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Review Article on Microbiota Gut Brain Axis

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Abstract: *It has long been understood how crucial the gut-brain axis is to preserving homeostasis. However, the microbiota—the trillions of bacteria on and within our bodies—has emerged in the last 15 years as one of the major regulators of gut-brain function, which has led to an understanding of the significance of a unique microbiota-gut-brain axis.and psychiatric illnesses are increasingly adopting this axis. Through a variety of pathways, including the immune system, tryptophan metabolism, the vagus nerve, and the enteric nervous system, the microbiota and the brain can interact. These pathways involve microbial metabolites such peptidoglycans, short-chain fatty acids, and branched chain amino acids.Numerous factors, such as illness, the way a is born, the use of antibiotics, the type of nourishment that is given, environmental stressors, and host genetics, can affect the composition of the microbiota in the early stages of life. On the other hand, as people age, their microbial diversity decreases. Throughout life, stress in particular can have a major effect on the gut-brain-microbiota axis. Recent research has linked a wide range of illnesses, including schizophrenia, Parkinson's myelination, animal models have proved crucial. Furthermore, the field will be substantially improved by continuing translational human investigations. Future research will try to clarify microbial-based intervention and therapy approaches for neuropsychiatric illnesses, as well as the mechanisms behind the microbiota-gut-brain axis.*

Keywords: brain-gut; microbiome; neurogastroenterology; second brain; stress

I. INTRODUCTION

The central nervous system (CNS) involves two-way communication . The gut microbiota's ability to influence the gut-brain axis has drawn a lot of interest lately. While "commensals" are germs that colonize a host without causing illness, "microbiota" refers to groups of microorganisms that live in a specific habitat.The variety of human microbiota has been better understood thanks to the development of omics technologies like metagenomics, which can identify DNA isolated from a particular environment, and culturomics, which can culture and identify an unknown bacteria . The following queries can be addressed as a result of improvements in microbiome research methodology: Which microorganisms make up the microbiota? Are there notable variations in alpha- or beta-diversity between experimental groups? Whereas beta-diversity describes the variation between samples, alpha-diversity describes richness (the number of taxa) or eveness (the abundance of texa) inside a sample. lastly do each group have biomarkers

In relation to neuropsychiatric illnesses, there has been a growing interest in finding answers to such concerns. A paradigm shift in neuroscience has been characterized by the discovery that the gut microbiota influences the gut-brain axis, which has provided fresh insight into the pathophysiology of illnesses , . Inflammation and psychological stress are frequent indicators of the pathophysiology of illnesses where microbiota may be involved. While inflammation is linked to depression , schizophrenia , autism spectrum disorder (ASD) ,Parkinson's disease , epilepsy and migraine , stress is linked to depression , schizophrenia , autism spectrum disorder [ASD] epilepsy , migraine , moreover the disorders listed above frequently coexist. ASD and depression for instance are frequent comorbidities in epilepsy .Migraines and depression frequently coexist . Additionally, gastrointestinal disorders such irritable bowel syndrome (IBS) and inflammatory bowel disease are more common among migraineurs.In order to present a current framework in this quickly developing field of study, we sought to compile information on the role of the microbiota-gut-brain axis in the pathophysiology of neuropsychiatric and neurological disorders, specifically depression, schizophrenia, ASD, Parkinson's disease, epilepsy, and migraine.

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1. Gut Brain Axis :-

The GI tract affects brain function, as was previously mentioned, and vice versa (see also sect. IV). Prior research on gut-brain communication mostly focused on satiety and digestive function, but more recent studies have focused on the higher-order cognitive and psychological impacts of gut-to-brain and brain-to-gut communication. We now have a better understanding of some of the pathophysiological effects of an abnormal reciprocal gut-brain network, such as altered reactions to acute and chronic stress, altered behavioral states, and worsened gut inflammatory problems Because of this, the gut-brain axis is a desirable target for the creation of new treatments for an increasing number of conditions affecting mental health and cognitive function, obesity, and gastrointestinal illnesses such inflammatory bowel disease (IBD) and IBS. It is anticipated that new illness treatments may be made possible by better targeting of the gut-brain axis, such as by using psychobiotics (targeted microbiota interventions that promote mental health

