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'Correlation between Brain-Gut Microbiota Axis and Alzheimer's Disease'

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Abstract
The gut–brain axis has various implications in pharmacology and is a common term for a wide range of functions and interrelations between the gut microbiome, the immune, endocrine, and nervous systems, and the brain. Researchers are now focusing on the ways in which microbiota can be at the centre of nutritional and therapeutic strategies to improve brain health and well-being.
Alzheimer's is a continuing neurodegenerative dementia caused by A plaques and neurofibrillary tangles, which cause a loss of cognitive and functional abilities.
Gut microbial metabolites and how they affect chemical changes in the brain of the host may raise or lower the risk of AD. An infection caused by a pathogenic microbe can also increase the likelihood of AD. Existing research suggests that AD may originate in the gut and is closely linked to the imbalance of gut microbiota.
This paper offers an in-depth review of the concept of gut-brain axis, the evolution of Alzheimer's Disease, the effect of gut-brain axis on AD through accumulation of protein aggregates, dysbiosis of microbes in the intestine, chronic inflammation and neuroinflammation, infections and CNS stress.
It specifically focuses on the non-drug approaches that can slow AD onset and progression and discusses some interventions that can be used to modulate the composition of gut microbiota and hence be used as a prospective target in AD. These include alternative treatments with herbs, probiotic treatment, traditional Indian medicine (Ayurveda) and traditional Chinese medicine (TCM); and dietary interventions which have been shown to be beneficial to AD patients.
This paper adds to the existing literature on AD and gut-brain axis and is a useful resource for students, researchers and medical practitioners.

Keywords: *Alzheimer's Disease, gut-brain axis, gut microbiota, alternative treatment, dietary interventions*

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I. Introduction

Recently, there has been a lot of research conducted on the significant role of the gut-brain axis on several neurodegenerative disorders. The gut-brain axis refers to the bidirectional communication between the central nervous system and the gastrointestinal tract. It consists of the extensive network of physical and chemical connections between the brain and the gut. The most common cause of dementia, Alzheimer's disease (AD), is defined by a progressive deterioration in cognitive ability and the development of amyloid beta plaques and neurofibrillary tangles (Kowalski &Mulak, 2019). AD is a multifaceted and genetically heterogeneous condition that affects 7–10% of people over 65 and approximately 40% of those over 80 (Sisodia, 1999).

Numerous metabolic and signalling pathways connect the stomach and brain, and each one has the potential to affect mental, brain, and cognitive function. Therefore, more research thinking is shifting to how the microbiota might be the focus of dietary and pharmacological approaches for enhanced brain health and wellbeing (Chakrabarti et al., 2022). The gut microbiota can play a role in disorders of memory, learning, anxiety, stress, and neurodevelopmental and neurodegenerative illnesses, according to an increasing number of association studies (Chakrabarti et al., 2022; Kowalski &Mulak, 2019; Peterson et al., 2022; Makin et al., 2021).

The increased permeability of the gut and blood-brain barrier caused by microbiota dysbiosis may play a role in the development of AD and other neurodegenerative diseases, especially those linked to getting older. Also, bacteria in the gut microbiota can make a lot of amyloids and lipopolysaccharides, which might help control signalling pathways and make proinflammatory cytokines that are linked to the development of AD (Jiang et al., 2017).

Maintaining a eubiotic gut environment may be important for healthy brain ageing, as dysbiosis could cause neuroinflammation that leads to AD. AD is becoming more common in the US, where it now affects more than 4 million people. This is due to major changes in life expectancy and demographics (Sisodia, 1999). AD is the leading cause of dementia in elders and accounts for 60 percent to 80 percent of all dementia cases

(Wierenga&Brondi, 2011). There are thought to be 44 million Alzheimer patients worldwide, and as the population ages, that figure will have more than doubled by 2050 (Lane et al., 2018).

There are several studies that report a strong connection between the gut-brain axis and AD, as well as interventions that can help AD patients by focusing on the gut microbiota. However, to the best of the researcher's knowledge, there is no collation of such research.

Therefore, this paper aims to review the effects of gut-brain axis on Alzheimer's Disease and also find out about interventions or treatments focused on gut-brain axis that can help AD patients. More specifically, the paper addresses the following research questions:

RQ1: What is the impact of gut-brain axis on human health?

RQ2. What is the impact of gut-brain axis on causing and aggravating AD?

