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Review

The Effect of Curcumin on the Gut-Brain Axis: Therapeutic Implications

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The gut-brain axis describes the bidirectional communication between the gut, the enteric nervous system, and the central nervous system. The gut-brain axis has attracted increasing attention owing to its regulatory effect on dysbiosis and a wide range of related diseases. Several types of nutrients, such as curcumin, have been proposed as regulators of the dysbiotic state, and preclinical experiments have suggested that curcumin is not only beneficial but also safe. This review focuses on the interplay between curcumin and the gut microbiota. Moreover, it provides a comprehensive review of the crosstalk between the gut-brain axis and disease, whilst also discussing curcumin-mediated gut-brain axis-dependent and -independent signaling about modulation of gut microbiota dysbiosis. This will help to define the utility of curcumin as a novel therapeutic agent to regulate intestinal microflora dysbiosis.
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Key Words
Curcumin; Dysbiosis; Gut-Brain axis; Gut microbiota; Health

Introduction

The gut microbiota (GM) is a term for the collection of microbes (Bacteria, Eukarya, and Archaea) that are inhabitants of the human gastrointestinal tract and regulate the physiological functions of the host.[1,2] The communication of bacteria, both with one another as well as with the host gut epithelium, can regulate host immunity, nutrition, digestion, and overall health (Fig. 1). However, certain diseases can disrupt, and even cause the gut microbiota towards involvement in both the intestinal and extra-intestinal disease process.[1] In recent years, reports have indicated that GM is not only critical to brain behavior and cognitive function but also that the brain communicates with the gut to maintain gut homeostasis.[2,3] This bidirectional communication is known as the GM-brain axis.

Recent research has focused on the GM-brain axis crosstalk in the mechanisms of health maintenance and disease.[1-5] Both neuronal and non-neuronal (hormones and the circulation, for example) mechanisms are involved in the communication between the brain and gut to regulate health and modulate induced stress.[3,6] Imbalance of GM which known as gut dysbiosis lead to unhealthy outcome and can indirectly promote the incidence of diseases such as stroke, mental disorders, hypertension, metabolic disorders, atherosclerosis, aging, and vascular dysfunction.[2,3] Nutrients such

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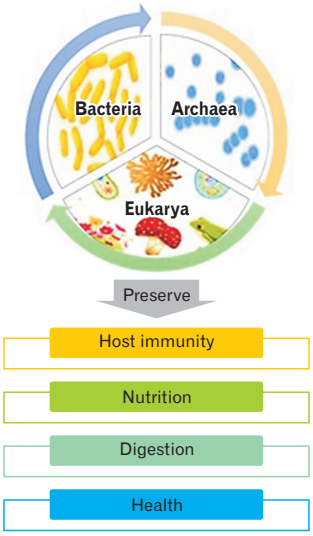

Figure 1. The beneficial effects of gut microbiota on the host system.

as curcumin have demonstrated the ability to reverse the dysbiotic state of the intestinal microflora back to a healthy state.[7]

Curcumin, $C_{21}H_{20}O_6$, is a crystalline yellow polyphenolic compound (MW: 368.39 g/mol) of the turmeric or *Curcuma longa* L. rhizome (Zingiberaceae); it accounts for 2-8% of turmeric substances and possesses anti-inflammatory, anti-atherosclerotic, neuroprotective and metabolic disorder-modulatory effects.[7-17] It can be modified chemically and conjugated with glucuronide and O-sulfate by the gut microbiota to exert its beneficial effects.[7,18] Indeed, the gut microbiota directly interacts with curcumin to produce small catabolites that can be absorbed through the intestinal wall, as confirmed by the high concentration of curcumin in the gut after oral administration.[18,19] In addition, curcumin influences the gut microbiota by promoting the growth of beneficial bacterial strains, improving microbial richness and diversity as well as enhancing intestinal barrier function. Therefore, there is a pivotal interplay between gut microbiota and curcumin to promote health.[18,19]

Curcumin also had beneficial effects on the gastric tissue of diabetic gastroparesis model rats, exhibiting anti-gastroparetic properties through improving ghrelin (a gut-brain peptide hormone) expression, thereby balancing energy and promoting gastrointestinal motility in the presence of oxidative stress.[20] Likewise, curcumin demonstrated a modulatory role on gastric emptying via enhancing stem cell factor/c-kit signaling (through reduction of oxidative stress) and the nuclear factor kappa B cascade in the stomach of a diabetic gastroparesis rat model.[21] In fact, curcumin may be one of the non-invasive alternatives to the invasive oral endoscopic gastric myotomy procedure, whose efficacy has not been confirmed in the treatment of gastroparesis.[22]

