

Pharmacology and Therapeutic Effects of Psilocybin

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Abstract. Psilocybin, a psychoactive alkaloid with hallucinogenic properties, exists in a variety of hallucinogenic mushrooms. As a study tool to imitate psychosis, psilocybin has aroused a lot of interest in the biological community due to its various possible therapeutic benefits. It is also a very popular and widely misused natural hallucinogens with distinct metabolism pathways and toxicity. In this paper, the metabolism and mechanism of psilocybin were summarized, and the toxicology and pharmacology of psilocybin were discussed in detail, and the positive effects of psilocybin on psychological illnesses like depression, addiction, anxiety, and obsessive-compulsive disorder were gathered and sorted out, and the drug's therapeutic potential for mental and psychological illnesses was systematically clarified. Understanding the mechanism and therapeutic ability of psilocybin is of great significance to its potential development. As a hallucinogenic agent with low toxicity and no side effects, its effective application in the treatment of psychological and mental diseases can provide new ideas for the treatment of various diseases.

Keywords: Psilocybin, toxicity, pharmacology, therapeutic effect.

1. Introduction

Hallucinogenic mushrooms, also known as magic mushrooms and sacred mushrooms, are large fungi that contain active tryptamine toxoid in their subsidiaries or mycelium and can cause neuro hallucinogenic poisoning in humans and other animals. The main pathogenic substances are psilocybin and psilocin, which belong to tryptamine compounds and are a class of neurogenic toxins. Psilocybin poisoning works by stimulating the autonomic nervous system and suppressing it. It is caused by the motor nervous system. 10 to 30 minutes after ingestion of toxic mushrooms containing psilocybin, cognitive impairment, thinking disorders, emotional changes and perceptual changes will appear, similar symptoms of schizophrenia, migraines, hyperreflexia, convulsions, tinnitus and paresthesia will also occur [1]. Psilocybin users report that its mind-altering effects continue longer than the typical 2 to 6 hours because the drug alters their time perception. The toxicity and risks of psilocybin are low. However, most nations forbid the consumption of psilocybin-containing mushrooms, and many classify them as a controlled narcotic under their respective drug laws.

Psilocybin is a substituted indole alkyl amine with the chemical formula $C_{12}H_{17}N_2O_4P$ and molecular mass 284.27. When psilocybin is ingested, it is rapidly converted into psilocin by phosphatase, and then psilocin binds to serotonin receptors which can be found in the human brain and then affects the mind. When psilocybin is consumed, it is absorbed and metabolized through the first channel in the liver before being rapidly dephosphorylated to the hallucinogenic compound psilocybin by an unknown enzyme. Psilocin enters the bloodstream and travels to the brain, where it affects the proper functioning of a person's nervous system. In living organisms, psilocybin goes through two stages of metabolism. The phase I metabolism process is as follows: psilocybin is oxidized to 4-hydroxyindole-3-acetaldehyde, and in the next step converted to 4-hydroxyindole-3-acetic acid or it would be reduced to 4-hydroxytryptophan. In phase II metabolism, psilocybin metabolites are psilocybin-glucoside conjugates. Enzymes involved in this metabolism include UGT1A10 enzymes which are found in the small intestine and UGT1A9 enzymes which are found in the liver (Figure 1). Then the kidneys get rid of those metabolites. Even though phase II reactions make up about 80% of metabolism, phase I reactions still make up a sizeable portion of it. According to studies, the elimination half-life of psilocybin in healthy individuals is about 2 to 5 hours. These are only the general metabolic pathways of psilocybin, and more detailed and complete pathways have not been further studied. Therefore, in order to further understand the metabolism of psilocybin

in human body, relevant studies are necessary. A study conducted by Agurell et al. found that tryptophan and tryptamine organisms had the potential to synthesize psilocybin, in the study of psilocybin synthesis, tryptophan has been shown to be a precursor, it is more worthy of utilization than D/L-tryptophan, but biosynthetic studies showed that labeled D/L-tryptophan and tryptamine activity combined to form psilocybin. Further studies have suggested that psilocybin may be produced in that ways as: tryptophan, tryptamine, N-methyltryptamine, N,N-dimethyltryptamine, psilocin, psilocybin [2].

