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The Gut-Brain Axis in Alzheimer's Disease:Mechanisms,Microbiota and Potential Therapeutic Strategies

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ABSTRACT

Introduction:

Alzheimer's disease (AD) is the most common form of dementia and represents a major challenge in modern medicine due to its global prevalence. In recent years, growing interest in the gut microbiota has revealed potential links between microbial dysbiosis and the development and progression of AD. These findings suggest novel perspectives in AD pathogenesis and therapeutic approaches.

Purpose:

This review aims to investigate the current evidence supporting the connection between gut microbiota and Alzheimer's disease, focusing on the gut-brain axis mechanisms and evaluating microbiome-targeted therapeutic strategies.

Methods:

A comprehensive literature review was conducted using peer-reviewed articles sourced from PubMed and other scientific databases. The search focused on studies exploring the gut-brain axis, neuroinflammation, microbiota composition in AD , and microbiome-based interventions from 2012 to 2025. Both animal and human studies were included.

Results:

Current research indicates that gut microbiota dysbiosis may contribute to Alzheimer's disease via direct microbial invasion and indirect neuroimmune mechanisms, such as systemic inflammation and blood-brain barrier disruption. AD patients often exhibit increased pro-inflammatory and decreased anti-inflammatory gut bacteria, correlating with neuroinflammation and accumulation of β-amyloid and tau. Emerging therapies like probiotics, fecal microbiota transplantation, and lifestyle changes show promise in modulating the microbiome and alleviating AD-related pathology.

Conclusions:

Gut microbiota dysbiosis appears to influence Alzheimer's disease progression via neuroinflammatory and neurodegenerative pathways. Targeting the gut-brain axis may offer promising therapeutic avenues. However, further research is necessary to clarify causality, optimize interventions, and validate findings in large-scale human trials.

Keywords: Alzheimer's disease, gut-brain axis, gut microbiota, neuroinflammation, microbiome-based therapy

1. METHODS

This narrative review was conducted to synthesize current knowledge on the relationship between gut microbiota and Alzheimer's Disease (AD), with a particular focus on the gut-brain axis mechanisms, microbial dysbiosis, and microbiome-targeted therapeutic strategies.

1.1. Literature Search Strategy:

A comprehensive literature search was performed across multiple scientific databases, primarily PubMed, Scopus, and Web of Science, covering publications from 2012 up to April 2025. The search terms included various combinations of keywords such as "Alzheimer's disease," "gut microbiota," "microbiome," "gut-brain axis," "neuroinflammation," "short-chain fatty acids," "fecal microbiota transplantation," "probiotics," and "microbiome-based therapy."

1.2. Inclusion and Exclusion Criteria:

The review included peer-reviewed original research articles, systematic reviews, meta-analyses, and relevant experimental studies involving both human subjects and animal models. Studies specifically addressing the role of gut microbiota in AD pathogenesis, diagnosis, mechanistic pathways (including microbial translocation, neuroimmune interactions, and blood-brain barrier disruption), and microbiome-based therapeutic interventions were considered. Articles focusing exclusively on other neurodegenerative diseases or dementia subtypes apart from AD were excluded.

1.3. Data Extraction and Synthesis:

Data regarding study objectives, designs, methodologies, main findings, and conclusions were independently extracted by the authors. A qualitative synthesis approach was applied to integrate evidence on gut microbiota alterations in AD, neuroinflammatory mechanisms, genetic and sex-dependent factors, and emerging therapeutic approaches such as fecal microbiota transplantation, probiotics, pharmacological modulation, and lifestyle factors (diet, exercise, sleep).

1.4. Reference Scope:

This review draws upon a broad and up-to-date collection of 48 key references that span foundational research and recent advances in the field. These references encompass microbial compositional changes in AD patients and animal models [5,6,7], mechanistic insights into the gut-brain axis and neuroinflammation [15,21,24], genetic influences such as APOE interactions [26,27,29], and clinical and preclinical evaluations of microbiome-targeted therapies [33,34,35,39,40].

1.5. Limitations:

Being a narrative review, this study does not follow the strict protocol of a systematic review or meta-analysis, which may introduce selection bias. Nevertheless, the broad scope of included literature provides a comprehensive overview of the current understanding of gut microbiota's role in AD and highlights promising directions for future research.

