Clinical and Medical Research and Studies

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Review Article **Clinical and Medical Research and Studies** **Open Access**

The Importance of Dysbiosis in Intestinal Flora Subsequent to Ischaemic Stroke: Implications in Therapeutic management and Biomarkers for Prognosis-A Narrative Review

DR Kulvinder Kochar Kaur[1], DR Gautam Nand K Allahbadia[2], DR Mandeep Singh[3]

1 Centre for Human Reproduction, India.

2 Ex-Rotunda-A Centre for Human Reproduction

3 Consultant Neurologist Swami Satyanand Hospital

***Corresponding Author:** Dr Kulvinder Kochar Kaur, Centre for Human Reproduction, India.

Received: January 20, 2023 | **Accepted:** January 27, 2023 | **Published:** January 30, 2023

Citation: Dr Kulvinder Kochar Kaur, DR Gautam Nand K Allahbadia, DR Mandeep Singh. The importance of Dysbiosis in Intestinal flora Subsequent to ischaemic Stroke: Implications in Therapeutic Management and Biomarkers for Prognosis-A Narrative Review, J. Clinical and Medical Research and Studies. 2(1).

Abstract

Stroke represents an acute cerebrovascular disease that puts the human life in significant danger besides a poorer quality of life.This adds a considerable burden on society in addition to their families.In the last decade the dysbiosis of Intestinal flora has evoked remarkable interest . Subsequent to stroke, Intestinal microbial dysbiosis results in escalated Intestinal permeability along with activation of the Intestinal immune system that in turn results in ectopic Intestinal bacteria along with roinflammatory cells which gainentry into the brain tissue via the injured blood brain barrier(BBB).This aggravates the ischaemia reperfusion damage by repression of post inflammatory reaction along with facilitates the healing of neurological function. Intriguingly, Subsequent to a stroke certain metabolites generated by the Intestinal flora ameliorated biological function .In this review the assessment of alterations in gut flora subsequent to stroke taking place along with emphasize on the immunomodulatory events of the post stroke gut flora.

Keywords: ischaemic Stroke(IS) ; brain gut axis; dysbiosis ; Intestinal flora ;SCFA's ischaemic stroke(IS) ; brain gut axis; dysbiosis ; intestinal flora ;SCFA's

1.Introduction

Stroke represents an acute cerebrovascular disease that can result in unanticipated burst of cerebral vessels or secondary to vascular blockade;further known as haemorragic Stroke(HS) or ischaemic Stroke(IS) respectively[1].The incidence of IS is considerably greater in contrast to HS which is implicated in about 80% of the full incidence of cerebrovascular damage.The disrupted blood provision to brain regions is associated with hypoxia,further results in IS correlated nerve cerebral injury. Numerous risk factors were implicated in the causation of or ischaemic Stroke that resulted in considerably greater burden regarding the patient's family along with that for the society in general [2]. Of the risk factors the ones of maximum significance are hypertension, Diabetes as well as atherosclerosis. ischaemic Stroke further is a complicated disease that takes place secondary to variable environmental along with genetic factors. Numerous local along with International studies illustrated that 2 kinds of risk factors are there regarding IS like i)non modifiable[3] (like gender ,age, genetic factors,family history,race) along with those that are modifiable(hypertension aberrant blood glucose, hyperlipidemia ,Atrial Fibrillation,greater homocysteine quantities,poor living conditions).For avoidance of risk factors they need to be tackled in particular the most inimical ones , like hypertension as wellas Diabetes for reduction of the incidence along with mortality of this disease.

Intestinal flora is inclusive of all the microorganisms present in the Gastrointestinal Tract (GIT), constitutedof amongst 150,000-36,000 bacterial species(spp)mostly made up of Firmicutes along with Bacteroides phyla [5]. Furthermore, an ecosystem comprised of trillions of commensals in the form of bacteria, archaea, protozoaas well as viruses along with bacteriophages whose collective microbiome is known as microbiotaor comprise the Intestinal flora [6]. Intestinal flora possess the **capacity** of controlling the metabolic activity along with controlling the Intestinal immune system as well as biological barriers [7], hence possess a part in the sustenance of health of the host [8]. The total quantities of bacteria along with species(spp') that constitute the Intestinal flora might be influenced by various factors *like* environment [9], diet [10], utilization of medicines along with genetics. Intestinal microbiome comprises of Intestinal flora with its surrounding Intestinal milieu,that works for the

sustenance of the homeostasis of the internal milieu in case of normal situations for humans as well as animals .On loss of homeostasis of the this internal micro-ecosystem different diseases are generated,that might implicate the central nervous system(CNS[11].The Intestinal microenvironment alterations results from alterations in the Intestinal micro-ecosystem, influence the Intestinal function regarding absorption along with metabolism,thus followed by IS[12], maximum directly or indirectly. Additionally, the enteric nervous system (ENS)alias the second ''human brain'' possesses the **capacity** of crosstalking with the CNS, autonomic nervous system (ANS) [13], hypothalamo-pituitary-adrenal (H-P-A) axis along with other structures to for generating a two-way controlling axis alias the brain-gut axis. Furthermore, intestinal flora has the **capacity** ofdecomposing the food particles that have been fermented to generate variable metabolites [14], which possess a significant part in the brain-gut axis. It might produce a network of nerve, immune along with endocrine controlling by stimulating neuroendocrine along with conduction pathways that represents the ''flora- gut -brain- axis''. Alterations in intestinal flora can alter the intestinal defense brain function along with intestinal permeability [15], that influence the ENS along with CNS.

