Review

Microbiota-gut-brain axis impairment in the pathogenesis of stroke: implication as a potent therapeutic target

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The human microbiota-gut-brain axis has an enormous role in the maintenance of homeostasis and health. Over the last two decades, it has received concerted research attention and focus due to a rapidly emerging volume of evidence that has established that impairment within the microbiota-gut-brain axis contributes to the development and progression of various diseases. Stroke is one of the entities identified to be associated with microbiota-gut-brain axis impairment. Currently, there are still limitations in the clinical treatment of stroke, and the presence of a non-nervous factor from gut microbiota that can alter the course of stroke presents a novel strategy towards the search for a therapeutic silver bullet against stroke. Hence, the aim herein, was to focus on the involvement of microbiota-gut-brain axis impairment in the pathogenesis stroke as well as elucidate its implications as a potent therapeutic target against stroke. The findings of studies to date have revealed and extended the role microbiota-gut-brain axis impairment in the pathogenesis of stroke, and studies have identified from both clinical and pre-clinical perspectives targets within the microbiota-gut-brain axis and successfully modulated the outcome of stroke. It was concluded that the microbiota-gut-brain axis stands as potent target to salvage the neurons in the ischemic penumbra for the treatment of stroke. Assessment of the microbiota profile and its metabolites status holds enormous clinical potentials as a non-invasive indicator for the early diagnosis and prognosis of stroke.

Key words: microbiota, gut-brain axis, stroke, therapy

INTRODUCTION

Stroke, also termed a cerebrovascular accident, is a non-communicable disease and constitutes the world's second most frequent cause of mortality after cardiovascular diseases [1]. It has been estimated to impact nearly 13.7 million people per year around the globe [2]. About one-third of this figure translates into mortalities, while another one-third represents stroke survivors with residual functional deficits, which constitute the leading cause of long-term neurological disability among adult populations [3] and the third most prominent cause of all disabilities globally [4].

The basic principle behind the manifestation of cerebral stroke is the loss of cerebral functions due to a cause of vascular origin or, more precisely, an aberration in blood supply. Stroke is broadly categorized based on the underlying cause into ischemic stroke, which accounts for 85% of all strokes, and hemorrhagic stroke, which accounts for 15% [5]. A therapeutic silver bullet against stroke is required and is still being researched for a several reasons: The two approved strategies, consisting of thrombolysis using recombinant tissue plasminogen activator (rTPA) and thrombectomy, available for the treatment of acute ischemic stroke are only accessible to about 5% of patients due to their highly restrictive time windows of application [6]. Also, it has been estimated that nearly 50% stroke survivors have residual disabilities despite all the medicinal and rehabilitative interventions [7]. Furthermore, the debilitating outcomes of stroke produce significant impacts on the quality of life of patients and their caregivers, and places an economic burden on healthcare budgets [8].

The most important region in the pathogenesis of acute ischemic stroke is the comparatively large component of surviving

neurons in the ischemic penumbra that surround the ischemic core. These neurons are potentially at risk of neuronal demise through evolving endogenous brain mechanisms such as neuro-inflammation, oxidative stress, and apoptosis [9]. Therefore, the ultimate goal of acute treatment of ischemic stroke is to rescue the neurons in the ischemic penumbra [10]. However, the roles of non-nervous system factors, such as the gut microbiota and its metabolites, are now increasingly identified in the pathogenesis of stroke as critical components to the viability of neurons in the ischemic penumbra [11]. Understanding this rapidly evolving concept of the microbiota-gut-brain axis, its impairment in the pathogenesis of stroke, and the several ways through which it could be modulated is critical to the search for more effective, novel strategies against stroke.

Microbiota is a general term defined as the collective community of microorganisms that inhabit the human/animal body. Thus, it encompasses microbes that colonize the skin and other mucosal cavities, such as the oral, nasal, reproductive, pulmonary, and gastrointestinal cavities. However, it is the gastrointestinal microbiota (gut microbiota) that has received concerted attention and focus within the last two decades. This is partly because there is an extraordinary density of trillions of microbiota in the gut, and partly because of the bidirectional communication of the gut microbiota with the brain via the microbiota-gut-brain axis, which has increasingly been identified as significantly influencing health and diseases [12, 13].

