Iranian Journal of NEUROSURGERY

2024, Volume 10, E29

Review Paper

Gut-brain Axis Roles in Brain Tumors: Pathophysiological Insights and Research Advances

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Citation Karimzadeh A, Yousefzadeh-Chabok Sh, Hemmati H, Andalib S. Gut-brain Axis Roles in Brain Tumors: Pathophysiological Insights and Research Advances. Iran J Neurosurg. 2024; 10:E29. http://dx.doi.org/10.32598/irjns.10.29

doi: http://dx.doi.org/10.32598/irjns.10.29

Article info:
Received: 24 Oct 2024
Accepted: 04 Dec 2024
Available Online: 30 Dec 2024

Keywords:
Gut-brain axis (GBA), Central nervous system (CNS), Malignancy, Brain tumor, Therapeutics

ABSTRACT

Background and Aim: This study reviewed the association between gut microbiota and primary brain malignancies, with a focus on underlying metabolic and immunologic mechanisms, and possible therapeutic approaches.

Methods and Materials/Patients: A literature search was carried out for a narrative review related to the microbial components of the gut-brain axis (GBA) and their potential effects on brain tumors' formation, growth, and course of treatment with a focus on recent publications.

Results: Studies have highlighted likely mechanisms of the crosstalk between the gut and brain through an anatomical and physiological pathway, known as the GBA. Moreover, the metabolites and signaling molecules produced by gut microbiota were found to be involved in maintaining the blood-brain barrier (BBB) integrity and brain homeostasis. In addition, studies have revealed the potential negative effect of gut dysbiosis on tumorigenesis and deleterious inflammatory and immunological cascades within the brain. Pre-clinical and clinical investigations indicated the role of modulation of gut microbiome in brain tumors.

Conclusion: Previous investigations on interactions between gut microbiome and central nervous system (CNS) have revealed potential pathways through which interventions on microbiota can regulate brain tumor epigenetics and microenvironment. The findings on modifying microbiota utilizing probiotics, fecal microbial transplantation, and supplemented dietary regimen were promising; nonetheless, further investigation is needed to translate these findings into clinical brain cancer treatment applications.

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Highlights

- Gut microbiome interacts with central nervous system (CNS), by sending on neurotransmitters and neurohormones.
- Gut microbiome is involved in maintaining blood-brain barrier (BBB) integrity and mediates neuroinflammation.
- Pre-clinical studies, mainly on glioma, reported an increase in tumor growth following gut dysbiosis.
- Clinical studies reported differences in the gut microbiome between brain tumor patients and healthy individuals.

Plain Language Summary

Developing cancer treatment strategies has been a major challenge, due to the heterogenic nature of tumors and the occurrence of genetic mutations. Apart from chemotherapeutic drugs including cell cycle inhibitors and antimetabolic agents, hormone-based therapeutics are among the factors that manipulate tumoral cell epigenetics, and in turn its behavior. There is a focus on cancer treatment with targeted immunotherapeutic methods, such as the development of anti-tumoral vaccines and Antibody-drug conjugates. The fact that tumoral cells rely on their surrounding microenvironment for growth and invasion has also come into focus on not only the malignant cells but also the components in their microenvironment. Gut microbiota plays a crucial role in digestion, metabolism, nutrient synthesis, and our immune system's response to pathogens. The role of gut microbiota malignancies has previously been investigated. The gut-brain axis (GBA), a bidirectional network linking the gastrointestinal (GI) tract and CNS, is valuable in cancer treatment; be that as it may, its role in neuro-oncology is a less-divulged topic. The present narrative review takes account of the role of GBA in primary CNS malignancies.

