

Psilocybin: revealing the enigmas of a revolutionary fungi

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Abstract

Psilocybin, a psychoactive compound found in certain mushroom species, has garnered significant attention for its potential therapeutic applications in mental health. This article provides a review of psilocybin's historical, cultural, and clinical relevance. The ancestral use of psilocybin-containing mushrooms in traditional rituals underscores its longstanding association with spiritual and healing practices. Scientific exploration has elucidated its mechanism of action, highlighting its similarity to serotonin and its ability to modulate neural activity through serotonin receptor binding, particularly 5-HT_{2A}. Clinical evidence from recent trials indicates that psilocybin, when administered in controlled settings, may provide substantial benefits in treating conditions such as depression, anxiety, and alcohol use disorder. Key studies have demonstrated sustained symptom relief and improvements in quality of life for patients, although challenges such as controlled usage, potential adverse effects, and regulatory status persist. A systematic literature search was conducted across PubMed, MEDLINE, Scopus, and ScienceDirect using keywords such as *psilocybin*, *psychedelic therapy*, and *mental health treatment*. From an initial pool of 30 articles, 10 studies were included based on relevance and alignment with the review objectives. The review also emphasises the importance of safe administration under professional supervision, focusing on the roles of "set" and "setting" in optimising therapeutic outcomes. Ongoing research is necessary to further substantiate these findings and integrate psilocybin into conventional mental health treatment protocols. This exploration provides valuable insights into the potential of psilocybin as a transformative tool in modern psychiatry, poised to offer alternatives for patients who have not responded to existing treatments.

Keywords: psychedelic-assisted treatment, mental health, psilocybin

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Introduction

For many years, psilocybin—a naturally occurring psychoactive substance present in some mushroom species—has captivated scientists, therapists, and psychonauts. Recent years have seen a significant increase in interest in this subject due to its unique capacity to induce profound altered states of consciousness as well as its potential for therapeutic and spiritual exploration applications.¹

There are now six known indigenous species of psychedelic mushrooms in the genus *Psilocybe*, after two new species from southern Africa were described. With about 140 identified species, *psilocybe* is one of the most well-known and researched genera of hallucinogenic mushrooms worldwide.² The two new species are identified as *Psilocybe ingeli* and *Psilocybe maluti* by researchers from Stellenbosch University (SU) and mycologists in a paper that was published in the journal *Mycologia*.²

Indigenous peoples in parts of Mexico and Central America have been using psilocybin, derived from specific types of mushrooms, for thousands of years as a part of a sacred and ancient tradition.¹ Psilocybin is now classified as a psychedelic, a type of substance that produces profound changes in perception, mood, and cognitive processes.¹ Psilocybin is sometimes referred to by the street names magic mushrooms, mushrooms, or shrooms.¹ This

piece explores the realm of psilocybin, including its usage, effects, potential as a medicine, and current research.

The historical use of psilocybin in Africa is not as extensively documented as in other regions, such as Central and South America, where psilocybin-containing mushrooms have a well-recorded history of ceremonial and medicinal use.¹ However, there is evidence to suggest that the use of psychoactive substances, including plants and fungi with psychoactive properties, has been a part of various traditional practices in Africa.¹

In some regions, indigenous communities are known to have employed psychoactive substances for spiritual, healing, and shamanic purposes.¹ The continent's vast biodiversity supports the possibility that certain fungi containing psychoactive compounds, including psilocybin, could have been part of local traditions.¹ Ethnobotanical records indicate that indigenous healers, known as shamans or traditional medicine practitioners, used various plants and mushrooms to induce altered states of consciousness for rituals, healing ceremonies, and connecting with the spiritual world.¹

However, while there is some anecdotal and speculative evidence pointing to the use of psychoactive mushrooms in parts of Africa, detailed documentation and scientific studies specific to psilocybin use are limited.¹ Further research and exploration

into ethnobotanical traditions may reveal more about the historical role of psilocybin-containing mushrooms and their potential applications in traditional African medicine.¹ This gap in documented history underscores the need for comprehensive anthropological and ethnobotanical studies to explore traditional African knowledge systems and their potential use of psychoactive substances.

Literature search strategy

The literature search for this narrative review on psilocybin was conducted across major scientific databases, including PubMed, MEDLINE, Scopus, and ScienceDirect, to identify relevant studies and articles published within the last five years. Keywords such as *psilocybin*, *psychedelic therapy*, *mental health*, *depression treatment*, and *serotonin receptor activity* were used. Additional sources were retrieved through cross-referencing citations from key articles.

