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Review of Berberine on Neuroinflammatory Disorder by Modulation of Gut-Brain Axis

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ABSTRACT:

Neurodegenerative diseases occur when nerve cells in the brain or peripheral nervous system loose it function over time and ultimately die. The factors aggravating Neurodegenerative Disease (NDDS) are age, decreased neurotransmitters levels, chronic inflammation, oxidative stress and apoptosis in neuronal cells. Gut-brain axis is one of the contributing factor of NDD, gut-brain axis support neuronal development and maintenance while gut dysbiosis manifests in neurological disease such as Alzheimer(AD) and Parkinson diseases(PD). Through the enteric nervous system, gut microbiota and the brain communicate bidirectionally through neural and humoral (systemic circulation) pathways to regulate gut physiology. Hence this study concluded that there is a correlation in alteration of gut microbiota which influence gut-brain axis leads to the development of neurodegenerative disorder. Berberine(BBR), as a natural alkaloid compound, is characterized by a diversity of pharmacological effects. In recent years, many researches focused on the role of berberine in central nervous system diseases. .Recent evidence suggests that berberine inhibits the production of neuroinflammation and oxidative stress. This review provides an overview of berberine in neurodegenerative diseases and its related mechanisms, and also provides new ideas for future research on berberine.

Keywords: Gut microbiota; Gut-brain axis; Neurodegenerative disease; Berberine

1 INTRODUCTION:

Neurodegenerative illnesses pose a serious risk to people's health. One factor contributing to the rise in these age-dependent illnesses is the recent increase in the number of elderly people(1).Amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, frontotemporal dementia, and spinocerebellar ataxias are a few examples of neurodegenerative disorders. The etiology of these disorders varies; some impair memory and cognition, while others disrupt breathing, movement, and speech (2, 3). We urgently need effective treatments, but they will only be possible after we have a thorough grasp of the mechanics and causes of each disease.

Although there are many different causes of neurodegenerative diseases, studies have identified a number of common pathways through which neurodegeneration occurs, such as the accumulation of insoluble protein aggregates, apoptosis, necrosis, excitotoxicity, and neuroinflammation. Other pathological mechanisms that contribute to neurodegeneration include mitochondrial dysfunction, downstream oxidative stress, and impaired autophagy/lysosomal activity. Additionally, impaired brain plasticity is a crucial pathological mechanism that underlies the progressive cognitive and motor deficits seen in neurodegenerative diseases(4).

The term "intestinal microbiome" describes the symbiotic microorganisms that reside in the human gut, including bacteria, viruses, fungus, and archaea. They have developed a complex and advantageous interaction with their hosts over thousands of years(5). The enteric nervous system (ENS) and central nervous system (CNS) are connected in both directions by the gut-brain axis (GBA). It involves both direct and indirect connections between peripheral intestine function and the brain's emotional and cognitive regions. One pathogenic feature of neurodegenerative disorders like Parkinson's disease (PD) and Alzheimer's disease (AD) is the progressive loss of populations of neurons that are specifically vulnerable.

Numerous studies have suggested that inflammation may have a role in the development of neurodegenerative illnesses, even though the exact cause of these conditions is still unknown(6). According to studies, intestinal microbes in AD patients have smaller colonies and are less dense. Additionally, pro-inflammatory bacteria are more abundant and anti-inflammatory bacteria (such as Bacillus fragilis, Eubacterium rectale, Eubacterium hallii, Faecalibacterium prausnitzii, and Bacteroides fragilis) are less prevalent in amyloid-positive patients than in healthy individuals(7). Specifically, the rise in gram-negative bacteria in AD patients may cause more lipopolysaccharide (LPS) to migrate from the gut into the bloodstream, which in turn causes neuroinflammation that either exacerbates or promotes AD pathogenesis(8).

According to clinical research, fecal samples from PD patients exhibit significantly higher levels of potential pathogens such Escherichia coli, Streptococcus, Proteus, and Enterococcus and significantly lower levels of cellulose-degrading bacteria than healthy controls(9). Notably, streptococci can permanently injure nerves by producing neurotoxins such streptomycin and streptokinase(10).

Therefore, it might be possible to reduce inflammation and slow down the development of neuroinflammatory illnesses if we can stabilize the gut flora and increase the amount of anti-inflammatory bacteria in AD and PD patients. One possible focus for the treatment of these illnesses is intestinal flora.

