ejpmr, 2025, 12(3), 145-155

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

RELATIONSHIP BETWEEN PSYCHEDELICS AND GUT MICROBIOME

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Article Received on 12/01/2025 **Article Revised on 02/02/2025** **Article Published on 23/02/2025**

ABSTRACT

The axis of the gut-brain is a network of neurological, immunological, and endocrine processes that connects the brain and gut microbiome in both directions in this review, the GBA's mechanics are investigated. with particular attention to how it affects gastrointestinal and mental health. Psychedelics have shown promise as treatment for mental health conditions like addiction, anxiety, and depression, especially serotonergic ones like psilocybin, LSD, and DMT. These substances modulate the GBA, impacting neural plasticity, immune responses, and neurotransmitter signaling with possible contributions to changing the composition of the gut microbiome. The interplay between gut microbiota and psychedelics offers insights into their therapeutic effects. While gut bacteria can influence serotonin synthesis and drug metabolism, psychedelics might reciprocally affect microbial diversity and composition. Preliminary findings suggest psychedelics could enhance neurogenesis, synaptic connectivity, and mental health outcomes via microbiome-mediated pathways. However, research on these interactions remains nascent, requiring further exploration of long-term effects and individual variability. This review highlights the potential of integrating gut microbiota into psychedelic therapies to enable personalized medicine. It emphasizes the need for standardized protocols, regulatory reforms, and expanded studies into broader medical applications, aiming to transform mental health and beyond through the GBA-psychedelic connection.

KEYWORDS: Gut microbiome, Gut brain axis, Psychedelics, HPA axis, Psilocybin, lysergic acid diethylamide.

1. INTRODUCTION TO GUT BRAIN AXIS AND PSYCHEDELICS

1.1 Brief overview of the brain-gut axis

The human body's gastrointestinal (GI) tract, skin, and mucosal surfaces are all home to a varied population of bacteria known as the microbiota.[1] Microbes and humans have developed a symbiotic relationship through co-evolution, which has influenced physiological development.[2]

Microbes, primarily bacteria, play a vital role in human health, with about 40 trillion microbial cells coexisting with 30 trillion human cells. The gut microbiota, consisting of bacteria, viruses, fungi, and archaea, is a key component, vastly outnumbering eukaryotic and archaeal cells.[1][3] The gut microbiome, 150 times larger than the human genome, supports metabolic functions like vitamin synthesis, fiber breakdown, and immune development by distinguishing pathogens from self-antigens.[4][5] The gut-brain axis (GBA), a two-way network of immune, hormonal, and neurological signals, links gut health to mental health, with its dysregulation tied to conditions like anxiety, depression, and cognitive decline.[6] Via pathways like the vagus nerve and HPA axis, the GBA facilitates top-down effects (e.g., stress affecting gut function) and bottom-up effects (e.g., gut microbes influencing behavior and brain function), emphasizing the connection between mental and gastrointestinal health.[7][2][8]

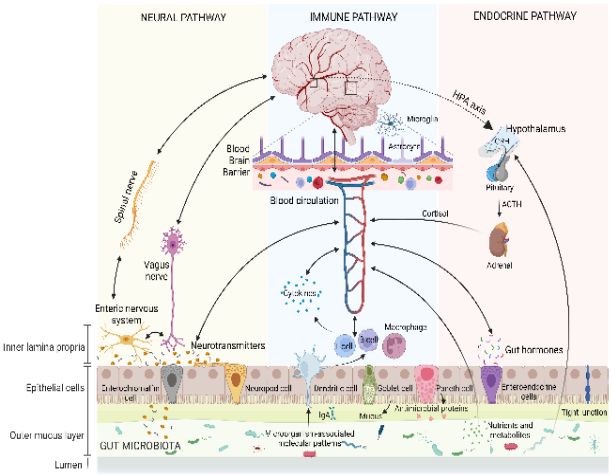

Fig. 1: Depicts the neurological, endocrine, and immune systems, among others.[8]

1.2 The Axis of the Gut-Brain and Addiction

Despite the societal impact of substance use disorders, effective therapies remain limited, highlighting the need

for new approaches.[9] Recent research shows the gut-brain axis influences behavior, medication responses, and processes like reward and satiety through chemical signals (metabolites, hormones, neurotransmitters) and the vagus nerve. Gut microbes also play a key role in immune system function.[10]

