

PSILOCYBIN GUIDE



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What is Psilocybin?

Psilocybin is a naturally occurring psychedelic compound found in over 200 species of mushrooms, often referred to as 'magic mushrooms', primarily belonging to the *Psilocybe* genus.¹ Psilocybin metabolizes into psilocin, a chemical that binds to serotonin receptors in the brain, triggering hallucinations and introspection.² In 1956, Roger Heim identified a psychoactive mushroom originating in Mexico as *Psilocybe*, and in 1958, Swiss Chemist Albert Hofmann, who also discovered lysergic acid diethylamide (LSD), first identified psilocybin and psilocin as the active compounds in these mushrooms.³

For centuries, psychedelic compounds, including these mushrooms, have held a prominent role in various cultures for their hallucinogenic and spiritual properties.⁴ In recent years, the field of psychedelic research has gained significant interest, exploring the potential therapeutic uses of psilocybin and related compounds in the treatment of both mental and physical health conditions.

This renaissance of psychedelic research in recent years has revealed numerous potential therapeutic applications for psilocybin. Clinical studies in the United States and from around the world have shown promising results in the treatment of various mental health issues, including depression,⁵ anxiety,⁶ addiction,⁷ and post-traumatic stress disorder (PTSD).⁸ Outside of clinical settings, a recent large-scale naturalistic study of psilocybin conducted by researchers at Unlimited Sciences, Johns Hopkins University, and Ohio State University found naturalistic psilocybin use is highly consistent with results from a growing body of clinical trials, including lasting improvements in mental health symptoms related to anxiety, depression, and substance misuse. Research is currently proposed or ongoing into psilocybin's effects on a number of physical health conditions as well, including migraine headache, cluster headache, chronic pain, cancer pain, functional neurological disorder, and post-treatment Lyme disease.

Use of Psilocybin Through the Ages

Different cultures (e.g., Olmec, Zapotec, Maya, and Aztec) have used psychoactive mushrooms for spiritual practices for thousands of years across different regions and societies around the world.⁹ Historical records, archaeological evidence, and academic articles allude to its use for religious, spiritual, and medicinal purposes. Psychedelic Singh, Gaughen, Hill, Morski, & Lowe. Psilocybin Guide. Page 5 of 38

substances, including psilocybin, have been recognized as a key component of religious and spiritual practices among several indigenous cultures.⁴ These substances are often used to facilitate communication with deities or ancestral spirits, allowing individuals to seek self-knowledge and healing, and providing opportunities for personal growth and transcendence.¹⁰

The earliest known evidence of ritualistic use of psilocybin dates back 6,000 years to the ancient Tassili n'Ajjer civilization in present-day Algeria.¹¹ Indigenous cultures, such as Native Mexican and Guatemalan groups, have long integrated psilocybin mushrooms into their spiritual and medicinal practices. Their use is often linked with divination, communication with ancestors, and connecting with the spirit world.¹² For example, the Mazatecs of Oaxaca, Mexico, use psilocybin mushrooms as a tool for healing and self-discovery.¹⁰ The mushrooms are often consumed in rituals supervised by experienced guides, who guide the participants through the process and interpret their experiences.

Ignited largely by the works of R. Gordon Wasson and researchers like Timothy Leary, the 20th century has seen a resurgence of interest in the use of psilocybin. Psilocybin has been utilized in modern contexts for personal growth, spiritual exploration, and as an adjunct to psychotherapy. Recent scientific research has explored the potential therapeutic benefits of psilocybin for a variety of mental health issues, further driving interest in its psycho-spiritual applications.

A growing number of people are participating in ceremonies that incorporate the traditional elements of indigenous practices, led by experienced facilitators in various settings. Additionally, certain religious groups, such as the Native American Church, have integrated psilocybin along with other entheogens into their religious practices.¹³

How is Psilocybin Used in Modern Medicine and Research

In recent years, there has been growing interest in the use of psilocybin in modern medicine and research. While psilocybin has long been used for spiritual and recreational purposes, more and more research is being conducted on the potential medical benefits of psilocybin.

