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RESEARCH ARTICLE

ASSOCIATION BETWEEN GUT BRAIN AXIS AND VARIOUS DISORDERS – A LITERATURE REVIEW.

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Abstract

Aim: The aim of this review is to identify and summarize the existing evidences on association between gut brain axis and various disorders.
Method: Research studies will be obtained from various data bases through computer based search in Pubmed, google scholar, Embase, and Cochrane. Obtained studies will be short listed according to inclusion criteria and its results will be reviewed and presented.
Result: A total of 20 studies were potentially identified by the authors. Studies published in English language were included in this review.
Conclusion: The gut microbe has been identified as the main source of highest biological variability confined in an individual and also provides constant antigenic stimulation shaping up the physiological immune response.

Introduction:-

The **gut–brain axis** is the biochemical signaling that takes place between the gastrointestinal tract and the central nervous system..[1] Broadly defined, the gut-brain axis includes the central nervous system, neuroendocrine and neuroimmune systems including the hypothalamic–pituitary–adrenal axis (HPA axis), sympathetic and parasympathetic arms of the autonomic nervous system including the enteric nervous system and the vagus nerve, and the gut microbiota.[1][3]The enteric nervous system has been described as a "second brain".[5] The enteric nervous system can operate autonomously.[5] It normally communicates with the central nervous system (CNS) through the parasympathetic (e.g., via the vagus nerve) and sympathetic (e.g., via the prevertebral ganglia) nervous systems.[5]Gut microorganisms benefit the host by collecting the energy from the fermentation of undigested carbohydrates and the subsequent absorption of short-chain fatty acids (SCFAs), acetate, butyrate, and propionate.[4][7] Intestinal bacteria also play a role in synthesizing vitamin B and vitamin K as well as metabolizing bile acids, sterols, and xenobiotics.[7] The systemic importance of the SCFAs and other compounds they produce are

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like hormones and the gut flora itself appears to function like an endocrine organ,[7] and dysregulation of the gut flora has been correlated with a host of inflammatory and autoimmune conditions.[4][8]

Gut-brain integration:
The gut–brain axis, a bidirectional neurohumoral communication system, is important for maintaining homeostasis and is regulated through the central and enteric nervous systems and the neural, endocrine, immune, and metabolic pathways, and especially including the hypothalamic–pituitary–adrenal axis (HPA axis).[1] That term has been expanded to include the role of the gut flora as part of the "microbiome-gut-brain axis", a linkage of functions including the gut flora.[1][3][2] The gut flora can produce a range of neuroactive molecules, such as acetylcholine, catecholamines, histamine, melatonin, and serotonin, which is essential for regulating peristalsis and sensation in the gut.[6] Changes in the composition of the gut flora due to diet, drugs, or disease correlate with changes in levels of circulating cytokines, some of which can affect brain function.[6] The gut flora also release molecules that can directly activate the vagus nerve which transmits information about the state of the intestines to the brain.[6] Likewise, chronic or acutely stressful situations activate the hypothalamic–pituitary–adrenal axis, causing changes in the gut flora and intestinal epithelium, and possibly having systemic effects.[6] Additionally, the cholinergic anti-inflammatory pathway, signaling through the vagus nerve, affects the gut epithelium and flora.[6] Hunger and satiety are integrated in the brain, and the presence or absence of food in the gut and types of food present, also affect the composition and activity of gut flora.[6]

Anxiety and mood disorders:
As of January 2016 work on the relationship between gut flora and anxiety disorders and mood disorders including depression was at an early stage, with insufficient evidence to draw conclusions about a causal role for gut flora changes in these conditions, nor for the efficacy of any probiotic treatment.[9]People with anxiety and mood disorders tend to have GI problems; small studies have been conducted to compare the gut flora of people with major depressive disorder and healthy people, but those studies have had contradictory results.[9]Much interest was generated in the potential role of gut flora in anxiety disorders, and more generally in the role of gut flora in the gut-brain axis, by studies published in 2004 showing that germ-free mice have an exaggerated HPA axis response to stress caused by being restrained, which was reversed by colonizing their gut with a Bifidobacterium species.[2]