A plethora of lines of emerging experimental evidence from both pre-clinical [14–18], and clinical studies [19–28] have established the bilateral interaction between the brain lesion in stroke and the gut microbiota via the microbiota-gut-brain axis. This pathway axis modulates the occurrence and development of myriad diseases and therefore provides a direction for rapidly evolving research into therapeutics against diseases. For instance, microbiota-gut-brain axis impairment and dysregulation, referred to as dysbiosis, have been strongly implicated in the pathogenesis and progression of not only neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis but also neuropsychiatric disorders such as autism spectrum disorder, schizophrenia, and major depressive disorder [29].

Numerous reviews have been carried out that buttress the link between the microbiota-gut-brain axis and brain-associated disorders and diseases [30–37]. These studies have focused on general disorders of the brain and lacked a specific focus on stroke as an entity. On the other hand, the review studies that have focused exclusively on stroke and the microbiota [38–44] have all been insufficient with respect to the rapidly evolving explosion of evidence concerning interventions that exert effects on stroke by modulating the microbiota-gut-brain axis. Hence, it was desirable to elucidate the concept of the microbiota-gut-brain axis and bring it up to speed with respect to the various preclinical and clinical evidences for targeting stroke via the microbiota-gut-brain axis. The aim herein was to focus on the involvement of microbiota-gut-brain axis impairment in the pathogenesis stroke as well as elucidate its implications as a potent therapeutic target against stroke.

MICROBIOTA-GUT-BRAIN AXIS IMPAIRMENT IN THE PATHOGENESIS OF STROKE

The gut-brain axis represents a bidirectional (two-way regulation) communication system between the gastrointestinal tract and the nervous system that is crucial for maintaining homeostasis throughout the body, including the gastrointestinal tract and the brain [45–47]. This highly interconnected interaction is mediated through neural, endocrine, immunological, and metabolic mechanisms. This interaction system can best be comprehended when viewed from the perspective of a top-down signaling pathway, which indicates the regulation of gastrointestinal homeostasis and function by the nervous system, and a bottom-up signaling pathway, which directs the sway of the gastrointestinal system impact on the central nervous system [48].

From the top-down regulation mode of the gut-brain axis, it is known that the nervous system control of the gastrointestinal system encompasses three levels neural control, the autonomic nervous system (ANS), enteric nervous system (ENS), and central nervous system (CNS). ANS sympathetic control operates via the pre-vertebral sympathetic nerves (splanchnic and pelvic spinal nerves) and vagal parasympathetic nerve, both of which exert autonomous functions (such as motility, blood flow, and secretions of glands) on the gastrointestinal system by antagonistic, synergistic, or independent functions [49]. The ENS comprises submucosal and myenteric plexuses that act to self-sufficiently regulate autonomous functions at the level of the gastrointestinal tract, such as motility, blood flow, and exchange of fluids between the gut and its lumen. This self-sufficiently gives the ENS a unique feature of being the single compartment of the peripheral nervous system that possesses extensive neural plexuses and circuits that can independently regulate gastrointestinal functions [50].