One-year administration of curcumin (3 g/day, orally) did not cause polyp regression in patients with familial adenomatous polyposis.[23] Other studies showed that curcumin (1%, 3%, and 5%) applied to peritoneal adhesions was not effective in treating postoperative intra-abdominal adhesions in rats, in spite of decreasing levels of tumor necrosis factor alpha (TNF-α), high sensitivity C-reactive protein, and isoprostane.[24] In this review, we discuss the crosstalk between the gut-brain axis and its dysfunction in disease as well as the impact of curcumin as adjunctive therapy to modulate GM dysbiosis and gut/brain communication, leading to the alleviation of disease.

Methods

A search strategy was done on preclinical (in vivo and in vitro) studies and clinical trials reporting the impact of curcumin on the gut-brain axis in disease modulation. Searches were conducted in PubMed, Scopus, and Google Scholar from January 2010 to December 2022. The terms "curcumin," "gut-brain axis," "gut microbiota-brain axis," and "disease" were carried out using a search strategy.

Interplay Between Curcumin and the Gut Microbiota

Two phenomena appear to play a crucial role in curcumin activity when interacting with gut microbiota: a direct influence of curcumin on gut microbiota and the effect of curcumin biotransformation by gut microbiota.[19] Thus, not only do the gut microbiota influence curcumin, but curcumin and its metabolites also impact the gut microbiota.[7,18,19] Curcumin accumulates in the gastrointestinal tract and exerts a regulatory effect primarily in the gut on the microbial richness, diversity, and composition of the intestinal microflora.[7,19] Oral administration of curcumin can alter the diversity and composition of beneficial/pathogenic microbes such as increasing the abundance of *Bifidobacterium* and *Lactobacilli*, as well as reducing the abundance of Coriobacterales, Prevotellaceae, Enterococci, Enterobacteria, and Rikenellaceae strains.[19,25]

Conversely, the specific pharmacological and pharmacokinetic properties of curcumin are influenced by its absorption rate and digestion via gut microbiota such as *Escherichia coli, Bifidobacteria pseudocatenulaum, Enterococcus faecalis, Bifidobacteria longum, Lactobacillus acidophilus*, and *Lactobacillus casei*.[7,18,19,25] Additionally, analyses of human feces indicated that *E. coli* impacted cur-

cumin activity through a reduction pathway (metabolic reduction) via nicotinamide adenine dinucleotide phosphate-dependent curcumin/dihydrocurcumin reductase (phase I metabolism). Almost 24% of curcumin is degraded to its metabolites by fecal microflora during 24 hours of fermentation.[7] In humans, 1-hour following high-dose oral administration, curcumin glucuronide conjugates, and curcumin sulfate conjugates (phase II metabolism) are found in blood, having been produced enzymatically by enterocytes and gut microbiota, leaving barely any intact curcumin remaining.[17,24] Thus, in the intestine, curcumin is transformed into various forms such as dihydrocurcumin and tetrahydrocurcumin, as well as undergoing hydroxylation, demethylation, demethoxylation, acetylation, or the combination of these processes via several steps involving microbial enzymes which are regulated by the gut microbiota.[18,19] Interestingly, gut bacteria can convert inactive glucuronide-conjugated and sulfate O-conjugated curcumin to active metabolites to enhance its beneficial biological effects.[18]