One of the most promising areas of research for psilocybin is its potential use as a treatment for various mental health conditions. Following a long hiatus stemming from a restrictive regulated drug schedule, the investigation of psychedelic compounds has reemerged with increased focus on potential applications of psychedelics in the treatment of mental health conditions.¹⁴ In 2018 the Food and Drug Administration (FDA) granted breakthrough therapy status to psilocybin for treatment-resistant depression.

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The Potential Therapeutic Uses of Psilocybin

Depression, anxiety, and PTSD

One of the most promising areas of research for psilocybin is its potential to treat mental health conditions such as depression, anxiety, and PTSD. Studies have shown that a single dose of psilocybin can lead to significant improvements in mood and decrease symptoms of treatment-resistant depression as compared to a placebo.¹⁵ A recent study reported that the effects of psilocybin-assisted therapy lasted up to twelve months after the initial dose.¹⁶ A recent meta-analysis of the effects of psilocybin found significant improvements in depression and anxiety symptoms¹⁷ while another study showed the clinical utility of treating symptoms of obsessive-compulsive disorder with psilocybin.¹⁸ A recent review on the use of psychedelics for the treatment of PTSD concluded that psychedelics offer a promising new approach for this chronic illness that is associated with high rates of comorbid psychiatric and medical issues.¹⁹ Outside of controlled research settings, naturalistic use of psilocybin has shown consistent results with clinical trials. Unlimited Sciences' prospective longitudinal data collected before and after a planned psilocybin experience outside of clinical settings showed persisting reductions in anxiety and depression.³⁹

Substance abuse and addiction treatment

Psilocybin has also shown promise in the treatment of substance abuse disorders. Studies have shown that participants with alcohol use disorder who received even a single dose of psilocybin had reduced cravings and increased abstinence rates compared to those who received a placebo.^{7,20} Consistent with these results, Unlimited Sciences' naturalistic research study on psilocybin use found significantly decreased alcohol misuse persisting for months after psilocybin ingestion.³⁹ Other studies have found that psilocybin-assisted therapy was effective in decreasing nicotine dependence²¹ and that 60% of participants remained smoking abstinent after a mean of 30 months.²² These results suggest that psilocybin may have a role to play in treating various types of addiction.

End-of-life distress

In addition to its potential for treating mental health conditions, psilocybin has also been studied as a treatment for end-of-life distress. One study showed that a single dose of psilocybin can lead to sustained improvements in satisfaction with life and mindfulness-related capacities in individuals facing terminal illness.²³ This is further supported by a randomized double-blind trial which found substantial and sustained decreases in depression and anxiety among patients with life-threatening cancer after receiving psilocybin-assisted therapy.

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Psychopharmacology of Psilocybin

When ingested, psilocybin is converted into a compound called psilocin. Psilocin then binds to serotonin receptors in the brain, specifically the 5-HT2A receptor.²⁴ This binding triggers a series of chemical and electrical reactions that result in altered perception, thought processes, and mood. These effects can last for several hours.

A drug's pharmacodynamics can be affected by physiologic changes due to:

- A disorder or disease
- The aging process
- The presence of other drugs

Absorption

The absorption of psilocybin occurs primarily in the gastrointestinal tract. After ingestion, it is broken down by enzymes in the body into its active form, psilocin.²⁵ This process can take anywhere from 30 minutes to an hour, depending on various factors such as dosage and individual metabolism. Once in its active form, psilocin can easily cross the blood-brain barrier, leading to its psychoactive effects.²⁶

Distribution and Metabolism

Once absorbed, psilocin is distributed throughout the body via the bloodstream. It then undergoes metabolism in the liver before being eliminated from the body. The exact process of metabolism is not yet fully understood. However, it is believed that liver enzymes break down psilocin into inactive forms. This process can take several hours, during which time an individual may experience a prolonged altered state of consciousness.²⁷

Elimination and Half-Life

The elimination of psilocin and its metabolites from the body occurs primarily through urine.²⁶ However, a small percentage may also be eliminated through breath and sweat.

