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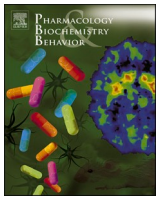

Review

Advancements in psychedelic research: Effects, mechanisms, and therapeutic potential as emerging antidepressants

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ABSTRACT

Major depressive disorder (MDD) causes great physical and mental suffering to patients while also imposing a tremendous economic burden on the global economy. Psychedelics, also known as serotonergic hallucinogens, are potent psychoactive compounds known for their ability to alter mood, perception, and a range of cognitive functions. Increasing evidence suggests that some psychedelics positively facilitate individual social functions, with rapid and sustained improvement in symptoms associated with MDD. Consequently, the application of psychedelics in the treatment of MDD has garnered considerable attention from researchers in recent years. This review examines recent advancements in evaluating the behavioral and physiological effects of psychedelics in both preclinical animal models and clinical trials focused on MDD. Additionally, we summarize and discuss the cellular, brain region, and circuit-level mechanisms, as well as potential intracellular signaling pathways, that may contribute to the antidepressant effects of psychedelics. Based on current evidence, we conclude that psychedelics hold significant promise as therapeutic agents for MDD.

1. Introduction

Major depressive disorder (MDD) is a common, chronic and debilitating disease that brings significant physical and emotional suffering to both patients and their families (Yuan et al., 2023). Studies indicate that around 300 million people worldwide are affected by MDD, which contributes to a substantial global economic burden (Yuan et al., 2023; Collaborators C-M D, 2021). The primary symptoms of MDD include persistent low mood, loss of interest, and decreased pleasure (Sidney, 2008). Additionally, MDD is often accompanied by cognitive impairment and a variety of physical symptoms, such as reduced appetite, sleep disturbances, weight loss, and abnormal behavioral activities (Madhukar, 2005). Pharmacotherapy remains the cornerstone of MDD treatment, with first-line antidepressants typically including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) (Dionisie et al., 2021). While these medications can relieve depressive symptoms in some patients, they present notable limitations, including a slow onset of action, low remission rates, and various side effects (Kasper et al., 2006). Thus, the development of novel, fast-acting antidepressants is an urgent research focus and a crucial clinical need.

Psychedelics are powerful psychoactive substances known to alter mood, perception, and various cognitive functions (N, 2016). In fact, as early as the mid-20th century, some studies reported that certain psychedelic could effectively alleviate symptoms of low mood and demonstrated substantial antidepressant potential. Despite this, research into the antidepressant effects and mechanisms of psychedelics faced a lengthy stagnation due to their perceptual distortions, hallucinogenic effects, and strict regulatory controls (Carhart-Harris and Goodwin, 2017). Since the late 20th century, however, with the advancement of science and technology, along with a renewed interest in the therapeutic potential of psychedelics, have led to a gradual resurgence in studying these substances for treating psychiatric disorders, particularly MDD. Numerous studies have demonstrated that psychedelics can significantly alleviate depression-like symptoms (e.g., low mood, anxiety, reduced quality of life, and negative life attitudes) in patients with MDD, treatment-resistant depression (TRD), and end-of-life distress in individuals with advanced-stage cancer, showing a high

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level of tolerability (Davis et al., 2021; Raison et al., 2023; Goodwin et al., 2022; Griffiths et al., 2016). This highlights the promising potential of psychedelics as innovative and effective antidepressants. In this review, we summarize and examine the antidepressant effects and underlying mechanisms of psychedelics, aiming to provide insights that may guide future directions in psychedelics-based therapies for MDD as well as the design and development of novel antidepressant treatments.

2. Definition and classification of psychedelics

Hallucinogens are a broad category of psychoactive substances that induce changes in consciousness, leading to pronounced shifts in thought, mood, perception, and more. Generally, hallucinogens are classified into three main types: psychedelics, dissociatives, and deliriants. Hollister and Glennon proposed that at therapeutic doses, psychedelics can alter perception and mood by directly binding to serotonin (5-HT) receptors, with minimal or no neuropsychiatric side effects and low potential for addiction (Hollister, 1964; Glennon, 1994). In academic contexts, psychedelics are often referred to as classical or serotonergic hallucinogens, which is the focus of this review.

