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Application of psilocybin in mental health disorders

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Abstract. Psilocybin is a naturally occurring psychoactive compound, which has been used for ages in traditional settings for religious and therapeutic use. Recent studies have renewed interest in psilocybin for its potential therapeutic benefits in treating depression and anxiety. The pharmacodynamics of psilocybin are complex, involving its rapid conversion to psilocin and its activity on various serotonin receptors, particularly the 5HT2A/C and 5HT1A receptors. In addition, psilocybin can increase glutamate release, which is believed to be an important mechanism underlying its therapeutic effects. Clinical trials have demonstrated that psilocybin has a long-lasting antidepressant effect, with little to no side effects. However, it is necessary to further study the mechanisms underlying its therapeutic potential and to optimize its use in clinical settings. Overall, the promising findings suggest that psilocybin may offer a valuable alternative to traditional antidepressant therapies for individuals suffering from depression and anxiety. Meanwhile, studies have shown that this drug also has certain benefits for mental disorders such as addiction and obsessive-compulsive disorder. Thus, it is necessary to continue exploring the potential of psilocybin as a novel strategy in treating mental health disorders.

Keywords: psilocybin, mental health disorders, application.

1. Introduction

Psilocybin, a prominent hallucinogenic substance, is mainly obtained from certain species of mushrooms found globally. However, the misuse of these drugs has led to detrimental effects among a growing number of psychedelic drug users, highlighting the need for careful consideration of its usage and effects [1].

The primary active metabolites of psilocybin, psilocin, and psilocybin is a predominant agonist on serotonin 5HT2A/C and 5HT1A receptors, while the 5HT2A receptor agonism is believed to be essential for hallucinogenic effects. This mechanism of action underpins the drug's psychoactive effects, which have been studied in the context of brain function and experimental therapies in the field of psychiatry since the mid-twentieth century [2]. However, the use of psilocybin in these studies fell out of favor in the 1960s, only to be revived in the early 21st century.

More and more studies have shown that as a hallucinogenic agent, psilocybin extract has relatively low addiction and fewer adverse reactions. Its combination with psychological support has a significant effect in treating depression, anxiety, substance addiction, obsessive-compulsive disorder, and other aspects. Among them, psilocybin extract has been granted breakthrough therapy status by the US FDA in treating refractory depression and severe depression. Psilocybin can trigger changes in

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the brain that result in an overall decrease in brain activity, which can lead to a decrease in symptoms of depression. While the effectiveness of psilocybin on depression has already been demonstrated through experiments, its effect duration and side effects compared to traditional depression drugs require further investigation.

This review aims to explore the mechanisms of psilocybin, with a focus on its therapeutic effects on depression in clinic. By exploring existing the research data and theoretical perspectives, this review will provide insights into the potential use of psilocybin as a promising therapy for depression, while also highlighting areas for future study and exploration, and prospect the current research hotspots, in order to provide reference and reference for relevant basic research and clinical treatment.

2. Chemical structure and metabolism

Psilocybin is a natural compound that exists in over 200 species of fungi, of which the psilocybe genus is the most potent source. Upon ingestion, Psilocybin undergoes rapid dephosphorylation in the intestinal mucosa to produce psilocin, which is considered the primary active metabolite of psilocybin. This process is facilitated by alkaline phosphatase and nonspecific esterase enzymes. Studies involving rats have shown that approximately 50% of the total volume of psilocin is absorbed from the digestive tract after ingestion. Then, through endoplasmic enzymes, specifically UDP-glucuronosyltransferase (UGTs), Psilocin is further metabolized to psilocin-O-glucuronide, which accounts for about 80% of the excreted form of psilocin.

The onset time of psilocybin extract is very fast, and after 15 minutes of oral administration, it can produce some subjective effects, such as feelings of happiness, happiness, and satisfaction. It reaches its highest blood concentration within 100 minutes, with a half-life of about 160 minutes, and its efficacy shows a significant dose-dependent effect. However, there is no clear consensus on the optimal therapeutic dose of naked mushroom extract in current research, The commonly used dosage in foreign clinical trials is based on a body weight of 0.3-0.429 mg/kg. In an animal experiment, it was found that psilocybin reached its maximum plasma level approximately 90 minutes after administration, and then distributed to all tissues, including the brain, which is also in line with common clinical situations. Interestingly, prior to accumulating in the brain, psilocin accumulates in the liver and kidneys. The precise mechanisms involved in the uptake, distribution, and metabolism of psilocin remain to be fully elucidated, which is an ongoing research field [3,4]. Nonetheless, understanding the pharmacokinetics of psilocybin and its active metabolite, psilocin, is crucial for the safe and effective use of psilocybin in therapeutic settings.