Gut-Brain Axis: Mechanism of Action and Therapeutic Targets in Disease

Anatomically, there are strong bidirectional connections between the gut and the central nervous system (CNS), termed the gut-brain axis, that can support health or promote disease in the host.[1] Communication between the gut microbiota and brain influences immunity, metabolism, and maintenance of the healthy state via impacts on neurons, hormones, blood, lymphatic vessels, immune cells, and microbial compounds.[3,26] This axis can promote disease via several pathways associated with inflammation, oxidative stress, circulation, and the nervous system.[6] The gut-brain axis has been linked to the pathogenesis of neurodegenerative disorders including Alzheimer's disease, autism, depression, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease.[1] Similarly, gut-brain axis dysbiosis leads to dysregulated and harmful effects on immune cells and cellular metabolism that can induce brain cancer through the neural, endocrine, lymphatic network, and immune pathways.[27,28] Moreover, the gut-brain axis can regulate cancer treatment-related psychoneurological symptoms such as pain, depression, anxiety, sleep disturbance, memory problems, cognitive dysfunction, and fatigue via, for example, cytokine Toll-like receptor 4 (TLR4) cascades, interleukin-2 (IL-2), interferon alpha, and TNF-α.[28,29] Dysbiosis of the gut microbiota has been linked to colorectal cancer (*Bacteroides fragilis, Streptococcus bovis, Helicobacter pylori, E. faecalis, E. coli, Clostridium septicum*, and *Fusobacterium* spp.).[30] Also, inflammatory bowel disease (IBD)[5] and irritable bowel syndrome (IBS) increase facultative anaerobes and decrease obligate anaerobes bacteria[5] by stimulating certain areas of the CNS, the autonomic nervous system, neuropeptides, neurotransmitters, hormones, enterochromaffin cells, interstitial cells of Cajal, smooth muscle cells, epithelial cells, and enteric neurons.[30] Moreover, a multi-omic analysis study indicated that microbiota dysbiosis is a key characteristic of eosinophilic esophagitis pathogenesis. The results of this study showed that abundant *Proteus vulgaris, Sulfodiicoccus acidophilus, Streptococcus mitis*, and *Hemophilus parainfuenzae* were increased in the blood in eosinophilic esophagitis, while the *Nitrosopumilus* sp. K4 was decreased; *Staphylococcus aureus, Malassezia restricta*, and *Plasmodium knowlesi* were unchanged.[31]

Additionally, the gut microbiota-brain axis may lead to heart disease and vascular dementia. The GM does affect the heart and the brain via gut-brain axis as a shunt in the complex disease such as coronary heart disease and Alzheimer's disease, where vascular links them.[32] Moreover, the gut-brain axis may exert influence by promoting the production of trimethylamine-*N*-oxide and diffusible bioactive gases such as hydrogen (H_2), hydrogen sulfide (H_2S), and oxygen (O_2) that have crosstalk with gut microbes.[32] A recent pilot clinical trial in women indicated that cardiac vagal activity correlated closely with gut microbiota and the gut-brain axis via the vagal nerve; additionally, vagal activity correlated inversely with inflammatory parameters.[33] *Clostridia, Lachnospira, Ruminococaceae, Faecalibacterium, Lactobacillales*, and *Streptococcaceae* were more abundant microbial species in subjects with higher cardiac vagal activity.[33] Therefore, the gut microbiota represents a promising candidate for controlling disease and a noninvasive predictor of prognosis.

Disease Modulation Activity of Curcumin on the Gut-Brain Axis (Preclinical and Clinical)

Central Nervous System

Curcumin has beneficial effects on the nervous system and exhibits neuroprotective properties through regulation of the gut-brain axis, via activation of the vagal nerve with the release of acetylcholine (ACh) in the presence of inflammatory or oxidative stress.[34-36] Likewise, curcumin directly/indirectly demonstrated a neuroprotective role via increasing antioxidant capacity through elevations in superoxide dismutase and catalase activity as well as anti-inflammatory effects via inducing nitric oxide and regulating reactive oxygen species in neurons (Fig. 2).[18]