2. INTRODUCTION

Alzheimer's Disease (AD) is the most prevalent form of dementia worldwide, accounting for approximately 60–70% of all cases. In recent years, a dramatic increase in incidence has been observed, and projections estimate that by 2050, the number of individuals affected by the AD may reach as high as 139 million. AD poses a significant challenge not only to patients and their families substantially diminishing their quality of life but also represents a considerable burden for healthcare systems and social policy frameworks[1].The clinical course of Alzheimer's Disease is

insidious, with initial symptoms often being nonspecific and subtle, which frequently delays diagnosis by several years. It is typically after the emergence of more pronounced symptoms such as progressive memory impairment (potentially culminating in complete memory loss), cognitive decline, behavioral changes, disturbances in balance and reflexes, as well as tremors and involuntary movements that a clinical diagnosis becomes feasible[1].

The diagnostic approach to AD increasingly incorporates the use of specific biomarkers, which serve as characteristic indicators of the disease. Among the most prominent are:

- β-amyloid (Aβ): The most extensively studied protein associated with Alzheimer's disease. Its pathological accumulation in the form of amyloid plaques within the brain is one of the primary neuropathological hallmarks of the disorder.
- Tau protein: A microtubule-associated protein predominantly found in neuronal axons, which undergoes hyperphosphorylation in the course of AD. The altered tau protein spreads to neighboring neurons and, as a result of neuronal death.
- Neurofilament light chain (NfL): A cytoskeletal protein primarily localized in axons, essential for the development and maintenance of the nervous system. Similar to tau, NfL levels in CSF rise in response to neuronal degeneration observed in AD.

The gut microbiota is a complex community of microorganisms including bacteria, fungi, viruses, and other microbes that inhabit the human gastrointestinal tract, with the highest concentration located in the colon. This microbial ecosystem performs a wide range of essential physiological functions. Among its key roles are the digestion of complex carbohydrates, synthesis of vitamins (such as vitamin K), and regulation of the host immune system. A particularly important function of the gut microbiota is the production of short-chain fatty acids (SCFAs), which reinforce the gut-vascular barrier and modulate host immune responses.The composition of the gut microbiota is influenced by numerous factors. Among the most significant environmental determinants are intestinal pH, oxygen concentration, the amount of mucus secreted, and the presence of antibodies and other antimicrobial molecules. The development of the gut microbiota begins in the neonatal period and continues until approximately 3–4 years of age, at which point a relatively stable and individualized microbial profile is established. Over the course of life, however, the microbiota remains subject to dynamic modifications influenced by various external factors, including diet and nutritional habits, antibiotic use, environmental pollution, physical activity, circadian rhythms, and the nature of social interactions. Internal factors such as age, genetic predisposition, host

metabolism (particularly hepatic metabolism and bile acid circulation) also play a crucial role in shaping the gut microbiota[8]

3. RESULTS

In recent years, a growing number of researchers have begun to associate the pathogenesis of Alzheimer's disease (AD) with disturbances in gut microbiota, reflecting the increasing scientific interest in the gut microbiome and its systemic impact on human health. In 2017, Cattaneo and her colleagues conducted a qualitative analysis of gut microbiota composition in AD patients using quantitative polymerase chain reaction (qPCR). Their findings revealed an increased presence of pro-inflammatory bacteria, primarily of the genera *Escherichia* and *Shigella*, alongside a reduction in anti-inflammatory species such as *Eubacterium rectale* [4]. In the same year, Vogt and collaborators employed 16S rRNA gene sequencing to analyze fecal samples from AD patients. Their results demonstrated a significantly reduced microbial diversity in individuals with Alzheimer's disease compared to healthy controls. Notably, a decrease in bacteria belonging to the phylum *Firmicutes* and the genus *Bifidobacterium* was observed, accompanied by an increase in *Bacteroidetes*[5]. It is important to note, however, that Vogt's study was conducted in a Caucasian population, which represents a critical contextual factor. In contrast, a separate investigation conducted among Chinese patients with AD reported a decrease in *Bacteroidetes* abundance an opposite trend to that observed in Vogt's findings[6]. These discrepancies may be attributable to ethnic and lifestyle differences between study populations, as well as methodological variations in the research protocols employed.The link between gut microbiota and Alzheimer's disease has also been explored in animal models. Brandscheid and colleagues, using the transgenic 5xFAD mouse model, demonstrated that these mice, compared to healthy controls, exhibited a reduced abundance of *Bacteroidetes*, further supporting a potential role for gut dysbiosis in AD pathophysiology.[7]