In general, psychedelics are divided into three categories based on their chemical structure: tryptamine psychedelics, including psilocybin and *N*,*N*-dimethyltryptamine (DMT); semisynthetic ergoline psychedelics, exemplified by lysergic acid diethylamide (LSD); and phenethylamine psychedelics, such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and mescaline, which are derived from cacti native to the Americas (Low et al., 2024). Psilocybin is a natural psychedelic substance primarily found in certain species of mushrooms, commonly referred to as 'magic mushrooms', and was first identified and isolated in 1958 by the Swiss chemists Albert Hofmann (Hofmann et al., 1958). DMT, the primary active component in ayahuasca, is also a potent tryptamine psychoactive substance with a rapid onset of action and strong effects (Szara, 1956). Ayahuasca is a psychoactive brew from South America that was historically utilized by indigenous communities and folk healers in the Amazon and Orinoco regions for spiritual rituals, divination practices, and various psychosomatic ailments (McKenna, 2004). LSD is a semisynthetic ergotamine hallucinogen first synthesized by Albert Hofmann in 1938 at Sandoz Laboratories in Basel (Hofmann, 1979; Hofmann, 2013). Taken orally, LSD induces profound psychoactive effects, with as little as 10 μg leading to euphoria and 50–200 μg resulting in significant alterations in consciousness and sustained hallucinations (Danilo et al., 2016). Some subjects have described feelings of acceleration or deceleration of the flow of time and even a sense of timelessness after using LSD, as well as experiencing spiritual 'epiphanies' and mystical experiences (L, 1968; Neil, 2002).

Mescaline, one of the earliest discovered natural psychedelics, was identified in Native American cultures as a key component of certain cacti, including Peyote and San Pedro (Vamvakopoulou et al., 2023). Used mainly in religious and healing rituals to evoke sacred hallucinatory experiences, mescaline was first isolated from cacti by German chemist Arthur Heffter in 1897, marking it as the first naturally occurring psychedelic isolated in the laboratory (Vamvakopoulou et al., 2023). Despite differences in chemical structure, these compounds share the ability to deeply alter consciousness, evoke intense and prolonged hallucinations, and show effectiveness in lifting depressive symptoms and enhancing positive emotions. DOI is a synthetic psychedelic compound classified as a substituted phenethylamine (Krupp et al., 2024; Sabanovic et al., 2024). It is structurally similar to mescaline and is recognized for its strong serotonergic effects, primarily acting as a partial agonist at the 5-HT_{2A} receptor (5-HT_{2A}R) (Karaki et al., 2014). DOI is commonly employed in research to investigate the impact of psychedelics on brain function and behavior, with a particular focus on its hallucinogenic properties. Although their precise mechanisms of action remain unclear, psychedelics hold substantial therapeutic potential for treating MDD. The following section will explore the antidepressant efficacy and potential mechanisms of action for representative psychedelics within the tryptamine, ergotamine, and phenylethylamine classes.

Table 1
The application and efficacy of psychedelics in MDD patients.

Psychedelics	Treatment dose	Therapeutic effects	References
Psilocybin	Two psilocybin sessions (oral doses of 20 mg/70 kg; 30 mg/70 kg)	Depressive symptoms showed significant improvement; Reassessment after 4 weeks indicated that the improvement was sustained.	(Davis et al., 2021)
Psilocybin	Single oral doses of 25 mg	Depressive symptoms were significantly alleviated, and no severe side effects were observed.	(Raison et al., 2023)
Psilocybin	Single oral doses of 25 mg	Effectively alleviates depressive symptoms in patients with TRD (treatment-resistant depression).	(Goodwin et al., 2022)
Psilocybin	Two oral doses of psilocybin at 20 mg/70 kg and 30 mg/70 kg spaced 2 weeks apart	The antidepressant effects of psilocybin-assisted therapy are durable, maintained for at least 12 months post-treatment.	(Gukasyan et al., 2022)
Psilocybin	Single dose of psilocybin 25 mg or 10 mg	Single dose of 25 mg psilocybin significantly improved depression, anxiety, affect and functioning at 3 weeks, with 10 mg showing lesser efficacy.	(Goodwin et al., 2023)
Psilocybin	Single dose of psilocybin 25 mg, 10 mg or 1 mg	The intensity of psychedelic experience overlaps widely across doses , and psychedelic experience correlated with depression improvement.	(Goodwin et al., 2025)
DMT	Two dosing sessions (inhaled 15 mg and 60 mg DMT) at least 1.5 h apart	Inhaled DMT shows rapid antidepressant and antisuicidal effects with a favorable safety and tolerability profile.	(Falchi-Carvalho et al., 2025)
DMT	Two dosing sessions (0.1 and 0.3 mg/kg intravenous DMT) at least 48 h apart	DMT (0.1–0.3 mg/kg) demonstrated good safety and potential next-day antidepressant effects in treatment-resistant MDD.	(D'Souza et al., 2022)
DMT	Single oral doses of 1 ml/kg (contain 0.36 mg/kg of N, N-DMT)	Relief from depressive symptoms began within hours and lasted for weeks or even months.	(Palhano-Fontes et al., 2019)