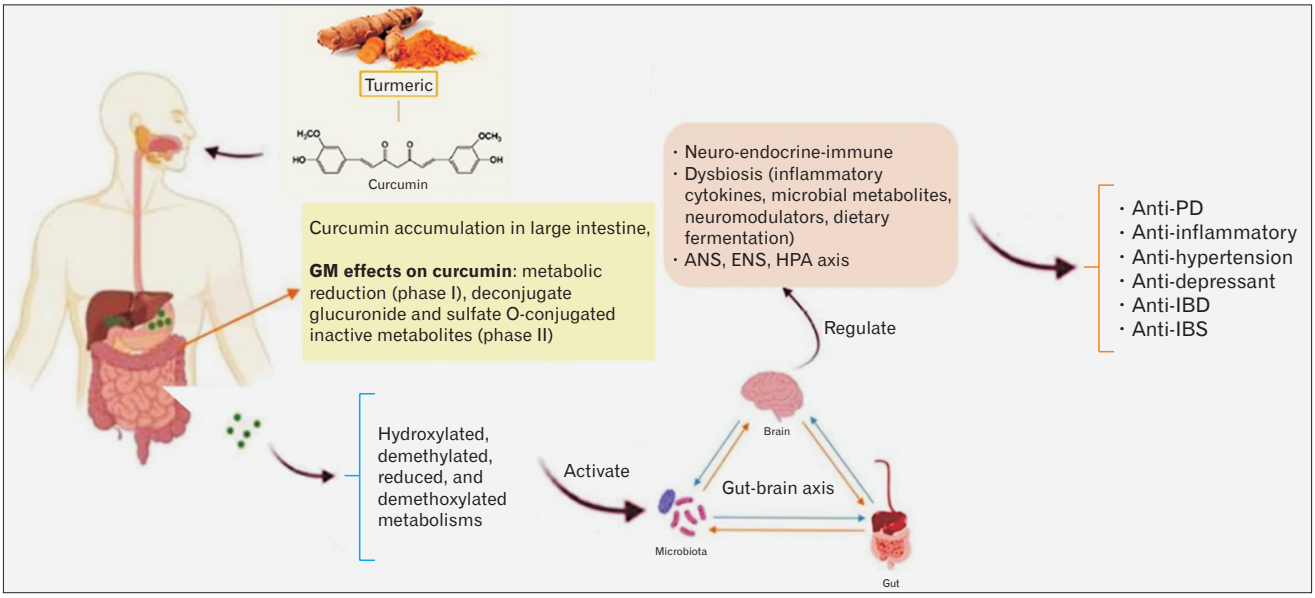

Figure 2. Impact of curcumin on gut-brain axis for disease management. GM, gut microbiota; ANS, autonomic nervous system; ENS, enteric nervous system; HPA axis, hypothalamic-pituitary-adrenal axis; PD, Parkinson's disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

Curcumin positively affects multiple pathways in Parkinson's disease (PD) treatment such as the inhibition of α-synuclein aggregation,[37,38] an increase in tyrosine hydroxylase, and reduction of N-acetylneuraminate degradation,[34] along with its influence on gut microbiota. Some in vivo studies have indicated that the protective effect of curcumin on neurodegenerative diseases and PD occurs through the regulation of the gut microbiota by curcumin (Table). In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, curcumin at all applied doses (40, 80, 160 mg/kg/day) improved dyskinesia and motor dysfunction, such as pole climbing time, suspension score and total distance moved, in PD mice.[34] The neuroprotective effects of curcumin, especially at higher doses, were effected through an increase in tyrosine hydroxylase-positive and dopamine-positive neurons, which could indicate the functional status of dopamine neurons, cell wrinkling, vacuolar degeneration, and cell survival.[34] Furthermore, curcumin also modulates the dysregulation of gut microbiota composition and prevents PD dose-dependently by reducing the relative abundance of Patescibacteria, Enterobacteriaceae, and Enterococcaceae and increasing the relative abundance of Eubacteriaceae, Rikenellaceae, Prevotellaceae, Anaeroplasmataceae, Eggerthellaceae, Ruminococcaceae, and Burkholderiaceae.[34] Notably, at higher doses, curcumin decreased N-acetylneuraminate degradation, diminished α-synuclein accumulation, and exerted antioxidant activity, thereby protecting against PD and neurotoxicity.[34] Recent research showed that curcumin (100 mg/kg/day) modulated the gut microbiota metabolite axis and suppressed the progression of PD, as indicated by improvements in motor deficits, glial cell activation, and α-synuclein aggregation in the MPTP mouse model.[38] Analysis showed that curcumin reduced the abundance of *Aerococcaceae* and Staphylococcaceae whilst enhancing Muribaculaceae, Lactobacillaceae, Lachnospiraceae, and Eggerthellaceae. In parallel with the gut microbiota alterations, a significant relationship was found between curcumin metabolites and the neuroprotective effects of curcumin in PD, where curcumin increased the levels of tyrosine, dopa, methionine, sarcosine, and creatine. Tyrosine is strongly related to motor function and Lactobacillaceae, Aerococcaceae, and Staphylococcaceae genera in the gut flora whilst, by contrast, sarcosine and creatine are negatively associated with Staphylococcaceae. Taken together, curcumin promoted tyrosine-dopa metabolism to elevate dopamine, thereby regulating the gut microbiota and activating the gut-brain-metabolic axis for PD prevention.[38] Interestingly, curcumin exerts anti-neuroinflammatory effects in PD by diminishing TNF-α, IL-1β, IL-6, IL-4, glial fibrillary acidic protein, as a marker of astrocytes, and ionized calcium-binding adaptor molecule 1, as a marker of microglia. Finally, curcumin inhibited α-synuclein aggregation, a PD-specific pathological hallmark in MPTP-induced PD mice.[38]