RQ3. What are the interventions/treatments that can help patients with AD by focusing on the GBA?

The paper is organized as follows. The next section deals with an in-depth literature review about gut-brain-axis and its effect on various human systems and processes, followed by a review of Alzheimer's Disease and its progression. This is followed by some interventions that can help treat Alzheimer's Disease by focusing on the gut-brain axis. Finally, the discussion section provides the practical implications of the study, limitations and further scope for research.

II. Methodology

This paper follows a systematic literature review methodology. Using the key words 'impact of gut-brain axis', 'gut-brain axis and Alzheimer's disease' and 'impact of gut-brain axis in Alzheimer's disease', the researcher searched prominent research databases such as Elsevier (Science Direct), Wiley Science, Sage and Springer. The initial search led to 1350 items. Using the exclusion criteria of only published papers and not conference papers or doctoral theses, the researcher finally used 100 research papers for this review.

The Gut-Brain Axis

The gut–brain axis is a functional unit that has various implications in pharmacology (Moore, Mathia and Valeur, 2018). The microbiota-gut-brain axis is a common term for a wide range of functions and interrelations between the gut microbiome, the immune, endocrine, and nervous systems, and the brain (Forsythe et al., 2016). It has been suggested that problems in the communication between the gut and the brain may be a cause of disorders like irritable bowel syndrome (IBS) and may also play a role in inflammatory bowel diseases (Bonaz& Bernstein, 2013).

Changing one goal on the gut–brain axis can have effects on the whole axis (Moore, Mathia and Valeur, 2018). González-Arancibia et al. (2016) believe that these changes can be caused by factors such as changes in the composition of microbiota (dysbiosis), changes in the function of the intestinal barrier, damage to the enteric nervous system, an unbalanced local immune response, and overreactions to stress.

The hormones, organs, and immune system of the body can talk to each other through the gut–brain (or brain–gut) axis. In a two-way connection, the central nervous system (CNS) transmits messages to the gut through the thoracolumbar, vagal, and lumbosacral nerve pathways or via soluble mediators like neurotransmitters, hormones, and cytokines (Brookes et al., 2013). According to Sandhu et al. (2017), the microbiota–gut–brain axis encompasses bacteria, viruses, fungi, and archaea in the gut microbes, as well as their metabolites and by-products, as parts of this two-way communication.

Researchers are now concentrating on how the microbiota can become the centre of nutritional and therapeutic strategies to enhance the health and well-being of the brain (Chakrabarti et al., 2022).

Evolution of the concept of Gut-Brain Axis

Scottish doctor Robert Whytt was one of the first to come up with the idea of "nervous sympathy" in 1765, to describe the ways he thought the organs inside the body were connected. He noticed that the gut had a lot of nerve endings that sent "nervous energy" to other parts of the body (Miller, 2018).

During the 19th century, people thought that the connection between the mind and the gut went both ways, as has been described in the works of researchers such as Miller (2018), Moore (2018) and Lillestol (2018). Lillestol (2018) mentions how the nineteenth century saw a growing interest in the interplay between the central nervous system and the gastrointestinal tract. This association was used to explain a wide range of phenomena, such as changing eating habits, suicide, and even radical politics.

The idea of the gut-brain axis became popular again at the beginning of the 20th century because of the work of psychologists, physiologists, psychoanalysts, and doctors like Water Cannon, Walter C. Alvarez, and Franz Alexander. They believed that the emotional health of a gastric patient was necessary to be taken into

account while diagnosing and treating; and that intestinal issues such as ulcers had psychological aspects (Alexander, 1934).

More recently, researchers have started to look into the possibility that the gut and brain can talk to each other by changing the resident microbiota through changes in diet, especially through prebiotics. A study by Li et al. (2009) was one of the first to show that changes in bacterial diversity caused by diet might affect behaviour.

De Vadder et al (2014) showed how the gut microbiota is essential for the development of the central nervous system, the enteric nervous system and for digestion-related metabolic processes like hunger, fullness, and glucose homeostasis. Forsythe et al. (2016) demonstrated that exposure to transient organisms orally can change brain chemistry and possibly behaviour.

Alzheimer's Disease

Alzheimer's is a progressive neurodegenerative dementia caused by A plaques and neurofibrillary tangles (NFTs), which cause a loss of cognitive and functional abilities (Wierenga&Brondi, 2011).