1. Introduction

The interconnections between neurological conditions and the gut are not a newly founded topic. As Avicenna wrote in his book, The Canon, the stomach plays a major role in many neurological disturbances [1]. A millennium later, the potential therapeutic approaches to many central nervous system (CNS) disorders are meticulously being investigated within another system, the gastrointestinal (GI) tract. Although the brain is an isolated Immune-privileged site in the human body, there is a growing body of evidence indicating that the primary pathogenesis of a few chronic neurological diseases originates in the gut. This change in our perspective has occurred in the past decade with the discovery of a new organ called "gut microbiota". Gut microbiota weighs roughly 1.5 kilograms [2] and encompasses more than 3 million genes, almost 140 times greater than that of the human genome [3]. These findings highlight the importance of these organisms' communication with our organs through metabolites, neurotransmitters, and the mucosal immune system.

Within the human CNS, primary malignancies are still a major challenge to tackle. One of the major reasons is that the expanding tumoral tissue is in an isolated physical and physiological environment. Therefore, brain cancer research has a focus on optimized targeted therapeutic approaches. These methods try to harness brain tumors not only by early detection and debulking the mass using neurosurgical techniques but also by changing their uncontrolled behavior to minimize the damage to the surrounding tissue. A potential intervention is through modifying the tumor's microenvironment.

A growing body of literature has deciphered molecular signals involved in the pathogenesis of brain tumors that are continuously being exchanged between the brain and gut, shedding light on new paths to modify diagnostic, prognostic, and therapeutic guidelines. These molecular signals have been classified based on their oncolytic or oncogenic effects [4]. Gut microbiota can impact the tumor microenvironment by changing the levels of immunomodulating agents, including interleukin (IL)-18, IL-17, IL-12, IL-6, tumor necrosis factor-α (TNF-α) [5], granulocyte-macrophage colony-stimulating factor signaling (GM-CSF), IL-4, IL-13, interferon-gamma (IFN-γ), and tumor necrosis factor-β (TGF-β) [4]. These chemokines and cytokines have been the targets of immunotherapy, although not enough to suppress malignant cells through apoptosis or autophagy mechanisms [6]. Gut microbiota plays a role in these pathways by modulating oxidative stress biomarkers such as reactive oxygen and nitrogen species [7]. Bacterial antigens and metabolites, namely short-chain

fatty acids (SCFAs), tryptophan, arginine, and other products are also involved in manipulating tumor microenvironment [4, 8]. The gut-brain axis (GBA) is a bidirectional network linking the GI tract and CNS. Gut dysbiosis is the alteration of gut microbiota and activity. In this narrative review, we provide a brief overview of the interconnections between gut microbiota and the pathophysiology of malignancies and CNS homeostasis, aiming to highlight the potential routes of intervention through the gut in CNS malignancies.

2. Methods and Materials/Patients

A literature search was conducted for a narrative review related to the microbial components of the GBA and their potential effects on brain tumors' formation, growth, and course of treatment with a focus on recent publications.

3. Results and Discussion

Gut microbiota and host immunity

Immediately after birth, human skin and mucous membranes are colonized with microbial flora, which is the beginning of interactions between the host and its microbiologically replete environment. Meanwhile, the host immune system is developed by consistently recruiting and training immune cells to maintain the integrity of immune barriers. The composition of the microbiota is affected by external factors and varies in health and disease. Previous studies indicated that microbiota in vaginally born infants were similar to their mother's vaginal microbiota, but the microbiota in those who were born via c-section was mainly composed of Propionibacterium and *Staphylococcus* species but lacked *Lactobacillus*, *Bifidobacterium*, and *Bacteroides* [9, 10]. This change is also affected by antibiotics used during hospitalization and maternal diet during pregnancy [9].

The gut mucosal immune system is functionally divided into two main sites. Introductory sites, where antigens are introduced in Peyer's patches, isolated lymphoid follicles, and mesenteric lymph nodes, and the action sites of epithelium and lamina propria where activated B and T lymphocytes are present [11]. Intestinal epithelial cells, macrophages, and dendritic cells in the introductory sites recognize the commensal or pathogen microorganisms via pattern recognition receptor systems (PRRs) [12, 13]. Microbe- or pathogen-associated molecular patterns (MAMPs or PAMPs) are identifiable by RPRs [14]. The immune response initiated following the interactions between PAMPS and RPRs leads to an immune tolerance or triggers an inflammatory cascade and production of pro-inflammatory cytokines [15]. Commensal microbiota regulates local and systemic inflammatory responses through induction of the IgA secretion [10], and production of fermentation metabolites that limit the growth of pathogens [16]. One of the key roles of microbiota in influencing host immune responses, whether through enhancement, suppression, or modulation—originates from their metabolic byproducts. These metabolites can impact the mucosal layers or enter systemic circulation. Accordingly, the host immune system and microbiota metabolism are interconnected mechanisms.