A naturally occurring pentacyclic isoquinoline alkaloid is referred as Berberine. It is a major component of numerous medicinal plants. The stems and roots of Berberis species, such as *B. aristata* [11,12], *B. darwinii* [13,14], *B. petiolaris* [15], and *B. vulgaris* [16], are the essential examples of berberine sources. One of berberine's distinguishing characteristics is its unique yellowish color which lends the parent plant materials their yellow to gold aspect. Numerous studies have examined the pharmacology of berberine, which includes properties that are anti-inflammatory [17,18], anticancer [19–21], antidiabetic [22–24], anti-obesity and anti-hyperlipidemic [23,25], cardioprotective [26,27], and boost spatial memory [28–30]. The wide range of pharmacological actions associated with berberine points to some particular impacts on biological targets, enzymes, and receptors in addition to additional broad effects like anti-inflammatory and antioxidant properties.

2.The Microbiota-Gut-Brain axis (MGB) and Neurodegenerative Disorders

2.1The signaling pathways of MGB axis: Neural and Humoral Routes

The neurological system and gut microorganisms most likely communicate primarily through the enteric nervous system (ENS). Because the ENS has neuronal complexity comparable to that of the brain and can operate as separate, autonomous units to control immune system and gut-related functions, it has been referred to as "the second brain"(31). Enteric neurons' excitability would probably be reduced in the absence of gut bacteria. The ENS facilitates bidirectional communication between the gut microbiota and the brain via humoral (systemic circulation) and neuronal pathways (32). Information is sent from the gut to the brain via the parasympathetic vagus afferent nerve(31). Almost all enteric neurons are innervated by motor neurons that make up the vagus nerve (33). This gives the brain some control over ENS function, particularly when it involves intestinal permeability and inflammation. Though not as well as vagal nerves, enteric neurons are also connected to the brain by sympathetic spinal nerves(31). Furthermore, microbial metabolites can reach systemic circulation and affect other parts of the body, including the brain, through the humoral route. Similarly, to control gut function, the brain also uses the humoral pathway to deliver chemical messengers such cytokines and glucocorticoids(32).

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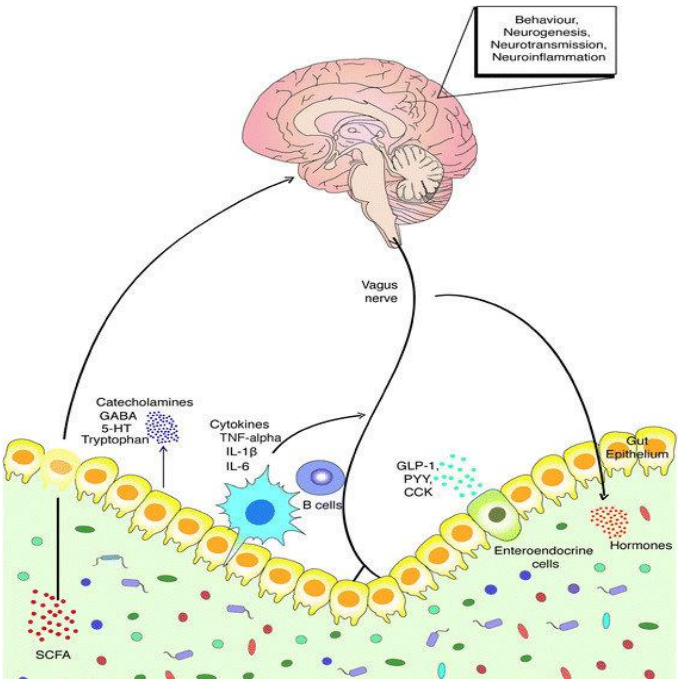

Figure 1: The signaling pathways of the microbiota–gut–brain axis Alzheimer disease- Key communication pathways of the microbiota–gut–brain axis. There are... | Download Scientific Diagram

2.2. MGB axis in neurodegenerative disorders

Neurodegenerative diseases like Parkinson's disease and AD, as well as psychiatric conditions like anxiety and depression, have been linked to MGB axis dysfunction(34).Healthy gut physiology depends on a stable intestinal microbiota, which also helps with proper signaling along the MGB, supporting both central nervous system (CNS) and physiological health. Misfolded amyloid species can accumulate as a result of intestinal dysbiosis' detrimental effects on gut physiology and aberrant MGB signalling(35). In the end, this may change the structure and functions of the CNS. Clinical and cognitive impairment are observed in patients with chronic CNS and gut condition, together with cortical shrinkage accompanied by subarachnoid space expansion, lateral ventricle enlargement, hippocampal atrophy, and Brain stem (BS) volume reduction(36).