Neurons in the hippocampus, cortex, amygdala, basal forebrain, anterior thalamus, and monoaminergic nuclei of the brainstem are affected by AD. Affected nerve cells build up NFTs, which are hard to dissolve filaments made of phosphorylated tau, a protein that is attached to microtubules (Sisodia, 1999).

The illness is a late-life syndrome that includes memory loss, problems with thinking, and dementia. It may impact verbal or physical skills, executive function, personality and behaviour, visual-spatial thinking, and the ability to make up new languages (Graff-Radford et al., 2021).

Risk factors for AD include having a head injury, not getting enough education, getting an oxidative injury, being depressed, never getting married, having few friends, or having mild cognitive impairment. This is a pre-dementia state in older people that is characterised by both subjective and objective memory loss and normal general cognition and functioning. African Americans and Hispanics are more likely than white Americans over 65 to have Alzheimer's or another form of dementia (Wierenga&Brondi, 2011).

Studies have found that 60–80% of the risk of Alzheimer's is genetic (Sultana et al., 2009). Alzheimer's disease is inherited, but the APOE 4 genotype does not fully explain it (Mandal et al., 2012). In contrast to amyloid deposition, tau-PET binding topography associated with cognitive deficits (van Harten et al., 2013), is unique to AD clinical phenotypes (Zhang et al., 2015), and is a sign of cognitive decline (Rabinovici et al., 2010) and atrophy (Sojkova& Resnick., 2011). Initial evidence suggests that amyloid may both cause more tau to form (Klunk et al., 2015).

When late-onset Alzheimer's causes memory loss, neurodegeneration happens over time, first in the medial temporal lobe and then in the posterior trans modal association cortex. AD that starts young and does not affect memory usually shows tau build-up and neurodegeneration in areas related to the domain that is not working well, leaving the hippocampal and medial temporal structures vulnerable (Graff-Radford et al., 2021). Amyloid- is found in the same places in all subtypes of Alzheimer's, but tau patterns closely match clinical presentation (Ossenkoppele et al., 2016).

Morris's (1996) clinical tests and quantitative post-mortem research show that the brain can stay healthy even as it gets older. People who are cognitively normal have mild neocortical pathology, but the number of SPs in the brains of people with early-stage AD is much higher. Based on these results, AD starts when -amyloid builds up in the form of SPs. It is believed that SPs speed up neurofibrillary degeneration, neuronal malfunction, and death (Sisodia, 1999).

Relation between Gut-Brain Axis and Alzheimer's Disease

Through the microbiota-gut-brain axis, gut microbiota can change how the brain works and how a person acts, including how they think. Gut microbiota disturbances can make the intestine and blood-brain barrier more permeable, which can make neurodegenerative disorders more likely (Hu et al, 2016). Gut microbial metabolites and their effect on chemical changes in the brain may raise or lower the risk of AD. Pathogenic microbial infection can also increase the risk of AD. Existing research suggests that AD may begin in the gut and is closely related to the imbalance of gut microbiota.

Some of the ways in which the gut-brain axis impacts AD is as follows:

Accumulation of Protein Aggregates

AD is linked to truncated A peptides, which are made when the transmembrane receptor amyloid precursor protein (APP) is split in an abnormal way (Jadhav et al., 2012). Protein clumps, which are made by either the repeat-expanded protein or the truncated protein, are a sign of these neurodegenerative diseases. The most well-known signs of AD are amyloid plaques made of A peptides and tau protein neurofibrillary tangles in affected neuronal cells (Jagust, 2018).

Dysbiosis

Dysbiosis is an imbalance in the types of bacteria in the gut. It has been linked to diseases like obesity, diabetes, and neurological conditions (Sherwin, Dinan and Cryan, 2018).

Some researchers have hypothesized that AD may be associated with a dysbiosis of microbes in the intestine (Jiang et al., 2017). This notion stems from the fact that the intestinal flora can influence the activity of the brain and cause its dysfunctions (Xin et al., 2018). The term "microbiota-gut-brain axis" (MGBA) was created because of an increasing amount of evidence to this effect (Quigley, 2017). The link between gut microbiota and AD is also linked to inflammation, which plays a key role in the development and progression of AD (Calsolaro& Edison, 2016). Some brain processes, like myelinization, neurogenesis, and microglial activation, cannot happen without the gut microbiota (Cenit et al., 2017).