1.3 Introduction to psychedelics

In the mid-2000s, research on gut microbiota's influence on host traits coincided with the "psychedelic renaissance," renewing interest in psychedelics for treating mental health conditions like treatment-resistant depression, anxiety, OCD, and addiction.[11] Traditionally used in healing rituals, psychedelics are now recognized for their therapeutic potential, supported by clinical trials demonstrating symptom relief and reduced addictive behaviors.[11][12][13] Derived from the Greek "psyche" (thought) and "delos" (reveal), psychedelics induce hallucinations, altered perceptions, cognitive shifts, and spiritual experiences.[14]

1.4 The relationship between the brain-gut axis and psychedelics

Psilocybin, a natural tryptamine alkaloid found in Psilocybin mushrooms, primarily targets serotonin 5-HT2A/C receptors. Traditionally, these mushrooms were used in cultural and religious rituals for divination. Psilocybin's psychological effects, akin to LSD, mescaline, and DMT, include altered perception, cognition, mood, sensory distortions, and dissociative experiences.[14] Emerging research on psychedelics and the brain-gut axis (GBA) implies that substances like psilocybin and LSD could have an impact mental well-being by altering microbiome in the gut. These changes can affect how the brain works. and mood through the GBA, potentially explaining their psychological effects and enabling personalized treatments based on microbiome variations.[15]

1.5 Objective and scope of the review

The gut microbiome may influence the psychological effects of psychedelics, though direct research is limited. Insights from serotonergic antidepressants will guide hypotheses on how serotonergic psychedelics interact with the microbiota-gut-brain axis, highlighting knowledge gaps. Understanding this interaction could revolutionize clinical practices by using individual microbiota variability to predict responses to psychedelic therapies, enabling personalized medicine. A framework incorporating the gut microbiome will be proposed to guide future psychedelic research.

2. GUT BRAIN AXIS MECHANISM AND PATHWAYS

2.1 Anatomy and function of the Gut Brain axis

2.1.1 Anatomy

The gut-brain axis is a complex network linking the central nervous system (CNS) to the digestive and metabolic systems, including the gastrointestinal tract, liver, and pancreas. This bidirectional communication occurs via pathways like the vagus, splanchnic, mesenteric, and pelvic nerves. Despite its simpler structure compared to the CNS, the gut-brain axis involves intricate neurochemical and anatomical interactions.[16]

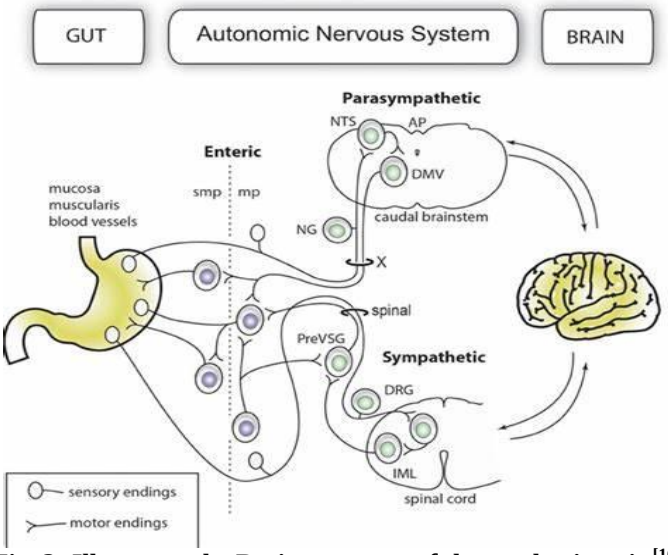

Fig. 2: Illustrates the Basic structure of the gut-brain axis.[16]

2.1.2 Functions

Strategies to study the microbiota–gut–brain axis include using germ-free mice to examine microbiota loss and its impact on CNS function or isolating effects of specific entities like probiotics. Transplanting human or disease-associated microbiota into germ-free mice enables research on microbiota "humanization." Probiotic administration in animals or humans helps evaluate bacterial effects on the host, with species-specific differences in their influence on the gut-brain axis. Infection studies explore how pathogenic bacteria affect behavior via immune activation, while antibiotics offer a

controlled means to alter microbiota composition, despite their systemic toxicity.[17][7]