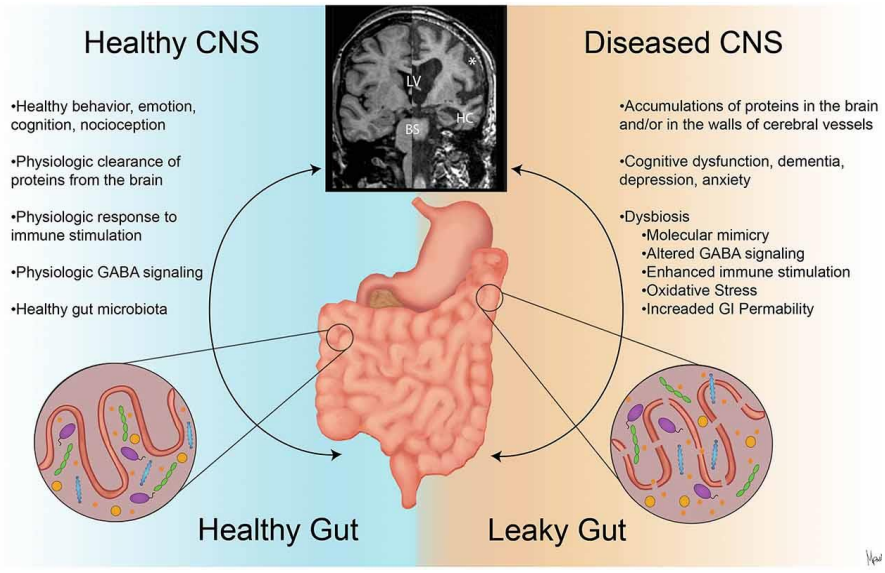

Figure 2: The contrasts of clinical presentations on the GBA in health and neurodegenerative diseases.(72)

2.3 Signaling Mechanisms of the MGB Axis: Immune and Berberine(BBR)

2.3.1. Immune system and MGB axis

The immune system is composed of about 70% of the gastrointestinal tract (Vighi et al., 2008). When immune cells cross the intestinal mucosal barrier, they release tool-like receptors (TLRs) that react to invading antigens like LPS. The production of inflammatory cytokines, primarily ILs, tumor necrosis factor TNF-α, and IFN- ɣ (37), is immediately triggered by inflammation. Numerous mechanisms allow these cytokines to enter the brain. Through the humoral pathway, cytokines can attach to carrier proteins that move through the blood-brain barrier or enter permeable regions of the BBB or circumventricular organs.The neurological pathway enables gut cytokines to activate particular brain regions through vagus and spinal afferents, including the brainstem, hypothalamus, and limbic systems. Through monocytes or macrophages, the cellular route enables cytokines to enter the brain. The brain may produce more cytokines as a result of these cytokines binding to receptors on microglia and astrocytes (38).

3.Pharmacological mechanism of neuroprotective effect of BBR

3.1Anti oxidative stress:

The excessive reactive oxygen species (ROS) can produce oxidative stress, resulting in an imbalance between oxidants and antioxidants. This imbalance can contribute to neurological disorders (39). Overexposure to reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) under oxidative stress can cause lipid peroxidation, protein oxidation, protein nitration, and sugar co-oxidation. The mechanism of BBR involves, reduction of lipid peroxidation and enhances glutathione and superoxide dismutase activity in cells (40). BBR can reduce ROS production in both cytoplasmic and mitochondrial cells (41). The decrease can be attributed to the activation of AMPK and SIRT1/FOXO1 pathways (42). BBR's antioxidative stress function has been associated to the PPAR transcription factor, which is activated by ligands. PPARs can act as antioxidants, and BBR can activate PPARδ to reduce ROS and provide neuroprotection (43). BBR may have antioxidant benefits via reducing iNOS, COX-2, and increasing HO-1.

3.2 Anti-neuroinflammation:

Neuroinflammation affects nerve tissue and can be caused by trauma or autoimmune conditions. Neuroinflammation arises from the ongoing activation of microglia and astrocytes, which can occur at several trigger sites (44). BBR may prevent neuroinflammation and serve as a potential treatment for central nervous system diseases induced by inflammation. According to (45)BBR may have neuroprotective effects by reducing neurotoxic compounds produced by activated microglia. Additionally, BBR has been shown to suppress NF-κB activation and phosphorylation of Akt, p38, and ERK. According to(46), BBR may reduce the PI3K/Akt and mitogen-activated protein kinase (MAPK) pathways, potentially inhibiting microglia's inflammatory response. BBR reduces inflammation by activating AMPK in BV-2 microglia. BBR significantly lowers the expression of iNOS and COX-2 in BV-2 microglia stimulated by LPS or IFN-γ. It also inhibits the formation of nitric oxide. Furthermore, BBR can regulate inflammatory factors. It reduces the production of pro-inflammatory cytokines TNF-α and IL-1β, as well as the expression of IL-6 in BV2 cells triggered by LPS (47,48). BBR reduces inflammation and GFAP synthesis, suppresses Sphk1/S1P signaling, and increases CREB signaling (49).