3. The therapeutic effects of psychedelics on MDD

Extensive research highlights the efficacy of psychedelics in alleviating depressive symptoms. The efficacy of psychedelics in MDD patients was summarized in Table 1. Psilocybin is an indole-derived secondary metabolite extracted from certain species of mushrooms, known for its potent neuropsychotropic effects (Johnson and Griffiths, 2017). As a serotonin receptor agonist, it exerts its effects primarily by activating the 5-HT_{2A} receptors in the brain. Psilocybin and its metabolite, psilocin, have shown therapeutic potential in the field of psychiatry, particularly in the treatment of mental disorders such as MDD and anxiety (Kargbo, 2020). In a randomized clinical trial, patients with MDD showed substantial symptom improvement just one day following an acute dose of psilocybin, with this effect sustained over four weeks of follow-up assessments (Davis et al., 2021). Another trial found that,

within six weeks of a single psilocybin administration, MDD patients experienced significant symptom relief, though it was not complete, with no serious adverse effects reported (Raison et al., 2023). TRD is generally defined as a form of MDD in which patients do not achieve adequate improvement after receiving at least two different classes of antidepressants at appropriate doses and durations. This population often endures a longer illness course and more severe symptoms, with higher hospitalization rates, suicide risks, and economic burdens on healthcare systems. Research suggests that psilocybin, whether administered alone or combined with psychosocial support, is highly effective in mitigating depressive symptoms in TRD patients (Goodwin et al., 2022; Carhart-Harris et al., 2017; Carhart-Harris et al., 2016; Carhart-Harris et al., 2018). In addition, trials involving patients with advanced-stage cancer and MDD have shown that psilocybin not only rapidly reduces depressive symptoms and enhances quality of life but also shifts negative perceptions of life. Impressively, approximately 80 % of these patients maintained these benefits for up to six months post-treatment (Griffiths et al., 2016; Ross et al., 2016; Paydary et al., 2023; Agrawal et al., 2024). Reflecting its promise, the U.S. Food and Drug Administration (FDA) awarded psilocybin breakthrough therapy designations for TRD and MDD in 2018 and 2019, respectively (Heal et al., 2023).

Other studies have shown that ayahuasca, rich in the tryptamine psychedelic DMT, has potent antidepressant and mood-elevating effects. Studies show that ayahuasca can relieve depressive symptoms within hours after a single dose, with effects lasting for several weeks or even months—often acting faster than traditional antidepressants (Palhano-Fontes et al., 2019; Uthaug et al., 2021; Jimenez-Garrido et al., 2020). The psychoactive component of ayahuasca, DMT, can guide users into a "decentered" psychological state, enabling them to observe their thoughts and emotions with a more objective, nonjudgmental perspective (Murphy-Beiner and Soar, 2020; Werle et al., 2024; Uthaug et al., 2018; Aicher et al., 2023). This shift may reduce the focus on negative self-reflection and mitigate self-criticism, providing emotional relief. Additionally, ayahuasca enhances the ability to recognize emotions in others, fostering improved social interactions and positive relationships, which can further alleviate depressive symptoms (Kiraga et al., 2021; Perkins et al., 2022).

Additionally, LSD has shown considerable therapeutic potential in enhancing mood. Clinical studies with healthy volunteers found that participants who received LSD, compared to those given a placebo, reported an enhanced sense of well-being, increased trust and social connectedness, and demonstrated more prosocial behaviors, with reduced expressions of sadness and fear (Dolder et al., 2016; Schmid et al., 2015). Further research demonstrated that a single dose of LSD sustained high levels of well-being and life satisfaction for up to 12 months without adverse effects (Liechti et al., 2017; Schmid and Liechti, 2018). Similar to psilocybin, DMT and LSD, mescaline also appears to rapidly and reliably improve mood. In a retrospective study, patients with anxiety and depression reported symptom improvements following mescaline administration, with many describing the experience as a profoundly positive, life-changing event (Agin-Liebes et al., 2021). Although the antidepressant effects of mescaline require further clinical validation, existing evidence suggests that psychedelics hold promise as an effective treatment option for enhancing mood and addressing MDD.

Animal studies have also demonstrated that psilocybin and DMT alleviate anhedonia in chronically stressed animals, enhance fear extinction, and produce rapid, sustained antidepressant-like effects (Hesselgrave et al., 2021; Xiangting et al., 2024; Du et al., 2023). Although no antidepressant effect was observed in rodents treated with a single dose of LSD, the administration of LSD for seven consecutive days effectively increased the social behavior of the animals, which might indirectly contribute to the amelioration of MDD (De Gregorio et al., 2021).