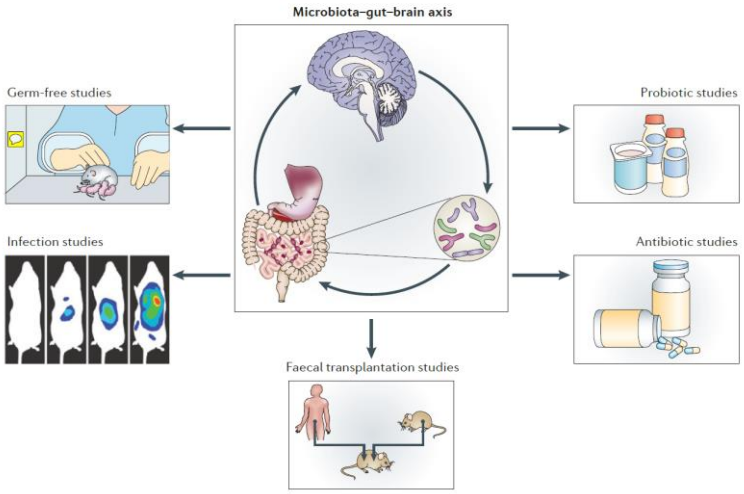

Fig. 3: Functions of Gut Brain axis.[17]

2.2 Factors Influencing

Dietary practices, antibiotic use, genetic predisposition, and environmental exposures are some of the factors that affect the variety and composition of gut microflora. Key contributors are**:**

1. **Diet:** Nutrient availability significantly shapes microbial populations. High-fiber diets foster beneficial bacteria, while high-fat, high-sugar diets can lead to dysbiosis.
2. **Antibiotics:** Antibiotic usage disrupts the microbiota, often leading to reduced diversity and the overgrowth of pathogenic strains.
3. **Host Genetics:** Genetic factors influence gut microbial composition, affecting immune system interactions and microbiome stability.
4. **Environmental Factors:** Lifestyle choices, stress, and exposure to toxins also play crucial roles.[18]

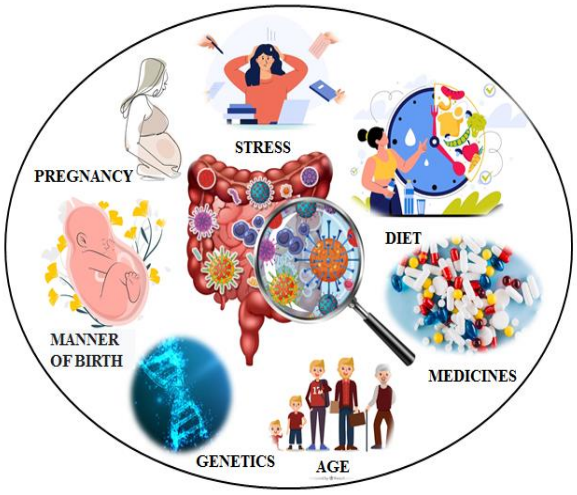

Fig. 4: Factors affecting the Gut Microbiota.[18]

2.3 The function of microbiota in Brain Gut Communication

There is evidence that psychedelics can change the gut microbiota's makeup, which may affect how body reacts to these drugs. This interaction likely affects gut-brain axis communication and behavior through mechanisms such as serotonergic neurotransmission, as both psychedelics and gut bacteria can modulate brain serotonin levels. Additional routes include effects on the vagus nerve and the enteric nervous system, immunological system, HPA axis, and psychedelics' common targets with the gut microbiota, which will be covered in more detail.[18]

2.3.1 Signaling through Immune system

Gut microbiota and psychedelics both influence the immune system, with psychedelics exhibiting immune-modulating and anti-inflammatory properties.[19][20] Gut microbiota plays a vital role in the development and function of the peripheral immune system and the maturation of microglia, the brain's innate immune cells.[21] Classical psychedelics modulate innate and adaptive immunity by inhibiting inflammatory and antigen presentation responses and affecting lymphocyte subtypes like cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells. While receptors associated with psychedelics' effects are present in immune and hematopoietic cells, their precise modulatory mechanisms in neuroimmune signaling remain largely unknown.[22]

