive research about the gut microbiota-depression link and the limitations of existing medications mean that many depression patients' needs remain unmet. Further research in this domain is essential to developing new antidepressants. Additionally, incorporating analyses of biological factors like gut microbiota into the therapy and follow-up of depression suffers could help prevent relapse, enhance quality of life, and expedite social reintegration.

DECLARATION

Author contributions

Sun XH and Li YR contributed equally to this work. Sun XH and Li YR developed the search strategy for the review and assisted with the method description. Sun XH, YX and Zhang LZ found and provided reference. Sun XH and Li YR completed the article screening and completed the data extraction. Sun XH created the tables. Sun XH performed the data analysis. Sun XH, Korban S, Zhang WL, Li XJ, Zhang YM, Chen H, Li W and Li TY helped interpret the results and correct grammatical errors in the article. All authors contributed equally to the article and approved the submitted version.

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Ethical approval
Not applicable.

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

Use of large language models, AI and machine learning tools
None declared.

Data availability statement
The original data presented in the review are from CDC (https://www.cdc.gov/), 2005-2016 Questionnaire Data—Continuous NHANES in the National Health and Nutrition Examination Survey prat. The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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