3.1. THE MECHANISMS OF GUT-BRAIN AXIS IN ALZHEIMER'S DISEASE

Direct Mechanism

The direct mechanism suggests that microorganisms can penetrate the central nervous system (CNS) directly. This concept, also referred to as the *"infectious hypothesis"*, was first proposed over 30 years ago when members of the *Herpesviridae* family particularly HSV-1, Epstein-Barr virus (EBV), and human cytomegalovirus (HCMV) were detected in the brains of patients with AD[9][10]. In recent years, this theory has regained attention. Several studies have implicated

Herpesviridae viruses, such as HHV-6, HHV-7, and HSV-1, in the pathogenesis of AD.[11] Notably, data from Taiwan's National Health Insurance Research Database have shown that antiviral treatment specifically with drugs like acyclovir is associated with a reduced risk of developing dementia[12]. One argument in favor of the infectious hypothesis is the observed increase in β-amyloid (Aβ) levels in response to microbial invasion. It has been proposed that Aβ may function as an antimicrobial peptide, forming a defensive barrier against pathogens in the brain. To investigate this hypothesis, Eimer and colleagues conducted an experiment in which young mice were infected with HSV-1. Both wild-type controls and transgenic 5xFAD mice (which overexpress human Aβ) were used. The results demonstrated that transgenic mice had increased Aβ plaque deposition in response to infection, which appeared to confer a degree of neuroprotection against HSV-1. These findings suggest that viral infections may influence Aβ dynamics in the CNS as part of a host immune defense mechanism.[13] However, it must be emphasized that while this effect has been observed in animal models, conclusive evidence in humans is still lacking. Moreover, Aβ deposition in the brains of AD patients typically begins 15–20 years before clinical symptoms appear, complicating the establishment of a clear causal link between infection and disease onset in individual patients. Some studies have further suggested that increased Aβ deposition may also be influenced by extracellular amyloid fibers produced by certain gut bacteria. These bacterial amyloids may act as seeds or modulators of endogenous Aβ aggregation in the host, potentially contributing to AD pathology. Microorganisms may access the CNS through multiple routes, including hematogenous spread, local invasion from adjacent tissues (e.g., paranasal sinuses or middle ear), or retrograde transmission along peripheral nerves such as the vagus nerve. For example, Wu et al. demonstrated that intravenous administration of *Candida albicans,* an opportunistic yeast that colonizes the gastrointestinal tract, can induce transient encephalitis in mice, accompanied by increased Aβ deposition, potentially relevant to AD pathogenesis[14]. The direct infection hypothesis posits that pathogens may contribute to the initiation or progression of AD. This view is supported by studies demonstrating correlations between specific microbial presence and disease development. However, it remains uncertain whether these microorganisms are causative agents in AD or whether they merely exacerbate disease progression possibly through reactivation of latent infections or by amplifying neuroinflammatory processes.

Indirect Pathway Linking Gut Microbiota to Alzheimer's Disease: The Neuroimmune-Inflammatory Mechanism

Among the proposed mechanisms connecting gut microbiota to Alzheimer's disease (AD), the indirect pathway mediated through immune and inflammatory modulation is considered the most plausible. This mechanism postulates that alterations in the gut microbiota influence the central nervous system (CNS) via immunoregulatory signals, thereby contributing to the pathogenesis of