A. Immunomodulatory effect of some Psychedelics

Psilocybin reduces inflammatory cytokines TNF-α and IL-1β in human macrophages after LPS stimulation, while psilocin and DMT decrease immune-related proteins (TLR4, p65, CD80) and increase TREM2 in mouse microglia, promoting immune balance.[23] LSD inhibits B cell growth, IL-2, IL-4, and IL-6 release, and CD8+ CTL activation at high concentrations (100 µM), but enhances NK cell activity at lower doses (0.0001–0.1 µM), suggesting dose-dependent effects on anti-tumor and anti-viral responses.[24] DMT also promotes anti-inflammatory functions by reducing p65, CD80, and TLR4 expression while increasing TREM2 mRNA in

microglia.[25] Ayahuasca use alters immune cell balance, lowering CD3 and CD4 lymphocyte counts while increasing NK cells.[26] The microbiota-immune system interaction, integral to the gut-brain axis, is essential for immune development, tolerance, and brain function.[27]

2.3.2 Signaling Through HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis, a key endocrine system, regulates stress responses, metabolism, and physiological processes. The microbiota-gut-brain axis (MGBA) plays a vital role within the HPA axis. Stress, including inflammatory signals like TNF and IL-6, activates the HPA axis, causing cortisol release to reduce inflammation and regulate immune activity while providing feedback to prevent overactivation.[27][28] Stress induces corticotropin-releasing hormone (CRH) from the hypothalamus, stimulating ACTH production by the pituitary and cortisol release from adrenal glands, affecting gut and brain functions.[29] Chronic HPA hyperactivity disrupts gut microbiota, weakens gut barriers ("leaky gut"), and triggers inflammation. Germ-free mice exhibit heightened stress responses and hyperactive HPA activity, emphasizing the gut microbiota's role in stress regulation and HPA balance.[30]

2.3.3 Using the vagus nerve to signal

The vagus nerve, the tenth cranial nerve, connects the brainstem to visceral organs, enabling gut-brain communication via 80–90% afferent and 10–20% efferent fibers. This pathway is vital for maintaining homeostasis, regulating mood, appetite, stress responses, and inflammation.[31] Vagal afferents influence the hypothalamic-pituitary-adrenal (HPA) axis, mediating cortisol release during stress, which affects the brain and other organs. Animal studies show that vagal disruption impairs stress responses, cognition, and hippocampal neurogenesis, while activating microglia and causing anxiety-like behaviors. Conversely, vagus nerve stimulation enhances synaptic plasticity, learning, memory, and hippocampal neurogenesis by increasing BDNF expression and modulating neurotransmitters.[32]

2.3.4 Signaling through the nervous system of the stomach

The enteric nervous system (ENS), with 200–600 million neurons, regulates intestinal stability by coordinating with the immune system, endocrine system, and gut microbiota.[33] Composed of submucosal and myenteric plexuses, it communicates with the CNS via the vagus nerve and prevertebral ganglia. Known as the "second brain," the ENS is influenced by microbiota through TLR-2 and TLR-4 pathways. Microbial metabolites like GABA, histamine, SCFAs, and serotonin impact ENS function and mucosal health. Germ-free and dysbiotic mice show impaired ENS structure, signaling, and neuronal function.[34][35]

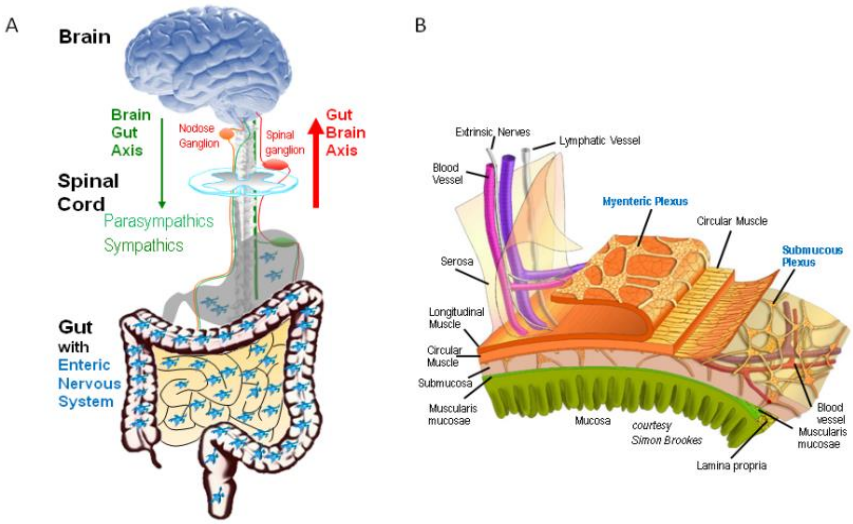

Fig. 5: The stomach's neurological system, "A little brain in the gut." Panel A illustrates gut regulation by the enteric nervous system (ENS) and its interaction with the brain via the gut-brain axis. Panel B highlights the ENS's complexity, focusing on the myenteric and submucosal plexuses (Prof. Simon Brookes, Flinders University).