4. Alzheimer's Disease and MGB axis

A progressive neurodegenerative disease such as Alzheimer's disease is characterized by hyperphosphorylated tau protein in the brain's cerebral cortex, locus coeruleus, and hippocampus, as well as senile plaques made of misfolded β-amyloid (Aβ) fibrils and oligomers(50).

Microbial dysbiosis is a theory that suggests the MGB axis has a role in the pathogenesis of neurodegenerative illnesses. It can be brought on by exposure to antibiotics, dietary modifications, probiotics, or a number of other medical situations. In particular, after high-fat diet feeding, a number of studies have demonstrated a connection between gut microbiome dysbiosis and the aggregation of Aβ peptides in intestinal epithelial cells and the central nervous system. Bacteria and other microbiota members can release an immunogenic mixture of amyloid species, exudates, and functional lipopolysaccharides (LPS) from their outer membranes into the rapid intestinal environment (51). Although LPS and amyloid species are often soluble, they have the ability to polymerize and create insoluble fibrous protein aggregates, which can trigger oxidative stress and spread further protein aggregation (52). Escherichia coli endotoxin, for instance, has been demonstrated to promote the development of Aβ fibrils. Additionally, it has been demonstrated that co-incubating Aβ peptide with LPS enhances amyloid fibrillogenesis(53).

The "Prion Concept" is another theory about the pathophysiology of misfolded protein aggregation. According to this theory, the development of prionopathies in the CNS(54) is comparable to the accumulation of fibrillary, misfolded proteins in numerous

neurodegenerative illnesses. The MGB axis and the local immune system are also involved in prionsopathy, as prions build up in dendritic cells in Peyer's patches and other lymphoid follicles after penetrating the intestinal epithelial layer . The misfolded protein may travel to the ENS and then propagate to the CNS compartment(55) through interactions with dendritic cells. Certain bacteria, including E. coli, Bacillus subtilis, Salmonella enterica, Salmonella typhimurium, and Staphylococcus aureus, have been shown to produce significant quantities of functional amyloid protein, which may contribute to the pathophysiology of AD by accumulating misfolded Aβ oligomers and fibrils(51). It is known that certain gram-positive bacterial species, including Lactobacillus and Bifidobacterium, can metabolize glutamate, a well-known primary excitatory neurotransmitter, to generate GABA, a well-known primary inhibitory neurotransmitter(56). These findings indicate that modifications to the gut flora could affect the body's natural production of GABA(57).

In turn, cognitive decline, AD, anxiety and depression have all been associated with changes in GABA transmission in the brain(56). On the other hand, gut bacteria can influence peripheral nerve activities by producing neuromodulatory metabolites such as short-chain fatty acids (SCFAs). In the colon, bacteria degrade dietary fiber to create SCFAs, such as acetic, butyric, and propionic acids(58). SCFAs have the ability to increase serotonin release from the sympathetic nervous system, which in turn affects CNS cognitive functions like memory and learning(59). Since progressive glucose dysmetabolism has been documented in AD patients, the breakdown of SCFAs to ketone bodies may also offer the brain an alternate source of ATP. Crucially, it has also been demonstrated that reduced SCFA levels impair immunological responses, epithelial cell proliferation, and potentially the operation of the central and peripheral nervous systems(58).

5. Berberine and MGB axis

The potential of berberine is to alter the composition of the gut microbiota is its most significant function in relation to the current communication. Previous research has demonstrated that berberine can kill dangerous gut bacteria while increasing the number of good bacteria, such as Lactobacillus acidophilus and Bifidobacterium adolescentis. The increasing predominance of pathogenic bacteria like E. Coli and enterococci, as well as the pathology-induced decrease in Lactobacilli and Bifidobacteria, can be reversed by BBR associated with gut inflammation. It has also been demonstrated that the mild diarrhoea that berberine causes clinically is associated with dysbiosis of the gut microbiota, as evidenced by elevated abundances of the groups Porphyromonadaceae(Gram –ve bacteria) and Prevotellaceae(Gram –ve bacteria) as well as the genera Parabacteroides, Prevotellaceae_UCG-001, and Prevotellaceae_NK3B31_group [60].