The half-life of psilocybin, the time it takes for half of the compound to be eliminated from the body, is approximately 160 minutes, while that of psilocin is around 50 minutes.²⁶ This means that after about six to eight hours, most traces of psilocybin are no longer detectable in the body. A drug is considered fully eliminated after 5 half-lives.

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Chemistry and forms of psilocybin

Psilocybin (O-phosphoryl-4-hydroxy-N, N-dimethyltryptamine) is a prodrug for the psychoactive compound psilocin (4-hydroxy-N, N-dimethyltryptamine).²⁶ A prodrug is a pharmacologically inactive medication or compound that, after intake, is metabolized, (meaning converted within the body) into a pharmacologically active drug. When ingested, psilocybin is converted to psilocin, which is responsible for the psychoactive effects. Psilocybin-containing mushrooms typically show variations in psilocybin and psilocin concentrations depending on factors like species, growth conditions, and preservation methods.²⁵

Psilocybin can be found in several different forms, each with varying potencies and effects. Here are some common forms:

- Raw mushrooms: The most natural form of psilocybin, typically consumed by ingesting dried magic mushrooms.
- Psilocybin extract: A concentrated form of the compound, created by extracting the psilocybin from the mushrooms.
- Psilocybin truffles: Also known as "philosopher's stones," these are underground fungal growths that contain psilocybin.
- Psilocybin edibles: Psilocybin can be infused into food or beverages, making it more palatable for consumption.
- Synthetic psilocybin: Chemically developed in a laboratory, allowing for precise dosing and purity.

Neurotransmitters involved

Psilocybin primarily targets the serotonin system, which is involved in regulating mood, behavior, and cognition. Specifically, psilocybin binds to serotonin receptors (5-HT2A) and activates them, leading to changes in brain activity and perception.²⁴

In addition to targeting serotonin, psilocybin also affects other neurotransmitters such as dopamine and glutamate.²⁸ Dopamine is known for its role in reward and motivation. Psilocybin has been found to increase dopamine levels in certain areas of the brain. This effect may explain why some users report feelings of euphoria and heightened creativity while under the influence of psilocybin. Glutamate, on the other hand, is involved in learning and memory. Psilocybin has been shown to disrupt glutamate signaling in certain brain regions, which could contribute to its hallucinogenic effects.

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It is important to note that psilocybin's effects on neurotransmitters are not fully understood yet. As mentioned earlier, research is still ongoing, and much remains to be discovered about this compound and its potential therapeutic uses.

Potential pathways/mechanism of action

Serotonin receptor interaction

Psilocybin is known to mimic the actions of serotonin, a neurotransmitter that regulates mood, cognition, and perception by primarily binding to the serotonin 2A receptor (5-HT2A), leading to alterations in brain activity and changes in perception.²⁹ The activation of these receptors may also promote neuroplasticity, which is the ability of the brain to adapt and form new connections.²⁴ This could potentially explain why psilocybin has been shown to have long-lasting effects on behavior and thought patterns.

Default mode network

The default mode network (DMN) is a group of brain regions that is active when an individual is at rest or not focused on a particular task. Studies have shown that psilocybin may decrease activity in the DMN, leading to a state of decreased self-awareness and ego dissolution.³⁰ This reduction in activity may also explain why individuals report feeling more connected and empathetic toward others after taking psilocybin. Further, it has been hypothesized that decreased activity in the DMN may allow for increased introspection and self-reflection, which could be beneficial for individuals struggling with mental health disorders.³¹

Neuroplasticity

As mentioned earlier, psilocybin has been found to promote neuroplasticity in the brain. This means that psilocybin can facilitate the growth of new neurons and connections between them, leading to changes in brain function and behavior.³² Studies have also shown that psilocybin may increase levels of brain-derived neurotrophic factor (BDNF), a protein that plays a crucial role in promoting neuroplasticity.^{33,34} These findings suggest that psilocybin may have potential therapeutic effects on conditions such as depression and anxiety, which are often associated with reduced BDNF levels.

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