Gut microbiota and host metabolism

With the emergence of high-throughput quantification of biological molecules and the development of techniques such as 16rRNA sequencing [17], many bacterial enzymes and consequently their metabolites have been traced. Bacterial enzymes metabolize a wide range of lipids, carbohydrates, and proteins, and are involved in the bioavailability of minerals and vitamins. Among this diverse range of metabolites, the immunoregulatory roles of SCFAs (SCFAs: Acetic acid, butyric acid, propionic acid), aryl hydrocarbon receptor (AHR) ligands, and polyamines were widely investigated [18]. Aside from providing an energy source for intestinal epithelial cells, SCFAs function as signaling molecules on polymorphonuclear leukocytes, macrophages, dendritic cells, and T regulatory cells. Subsequently, the nuclear factor-κB (NF-κB) is inactivated, which leads to a decrease in pro-inflammatory cytokines including tumor necrosis factor (TNF) [18]. Moreover, SCFAs cross through the blood-brain barrier (BBB) [19] and inactivate inflammatory microglia [20]. The essential amino acid tryptophan is metabolized by host cells to the neurotransmitter serotonin, vitamin B3 (niacin), kynurenines, and the hormone melatonin [21, 22]. It is also metabolized by a specific group of bacteria such as Lactobacilli species to produce AHR ligands, indole, indolic acid, skatole, and tryptamine which plays a crucial role in mucosal barrier integrity and immunosuppression in tumors [22, 23].

Healthy gut and tumor suppression

In the field of cancer immunotherapy, many attempts have been made to modulate the tumor microenvironment by modifying the gut microbiota. Microbiota can metabolize dietary ingredients to oncogenic metabolites such as hydrogen sulfide and secondary bile acids or tumor-suppressive agents such as SCFAs and urolithins [24]. Such an interplay between the microbiota and diet is also a subject of epigenetic modifications. Moreover, some species of commensal bacteria such as *Akkermansia muciniphila*, *Bacteroides fragilis*, *Bifidobacterium* species, and *Faecalibacterium* species enhance the effect of anti-tumor therapy when targeting T lymphocytes by blocking

the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) [25-28].

Manipulation of gut microbiota using oral antibiotics was shown to potentially change the behavior of solid tumors including melanoma, pancreatic, and colon cancers in mice; however, a healthy functioning mature lymphoid cell lineage is needed for immunotherapeutic interventions through the gut [29]. In a recent study, Puerarin, which is a bioactive agent derived from Chinese herbal medicine, was shown to have the ability to change gut microbiota composition [30]. Through analysis of metabolic pathways, it was demonstrated that changes in ovarian cancer tumoral metabolism were affected by microbial metabolites, and subsequently led to the activation of apoptotic signals [30].

Gut dysbiosis and tumorigenesis

The term Oncobiome was coined since genomic research has expanded our understanding of the relationship between the gut microbiota genetic material and carcinogenesis [31]. *Helicobacter pylori* is the first pathogen whose strong association with GI cancers was discovered. In the context of chronic inflammation, its virulence factors including cytotoxin-associated gene A (*CagA*), vacuolating cytotoxin (VacA), and outer membrane proteins (OMPs) can lead to mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma [32, 33]. Unlike *H. pylori*, which is not a commensal microorganism in the colon, some cancer-related bacteria are considered opportunistic pathogens that are related to a specific stage of cancer [34, 35]. Dysbiosis, the alteration in composition and activity of microbiota, may result from either host-specific or environmental factors [36] and was previously observed in saliva, bile culture, and feces in pancreatic, gall bladder, and colorectal cancer patients, respectively [37].