4. Mechanisms of psychedelics in the treatment of MDD

4.1. Generation and impact of mystical experiences

Substantial evidence indicates that the psychoactive effects of psychedelics are primarily mediated through agonism of the 5-HT_{2A}R (de la Fuente Revenga et al., 2022). These effects can be inhibited by pretreatment with 5-HT_{2A}R antagonists such as ketanserin or risperidone (FX et al., 1998). Activation of 5-HT_{2A}R in the prefrontal cortex facilitates intrinsic network activity by directly enhancing the excitability of a discrete subpopulation of pyramidal neurons, leading to a robust increase in spontaneous glutamatergic synaptic activity (Beique et al., 2007). Preclinical and clinical evidence indicates that reduced 5-HT_{2A}R-mediated neurotransmission—in Htr2a knock-out mice and MDD patients carrying HTR2A risk alleles (e.g., C allele of rs6313)—is associated with increased susceptibility and severity of depressive episodes, while certain 5-HT_{2A}R polymorphisms have been linked to higher antidepressant remission rates (Petit et al., 2014; Lin et al., 2014). Furthermore, the 5-HT_{2A}R physically and functionally interacts with the mGlu2 glutamate receptor, forming a heteromeric complex (Lopez-Gimenez and Gonzalez-Maeso, 2018). This heterocomplex is crucial for the psychoactive effects, as the mGlu2 receptor acts as a physiological brake on 5-HT_{2A}R-mediated excitation. Disruption of this intricate serotonin-glutamate balance represents a key model for understanding psychosis (Lopez-Gimenez and Gonzalez-Maeso, 2018).

Other research has suggested that psychedelics may activate the 5-HT_{2A}R, leading to a transformative "epiphany" during an acute hallucinogenic experience, which fosters positive emotions and helps alleviate depressive symptoms in patients with MDD (Majic et al., 2015). Some participants reported that the profound experience of using hallucinogens altered their perspectives on people, events, and the world. This shift influenced their attitudes toward handling various situations and reshaped how they dealt with relationships (Griffiths et al., 2016; Ross et al., 2016). These findings have fueled the hypothesis that mystical-type experiences may serve as a psychological mediator of the antidepressant response. However, accumulating evidence challenges the notion that hallucinogenic or mystical properties are either necessary or sufficient for therapeutic benefit (Hashimoto, 2025). Longitudinal follow-up of psilocybin-assisted therapy in patients with severe MDD showed sustained reductions in depressive symptoms, yet the intensity of mystical or spiritual experiences did not consistently predict clinical improvement (Gukasyan et al., 2022). Similarly, a large-scale naturalistic study suggested that factors such as treatment motivation, prior psychedelic use, dosage, and the occurrence of emotional breakthrough played a more prominent role in shaping symptom reduction than mystical intensity alone (Nygart et al., 2022). In a placebo-controlled trial, the subjective intensity of mystical experiences sometimes failed to correlate with reductions in MDD severity (Sloshower et al., 2023). Moreover, a case report demonstrated that psilocybin produced antidepressant benefits even when combined with trazodone, a 5-HT_{2A}R antagonist, suggesting that its therapeutic efficacy may not be strictly dependent on hallucinogenic or mystical properties (Rosenblat et al., 2023). Collectively, these findings indicate that while mystical experiences may enhance well-being for some individuals, they are unlikely to serve as a universal or necessary mediator of the antidepressant effects of psychedelics.

Building on this, the role of 5-HT_{2A}R activation in antidepressant efficacy also appears more complex than initially assumed. Evidence from preclinical studies shows that specific symptoms associated with hallucination in rodents (e.g., head twitch response) were found to be blocked, but not the antidepressant effects caused by psychedelics, either by using 5-HT_{2A}R knockout transgenic mice or by administering a 5-HT_{2A}R antagonist prior to administration of psychedelics (Hesselgrave et al., 2021; Sekssaoui et al., 2024). This dissociation suggests that hallucinatory phenomena are not indispensable for therapeutic efficacy. Yet, it would be premature to dismiss their influence entirely, as the

nature and meaning of hallucinatory experiences are strongly shaped by individual perceptions, context, and prior experiences. Although findings from psychedelic research remain somewhat inconsistent, multiple studies have demonstrated that mystical-type experiences are associated with antidepressant outcomes, serving as important predictors of symptom reduction and improved quality of life (Carhart-Harris et al., 2018; Roseman et al., 2017; Ko et al., 2022). Beyond receptor-level mechanisms, psychedelics are also known to enhance neuroplasticity, modulate immune signaling, and influence neurotransmitter systems, highlighting the multifactorial basis of their antidepressant efficacy (Inserra et al., 2021). Within this framework, mystical or hallucinatory experiences may amplify therapeutic effects, but they are unlikely to serve as the sole determinants of clinical improvement.