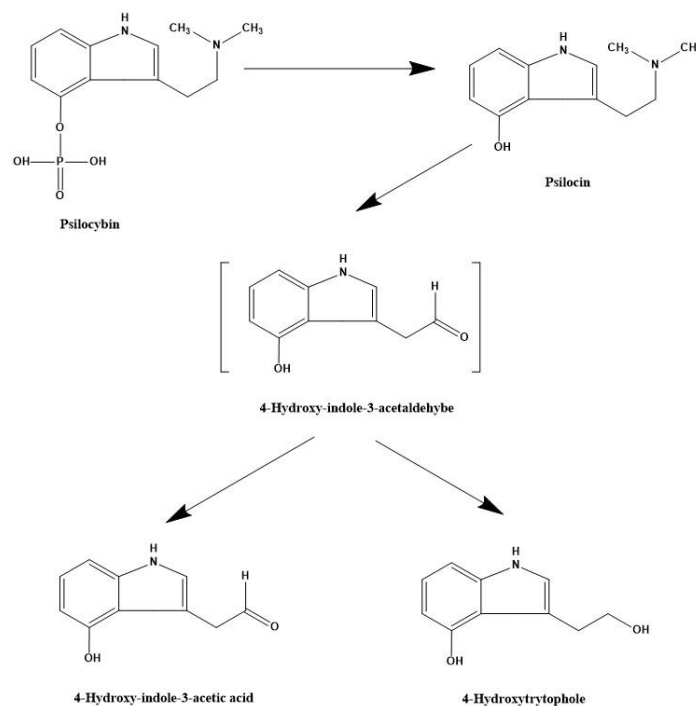


Figure 1. Metabolic pathway of psilocybin

More and more research in recent years suggests that psilocybin may have medical benefits, and some studies have found that psilocybin can increase good mood and have suggested that psilocybin may have antidepressant effects. Many pieces of evidence point to potential clinical applications of psilocybin in the management of addiction. Today, psilocybin has been proved to be able to be absorbed by the human body with a relatively high absorption rate and a longer effect on people, with few side effects, it can be used in psychological and neurological diseases has a bright prospect. It has recently attracted a great attention from the scientific community because it has potential therapeutic effects and can be used as a tool in psychiatric simulations.

2. Toxicity of Psilocybin

2.1. Dosage

Research on psilocybin has shown that the effects of the drug can vary based on the dosage and time course of administration. A pooled analysis of experimental studies by Studerus and colleagues found that higher doses of psilocybin were associated with more intense subjective effects and a longer duration of action. In a double-blind experiment conducted by Moreno and colleagues, nine obsessive-compulsive subjects took four distinct doses of psilocybin (25mg/kg, 100mg/kg, 200mg/kg, 300mg/kg) respectively, only one of them developed symptoms of hypertension unrelated to the disorder and had no adverse effects. Psilocybin was well tolerated, safe to measure and had no serious side effects [3]. Krebs and Johansen reported that population studies have suggested that psychedelics, including psilocybin, may have positive effects on mental health, but it is important to consider dosage and set and setting when using these drugs [4]. While psilocybin is generally considered safe, there is a risk of adverse effects, including potentially dangerous psychological reactions such as

panic, paranoia, or psychosis. In summary, psilocybin can have subjective effects on healthy individuals and may be effective in treating certain mental health conditions, but dose and timing need to be carefully considered because they are important factors. Although psilocybin is generally proven to be safe, there is a risk of adverse reactions, and it is important to use it under the guidance of a trained professional in a safe and supportive setting. Compared to other drugs, psilocybin has a low potential for harm.

2.2. Effects on the Metabolic System

Several studies have examined the potential toxicity of psilocybin on somatic, physiological, and endocrine functions, and have produced some interesting findings. For instance, in a clinical research by Hasler et al., eight volunteers received oral doses of psilocybin at $212 \pm 25 \mu\text{g}/\text{kg}$, collected urine for 24 hours, and used electrochemical detection and high performance liquid chromatography column switching to explore psilocybin elimination kinetics, they found that psilocybin can be excreted through the body's kidneys, suggesting that the compound can be processed by the body and removed from the body [5]. Vollenweider and Kometer explored the neurobiology of psilocybin and its potential use for treating mood disorders, highlighting the compound's effects on serotonin receptors in the brain. Other studies, such as Griffiths et al. have investigated the potential for psilocybin to occasion mystical-type experiences that have personal and spiritual significance, but more studies are needed to fully understand the long-term implications of these experiences [6]. Riba et al. studied the cardiovascular and monoamine metabolite effects of ayahuasca, a psychedelic brew containing psilocybin, and found that it produced changes in heart rate and blood pressure, and also some alterations in the excretion of certain monoamine metabolites [7]. Overall, while these studies provide some insight into the potential toxicity of psilocybin on various physiological functions, if we want to fully understand its effects on the human body, we need to conduct more relevant research to explore. However, the results of these experiments suggest that psilocybin can have potential for treatment to treat a variety of conditions and can be relatively safe when used in controlled environments.