3. Pharmacodynamics

Psilocybin and psilocin are two indoleamine compounds that have been widely investigated for their pharmacological properties, including their predominant agonist activity on serotonin receptors. Specifically, psilocybin and psilocin are known to exhibit agonist activity on the 5HT2A/C and 5HT1A receptors, with 5HT2A receptor agonism being vital for the development of hallucinogenic effects [2].

Psilocin has been found to have a broader receptor-binding profile than psilocybin, with weak affinity for receptors such as Imidazoline1, Alpha2A/B/C, and 5HT transporters, as well as dopamine receptors [5]. Research has suggested that psilocin may increase glutamate release through presynaptic 5-HT2ARs located on thalamocortical terminals in the neocortex, thereby contributing to its hallucinogenic properties.

Recent studies have also revealed that psilocybin can modulate dopamine release in humans, likely via 5HT receptor-mediated mechanisms. Specifically, psilocybin has been reported to indirectly improve the release of dopamine in the ventral striatum, which was found to be correlated with symptoms of depersonalization and euphoria [6].

Additionally, psilocybin has been shown to inhibit dorsal raphe nucleus activity via 5-HT1A autoreceptors[4]. This modulation of 5-HT1A autoreceptor activity is thought to contribute to psilocybin's antidepressant effects, which have been observed in several clinical studies.

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Also, psilocybin has been shown to affect gene expression in the brain. Specifically, it has been shown that psilocybin can increase the expression levels of early genes, which can be rapidly activated by a variety of cellular stimuli, including erg-1, erg-2, c-fos, jun-B, period-1, gpcr-26, fra-1, N-10, and I-κBα. Psilocybin has also been found to reduce the expression of sty-kinase, a protein involved in cellular signaling pathways [7]. However, the exact signaling pathway leading from receptor activation to the modulation of early gene expression remains to be fully understood, thus requiring further investigation.

In conclusion, the complex pharmacological actions of psilocybin and psilocin on various receptor systems, neurotransmitter pathways, and gene expression suggest their potential as therapeutic agents for a range of neuropsychiatric disorders. Further studies are needed to fully elucidate their mechanisms of action and clinical efficacy.

4. Effect duration

4.1. Depression

As a natural compound existing in certain species of mushrooms, psilocybin has been noted for its potent hallucinogenic effects. However, recent research has demonstrated that psilocybin may also have therapeutic benefits in treating depression. In a groundbreaking open-label study, a cohort of 12 participants (six males and six females) with moderate-to-severe depression were administered two doses of psilocybin (10 mg and 75 mg) and were monitored for six weeks [8]. The study employed a brief inventory of depressive symptoms to assess levels of anxiety in participants before and after treatment. The study's results were highly encouraging. After receiving psilocybin treatment, participants reported a significant reduction in the activeness of negative emotions, suggesting psilocybin's potential efficacy as a tool for managing depression. Intriguingly, all participants reported similar experiences of an emotional "confrontation" during treatment sessions. Such emotional breakthrough and resolution are believed to stem from the recovery of past traumas, which participants could confront and work through in their psilocybin sessions.

The study represents a notable advancement in the understanding of psilocybin's potential therapeutic benefits. While further studies are needed to establish its mechanisms of action and long-term effects, this study provides compelling evidence supporting psilocybin's potential value in treating depression. It opens up new avenues for research into the area, presenting a promising opportunity to explore the intersection of psychedelics and mental health treatment.

There was an observable effect on depression severity in the first week after taking psilocybin, indicating its effectiveness. The effect of the drug reached its peak in about two weeks, and then decreased, but it was still effective after three months [9].

The long persisting therapeutic effects after acute drug effects challenges biological theories of classic therapeutic psychedelic effects, and a possible hypothesis is that psilocybin acute destabilizes brain networks, and it may have the occasion to alter brain network activity persistently [10]. Clinical trial also shows that the result can remain significant 6 months post-treatment in a treatment-resistant cohort [11].