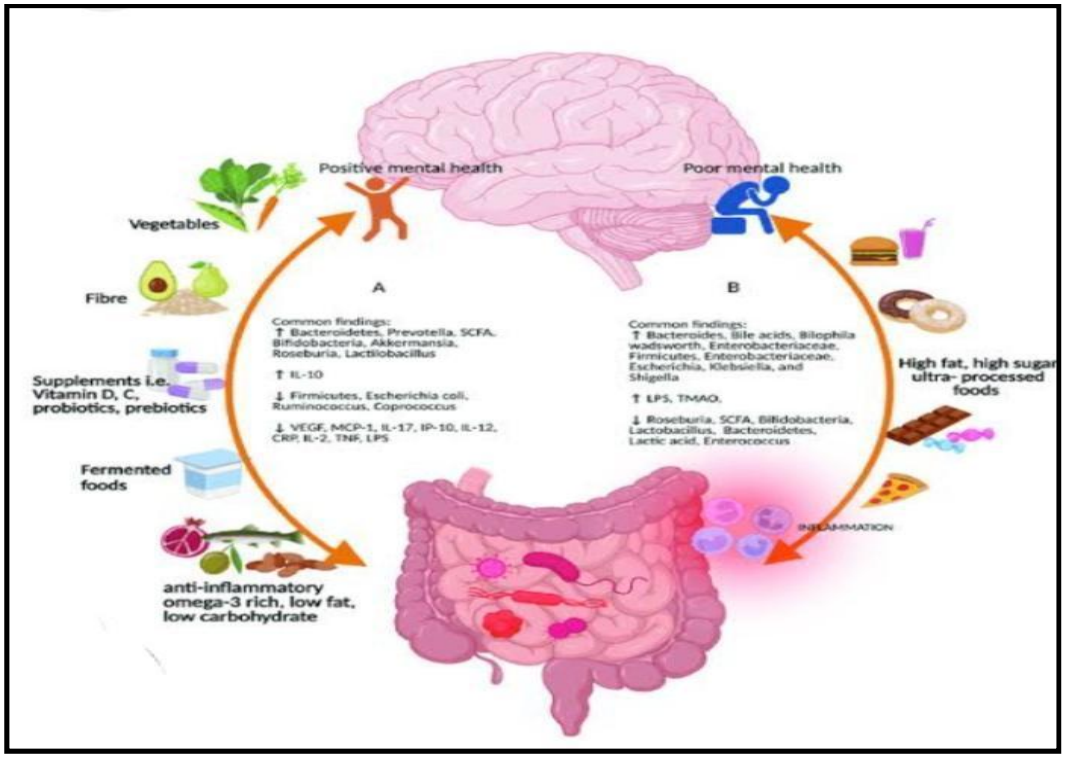

Fig. no.1

2. Microbiota Gut Brain Axis :-

The disciplines of neuroscience and microbiology have grown more intertwined in recent decades. It is becoming more widely acknowledged that the resident microbiota can have a significant impact on host behavior, even though the idea of a microbiota-gut-brain axis is still relatively new. We will demonstrate this in sections VI (Behavior and the Microbiota-Gut-Brain Axis) and VIII (Diseases and Disease Processes). A key component of the microbiota-host synergy in accessing gut-brain signaling pathways to modify the host's brain and behaviour is bidirection communication along the gut brain axis

GF rodents (see), antibiotic-induced depletion, prebiotic/probiotic supplementation GI infection, and fecal microbiota transplantation (FMT) (see sect. IIC) are some of the distinct but complementary microbiota interventions used in the studies to identify and investigate the microbiota-gut-brain axis. All of these will be covered in more detail in section IV.

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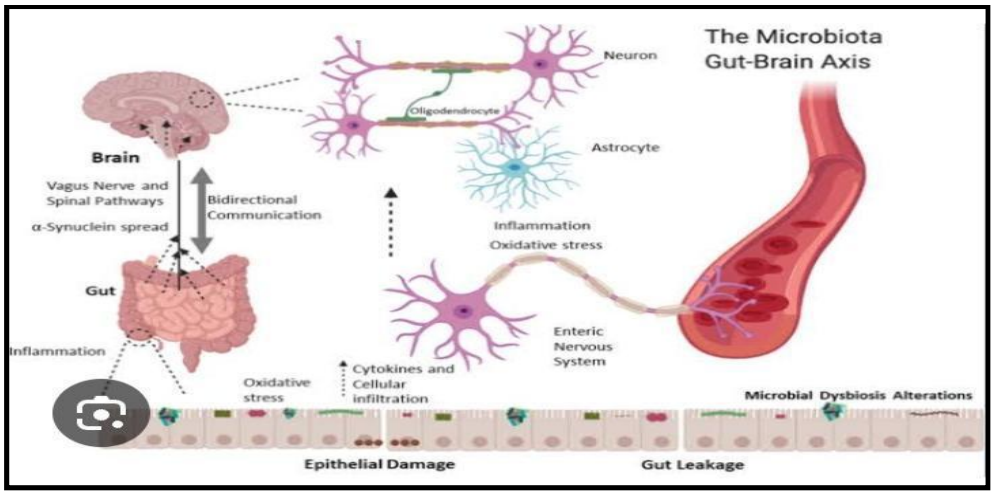

Fig.no.2

3. Role of intestinal microbiota in the hostel organism :-

The intestinal microbiota serves a variety of vital purposes in the macroorganism. In the first place, it keeps the intestines functioning properly by maintaining a healthy pH, normal intestinal peristalsis, and a regular bowel movement rhythm. By secreting digestive enzymes, breaking down complex nutrients into simpler organic compounds, and promoting fat metabolism, microorganisms that colonize the intestines not only aid in food digestion but also aid in the absorption of food that has been broken down. Apart from the aforementioned roles, the gut microbiota is in charge of vitamin synthesis, primary group B vitamin intestinal microbes generate short chain fatty acids (SCFAs) by anaerobic fermentation of indigestible carbohydrates mostly dietary fiber. These SCFAs serves as the main energy source for colonocytes which are colon epithelial cells.

The most crucial component in nourishing these cells is butyric acid, which also plays a significant role in promoting their proliferation and differentiation [19]. The intestinal microbiota's ability to neutralize poisons and carcinogens is another crucial function. Additionally, intestinal microbes produce the intestinal barrier, which shields the macroorganism from harmful substances.. It should be noted that the intestinal microbiota has a major impact on the immune system's activity and operation. It is thought to be the largest lymphatic organ in the human body, has immunomodulatory properties, and interacts with the digestive tract's lymphatic tissue to control cytokine levels [22]. Considering the aforementioned, it is undeniable that any disruptions in the quantity and makeup of the intestinal microbiota (intestinal dysbiosis) result in a variety of abnormalities, including disruptions of intestinal peristalsis, problem with digestion and absorption problem with vitamin production or metabolism and trouble digesting fats additionally the intestinal barrier is destroyed and the immune system is overstimulated were brought up in a completely sterile environment with no intestinal microbiota, and investigations on the application of probiotic and antibiotic therapy, fecal microbiota transplantation (FMT), and infectious research.

