1 Introduction

Depression affects over 264 million people worldwide and is primarily treated with antidepressants like SSRIs (Selective Serotonin Reuptake Inhibitors), NRIs (Norepinephrine Reuptake Inhibitor), or SNRIs (Sero-tonin and Norepinephrine Reuptake Inhibitors) targeting serotonergic mechanisms, and/or through psychotherapy [1, 2]. However, antidepressants often have a moderate success rate and can cause side effects such as sexual dysfunction and emotional blunting [3, 4]. Moreover, they require long periods to take effect and multiple courses of treatment are necessary [1, 2]. Psychotherapy may be inaccessible due to high costs and long wait-lists and often demands high motivation levels, which can be challenging for depressed patients [1, 5]. When patients do not respond to two adequate treatments with conventional antidepressants, their condition is classified as Treatment-Resistant Depression (TRD) [6]. This occurs in approximately one third of depressed patients [7], highlighting the urgent need for innovative treatments beyond the traditional methods.

Psilocybin is a naturally occurring psychedelic compound found in the Psilocybe genus of mushrooms, often referred to as “magic mushrooms” [2]. As a classic psychedelic, psilocybin belongs to the tryptamine class, structurally similar to serotonin [8]. It has been used for centuries by indigenous populations for religious ceremonies [9]. After Albert Hofmann and colleagues [10] managed to isolate the active compound psilocybin from the mushrooms in 1958, it became highly researched. These studies, although not up to modern scientific standards, indicated promising outcomes, with 80% of patients showing improvement [1, 8]. Around this same time, there was a global increase in recreational use of psychedelics (mostly LSD). Concerns over the unpredictable psychological effects and the sensationalized media portrayal of negative incidents involving psychedelics further fueled public fear and moral panic [11]. This resulted in the U.S. Controlled Substances Act of 1970, which classified psychedelics as Schedule I drugs, making research into their beneficial effects complicated.

2 Results from recent clinical trials

Despite psilocybin’s illegal status, obstacles to research have loosened over time. Recent studies have sparked renewed interest in psilocybin,
particularly for treating mood disorders [6, 8]. Notably, groundbreaking research in 2016 [12, 13] demonstrated that psychedelic-assisted psychotherapy is highly effective in treating depression. These studies marked a crucial resurgence of interest in psilocybin as a viable therapeutic option [9].

From 2016 to 2023, a series of clinical trials have underscored the effectiveness of psilocybin therapy in managing major depressive disorder (MDD) and treatment-resistant depression (TRD). These trials administered psilocybin in conjunction with psychological support from trained therapists [6, 13–17]. Results have consistently shown that a single dose of psilocybin can lead to statistically and clinically significant reductions in depressive symptoms, alleviating depression severity, anxiety, and functional outcomes, and notably decreasing the number of lost or ineffective days. These benefits have been observed to last for the duration of the studies, typically 6 to 12 weeks. Moreover, a long-term follow-up study conducted 4.5 years post-treatment, indicated that 60-80% of participants sustained significant antidepressant responses, with 71-100% reporting that the psilocybin-assisted therapy contributed to positive life changes [17]. The promising results from clinical studies on psilocybin led to further research aimed at elucidating the mechanisms underlying its potential therapeutic effects [9].

3 Metabolism of psilocybin

Psilocybin is a prodrug, meaning it must be converted into its active form, psilocin, to be effective (Fig. 1). This conversion involves a dephosphorylation reaction, catalyzed by alkaline phosphatases. The reaction primarily occurs in the intestines, although it also takes place to a lesser extent in the stomach, kidneys, and blood [2]. Once converted to psilocin, it induces a hallucinogenic phase lasting between 2 to 6 hours, characterized by a range of subjective effects including visual hallucinations, euphoria, a loss of sense-of-self, and spiritual experiences [2, 9]. Psilocin undergoes further metabolism in the liver, primarily through demethylation and oxidative deamination by enzymes such as monoamine oxidase and aldehyde dehydrogenase. This metabolic process gradually reduces the hallucinogenic effects [2].

4 Psilocybin action through serotonin receptor 5-HT2A

Psilocybin closely resembles the structure of serotonin (5-hydroxytryptamine, 5-HT) [8] (Fig. 1). Despite psilocybin being a prodrug with pharmacologically negligible effects itself, its active metabolite, psilocin, engages with multiple receptors. Psilocin binds with moderate affinity to the 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT2C receptors, as well as to the histamine H1 receptor. It shows higher affinities to the 5-HT2B and 5-HT7 receptors. This multi-target interaction contributes to the complex therapeutic effects observed in the treatment of depression [9].