Simultaneously intestinal flora have a significant part in the generation of the CNS [16, rev by us in17,18]. Different studies have **illustrated** that gut microbiota possess the **capacity** of controlling neurotrophic factors or proteins implicated in brain generation along with plasticity like the brain derived neurotrophic factors (BDNF) [19], synaptophysin as well as post synaptic dense region proteins. The sterile status of sterile animals can result in alterations in the nervous system like escalated permeability of the blood brain barrier(BBB). Microglial cells are variable from canonical bacterial colonization animals in morphology along with function [20]. Additionally, intestinal flora is further implicated in CNS actions like anxiety, depression along with stress reactions [21]. Having reviewed earlier the role of Gut Microbiota inavoidance of obesity, Type 1 Diabetes (T1D), associated with generation of neurodegenerative along with neuropsychiatric diseases [22-27]. Here we reviewed how imbalanced intestinal flora presence there can be enhanced risk of stroke via various mode. Normally intestinal flora that continue to be in steady state has a considerably significant part in sustenance of normal brain function along with healing. On imbalanced intestinal flora presence there can be enhanced risk of stroke via various modes.

Methods

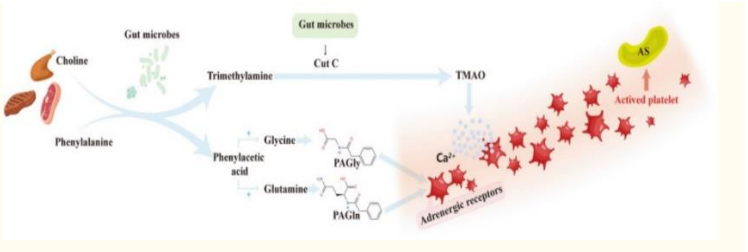
Here we conducted a narrative review utilizing search engine pubmed,google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like ischaemic Stroke(IS); Intestinal flora; 'flora- gut -brain- axis''; BDNF; BBB; atherosclerotic plaque; Porphyromonas gingivalis; short chain fatty acids (SCFA); toll like receptors (TLRs); trimethylamine-N-oxide(TMAO); phenylacetic acid glutamine (PAGln); Intestinal junctional proteins; Intestinal permeability *Lactobacillus rhamnosus* from 1975 till 2022 till date.

Results

We found a total of 300 articles out of which we selected 119 articles for this review.No meta-analysis was done.

2.Intestinal flora along with their products result in stroke by atherosclerosis Induction

Activation of platelets, their adherence along with atherosclerotic plaque production represent significant factors regarding pathogenesis of IS(Figure1)[rev in 28].



Legend for Figure 1

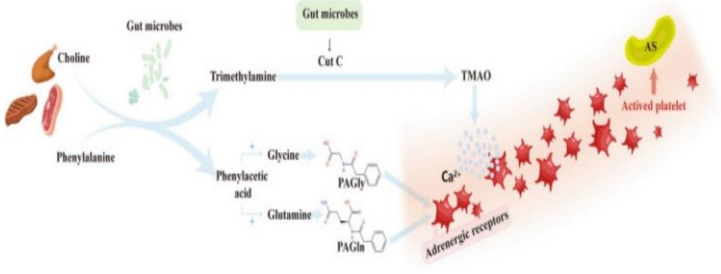
Courtesy ref no- 28 -Some intestinal metabolites promote the development of atherosclerosis. Choline in food is transformed into trimethylamine by the action of intestinal bacteria, and the latter is formed into TMAO by the action of a specific group of bacteria containing the CutC gene. TMAO evokes the release of intracellular calcium stores and promotes platelet activation and atherosclerotic plaque formation. Phenylalanine in food is converted to phenylacetic acid by the action of porA gene-containing enteric flora, which synthesizes PAGln or PAGly with glutamine or glycine and binds to platelet adrenergic receptors to induce platelet hyperreactivity and promote atherogenic plaque formation

More recently studies have illustrated that intestinal flora a significant part in the atherosclerotic plaque generation. There are3 modes by which intestinal flora possess participate in the formation of atherosclerotic plaques; namely i) Activation of the immune system by the bacterial infections [29],by impacting different immune cells [30]. Furthermore, the expression of toll like receptors (TLRs) by macrophages result in escalated proinflammatory cytokines as well as chemokines , that aggravates the propagation of atherosclerotic plaques along with result in the generation of a susceptible plaque generation.For facilitation of atherosclerosis,the microbes implicated are Porphyromonas gingivalis[31],Aggregatibacter actinomycetemcomitans, Chlamydia Pneumoniae[32], along with othersii)Food metabolism by intestinal flora like of cholesterol as well as fat influence the generation of atherosclerotic plaques[33]. Proinflammatory microorganisms transplantation possess the capacity of reduction of kinds of microorganisms,that generate short chain fatty acids (SCFA)in mice,escalate the inflammatory reaction along with facilitate atherosclerosis generation[34].Some types of bacteria like Lactobacillus rhamnosus (LGG)or certain pharmacological substances like telmisartan(TLM) supplementation possess the capacity of changing bacterial genera along with reduction of α-diversity , possessing significant association with atherosclerotic plaque size,plasma -A- fatty acids binding protein (FABP) along with cholesterol quantities[35].iii)Some metabolites like, trimethylamine-N-oxide(TMAO), generated by intestinal flora facilitate atherosclerotic plaque generation by activating platelets activities.The TMAO pathway is believed to be the pathway being maximum direct one ,where intestinal flora impact the event of atherosclerosis[36].

Choline from the diet undergoes metabolism by intestinal flora to form trimethylamine,that gets oxidized to TMAO, subsequent to gaining entry in liver through liver-gut circulation. TMAO facilitates the liberation of intracellular Ca^{2+} ions in an extracellular manner that is in a platelets activator fashion,hence modulates the greater platelets reactivity along with escalates the risk of thrombosis generation[37].