AD. Experimental evidence supporting this hypothesis was provided by Erny and colleagues in a 2015 study. They demonstrated that depletion of the gut microbiota in mice using broad-spectrum antibiotics impaired microglial maturation, resulting in reduced responsiveness to viral infections[15]. The study also highlighted the pivotal role of short-chain fatty acids (SCFAs), produced by gut microbiota bacteria, as signaling molecules in the gut-brain axis and in the regulation of microglial function. SCFA receptors, including GPR41 and GPR43, are expressed on the surface of microglia. Through these receptors, SCFAs modulate cytokine production by immune cells such as neutrophils, macrophages, and dendritic cells, and influence the differentiation and proliferation of T and B lymphocytes. Erny et al. further showed that SCFAs, particularly acetate, can modulate microglial activity via epigenetic mechanisms and mitochondrial metabolism[15]. Glial cells, astrocytes and microglia play a crucial role in this mechanism. These cells are well recognized in neurophysiology for their fundamental functions in maintaining brain homeostasis, including neuronal protection, metabolic support, and clearance of apoptotic cells. However, when their function is disrupted particularly in the context of neuroinflammation triggered by gut microbiota dysbiosis this homeostatic balance is impaired.[16][17]. Such dysregulation leads to increased accumulation of β-amyloid and tau proteins, overproduction of pro-inflammatory cytokines, and the generation of reactive oxygen species (ROS). These changes further compromise the integrity of the blood brain barrier (BBB), increasing its permeability and facilitating the progression of neurodegenerative processes[18][19]. Delving into cytological mechanisms, gut dysbiosis may promote the aggregation of β-amyloid and tau proteins through activation of the C/EBPβ–AEP signaling pathway. The transcription factor C/EBPβ, known to facilitate β-amyloid aggregation, is a pro-inflammatory cytokine that regulates the activity of asparagine endopeptidase (AEP). AEP cleaves precursor protein chains of both β-amyloid and tau, thereby promoting their formation and deposition initially within the gut. These pathological protein aggregates can propagate to the brain via the vagus nerve, ultimately contributing to central nervous system deposition and neurodegeneration[20][21][22]. Moreover, pro-inflammatory cytokines released as a result of gut dysbiosis may cross the blood–brain barrier and activate Toll-like receptors (TLRs), specifically TLR1 and TLR2. This activation leads to the stimulation of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway, a well-established pro-inflammatory cascade. Subsequent activation of this pathway may further facilitate the aggregation of β-amyloid and tau proteins in the brain[23]. Animal model studies have consistently shown that manipulation of the gut microbiota composition alters gene expression profiles in glial cells. Although the precise molecular mechanisms underlying the indirect neuroimmune pathway remain incompletely understood, it is increasingly evident that the gut microbiota plays a critical role in maintaining immunological homeostasis by modulating the balance between pro-inflammatory and

anti-inflammatory responses within the gut-brain axis. Dysbiosis-induced immune activation leads to elevated levels of systemic pro-inflammatory cytokines and promotes the migration of activated leukocytes across the blood–brain barrier (BBB). Factors that influence BBB permeability such as aging and genetic predisposition may further increase susceptibility to neuroinflammatory conditions associated with AD.

3.2. SHORT-CHAIN FATTY ACIDS (SCFAs)

Short-chain fatty acids (SCFAs) are carboxylic organic acids containing up to six carbon atoms and are the main end-products of the microbial fermentation of indigestible polysaccharides (dietary fiber) by gut bacteria. The most prominent SCFAs include acetate, propionate, and butyrate. These metabolites play a crucial role not only in maintaining intestinal homeostasis but also in gut–brain communication. SCFAs can directly influence glial cell function, as demonstrated in the aforementioned study by Erny et al. (2015), which highlighted their involvement in microglial maturation and responsiveness[15]. Beyond their roles in the gut, SCFAs are increasingly recognized for their immunomodulatory and neuroprotective effects. Experimental studies have shown that SCFAs are involved in immune responses following ischemic stroke, in multiple sclerosis, and in recovery after traumatic brain injury[24]. However, despite their many beneficial properties, certain studies suggest that SCFAs may exert context-dependent deleterious effects. For instance, sodium butyrate administration in the absence of gut microbiota has been associated with increased susceptibility to neuroinfections and exacerbation of neurodegenerative processes[25]. This effect was particularly evident in older mice (35 weeks of age) in tauopathy models, but not in younger animals (15 weeks), indicating a possible age- and microbiota-dependent response[26]