Cardiovascular

In addition, curcumin at 100 mg/kg can ameliorate hyperten-

Table. Modulatory Effects of Curcumin on the Gut-Brain Axis in Disease

Category of disease	Experimental model	Dose of curcumin	Main objective	Dose-dependent promoted bacteria	Mechanism	Ref.
Parkinson's disease	MPTP mice	40, 80, 160 mg/kg, IP, 14 day	Improved motor dysfunction, anti-Parkinson's disease, reduced neurotoxicity, protected dopamine neurons, regulated composition of gut microbiota, reduced pole climbing time, increased suspension score, enhanced total distance, improved cell wrinkling, increased vacuolar degeneration, improved cell survival	*Cyanobacteria, Actinobacteria, Acidobacteria, Firmicutes, Tenericutes, Clostridiales-unclassified, Rikenellaceae, Prevotellaceae, Anaeroplasmataceae, Eggerthellaceae, Erysipelotrichaceae, Ruminococcaceae, Burkholderiaceae, Bacteroidaceae, Pseudomonadaceae, Solirubrobacteraceae*	(+) TH (−) N-acetylneuraminate degradation, an abundance of *Patescibacteria, Enterobacteriaceae, Enterococcaceae*	34
Inflammation	Collagen-induced arthritis in rat	100 mg/kg/day, orally, 2 wk	Balanced sympathetic and parasympathetic tones, increased vagus neuronal excitability, anti-arthritic, increased cholinergic function, increased body weight, decreased arthritis index scores, reduced hind paws swelling, anti-inflammatory, decreased (inflammatory cell infiltration, synovial hyperplasia, congestion, pannus formation, cartilage, and bone erosion)	-	(+) ChAT, VAChT, SDNN, RMSSD, HF, IL-10, TGF-β, rheobase, spike frequency (−) LF/HF, TNF-α, IL-1β, IL-17A, IL-6, first spike latency, membrane potential	35
Hypertension	Spontaneously hypertensive rat	100, 300 mg/kg, once every 2 day, intragastric, 12 wk	Decreased blood pressure, ameliorated cardiac hypertrophy, reduced neuroinflammation, inhibited oxidatively stress, reshaped gut microbiota composition, attenuated sympathetic activity, anti-inflammatory, enhanced gut-brain communication	*Lachnospiraceae_NK4A136_group, Ruminococcaceae_UCG_005, Ruminococcaceae_UCG_014, Ruminococcus_1, and Roseburia*	(+) butyrate, GPR 43, Chao1 richness, shannon diversity, lachnospiraveae_NK4A136_ group, roseburia, goblet cells, villi lengths, Tjp1, Ocln, Cldn4 (−) SBP, MAP, HW/BW, LVW/BW, Firmicutes/Bacteroidetes, TH, norepinephrine, fibrotic area, tunica muscularis, TNF-α, IL-1β, IL-6, TLR4, TLR2, microglia (number and activated), $gp91^{phox}$, $p22^{phox}$	36