Search outcome

The initial search yielded 30 articles. After applying inclusion and exclusion criteria, a total of 10 studies were included in the final review.

Inclusion and exclusion criteria

- **Inclusion criteria:** Peer-reviewed articles, clinical trial reports, and reviews discussing psilocybin's pharmacological properties, therapeutic potential, and safety in mental health treatment.
- **Exclusion criteria:** Studies not published in English, non-peer-reviewed literature, articles focusing solely on non-clinical uses of psilocybin, and publications older than five years unless seminal to the topic.

Ancestral history

Mushrooms containing psilocybin have been used for thousands of years. Indigenous cultures have used these mushrooms in shamanic and spiritual rituals throughout the Americas and other parts of the world.³ Species like *Psilocybe cubensis* and *Psilocybe mexicana* have been used ceremonially by indigenous people in Central and South America for many generations; this provides insight into the profound cultural significance of these fungi.³ Cultural use of the *Psilocybe maluti* species, which was found in Lesotho's highlands, has been documented.² As one of the first hallucinogenic mushrooms with confirmed indigenous uses in Africa, *P. maluti* (locally known as koae-ea-lekhoaba) is reportedly incorporated into spiritual practices by Basotho traditional healers.²

The science of psilocybin

The indole alkaloid psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) was first isolated from fungi, mainly from species of *Psilocybe* (*Fr.* Kumm.³ Psilocybin is converted to the bioactive substance psilocin in the body by dephosphorylation.³ From a structural perspective, psilocybin and psilocin resemble the neurotransmitter serotonin (5-hydroxytryptamine).³

5-hydroxytryptamine (5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}) receptors are bindable to serotonin and psilocin, which disrupts serotonergic neurotransmission and produces physiological effects.³ Changes in mood, awareness, and perception result from this interaction.³ Psilocybin is distinct from other psychedelics due to its pharmacological effects. Like other tryptamines, psilocybin, the active ingredient in psychedelic mushrooms, works by binding to serotonin receptors, especially the 5-HT_{2A} receptor. DMT (N,N-Dimethyltryptamine), 5-MeO-DMT, and LSD (Lysergic acid diethylamide) are tryptamines that have comparable effects and mechanisms.³

Effects of psilocybin

Psilocybin consumption can result in a variety of subjective effects, such as altered emotional states, improved creativity, altered perceptions, and changes in sensory perception.⁴ Users frequently describe vivid visual experiences, including enhanced colours and geometric patterns.⁴ Furthermore, experiencing a sense of oneness with everything or a sense of interconnectedness with the universe is not unusual.⁴

Known for its ability to bring about profound insights and a sense of unity, psilocybin is also known for inducing what is commonly called a "mystical experience" which possesses the following qualities: ineffability, noetic quality, timelessness and spacelessness, sacredness, and ego transcendence.⁴ A person's life may be profoundly impacted by these mystical encounters, which may result in increased spiritual or existential awareness and personal development.

Psilocybin, a naturally occurring psychoactive compound found in certain mushrooms, has significant effects on the brain's default mode network (DMN).⁴ The DMN is a network of brain regions that are active when the mind is at rest and engaged in introspection, self-referential thought, or daydreaming.⁴ It plays a crucial role in maintaining an individual's sense of self, or "ego", and is associated with conditions like depression and anxiety when it becomes overactive or rigid.⁴

Research has shown that psilocybin disrupts the usual patterns of activity within the DMN, leading to a state of "ego dissolution", where an individual feels a reduced sense of self and a greater connection to the external world.⁴ This altered activity allows for new connections and communication between brain regions that do not typically interact, promoting a state of cognitive flexibility.⁴ Such changes have been linked to therapeutic benefits, particularly in patients with depression, where an overactive DMN is associated with rumination and negative self-focus.⁴

Psilocybin's modulation of the DMN helps break entrenched patterns of thought and behaviour by reducing its activity and increasing brain network integration.⁴ This can lead to insights, shifts in perspective, and improved emotional processing, potentially offering lasting mental health benefits when combined with guided therapy sessions.⁴ Studies suggest that these changes can promote long-term improvements in mood and mental

health, supporting its potential as a treatment for depression, anxiety, and other disorders involving the DMN.⁴

Potential for therapeutics

In recent years, psilocybin's therapeutic potential has drawn a lot of attention. Its effectiveness in treating mental health conditions like depression, anxiety and alcohol use disorders has been shown in clinical studies.