Besides animal experiments , clinical studies have further illustrated the implications of TMAO in atherosclerosis generation, that is significantly associated with the risk of cerebrovascular along with cardiovascular

processes.A study performed by Tang etal.[38], implicating 4007 individuals, followed up for3yrs for assessment of correlation amongst the quantities of plasma TMAO along with the risk of cerebrovascular along with cardiovascular processes.Their outcomes obtained illustrated a positive association with the risk of thrombosis in a dose based fashion,an action independent of canonical cardiovascular disease (CVD) along with cerebrovascular disease risk factors. However, Yin etal.[39], in their **study** did not observe escalated plasma TMAO quantities in case of stroke patients or patients presenting with transient ischaemic attack (TIA). They further evaluated the variations in the intestinal flora components along with TMAO quantities in asymptomatic patients with atherosclerosis, stroke or TIA. Their outcomes obtained demonstrated that the TMAO quantities along with intestinal flora constituents were akin in asymptomatic patients with atherosclerosis,with or without carotid plaques. Nevertheless, intestinal flora composition in stroke or TIA patients was considerably significantly variable from those of asymptomatic atherosclerosis patients. Noticeably,despite the TMAO quantities were not escalated as anticipated ,the quantities were still lesser in contrast to those seen in asymptomatic atherosclerosis patients. Tang etal.[38], reasoned that the utilization of medicines for stroke treatment might decrease the TMAO quantities.Hence the association amongst the intestinal flora product TMAO as well as stroke requires further assessment to prove this posit.It was observed that the microbial cut C gene was implicated in, trimethylamine(TMA) transformation along with escalated the size of infarction,thus this gene can be believed to facilitate dysfunctional neurological function by genetic engineering bacterial transplants by modifications in germ free(GF) mice,pointing that GM possess the capacity of exaggerating infarcts by generating TMAO[40]. Other than TMAO,other metabolites of intestinal flora possessing the capacity of platelet activation inclusive of phenylacetic acid glutamine (PAGln) along with phenylacetic acid glycine (PAGly)[41].These reflect phenylacetic acid whose consumption occurs in diet followed by transformation to phenyl alanine by intestinal flora along with finally into glutamine as well as glycine respectively. PAGln along with PAGly are akin in structure to adrenergic receptors,hence possess the capacity of binding to plateletβ2 receptors in the body along with capacity of platelet activation for facilitating thrombosis. Nevertheless, certain studies observed that **PAGly** possesses the capacity of activating Gαi/PI3K/AKT signaling cascade via stimulation of β2AR, thus cell apoptosis in addition to reduction of the region of myocardial infarction (MI) that occurred due to ischaemia /reperfusion (I/R) damage. Nevertheless, therapy with greater dosage would result in greater mortality rate [42]. It can be seen that the part of PAGly in body is intricately correlated with its dosage. Nevertheless, the part of PAGly subsequent to IS along with the modes by which it works have not been clarified till now, thus needs greater assessment (Figure1).



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Courtesy ref no- 28 -Some intestinal metabolites promote the development of atherosclerosis. Choline in food is transformed into trimethylamine by the action of intestinal bacteria, and the latter is formed into TMAO by the action of a specific group of bacteria containing the CutC gene. TMAO evokes the release of intracellular calcium stores and promotes platelet activation and atherosclerotic plaque formation. Phenylalanine in food is converted to phenylacetic acid by the action of porA gene-containing enteric flora, which synthesizes PAGln or PAGly with glutamine or glycine and binds to platelet adrenergic receptors to induce platelet hyperreactivity and promote atherogenic plaque formation Porphyromonas gingivalis,that resides in oral cavity was also observed to be correlated with stroke generation further has to be borne in mind[43].

3.Alterations in intestinal flora can influence brain healing subsequent to stroke

The ''flora- intestine- brain'' area is a newer abstraction.It has beena prior needed posit,that illustrated in the model of middle cerebral artery occlusion(MCAO), intestinal flora possessed a considerably important influence on stroke prognosis.Benakis etal.[44],revealed that secondary to antibiotics,dysbiosis possessed the capacity of reduction of α-diversity of intestinal flora along with escalate the prognosis;the histology demonstrated a reduction of volume of the ischaemic tissue.This action takes place secondary to the reduction of IL-17^{+}γδ T cells along with the escalation of Treg cells in the small intestine,thus restricted the infiltration of inimical substances into the brain membrane of IL-17^{+}γδ T cells.Sun et al.[45], observed that the butyric acid bacteria possessed the capacity of reduction of cerebral I/R damage in diabetic mice by controlling intestinal flora 16S RNA gene sequencing in combination with liquid chromatography(LC)-MS(high resolution mass spectrometry) assessment illustrated that incase of rats with IS there were alterations of intestinal flora along with plasma metabolites. Furthermore,it was demonstrated that the enrichment of Proteobacteria**,** Firmicutes in addition to Defferibacteres was significantly variable amongst Sham along with IS groups.A robust association amongst the gut microbiota(GM) with the dyscontrolled metabolites was present[46].Xu etal.[47], observed that the MCAO mice expanded the dynamic dysbiosis at fast pace .The escalated Enterobacteriaceae bacteria accelerates cerebral infarction by escalating systemic inflammation. Akin studies illustrated that dyscontrolled microbiotais partly implicated in poor prognosis of patients presenting with primary stroke. The utilization of aminoguanidine or superoxide dismutase(SOD) for reduction of nitrate generation or by utilizing tungstate for hampering nitrate respiration possesses the capacity of hampering Enterobacteriaceae bacteria overgrowth,decrease systemic inflammation along with reduction of risk of cerebral infarction.These therapeutic actions are based on the GM, that pointed to the translational importance of gut- brain axis regarding the treatment of stroke.Wang etal.[48],validated that in the patients of T2D subsequent to AIS the serum quantities of lipopolysaccharides (LPS) as well as D-lactate enhanced in a clear manner. Additionally, she demonstrated that the butyrate generating bacteria inclusive of Lachnospira, Blautia along with Butyricoccus reduced. On replenishment of BS, the mice demonstrated lesser quantities of proinflammatory cytokines besides illustrating smaller volume of infarction. Furthermore,it illustrated that fecal transplantation possessed the capacity of ameliorating ischaemic stroke damage by conferring protection to the BBB.One day subsequent to stroke MCAO models of pigs [49], demonstrated a reduction in microbial diversity as well as on day3 there existed a negative association of the volume of the injured area with microbial diversity. In correlation with the models the enrichment of Proteobacteria was significantly

escalated, whereas reduction of Firmicutes, other lactic acid bacteria, Lactobacillus took place on day3 post stroke .These outcomes from a pig model point to the plasticity of gut microbiome at the time of acute phase of stroke besides impacting the injury.