Schizophrenia:
People with schizophrenia tend to also have GI problems,[6] but as of 2015, no studies had been carried out to compare the gut flora of people with schizophrenia with healthy people.[3] Research causing schizophrenia-like symptoms in mice by giving them phencyclidine (PCP) has found changes to the gut flora of the treated mice compared with untreated mice.[3]

Autism:
Around 70% of people with autism also have GI problems, and autism is often diagnosed at the time that the gut flora becomes established, indicating that there may be a connection between autism and gut flora.[10]Some studies have found differences in the gut flora of children with autism compared with normal children – most notably elevations in the amount of Clostridium in the stools of children with autism compared with the stools of the children without[11] – but these results have not been consistently replicated.[10]Many of the environmental factors thought to be relevant to the development of autism would also affect the gut flora, leaving open the question whether specific developments in the gut flora drive the development of autism or whether those developments happen concurrently.[3][10] As of 2016, studies with probiotics had only been conducted with animals; studies of other dietary changes to treat autism have been inconclusive.[9]

Parkinson's disease:
As of 2015 one study had been conducted comparing the gut flora of people with Parkinson's disease to healthy controls; in that study people with Parkinsons had lower levels of Prevotellaceae and people with Parkinsons who had higher levels of Enterobacteriaceae had more clinically severe symptoms; the authors of the study drew no conclusions about whether gut flora changes were driving the disease or vice versa.[3]

Method:-
The gut–brain axis, a bidirectional neurohumoral communication system, is important for maintaining homeostasis and is regulated through the central and enteric nervous systems and the neural, endocrine, immune, and metabolic pathways, and especially including the hypothalamic–pituitary–adrenal axis (HPA axis). The gut flora also release

molecules that can directly activate the vagus nerve which transmits information about the state of the intestines to the brain. Mood disorders, Schizophrenia, Autism, and Parkinson's disease are the specific conditions which associates with gut-brain-axis. This review is to identify and summarize the existing evidences on association between gut brain axis and various disorders. Studies were identifies by using following database.Pubmed, Google scholar, Embase, Cochrane, Pedro and Medline

Review of Literature

S.NO	AUTHOR	TITLE	YEAR	METHODOLOGY	CONCLUSION
1.	Caso. JR, Balanza Martinez. V, Palomo. T, Garcia Bueno. B	The microbiota and gut brain axis: contributions to immunopathogenesis of schizophrenia	2016	Considering the study on microbiome and several research shows the potential role of gut microbiota on various neurologic and psychiatric conditions. The aim is to study the possible effect of these organisms in immunopathogenesis of schizophrenia.	It is to conclude that the following research needs to improve certain advancements in personalized medicine and the future research should include several microbiota and certain therapies in order to improve symptoms and to decrease immue dysfunction in patient with schizophrenia.[12]
2.	Hu. X, Wang. T, Jin. F	Alzheimer's disease and gut microbiota	2016	The host brain function and cognitive behavior can be modulated by gut microbiota via microbiota-gut brain axis. The alterations in host cognitive behaviour, gut microbiota and gut physiology will increasing or decreasing risks of AD. Gut microbiota disturbance can induce increased permeability of intestine and blood brain barrier and it will raise the incidence of neurodegeneration disorder. The onset of AD support the hygiene hypothesis.	All the results suggest that AD is closely related to the imbalance of gut microbe and it may begin in the gut. The personalized diet or intervention will probably become a new treatment for AD.[13]
3.	Maqsood. R, Stone. TW	The gut brain axis, BDNF, NMDA and CNS disorders	2016	This review mainly focuses on the influence of GI tract on BDNF and its relationship with receptors for (N-methyl-D-aspartate) which is associated with the development of schizophrenia and other psychopathologies, as these are believed to be involved in synaptic plasticity and cognitive function. GI microbiota will contribute to the pathophysiology of BDNF induced NMDAR dysfunction which is relevant	The changes in the gut microbiota by using probiotics, prebiotics or antimicrobial drugs has been found promising as a therapeutic measure to counteract behavioural deficits which is useful to supplement the actions of drugs in the treatment of CNS disorders.[14]