4. Factors affecting gut microbiota :-

4.1 Mode of delivery :-

Bidirectional communication between GM and the central nervous system (CNS) starts during intrauterine life and is influenced by a variety of internal and external factors, including the host's circadian rhythm, lifestyle choices, living arrangements (rural or urban), food and medication consumption, and vaginal or caesarean delivery.

Delivery Method Although some research show that the newborn microbiota colonization begins in utero, it has long been believed that the "sterile womb dogma" states that the human fetus is sterile until delivery and that microorganisms begin to colonize the human GI after birth . Its transport from the mother's gut into the bloodstream and placenta may be linked to the infant's colonization by Escherichia coli, Enterococcus fecium, and Staphylococcus

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epidermidis . The microbiota found in the placenta and the amniotic fluid environment was described by Collado et al. as having low richness and diversity, with Proteobacteria predominating.

The technique of delivery has a significant impact on how the GI tract colonizes babies . Despite the absence of medical guidelines, the number of cesarean sections (CS) performed globally has risen in recent decades. Over 50% of births in some nations take place in this manner . According to research, the intestinal microbiota of vaginally delivered (VD) babies seems to have a similar makeup to the mother's vaginal microbiota: Lactobacillus predominates, followed by Senathia species and Prevotella, the majority of which are anaerobic bacteria. CS causes the gut microbiota of infants to become unbalanced and less diverse. The hospital setting and the mother's skin serve as their initial points of contact because they are deprived of the chance to interact with the maternal vaginal microbiota.

The way the GI tract colonizes infants is greatly influenced by the delivery method . The number of cesarean sections (CS) performed worldwide has increased in recent decades despite the lack of medical guidelines. In certain countries, more than half of births occur in this way . Research indicates that the intestinal microbiota of kids born vaginally (VD) appears to be comparable to the mother's vaginal microbiota: Lactobacillus is the predominant anaerobic bacterium, followed by Senathia species and Prevotella. Infants with CS have an imbalanced and less diversified gut microbiome.

Their first interaction is with the mother's skin and the hospital setting because they are unable to interact with the mother's vaginal microbiota. This has led to the discovery of hospital-associated infections (Klebsiella, Enterobacter, and Enterococcus) in their intestines . In the intestinal microbiota of the baby born via caesarean section, Bifidobacteria, Bacteroides, Staphylococcus, Corynebacterium, and a Propionibacterium species are less prevalent. Lactobacillus, Prevotella, Sneathia spp., and Clostridium difficile were identified in greater amounts than in children with VD .

It should be noted that dysbiosis and an elevated risk of obesity may result from a large abundance of C. difficile . Because of the proper development of the brain, immune system, and metabolism in the subsequent stages of life, GM colonization thus seems to be important for the infant's health and development. It's interesting to note that feeding practices can also affect the development of particular bacterial strains in the infant's GM. For instance, Bifidobacterium longum competes with Clostridium perfringens and E. coli by using oligosaccharides in mother's milk .Additionally, Lactobacillus acidophilus LB may lessen necrotizing enterocolitis in preterm newborns, according to primary investigations . To guarantee the best possible microbial colonization of the newborn's intestine, additional study on probiotic, prebiotic, and synbiotic supplements in the infant meal is necessary . Additionally, there is evidence that stress, a pregnant woman's vaginal microbiota, and the development of her unborn child's nervous system are related . By altering the makeup of the vaginal microbiota, stress exposure during pregnancy may have an impact on the development of the offspring's nervous system.This causes disruptions in the intestinal microbiome's development in a baby, which impacts not only the digestive system's growth and operation but also the immune and neurological systems .

4.2 Probiotics *:-*

Probiotics are currently being used to treat mental, neurological, and developmental diseases, such as depression, anxiety, autism, schizophrenia, or bipolar disorder, where increased intestinal permeability has been shown [50]. Probiotic microbes work by regulating the immune system, producing SCAFs, or maintaining the integrity of the intestinal barrier, among other things [51]. The variety and specificity of probiotic strains' effects on the brain were demonstrated by numerous research. Huang et al.'s meta-analysis [52] found that probiotic use considerably reduced the symptoms of depression in those who had it. The research conducted by Messaoudi et al.In a study involving a group of healthy human volunteers, it was demonstrated that taking probiotics containing Lactobacillus helveticus R0052 and B. longum R0175 for 30 days reduced anxiety and depression symptoms, as evidenced by lower Hospital Anxiety and Depression Scale (HADS) scores than the placebo control group. According to another investigation, several bacteria, including Streptococcus thermophilus, Lactobacillus bulgaricus, Bifidobacterium animals lactis, Bifidobacterium longum, Bifidobacterium helveticus, and Lactobacillus lactis, lower stress levels and lessen depressive symptoms [54]. Additionally, children with ASD were also shown to benefit from probiotic use. Critchfield and associates.demonstrated how probiotic supplements can reduce inflammation and improve behavioral issues in kids with ASD. The effects of probiotics on SCZ in the human model have not been well studied. However, it should be

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mentioned that Severance et al. [56] suggested a link between dietary antigen-associated immune activation and gastrointestinal inflammation in SCZ patients. Additionally, a study by Ghaderi et al. [57] found that probiotic strains like Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus acidophilus, and Bifidobacterium bifidum (2 × 109 each) were beneficial for the general and total PANSS (Positive and Negative Syndrome Scale) score when vitamin D was administered to patients with SCZ for 12 weeks.There is a temptation to investigate the topic of the influence of probiotic strains and prebiotics on the development and course of SCZ, even though the influence of prebiotics on SCZ does not explain the molecular mechanism of action and research in this area does not provide crystalline and unambiguous conclusions. Scientists have lately brought up the intriguing question of how probiotics affect mood enhancement during COVID-19. In addition to reestablishing intestinal equilibrium, probiotics lower the chance of opportunistic infections colonizing the intestine [58]. Rogers et al. [59] state that