Serotonin receptors are implicated in numerous physiological functions, including vision, immune response, and neurotransmitter signaling, highlighting their extensive influence across body systems. The acute subjective effects of psilocybin include visual hallucinations, altered perception, and emotional experiences often described as mystical or spiritual. These effects are mediated primarily through the activation of the 5-HT2A receptors, which are prominently expressed in the visual cortex. Psilocybin’s interaction with these receptors leads to profound sensory and perceptual changes, supported by physiological responses such as changes in heart rate, blood pressure, and temperature, reflecting the receptor’s widespread influence [9].

Activation of the 5-HT2A receptor by psilocybin is critical for its hallucinogenic effects. This was confirmed through studies employing 5-HT2A receptor antagonists like ketanserin that have shown that blocking this receptor significantly attenuates the psychedelic effects [19]. 5-HT2A receptor activation triggers a series of downstream effects mediated by secondary messenger systems, leading to alterations in gene expression and protein activity that are characteristic of psilocybin’s acute impacts [2]. Interestingly, the antidepressant effects of psilocybin are not solely dependent on 5-HT2A receptor activation. Experiments using psilocybin in conjunction with ketanserin demonstrated that other serotonin receptors also contribute to its antidepressant properties [19]. This indicates that psilocybin’s therapeutic effects may involve a broader array of receptor interactions, including but not limited to 5-HT2B and 5-HT2C, and potentially non-serotonergic pathways as well [19]. Therefore, while current literature mostly focusses on 5-HT2A receptor dependent mechanisms, 5-HT2A receptor independent signalling pathways also exist [9]. Furthermore, continuous activation of 5-HT2A by psilocybin leads to receptor down-regulation, a process likely involved in the desensitization mechanisms that underlie long-term therapeutic effects, because previous studies have suggested that overexpression of 5-HT2A receptors is present in patients with MDD, with expression correlating positively to the severity and duration of depression [2].

5 Anti-inflammatory effect

Next to 5-HT2A receptor’s role in the hallucinogenic effects of psilocybin, it is essential to explore another aspect — its influence on inflammatory processes. Chronic low-grade inflammation is increasingly recognized as a significant factor in the pathogenesis of mood disorders such as depression [1]. This inflammation is characterized by elevated levels of pro-inflammatory cytokines like IL-1α, IL-1β, IL-6, and TNF-α, along with acute-phase proteins such as C-reactive protein (CRP). These markers are not only elevated due to psychosocial stressors but also play a role in the onset and maintenance of depressive disorders [2, 20].

Psilocybin’s agonism at the 5-HT2A receptor leads initially to a reduction in TNF-α, a key pro-inflammatory cytokine. The inhibition of TNF-α is crucial because it can induce IL-6 synthesis through the activation of the NFKB and MAPK pathways, particularly phosphorylation of p38 MAPK [2]. IL-6, in turn, is a direct inducer of CRP synthesis in the liver, which is considered an important circulating biomarker.
of inflammation in clinical practice. Studies indicate an immediate reduction in TNF-α levels following psilocybin administration, with these levels returning to baseline within seven days. However, the levels of IL-6 and CRP remain reduced, suggesting a long-term anti-inflammatory effect. This persistent reduction correlates with sustained improvements in mood and prosocial behavior [20].

TNF-α is not only a critical mediator of systemic inflammation but also a potent inducer of the kynurenic pathway. This pathway metabolizes tryptophan into kynurenic, diverting it from serotonin synthesis, which can lead to reduced serotonin availability and contribute to depressive symptoms. More critically, certain metabolites within the kynurenic pathway, such as quinolinic acid, are neurotoxic and have been implicated in neurodegeneration and the pathophysiology of depression. By modulating this pathway, psilocybin may reduce harmful kynurenic metabolites and neuroinflammation, thereby potentially alleviating symptoms of depression [1].

6 Neuroplasticity

Neuronal atrophy in the prefrontal cortex (PFC) is a significant feature of many stress-related neuropsychiatric disorders, including depression. Psilocybin has demonstrated the potential to counteract these deficits by promoting structural and functional neuroplasticity in the PFC [21]. Research has shown that even a single administration of psilocybin can lead to robust and lasting changes in cortical neuron growth, significantly increasing spine density in the PFC for at least a month. Additionally, psilocybin has been shown to promote dendritic growth both in vivo and ex vivo, enhance excitatory postsynaptic potential in hippocampal neurons, and induce behavioral changes suggestive of antidepressant-like activity. These structural changes are supported by further studies demonstrating that psilocybin effectively promotes neuritogenesis, spinogenesis, and synaptogenesis in rat embryonic cortical cultures, further illustrating its profound impact on brain plasticity [9, 21].