Of the community of commensal bacteria, E. coli and *Bacteroides fragilis* can accelerate the progression of colorectal cancers (CRC) in genetically susceptible individuals (familial adenomatous polyposis) via damaging DNA and IL-17-induced inflammation. Additionally, *Fusobacterium nucleatum* is involved in the occurrence of CRC and metastasis through the up-regulation of microRNA-21 and nuclear Factor-kappaB signaling pathway [38]. The role of lymphoid cells, namely the proinflammatory T-helper 17 (TH17) and T-regulatory (T reg), are not fully understood in the tumor microenvironment [39]. Studies in germ-free mice discovered the dependence of TH17 on microbiota [39]. Naive Tregs also depend on Butyrate-mediated microbiota metabolites to mature. These findings highlight the need for further investigations to elucidate the precise mechanisms underlying immune dysregulation and chronic inflammation because of gut dysbiosis.

The gut and the brain

GBA is said to be a physiologically interconnected system composed of the CNS, the enteric nervous system (ENS), the autonomic nervous system (ANS), the hypothalamic pituitary adrenal (HPA) axis and the entero-endocrine system (EES) [40]. It functions as a pathway for the microbiome to send signals to the brain and vice versa. SCFAs are among these signals and can circulate throughout the body and maintain not only the stability of the intestinal epithelial barrier but also the BBB, by regulating the expression of Occludin, a transmembrane protein [41]. Therefore, changes in microbiota metabolome can endanger the integrity of BBB. Furthermore, a study on germ-free mice indicated that SFCAs are essential for microglial maturation [42]. Microglia, the immune regulator of the brain, constitutes 10-15 % of all CNS cells. They have two opposite phenotypes. M1 phenotype promotes inflammation and neurotoxicity, and M2 induces anti-inflammatory and neuroprotective effects [43]. The transformation of microglia to either one of these phenotypes is under the control of cytokines released from T helper lymphocytes. Overstimulation by anti-inflammatory cytokines, such as IL-4 and IL-13, turn microglia into M2 and has been shown to cause exhaustive tissue remodeling and eventually the formation of tumoral mass in the brain [44]. As a result, maintaining an immune balance, in addition to a favorable metabolic state, is vital in preventing the formation and growth of tumoral cells.

Gut microbiota and CNS malignancies in pre-clinical investigations

Many attempts have been made to enhance the efficacy of anti-tumor therapies in brain tumors by modifying the GBA. A study evaluated the effects of manipulated gut microbiota on glioma growth and innate immune cells including microglia, monocytes/macrophages, and infiltrating T and NK cells [45]. In this study, 5 weeks of oral non-absorbable antibiotic therapy with vancomycin and gentamicin in a glioma syngenetic mouse model, led to the growth of Burkholderiales families and a decrease in the Prevotellaceae, Rikenellacaea, and Helicobacteraceae families. The results of the flowcytometric analysis showed a reduction in the cytotoxic NK cell (CD27+/CD11b+) population, while the immature NK cell (CD27+/CD11b-) subset increased relatively in the tumoral hemisphere. An overall growth in the size of the tumor was also observed in the experimental group whose microbiota composition was altered [45].

Findings of the effects of microbiota modulation on brain glioma growth were promising. A probiotic regimen containing *Bifidobacterium lactis* and *Lactobacillus plantarum*, inhibited the PI3K/AKT pathway and decreased the expression of Ki-67 and N-cadherin, therefore slowing down the growth of glioma in mice models [46]. Another study modified the gut microbiota of GL261 syngeneic glioblastoma mice by adding high-glucose drinks to their diet for a short period, during which high-sugar metabolic complications were not observed [47]. This study demonstrated that the increase in the Desulfovibrionaceae family in the gut microbiota resulting from the modified diet was related to enhanced cytotoxic CD4+ T cell immune response and tumor growth restriction [47]. Elsewhere, the regimen of two types of glioblastoma mouse models (orthotopic implantation and genetically engineered GBM models) was supplemented with tryptophan [48]. This intervention caused a rise in CD8+ T cell numbers in circulation and boosted the antitumor response synergized with anti-PD-1 cancer immunotherapy [48].