3.2 Alterations in intestinal mucosal permeability can impact stroke results

Intestinal mucosal barrier which is unbroken represents a significant defense for the body for avoidance of inimical external factors. At the time of IS alteration of intestinal permeability takes place secondary to different explainations, usually presenting in the form of escalated intestinal permeability. This causes enhanced toxic products entering blood circulation via the intestinal mucosal, followed by entry into the nervous system resulting in injury. The dysfunctional Intestinal barrier function in patients with cerebral infarction might be associated with these factors detailed hereafter.

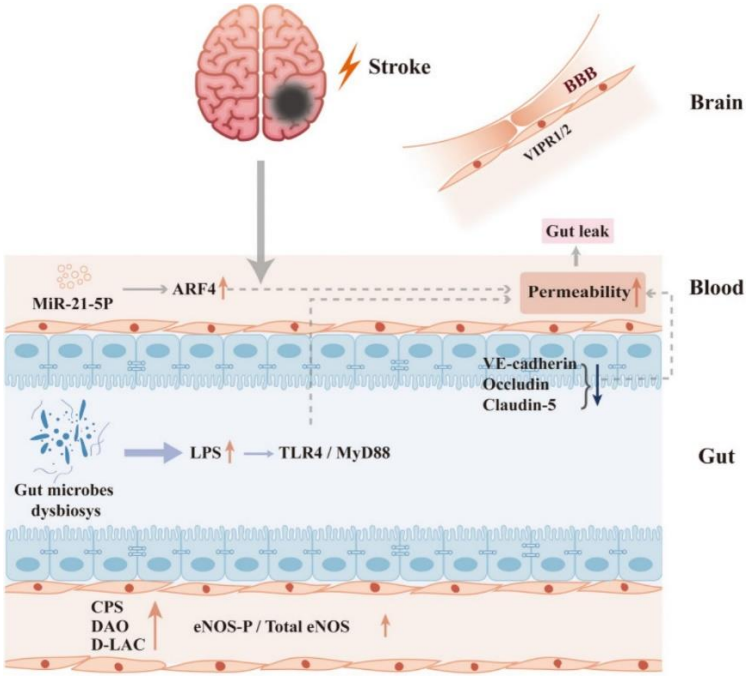
3.2A**Ischaemic Stroke results in the reduction of expression of Intestinal junctional proteins**

The Intestinal mucosa inclusive of the structure of tight junctions (TJ) are comprised of numerous proteins subunits [50], of whom claudins as well as occludins are of considerable importance in view of their crucial structural part. Numerous studies [51], have evaluated their expressional quantities in the form of changed mucosal permeability. A reduction in the expression of zonula occludens 1(ZO1), occludins along with claudins takes place subsequent to stroke[52]. Cerebral infarction reduces the expression of Intestinal mucosa tight junction proteins. Occludin which results in the breakdown of tight junctions, injures the Intestinal barrier as well as enhances intestinal permeability. Xia etal.[53], observed that the expression of ZO1, VE-cadherin, occludins along with claudin 5 in case of rats of MCAO group were apparently decreased in variable extents. Delivery of Shengui Shansheng Pulvis(SSP) resulted in restoration of these proteins in the intestinal mucosal epithelium with simultaneous reduction of MCAO induction of brain oedema along with enhanced the expression of VIPR1/2 in the OGD BBB models decreasing endothelial damage.

3.2BEnhanced Intestinal epithelium permeability stimulated by micro-RNA subsequent to stroke

microRNA represents a type of small noncoding ribonucleic acid which take part in different pathophysiological events of the body.miR-21-5p represents a type of mi RNAs.Wu etal.[54], observed that there was significantly enhanced miR-21-5p in serum of patients with cerebral infarction. In different studies it has been observed that miR-21-5p possesses the capacity of escalating intestinal epithelium permeability by causing upregulation of small GTPase-ADP-ribosylation factor 4(ARF4) [55].The capacity of miR-21-5p to escalate vascular permeability has been illustrated in akin studies of colorectal cancer along with that might be correlated to its targeting of Krev interaction protein1 along with activation of the β-catenin signaling pathway .Impairment of intestinal flora subsequent to stroke, generates toxic metaboliies working on the intestinal mucosal epithelium .

LPS along withK99 pili protein localized in the brain 24h subsequent to stroke was observed by Kurita etal.[56], that was present in the Iba-1 positive neurons, microglia along with endothelial cells. These outcomes obtained pointed that ischaemia Induction of Enterobacteriaceae proliferation resulted in escalated luminal LPS quantities, caused weakening of the tight junctions of the epithelial cells along with facilitated the entry of LPS in the circulatory system. Singh etal.[57], observed that the intestinal flora could be impacted subsequent to stroke. Once intestinal flora imbalanced, opportunistic pathogens can generate ion different inimical substances, like LPS. LPS comprises of the cell wall constituent of gram negative bacteria alias endotoxin, that possesses the capacity of impacting tight junctions of the intestinal epithelium along with result in escalated intestinal permeability by modulating the TLR4/MyD88, signal transduction pathway. Escalation of TLR4 positive cells got initiated 1h subsequent to MCAO, persisting for22 h. In particular knockout of TLR4had the capacity to generate a protective action against Ischaemic stroke .Thus it is clear that TLR4 is an important target in case of stroke[58]. Interference of GM could result in cerebral endothelial cells via the endothelial nitric oxide synthase(eNOS) reduction of activity [59]. Stroke can result in escalated enrichment of gram negative Enterobacteriaceae bacteria along with further escalate circulatory LPS quantities [56,60], that might initiate inflammation through TLR4[61] along with change intestinal mucosal ligand protein expression quantities causing a leaky gut. In the meantime LPS causes induction of an inflammatory reaction that further aggravates stroke damage .This pointed that stroke along with changed intestinal flora are biphasic. Furthermore, cerebral artery lysates of **antibiotics** treated rats the eNOS-P/total eNOS ratio was reduced in contrast to controls. Utilization of antibiotics causes the interference of GM leading to cerebral endothelial impairment. Nevertheless, this study was converse of that by Benakis etal.[44]. The intestinal barrier is the main defense against the external environment that possesses a significant part in guaranteeing the stability of internal milieu of the body. Blood DAO (diamine oxidase), D-Lac(D-lactate) along with endotoxins [64], are dependable pointers that towards the function of intestinal barrier. Mice having hyperuricemia were observed to have injured intestinal barrier along with escalated Intestinal permeability that result in an induced inflammatory event. Escalated serum uric acid quantities were observed to be correlated with an escalated risk of Ischaemic Stroke, however the mode is not clear. Actually, Joshua etal.[63], observed akin outcomes in animal studies. Nevertheless, various studies [64], concluded that not enough validation for alterations in the morphology along with expression of permeability proteins in the intestinal mucosal epithelium subsequent to MCAO (Fig2).