The CNS components that affect the gastrointestinal tract include the hypothalamus, nucleus of the solitary tract in the medulla, medial prefrontal cortex, and amygdala, among others [51]. It is known that the descending tract for the ANS originates from the hypothalamus and that fibers that control the thoracolumbar outflow of the sympathetic nervous system extend from the anterior hypothalamic nuclei, while descending parasympathetic fibers that control the craniosacral outflow of the parasympathetic nervous system extend from the posterior hypothalamic nucleus. Thus, the CNS controls the activity of the ANS, and the activity of the ENS in turn is modulated by the ANS, creating a neuronal feedback pathway that is intricately fundamental to the bidirectional communication of the gut-brain axis. A typical illustration of the functionality of this neural connection that regulates the activity of the gastrointestinal system can be seen in cephalic reflex action, local myenteric reflex and vagovagal reflex [52]. One of the conspicuous endocrinal pathways in gut-brain axis communication is the hypothalamus-pituitary-adrenal (HPA) axis. In response to physical, physiological, or psychological stressors, the HPA axis becomes primed to release corticotropin-releasing factor (CRF) from the hypothalamus, this subsequently excites the release adrenocorticotropic hormone (ACTH) secretion from the pituitary gland, and then ACTH leads to the release of cortisol hormone from adrenal glands. Cortisol affects many changes in various organs, including the gastrointestinal tract and brain itself to propagate cellular responses to stress.

The bottom-up signaling of the gut-brain axis involves the intestinal cells and the microbes within the gut, which are referred to as microbiota. The gut microbiota and its metabolites constitute a major key drivers in the bottom-up signaling pathway that communicates with the brain, hence the term microbiota-gut-brain axis [29]. Intestinal cells such as enterochromaffin and enteroendocrine cells produce bioactive molecules such as serotonin (5-hydroxytryptamine, 5-HT), cholecystokinin (CCK), neuropeptides Y, ghrelin, and glucagon-like peptide-1 (GLP-1), and these substances act as hormones, neurotransmitters, neuromodulators, or neurotrophic factors. 5-HT is synthesized from the essential amino acid precursor tryptophan by enterochromaffin cells; 5-HT in turn mediates serotoninergic signaling in the brain, thereby maintaining brain functions, either by affecting exogenous primary afferent neuron cell bodies itself or through its precursor tryptophan, which can cross the blood-brain barrier (BBB) [53, 54]. 5-HT also mediates the vascular tone of the CNS by modulating the nitrergic neurons to the smooth muscle tissue of the vascular wall [55].

The gut microbiota is composed of an exceptional arrangement of symbiotic microbes within the gut consisting of bacteria, fungi, archaea, viruses, and protozoa, and together with the collective genomes of its constituent microbes, collectively referred to as the microbiome. It comprehensibly plays a monumental role in orchestrating homeostasis and health such that alterations in their balance referred to as dysbiosis, have been convincingly implicated in the pathogenesis of numerous diseases [56–58]. There are trillions of microbiota resident within the gut, representing about ten times the total number of human cells in the body, and the vast majority of the microbiota are bacteria dominated by three specific phyla, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, that cumulatively constitute over 90% of the gut microbiota [59, 60]. Although there is variation in gut microbiota among populations, the three phyla of bacteria remain the core dominant microbes among individuals. The established traditional roles of the microbiota include digestion of food fibers, priming of innate immunity to identify potentially harmful pathogens, and production of enzymes that facilitate biotransformation of ingested food [61, 62]. Nevertheless, the rapidly evolving explosion in the amount of evidence from microbiota-gut-brain axis studies has now extended such roles to other imperative functions, such as the regulation of brain development, behavior, and functions, as well as immune cell homeostasis. Due to these critical roles, the microbiota has been suggested by various researchers to be a 'second brain' [45].

The microbiota activity within the gastrointestinal system produces metabolites including short-chain fatty acids (SCFAs), metabolites of tryptophan, and secondary bile acids, among others [12]. However, SCFAs (butyrate, acetate, and propionate) are compounds with one to six carbon atoms that constitute the mainstream metabolic products of the gut microbiota [63]. SCFAs enter the circulation and directly enter the brain to signal numerous pathways that mediate brain functions. These include maintaining the integrity of the blood-brain barrier by mediating tight junction proteins, acting as a source of biomolecules for energy supply, control of serotoninergic transmission through control of the activity of tryptophan hydroxylase (an enzyme responsible for the synthesis of 5-HT), and activation of endogenous brain neurotrophic factors [64]. The immunological mechanisms of SCFA-mediated actions in the brain include the maturation and activation of glial cells, regulation of T-cell homeostasis, and release of cytokines/chemokines by these immune cells [65, 66].