3.3. GENETICS AND SEX-RELATED FACTORS

While gut microbiota composition is shaped by a variety of environmental and internal factors, host genotype is one of the key determinants. Particular attention has been given to the role of apolipoprotein E (APOE), a well-established genetic risk factor for Alzheimer’s Disease and other neurodegenerative conditions. Studies have shown that allelic variants of APOE are associated with distinct microbial signatures. Individuals carrying the APOE2 allele exhibit a higher abundance of SCFA-producing bacteria, particularly members of the *Ruminococcaceae* and *Lachnospiraceae* families, compared to APOE3 carriers. Conversely, the lowest levels of these beneficial microbes have been observed in APOE4 carriers, who also possess the highest genetic risk for AD. This relationship may be mediated by the role of apolipoprotein E in lipid metabolism and transport across the gut–blood barrier. Each APOE isoform differs in its influence on lipid absorption and distribution, which can directly alter the intestinal microenvironment and, consequently, microbiota composition.[27][28][29] In addition to genetic variation, biological sex is increasingly recognized

as a significant factor influencing gut microbiota composition and immune responses to pathogens.There is influence of the gut microbiota on microglial maturation during development exhibits a sex-specific pattern [31][32] Females typically exhibit a more robust innate immune response, more rapid T cell activation, and heightened antibody production compared to males[20]. These sex-related differences may be partially attributed to the effects of sex hormones particularly estrogen which modulates both immune and neuroinflammatory responses. Furthermore, hormonal differences between sexes can influence the microbiota's response to antibiotics, which has important implications for microbiome-targeted therapies and treatment strategies in neuroimmune and neurodegenerative diseases.[31][32]

4. THERAPEUTIC STRATEGIES TARGETING THE GUT MICROBIOTA IN ALZHEIMER'S DISEASE

4.1. Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) is a therapeutic strategy widely recognized for its efficacy in treating *Clostridioides difficile* infection and is increasingly being considered as a potential intervention to slow the progression of Alzheimer's disease (AD). The procedure involves transferring gut microbiota from a healthy donor to the gastrointestinal tract of a recipient, aiming to restore microbial balance and reduce neuroinflammation[33]. In a study by Sun et al., transplantation of fecal microbiota from healthy mice into APP/PS1 transgenic models resulted in decreased levels of β-amyloid and hyperphosphorylated tau after four weeks of treatment[34]. Similarly, Kim and colleagues used FMT from healthy donors in ADLPAPT mouse models and observed a reduction in pathological proteins, increased expression of glial fibrillary acidic protein (GFAP), elevated monocyte counts, and improved behavioral outcomes[35]. However, it is important to note that some studies have reported opposing effects, such as increased β-amyloid deposition following FMT, highlighting the need for further investigation[20]. Other clinical reports suggest potential cognitive benefits of FMT in AD patients. For example, cognitive improvement was observed in an 82-year-old male patient following FMT from his healthy 85-year-old wife [36] A similar case involved a 90-year-old woman who received a transplant from a 27-year-old donor, resulting in increased microbial diversity and SCFA levels, which correlated with improved cognitive performance[37]. Nonetheless, due to the limited number of clinical trials, robust, controlled studies are required to validate these preliminary findings.

4.2. Probiotics

Probiotics primarily consisting of strains from the *Lactobacillus* and *Bifidobacterium* genera are commonly used in clinical settings to restore gut microbial balance after antibiotic treatment or in gastrointestinal disorders. Given the association between gut dysbiosis and AD, probiotics may offer neuroprotective effects that could slow the progression of dementia. In a study by Kaur et al., administration of the probiotic formulation VSL#3 to 6-month-old APP^NL-G-F mice for 8 weeks increased the abundance of *Clostridia*, *Lachnospiraceae*, and *Akkermansia*, along with elevated SCFA levels[38]. Similarly, Abdelhamid and colleagues reported that supplementation with *Bifidobacterium breve* for 4 months in 3-month-old mice reduced β-amyloid accumulation and pro-inflammatory cytokines[39]. In a randomized, double-blind clinical trial, patients with Alzheimer's disease were divided into two groups: one receiving a probiotic supplement and the other receiving a placebo. The results demonstrated that individuals in the probiotic group showed significantly improved performance in cognitive function tests, particularly in executive functioning and memory. Additionally, these patients exhibited reduced levels of inflammatory markers, lipid concentrations, and insulin resistance parameters commonly elevated in individuals with Alzheimer's disease.[40] However, in another study, patients with Alzheimer’s disease, aged 65 to 90 years, were randomly assigned to two groups: one receiving a probiotic and the other a placebo. After 12 weeks of probiotic supplementation, the researchers observed no significant differences between the groups the levels of pro-inflammatory markers remained comparable[41]. The efficacy of probiotic interventions likely depends on various factors, including strain composition, dosage, treatment duration, and the individual’s microbiome profile. Further standardized and large-scale clinical trials are needed to optimize probiotic strategies for AD management.