Legend for Figure. 2

Courtesy ref no- 28 -Post-stroke intestinal changes and their impacts on cerebral organization. Stroke causes a reduction in the expression of intestinal epithelial tight junction proteins including VE-cadherin, Occludin and Claudin-5; more LPS is produced by post-stroke intestinal flora, which induces damage by binding to TLR4/MyD88 in the downstream inflammatory response; LPS also contributes to an increase in eNOS-P/total eNOS, causing vascular endothelial damage; stroke causes an increase in miR-21-5p and further upregulated ARF4; the aforementioned factors combined lead to increased intestinal mucosal permeability and leaky gut. The blood LPS, DAO and D-LAC elevated after vascular endothelial injury and BBB endothelial injury accompanied by VIPR1/2 decreasing

4.Cytokines liberated by gliacytes along with other Cell kinds Post Ischaemic Stroke might either Exaggerate or Benefit Injury

Ischaemia along with hyoxia in brain tissue from different etiologies stimulate a series of stepwise reactions inclusive of glial cell activation along with liberation proinflammatory mediators, resulting in activation of endothelial cells that express adhesion molecule along with enrol inflammatory in addition to immune cells from circulation at the region of stroke damage. The concomitant liberation of damage–associated molecular pattern receptor (DAMP)/ cytokines besides the activation of the vagal nerves causes disordered intestinal motility, other intestinal aberrations in addition to escalated Intestinal permeability. Vila etal.[65], observed that serum quantities of Tumor necrosis factor alpha(TNFα) as well as interleukin-6(IL-6) during admission possessed a robust correlation with early neurological inimical effects . Nevertheless, the precise source of IL-6 along with TNFα were not revealed in the study. Numerous studies [66] illustrated that the time period subsequent to a stroke could cause escalated expression proinflammatory/inflammatory factors in the serum along with in the brain tissue. This aggravated local or systemic inflammatory reaction along with further exacerbates the brain tissue injury. Primary culture astrocytes were observed to be expressing minimal quantities of TLR2, TLR4, TLR5 along with TLR9 at the time of resting culture situations, however their mRNA expression quantities were remarkably upregulated on exposure of cells to particular bacteria obtained ligands[67]. Triggering receptor expressed on myeloid cells 1 (TREM1) gets generated by Ly6C^{+} MHCII^{+} macrophages that are present in lamina propriaof the intestinal mucosa subsequen**t** toa stroke;its capacity of escalating mucosal epithelial permeability facilitates bacterial translocation across the intestinal barrier into the brain tissue[68].This has relevance regardingthe peripheral TREM1 results in escalated proinflammatory reaction to brain obtained as well as gut obtained immunogenic constituents. Hampering TREM1 has the capacity of decreasing brain injury via this particular innate immune pathway.Earlier activation of PMN in the ischaemic braintissue might be secondaryto fast liberation of DAMPs along with ultimately result in the liberation of IL-1b[69].This is an event that facilitates the initiation of vesicle generation by activation of immune cell surface receptors besides the activation of the NLRP3 pathway.On elimination of infiltration of penumbra PMNsubsequent to initiation of stroke,the early brain injury does not influence the animal's behavioral performance significantly[70].

It is not tough to appreciate regarding the significance of an inflammatory state being key for eliciting the neurotoxic potential of the invader.Resting state PMN illustrated no neurotoxic action in brain slices without Ischaemic prior damage along with just LPS stimulated PMN illustrated this action.An akin escalation of TREM1 takes place at the time of Intestinal ischaemia reperfusion, however utilization of the hamper**ing** agent LP-17 postpones demise in experimental animals[71].The intestinal tract comprises of the major immune numerous organs possessing abundant or biggest immune cell pool that is implicated in 70% of the total immune system[72]. Intestinal microorganismson displacement can i) cause stimulation of intestinal associated lymphoid issue along with differentiation of immune cell subsetsii) facilitate the inflammatory reaction taking **place** in addition toiii) exacerbate the probability of systemic inflammatory reaction along with numerous organs impairment.

Microglia are obtained from the myeloid cellsof the yolk sac that have placement in the CNS early at the time of individual generation along with represent the resident immune cells of the CNS[73].The morphology of dendrites along with axons in case of neurons of germ free(GF) mice gets impacted at the time of generation as well as these kinds of generational abnormalities are usually correlated with immature microglial phenotype. This points to the key significance of gut microbial colonization at the time of generation of the brain[74]. Microglia possess the capacity of proliferation as well as polarization besides during a pathological situation from branching during resting state to an amoeboid state when activated [75].