4.2. Changes in synaptic plasticity and neurogenesis

Previous studies have reported impaired neuroplasticity in the brains of patients and animal models of MDD, and psychedelics can improve neuroplasticity and enhance neurogenesis in relevant brain regions (Haniff et al., 2024). A single dose of psilocybin administered intravenously to pigs resulted in an increase in the density of dendritic spines on hippocampal and prefrontal neurons, as detected by radiographic autoradiography 24 h later (Raval et al., 2021). Similarly, after intraperitoneal injection of psilocybin in mice, an increase in spine density and size in frontal cortical pyramidal cells was noted, with structural remodeling occurring rapidly within 24 h and persisting for over a month (Shao et al., 2021). Another study demonstrated that psilocybin not only enhances neuronal plasticity in prefrontal areas but also activates the brain-derived neurotrophic factor (BDNF)-mTOR signaling pathway in the hippocampus, supporting neurogenesis (Xiangting et al., 2024).

BDNF is widely considered a key factor in synaptic plasticity and neurogenesis, with reduced BDNF levels often detected in patients with MDD (Chen et al., 2024). Notably, the extent of BDNF reduction is strongly correlated with suicidal behaviors, while higher baseline BDNF levels have been linked to improved response to SSRIs in MDD (Dwivedi, 2010; Yoshimura et al., 2023; Flores-Ramos et al., 2024). In animal models, 28-day administration of ayahuasca significantly raised BDNF levels in the hippocampus of rats (Colaco et al., 2021). Similarly, circulating BDNF levels are increased in both healthy individuals and patients with TRD after 48 h of administration of a single dose of ayahuasca, and serum BDNF levels are negatively correlated with the severity of depressive symptoms in patients with TRD (de Almeida et al., 2019). A comparable effect was reported in another study on LSD, in which low doses acutely increased BDNF levels in the plasma of healthy volunteers (Hutten et al., 2021). Further research is essential to clarify the connections among depression, synaptic plasticity/neurogenesis, and psychedelics.

4.3. Connectivity alterations in the brain as a whole or within specific subregions

Numerous studies utilizing functional magnetic resonance imaging (fMRI) have been conducted to evaluate the effects of psychedelics on brain activity and connectivity, helping to clarify the mechanisms underlying their therapeutic potential (Copa et al., 2024). fMRI detects changes in cerebral blood flow (CBF) and blood oxygen level-dependent (BOLD) resting-state functional connectivity (RSFC) to measure the activity and network connections between various brain regions. A clinical trial demonstrated that psilocybin can reduce the modularity of brain networks in patients with MDD, leading to enhanced connectivity between various functional brain networks (Daws et al., 2022). Compared to traditional SSRI antidepressants, such as escitalopram, psilocybin induces more significant alterations in brain network integration, which correlate with sustained antidepressant effects (Daws et al., 2022). Additionally, another neuroimaging study found that posttreatment with psilocybin in TRD patients decreased CBF in the amygdala and enhanced the RSFC in the DMN (Carhart-Harris et al., 2017). Notably, RSFC was increased between the ventral medial prefrontal cortex and bilateral inferior lateral parietal cortex, while RSFC was decreased in the parahippocampal-prefrontal circuits, all of which changes were able to predict the therapeutic response to the drug (Carhart-Harris et al., 2017). Moreover, psilocybin not only affects the activity of the amygdala but also enhances its functional connectivity with other brain regions involved in facial expression processing, which may contribute to the therapeutic effects in MDD patients after treatment. During facial processing, increased responses to faces with different expressions were observed in the right amygdala post-treatment, and the increased activity of amygdala in response to fearful faces can predict clinical improvements (Roseman et al., 2018; Grimm et al., 2018). The amygdala response induced by psilocybin is the opposite of that previously reported for SSRI drugs (Godlewska et al., 2012). Therefore, fundamental differences in the therapeutic actions of these treatments can be inferred. In brief, the SSRI primarily relieve negative emotions, but psilocybin can empower patients to confront and overcome those emotions (Roseman et al., 2018).

However, in healthy volunteers, decreased amygdala reactivity induced by psilocybin was found to be associated with increased positive emotions (Rainer et al., 2015). Additionally, whole-brain analyses revealed enhanced functional connectivity between the amygdala and the ventromedial prefrontal cortex to the occipital-parietal cortices during facial processing (Mertens et al., 2020). Similar findings were reported in a study on LSD, in which post-treatment reduced the reactivity of the amygdala and medial prefrontal cortex during the presentation of fearful faces (M et al., 2017).

Another study revealed that alterations in global connectivity and thalamic brain connectivity were also detected during LSD-induced altered states of consciousness, with this effect being 5-HT_{2A}R-dependent (Katrin et al., 2018; Enzo et al., 2016). Like psilocybin, the LSD and ayahuasca can also modulate the activity and connectivity of the DMN (Jana et al., 2016; Fernanda et al., 2015). Given the effects of psychedelics on the mental activity and brain networks of depressive patients, a 'reset' therapeutic mechanism is thought to be the basis for the antidepressant effects of psychedelics, meaning that psychedelic can breakdown pre-existing solidified patterns of network connectivity in the brain and help patients with MDD overcome their negative thoughts and experience refreshment of cognition and emotion (Carhart-Harris et al., 2017).

