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REVIEW ARTICLE

Psilocybin: Chemical Foundations and Emerging Therapeutic Potential

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Abstract: Psilocybin, chemically known as (4-phosphoryloxy-N, N-dimethyltryptamine, 4-PO-DMT), is derived from the psychoactive mushroom genus, *Psilocybe*. Of the four active metabolites, psilocin readily enters systemic circulation. The psychoactive effects of psilocin are thought to arise through partial agonist effects at the 5-HT2A receptor. Psychedelic drugs, including psilocybin, are having a renaissance, especially in mental health disorders, addiction, and cancer-related depression. The beneficial effects of psilocybin are expanding into brain injury and lifespan due to its ability to enhance neuroplasticity. However, the large-scale synthesis of psilocybin was the main challenge for the scientific community after the FDA's breakthrough therapy designation in 2018 for Treatment-Resistant Depression (TRD) and for Major Depressive Disorder (MDD) in 2019. Synthesizing psilocybin is challenging due to the complex reactions, a multi-step process that requires strict temperature control, hazardous reagents, and purification difficulties. The very first Hoffman's synthetic method was successfully modified by several medicinal chemistry research groups to obtain it on a kilogram scale to conduct important clinical trials. This mini review comprises a brief history, chemistry, and pharmacology, along with the therapeutic use in depression of this naturally occurring psychedelic.

Keywords: Psilocybin, psychedelic, psilocin, drug, depression; structure-activity relationship.

1. INTRODUCTION

The therapeutic use of psychedelics is one of the most transformative discoveries in modern medicine, due to their rapid and long-lasting beneficial effects on an array of neuropsychiatric disorders [1-3]. However, psychedelic research has been greatly hindered by government restrictions in some countries. In the USA, psychedelics were declared controlled substances in 1970 [4]. The banning of psychedelics led to research stagnating for several years. Yet, recently, restrictions were lifted on the scientific community to advance research on the therapeutic use of psychedelics. The psychedelic drug market size is now expected to reach USD 8.50 Bn by 2032 in the USA, making it important to understand their history, chemistry, mechanisms, and potential side effects [5]. Psychedelics are generally known as hallucinogens because they can have a hallucinogenic effect or altered perception when consumed. Thus, psychedelics are a class of psychoactive molecules, including but not limited to psilocybin (**1**) (4-phosphoryloxy-N, N-dimethyltryptamine, 4-PO-DMT) (CAS Number: 520-52-5) (Fig. **1**). The word psychedelic is originally derived from the Greek words psyche (mind) and delein (to manifest), hence the term "mind manifesting". The British psychiatrist Humphry Osmond coined the word psychedelic in 1957, and David Nichols defined it as "powerful psychoactive substances that alter perception and mood and numerous cognitive processes [6, 7]".

The use of psychedelics goes back centuries, and a few ethnic groups still use them in religious ceremonies to experience a mystical or higher state of awareness [8, 9]. In the modern era, the use of psychedelics can be traced back to Albert Hofmann, the Sandoz chemist who first prepared lysergic acid diethylamide, usually referred to as LSD, in 1938. He later became the first person to test LSD on himself [10, 11]. This breakthrough research on LSD from Hofmann paved the way for the medicinal use of LSD and other psychedelics such as 4-PO-DMT. The most commonly used psychedelic substances are psilocybin (1), dimethyltryptamine (2), lysergic acid diethylamide (3), ketamine (4), mescaline (5), and ecstasy (6), and ergine (7) (Fig. **1**). The structure of these psychedelics comprises two backbone pharmacophores, tryptamine or phenethylamine. The presence of the tryptamine moiety in psilocybin is notable as this pharmacophore is found in the endogenous neurotransmitter serotonin