AD patients have gut dysbiosis, and the composition of their intestinal microbiome is very different from that of healthy people (Vogt et al., 2017).In particular, people with AD have lower levels of bacteria in the groups Actinobacteria (in particular, bacteria of the genus Bifidobacterium) and Firmicutes. (Underwood et al. (2015) show that some types of Bifidobacterium are linked to anti-inflammatory effects and less intestinal permeability.

Gram-positive Lactobacillus and Bifidobacterium in the intestines, like Lactobacillus brevis and Bifidobacterium dentium, can break down glutamate to make gamma-aminobutyric acid (GABA) (Barrett et al., 2012). GABA is the main neurotransmitter in the CNS that slows down nerve signals. Cognitive impairment may be caused by problems with the GABAergic system (Lanctot et al., 2004). There is a link between the rise of GABA in the GI tract and the increment of GABA in the CNS. When there is an imbalance in the gut microbiota, especially an absence of Lactobacillus and Bifidobacterium, it will affect how much GABA is made in the gut, which will then lead to less GABA in the CNS. A post-mortem study of Alzheimer's disease patients found that their frontal, temporal, and parietal cortexes had lower GABA levels (Lanctot et al., 2004).

Different diseases, such as depression (Wang et al., 2017) and neurodegenerative disorders, can also change the gut microbiota (Parashar &Udayabanu, 2017). Tremlett et al. (2017) discussed the contribution of the brain-gut-microbiota axis to brain disorders such as AD (Chen et al., 2018), autism, schizophrenia or multiple sclerosis (Quigley, 2017).

Amyloids can be found in large amounts in the gut microbiota (Cherny et al., 2005). The generation of amyloid proteins enables bacterial cells stick together to form biofilms that cannot be destroyed by the body's immune system or by physical forces (Friedland & Chapman, 2017). The exposure to bacterial amyloid proteins in the gut may cause priming of the immune system, consequently enhancing immune response to endogenous production of neuronal amyloid in the brain (Zhao et al., 2017).

Gut microbiota dysbiosis causes epithelial colon cells to make less tight junction proteins, which causes inflammation in the colon. When the function of the gut barrier is changed, microbial metabolites are released into the bloodstream. This makes inflammation worse. So, when the Blood Brain Barrier (BBB) breaks down, more pro-inflammatory cytokines could leak into the CNS and cause neuroinflammation by turning on microglia and astrocytes (Rothhammer et al., 2016).

Changes in gut microbiota may directly cause higher intestinal permeability (leaky gut) and BBB permeability (leaky brain) and systemic and central nervous system (CNS) inflammation, which can lead to neurological disorders. Gut microbiota metabolites and their effects on neurochemical changes may also increase or decrease the risk of AD (Hu et al, 2016).

Chronic Inflammation

The brain can start an immune response after being hurt by pathogens or anything else that is harmful for the body. Under normal circumstances, this immune response is started by microglia and ends when pathogens, dead cells, or other cellular debris are gone and the tissue is repaired. Chronic inflammation could be harmful for neurons, though, if the injury lasts or if the immune response is changed or weakened. Neuroinflammation is the release of substances by neurons that keep the inflammatory process and immune response going (Angelucchi et al., 2019).

Jouanne et al (2017) believe that the most notable feature about Alzheimer's disease is the buildup of amyloid beta (A), which is then followed by the formation of plaques and neurofibrillary tangles made of hyperphosphorylated tau protein. According to Kohler et al. (2016) these deposits cause neuroinflammation, which leads to the loss of synapses and the death of neurons. Still not much is known about what causes amyloid plaques to form, but the gut microbiota is a big part of the process (Kowalski and Mulak, 2019). Patients with brain amyloidosis and cognitive impairment were found to have higher levels of proinflammatory cytokines in their blood, as well as more proinflammatory gut microbes (Escherichia/Shighella) and less anti-inflammatory gut microbes (Escherichia rectale) (Cattaneo et al., 2017). Neuroinflammation, which is shown by activated microglia, reactive astrocytes, and complement in the area of amyloid plaques, is a well-known sign of AD (Cattaneo et al., 2017).

AD patients' blood and cerebrospinal fluid show that they have a higher inflammatory response (Cattaneo et al., 2017). Recent studies show that AD neuroinflammation can be affected by how the gut microbiota is made up. It has been suggested that a change in gut microbiota and intestinal permeability can cause inflammation not

only in the gut but also in the CNS because pro-inflammatory cytokines can penetrate the bloodstream and affect the brain (Kelly et al., 2015).