One notable limitation in many of the psychedelic studies discussed here is the small sample size, which restricts the generalizability and robustness of the findings. Consequently, there is a substantial need for larger-scale studies to thoroughly explore how psychedelics influence brain region activity and functional connectivity across different areas of the brain to produce antidepressant effects. Larger studies with more diverse and representative samples would help validate and expand upon current findings, allowing researchers to better understand the specific neural mechanisms and potentially identify patterns or biomarkers that could predict individual responses to psychedelic therapies. In addition, foundational research is essential for unveiling the underlying mechanisms of psychedelics. Integrating methods such as fMRI, electrophysiology, and advanced molecular biology techniques could provide insights into how psychedelics influence connectivity within targeted brain regions and across broader networks, shedding light on their impact on neuronal and glial cell function over time. This comprehensive approach would deepen our understanding of the complex, multi-level effects psychedelics have on brain circuitry and cellular processes.

4.4. Anti-inflammatory and immunomodulatory effects

MDD is currently regarded as a neuroimmune dysregulation disorder, with clinical evidence showing that autoimmune diseases and

severe infections can heighten the risk of developing mood disorders (Michael et al., 2013). Immune system disruption is a key feature in psychiatric conditions, such as mood disorders (Morrens et al., 2020), characterized by central immune changes, including changes in microglial activity, as well as shifts in peripheral cytokine levels. Microglia are specialized macrophages within the central nervous system (CNS) with a primary role in clearing necrotic cells, tissue, and invading pathogens. They perform immune surveillance functions and maintain CNS homeostasis (Li et al., 2019). Clinical studies have observed elevated peripheral pro-inflammatory factors in patients with MDD. Following blood-brain barrier disruption, microglia become excessively activated, with a concurrent increase in the release of pro-inflammatory factors (Torres-Platas et al., 2014). Additionally, basic research indicates that in chronically stressed mice, negative behavioral impairments are linked to microglial activation, which triggers central inflammatory signaling pathways and reduces neurogenesis (Belleau et al., 2019).

The brain possesses a highly intricate immune regulatory system, where activated immune cells synthesize and release inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (Li et al., 2023). These cytokines serve as primary mediators of immune responses. Extensive research has shown that the development of MDD may be linked to increased secretion of pro-inflammatory cytokines resulting from immune activation (Maes et al., 2012). Inflammatory markers such as IL-6, IL-1β, TNF-α and C-reactive protein (CRP) are involved in regulating neuronal development, neuropeptide release, and synaptic plasticity (Diz-Chaves et al., 2013), and typically elevated in both MDD patients and animal models (Dowlati et al., 2010; Chamberlain et al., 2019; Ma et al., 2016). Furthermore, pro-inflammatory cytokines can activate the hypothalamic-pituitary-adrenal (HPA) axis, cross the blood-brain barrier, and inhibit monoamine neurotransmitters, thereby influencing neurogenesis and synaptic function, and contributing to the pathogenesis and therapeutic mechanisms of MDD and other psychiatric disorders (Milenkovic et al., 2019).

Recent evidence has highlighted the immune-regulatory and anti-inflammatory effects of classical psychedelics. In the CNS, they can modulate the immune responses of astrocytes and microglia through 5-HT_{2A}R and sigma-1 receptors (Sig-1R) (Low et al., 2024; Nichols, 2022). For instance, 5-HT_{2A}R agonists such as (*R*)-DOI effectively suppress TNF-α–induced inflammatory responses in vitro and in vivo at sub-behavioral doses (Flanagan et al., 2019a; Flanagan et al., 2019b). Mechanistically, 5-HT_{2A}R activation modulates key pro-inflammatory signaling pathways, notably inhibiting NF-κB activation, which attenuates the expression of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 (Szabo, 2015). In parallel, psychedelics regulate additional signaling cascades such as PI3K/Akt and mTOR, promoting neuronal survival and synaptic plasticity, and facilitate a shift in microglia from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype (Ornelas et al., 2022; de Deus et al., 2025). Collectively, these actions attenuate neuroinflammation and strengthen neuroprotective mechanisms. In addition, DMT has been identified as an endogenous modulator of Sig-1R (Fontanilla et al., 2009). This receptor is abundantly expressed in CNS-resident immune cells, and its activation attenuates the reactivity of microglia and astrocytes, thereby exerting anti-inflammatory effects and inhibiting the release of pro-inflammatory mediators, including TNF-α and IL-1β (Guo et al., 2021; Wu et al., 2015). Sig-1R activation also promotes a shift in microglial polarization toward an anti-inflammatory phenotype, further contributing to the resolution of neuroinflammation (Chao et al., 2017). Notably, under hypoxic or oxidative stress conditions, DMT-mediated activation of Sig-1R significantly enhances the survival of cortical neurons and immune cells (macrophages and dendritic cells), attenuating hypoxia-induced cellular damage and apoptosis (Gupta et al., 2025; Szabo et al., 2016). These actions suggest that DMT may serve as a potential therapeutic agent for neuroinflammation, particularly in immune modulation for psychiatric disorders including MDD, where Sig-1R activation may represent a novel interventional strategy (Falchi-Carvalho et al., 2025; do Nascimento Sousa et al., 2025).