An infection with COVID-19 may cause PTSD (posttraumatic stress disorder). Intestinal nutrition transport is disrupted by the dysbiosis of the gut microbiota caused by SARS-CoV-2 infection [60]. Gu et al. [61] demonstrated that, in contrast to healthy patients, patients with COVID-19 and H1N1 had a decrease in beneficial symbionts and an increase in opportunistic pathogens like Streptococcus, Rothia, Veillonella, and Actinomyces. Thus, research showing the effects of probiotic supplementation on COVID-19-induced depression may out to be very beneficial. According to a survey by d'Ettorre et al. [62], patients with COVID-19 who took a special probiotic formulation (three doses of 2400 billion bacteria each day) had a lower chance of developing a severe phase of the illness.Streptococcus thermophilus DSM 32345, Lactobacillus acidophilus DSM 32241, Lactobacillus helveticus DSM 32242, Lactobacillus paracasei DSM 32243, Lactobacillus plantarum DSM 32244, Lactobacillus brevis DSM 27961, Lactobacillus lactis DSM 32246, and Lactobacillus lactis DSM 32247 were the components of this formulation. However, there were no appreciable differences in recognized stress or indicators of viral disease among nurses who took the probiotic Lactobacillus rhamnosus HN001 for 12 weeks during the 2020 pandemic year in New Zealand, according to a study by Slykerman and Li [63]. Additionally, it should be mentioned that probiotic supplements have certain restrictions; for instance, individuals who are immunocompromised and receiving corticosteroid treatment are not advised to use them [64].Although there are no global approved ordinances on probiotic supplementation of probiotics in patients with COVID-19, probiotics could potentially find application in the prevention and complementary therapy of this disease.

4.3 Stress :-

A correlation between stress and alterations in the quantity and makeup of gut microbiota has also been demonstrated by a number of reviews. It has been demonstrated that stress drastically reduces the amount of Bifidobacterium and Lactobacillus species in humans. The quantity of bacteria from the genus Clostridium spp. rose in mice under stress, whereas the number of Lactobacillus species decreased [65]. However, the number of harmful and non-pathogenic strains of E. coli rose, possibly as a result of the generation and secretion of catecholamines, adrenaline, and norepinephrine.According to the majority of psychological theories, stress and the likelihood of contracting a physical or mental illness are clearly related. For instance, it has been shown that sadness and disruptions brought on by stressful stimuli, particularly those that have long-term impacts, are significantly correlated [66,67]. Numerous stressors raise the incidence of mental illnesses such affective and anxiety disorders, particularly in children. The mechanism underlying this phenomena heavily relies on the hypothalamic-pituitary-adrenal axis (HPA) malfunction. Corticotropin-releasing hormone (CRH), sometimes referred to as corticotropin-releasing factor (CRF) or corticoliberin, is linked to an increase in its release [31].Arginine vasopressin (AVP), released simultaneously with CRH during stress, operates synergistically. Thanks to discovering the directions and mechanisms of CRH activity, the knowledge about the endocrine system's participation in the etiopathogenesis of depression and how antidepressants work has expanded [68]. CRH plays a critical function in the body's reaction to stress stimuli, boosting the release of adrenocorticotropic hormone (ACTH) and cortisol [69]. Additionally, it has strong psychotropic effects, with anxiety and depression being the most common reactions, along with disruptions in sleep and nutrition regulation [70].In order for the neurological and endocrine systems to carry out regulatory tasks in the body, they must also form an inseparable, complementary, and mutually interacting structural and functional whole [71]. Increased activity and dysregulation of the limbic–hypothalamic–pituitary–adrenal (LHPA) axis, as well as disruption of serotonergic (5-HT, 5-hydroxytryptamine)

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transmission, are also noted in depression [72]. Serotonin and glucocorticoids, two previously distinct theories of depression, appear to be related because these phenomena most likely play a significant role in their pathogenesis.These alterations, which include a decrease in cell count and a weakened neurogenesis and neural plasticity process, mostly impact the structures of the hippocampus and prefrontal cortex [73]. According to the aforementioned overview, genetic and molecular research findings, and neurobiological information gleaned from biochemical and neuroimaging investigations, depression appears to be well understood in terms of its etiopathogenesis, management, and therapeutic approaches. However, more and more people suffer from this serious disease, resulting to a considerable decline in patient quality of life and many suicide attempts. Thus, new theories of affective disorders may emerge in the near future, enabling a fresh perspective on the etiology and management of these conditions.

4.4 *Circadian Clock System*

The relationship between the host's circadian rhythm and gut bacteria is another intriguing feature. Most organisms have an innate rhythm called the circadian rhythm, which coordinates several bodily functions [74]. A central circadian clock, housed in the hypothalamic suprachiasmatic nucleus (SCN), and peripheral circadian clocks, found in organs such the kidneys, skeletal muscles, liver, heart, pancreas, and intestine, make up the circadian clock system. Phase shifting (jet lag), shift work, light, sleep, dietary nutrition, and stress can all have an impact on GM's diurnal oscillations [75,76,77].As described in Section 3.3, stress has a tremendous effect on the human organism and causes dysregulation of the intestinal microbiota. Galley et al. [78] revealed that exposure to even 2 h of a social stressor, often known as social disruption, can change microbial populations of the colonic mucosa. The alterations included the decrease in relative and absolute abundance of the species Lactobacillus, which has immunomodulatory effects in the colon, and probiotic efficacy in reducing inflammation. Circadian rhythm has been linked to metabolic and mental health issues, according to some researchers [74].The disruption of the circadian clock system causes brain signals to synchronize the gut's peripheral clock, which in turn leads to bacterial translocation, inflammation, and dysbiosis of the gut microbiota, all of which increase the risk of metabolic disorders [79]. Shift work or evening chronotype (desire for evening activities) have been linked to higher frequency or aggravation of BD and MDD [81], according to Takaesu [80]. Additionally, some research show that "clock genes" including Per, Cry, Bmal1, and the host bacteria's clock regulate human behavior in a circadian fashion. Melatonin, which is secreted in the GI tract, increased the amount of swarming in Enterobacter aerogenes cultures, according to Paulose et al. [76].This commensal bacterium occurs in the human GI tract. Although the precise mechanism for this synchronization remains not fully understood, the data obtained illustrate that the circadian system of the host may regulate its microbiome through signals from bacterial clocks. The gut microbiota plays a crucial role in the liver's clock reprogramming and circadian homeostasis [82]. Murakami et al. [83] demonstrated that, as a result of a high-fat diet (HFD), GM stimulates through peroxisome proliferator-activated receptor-γ (PPARγ) transcriptional reprogramming in the liver.