There is emerging robust evidence about the role of microbiota-gut-brain axis impairment as one of the key factor in the pathogenesis of stroke. Interactions between the brain and gut microbiota during stroke occur via the microbiota-gut-brain axis and follow top-down and bottom-up signaling pathways. Brain lesions due to stroke either affect areas of the brain that control the ANS or the HPA axis, which in turn perturb normal gut microbiota-host interaction [67]. The consequential changes from this perturbation of the gut include a reduction in gut motility, increase in gut permeability, and alteration in the access of luminal bacteria and antigens to immune cells in the gut. Another way by which stroke affects the gut microbiota is through immune signaling, in which stroke lesions result in the suppression of peripheral immune cells by decreasing their numbers and functions; this is referred to as stroke-induced immunodepression. This systemic effect of stroke affects the integrity of the gut mucosal barrier, thus allowing the translocation of gut microbiota to the blood stream and lymphatic organs [68].

The major drivers of bottom-up signaling under the conditions of stroke are the gut microbiota and its metabolites, as well as molecules from intestinal cells. Biomolecules from the gastrointestinal tract, such as SCFAs, gamma amino-butyric acid, tryptophan, serotonin, catecholamines, and metabolites of bile acids, can interact with the brain with stroke lesions at three levels. The first is through their cognate receptors in the gut wall and the ENS, which subsequently communicate signals to the brain via afferent vagal pathways. The second is through direct invasion through the BBB by molecules such as SCFAs from the circulation. The third is through the indirect effects of amplifying the regional and systemic effects of stroke-induced immunosuppression impact on the immune system and inflammation by gut bacteria and their component endotoxins [69]. These gut bacteria and their component endotoxins, such as lipopolysaccharide (LPS), have also been documented to overwhelm the integrity of the cerebral blood-brain barrier [70].

Figure 1 shows a schematic representation illustrating the bidirectional interaction between stroke and gut microbiota via the gut-brain axis. The impact of the brain lesion due to stroke together with the associated stroke-induced immunosuppression cause negative effects on microbiota via top-down signaling. The effects include post-stroke dysbiosis, intestinal immune dysfunction, and compromise of the gut barrier. The resultant consequences from the gut microbiota range from up-regulation of pro-inflammatory immune cells (T cells) and their secreted cytokines, to increases in the permeability of microbes and their components. These collectively in turn lead to the exacerbation of stroke injury by increasing neuro-inflammation and disrupting the integrity of the BBB.