Beyond immunoregulation, Sig-1R activation also mediates substantial neuroprotective, antioxidative, and neural circuit-modulatory effects (Gupta et al., 2025). DMT enhances synaptic connectivity and plasticity via Sig-1R, leading to altered functional dynamics within neural network (Barker, 2018). Activation of Sig-1R in the cortical and limbic regions supports neuronal homeostasis through the regulation of multiple signaling pathways, potentially influencing stress resilience, emotional regulation, memory processing, and sensory integration, which are critical for adaptive neural function in response to pathological stressors (Winkelman et al., 2023; Ryskamp et al., 2019a). Furthermore, Sig-1R activation is associated with enhanced neuroplasticity within the hippocampus, facilitating synaptic remodeling and promoting neurogenesis (Ryskamp et al., 2019b; Moriguchi et al., 2013). These actions may underlie not only the psychedelic effects of DMT but also its therapeutic potential in neurodegenerative and cognitive disorders, including Alzheimer's disease, by restoring synaptic stability and enhancing cellular resilience to stress (Winkelman et al., 2023). Through these pathways, Sig-1R activation could play a pivotal role in both the therapeutic and psychoactive properties of DMT.

In addition, studies have demonstrated that combined treatment with psilocybin and eugenol can alleviate neuroinflammation in LPS-induced mice by preventing the upregulation of IL-6, COX-2, and TNF-α (Zanikov et al., 2023). Similarly, in a chronic stress model, the psychedelic (*R*)-DOI was found to effectively suppress the increase in pro-inflammatory cytokines TNF-α levels in central and peripheral tissues, thereby improving immune-inflammatory responses and ameliorating depressive-like phenotypes in the mice (Krupp et al., 2024). Beyond reducing inflammatory marker production, psychedelics can also change the number of inflammatory cells, such as leukocytes and natural killer cells (Dos Santos et al., 2012). Overall, these findings suggest that the modulation of the immune system by psychedelics may play a key role in their antidepressant effects. Minocycline, a second-generation tetracycline antibiotic, also exhibits notable immunomodulatory actions, such as inhibition of microglial activation, suppression of TNF-α and IL-1β release, and attenuation of oxidative stress and apoptosis (Husain et al., 2020; Takahashi et al., 2024). These properties initially positioned minocycline as a promising candidate for MDD, with early pilot trials reporting significant benefits in treatment-resistant cases (Husain et al., 2020). However, subsequent large-scale randomized controlled trials failed to replicate these results consistently, thereby limiting its clinical application (Huang et al., 2025). Ketamine, another rapid-acting antidepressant, has been proposed to exert anti-inflammatory effects, but evidence remains inconsistent. Meta-analytic findings showed no statistically significant association between baseline or longitudinal levels of pro-inflammatory markers and treatment response, with CRP showing only a modest and non-significant effect (Medeiros et al., 2022). In contrast, psychedelics appear to combine direct immunomodulatory effects, partly mediated by 5-HT_{2A}R and Sig-1R signaling, with robust enhancements in neuroplasticity and functional connectivity. This dual mechanism may offer a more comprehensive therapeutic strategy for major depressive disorder, bridging immune regulation with plasticity-driven neural circuit remodeling.

Based on this, psychedelic compounds have opened a novel avenue for the development of rapid-acting antidepressant strategies, with their mechanisms of action and clinical potential gradually being elucidated. Future research should focus on systematically clarifying the causal relationships between psychedelic-induced subjective experiences, neuroplasticity, alterations in brain connectivity, immune modulation, and clinical outcomes, as well as investigating the synergistic effects across distinct receptor pathways and mechanisms. From a drug development perspective, strategies such as "preserving therapeutic efficacy while minimizing hallucinogenic effects" and "shortening duration of action to enhance accessibility" are particularly promising. In this context, the