Conversely, the effects of glioma on fecal neurotransmitters and metabolites have also been explored. In a study, a decline in the levels of SCFAs (butyrate, propionate, and acetate) and neurotransmitters, including norepinephrine were observed in fecal samples of both glioma patients and glioma-transplanted mouse models [49]. Whereas the detected levels of serotonin, 3-methyl valerate, caproate, and acetylcholine increased following tumor growth. These changes in metabolic pathways also impacted the gut microbiota composition. Results of the study showed a deterioration in *Bacteroidetes* and Firmicutes phyla levels and a rise in Verrucomicrobia phylum, in mice [49]. Consistent with these findings, another study reported that Firmicutes to Bacteroides ratio significantly decreased in glioma-induced models, and Verrucomicrobia phyla, specifically the Akkermansiaceae family in this phylum, demonstrated a relative growth and subsequent gut dysbiosis [50].

Gut microbiota dysbiosis can also result from the administration of chemotherapy agents within the course of treatment. Temozolomide, an oral alkylating agent used in the treatment of glioblastoma multiforme and anaplastic astrocytoma [51], can directly affect gut microbiota composition [52]. In a mouse model of brain glioma, the relative amounts of *Akkermansia* and *Bifidobacterium* increased in fecal samples of mice treated with temozolomide compared to control subjects [52]. Both bacteria are beneficial components of microbiota because of their role in metabolism and immunomodulation [53, 54].

In a recent study, it was shown that gut dysbiosis caused by oral antibiotics led to a decrease in the expression of Foxp3, a key transcriptional regulator in the function of Regulatory T lymphocytes, and fecal microbial transplantation successfully restored its expression in glioma-induced mice [55]. Within the GBA, the inflammatory pathways have been investigated in pre-clinical studies.

It was shown that acute and chronic inflammatory processes in the colon of inflammatory bowel disease models resulted in astrocyte activation in the hippocampus of mice and interfered with the process of adult hippocampal neurogenesis [56]. In this study, colitis was indicated by the raised levels of oxidative stress markers (Il-6 and iNOS) and macrophage infiltration. However, intestinal inflammation was not related to medulloblastoma tumorigenesis measured by tumor markers of Gfap and Ki67.

More recent studies are equipped with the powerful tool of multi-omics analyses to integrate biological findings related to the physiological pathways between the gut and the brain. In a multi-omics-based investigation, gut microbiota modification with oral administration of a mixture containing *Bifidobacterium* species in a mouse model of glioma successfully inhibited tumoral expansion and increased the survival time [57]. In this investigation, transcriptome sequencing revealed that the suppression of MEK/ERK cascade and Wnt5a mRNA levels was the underlying mechanism of growth arrest in glioma. Table 1 summarizes pre-clinical studies used in this narrative review article.

Table 1. A summary of preclinical studies used in this narrative article

Species/Sex	Model	Intervention	Most Important Results	Reference
Mice/Male	Syngeneic glioma mice	NK cell depletion, Gut microbiota alteration by Antibiotic treatment	1. Increase in tumor size as a result of immune dysfunction related to gut dysbiosis	D'Alessandro et al. 2020 [45]
Mice/Male	Glioma	Gavage of a probiotic mixture	1. Decrease in tumor size, increase in survival time, and restore some damage to the intestinal epithelial barrier	Wang et al. 2022 [46]