Changes in the environment of the gut can destroy the brain's ability to protect itself from harmful substances over time. When inflammation is caused by a leaky gut, it will lead to a leaky brain, resulting in the BBB becoming more permeable.

Infections

Most of the negative outcomes for AD patients, like inflammation, brain atrophy, immune system problems, amyloid formation, changes in gene expression, and mental decline, are thought to be caused by microbial infections (Heintz and Mair, 2014). In normal conditions, the gut microbiota and the host form a complex of mutualistic symbiosis, and the symbiotic environment can effectively prevent pathogenic microorganisms from taking hold. When the symbiotic environment is severely damaged, the number of potential pathogens will grow quickly. This will lead to diseases like diabetes, autoimmune disease, metabolic syndrome, obesity, and stress-related mental illnesses like autism, schizophrenia, and AD.

A viral or bacterial infection has been shown in many studies to be one of the factors that can lead to AD. Chronic Helicobacter (H.) pylori infection in AD patients causes inflammatory mediators to be released. AD patients with H. pylori infection had relatively low MMSE scores, which is a sign of more severe cognitive impairment (Kountouras et al., 2009). Also, the levels of A40 and A42 in the blood of Alzheimer's patients who are infected with H. pylori or other bacteria like Borrelia burgdorferi and Chlamydia pneumoniae are higher (Bu et al., 2015). It was also shown that exposing neuroblastoma cells to H. pylori filtrate causes tau hyperphosphorylation similar to the pathology of AD tau (Wang et al., 2017).

LPS was found in high amounts in the hippocampal and temporal lobe lysates of AD patients' brains (Zhao & Jaber, 2017). Hauss-Wegrzyniak et al. (2000) found that injecting bacterial LPS into the fourth ventricle of an animal's brain mimics many of the inflammatory and pathological symptoms of AD. In vitro tests showed that bacterial LPS encourages the formation of amyloid fibrils (Asti &Gioglio, 2013). The amount of LPS in the plasma of people with AD is also significantly greater than in healthy individuals (Zhang et al., 2009). Other bacterial products such as E.coli pili protein (Zhan et al., 2016)or nucleic acids (Emery et al., 2017)were also found more prevalent in AD patients.

Many studies have linked the presence of microbiota in the brain to the cause of AD (Frost & Diamond, 2010). These pathogens include Chlamydophila pneumoniae (Hammond et al., 2010),Borrelia burgdorferi, and other spirochetes (Miklossy, 2016)or herpes simplex virus type 1 (Carter, 2011).

CNS Stress

CNS stress levels may change the physiology and the composition of the gut (Pistollato et al., 2016). Stress may cause hormones and neurotransmitters to be released, which could change gut physiology and microbiome habitat, making it easier for certain strains to grow (Cenit et al., 2017). Also, stress can cause big changes in the microbiota and the way the gut works, like making macromolecules more permeable and making the gut make more secretions (Zareie et al., 2006).

Treatment

Current medication

There is presently no drug that can stop the progression of Alzheimer's, cure it, or even significantly slow down symptoms. Instead, existing treatments are approved for the symptomatic treatment of mild to moderately severe AD dementia (Joe &Ringmans, 2019). Only six medications, including tacrine, donepezil, galantamine, rivastigmine, an NMDA receptor blocker called memantine, and an orexin receptor antagonist called Suvorexant (Belsomra, MK-4305), are currently FDA-approved for treating Alzheimer's disease. These medications all work by modifying symptoms (Howard et al., 2012).

There is no approved drug therapy for AD that changes the way the disease develops. Some evidence suggests that diet, cognitive and physical exercise, and good cerebrovascular health may slow disease onset and progression (Wierenga&Brondi, 2011).

Non-Drug Approaches

Non-drug approaches that have been used with benefit for AD patients include aromatherapy, bright light therapy, music or dance, massage, pet therapy, and multisensory stimulation. However, research on these typically lacks randomized controlled trials, and have not been found to be particularly efficacious (Sink et al., 2005).

Alternative therapy approaches for AD need to be investigated because of the current medical system's ineffectiveness, side effects, and low patient compliance.

Focus on Gut-Brain Axis

There is increasing evidence for the gut microbiota contribution to the pathogenesis of AD, as seen in the previous section. Hence, modifying the makeup of the gut microbiota could be used as a possible treatment for AD (Kowalski &Mulak, 2019).