Additionally, T lymphocytes possess a significant part in the stroke event. The Induction of dysbiosis during acute phase of stroke facilitates proinflammatory Th1 along with Th17 modulated immune reaction obtained from peyers lymph nodes as well as aids in brain damage[57,76].On attainment of intestinal microecological homeostasis subsequen**t** **to** during fecal microbiota transplantation (FMT),the quantities of Tregs escalate within the ischaemic brain area[78].Chronic colitis in combination with stroke, migration of intestinal obtained CD4+Tcells takes place from intestines to the meninges along with might crosstalk with meningeal macrophages resulting in non-intestine obtained CD4+Tcells infiltration along with Tcells imbalanced M1 as well as M2 Microglia /macrophagesthat aggravates the brain damage in ischaemic Stroke[79]. Simultaneously, it might further facilitate the migration of immune cells from the intestines to the damaged area of cerebral infarction as well as exaggerate the local damage. This might give us greater understanding regarding positive association amongst the intestinal barrier impairment as well as the extent of

neurological sequelae in case of patients with cerebral infarction. tissue

4.2Ectopic bacterial Placement subsequent to stroke result in infections of other tissues along with organs

Stroke can result in bacterial infections. A neurological central damage like stroke can cause a breakdown of the initial balance amongst the CNS in addition to the immune system, secondary immunodeficiency or immunesuppression. Finally this results in in the generation of infection[79].The ectopic bacteria that cause infection are exclusively species that are the ones part of intestinal flora which gain entry in the blood circulation followed by invasion of other tissues subsequent to stroke. An explanation offered for this is the escalated permeability of Intestinal mucosa, colonization along with result in infections. Wen etal.[80], illustrated that there is aggravated impairment of the Intestinal barrier with advancement of age facilitates translocation of gut obtained bacteria, aiding in escalated risk of post stroke bacterial infection .In an animal MCAO model, Tascilar etal.[81], observed that in post stroke Intestinal mucosa breakdown along with bacterial translocation inclusive of lung ,liver ,spleen along with mesenteric lymph nodes. The common**est** pathogen is the coagulase negative *Staphylococcus aureus* .The dysfunctional Intestinal barrier function generates a beneficial situation for Intestinal microbial translocation.

Nevertheless, Oyerna etal.[64], pointed to no significant variation in Intestinal mucosa alterations in animals at the time of acute phase of stroke: furthermore, their colonization in the lung might be associated with unintentional aspiration of the Intestinal flora into the trachea followed by in the lung at the time of gavage. Additionally, post stroke stress is further correlated with bacterial translocation from the colon into other tissue(like mesenteric lymph nodes, liver along with spleen) , escalates the inflammatory phenotype of the Intestinal mucosa(like COX2,iNOS) along with decreased the quantities of locally liberated IgA[82].This poststroke stress is correlated with stroke results[83].Irrespective of post stroke infection being the commonest complication, besides the maximum robust complication its mode required further evaluation.

5.Alterations of intestinal flora are intricately associated with poststroke depression

The brain -gut axis is a bidirectional controlling axis of the crosstalk amongst the brain as well as the Gastrointestinal Tract (GIT). Gastrointestinal unease is usually correlated with emotional responses, that in turn can stimulate neur**al** activities of the associated CNS regions. Simultaneously the controlling knowledge gets transferred to the GIT downwards via the brain -gut axis. This alters its dynamic besides the liberating functions, causes activation of Intestinal mucosal immunity along with impacting the Intestinal mucosal barrier function. Like in case of patients with gastroesophageal reflux, a robust association amongst anxiety, depression along with gastrointestinal symptoms like erosions of the gastric mucosa. Additionally, psychological or antidepressant therapy is efficacious for certain patients [84].In Psychiatric patients, depression along with generalized anxiety conditions are usually correlated with gastrointestinal unease[85]. Numerous patients with generalized anxiety conditions are usually initially diagnosed as having a gastroenterologic conditions [86]. Hence brain -gut axis impairment might participate in the formation of mental illnesses. Nevertheless, with regards to the mode, the present work suggests the implications of gut flora [87]. Alterations of BBB permeability takes place in the case of pathological condition [88] with different inflammatory factors gaining entry into the CNS. On transmission of inflammatory signals to the CNS, glial cell activation takes place via the NFκB pathway for facilitation of depression [89].

Post stroke depression gets frequently encountered in the post stroke population [90]. Patients in the post stroke phase in combination with cognitive dysfunction as well as depression usually possessed dysbiosis of the intestinal flora. PSCCID patients in contrast to non PSCCID patients, illustrated escalated enrichment of Proteobacteria**,** inclusive of, Gamma proteobacteria, Enterobacteriales along with Enterobacteriaceae besides reduction of Short chain fatty acids (SCFA) generating bacteria[91].

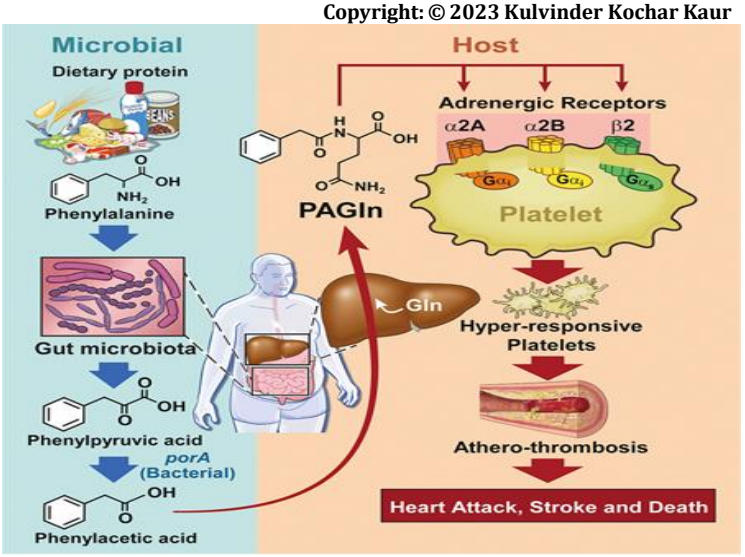
LPS delivery was observed to simulate depression like behavior in experimental animals. A remarkable inflammatory reaction in the CNS was seen that pointed that inflammatory reaction Induction by bacteria l with bacteria product like LPS possess the capacity of impacting CNS along with facilitation of depression generation [92]. Chronic mild stress results in escalated IL-1β, COX2 as well as PGE2 expression in blood along with reduction inexpression of 15d PGE2 quantities in brain tissue. utilization of antibiotics could decrease inflammation through hampering TLR signaling pathway, hence this target needs evaluation regarding depression[93]. Hampering or blockade of TLRs implicated in CNS inflammation along with depression like behavior Induced by Chronic mild stress can result in recovery of inflammation along with behavior of the animal [94]. The Clinical manifestations of depression along with Chronic mild stress are akin to each other. The conclusions drawn from these present studies is that both share an akin pathogenesis. Nevertheless, recent studies have further demonstrated that the correlation amongst gut flora are not particular for Post stroke depression, advocating greater evaluation. Hence future experimental in addition to Clinical studies regarding the assessment of actions of intestinal flora on Post stroke depression.