Species/Sex	Model	Intervention	Most Important Results	Reference
Mice/Male	Syngeneic glioblastoma mice	20% dextrose water supply, Intraperitoneal injection of anti-mouse CD4 depletion antibody for CD4+ and CD8+ T cell depletion, Antibiotic treatment to deplete gut microbiota, Immune checkpoint blockade by intraperitoneal injection of anti-PD-1 ICI	1. Enhancement in T cell-mediated anti-tumor immune response as a result of gut microbiota regulation with a high-sugar diet	Kim et al. 2023 [47]
Mice/Male	Germ-free mice, gene-edited glioblastoma model	0.2% Tryptophan-supplemented drinking water before intracranial implantation of tumoral cells, Fecal microbiota transplantation, Intraperitoneal injection of anti-CD8α antibodies for CD8α+ cell depletion, Intraperitoneal injection of anti-PD-1 blocking antibody for immunotherapy	1. Modulation of gut microbiota dysbiosis as a result of tumoral growth by tryptophan 2. Mitigation of gut microbiota dysbiosis improved survival rates and T-cell immune responses	Kim et al. 2024 [48]
Mice/Male	Glioma	Fecal metabolite assessments in glioma models with or without oral temozolomide treatment	1. Reduction in 5-hydroxyindoleaceic acid and norepinephrine levels in glioma models 2. Temozolomide treatment partially reversed tumoral effects on fecal metabolite.	Dono et al. 2020 [49]
Mice/Male	Glioma	Oral temozolomide treatment	1. Temozolomide treatment partially reversed tumoral effects on fecal microbial composition.	Patrizz et al. 2020 [50]
Mice/Male	Germ-free mice, glioblastoma model	Oral temozolomide treatment	1. Temozolomide treatment showed an increase in *Akkermansia* and *Bifidobacterium* while preventing the decrease of Anaerotruncus.	Li et al. 2021 [52]
Mice/Female and Male	Germ-free mice, Glioma	Antibiotic treatment, Antibiotic treatment+ fecal microbial transplantation	1. Gut dysbiosis can accelerate glioma growth	Fan et al. 2022 [55]
Mice/Male	Medulloblastoma mouse model	0.7% dextran sodium sulfate for induction of colitis	1. Chronic intestinal inflammation is related to neuroinflammatory response. 2. Medulloblastoma oncogenesis was not precipitated in the setting of chronic colitis.	Vitali et al. 2022 [56]
Mice/Female	Glioma	Gavages of a *Bifidobacterium* mixture	1. A decrease in tumor size and an increase in survival time	Fan et al. 2024 [57]

Gut microbiota and CNS malignancies in clinical investigations

Intricate molecular findings of gut microbiota and CNS malignancies have been translated into clinical research, expanding the survival rates and improving the clinical outcomes of aggressive brain malignancies, such as glioblastoma. Many attempts have been made to enhance treatment protocols in brain tumor patients.

In a case-control study, the association between five oral microbiota and high-grade human brain glioma, as opposed to low-grade glioma, was investigated [58]. Additionally, the bacterial genes that are related to glioma grade were analyzed functionally. These genes play various roles in cell adhesion, focal adhesion, extracellular matrix molecule-receptor interaction, and modulation of actin cytoskeleton [58]. To detect the gut microbial biomarkers that are distinguishable in brain tumor patients compared with healthy individuals, a shortage of SCFA-producing bacteria was reported in the fecal samples of benign meningioma and malignant glioma patients [59].

An investigation of fecal microbiota composition in 101 brain tumor patients (65 benign and 36 malignant types) compared with 57 healthy controls, revealed that the levels of pathogenic bacteria, such as Fusobacteriota and Proteobacteria increased, while the amounts of probiotic bacteria, such as *Bifidobacterium* or Lachnospira deteriorated [60].

In a multi-omics study on fecal samples of primary CNS lymphoma (PCNSL) patients and healthy individuals, increased ratios of the Firmicutes/Bacteroides (F/B) and the proteobacteria were observed in PCNSL cases [61]. More to the point, amino acids, thiamine, biotin, and 2- oxocarboxylic acid metabolic pathways were diverted in PCNSL patients as compared with controls. Similarly, another study on changes in the gut microbiome and metabolome in patients with meningioma, glioma, and brain metastasis, reported a remarkable reduction of Gram-positive bacteria such as Lachnospiraceae and a considerable growth of Gram-negative bacteria such as Enterobacteriaceae [62]. A shift in metabolite composition was also detected; however, most fatty acid and amino acid metabolites increased, and bile acids (BAs) and carbohydrates decreased [62]. Multi-omics studies of gut microbiota have also been performed on different types of intracranial neoplasia, such as craniopharyngioma, and yielded consistent results [63]. A more recent study investigated gut dysbiosis in glioblastoma patients at the phylum, family, and genus levels using polymerase chain reaction-denature gradient gel electrophoreses (PCR-DGGE) analysis, and revealed major changes in microbial diversity in these patients [64]. Table 2 summarizes clinical studies used in this narrative review article.