4.5 Occupational and Environmental Exposure

Another factor influencing GM is occupational exposure at work. Based on the earliest publications, researchers have focused mainly on workers in cotton textile and livestock farmers' factories [84].Because people work for the majority of their lives, occupational exposure to physical, chemical, and biological dangers at work has a significant role in shaping the microbiota [85]. The review by Mucci et al. [75] found that exposure to biological agents (direct contact with animals and healthcare workers) and chemical agents (metalworking fluids, dust, and pesticides) as well as the pressure of work and altered eating habits due to long travel times and microclimate conditions were the most harmful agents causing changes in workers' microbiomes. Streptococcus gordonii and Klebsiella pneumoniae, for instance, have increased in the microbiome of sailors following a 30-day sea cruise [86]. According to the shift workers, an intriguing outcome was achieved.Workers on the day shift had high levels of Faecalibacterium [79]. These investigations, which show variations in the makeup of microbiomes and the presence of particular genera, may be used as biomarkers for the diagnosis and health monitoring of employees [75]. The risk of environmental pollutants came from human activity, agriculture, and industry in addition to occupational exposure. Heavy metals, pesticides, herbicides, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls (PCBs) are examples of xenobiotics (exogenous compounds)

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[87]. Environmental heavy metals have the ability to alter GM's composition, which can have an impact on human health [88]. The dose and age of exposure to the pollutants determine how xenobiotics affect the brain and microbiota. Voorhees et al. [89] claim that early exposure to the organophosphate insecticide chlorpyrifos (CPF) increased the incidence of Alzheimer's dementia (AD) in both males and females by causing persistent microglial dysregulation and accelerating neurodegeneration. However, microbes have evolved a number of systems that allow for biotransformation. However, end- or by-products of such reactions can occasionally be more harmful than the original molecule [20]. Smoke from cigarettes and grilled meats contain PAHs, which are created when trash and fuels are not completely burned. It has been demonstrated that smokers have a higher proportion of the phylum Bacteroidetes and a lower fraction of the phylum Firmicutes and Proteobacteria than nonsmokers.

However, it takes some time for the GM to change after quitting smoking, but eventually it returns to its non-smoking condition. Because of this, the best way to treat disorders associated with altered GM composition is still to stop smoking [90,91].

4.6 Diet :-

Diet is one of the main variables influencing gut microbiota diversity and abundance while also fostering immune responses [92]. Vitamins, minerals, polyunsaturated fatty acids (PUFAs), and amino acids are among the dietary components that are essential for preserving the structure and functionality of the brain. They take involvement in the creation of neurotransmitters, glucose and lipid metabolism, cell signaling, and other metabolic pathways [93]. SCFAs are byproducts of the microbiota's metabolism of nutrients that are supplied to the host through food, particularly dietary fiber (more on this in Section 4.6). According to a study by Parletta et al. [93], as compared to control conditions, the Mediterranean diet (MedDiet) enhanced with fish oil can lessen depression symptoms.There was discussion of data showing that vegetarian and vegan diets have an effect on depression. Of the studies that were examined, 44% of the findings showed a link between vegetarian and vegan diets and an increased risk of depression. In contrast, 28% of studies found no link between vegetarian and vegan diets and depression, whereas 28% of records demonstrated the benefits of these diets on MDD. Therefore, more research is required as the evidence regarding the impact of vegetarian and vegan diets on depression is still equivocal. The ketogenic diet, a low-carb, high-fat diet that encourages the body to burn fat, is another example [95].Numerous clinical trials have demonstrated that a ketogenic diet can help people with AD by lowering their blood ketone levels, which enhances memory and cognitive function [96]. Interestingly, there is also a theory that lean and obese people have different ratios of Firmicutes and Bacteroidetes in their fecal microbiota [97]. However, when obese people follow reduced-carb diets for weight loss, Duncan et al. [98] found no discernible change in the Bacteroidets ratio in their fecal samples.Furthermore, this analysis confirmed that response to diet (especially amount and type of carbohydrate) decreased the proportions of *Roseburia* and *Eubacterium rectale* group, responsible for butyrate production and probably colonic health maintenance. Therefore, the described changes of GM determined by diet affect the proper work of the colon and whole human metabolism, and further studies can better understand these dependencies.

5.Gut microbiota and neurological disorders :-

Alterations in gut microbiota composition are linked to neurological and neuropsychiatric illnesses (Cryan et al., 2019; Tian et al., 2023). Problems affecting the brain, spinal cord, cranial and peripheral nerves, autonomous nervous system, nerve roots, and neuromuscular plaque are referred to as neurological disorders. Brain bleeding can result from a variety of ailments, such as blood vessel diseases, disorders resulting from problems with the development of the nervous system, brain or spinal cord injuries, and brain malignancies (Dugger and Dickson, 2017).