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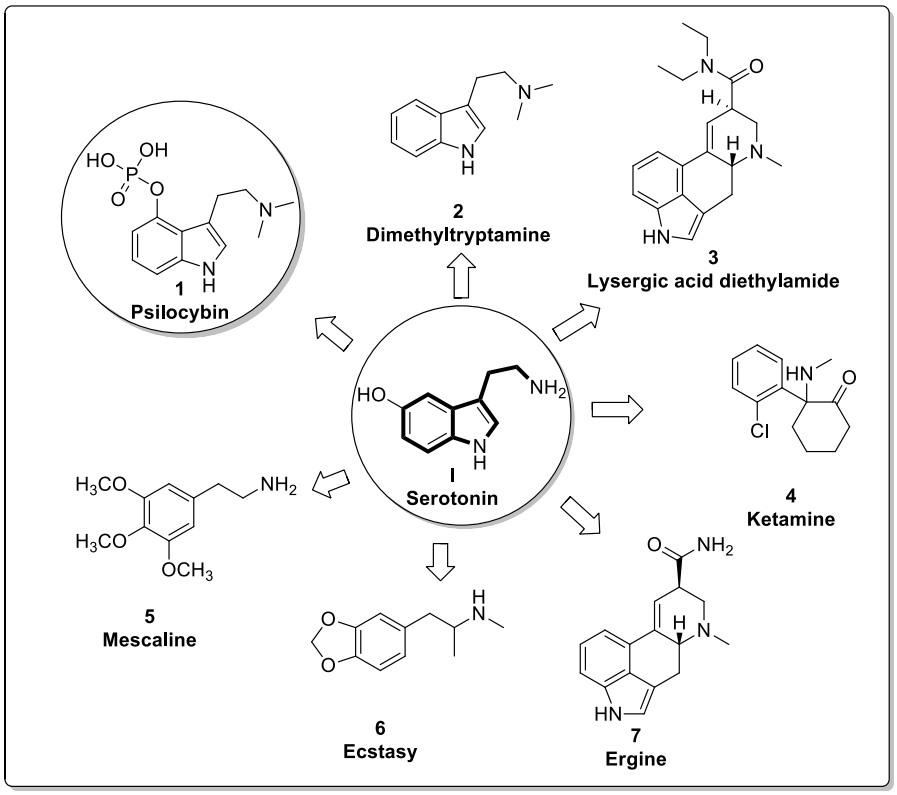


Fig. (1). Most commonly used psychedelic substances.

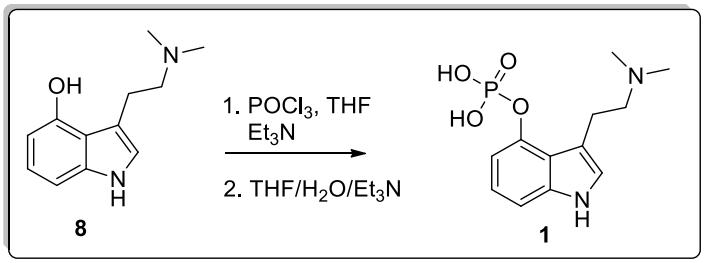


Fig. (2). Prodrug psilocybin (8) and its active ingredient psilocin (1).

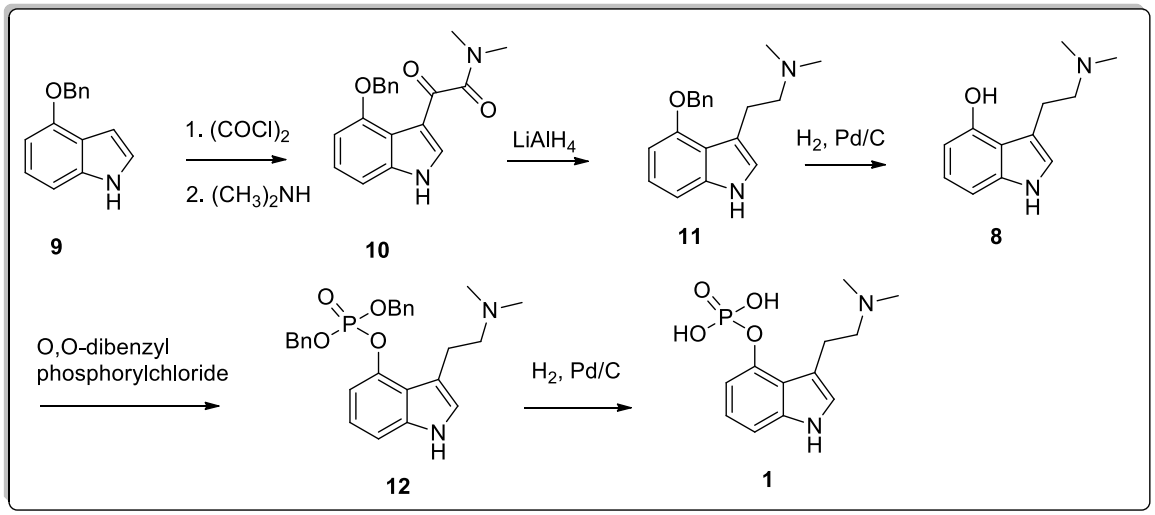
(5-hydroxytryptamine) (**I**) (Fig. **1**) [12-19]. This review will focus on psilocybin because of its effectiveness in a wide range of diseases.