The activation of the 5-HT2A receptor by psilocin, triggers an increased release of glutamate, which is the main excitatory neurotransmitter in the brain responsible for promoting neuronal communication and activation [9]. Furthermore, when psilocin binds to the 5-HT2A/mGlu2 receptor complex, it likely results in the inhibition of mGlu2 activity, which typically acts to suppress the synaptic release of glutamate. Therefore, its inhibition by psilocin can lead to further increase in glutamatergic transmission [2]. This glutamatergic surge is critical, as it facilitates the activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors, enhancing synaptic plasticity and excitatory signaling within neural networks [11].

Activation of AMPA and NMDA receptors results in an upregulation of brain-derived neurotrophic factor (BDNF), a protein that plays a key role in the survival, growth, and maintenance of neurons in the developing and adult brain [1]. BDNF then binds to tropomyosin receptor kinase B (TrkB), initiating a signal transduction cascade that leads to the activation of the mTOR (mammalian target of rapamycin) pathway, crucial for protein synthesis that support synaptic strength and adaptation. These processes, stimulated by BDNF-TrkB signaling, underscore the essential role in enhancing synaptic plasticity and facilitation of late-phase Long-Term Potentiation (LTP) in hippocampal neurons [2].

Overall, the mechanisms described in this review and depicted in Figure 2 illustrate the complex and multifaceted ways in which psilocybin influences brain function and structure, particularly through its impact on the immune system and neuroplasticity. These processes, combined with additional mechanisms not covered in this review, as well as those that may be uncovered through ongoing and future research, underscore the broad spectrum of actions through which psilocybin can exert its therapeutic effects beneficial for treating mood disorders, including major depressive disorder (MDD) and treatment-resistant depression (TRD).

7 Safety of psilocybin treatments

Effective doses of psilocybin range from 1–5 g of dried mushrooms (20–40 mg of psilocybin), with effects lasting 6–8 hours [9]. It is generally well-tolerated, with common side effects including nausea and headache. Psychological effects can include anxiety and emotional distress during sessions, but no long-lasting adverse effects have been reported [8]. Psilocin acts as a partial, not complete, agonist at the 5HT2A receptor, significantly reducing the risk of serotonin syndrome. While an overdose of psilocybin is not physiologically dangerous, it can lead to risky behaviors (e.g. acting on delusions such as capabilites to fly) if used without supervision. The development of psychosis has not been associated with psilocybin use, though there might be a potential risk for individuals with a family history predisposing them to psychosis. Overall, expert consensus ranks psilocybin among the safest recreational drugs used [8].

8 Benefits of psilocybin treatments

Psilocybin induces a rapid-acting antidepressant effect, noticeable within days after a single dose, with long-lasting benefits that persist for at least 12 weeks. This rapid efficacy far exceeds that of traditional antidepressants, which typically require 1-4 weeks to begin showing effects [6, 8, 22]. Additionally, unlike many standard medications,
Psilocybin does not induce emotional blunting and is associated with minimal dependency issues and withdrawal symptoms, making it an appealing option for treatment [2, 8, 22].

9 Conclusion

The resurgence of interest in psilocybin as a therapeutic agent marks a significant shift in the treatment landscape for major depressive disorder (MDD) and treatment-resistant depression (TRD). Over the past few years, an accumulating body of evidence from clinical trials has demonstrated the remarkable efficacy of psilocybin-assisted therapy in alleviating depressive symptoms, often with effects lasting significantly longer than those observed with traditional antidepressants. Unlike conventional treatments, which might take weeks to show benefits and often come with undesirable side effects like emotional blunting and dependency issues, psilocybin offers a rapid onset of action and minimal side effects. Its ability to induce lasting neuroplastic changes following a single dose, coupled with its low toxicity and absence of significant physiological dangers, positions psilocybin as a promising alternative to traditional pharmacotherapy. The molecular mechanisms underlying its benefits extend beyond simple serotonin receptor modulation, involving complex interactions that promote synaptic plasticity and reduce inflammation, potentially addressing foundational biological aspects of depression.

Furthermore, the integration of psychedelic-assisted psychotherapy into mental health treatments could potentially reshape patient care strategies, offering more effective and enduring solutions for those suffering from persistent depressive symptoms with a major reduction in the amount of therapeutic session. This would benefit not only the patients, but also reduce the pressure on the health care system by reducing waitlists and therapy cost.

Ultimately, the continued exploration of psilocybin not only broadens our understanding of psychopharmacology but also enhances our ability to confront the complexities of mental health. Overall, psilocybin therapy offers hope for a brighter future in the management of depression and related mood disorders.

References


Fig. 2: Overview of molecular psilocybin effect on neuroplasticity and anti-inflammation