The development of amyloid plaques and an inflammatory response in microglia are two of the most prominent characteristics of Alzheimer's disease (AD), a group of brain dysfunction syndromes brought on by ongoing or progressive organic damage to brain structures. 11. It is now widely acknowledged that patients have deposits of β-amyloid (Aβ) in the brain, which lead to the development of senile plaques, hyperphosphorylation of Tau protein, which causes neurofibrillary tangles (NFTs), and loss of neurons, along with the proliferation of glial cells and, ultimately, progressive cognitive decline and behavioral abnormalities.

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On the other hand, the microbiota compositions of neurological illness patients and healthy controls differ significantly (Sampson et al., 2016; Blacher et al., 2019; Valles-Colomer et al., 2019). Crucially, neurodevelopmental (like ASD), neurodegenerative (like PD and AD), and behavioral (like depression and anxiety) disorders all exhibit communication along the gut microbiota–brain axis throughout childhood (Figure 1). Recent studies in humans and animals, the majority of which were association studies, have shown that changes in microbial diversity are associated with adverse health outcomes and may result in changes in the central nervous system (CNS) (Table 1), which are linked to anxiety, depression, and ASD (Felice and O'Mahony, 2017).

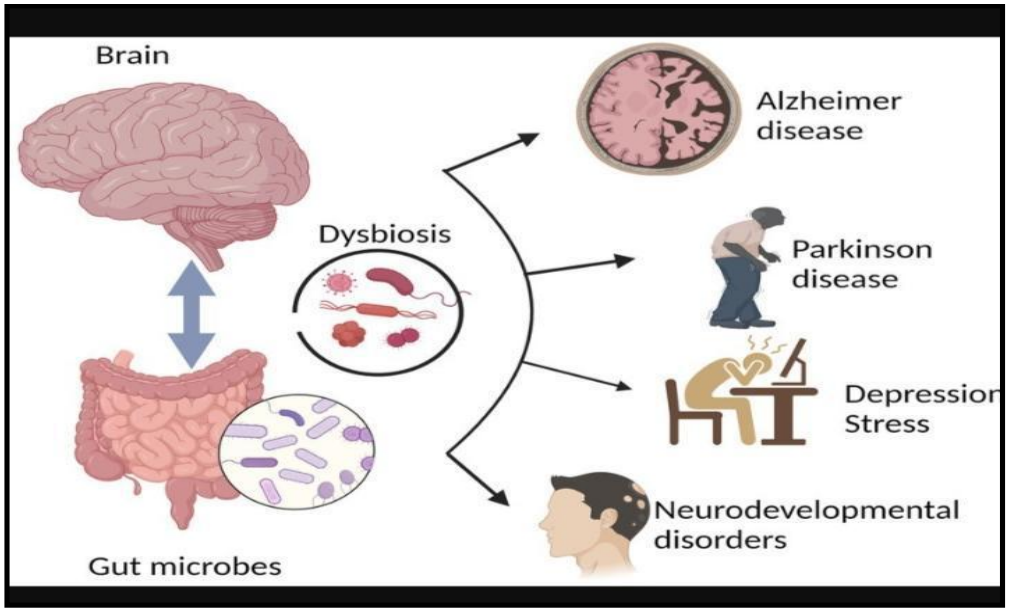

Fig no.3

Alterations in gut microbiota composition are linked to neurological and neuropsychiatric illnesses (Cryan et al., 2019; Tian et al., 2023). Problems affecting the brain, spinal cord, cranial and peripheral nerves, autonomous nervous system, nerve roots, and neuromuscular plaque are referred to as neurological disorders. Brain bleeding can result from a variety of ailments, such as blood vessel diseases, disorders resulting from problems with the development of the nervous system, brain or spinal cord injuries, and brain malignancies (Dugger and Dickson, 2017). Dysbiosis of the human gut microbiota is linked to a wide range of neurological disorders (Frank et al., 2007; Bibbo et al., 2017; Gavin et al., 2018; Kasselman et al., 2018; Duan et al., 2019).Additional connections between the composition of the microbiota and ASD, depression, and anxiety have been documented by several studies (Bercik et al., 2010; Sekirov et al., 2010; Claesson et al., 2012). As a result, changes in the microbiota's makeup over time may affect how the brain functions. We examine new advances in neuromicrobiology in this Perspective, with a focus on the connections between neurological disorders and gut microbiota. We specifically examined ASD, AD, PD, depression, and anxiety disorders in order to investigate the function that gut microorganisms play in neurological illnesses.

5.1 Alzheimer's disease :-

About 50 million people worldwide suffer with Alzheimer's disease (AD), which is the most common cause of progressive, chronic, irreversible neurological disease and the most prevalent form of dementia in the elderly. Even the most fundamental daily activities may become substantially compromised when the illness worsens due to symptoms that affect thinking and memory (Scheltens et al., 2016; Rutsch et al., 2020). AD symptoms include neuronal loss and increasingly severe synaptic dysfunction (Tiraboschi et al., 2004; Alzheimer's, 2016).According to Scheltens et al. (2016), AD is brought on by the accumulation of polymerized forms of β-amyloid precursor protein (Aβ) in soluble multimeric and/or insoluble amyloid deposits in the brain. These deposits set off a series of pathological events that