Table. Continued

Category of disease	Experimental model	Dose of curcumin	Main objective	Dose-dependent promoted bacteria	Mechanism	Ref.
Parkinson's disease	MPTP-induced mouse model of Parkinson's disease	25, 100, 400 mg/kg/day, intragastric, 4 wk	Improved motor deficits, glial cell activation, and the aggregation of α-synuclein, neuroprotection, modulated gut microbiota-metabolite axis, ameliorated motor impairments and dopaminergic neuronal loss, suppressed neuroinflammation	*Lachnospiraceae, Lactobacillaceae*	(+) Tyrosine, levodopa, methionine, sarcosine, creatine, IL-10 (−) α-synuclein, TNF-α, IL-1β, IL-6, IL-4, GFAP, Iba1, *Aerococcaceae, Staphylococcaceae*	38
Inflammatory bowel disease	DSS-induced anxiety-like behaviors in mice	100 mg/kg/day, drinking water, 8 day	Increased weight, improved colon length, suppressed anxiety-like behaviors, reprogramed gut microbiota, changed fecal metabolites, changed prefrontal cortex metabolomics, improved motion tracks, *Muribaculaceae* a key component of gut microbiota-brain axis	*Firmicutes, Actinobacteria, Cyanobacteriam, Muribaculaceae_unclassified, Bilophila, Bacteroides*	(+) Total distance, center distance, center time, open arm entry, time in the open arm, alpha diversity indexes, *Bacteroidetes, Deinococcus-Thermus, Muribaculaceae_unclassified, Phylum Firmicutes, genera Kineothrix, genera Odoribacter* (−) *Ruminococcaceae_unclassified, Bacteroides*	39
Irritable bowel syndrome	Irritable bowel syndrome rats	10, 20, 40 mg/kg/day, p.o, 21 day	Decreased immobility time and number of buried marbles, reduced fecal output, diminished AWR response, ameliorated the depressive- and anxiety-like behaviors, anti-irritable bowel syndrome	-	(+) Hippocampus: 5-HT, BDNF, p-CREB/CREB (−) Hippocampus: 5-HIAA/5-HT Colon: 5-HT, BDNF, p- CREB/CREB	40
Depression (*Lacticaseibacillus rhamnosus* GG, glutamine, curcumin)	Chronic unpredictable mild stress-induced depression in mouse	1.2 mg, oral, 21 day	Suppressed anxiety and depression, decreased time spent with open arms, increased immobility, increased time in the central area, decreased time spent climbing	-	(+) - (−) -	49
Gastrointestinal	Adults with self-reported digestive complaints (Clinical trial: ACTRN12619001236189)	500 mg/day (curcumin extract), 8 wk	Reduced GSRS total score, decreased DASS-21 anxiety score, intestinal microbial profile, and SIBO test had no significant effect		(+) - (−) -	41

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; IP, intraperitoneal; DSS, dextran sulfate sodium salt; GSRS, Gastrointestinal Symptom Rating Scale; DASS-21, Depression Anxiety Stress Scale 21; SIBO, small intestinal bacteria overgrowth; TH, tyrosine hydroxylase-positive and dopamine; ChAT, choline acetyltransferase; VAChT, vesicular acetylcholine transporter; SDNN, standard deviation of all R-R intervals; RMSSD, root of the mean of the sum of the squares of differences between adjacent R-R intervals; HF, high-frequency power; LF, low-frequency power; GPR43, G protein-coupled receptor 43; Tjp1, tight junction protein 1; Ocln, occludin; Cldn4, claudin 4; SBP, systolic blood pressure; MAP, mean arterial pressure; HW, heart weight; BW, body weight; LVW, left ventricle weight; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium-binding adaptor molecule 1; p.o., per os; 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor; p-CREB, phosphorylation of cAMP response element-binding protein; CREB, cAMP response element-binding protein; 5-HIAA, 5-hydroxyindoleacetic acid.

sion, a common pathology in cardiovascular disease, and improve dysregulation of the gut-brain axis via reshaping the composition of gut microbiota (Table).[36] Curcumin reduces sympathetic activity and the Firmicutes/Bacteroidetes ratio through the downregulation of norepinephrine and tyrosine hydroxylase as well as upregulation of Chao1 richness and Shannon diversity. However, curcumin enhanced the levels of butyrate-producing bacteria such as the Lachnospiraceae_NK4A136_group, Ruminococcaceae_UCG_005, Ruminococcaceae_UCG_014, Ruminococcus_1, and Roseburia.[36]