TABLE 1: Inhibition of gut inflammation by berberine via modulation of the gut microbiota.

Bioassay model	Dosage	Key finding	References
Diarrhoea from irritable bowel syndrome(IBS-D) patients transplanted to GF Sprague Dawley (SD) rats	200 mg/kg, p.o. for 2 weeks	Modify the amount of Faecalibacterium, fecal formate, acetate, and propionate by adjusting the composition of the gut microbiome; lower the ratio of Firmicutes to Bacteroides at the phylum level; lower the ratio of Faecalibacterium to Bacteroides at the genus level	61
db/db mice	136.5 mg/kg or metformin at 113.75 mg/kg i.g for 11 weeks	Lower blood LPS levels; raise the amount of SCFA in feces; adjust the ratio of Firmicutes to Bacteriodites; raise the percentages of Lactobacillus and Butyricimonas; and lower the percentages of Proteus and Prevotella.	62
DSS-induced colitis in mice	40 mg/kg BBR for 10 days	In the disease model, the relative abundance of Eubacterium increased while Desulfovibrio decreased; Bacteroides abundance was even higher than in healthy animals; and the impact on Treg/Th17 balance was lessened following the depletion of gut microbiota (by ciprofloxacin and metronidazole treatment).	63

6.Challenges and Perspectives for BBR as treatment for ND

Over the past decade, numerous studies have demonstrated the effectiveness of BBR in treating brain disorders. The gut microbiota plays a crucial role in human health and is regarded as a hidden organ. Gut microbiota dysbiosis has been linked to brain problems and may potentially contribute to illness development(64,65).Our previous research found that BBR can stimulate neurogenesis in vitro [66]. PPAR, a ligand-inducible transcription factor, regulates brain processes such as cell differentiation, proliferation, and development [67]. It is possible that PPAR is a key gene in BBR treatment for neurological illnesses. BBR's limited bioavailability raises concerns about its capacity to exert its pharmacological effects on the brain.

There are two elements to consider when treating Parkinson's disease with BBR. BBR reduces neuron loss and promotes neurogenesis in Parkinson's disease models. Second, Wang et al. found that BBR improved Parkinson's disease symptoms by increasing the manufacture of L-dopa in the gut microbiota, similar to a vitamin [68]. This suggests an indirect impact of BBR. This type of dual action is also seen in hyperlipidemia. BBR has been shown to reduce hyperlipidemia both directly and indirectly through the gut microbiota's butyrate levels [69]. The gut microbiome has been linked to BBR's effectiveness in treating Parkinson's disease and anxiety (68,70).

It has been suggest that BBR affects gut microbiome structure and increases active microbial metabolites such as L-dopa and equol. BBR has been shown to regulate SCFA levels and reduce intestinal permeability in metabolic syndrome [71]. However, it is unclear if these effects contribute to the effectiveness of BBR in treating neurological illnesses. Further research is needed to examine how BBR affects gut microbiota and metabolites in neurological disorders.

7.Conclusion:

Neurodegenerative diseases (NDs), including Parkinson's disease (PD) and Alzheimer's disease (AD), are linked to gut-brain axis dysfunction, neuroinflammation, and oxidative stress. The pathophysiology and development of many illnesses are significantly influenced by the gut microbiome. New research shows that altering gut bacteria may help rebalance the gut-brain axis and open up new treatment options for NDs.

The natural alkaloid berberine (BBR), which possesses a variety of pharmacological characteristics, has demonstrated potential in the treatment of neurodegenerative illnesses. It restores the balance of the gut microbiota, inhibits neuroinflammation, and lowers oxidative stress to have neuroprotective effects. In preclinical models, BBR improves cognitive and motor functions, controls immunological responses, and increases the production of short-chain fatty acids (SCFAs) by encouraging the growth of good gut bacteria and decreasing populations of dangerous bacteria.

Even with these encouraging findings, BBR's low bioavailability is still a major problem. In order to improve brain-targeted delivery and better understand its mechanisms in human studies, future research should concentrate on refining BBR formulations. To verify its therapeutic potential, establish the best dosages, and evaluate its long-term safety, clinical trials are crucial. In the fight to treat and prevent neurodegenerative illnesses, altering the gut-brain axis with natural substances like BBR shows promise.

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