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result in the development of neurofibrillary tangles, aggregates of hyperphosphorylated tau proteins, neurofibrillary lesions, and dementia. Since increased expression of IL-1β and IL-18 has been seen in the microglia, astrocytes, and neurons surrounding Ab plaques or in the plasma of AD patients, the inflammasome and its byproducts have been linked to the pathophysiology of AD (Malaguarnera et al., 2006; Ojala et al., 2009).Additionally, AD patients' peripheral blood mononuclear cells (PBMCs) had higher levels of NLRP3, ASC, caspase-1, caspase-5, IL-1β, and IL-18 (Saresella et al., 2016). Cleaved caspase-1, ASC, and mature IL-1β are often elevated in the cortex of patients with tauopathies, neurodegenerative illnesses marked by the buildup of abnormal tau protein in the brain (Ising et al., 2019). There is strong evidence that the NLRP3 inflammasome-induced neuroinflammation contributes to the onset and progression of AD. Numerous microbiological factors have been linked to the etiology of AD (Atarashi et al., 2011; Geuking et al., 2011).Stool samples from AD patients had lower levels of Firmicutes and Actinobacteria and higher levels of Bacteroidetes when compared to controls. AD patients had lower abundances of the Firmicutes families Ruminococcaceae, Turicibacteraceae, and Clostridiaceae (Vogt et al., 2017). According to several studies, there may be mechanistic links between the pathophysiology of AD and other microbes, such spirochaetes, fungi, and Chlamydia pneumoniae (Lim et al., 2014; Stojkovi et al., 2020).The gut microbiota has also been linked to the etiology of AD in recent studies. A metabolite microbiota-derived protein found in the cerebral fluid of AD patients and linked to two disease-related biomarkers (phosphorylated tau and phosphorylated tau/A-42) suggests that the gut microbiome may be involved in the etiology of AD (Vogt et al., 2018). When comparing fecal microbiomes and fecal SCFAs between AD-affected mice and wild-type mice at different ages, AD mice showed marked decreases in Butyricicoccus and Ruminococcus and dramatic increases in Proteobacteria and Verrucomicrobia, indicating altered microbiota diversity and composition. The decreased level of SCFAs also suggests changes in numerous metabolic pathways (Zhang et al., 2017).It was shown that the gut microbiota diversity of the widely used APP/PS1 double transgenic mice, which produce a mutant human presenilin 1 (PS1) and a chimeric mouse/human amyloid precursor protein (APP), was significantly altered in comparison to non-transgenic wild-type animals. Furthermore, germ-free APP/PS1 transgenic mice exhibit a markedly lower level of cerebral β-amyloid pathology in comparison to healthy control mice with gut microbiota (Harach et al., 2017). Similar results about the change in microbiota composition in the transgenic APP/PS1 mouse model, which exhibits higher numbers of the closely related inflammatory Erysipelotrichaceae family, were published by Bäuerl et al. (2018). Additionally, compared to ordinary mice, germ-free APP/PS1 mice displayed less amyloid pathology (Radde et al., 2006).

5.2 Parkinson's disease :-

The second most common neurodegenerative disease after AD is Parkinson's disease (PD), which affects around 1% of the aged population and 0.3% of the general population globally (Tysnes and Storstein, 2017). The incapacity to regulate voluntary movements due to significant changes in the substantia nigra and striatum's function is a hallmark of Parkinson's disease (PD), a progressive neurodegenerative illness. According to Blancdini et al. (2000), these changes include the death of dopaminergic neurons, the build-up of phosphorylated forms of the neuronal protein α-synuclein (αSyn), mitochondrial dysfunction, an overabundance of reactive oxygen species, and an increase in microglia activation.Two important pathogenic processes that underlie α-synucleinopathies like Parkinson's disease are inflammation and α-synuclein misfolding (Lema Tom et al., 2013). The buildup of α-synuclein is a major factor in the pathophysiology of Parkinson's disease. The 140 amino acid protein known as α-synuclein is found on chromosome 4q21.3-q22 and contains five exons (Mehra et al., 2019). Tremors, difficulty walking, a stooped posture, and muscle rigidity are all signs of Parkinson's disease. Up to 80% of patients with Parkinson's disease may experience digestive problems, most commonly constipation (Chen et al., 2015), which can occur years before PD is diagnosed (Cersosimo et al., 2013).

The high-throughput sequencing techniques, and features of the altered microbiota profiles in PD patients have been found (Zhu et al., 2022). Numerous earlier studies found that PD patients had higher α-diversity but lower bacterial diversity than healthy people (Qian et al., 2018; Barichella et al., 2019). Additionally, one study revealed that there were differences in β-diversity (between samples) between PD patients and controls (Boertien et al., 2019). There has been a connection between the clinical characteristics of PD and the decline in bacterial diversity, which is primarily

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assessed using α-diversity indexes such as Shannon and Simpson. According to a recent study by Heinzel et al. (2021).Certain symptoms of Parkinson's disease (PD), such as constipation, subthreshold parkinsonism, smoking, urate levels, physical inactivity, and potential RBD, may be especially linked to the prodromal microbiome. Constipation, occupational solvent exposure, and smoking were all associated with β-diversity, in contrast to sex, inactivity, suspected RBD, constipation, and smoking. Both α and β-diversity were associated with age and urate-lowering drugs (Heinzel et al., 2021). However, α-diversity in the gut microbiota is not a biomarker of Parkinson's disease, according to studies by Plassais et al. (2021).The intestinal neural plexus may be exposed to toxins like lipopolysaccharide (LPS) and pesticides due to intestinal permeability and inflammation brought on by the gut dysbiosis linked to Parkinson's disease (PD), such as decreased SCFA-producing bacteria and increased Akkermansia. This can result in abnormal α-synuclein fibril aggregation and the formation of Lewy bodies (Hirayama and Ohno, 2021). The microbiome makeup of individuals with Parkinson's disease (PD) differs from that of those with other neurological disorders or those in good health (Hasegawa et al., 2015; Keshavarzian et al., 2015; Scheperjans et al., 2015).The intestinal flora of patients with Parkinson's disease (PD) is deficient in bacteria that produce SCFAs (primarily butyrate), such as Faecalibacterium prausnitzii (Keshavarzian et al., 2015; Unger et al., 2016) and taxa from the Lachnospiraceae family (Hill-Burns et al., 2017; Petrov et al., 2017; Barichella et al., 2019). Furthermore, PD-like illness may be brought on by specific bacterial species, such as Proteus mirabilis, which impairs mice's motor skills (Choi et al., 2018). To monitor the progression of the illness and describe alterations in the taxonomic makeup of the microbiome that either influenced or might have defined the clinical state, prospective long-term longitudinal microbiome studies are necessary. The exact mechanism by which the gut microbiota may influence Parkinson's disease symptoms is still unknown.