GUT-BRAIN AXIS IMPAIRMENT AS A THERAPEUTIC TARGET IN STROKE

Table 1 depicts a summary of studies that used various interventions to modulate stroke outcome via the microbiota-gut-brain axis. The table shows the diversity of microbiome-based interventions that have successfully modulated the microbiota-gut-brain axis and affected stroke outcome. These interventions ranged from bacteriotherapy-based interventions in the form of
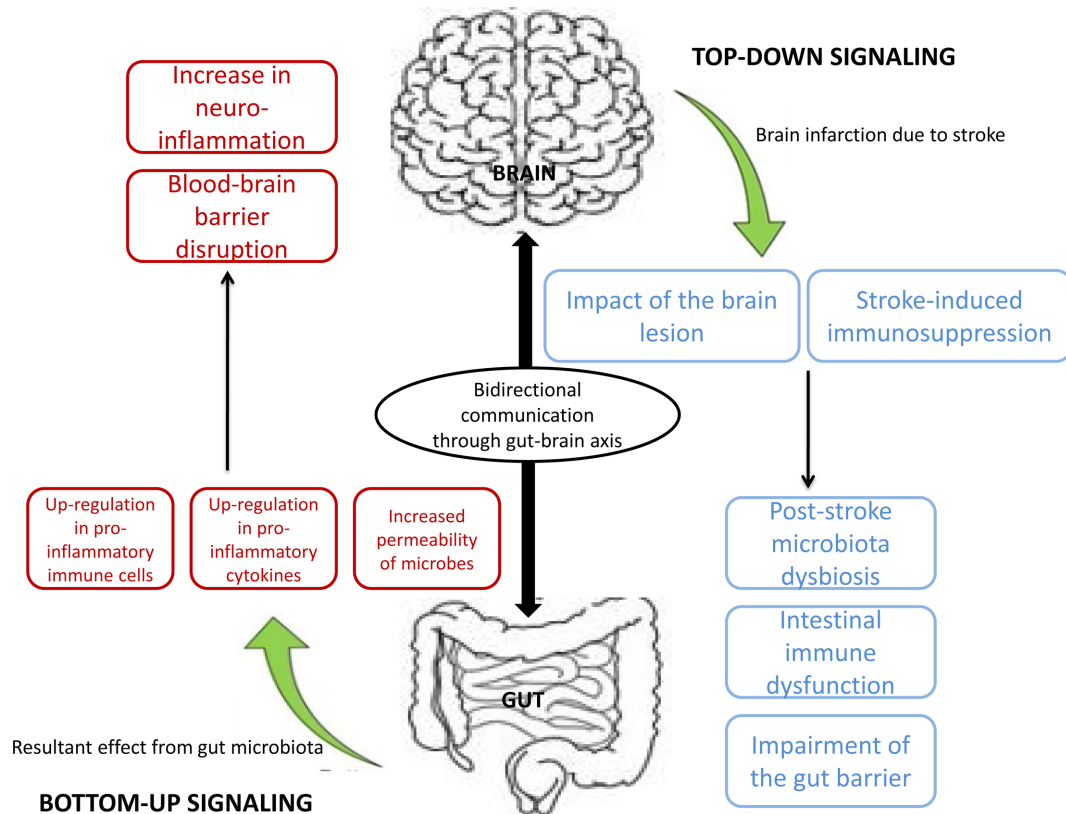
Fig. 1. Schematic representation illustrating bidirectional interaction between stroke and the gut microbiota via the gut-brain axis.

synbiotic, probiotic, prebiotic, postbiotic, and fecal microbiota transplantation (FMT) to traditional medicines in the form of a tanhuo decoction, a combination of puerariae lobatae radix and chuanxiong rhizome, and to natural products such as resveratrol and baicalin. The diversity of different categories here also points to the importance in terms of the prospect of combining two or more categories to synergistically work together and improve stroke outcome.

Additionally, assessment of the microbiota profile and status of microbiota metabolites holds enormous clinical potentials as a non-invasive indicator for the early diagnosis and prognosis of stroke. This is particularly essential considering the fact that diagnostic techniques for stroke can be expensive and, in some cases, may be invasive and painful. Therefore, clinical assessment of the microbiota profile and status of microbiota metabolites among stroke patients could provide cost-effective and non-invasive methods for clinicians to make accurate clinical inferences about stroke. A previous study compared the gut microbiota statuses of acute ischemic stroke patients with those of matched healthy controls and demonstrated that the stroke dysbiosis index (SDI) formulated from assessment of the gut microbiota composition was significantly correlated with patient outcome [71].

NATURAL PRODUCTS IN THE GUT MICROBIOTA AND STROKE

Natural products in the form dietary therapy, nutraceutical supplements, and edible medicinal plants have been used

for centuries to promote health and treat disorders. As a cerebrovascular disorder, stroke has well-established record of being improved using natural products [72]. With the prevailing irrefutable evidence of the involvement of the gut-brain axis in the pathogenesis of stroke, natural products represent a promising factor that could modulate the microbiota and impact the outcome of stroke.