6.Modes possessing the capacity of conferring protection against Stroke via intestinal flora

The intestinal flora further possess the capacity of generating metabolites which promote improvement in stroke, out of which Short chain fatty acids (SCFA) is the one that has been maximum evaluated . SCFA represent one of the maximum frequent microbial metabolites obtained from *the i*ndigestible carbohydrate . SCFAs are comprised of acetate, butyrate, propionate in humans [95] besides lesser quantities of formate, valerate along with caproate[96].The absorption of SCFA into the circulation takes place actively with the use of monocarboxylate transporters(MCTs) 97]. Furthermore, they possess the capacity of crossing blood brain Intestinal barrier (BBIB) [98]. In the Clinical studies it has been observed that lesser quantities of SCFAs have a robust association with Stroke along with stroke correlated Pneumonia (SAP) [99]. Fecal transplantation or SCFAs delivery cause enhanced stroke prognosis, of the lot butyric acid possesses maximum significance action, escalating the quantities of advantageous Lactobacilli along with reduction of intestinal mucosal permeability [100]. The assessment of intestinal microbiota in young along with elderly mice was conducted separately. Identification of greater quantities of SCFAs along with the strains which generate in the feces were seen in young mice. Bacteria forming SCFAs(*Bifidobacterium longum,Clostridium symbiosum, Faecalibacterium Prausnitzii* along with *Lactobacillusfermentum)* transplantation caused an escalated intestinal mucosal intactness, escalated SCFAs in blood along with brain tissue, Escalated Treg in brain tissue decreased IL-17^{+}γδ T cells, decreased neuroinflammation, besides significantly enhanced behavior scores [101]As per Sadleret al.[102], multiple observations were noticeable i) reduction of quantities of SCFAs subsequent to strokeii)on artificial administration of SCFAs decreased the expression of CD68 in Iba-1^{+} along with caused reduction of microglia activation that decreased the

inflammatory reaction in the brain group subsequent to stroke. This in turn escalated synaptic plasticity in the semidark cortical zone, along with improvement of prognosis of stroke besides cortical reconstruction. This pointed that SCFAs generated by intestinal flora act in the form of basis of metabolites regarding the function of the gut brain axis .Besides complicated SCFAs, SCFAs species can work like butyrate by itself can confer neuroprotective actions.[103]. On liberation of bile in the intestine, metabolism of Bile Acid (BAs) into a pool of Bile Acids occur by the intestinal flora action. Subsequent to metabolism primary Bile Acids like cholic acid(CA), chenodeoxcholic acid(CDCA) Ursodeoxycholic acid(UDCA) are generated, followed by secondary Bile Acids like deoxycholic acid(DCA),lithocholic acid(LCA) get generated. These metabolites possess the capacity of binding different receptors in the brain, like Far Senoid Xreceptor(FXR)[104], TGR5(105), N-methyl-D aspartate receptor (NMDAR)[106], along with PXR[107], following which biological action gets exerted. TauroUrsodeoxycholic acid(TUDCA)injection 1h subsequent to ischaemia escalated quantities of intracerebral BAs), decreased the size of infarction besides reducing neuronal apoptosis by escalating mitochondrial stability. sustenance of this protective actions lasted for7d [108]. TUDCA possess the capacity of reduction of serum glutamate,TG,TC,LDL-C quantities, reduce the inflammatory factor expression, escalated super oxide dismutase (SOD), catalase(CAT), glutathione peroxidase(GPx) expression, decreased OS injury as well as downregulated nuclear factor erythroid-2-related factor-2((Nrf2) signaling pathway in addition to proapoptotic protein quantities in cerebral ischaemic rats,hence confer neuroprotective actions[109]. Taking into account the broad kind of metabolites along with their continuous invention,the part of other species of BAs in Ischaemic Stroke requires further evaluation. Additionally, the Induction of neuroprotective actions of advantageous BAs species is feasible by manipulating intestinal flora.

Microorganisms that express tryptophanase in the intestine transform tryptophan to indoles,that on binding to aromatic hydrocarbons receptors facilitates the expression of β-catenin, Neurog 2 along with VEGF-α as well as facilitates neurogenesis in the hippocampus[110].This is remarkably in agreement with the observations of Mohle etal. [111], that observed that antibiotics therapy decreased hippocampal neurogenesis along with memory generation in adult mice, nevertheless, adoptive shift of Ly6C(hi) monocytes rescued this damage. SCFAs in physiological quantities possess the capacity of facilitating the growth rate of human neural progenitor cells(hNPCs), besides cause Induction of mitosis [112]. Facilitating neurogenesis or neural stem cells regeneration(figure3) can promote neurological recovery subsequent to stroke, hence intestinal flora might further escalate stroke results by facilitating the neural stem cells regeneration(figure3).