2.3.5 Signaling Through Neurotransmitter

The gut-brain axis (GBA) relies on neurotransmitters (NTs) and stress hormones for bidirectional communication, regulating gut functions like blood flow, nutrient absorption, immunity, motility, and microbiota activity.[36][37] Key NTs, including dopamine, serotonin, adrenaline, and norepinephrine, play crucial roles in gut health, mood, memory, sleep, and cognition while supporting neuron growth and survival. Imbalances in NTs are linked to mental health issues and neurodegenerative diseases. Although NTs cannot cross the blood-brain barrier, they influence brain function through vagus nerve signals and the enteric nervous system.[37][38]

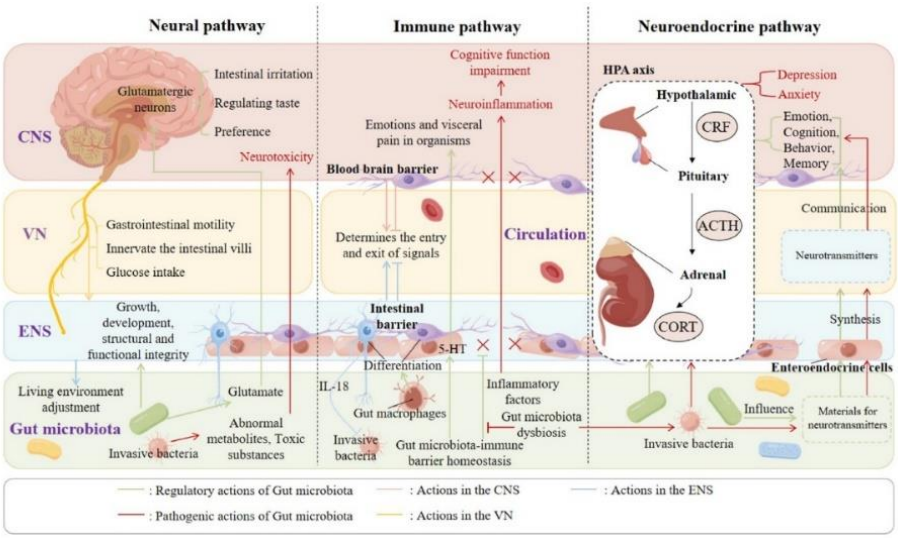

Fig. 6: The brain-gut axis (GBA) is maintained by the neuronal, immunological, and neuroendocrine mechanisms of Interaction between gut microorganisms and the host.[39]

3. PSYCHEDELICS: CLASSIFICATION AND MECHANISM OF ACTION

3.1 Classification

Psychedelics encompass a variety of substances that induce altered states of consciousness (ASC) and "mystical-type" experiences. The term "psychedelic," meaning "mind manifesting," was coined by Humphrey Osmond in 1956 as a positive alternative to "psychomimetic," meaning "mimicking madness".[40] Psychedelics, taken orally, inhaled, or absorbed, produce ASCs marked by changes in perception, cognition, and mood. These experiences vary based on factors like environment, emotion, and cognition. Recent studies highlight their therapeutic potential for conditions like depression, OCD, anorexia nervosa, alcohol use disorder, anxiety, and even anti-inflammatory effects.[41]

Classic psychedelics fall into three chemical classes: indoleamines (e.g., DMT, psilocybin, psilocin), synthetic amphetamines and phenylalkylamines (e.g., mescaline, Iodoamphetamine), and semi-synthetic ergolines (e.g., LSD). Phenylalkylamines primarily act as selective agonists of 5-HT2 receptors, including types A, B, and C receptor.[42]

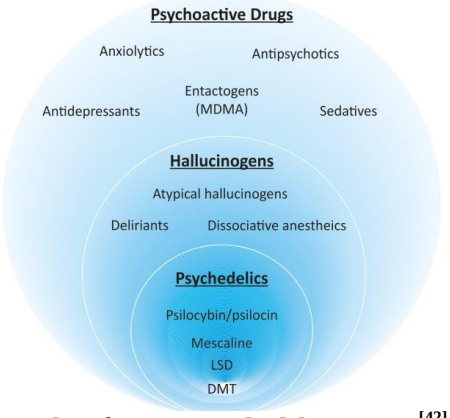

Fig. 7: Classification Psychedelics Drugs.[42]