The diet is the major source natural products that determine the gut microbiota composition and function [73, 74]. The relationship between the diet and gut microbiota has the potential to be associated with stroke from the perspective of both prevention and treatment. The presence of stroke risk factors accounts for more than 90% of all stroke etiologies [75]. These risk factors are categorized into non-modifiable factors, including age, sex, and genetic predisposition, and modifiable factors, including hypertension, diabetes mellitus, hyperlipidemia, alcohol consumption, and smoking, among others. These risk factors are associated with an increased risk of atherosclerotic plaque formation within the blood vessels and consequent thrombus formation and occlusion. Modifiable risk factors can be changed, and this forms the core pivot in stroke prevention strategies. Modifiable risk factors are inherent in a condition referred to as metabolic syndrome (MetS), a term that encompasses a cluster of conditions associated with glucose intolerance, central obesity, dyslipidemia, and hypertension [76].

It has been established recently that a gut microbiota-derived metabolite, trimethylamine N-oxide (TMAO), is the major factor in the development atherosclerosis and thrombosis [77–79]. There exists a meta-organismal pathway in which trimethylamine

Table 1. Studies that successfully utilized various interventions to modulate stroke outcome via the microbiota-gut-brain axis

Intervention	Study design	Major findings	Proposed mechanism
Traditional Chinese medicine (TCM): Tanhuo decoction (THD) [95]	Case-control study involving acute ischemic stroke patients	THD treatment showed better outcomes for clinical indices and the characteristics of gut microbiota.	THD exerts effects via modulation of microbiota-gut-brain axis, where THD regulates several gut bacteria to lower microbial metabolites such as lipopolysaccharide (LPS) and trimethylamine N-oxide (TMAO).
Gut microbiota from mice exposed to ischemia-reperfusion (I/R) injury [18]	Germ-free C57BL/6J mice with cerebral I/R injury induced by bilateral common carotid artery occlusion (BCCO)	Microbiota from I/R colonized mice led to decreased functional connectivity strengths of the cingulate cortex, hippocampus, and thalamus.	Cerebral I/R injury-induced dysbiosis is associated with the brain via neuronal plasticity and neuro-inflammation.
Fecal microbiota transplant (FMT) from healthy mice [96]	Specific pathogen-free C57 mice exposed to stereotaxic intracerebral hemorrhage (ICH)	FMT led to amelioration of functional deficits and neuro-inflammation caused by ICH.	ICH-induced dysbiosis was ameliorated by FMT via the maintenance of T-cell homeostasis.
Synbiotic consisting of probiotics and a prebiotic. Probiotics: SCFA-producing probiotics consisting of *Bifidobacterium longum, Clostridium symbiosum, Faecalibacterium prausnitzii* and *Limosilactobacillus fermentum.* Prebiotic: inulin [97]	MCAO in aged mice	Significant reduction in functional impairment, as well as significant attenuation of neuro-inflammation markers.	Through restoration of stroke-induced SCFA impairments and consequent restoration of SCFA-mediated functions, such as the regulation of T-cell homeostasis, thereby enhancing host immunity and gut barrier integrity.
Baicalin (flavonoid) [98]	C57BL/6J mice exposed to repeated ischemia reperfusion injury by bilateral common carotid artery occlusion (BCCO)	A baicalin-mediated decrease in the microbiota-dependent metabolite TMAO (trimethylamine-*N*-oxide) was observed in plasma.	Reduced TMAO activity provided neuro-protection by attenuating neuro inflammation and improved cognition, short-term memory, LTP, and the plasticity of hippocampal neurons.
Postbiotics: Synthetic short-chain fatty acids (SCFAs) [99]	Specific pathogen-free C57BL/6J mice were exposed to MCAO	SCFA supplementation led to reversal of low stroke-induced SCFA concentrations as well as consequent improvements in behavioral recovery, cortical connectivity, and microglial function.	Microbiota- derived SCFA molecules exert their effect in the brain via the modulation of immune cells and neuroplasticity by influencing the gut-brain axis.
Resveratrol (natural product) [94]	C57BL/6 mice exposed to a cerebral I/R injury induced by middle cerebral artery occlusion (MCAO)	Resveratrol-treated mice showed a decrease in infarct volume and small intestinal pro-inflammatory cytokines expression.	Resveratrol exerts its effect through attenuation of the cerebral ischemia-induced compromise in intestinal integrity as well as modulation of the intestinal immune cell-mediated inflammatory response, to consequently ameliorate pro-inflammatory cytokine-mediated BBB disruption and neuro-inflammation.
Traditional Chinese medicine (TCM): combination of puerariae lobatae radix (PLR) and chuanxiong rhizoma (CXR) [100]	Rat subjected to MCAO	The combination concoction led to reparation of stroke-induced neurological impairments, dysbiosis, and intestinal barrier disruption.	Through modulation of intestinal bacteria that promote neuroprotection.
Fecal microbiota transplant (FMT) from the distal colon in young and aged mice [67]	C57BL/6 mice with cerebral ischemia surgically induced by middle cerebral artery occlusion (MCAO)	Stroke produced gut dysbiosis in both young and aged mice. However, young mouse microbiota improved outcomes of stroke in aged mice, while aged-mouse microbiota impaired stroke outcomes in young mice.	The observed benefit was via stabilization of gut barrier integrity, modulation of neuro-inflammatory cytokine production, and regulation of adaptive immune cells.
Antibiotics: cocktail of 5 antibiotics consisting of ampicillin, vancomycin, ciprofloxacin, imipenem, and metronidazole [68]	C57BL/6J mice with focal cerebral ischemia induced by middle cerebral artery occlusion (MCAO)	Microbiota-depleted mice produced by pretreatment with antibiotics showed a decreased survival rate after MCAO.	Dysbiosis affected the stroke outcome by altering the intestinal barrier integrity.
Fecal microbiota transplant (FMT) of extracts from cecal contents of two donor mice. Antibiotics: amoxicillin/clavulanic acid, as well as vancomycin pretreatment prior to MCAO [101]	Specific-pathogen-free C57BL/6 mice subjected to transient focal cerebral ischemia induced by MCAO	Altered intestinal flora resulted in effects on stroke outcome by inducing changes in immune homeostasis.	Dysbiosis resulted in alteration of immune homeostasis by suppressing the trafficking of effector T cells from the gut to the leptomeninges after stroke.