Furthermore, curcumin reduced the fibrotic area, collagen decomposition, and thickness of the tunica muscularis layer, along with promoting an increase in goblet cells and villi length. Quantitative reverse transcription polymerase chain reaction analysis showed that curcumin attenuated the expression of TNF-α, IL-1β (as pro-inflammatory cytokines), high-mobility group box 1 (as an inflammatory mediator) and Toll-like receptors (TLR2 and TLR4) in the small intestine. In addition, curcumin restored the mRNA levels of tight junction protein 1 and occludin in the intestine, which were reduced in spontaneously hypertensive rats.[36] Conversely, curcumin diminished neuroinflammation through inhibition of TNF-α and IL-1β as well as decreasing oxidative stress by reducing superoxide anion mRNA levels of $gp91^{phox}$ and $p22^{phox}$ in the hypothalamus paraventricular nucleus (PVN) of spontaneously hypertensive rats. Curcumin also activated G protein-coupled receptor 43 (GPR43), a major binding receptor of butyrate, indicating that its antihypertensive effect is exerted via the butyrate-GPR43 pathway in the PVN. Thus, curcumin's antihypertensive effects are associated with the gut-brain axis and work through amelioration of gut-brain dysregulation; this occurs, at least partially, by the alternation of gut microbial composition to maintain intestinal homeostasis leading to suppression of neuroinflammation and oxidative stress with activation of GPR43 in the PVN of spontaneously hypertensive rats.[36]

Inflammatory and Gastrointestinal Diseases

In inflammatory and GI disorders, such as arthritis, IBD, and IBS, curcumin can improve depressive- and anxiety-like behaviors and modulate the intestinal system through activation of the gut-brain axis (Table).[35,39,40] The balance of sympathetic and parasympathetic tones plays a pivotal role in the treatment of inflammatory diseases.[35,39,40] Curcumin may exert its anti-inflammatory effects through increasing vesicular ACh transporter and choline acetyltransferase in the gut, brain, and synovium to improve the inflammation and arthritis.[35] Using curcumin at 100 mg/kg/day for the treatment of collagen-induced arthritis in rats showed that curcumin prevented arthritis by balancing the sympathetic (reduction) and parasympathetic (increase) tones and increasing vagus nerve activity. However, curcumin only promoted ACh biosynthesis/transportation but did not affect ACh hydrolyzation or choline uptake in the gut or brain.[35] Curcumin's anti-arthritic effect is mediated by the α7 nicotinic ACh receptor and the cholinergic anti-inflammatory pathway causing a reduction in the levels of TNF-α, IL-1β, IL-6, and IL-17A as well as an increase in IL-10 and TGF-β markers. These findings indicate that curcumin's anti-arthritic effects are mediated via the gut-brain axis and this could be a promising therapeutic approach for arthritis.[35]

In the previous study, curcumin attenuated dextran sulfate sodium salt-induced anxiety-like behavior through the gut-brain axis via alleviating gut microbiota disturbances, especially regulation of Muribaculaceae, and increasing phosphatidylcholine, a biomarker of psychiatric disorders, in the prefrontal cortex. Additionally, curcumin ameliorated systemic disorders of lipid metabolism triggered by dextran sulfate sodium salt by diminishing glycerophospholipid metabolism of the gut-brain axis.[39] Moreover, in IBS rats, curcumin showed a significant reduction in behavior and function, abdominal withdrawal reflex score, and the frequency of fecal output in IBS rats. In the hippocampus, curcumin increased the levels of serotonin, brain-derived neurotrophic factor (BDNF), and phosphorylation of cAMP response element-binding protein (pCREB) dose-dependently; by contrast, curcumin decreased serotonin, BDNF and pCREB in the colon. Hence, curcumin exhibited an enhancement in the visceral nociceptive response, and antidepressant- and anti-anxiety-like effects by regulating serotonin and its downstream pathways in both the hippocampus and intestinal system.[40]

Clinical Trials

Furthermore, one clinical trial reported that curcumin extract (500 mg, Curcugen) improved digestive complaints and anxiety levels as assessed by a reduction in symptoms such as abdominal pain, reflux, diarrhea, indigestion, and constipation using the Gastrointestinal Symptom Rating Scale, and a reduction in the Depression Anxiety Stress Scale 21 (Table).[41] However, there were not any significant changes in selected gut microbiota diversity between curcumin and placebo groups including Bacteroidetes (phyla), Firmicutes (phyla), Clostridia (class), Enterobacteriaceae (family), *Bacteroides* (genus), *Clostridiales* (genus), *Faecalibacterium* (genus), and *Bifidobacterium* (genus) (significant bacteria associated with IBS). However, the Shannon and Simpson index showed a statistically significant difference between the groups at the genus level, with curcumin decreasing the Shannon diversity index.[41] It can be postulated that curcumin extract leads to attenuation of di-

gestive complaints and anxiety levels and is thus ultimately protective against symptoms through a difference in gut microbiota diversity at the genus level and/or may affect other intestinal bacteria.