Psilocybin may be useful for alcohol use disorder, according to one study. In a 2022 study, 93 individuals with moderate alcohol use disorders were enrolled in psychotherapy plus two psilocybin sessions versus psychotherapy plus a placebo.⁵ Over the course of 32 weeks, there were fewer days when the participants in the psilocybin-assisted psychotherapy engaged in heavy drinking, indicating that psilocybin may be beneficial for treating alcohol use disorder.⁵ Nonetheless, the majority of study participants accurately identified the therapy they had received, and it's unclear if the psilocybin effect persisted for more than 32 weeks.⁵

The use of psilocybin for anxiety and existential distress in serious medical illnesses such as advanced cancer has been the subject of a small amount of research. According to a 2020 analysis of four small studies involving 117 participants, the majority of whom had life-threatening cancer, psilocybin in combination with psychotherapy may be a safe and useful way to improve quality of life and alleviate symptoms of anxiety, depression, and existential distress.⁶ The authors acknowledge that there may have been bias in the conclusions due to factors such as small sample size and health status of the participants, as well as limitations in the study design.⁶

Psilocybin in conjunction with psychotherapy may be beneficial for depression in the short and medium term, according to an increasing amount of research. A 2023 evaluation and analysis of five trials involving 215 depressed individuals discovered that psilocybin therapy along with psychological support could alleviate depressive symptoms for up to five weeks.⁷ Although there was insufficient data to make a firm conclusion, it is feasible that the advantages will persist longer than five weeks.⁷

According to a 2023 study involving 104 depressed individuals, psychotherapy aided by a single dose of psilocybin significantly decreased depressive symptoms in eight days, with benefits continuing for six weeks.⁸

Psilocybin has garnered significant interest for its potential therapeutic effects in treating mental health conditions such as depression and anxiety.⁵ While psilocybin is generally considered to have a favourable safety profile when used in controlled settings, it is not without risks. One of the primary concerns is the potential for serotonin syndrome, a potentially life-threatening condition caused by excessive serotonin activity in the central nervous system.⁶

This syndrome can occur when psilocybin is combined with other serotonergic agents, leading to symptoms such as agitation,

confusion, rapid heart rate, and hyperthermia.⁶ Additionally, psilocybin can trigger acute psychotic episodes or exacerbate existing mental health conditions, particularly in individuals with a history of schizophrenia or those in the prodromal phase of the disorder.⁷ This risk underscores the importance of thorough psychological screening and the need for administration under professional supervision. Ensuring that contraindications and patient history are carefully evaluated is essential to minimising the risks and enhancing the therapeutic potential of psilocybin.⁷

Psilocybin produces altered states of consciousness that encourage self-reflection and emotional breakthroughs by binding to serotonin receptors in the brain. Clinical research has shown that it can provide patients with terminal illnesses with a sense of acceptance and serenity while also reducing anxiety and depressive symptoms. Furthermore, by assisting patients in reframing their thought processes and behavioural patterns, psilocybin-assisted therapy has demonstrated promise in easing the symptoms of substance use disorders, including alcohol and nicotine addiction. To create standardised treatment protocols and gain a complete understanding of the mechanisms of action and long-term effects of psilocybin, more research is necessary.

Safety of psilocybin

Psilocybin is not thought to be physically addictive and has a comparatively low toxicity profile. But it's important to remember that psilocybin has risks just like any other drug, particularly when used carelessly and without supervision. Unfavourable or difficult side effects that users may encounter include confusion, anxiety, and paranoia.⁹ Consequently, it is impossible to exaggerate the significance of using psilocybin in a monitored and controlled environment. An essential component of psilocybin safety is the "set" and "setting". The term "set" describes the psilocybin user's mental state at the moment of ingestion, including their mood, expectations, and underlying psychological state.⁹ The term "setting", however, describes the social and physical context in which the experience occurs, encompassing elements like the location, the presence of helpful people (like facilitators or guides), and the sensory elements of the surroundings.⁹

Psilocybin safety has been questioned for a number of reasons:

- One article published in 2022 for palliative care clinicians recommends that individuals take psilocybin only while receiving supervision from a qualified therapist or facilitator.⁶ According to the article, the therapist is responsible for overseeing the participant's mental state when they enter the experience, as well as the physical surroundings, personnel, and additional elements surrounding the experience, like music.⁶ These are crucial components of safety for psychedelic-assisted therapy.
- People's experiences can be erratic and vary based on their personality, mood, expectations, and environment (such as the presence of a trained facilitator, the type of light and music, and whether the setting is indoors or outdoors), in addition to how much psilocybin they take.¹⁰ Other variables that may impact

the encounter include the user's health, the kind of mushroom, prior exposure to comparable substances, and concurrent use of other medications.¹⁰