Recently, psilocybin has gained growing attention as a potential therapeutic agent for various mental illnesses, including depression, anxiety, and addiction. Emerging evidence suggests that psilocybin has a longer-lasting therapeutic effect compared to conventional medications used for treating these conditions. For instance, a study investigated the long-term effects of psilocybin therapy on depression and anxiety, and found that a significant therapeutic effect was observed up to 12 months after treatment [11]. The study involved 27 participants who were randomized into immediate and delayed treatment groups, and the results showed that all participants had higher baseline GRID-HAMD scores at the 12-month timepoint, except for three subjects who did not meet the treatment response criteria at any timepoint after treatment.

Moreover, a study reported that within 4.5 years after patients with cancer-related distress received treatment, psilocybin treatment showed a significant decrease in depressive symptoms, indicating a

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possibility of a longer-lasting effect of psilocybin treatment in major depressive disease [12]. A phase II clinical trial involving 233 patients with the severe depression who received different doses (1mg, 10mg, 25mg) of psilocybin for 3 weeks. The results showed that a single dose of 25mg (not 10mg) psilocybin showed the significant decrease in the depression scores compared to 1mg after 3 weeks of treatment, but may also be accompanied by larger side effects [13].

In a clinical trial, 19 patients with intractable depression were included, and they were treated with 25 mg psilocybin in combination with psychotherapy. At the same time, the emotional face task was used to test the response of the patients to different facial stimuli. After treatment, the depression of the patients was significantly reduced, and the response of the right amygdala nucleus to fear and neutral facial stimuli was significantly increased, and the change of the amygdala nucleus stimulus response was significantly related to the improvement of depression symptoms. It shows that the mechanism of action of psilocybin on amygdala is different from that of traditional antidepressants, due to the mechanisms of action of traditional antidepressants is to reduce the response of amygdala nucleus to negative stimulation [14]. More clinical trials with different doses and times are needed to further verify its efficacy and safety.

4.2. Addiction

In addition, psilocybin has also been found to have a long-term effect in suppressing addiction, particularly smoking cessation. A study involved 15 smokers, including heavy smokers who smoked an average of 19 cigarettes per day over the past 31 years [15]. The subjects received a 15-week combination treatment including cognitive-behavioral therapy (CBT), elements of mindfulness training, and guided imagery for smoking cessation. The subjects received a moderate dose of psilocybin at week 5 of treatment, which served as the Target-Quit Date (TQD), and a high dose of psilocybin approximately 2 weeks later. After the study, at the 12-month follow-up, 10 participants (67%) were biologically confirmed to be quitters. This finding is further supported by previous studies suggesting high rates of positive results of psychedelic-facilitated treatment of alcoholism. Therefore, the effectiveness of psilocybin in treating addiction can be considered significant, and research is required to further explore its potential in this area.

A systematic review of four clinical trials combining psilocybin with psychotherapy found a significant positive effect of therapy which psilocybin is used in subjects with either addiction of tobacco or alcohol use. Three of the trials were single-arm pilot studies with a substantial risk of bias, but one trial was a double-blind, placebo-controlled randomized controlled trial (RCT).

The proposed mechanisms by which psychedelics, including psilocybin, improve the symptom of addiction are both biological and psychological. Biological mechanisms include inducing brain neuroplasticity via ascending the levels of brain-derived neurotrophic factor (BDNF), which are reduced under psychiatric conditions. Psychological mechanisms include inducing a experience of mystical during the psilocybin session, which seems to cause behavioral change in patients with addiction [16].

4.3. Obsession

Nine adults (seven males and two females) with prior experience with psychedelic drugs and symptomatic OCD were provided with repeated psilocybin doses in a clinical trial. On average, the participants did not show improvement even after receiving 3.4 rounds of medication that are typically used to treat obsessive behavior. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is employed to investigate the severity of symptoms, and all participants signed informed consent. Psilocybin reported to cause a psychedelic experience in a dose-dependent manner, and no participants experienced psychotic symptoms or dangerous behaviors. The most significant observation during the clinical study was the sudden decrease in OCD symptoms in all participants during one or more testing sessions. The extent of improvement varied from minor to complete, but it was temporary [17].