5.3 Anxiety and Depression :-

A quarter of the world's population suffers from mental and neurological conditions like anxiety and depression. Given that 90% of those with anxiety disorders and 85% of those with depression suffer significant anxiety, it would seem that these two clinical illnesses are closely associated (Bui and Fava, 2017; Maiuolo et al., 2021). Clinical manifestations of these diseases varied markedly in their early and late phases (Groeneweg-Koolhoven et al., 2017). The growth in depressed symptoms has led to a rise in teenage suicide deaths in recent decades (Jorm et al., 2017; Matsumoto et al., 2017; Weinberger et al., 2018; Twenge et al., 2019).Numerous studies have examined the connection between anxiety and depression and alterations in the stability and makeup of the gut microbiota (Tognini, 2016; Zhao et al., 2018; Bastiaanssen et al., 2019). The connection between individuals with anxiety and mood problems and their gut flora has been the subject of numerous studies in recent years. Specifically, human studies have shown that there is often some difference in the fecal microbiota between patients and healthy controls when accounting for microbial diversity and taxonomic makeup.Furthermore, it was shown that specific bacteria were connected to inflammatory or metabolic profiles as well as clinical characteristics (Huang et al., 2019). Studies on human microbial diversity have been conducted, however most of them have failed to find a link between depressive illnesses and low microbial diversity (Chen et al., 2014; Naseribafrouei et al., 2014; Zheng et al., 2016). While alpha diversity is the number of species that may be detected in a microbial ecosystem, only one study indicated that people with major depressive disorder (MDD) had a higher alpha diversity of the gut microbiota than healthy patients (Jiang et al., 2015).Patients with MDD had increased fecal a-diversity (higher levels of Enterobacteriaceae and Alistipes but lower levels of Faecalibacterium) when compared to drug-responding patients with healthy controls. For this reason, the scientists found a negative correlation between Faecalibacterium and the severity of depressive symptoms (Jiang et al., 2015). Patients with anxiety problems have also been shown to have intriguing alterations in their fecal microbiome. According to Jiang et al. (2018), they found that patients with generalized anxiety disorder (GAD) had lower levels of microbial diversity and richness, which was associated with higher levels of Ruminococcus, Escherichia, Shigella, and Fusobacterium and lower levels of short-chain fatty acid producers like Eubacterium rectale and Fecalibacterium.Another study found that when compared to a placebo, probiotics (Bifidobacterium bifidum, Lactobacillus acidophilus, and Lactobacillus casei) significantly decreased symptoms of depression in MDD patients (Akkasheh et al., 2016). According to fecal metagenomic data, the ability of bacteria to produce 3,4-dihydroxyphenylacetic acid, a metabolite of dopamine, correlates favorably with mental health. This suggests that microbes may contribute to the production of distinct

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neuroactive molecules during depression as opposed to normal conditions (Valles-Colomer et al., 2019). Lactobacillus rhamnosus has been shown to reduce sadness and anxiety-like behaviors in rats by releasing GABA and activating GABA receptors in the brain, namely GABA Aα2 and GABA B1b receptors (Bravo et al., 2011).

II. CONCLUSION

The majority of research on the topic to date has only identified correlations between specific clinical diseases and bacterial profiles, despite the fact that the gut microbiome is crucial for the host's health and disease states. Because the intestine and neurological system interact in both ways, the gut microbiota significantly affects the physiology and pathology of the brain.Despite the fact that the gut microbiome is essential for the host's health and disease states, most of the study on the subject to now has only found associations between particular clinical disorders and bacterial profiles. The gut microbiota has a major impact on the physiology and pathophysiology of the brain because of the reciprocal interactions between the intestine and neurological system.The majority of research on the topic to date has only discovered correlations between specific clinical diseases and bacterial profiles, despite the fact that the gut microbiome is crucial for the host's health and disease states. Due to the mutual interactions between the neurological system and the colon, the gut microbiota has a significant influence on the physiology and pathology of the brain.The GM is essential for brain development and function, according to numerous studies. The relationship between the GIT microbiota in the GBA and a variety of neurological conditions, including AD, MS, PD, ASD, epilepsy, stroke, and brain injury, has been examined in a number of preclinical and clinical research studies. To fully comprehend GM's method of action, role in the pathophysiology of disease, and potential future applications in treatment or prognosis, more investigation is necessary. Future research is still required to clarify the effect on the GM and the makeup of their beneficial species in the GBA. More research is required to elucidate any potential GM–drug interactions because many patients are prescribed multiple medications.Future neurotherapeutic research will shed important light on the GM, a new line that distinguishes human health from a range of illnesses. Even though our knowledge of the GBA has advanced recently, more investigation is necessary to ascertain whether this information can be useful in a clinical setting. Future research must elucidate the fundamental connections between GM and different neurological conditions and ascertain whether microbiota therapy is a safe and efficient treatment option. If conventional brain disorders are now seen holistically and as whole conditions with a major role for the gastrointestinal tract, it may be possible to create methods that target the gut microbiota to provide novel, safe, and effective treatment options for neurodegenerative disorders.

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