3.2 Mechanism of action

The primary way that hallucinogens cause their psychedelic effects is by functioning as agonists at the cortex's 5-HT2A receptor.[41] The 5-HT2A receptor is a member of the G-protein-coupled receptor (GPCR) family and is connected to the Gq/11 protein. When activated, it starts the hydrolysis of phosphoinositide, which yields inositol triphosphate (IP3) and diacylglycerol (DAG). This mechanism depolarizes the membrane and releases intracellular calcium reserves, both of which are essential for signal transduction and the physiological consequences of the receptor.[43]

3.2.1 5-HT2A Receptor as Psychedelics' Main Target

The intensity of psychedelic experiences correlates with 5-HT2A receptor activation, particularly in the prefrontal cortex (PFC).[44] Psychedelics like psilocybin, DMT, LSD, mescaline, and DOI act as agonists at serotonin receptors (5-HT1, 5-HT2, 5-HT6, 5-HT7) and also affect adrenergic and dopaminergic receptors, with 5-HT2A, 5-HT2B, and 5-HT2C as primary targets. Activation of 5-HT2A receptors in the PFC alters blood flow and connectivity in brain regions like the hippocampus, thalamus, amygdala, and cingulate cortex, contributing to psychedelics' effects on perception and cognition.[45]

A unique subpopulation of neurons in rat brains, primarily in the PFC and claustrum, responds directly to psychedelics. These neurons, with higher 5-HT2A receptor gene expression, trigger a response involving astrocytes and other cells, such as GABAergic interneurons expressing parvalbumin and somatostatin.[46]

3.2.2 5-HT2A Receptor Activation's Effect on Behavior

The receptor 5-HT2A is a good indicator of hallucinogenic activity in animal studies and is essential for producing psychedelic experiences in humans. The

head-twitch response (HTR) or wet dog shake (WDS) test is one way to gauge this, and it has good construct validity. This test measures the rhythmic head movements that occur in rodents when psychedelic substances that function as 5-HT2A receptor agonists are administered. Although 5-HT2A receptor agonists are the primary target of the head-twitch response (HTR) assay, false positives have been reported for compounds like 5-hydroxytryptophan, p-chloroamphetamine, and fenfluramine. Despite these limitations, the HTR assay demonstrates strong predictive validity and sensitivity for identifying drugs with psychedelic effects. However, the assay has low face validity, as not all individuals exhibit head-twitching behavior when exposed to psychoactive substances. For instance, Lisuride, a non-psychedelic 5-HT2A receptor agonist, does not induce the head-twitch response.[47]

3.3 Overview of classic Psychedelics

Psilocybin

Psilocybin, a naturally occurring alkaloid in the tryptamine class, primarily affects serotonin receptors, particularly 5HT2A and 5-HT2C, to induce psychedelic effects. Found in Psilocybe mushrooms, its psychological effects include alterations in perception, emotion, cognition, and body awareness, such as mood swings, dissociative states, cognitive difficulties, and sensory distortions like visual and auditory changes. These effects influence how individuals perceive and understand their environment and mental states, including both sensory enhancements and disruptions.[48]

LSD

Lysergic acid diethylamide (LSD), a classic serotonergic psychedelic, produces psychotropic effects by binding to the serotonin 5-HT2A receptor. Derived from the ergot fungus, LSD is being reexamined as a potential treatment for anxiety, depression, and other mental health issues. Its effects, lasting eight to twelve hours, significantly impact emotional states, cognition, and sensory perception.[49]

DMT

N, N-dimethyltryptamine (DMT), a potent serotonergic psychedelic acting on the 5-HT2A receptor, is found in various plants, including those used to make ayahuasca.[50] DMT induces profound changes in perception, thought, and emotion, often involving vivid sensory experiences, altered reality or self-perception, and mystical states.[51]

Ayahuasca

Ayahuasca, a traditional Amazonian beverage, is made by boiling the leaves of *Psychotria viridis* (rich in DMT) with the stems of *Banisteriopsis caapi* (containing β-carbolines like harmine, THH, and harmaline). These β-carbolines inhibit monoamine oxidase A (MAO-A), preventing DMT from being broken down and allowing it to cross the blood-brain barrier. DMT then activates serotonin receptors (5-HT1A, 5-HT2A, and 5-HT2C) in the brain, inducing psychedelic effects.[52]