In summary, as a potential drug for treating depression, anxiety, and addiction, psilocybin has shown promising results. Its long-lasting therapeutic effects have been observed up to 12 months after

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treatment for depression and anxiety, and even longer in some cases. These findings provide a solid foundation for future research on the potential of psilocybin in treating mental illnesses and addiction, while caution should still be taken for its clinical applications, given its controlled substance status.

5. Side effect

Among psychedelic drugs, psilocybin is considered to be the safest. A wealth of past evidence and modern scientific research have shown that psilocybin is not highly toxic, not addictive, and does not have any sustained harmful physiological or psychological effects during or after use. It is also known to have safe psychological responses [18].

The low physical harm has been proven by complicated comparison [19,20]. However, the side effects were still found in clinical trials.

Psilocybin has an acute psychedelic effect. The effects of the drug usually became noticeable within 30 to 60 minutes after taking it, reached their highest point between 2 and 3 hours after ingestion, and eventually decreased to a point where the patient could be discharged and evaluated safely at least 6 hours after taking the drug [20]. According to a survey study that examined the impact of psilocybin consumption, 10.7% of participants reported behaviors that put themselves or others in danger of physical harm. Additionally, 2.6% of participants reported experiencing physically aggressive or violent behavior, while 2.7% of participants sought medical treatment from a hospital or emergency department during the research period [21]. While some of the participants with suicidal ideation reported reduced related thoughts, the other ones that have pre-existing suicidal thoughts or depression experienced more severe imagination on suicide. Two of them attempted suicide but was unsuccessful, and in total, a third of them reported suicide attempt besides two reporting severe suicidal ideation during the session. Three of the participants who were psychiatrically healthy before the psilocybin experience went through psychotic symptoms, including hallucination, depersonalization, very disturbing visual hallucination, etc. Each of them was subsequently diagnosed with psychotic conditions such as schizophrenia, bipolar disorder, and post-traumatic stress disorder (PTSD).

Another study showed that typical adverse events after taking psylosibin were transient anxiety (mostly mild) during drug onset, temporary thought disturbance or confusion, mild and temporary nausea, and temporary headache [11]. In addition to that, visions of an autobiographical nature were reported by 14 out of 20 participants, but the patient subsequently improved after open and compassionate listening was maintained. This evidence suggests that, despite the therapeutic effect on psychotically healthy people as mentioned previously, the ingestion of psilocybin could result in the exacerbation of mental illness or even the onset of mental illness. However, these appeared side effects are considered mild, and limited to a short period after dosing [22].

6. Conclusion

Psilocybin, one of the naturally occurring psychedelics found in certain species of mushrooms, has shown promising therapeutic effects in treating anxiety and depression, making it a popular focus of research in the field of mental illness treatment. The current body of research suggests that psilocybin may have considerable therapeutic potential, as it produces effects that last up to three months and has shown superior efficacy in managing moderate to severe depression compared to other available drugs, while also causing fewer and milder side effects.

The recent emergence of psilocybin as a possible treatment for depression is particularly exciting, given the limitations of currently available therapies. Traditional antidepressants, for instance, can take weeks or even months to produce a noticeable effect and can be accompanied by a series of adverse effects, including weight gain, sexual dysfunction, and gastrointestinal disturbances. On the contrary, psilocybin has been confirmed to produce rapid and lasting therapeutic effects, making it a potentially powerful tool for treating depression.

Despite these promising findings, psilocybin remains a Schedule I controlled substance under the 1971 United Nations Convention on Psychotropic Substances. This legal classification poses a

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significant obstacle to conducting further research and clinical trials on the application of psilocybin, as it restricts access to the drug and limits its availability for research purposes.

While psilocybin has shown great potential, it is not without risks. Negative side effects have been observed in some patients, including temporary increases in anxiety, paranoia, and dissociation. It is also important to note that psilocybin can have powerful and potentially unpredictable effects on the mind, and as such, it should be used with caution in clinical settings.

Nonetheless, the promising treatment effects of psilocybin in treating the mental disorders have resulted in a reignited interest in the drug, and more research is being conducted to better understand its mechanisms of action and potential clinical applications. With further research, psilocybin may be regarded as a useful tool in treating mental illness, providing new hope for patients suffering from depression and other conditions.