- Unpleasant experiences, sometimes referred to as “bad trips,” involving intense fear, perplexity, or panic have been reported by certain individuals.⁹
- High blood pressure and heart rate, headache, nausea, dizziness, exhaustion, restless nights, anxiety, paranoia, psychosis, and hallucinations are some of the negative effects of psilocybin.⁹
- Sleeplessness, elevated anxiety and depression, low mood, low energy, physical discomfort (such as headaches, gastrointestinal symptoms, impaired sense of smell, temperature dysfunction), poor focus and cognitive functioning, and hampered social skills can all result from microdosing on psilocybin.¹¹
- People with severe forms of bipolar disorder, borderline personality disorder, schizoaffective disorder, or other psychotic conditions should not take psilocybin.^{12,13}

Current views

Psilocybin research is growing quickly as researchers look into possible uses and improve our understanding of the drug's mechanisms of action. Research is being conducted to examine its potential applications in the management of various ailments.

Since many people do not tolerate the current pharmaceutical treatments well and they do not work for everyone, patients need to be given options. The side effects of the current depression medications can include sexual, mood, weight, cognitive, and other issues.^{14,15} It frequently takes weeks or months of trying various medications before finding one that works or doesn't work.¹⁵ The side effect profile of psilocybin is much better: mild to moderate transient anxiety and a transient headache that can be relieved with over-the-counter drugs.

Psilocybin has long intrigued scientists due to its profound mind-altering properties and potential therapeutic benefits.

In recent years, research into how psilocybin affects the brain has expanded, aiming to unravel the mechanisms behind its influence on perception, cognition, and mental health. A groundbreaking study led by Dr Nico Dosenbach, an associate professor of neurology at Washington University School of Medicine in St Louis, took this exploration a step further. Dr Nico Dosenbach had done dozens of brain scans on himself in the name of science. However, this was the first time he'd taken something that defied logic before entering an MRI machine.¹⁶ It was his colleagues who had given Dosenbach a high dose of psilocybin.¹⁶ All of this was done as part of a study published in *Nature* to demonstrate how psilocybin causes its mind-altering effects.¹⁶ “It was definitely an awesome experience for a neuroscientist. It's really fascinating how your brain can fall apart — because how something breaks tells you how something works”, he stated.¹⁶ His findings indicated that psilocybin «desynchronized» the *brain*, but also produced subtle, lasting effects in boosting plasticity.¹⁶

All things considered, the study has offered us a promising look at the science underlying the mystique of magic mushrooms and serves as an example of what can be accomplished by the renewed interest in psychedelic medicine. Figure 1 depicts that the depressed brain encourages rigid thought patterns that impact well-being. This can be viewed as a “landscape” with deep wells that make it difficult for patients to “move between” different thoughts and perspectives.¹⁷ Figure 2 indicates psilocybin's mechanism of action.

Conclusion

The exploration of psilocybin's therapeutic potential has brought renewed attention to the power of natural compounds in addressing mental health challenges. With a rich history of cultural and ceremonial use, psilocybin has transitioned from a traditional context to being a focal point of modern scientific inquiry. Research has demonstrated its promise in treating various mental health conditions, including depression, anxiety, and substance