				to developing novel therapeutics for schizophrenia and other related disorder. The central BDNF levels are reduced during the absence of GI microbes and this inhibits the maintenance of NMDAR production. The disinhibition of glutametergic output will disrupts the central signal to noise ratio and leads to aberrant synaptic behaviour and cognitive deficits. The BDNF function in the CNS can be modulated by gut microbiota via changes in neurotransmitter function by affection modulatory mechanisms such as the Kyneurenine pathway, or by changes in actions of short chain fatty acids in brain.	
4.	Cepeda. MS, Katz. EG and Blacketer. C	Microbiome-Gut brain axis: Probiotics and their association with depression	2016	A large population based cross sectional study was conducted by National health to assess the association of probiotics with depression. During interview days they consume any probiotic food or supplement and the subjects were classified as depressed if patient health questionare scores were greater than or equal to 10. Unadjusted analysis suggest the subjects those who consume probiotics had lower adds of depression and after adjustment the effect was attenuated.	As a result there is a lower rate of depression in the national sample and it should not associated with the use of probiotics.[15]
5.	Luna. RA, Savidge. TC, Williams. KC	The Brain-Gut-Microbiome Axis: what role does it play in Autism spectrum disorder?	2016	The interactions between the CNS, GI system and micro-organisms that live in the GI tract can be called as brain-gut-microbiome axis. FGIDs commonly occur in children with ASD and is closely associated with the signs of brain-gut-microbiome axis.	The studies suggest that the gut microbiome changes associated with ASD and with GI disorders in children with ASD. The following studies should be treating ASD behaviours with novel therapies and new techniques for identifying GI disorders in children with ASD.[16]
6.	Kennedy PJ, Cryan				

	JF, Dinan TG, Clarke G	Kynurenine pathway metabolism and the microbiota-gut-brain axis	2016	Kynurenine pathway metabolism focuses mainly on structural and functional dynamics of gut microbiota and signaling pathway of brain gut axis. It is regulated by microbial control of neuroendocrine function and components of immune system.	As a result, the gut microbiota represents a tractable target to modulate the kynurenine pathway metabolism.[17]
7.	Santocchi E, Guiducci L, Fulceri F, Billeci L, Buzzigoli E, Apicella F, Calderoni S, Grossi E, Morales MA, Muratori F	Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical ad neurophysiological parameters	2016	A group of 100 preschoolers with ASD can be classified into two groups and it will be randomized 1:1 to regular diet with probiotics or with placebo for six month. After six months from baseline in order to evaluate the possible changes in: (1) GI symptoms; (2) autism symptoms severity; (3) affective and behavioral comorbid symptoms; (4) plasmatic, urinary and fecal biomarkers related to abnormal intestinal function; (5) neurophysiological patterns.	As results could add information to the relationship between phthalates levels, clinical features and neurophysiological patterns in ASD.[18]
8.	Emge JR, Huynh K, Miller EN, Kaur M, Reardon C, Barrett KE, Gareau MG	Modulation of the microbiota-gut-brain axis by probiotics in a murine model of inflammatory bowel disease	2016	DSS (5 days) was administered via drinking water followed by 3 or 9 days of normal drinking water to assess behavior during active or resolving inflammation, respectively. Disease (weight, colon length, and histology) was assessed and the composition of the gut microbiota was characterized by using qPCR on fecal pellet DNA. In a subset of mice, pretreatment with probiotics was started 1 wk prior to commencing DSS. During active inflammation (8 days), mice demonstrated impaired recognition memory and exhibited anxiety-like behavior vs.	As a resut, mood and behavior are present during acute inflammation in murine IBD and associated with dysbiosis and that these outcomes can be prevented by the administration of probiotics.[19]
9.	Brzozowski B, Mazur-Bialy A, Pajdo R, Kwiecien S, Bilski J, Zwolinska-Wcislo M, Mach	Mechanisms by which stress affects the experimental and clinical inflammatory bowel disease (IBD). Role	2016	It is to provide an overview of experimental and clinical evidences that stress activates the brain-gut axis which results in a mucosal mast cells activation	It is to conclude that, an increased microbial load in the colonic tissue, excessive cytokine release and a partially blunted