4. PSYCHEDELICS AND NEUROPLASTICITY

Neuroplasticity, essential for mental health, enables the brain to adapt through structural and functional changes.[53] Psychedelics promote neuroplasticity and neural repair, benefiting conditions like chronic stress, neuroinflammation, and depression.[54] The vagus nerve influences neuroplasticity by modulating gut flora and BDNF levels, vital for neurogenesis, while its disruption lowers BDNF, affecting conditions like autism and depression.[55][56] Dysbiosis impairs neurogenesis and LTP via microglia activation, but probiotics restore cortical plasticity in antibiotic-treated mice.[57][58][59] Psychedelics affect neurogenesis differently: psilocybin inhibits hippocampal regeneration at high doses but stimulates it at lower doses, while extended high doses promote neuron growth. DMT and 5-MeO-DMT enhance neurogenesis, while LSD and DOI show no significant effects. Psychedelics support synapse and dendritic growth, LTP, and neuroplasticity-related gene expression, highlighting their role in brain recovery.[60][61]

5. INFLUENCE OF GUT MICROBIOTA ON PSYCHEDELICS

Gut microbiota significantly influences drug metabolism, impacting drug availability, efficacy, and safety, with potential for toxicity. The efficacy of SSRIs in depression treatment is linked to gut bacteria like Blautia, Bifidobacterium, and Coprococcus.[62][63] In a mouse model of maternal immune activation (MIA), changes in gut microbiota enhanced the effects of the psychedelic DOI by upregulating 5-HT2A receptors in the frontal cortex. Bacteria like Candidatus and Ruminococcaceae negatively correlated with receptor density, while Lactobacillaceae showed a positive correlation, demonstrating how gut bacteria modulate psychedelic effects.[64][65]

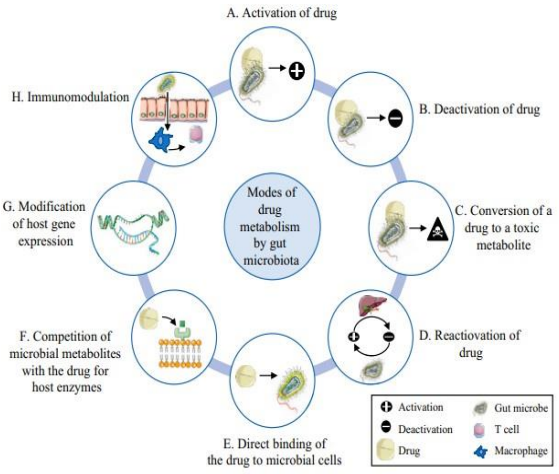

Fig. 8: Drug metabolism is influenced by the gut flora in a number of ways.[65]

6. INFLUENCE OF PSYCHEDELICS ON GUT MICROBIOTA

Studies on serotonergic psychedelics like psilocybin and its effects on gut microbiota are limited. A preliminary study showed that psilocybin increased Verrucomicrobia and Actinobacteria while reducing Proteobacteria in rats, suggesting a microbiota influence.[2] SSRIs also alter gut microbiota and have antibacterial effects.[66] Psychedelics like ayahuasca may impact the gut microbiome through laxative effects mediated by 5-HT2A receptors, aligning with serotonin's effects on peristalsis and secretion.[66][67] Gut bacteria influence serotonin production, affecting mood and gastrointestinal function.[68] Oral serotonin increases spore-forming bacteria, with Turicibacter sanguinis absorbing serotonin via a protein similar to the mammalian serotonin reuptake transporter.[2] These findings suggest psychedelics may alter gut microbiota composition, influencing brain function via the gut-brain axis.