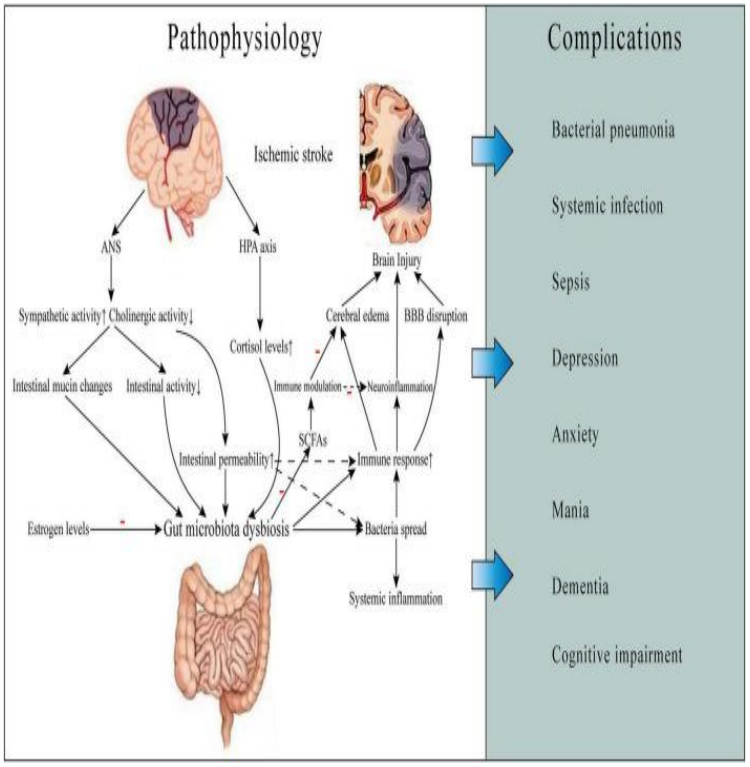
Courtesy ref no- 28 -Certain intestinal flora metabolites promote post-stroke recovery. Certain foods, such as high-fiber foods, can be metabolized by intestinal flora to produce SCFA, which is transported and absorbed by MCTs and enters the brain, reducing IL-17 + γδ T cells, diminishing activated microglia, and increasing synaptic plasticity; bile acids are transformed by intestinal bacteria into primary bile acids, which are then transformed into secondary bile acids and enter the blood or cross the blood–brain barrier, bind to receptors and upregulate SOD and GPX Tryptophan in food can be metabolized by enterobacteria to indole, which binds to intestinal mucosal aromatic hydrocarbon receptors and promotes the growth rate of human neural progenitor cells (hNPCs) by promoting β-catenin, Neurog2, and VEGF-α expression

7.Conclusions

Thus here we have summarized the alterations in gut microbiota(GM)that take place during IS.As we already know limited options of treating IS are available namely thrombolysis along with thrombectomy however a very short time window exists for same. Despite observing excitotoxicity, neuroinflammation along with oxidative stress (OS) working as the pathogenetic modes no clinical translation has been feasible. As earlier emphasized by us GM are implicated in the generation of unique immune abberations,metabolic abnormalities along with neurodegeneration(as reviewed by us earlier).Here we have further concentrated on the alterations in GM subsequent to ischemic stroke along with future utilization of this insight gained in treating IS besides getting biomarkers for prognosis

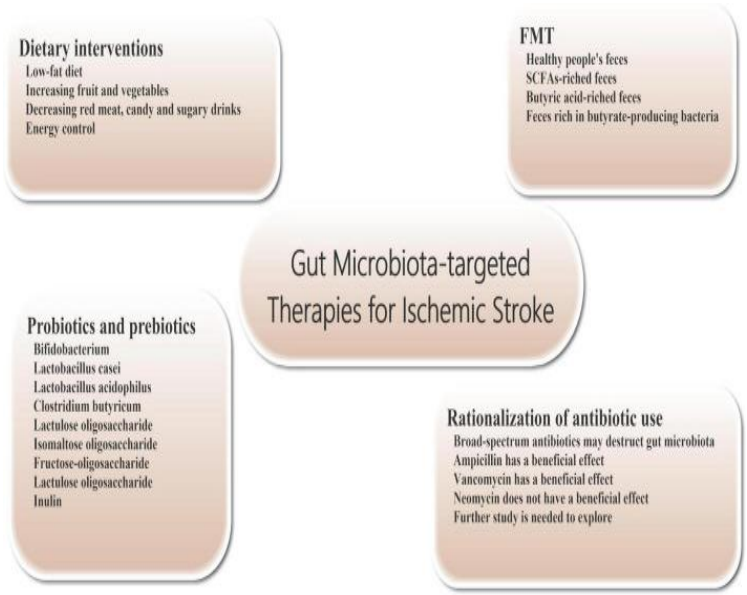
Additionally,as detailed earlier like age at initiation of stroke as well as gender[113-14],can further impact the results by influencing gut flora.MCAO, with the utilization of SD rats of separate genders documented that male SD rats displayed greater escalated intestinal mucosal permeability, greater escalated proinflammatory cytokines in the blood,having greater mortality in contrast to female SD rats[115]. In contrast to bacteria the part of fungi [116,117] in the gut has not been appropriately evaluated. Additionally,the name coined as the intestinal dark matter alias viruses[118](inclusive of phages)are further presumed to possess greater significance in the disease despite lesser research has been conducted in this field.Thus factors that possess the capacity of alteration of intestinal flora require refinement followed by integration overall in the future studies planned.Basically every organism is indistinguishably correlated with each other instead of having independent existence with the presentation of microbiota -gut-brain axis in this particular fashion .Thus the

evaluation on intestinal flora along with Ischaemic Stroke is presently in budding stage.We anticipate intestinal flora might become the newer target regarding nerve protection via multiple pathways in post stroke damage healing.Hence in future this intestinal flora targeting will have a significant part in primary as well as, secondary protection of Ischaemic Stroke[see figure4 &5 for details)[rev in ref 119].



Legend for Figure 4

Courtesy ref no-119-Gut microbiota-related ischemic stroke pathophysiology and complications. Ischemic stroke can cause gut microbiota dysbiosis, which may result in increased gut permeability and worsening brain injury, thereby leading to some complications such as infections and neuropsychiatric disorders and poor prognosis. The mechanisms involved include neuroendocrine pathways, bacterial metabolite, and immune response. ANS, autonomic nervous system; HPA, hypothalamic-pituitary-adrenal; BBB, blood-brain barrier; SCFAs, short-chain fatty acids.



Legend for Figure 5

Courtesy ref no-119-Gut microbiota-targeted treatments and managements for ischemic stroke. Gut microbiota-targeted treatments and managements can be considered for patients with ischemic stroke, including dietary interventions, probiotics and prebiotics supplementation, FMT, and rationalization of antibiotic use. FMT, fecal microbiome transplantation.

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