	T, Brzozowski T.	of Brain-Gut axis		and an increase in the production of proinflammatory cytokines and other endocrine and humoral mediators.	immune reactivity in response to stress result in its negative impact on IBD.[20]
10.	Li Q, Zhou JM	The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder	2016	Gastrointestinal symptoms and compositional changes in the gut microbiota frequently accompany cerebral disorders in patients with ASD. A disturbance in the gut microbiota, which is usually induced by a bacterial infection or chronic antibiotic exposure, has been implicated as a potential contributor to ASD.	As a result, the salient observations of the disruptions of the microbiota-gut-brain axis in the pathogenesis of ASD and reveals its potential therapeutic role in autistic deficits.[21]
11.	RM. Stilling, TG. Dinan, JF. Cryan	Microbial genes, brain and behaviour – epigenetic regulation of the gut – brain axis	2014	The microbial composition is associated with alterations in behaviour and cognition has significantly contributed to establishing the microbiota gut brain axis. A role for this axis in health and disease, ranging from stress related disorders such as depression, anxiety and irritable bowel syndrome to neurodevelopmental disorders such as autism.	In conclusion, the fields of epigenetics and microbiology are converging at many levels and more interdisciplinary studies are necessary to unravel the full range of this interaction.[22]
12.	John F. Cryan, Timothy G. Dianan	Mind – altering micro – organisms: The impact of the gut microbiota on brain and behaviour	2012	The gut microbiota also communicates with the CNS possibly through neural, endocrine and immune pathways and thereby influences brain function and behaviour. Studies in germ free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain.	It suggest that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.[23]
13.	Paul Forsythe, Mobuyuki Sudo, Timothy Dinan, Valerie H Taylor, John Bienenstock	Mood and gut feelings	2010	The mass of intestinal bacteria represents a virtual inner organ with 100 times the total genetic material contained in all the cells in the human body. Commencal organisms live in a state of harmonious symbiosis with each other and their host, however, a disordered balance amongst gut	As a result, this review focuses on these data and suggests that the concept should be explored further to increase our understanding of mood disorders, and possibly even uncover missing links to a

				microbes is now thought to be an associated or even causal factor for chronic medical conditions as varied as obesity and inflammatory bowel diseases. While evidence is still limited in psychiatric illnesses, there are rapidly coalescing clusters of evidence which point to the possibility that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system.	number of co-morbid diseases.[24]
14.	Timothy G. Dinan, John F. Cryan	Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology	2012	The animals treated with probiotics have a blunted HPA response. Stress induces increased permeability of the gut allowing bacteria and bacteria antigens to cross the epithelial barrier and activate a mucosal immune response, which in turn alters the composition of the microbiome and leads to enhanced HPA drive.	The gut microbiota must be taken into account when considering the factors regulating with HPA.[25]
15.	Jane A. Foster, Karen – Anne Mcvey Nessfeld	Gut-brain axis: how the microbiome influences anxiety and depression	2013	Studies reveal the importance of gut microbiota to the function of the CNS. Bidirectional communication between the brain and the gut has long been recognized.	Gut microbiota are an important player in how the body influences the brain, contribute to normal healthy homeostasis, and influence risk of disease, including anxiety and mood disorders.[26]
16.	Elaine Y Hsian, Sara W. McBride, Sophia Hsien	Microbiota modulate behavioural and physiological abnormalities associated with neurodevelopmental disorders	2013	A serious neurodevelopmental condition that is diagnosed based on the presence and severity of stereotypic behavior and deficits in language and social interaction.	Adult offspring of immune-activated mothers exhibit increased gut permeability and abnormal intestinal cytokine profiles.[27]
17.	Anderson G, Seo M, Berk M, Carvalho AF, Maes M	Gut permeability and microbiota in parkinson's disease: Role of depression, Tryptophan catabolities, Oxidative and	2016	It integrate the wider biological changes in PD, including increased oxidative and nitrosative stress, immune inflammatory processessm tryptophan catabolities and alterations in	As a result, by driving tryptophan down the kynurenine pathway pro inflammatory cytokines and chronic stress driven activation of the