The microbiota composition has been demonstrated to be impacted by a variety of factors, including food (Gentile & Weir, 2018; Yang et al., 2017), alcohol use (Hillemacher et al., 2018), smoking (Savin et al., 2018), and variations in circadian rhythm (Kaczmarek et al., 2017).

According to González-Arancibia et al. (2016), changing the microbiota with antibiotics, probiotic bacteria, and prebiotic compounds may be able to help not only gastrointestinal changes but also changes in behaviour and neurochemistry that are caused by stress. Treatment with antibiotics can help in regulating the gut microbiota and can be used to treat small intestinal bacterial overgrowth (SIBO) and intestinal colonisation by pathogenic strains (Fasano et al., 2013).

Alternative Treatments

Several alternative treatments have been found to be effective in the treatment and prevention of AD, as per the findings of various studies.

The herb bacopa has been shown to have anti-oxidant free radical scavenging potential in animal studies (Sadhu et al., 2014).Patients with age-related memory loss and healthy older people who took part in clinical trials show that bacopa improves focus, memory, and learning (Nemetchek et al., 2017). Kuboyama et al. (2014) observed that bacopa in a mixture of herbs positively affected markers of inflammation, oxidative stress, and cognitive function.

Curcumin therapy for AD patients showed better phagocytosis of amyloid plaque and higher clearance of amyloid protein (Mishra &Palanivelu, 2008). When compared to a placebo, curcumin treatment of 400 mg/day significantly enhanced working memory and sustained attention in healthy persons over the age of 60 (Cox, Pipingas and Scholey, 2015). According to Rainey-Smith et al. (2016), community-dwelling older persons who receive 1500 mg/day of curcumin saw no cognitive decline while the placebo group experienced cognitive decline

Probiotic therapy

Research shows that probiotic therapy can enhance nitric oxide bioavailability and lower indicators of DNA damage, oxidative stress, inflammation, and serum protein oxidation. Thus, probiotic therapy may enhance AD-related cognitive performance, inflammation, oxidative stress, and several metabolic markers (Peterson et al., 2022).

Healthy eating habits that include high levels of probiotics and prebiotics, along with other nutrients, slow down cognitive decline and lower the risk of AD (Pistollato et al., 2018). Tillisch et al. (2013) showed that adding probiotics to a person's diet not only affects normal brain activity but also makes a big difference in how well a person thinks. These effects may be caused by restoring gut microbiota, but they may also be caused by the opposite effect on other AD-related pathological events, like oxidative stress and insulin resistance (Athari et al., 2018).

Musa et al. (2017) suggested that probiotics could help reduce LPS-induced neuroinflammation and memory loss by preventing acetylcholinesterase activity and acting as antioxidants. In another clinical study, taking Lactobacilli and Bifidobacteria-based probiotics led to AD patients' MMSE scores going up substantially (Akbari et al., 2016). Fermented dairy products have been linked to healthy brain function (Kato-Kataoka et al., 2016). In fact, many studies show that a healthy microbiota assists in maintaining the brain's homeostasis by reducing inflammation in the CNS, vascular pathology, and the clumping together of misfolded proteins. So, probiotic treatment could improve cognitive function, inflammation, oxidative stress, and some metabolic parameters in AD, but more clinical studies are needed to fully comprehend the therapeutic benefits (Peterson et al., 2022).

Ayurveda and Traditional Chinese Medicine

Herbal and traditional therapies like traditional Indian medicine (Ayurveda) and traditional Chinese medicine (TCM) are being investigated for AD due to their natural approach and negligible side effects. These practises have a number of useful medical plants, substances, and innovative management techniques (Patwardhan, 2000). However, it should be noted that research on their overall therapeutic benefits is insufficient, and thus evidence-based recommendations are not obtainable.

Spices like ginger, cinnamon, rosemary, turmeric and sage used in these traditional therapies can help prevent AD and other neurological diseases because they contain phytochemicals (Hügel, 2015). Memory and learning skills are commonly improved with Panax notoginseng (Li et al., 2015). The neuronal toxicity brought on by AD is lessened by notoginsenoside R1, which has been shown to increase neuronal excitability and ameliorate synaptic and memory impairment (Yan et al., 2014). Chinese plant extracts like galantamine, ginkgo biloba and huperzine have been shown to be effective to thwart AD pathogenesis (Malve, 2017).