3. Pharmacology of Psilocybin

Studies of rodent tissues have shown that psilocybin enters the systemic circulation through complete conversion to psilocin. Therefore, the study target of kinetics is mainly its metabolite psilocin. In fact, in some experiments, following oral psilocybin dosage increases, neither plasma nor urine samples of the parent substance were found. [8]. Human pharmacokinetics are rarely studied, so the details of these aspects are not fully known.

As a structural analogue and antagonist of 5-hydroxytryptamine (5-HT), psilocybin mainly interacts with 5-HT receptors (5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A} and 5-HT_{2c} subtypes), and then affects 5-HT neurotransmission. Among them, the affinity with 5-HT_{2A} is the strongest. With the weakest effect of 5-HT, early studies have shown that $100 \mu\text{g}$ of psilocybin is equivalent to $1 \mu\text{g}$ LSD and $1000 \mu\text{g}$ of mescaline [9]. Repeated use of psilocybin can lead to severe resistance, but no drug dependence. Oral dose of 12~20mg psilocybin, can produce controlled changes in consciousness, the main characteristics are to improve the ability of introspection and guide hypnosis, especially can cause perceptual changes, hallucinations, synesthesia, emotion and change thinking and time awareness. The psychological effects of psilocybin can last for 3~6h. The median lethal dose of psilocybin in mice is $280 \text{mg}/\text{kg}$ intravenously, and higher concentrations may be required for human action. In many in vitro experiments, psilocybin has no specific effect on specific organs (such as the heart, small intestine, etc.) [10]. The autonomic effects of $10 \text{mg}/\text{kg}$ intravenous injection on the autonomic nervous system of experimental animals (mice, rats, rabbits, dogs, cats) include dilated pupils, erect hair, irregular heartbeat and respiratory rates, discontinuous hyperglycemia and hypertonic effects. The cause of these effects is the concentrated stimulation of the sympathetic nervous system in excitation syndrome. In non-blind trials of healthy people, 93% of subjects had

dilated pupils, 80% had increased knee jerk reflexes, 56% had increased heart rate, 44% had nausea and 34% had decreased arterial blood pressure. Detailed physical tests have shown that psilocybin does not have any adverse effects on human health.

4. Therapeutic Effects of Psilocybin

Hallucinogens are considered as key tools in understanding the causes of some mental illnesses. As a hallucinogenic drug with low toxicity and low addiction, psilocybin has strong research potential in the treatment of mental and psychological diseases

4.1. Depression Treatment

In 2021, 24 patients with severe depression were randomly allocated to receive instant therapy or wait for eight weeks before receiving it in a randomized controlled study by Davis et al. Psilocybin was given to the immediate treatment group at weeks 3 and 4, on the other hand, it was given to the postponed treatment group at weeks 11 and 12. In the process of data collection, the GRID-Hamilton Depression Assessment Scale was used to evaluate the depressive symptoms of the two groups of patients after psilocybin injection at different times [11]. In the measurements of this experiment, at weeks 5 and 8, compared to the postponed therapy group, there was a clear downward trend in the GRID-HAHD score in the receiving immediate treatment group. People with major depressive disorder have conditions that change over time, the study reduced this effect using a delayed control group, and the result showed that psilocybin can effectively treat major depressive disorder. In 2016, a similar conclusion was reached in a clinical trial conducted by Carhart-Harris et al. to explore whether psilocybin combined with psychotherapy has therapeutic effect on TRD (treatment-resistant depression) patients, twelve moderate-to-severe patients with TRD were selected and given 10mg and 25mg of psilocybin, with a 7-day interval between administration and non-guiding supportive psychotherapy before, during, and after each treatment. The rapid inventory of depressive symptoms and the Beck depression inventory were used to measure the severity of depression. Results showed that depression scores for all patients decreased significantly after 1 week and 3 months of administering 25 milligrams of psilocybin. It showed that psilocybin combined with psychotherapy may have certain therapeutic effect on TRD patients, and its anti-depression effect is fast [12]. Studies have shown that depressed patients who receive psilocybin therapy can significantly improve their executive function, social skills, and depressive mood, and combined psychotherapy may further enhance this effect. Since the drug amplifies the emotional state of the drug, a more comfortable environment should be provided before psilocybin is administered in the future to achieve a better therapeutic effect.