Recently, functional gastrointestinal disorders have been better known as Disorders of Gut–Brain Interaction (DBGI); these disorders are a group of non-structural abnormalities and include IBS and chronic gastrointestinal diseases.[42-44] The pathophysiology of DBGI is associated with psychological stress, diet and microbiota alterations.[43] In fact, DGBI is indicative of the brain-gut connection and the complex interplay between central and peripheral nervous system and gastrointestinal alterations.[42] Likewise, this study showed that the level of histamine-producing bacteria (such as *Enterobacter aerogenes, Raoultella ornytolytica, Morganella morganii*, and Lactobacilli) was increased in the GM of patients with IBS/IBD and asthma.[43] In addition, one case control study showed that IBS is independently linked to small intestinal bacteria overgrowth (SIBO)[45] and another study showed that patients with IBS and concomitant SIBO has more severe symptoms and impaired quality of life.[46]

Moreover, a clinical study reported that combination therapy of curcumin (500 mg) and famotidine (40 mg) for 30 days significantly reduced the severity of functional dyspepsia and the frequency of *H. pylori* infection in patients with functional dyspepsia.[47] Another study indicated that supplements containing curcumin (17-23% w/w) and boswellia extracts (7-11% w/w) diminished bloating, abdominal pain and indican values and enhanced global assessment of efficacy after 30 days of intervention in patients with IBS or small bowel dysbiosis.[48]

However, microbial diversity may be affected by gastrointestinal or other disorders (such as IBS and IBD), and can cause dysbiosis in the gut, which could be utilized as a marker of disease or other disorders such as inflammation. Oral administration of curcumin can alter the diversity of beneficial or pathogenic bacteria according to the dose, duration of treatment or formulation. In addition, curcumin and its metabolites may have a direct impact on neurons, hormones, blood, lymphatic vessels, and immune cells; thus, it is likely that the direct and indirect effects of curcumin (gut-brain axis) act together synergistically to modulate disease and improve host health. Further research is needed using more accurate testing methods to determine curcumin's beneficial effects on the gut-brain axis and the synergism of its direct or indirect effects. In addition, whole-genome sequencing should be employed to provide a more detailed analysis of gut microbiota in the presence of curcumin, together with an evaluation of standard curcumin administration compared to experimental doses and formulations for each disease state.

Limitations

Some limitations of this review include the lack to date of available animal and clinical studies related to curcumin's effects on the gut-brain axis and the difficulty of generalizing animal studies to the clinic; secondly, there is insufficient evidence as investigation of gut microbiota profiles in the available studies has been inadequate. Finally, evaluation of the pharmacokinetic characteristics and bioavailability of curcumin about gut microbiota interaction (and vice versa) is lacking, so information to guide dosage and treatment regimen is required. Thus, further preclinical and clinical investigations to delineate the interplay of curcumin on the gut-brain axis are required to manage diseases with a known mechanism of action and to understand the impact on intestinal bacterial diversity and effective dosing.

Conclusions and Outlook

Based on the beneficial effects of curcumin on health- promotion, disease management, and its wide application as a spice in daily food, this review has sought to understand the interplay between curcumin and the gut-brain axis in multiple diseases, mainly based on available in vivo experimental models (Table).[49] The findings presented here indicate that curcumin has promising potential, with acceptable efficacy, as a regulator of the gut-brain axis in several diseases associated with GM dysbiosis. In addition, curcumin can not only act as a treatment but is also able to interact with intestinal microflora in dysbiosis to target microbiota activation or suppression, thereby enhancing its therapeutic effect through the production of more active metabolites and better pharmacokinetics.

It would be expected that, in the not-too-distant future, extensive research will utilize the gut microbiota as a biomarker for the diagnosis or treatment of many diseases, and that curcumin and other natural products will act as agents to treat dysbiosis-associated diseases. However, at present, there is a lack of clinical trials to assess curcumin's impact on the gut-brain axis and dysbiosis. Further in vitro and in vivo studies, followed by clinical trials with optimally selected patients, together with advanced analytical techniques to enable understanding of microflora composition modifications in response to curcumin treatment, are needed. Furthermore, more research on the metabolic pathways and enzymes involved in curcumin's mechanism of action is needed. Finally, the impact of curcumin on the gut-brain axis in managing disease may lead to new strategies to protect health through gut microbiota modulation and

may represent a novel therapeutic use for curcumin.

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