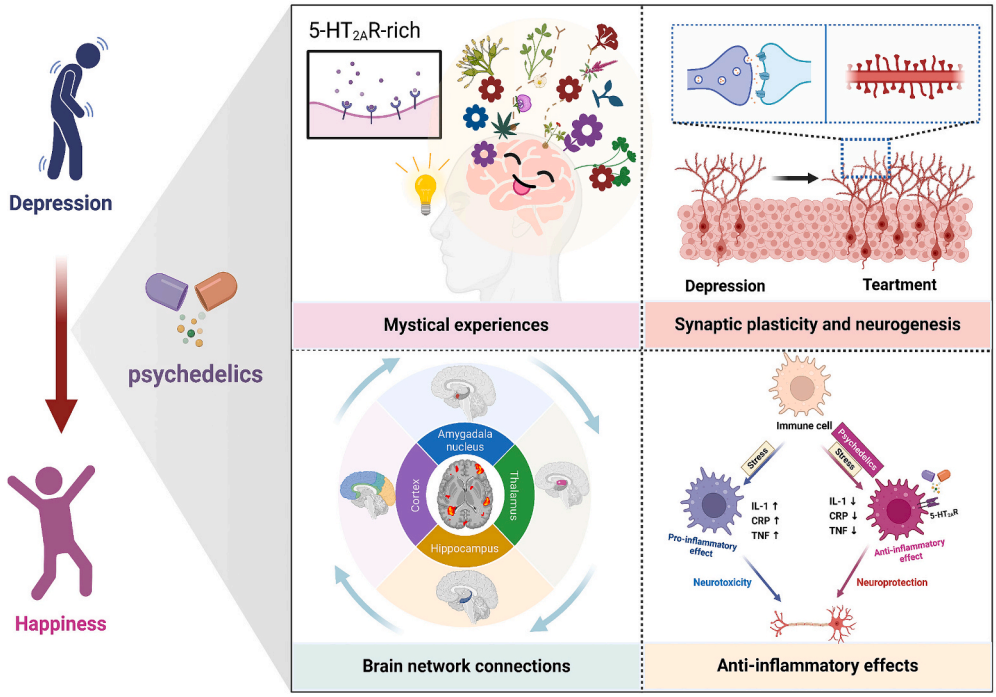

Fig. 1. An overview of the main hypothesized mechanisms of psychedelics act on MDD: mystical experiences, synaptic plasticity, neurogenesis, brain network connections, and immuno-inflammatory modulation (created with BioRender.com).

identification of non-hallucinogenic analogs capable of enhancing neuroplasticity may drive a paradigm shift in therapeutic approaches for neuropsychiatric disorders and is especially important for resolving the longstanding debate over whether the subjective effects of psychedelics are necessary for their therapeutic efficacy (Ly et al., 2018). Non-hallucinogenic 5-HT_{2A} receptor agonists and ultra-short-acting tryptamines exemplify these approaches, as they retain the capacity to modulate synaptic and circuit-level plasticity while avoiding the limitations associated with classical psychedelics (Lima da Cruz et al., 2024). In addition, generating robust clinical evidence, identifying target patient populations, and optimizing assessments of long-term efficacy and safety remain critical challenges for clinical translation. With the advancement of interdisciplinary research, the application of cutting-edge technologies, and the establishment of standardized training and regulatory frameworks, psychedelic-based therapies are expected to evolve into a safe, controllable, and broadly accessible antidepressant strategy, while simultaneously reshaping paradigms in psychiatric treatment and drug development (Fig. 1).

5. Conclusion

Although psychedelics were found to produce significant antidepressant effects in the middle of the 20th century, their psychedelic effects, neurotoxicity, and risk of abuse led to strict controls, which prevented researchers from investigating antidepressant efficacy and mechanisms. This resulted in a long period of stagnation in psychedelic research. Traditional antidepressants have shown limited effectiveness in treating MDD. In recent years, psychedelics, which exhibit potent antidepressant effects and good tolerance, have attracted increasing attention from researchers. While the profound perceptual changes induced by psychedelics have traditionally obstructed their clinical application, efforts have been made to modify these compounds in hopes of separating their hallucinogenic effects from their therapeutic benefits. Nevertheless, some researchers argue that the psychedelic experience itself is integral to improving a patient's depressive symptoms. Despite ongoing skepticism and challenges, research into psychedelic drugs continues to suggest that they hold great promise for the future of MDD treatment.

CRediT authorship contribution statement

Xian-Qiang Zhang: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **De-Nong Liu:** Writing – original draft, Methodology, Formal analysis. **Qing-Shan Miao:** Writing – review & editing, Formal analysis. **Xu Cai:** Methodology, Formal analysis. **Lu-Xin Zong:** Writing – review & editing, Formal analysis. **Yu-Kun Hou:** Writing – original draft, Formal analysis. **Jing Xiong:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare no conflicts of interest or financial relationships that could have influenced the research presented in this paper.

Data availability

No data was used for the research described in the article.

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