		Nitrosative stress and Melatonergic pathways		serotoninergic and melatoninergic pathways.	hipothlamic pituitary adrenal axis decrease the availability of serotonin as a precursor for activation of the melatonergic pathways.[28]
18.	Kohler CA, Maes M, Slyepchenko A, Berk M, Solmi M, Lanctot KL, Carvalho AF	The Gut-brain axis, including the microbiome, Leaky gut and bacterial translocation: Mechanisms and pathophysiological role in Alzheimer's disease	2016	The most prevalent hypothesis for AD is the amyloid hypothesis, which states that changes in the proteolytic processing of the amyloid precursor protein leads to the accumulation of the amyloid beta peptide. Amyloid beta then triggers an immune response that drives neuroinflammation and neurodegeneration in AD. The specific role of gut microbiota in modulating neuroimmune functions well beyond the gastrointestinal tract may constitute an important influence on the process of neurodegeneration.	As a result, we summarize possible mechanisms that could mediate the involvement of gut brain axis in AD physiopathology, and propose an integrative model.[29]
19.	Karakula-Juchnowicz H, Dzikowski M, Pelczarska A, Dzikowska I, Juchnowicz D	The brain-gut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia	2016	The factors which is involved in the functioning of brain gut axis and important for the development of schizophrenia, i.e, 1, intestinal microbiome, 2. Permeable intestine, 3. Hypersensitivity to food antigens, including gluten and casein of cow's milk. It indicate the probiotics, and the implementation of antibiotic therapy of specific treatment groups.	As a result, further research is needed on links between the intestinal microbiome and intestinal function as factors mediating the activation of the immune system and the development and further course of schizophrenia.[30]
20.	GB Rogers, DJ Keating, RL Young, M-L Wong, J Licinio and S Wesselingh	From gut dysiosis to altered brain function and mental illness: mechanisms and pathways	2016	The potential of dysbiosis to contribute to psychopathology and the evidence linking disruption of gut microbiota with specific psychiatric disorders. We examine the role of the microbiome in neurological development and regulation, and consider its contribution to aging-related morbidity.	As a result, the potential for modification of the gut microbiome to provide clinical benefit in the context of altered brain function.[31]

Discussion:-

This study shows various associated disorders of the gut brain axis. As of January 2016 work on the relationship between gut flora and anxiety disorders and mood disorders including depression was at an early stage, with insufficient evidence to draw conclusions about a causal role for gut flora changes in these conditions, nor for the efficacy of any probiotic treatment.[9] Caso et all reported about the future research should include several microbiota and certain therapies in order to improve symptoms and to increase dysfunction in patient with schizophrenia.[12] Hu X et all reported that the personalized diet or intervention will probably became a new treatment for AD.[13] Luna RA, et all reported that the following studies should be treating ASD behaviours with novel therapies and new techniques for identifying GI disorders in children with ASD.[16 Cepeda MS, et all reported that the lower rate of depression in the national sample and it should not associated with the use of probiotics.[15] Maqsood R, et all reported that the changes in the gut microbiota by using probiotics, prebiotics or antimicrobial drugs has been found promising as a therapeutic measure to counteract behavioural deficits which is useful to supplement the actions of drugs in the treatment of CNS disorders.[14] Kennedy PJ, et all reported that the gut microbiota represents a tractable target to modulate the kynurenine pathway metabolism.[17] Emge JR, et all reported that the mood and behavior are present during acute inflammation in murine IBD and associated with dysbiosis and that these outcomes can be prevented by the administration of probiotics.[19] Timothy G, et all reported that the gut microbiota must be taken into account when considering the factors regulating with HPA.[25] Elaine Y Hsian, et all reported that the adult offspring of immune-activated mothers exhibit increased gut permeability and abnormal intestinal cytokine profiles.[27]

Conclusion:-

The reviewed article shows the various disorders of the gut brain axis. The gut microbe has been identified as the main source of highest biological variability confined in an individual and also provides constant antigenic stimulation shaping up the physiological immune response. Studies of microbiota gut brain axis could provide a deeper understanding of the relationship between the intestinal bacteria and their hosts which could help to suggest potential therapeutic strategies through affecting the composition of gut microbiota.

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