Ayurveda recommends Nasya (nasal administration) for all head and neck disorders, which may have a therapeutic benefit for AD patients (Amin & Sharma, 2015). These treatments are frequently used to treat AD behavioural symptoms, including rage, aggression, despair, irritability, and wandering. Ashwagandha, which is the common name for the herb Withaniasomnifera, has been shown to help the immune system and nervous system in both health and illness (Zhao et al., 2002). Studies have shown that it affects the CNS positively by

reducing oxidative stress and changing the way key proteins help neural cells grow, change, and talk to each other (Prakash et al., 2013).Brahmi was shown to enhance spatial working memory (Stough et al., 2008), lead to better cognitive performance for elderly patients (Calabrese et al., 2008), enhance verbal learning, memory development, and delayed recall (Morgan & Stevens, 2010) and better short-term memory (Roodenrys et al., 2002).

Dwivedi, Tripathi, Mutsuddi and Lakhotia (2013) investigated the beneficial effects of traditional Ayurvedic formulations in suppressing inherited neurodegenerative disorders. Further studies on Ayurvedic formulations will be useful in developing them as therapeutic formulations for combating neurodegenerative disorders (Lakhotia, 2013).

Food based therapies

Dietary intervention is one of the most effective ways to change the gut microbiota. Food-based therapies could change the gut microbiota or directly affect how neurons in the ENS and CNS work (Szablewski, 2018).

Several studies show that AD and other neurodegenerative diseases may be linked to low levels of Omega-3 polyunsaturated fatty acids (Omega-3 PUFAs). A healthy diet that is high in probiotics, plant-based foods, antioxidants, nuts, soybeans, and omega-3 polyunsaturated fatty acids and low in animal-derived proteins, saturated fats, and refined sugar has been shown to reduce inflammation, lower insulin resistance, and lower the risk of neurocognitive impairment as well as the risk of AD (Pistollato et al., 2018).

Jacka et al. (2015) found that older people whose intake of unhealthy foods went up over four years had smaller hippocampus volumes. On the other hand, it was found that eating healthy foods was linked to better brain function (Wu et al., 2019). The risk of AD can be lowered by eating fruits and vegetables (Hughes et al., 2010), and nuts, fish, and vegetable oils, which are all high in antioxidants and Omega-3 PUFAs (Okubo et al., 2017).

A high-fat diet can cause memory problems and raise the risk of AD. Research shows that high-fat diets and obesity are linked to problems with memory and learning (Sabia et al., 2009), and likely also to lead to brain atrophy (Enzinger et al., 2005). Also, obesity in middle age increases the risk of getting AD later in life (Anstey et al., 2011).

Gardener et al. (2012) found that AD and mild cognitive impairment were far more common in people who did not follow the Mediterranean diet. On the other hand, people who did follow the Mediterranean diet were less likely to get AD (Scarmeas et al., 2006). The Mediterranean diet was discovered to lower biomarkers of inflammation and normalise the gut microbiota by making Bacteroidetes and Clostridium more common and Proteobacteria and Bacillaceae less common (Marlow et al., 2013). This implies that the Mediterranean diet could help control AD by keeping the gut microbiota in balance (Del Chierico et al., 2014).

III. Conclusion

This paper offers an in-depth review of the concept of gut-brain axis, the evolution of Alzheimer's Disease, the effect of gut-brain axis on AD and some alternative approaches to treatment of AD by focusing on the gut-brain axis.

The microbiota-gut-brain axis is a common term for a wide range of functions and interrelations between the gut microbiome, the immune, endocrine, and nervous systems, and the brain. AD is a progressive neurodegenerative dementia caused by A plaques and neurofibrillary tangles, which cause a loss of cognitive and functional abilities.

Existing research suggests that the gut-brain axis impacts AD through accumulation of protein aggregates, dysbiosis of microbes in the intestine, chronic inflammation and neuroinflammation, infections and CNS stress.

This paper specifically focuses on the non-drug approaches that can slow AD onset and progression and discusses some interventions that can be used to modulate the composition of gut microbiota.

This paper adds to the existing literature on AD and gut-brain axis and is a useful resource for students, researchers and medical practitioners.

Future studies can study the effect of the gut-brain axis on specific symptoms of AD, or can focus on the effect of numerous confounding factors such as diet, concomitant diseases and drugs that impact incidence and progression of AD through the gut-brain axis.

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