TCM: traditional Chinese medicine; THD: tanhuo decoction; LPS: lipopolysaccharide; TMAO: trimethylamine N-oxide; FMT: fecal microbiota transplantation; I/R: ischemia-reperfusion; BCCO: bilateral common carotid artery occlusion; LTP: long-term potentiation; ICH: intracerebral hemorrhage; SCFAs: short-chain fatty acids; MCAO: middle cerebral artery occlusion; PLR: puerariae lobatae radix; CXR: chuanxiong rhizome.

(TMA) is synthesized as a by-product of gut microbiota metabolism of dietary nutrients, such as the phosphatidylcholine, choline, carnitine, and betaine found abundantly in red meat and eggs. This TMA precursor enters the liver via the portal circulation and is further converted into TMAO by a family of endogenous liver enzymes called flavin monooxygenases (FMOs) [80].

Several natural products have been widely recognized to modulate gut microbiota and influence health in human *in vivo* and *in vitro* studies. For instance, polyphenol-rich diets [81], an edible leguminous mung bean (*Vignaradiata* L.) supplement [82], blueberry proanthocyanidins [83], a wasabi supplement [84], polyphenols rich in high-quality extra-virgin olive oil in combination with a Mediterranean diet [85], sulfated polysaccharides from the flesh of *Callosobruchus chinensis* [86], cranberry (*Vaccinium macrocarpon*) fruits [87], apple procyanidin polyphenols [88], resveratrol polyphenol [89], a supplement mixture of quercetin and catechin polyphenols [90], dietary fiber from Apple-derived pectin [91], a dietary quercetin [92], and the phytochemical allicin phytochemical from garlic [93] all modulate gut microbiota and confer improvements in metabolic health profile, as well as anti-arthrosclerosis effects. This shows the promising role of natural products in stroke prevention.