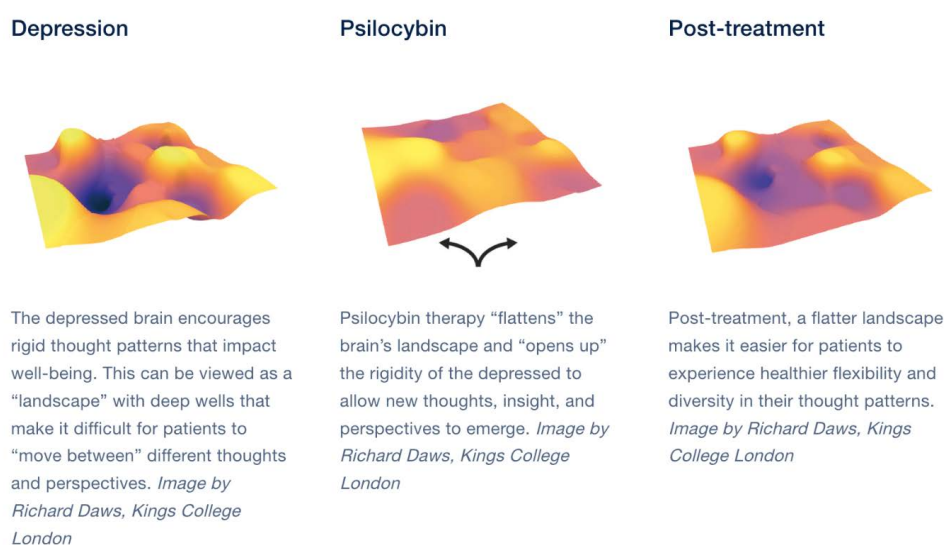


Figure 1: Depiction of the rigid thought patterns of depressed patients that change post-treatment with psilocybin.¹⁷ Credit: Richard Daws, Kings College London

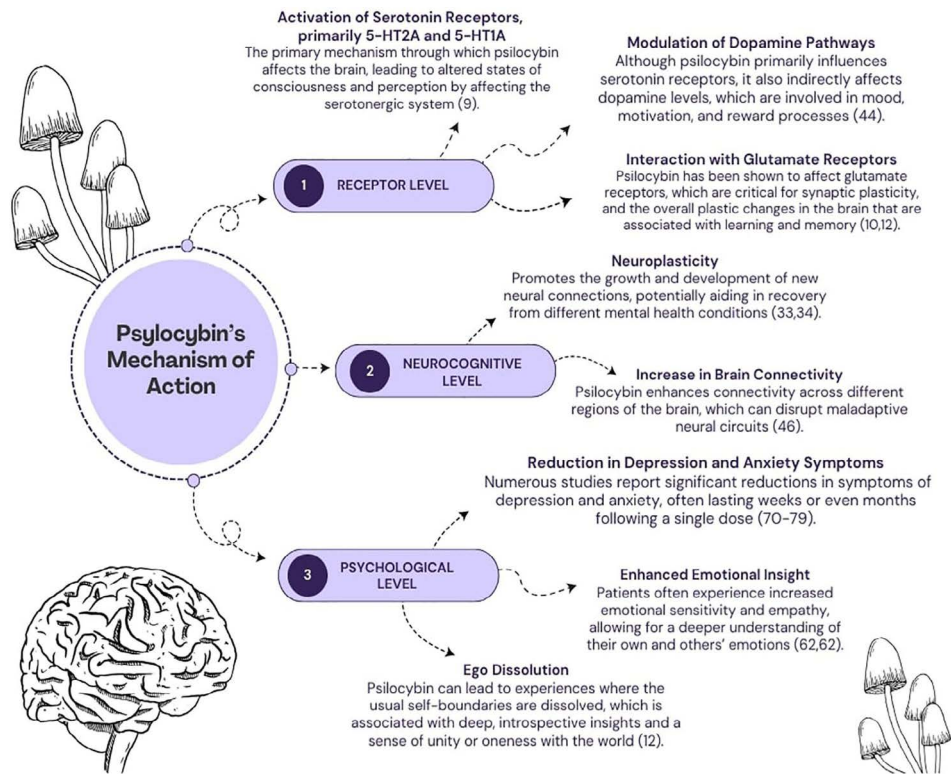


Figure 2: A diagram depicting several mechanisms of psilocybin's action. The effects of its action are categorised into three levels: (1) pharmacological, (2) neurocognitive, (3) psychological.¹⁸

use disorders. Clinical trials have shown that, when administered in controlled settings with professional oversight, psilocybin can facilitate profound psychological experiences that contribute to significant symptom relief and personal growth.

Despite these promising findings, the path to integrating psilocybin into mainstream treatment is complex. Concerns related to safety, optimal treatment protocols, long-term effects, and the potential for misuse must be addressed through rigorous, ongoing research. Additionally, the legal status of psilocybin remains a barrier in many parts of the world, necessitating policy changes informed by scientific evidence to ensure safe and ethical use.

In conclusion, psilocybin holds considerable potential to revolutionise the treatment of mental health disorders, offering an alternative for patients unresponsive to conventional therapies. Future research and evolving public perception may pave the way for psilocybin to become a standard component of psychiatric care. Continued exploration, robust clinical trials, and interdisciplinary collaboration will be essential in transforming this potential into widespread clinical application.

Conflict of interest

The author declares no conflict of interest.

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