4.3. Pharmacological Modulation of the Microbiota

Pharmacotherapy can also alter gut microbial composition. While antibiotics induce dysbiosis by indiscriminately eliminating both harmful and beneficial bacteria, other drugs such as metformin, used in type 2 diabetes can modulate the gut microbiome in ways that may impact neurological health[42][43], Understanding how specific medications affect the microbiota may enable the development of personalized pharmacological interventions. This approach, often referred to as pharmacomicrobiomics, could enhance therapeutic efficacy in neurodegenerative diseases by integrating microbiome-based considerations into drug therapy design.

4.4. Lifestyle Factors: Diet, Physical Activity, and Sleep

Lifestyle plays a fundamental role in shaping the gut microbiota and, by extension, influences the risk and progression of Alzheimer’s disease.

- Diet: The Western dietary pattern rich in saturated fats and simple sugars promotes the growth of bacteria that produce trimethylamine N-oxide (TMAO), a metabolite linked to neurodegeneration.[44] In contrast, the Mediterranean diet, characterized by high fiber and vegetable intake, enhances SCFA production and is associated with a reduced risk of AD[45].
- Physical Activity: Research by Mitchell et al. demonstrated that regular exercise increases the abundance of butyrate-producing bacteria (e.g., *Faecalibacterium*) in both rodents and humans. Exercise appears to exert anti-inflammatory effects by modulating gut microbiota and enhancing intestinal barrier integrity[46].
- Sleep: A bidirectional relationship exists between sleep quality and gut microbiota composition. Dysbiosis can disrupt circadian rhythms and impair sleep, while poor sleep reduces microbial diversity. The hypothalamic–pituitary–adrenal (HPA) axis is thought to mediate this interaction. Both dysbiosis and sleep disturbances have been implicated in the pathogenesis of AD.[47][48]

5. DISCUSSION

The findings of this review support a growing body of evidence suggesting that gut microbiota plays a significant role in the pathophysiology of Alzheimer's disease (AD). Dysbiosis, characterized by an imbalance between pro-inflammatory and anti-inflammatory bacterial species, may exacerbate neurodegenerative processes through both direct and indirect pathways.Direct mechanisms involve translocation of pathogens across a compromised intestinal barrier and blood-brain barrier, potentially triggering amyloid-β aggregation and neuroinflammation. Indirectly, gut-derived systemic inflammation activates microglia and astrocytes, leading to neuronal damage. These mechanisms align with emerging concepts of the gut-brain axis and its role in central nervous system (CNS) homeostasis.Notably, interventions such as probiotic supplementation, fecal microbiota transplantation (FMT), and dietary modification have demonstrated neuroprotective effects in preclinical models and small-scale clinical studies. While promising, these therapies require validation in larger, controlled human trials to determine efficacy, safety, and long-term outcomes. Furthermore, factors such as APOE genotype, sex differences, and age-related immune changes appear to modulate the gut-brain relationship, underscoring the complexity of personalized approaches in AD prevention and treatment. Overall, targeting the gut microbiota represents an innovative and potentially transformative direction in AD research. However, causality remains difficult to establish, and future studies should aim to integrate microbiome data with genomics and

clinical phenotypes to better understand individual variability in disease progression and therapeutic response.

6. CONCLUSION

Current evidence highlights a significant link between gut microbiota composition and the pathogenesis of Alzheimer's disease. Dysbiosis appears to contribute to neuroinflammation, blood-brain barrier disruption, and accumulation of amyloid-β and tau proteins via gut-brain axis mechanisms. Interventions targeting the microbiome such as probiotics, fecal microbiota transplantation, dietary changes, and lifestyle modifications have shown potential in modulating these pathways and improving cognitive outcomes, particularly in early disease stages.Although results from animal models and preliminary human studies are promising, larger, well-controlled clinical trials are needed to confirm these findings and to establish safe and effective microbiota-targeted therapies for AD. Understanding individual variability including genetic, immune, and lifestyle factors will be crucial for developing personalized interventions.

7. DISCLOSURE:

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