The role of natural products in the treatment of stroke by modulating gut microbiota is only just emerging. Dou et al. [94] investigated whether modulation of the gut-brain axis by resveratrol (a natural polyphenol) could exert a neuro-protective effect in acute ischemic stroke model. The findings from their study revealed that resveratrol attenuates the stroke-induced compromise of intestinal integrity and restores the gastrointestinal immune balance altered by stroke. Their study holds as a basic premise the idea that natural products can be an integral part of evolving interventions that modulate stroke outcome via the microbiota-gut-brain axis. Development of two or more appropriate combinations of natural products that are rich in fibers, polyphenols, or fermented product that can modulate microbiota holds enormous potential for both the prevention and treatment of stroke. The use of natural products in combination with prebiotics, probiotics, synbiotics or postbiotics that can mediate TMAO metabolites could also be a potent strategy for therapeutics against stroke.

Figure 2 shows a schematic illustration of the meta-organismal pathway involving the gut microbiota and hepatocytes. The accumulation of conditions rooted in metabolic syndrome leads to perturbation of the gut microbiota balance (dysbiosis). This result in an abnormal increase in the proportion of TMA-producing bacteria, which generates the metabolite TMA that sequentially gets further converted into TMAO in the liver by the action of FMOs. TMAO is associated with the development of atherosclerosis and consequent thrombus formation, thereby increasing the risk of the development of stroke. Natural products possess the potentiality to prevent stroke by modulating gut microbiota to inhibit this meta-organismal pathway.

CONCLUSION

The findings discussed herein provide insights to further establish that microbiota-gut-brain axis impairment is compellingly involved in the pathogenesis of stroke. This suggests that it could be potentially modified as a therapeutic target to influence the outcome of stroke, and evidence from studies that have modulated stroke via the microbiota-gut-brain axis extends the point that the microbiota-gut-brain axis holds promising
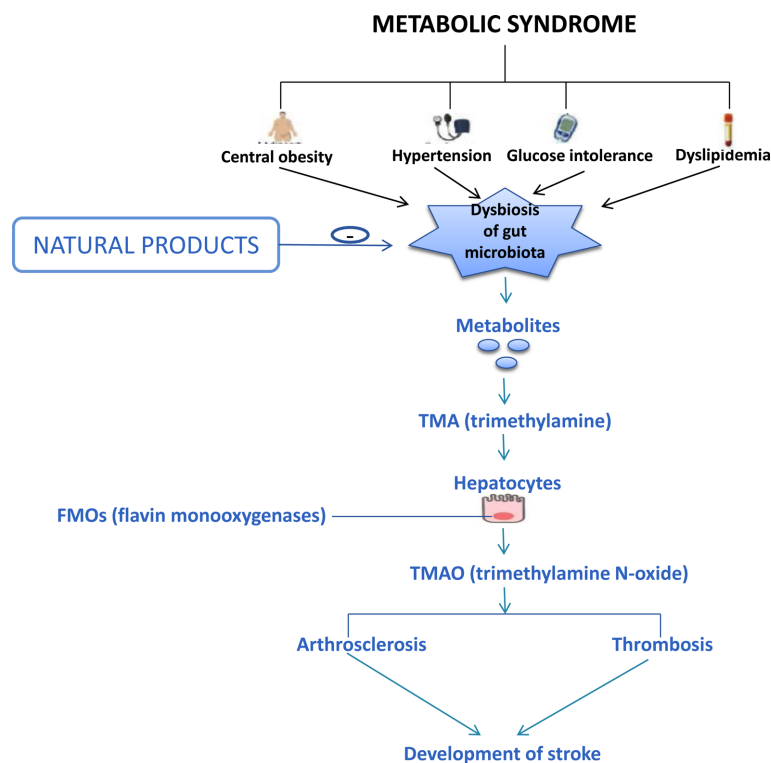

Fig. 2. Schematic representation illustrating meta-organismal pathway involving the gut microbiota and hepatocytes.

implications for the therapeutic treatment of stroke as well as the prevention of stroke. Assessment of the microbiota profile and status of microbiota metabolites holds enormous clinical potential as a non-invasive indicator for the early diagnosis and prognosis of stroke.

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