4.2. Addiction Inhibition

In one trial, psilocybin was administered as a psychobehavioral treatment for 15 tobacco and nicotine-dependent smokers. Ten of the fifteen subjects were discovered to be abstinent at the one-year follow-up, and psilocybin had no discernible adverse effects. The positive effect of psilocybin on smoking cessation is also supported by an online study of 358 people who reported quitting or reducing the frequency of smoking after receiving traditional hallucinogenic treatment. The subjects clearly indicated that the mood withdrawal side effects of psilocybin drugs were less severe than those of traditional hallucinogens used previously [13]. Psilocybin additionally has therapeutic effects on alcoholism. In a single-group and proof-of-concept trial, oral psilocybin was administered for one to two sessions together with motivational enhancement therapy that specifically targeted psilocybin to 10 participants with alcohol dependency as described by the DSMIV. According to the findings, abstinence did not significantly increase among those who had not yet started receiving psilocybin therapy but did so after doing so. The majority of the withdrawal effects were still present after 36 weeks of follow-up [14].

4.3. Anxiety and Obsessive-Compulsive Disorder Reduction

Ross et al. conducted a crossover, randomized, controlled, double-blind trial, in which 29 patients with cancer complicated with depression and anxiety were randomly divided into psilocybin group and niacin group. After 7 weeks, the psilocybin group was crossed with the niacin group, and symptom changes were assessed by the hospital anxiety and depression scale. The findings demonstrated that following administration and up until the crossover at seven weeks, the scores on all scales within the psilocybin group were considerably lower than the control group. While in the niacin group, all scales scores did not decrease significantly before crossover, and the scores of five scales decreased significantly after taking psilocybin. These data the transformation trend indicate that psilocybin may be effective in anxiety reduction in addition to treating depression [15].

In another study of nine patients who had OCD (obsessive-compulsive disorder), Moreno et al. Had them ingest four single doses of psilocybin, with the low dose being 100mg/kg, the medium dose 200mg/kg, the high dose 300mg/kg, patients ingested psilocybin from low to high doses, and during the intake of these doses, after the first dose, very low doses (25mg/kg) of psilocybin will be administered at a random time in a double-blind format. During the course of the experiment, the tests were conducted at least one week apart, and each session lasts for more than 8 hours in a strictly controlled outpatient setting, after which subjects were transferred to a psychiatric inpatient ward, and their behavior and mental state were observed and recorded during the night. At 0, 4, 8 and 24 hours after ingestion of psilocybin, the experiment used Yell-Brown obsessive-compulsive disorder Scale and visual analogue Scale to measure the scores of the patients in the experiment, so as to judge the severity of their obsessive-compulsive disorder symptoms. 8 hours after ingesting psychedelic drugs, Patients were evaluated and graded, and after psilocybin injection, patients had their vital signs measured and accurately recorded at 0, 1, 4, 8, and 24 hours. The effective results of this study indicate that psilocybin is safe and reliable in patients with OCD in a clinical setting which are controlled, and in several subjects, their OCD symptoms were confirmed to be reduced by the effects of psilocybin [3].

4.4. Safety of Psilocybin

Psilocybin has been shown to be effective in treating mental disorders such as depression, but it is still not an approved drug for use. Studies have shown that psilocybin use often has a variety of side effects including transient headache, anxiety, nausea and vomiting, psychotic symptoms, and increases in blood pressure and heart rate [12]. Psilocybin is less toxic, its action is more mild, less addictive, is suitable for psychiatric and psychological research a drug. The vast majority of adverse events were mild, self-limited, did not require specific treatment, and no serious adverse events occurred during medication. However, as a hallucinogen, there are still great obstacles to its clinical application. In the future, a great deal of clinical studies are needed to confirm its safety, feasibility and effectiveness.

5. Conclusion

To sum up, psilocybin has strong research and therapeutic potential. Because its toxicology, pharmacology and the mechanism of its action has been well studied and understood, and many important experiments on it have also made effective discoveries. At the same time, it has been found to be a useful tool for studying the neurobiology of psychosis, and psilocybin treatment of psychosis plays a key role in the development of new treatments for psychosis. However, there are still great limitations in the application of psilocybin. First of all, among the drugs currently studied, psilocybin needs to be combined with psychotherapy to play its role, and the effect of psilocybin alone is still unclear, which should be further explored in future studies. Secondly, most current studies lack placebo control, which is too difficult to form control. Future studies may try to use drugs with the same psychedelic effect or low-dose psilocybin for placebo control. Although psilocybin is safer, it

still has some side effects and is less addictive, in future studies, assurance of the safety and effectiveness of psilocybin will be an important development direction of psilocybin research.

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