Table 2. A summary of clinical studies used in this review article

Study Type	Tumor Type	Intervention/ Objectives/ Outcome Measures	Most Important Results	Country	Reference
Case-control	Glioma	Oral microbiota diversity	1. Negative association between the genera *Capnocytophaga*, *Leptotrichia*, and the phylum Patescibacteria with glioma grade 2. Positive correlation between the genera *Bergeyella* and *Capnocytophaga* with the IDH1 mutation in gliomas 3. Identification of 5 oral microbial qualities that have discriminative value for high-grade and low-grade gliomas	China	Wen et al. [58]
Clinical trial (a pilot study)	Benign meningioma, malignant glioma	Gut microbiota diversity	1. Introduction of a microbial biomarker panel that has discriminative value between brain tumor patients and healthy patients	China	Jiang et al. [59]
Case-control	Glioma, meningioma, pituitary tumors, brain metastases, and other brain tumors	Gut microbiota diversity	1. Introduction of a microbial biomarker panel that has discriminative value between brain tumor patients and healthy patients 2. A rise in the abundance of pathogenic bacteria (e.g. Fusobacteriota and Proteobacteria) in patients 3. A decrease in the abundance of probiotic bacteria (*Bifidobacterium* and *Lachnospira*) in patients	China	Li et al. [60]
Case-control	Primary CNS lymphoma	Fecal metagenomics and metabolomics	1. Alterations in gut microbiota composition and metabolic pathways were detected.	China	Kang et al. [61]
Cross-sectional	Glioma, meningioma, brain metastases,	Gut profiles multi-omics analysis	1. Significant differences in gut microbiota abundance and metabolome between patients and healthy controls were detected. 2. Introduction of markers according to gut flora and metabolome that have discriminative value	China	Zhou et al. [62]
Cohort	Craniopharyngioma	Gut microbiota diversity	1. Alterations in gut microbiota composition and metabolic pathways were detected.	China	Liu et al. [63]
Case-control	Glioblastoma	Gut microbiota diversity	1. Significant dysbiosis in patients was reported using high throughput screenings.	China	Ishaq et al. [64]

The present article is a narrative review, and therefore there are caveats to be taken into account. Narrative reviews do not have the methodology seen commonly in systematic reviews. Narrative reviews have inherent weaknesses of non-standardized literature search, potential bias in the extracted articles' appraisal, and findings' interpretation; nevertheless, they provide readers with sources of quick up-to-date reference on specific areas of interest [65].

4. Conclusion

The amount and diversity of essential dietary nutrients that are synthesized by microbial enzymes is manifold. The role of microbiota in the metabolism of many ingredients that are otherwise not consumable by intestinal cells has been previously studied; however, the role of such microbial products that enter our systemic circulation could be a subject of future studies. Many of these products are neurotransmitters and signaling molecules that act as ligands on immune cell receptors, playing a pivotal role in their maturation and function. These findings highlight the significant role of healthy gut microbiota in regulating immunologic responses and inflammatory cascades within the CNS. This fact led researchers to be wary of possible interventions that can be made through gut microbiomes for brain cancer treatment; however, their effects should be further investigated. Effective interventions should not only emphasize applicable methods as adjunct treatments in the management of brain tumors but also investigate the long-term effects of microbiome modulation on brain tumor outcomes.

Ethical Considerations

Compliance with ethical guidelines

This article is a narrative review with no human or animal sample.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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