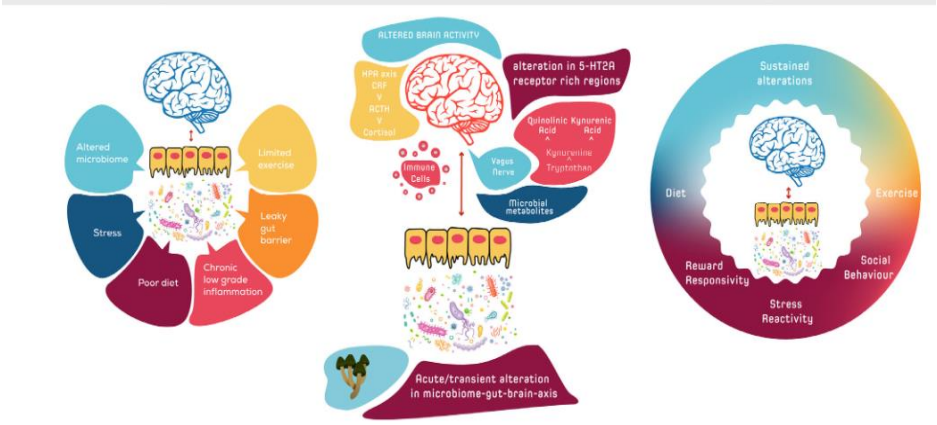

Fig. 9: The Psilocybiome's host-microbiota-psychedelic interactions suggest that the MGB axis plays a significant role in controlling the effects of psychedelic therapy.[69]

7. LIMITATION AND FUTURE DIRECTIONS OF PSYCHEDELICS ON GUT BRAIN AXIS

Although psychedelics show promise for treating mental health conditions, several challenges remain. The variability of psychedelic experiences, influenced by factors like environment, mindset, and therapeutic relationships, leads to inconsistent clinical outcomes, highlighting the need for standardization. Genetic differences in drug metabolism further affect safety and efficacy, necessitating tailored approaches like pharmacogenomics and optimized dosing strategies.

Long-term effects of psychedelic therapy remain poorly understood, requiring follow-up studies to assess outcome sustainability and detect late-onset risks. Integration therapy, essential for applying psychedelic insights to daily life, is hindered by limited training and protocols, calling for further research. Legal and regulatory barriers also restrict access, emphasizing the need for evidence-based policy reform.

Emerging research suggests gut microbiota may influence psychedelic effects, presenting opportunities for microbiome-targeted therapies, which should be explored in controlled trials. Additionally, preventing adverse effects like hallucinogen-persisting perception disorder (HPPD) and psychosis is crucial, especially for vulnerable individuals. Beyond mental health, future research should explore psychedelic applications in immunology, neurology, and other medical fields.[70]

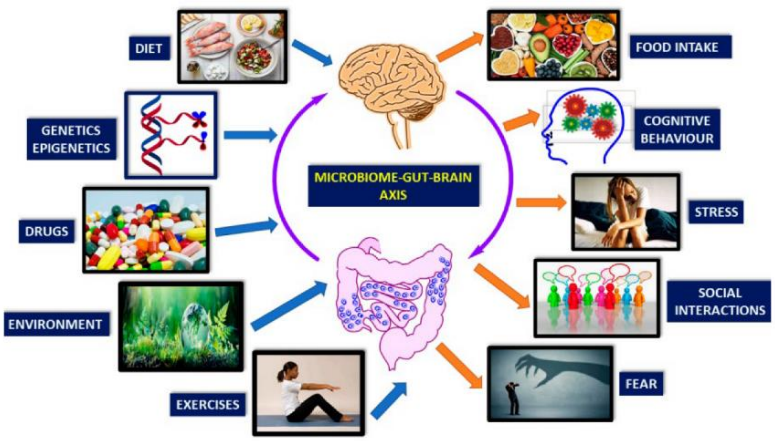

Fig. 10: Research Opportunities and Knowledge Gaps in the Brain-Gut-Microbiota Axis.[70]

8. CONCLUSION

The relationship between gut microbiota, psychedelics, and the gut-brain axis (GBA) offers a promising way to understand and treat complex mental health conditions. The GBA is impacted by psychedelics, especially serotonergic substances like psilocybin, LSD, and DMT, which alter immunological responses, gut microbiota composition, and neurotransmission. By increasing neuroplasticity, decreasing inflammation, and customizing therapy responses according to individual microbiome profiles, these interactions have the potential to improve mental health outcomes. There are still a number of unanswered questions regarding the long-term impacts and underlying mechanisms of the gut-microbiota-psychedelic interactions, despite tremendous progress.

The necessity for tailored therapies is highlighted by the variation in therapy responses, which can be influenced by human characteristics such as genetics, gut microbiota makeup, and environmental circumstances. Moreover, there is still a lack of research on how to incorporate psychedelic experiences into everyday life and create standard procedures.

Future studies should concentrate on resolving these issues, investigating how the microbiota influences the results of psychedelic therapy, and broadening the use of psychedelics in neurological, immunological, and other medical domains. Filling up these information gaps may lead to novel, microbiome-focused treatments, which would change treatment methods and enhance patient outcomes.

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