References

[1] Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2006). The pharmacology of Psilocybin. Addiction Biology, 7(4), 357–364.

[2] Nichols, D. E. (2004). Hallucinogens. Pharmacology & Therapeutics, 101(2), 131-181.

[3] Horita, A., & Weber, L. J. (1962). Dephosphorylation of psilocybin in the intact mouse. Toxicology and Applied Pharmacology, 4(6), 730-737.

[4] Sellers, E. M., Romach, M. K., & Leiderman, D. B. (2018). Studies with psychedelic drugs in human volunteers. Neuropharmacology, 142, 116–134.

[5] Ray TS (2010) Psychedelics and the Human Receptorome. PLoS ONE 5(2): e9019.

[6] Vollenweider, Franz X.1,3; Vollenweider-Scherpenhuyzen, Margreet F. I.2; Bäbler, Andreas1; Vogel, Helen1; Hell, Daniel1 Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action, NeuroReport: December 1, 1998 - Volume 9 - Issue 17 - p 3897-3902

[7] González-Maeso, J., Weisstaub, N. V., Zhou, M., Chan, P., Ivic, L., Ang, R., Lira, A., Bradley-Moore, M., Ge, Y., Zhou, Q., Sealfon, S. C., & Gingrich, J. A. (2007). Hallucinogens Recruit Specific Cortical 5-HT2A Receptor-Mediated Signaling Pathways to Affect Behavior. Neuron, 53(3), 439-452.

[8] Leor Roseman, Lysia Demetriou, Matthew B. Wall, David J. Nutt, Robin L. Carhart-Harris, Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression, Neuropharmacology, Volume 142, 2018, Pages 263-269.

[9] Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V.H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The lancet. Psychiatry, 3(7), 619–627.

[10] Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2016). Psychedelics as medicines: An emerging new paradigm. Clinical Pharmacology & Therapeutics, 101(2), 209–219.

[11] Carhart-Harris, R. L., Bolstridge, M., Day, C. M., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2017). Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up.

[12] Agin-Liebes, G. I., Malone, T., Yalch, M. M., Mennenga, S. E., Ponté, K. L., Guss, J., Bossis, A. P., Grigsby, J., Fischer, S., & Ross, S. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. Journal of Psychopharmacology, 34(2), 155–166.

[13] Roseman, L., Demetriou, L., Wall, M. B., Nutt, D. J., & Carhart-Harris, R. L. (2018). Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology, 142, 263–269.

[14] Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R.,

Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., Forbes, M., … Malievskaia, E. (2022). Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. The New England journal of medicine, 387(18), 1637–1648.

[15] Johnson, M. W., & Griffiths, R. R. (2017). Potential therapeutic effects of psilocybin. Neurotherapeutics, 14(3), 734–740.

[16] Lowe, H., Toyang, N., Steele, B., Valentine, H., Grant, J., Ali, A., Ngwa, W., & Gordon, L. (2021). The therapeutic potential of psilocybin. Molecules, 26(10), 2948.

[17] van der Meer PB, Fuentes JJ, Kaptein AA, Schoones JW, de Waal MM, Goudriaan AE, Kramers K, Schellekens A, Somers M, Bossong MG, Batalla A. Therapeutic effect of psilocybin in addiction: A systematic review. Front Psychiatry. 2023 Feb 9;14:1134454.

[18] Ehrmann, K., Allen, J. J. B., & Moreno, F. A. (2022). Psilocybin for the Treatment of Obsessive-Compulsive Disorders. Current topics in behavioral neurosciences, 56, 247–259.

[19] Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction, 99(6), 686–696.

[20] Gable, R. S. (1993). Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. The American Journal of Drug and Alcohol Abuse, 19(3), 263–281.

[21] Carbonaro, T. M., Bradstreet, M. P., Barrett, F. S., MacLean, K. A., Jesse, R., Johnson, M. W., Griffiths, R. R. (2016). Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. Journal of psychopharmacology (Oxford, England). Retrieved February 17, 2022.

[22] Prouzeau, D., Conejero, I., Voyvodic, P. L., Becamel, C., Abbar, M., & Lopez-Castroman, J. (2022). Psilocybin efficacy and mechanisms of action in major depressive disorder: A Review. Current Psychiatry Reports.