2. PSILOCYBIN AND ITS ACTIVE INGREDIENT PSILOCIN

4-PO-DMT is an indole alkaloid derived from the psychoactive mushroom genus *Psilocybe*. Compounds with indole rings are one of the most widely distributed nitrogen heterocyclic analogs in nature, with very high biological significance [20, 21]. Due to their pharmacological importance, they continue to attract medicinal chemists and biologists alike to identify novel indole-derived natural or unnatural pharmaceutical compounds with new therapeutic uses. We have been actively involved in indole research and have written several articles on the chemical synthesis and biological activities of indoles [22-26].

Structurally related to serotonin with a dimethyl tertiary amine, 4-PO-DMT is a simple and achiral molecule with molecular weight m/z = 284.1 and molecular formula $C_{12}H_{17}N_2O_4P$. After ingestion, 4-PO-DMT (prodrug) is rapidly dephosphorylated in the stomach to the pharmacologically active ingredient psilocin (**8**), a 4-hydroxy-*N, N*-dimethyltryptamine (Fig. **2**). 4-PO-DMT (**1**) is the main product isolated from mushrooms of the *Psilocybe,* but psilocin (**8**) is also present in significant quantities [27].

Both indole analogs, 4-PO-DMT (**1**) (prodrug) and psilocin (**8**) (active metabolite), are very closely related to the neurotransmitter serotonin and were identified in 1958; they were subsequently prepared in 1959 by Hofmann and colleagues at Sandoz [28, 29]. The Sandoz company then provided 4-PO-DMT (brand name: Indocybin) to the psychiatric community to explore its therapeutic use. Early work showed therapeutic potential within psychologically supportive



Scheme 1. Preparation of psilocybin by Hofmann and co-workers.

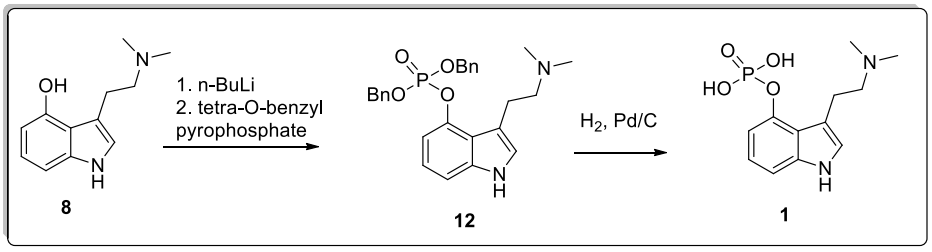
contexts and low-risk toxicity in a wide variety of clinical populations with non-psychotic mental health problems [30]. However, in 1967, medicinal use and research ceased due to the Schedule 1 designation. Research has since resumed, and in 2006, the first modern clinical trial was published examining the safety, tolerability, and efficacy of psilocybin for obsessive-compulsive disorder [31]. The initial mechanistic investigations linking 4-PO-DMT with serotonergic neurons in the sensory cortex, in general, provided the possibility for treating depression-related disorders [32]. Most antidepressants are taken daily to have a beneficial effect, whereas a single dose of 4-PO-DMT could produce a large antidepressant effect that is long-lasting [33].

Pharmacology of prodrug psilocybin (**1**) revealed that its active ingredient psilocin (**8**) interferes with serotonergic neurotransmission and produces the pharmacologic effects of a partial or non-selective agonist of multiple serotonin (5-HT) receptors. Psilocin binds to 5-hydroxytryptamine (5-$HT)_{2A}$ and (5-$HT)_{2C}$ and to a lesser extent to (5-$HT)_{1A}$ of the human nervous system [34-36]. Psilocin binds to (5-$HT)_{2A}$ receptors very potently with binding affinity Ki = 6.0 nM and to (5-$HT)_{2C}$ receptors with Ki = 10 nM. Binding potency is lowered towards (5-$HT)_{2B}$ with Ki = 410 nM [37]. Usually, after ingesting approximately 4-10 mg, 4-PO-DMT will take between 10-40 minutes, peaking around 60-90 minutes, and effects will diminish around six hours [38-40]. The pharmacokinetics of escalating oral doses (0.3, 0.45, and 0.6 mg/kg) of 4-PO-DMT in 12 healthy adults revealed that increasing dosages are also well tolerated with minimal side effects [33]. Overall, 4-PO-DMT's preliminary results have demonstrated benefits for various psychiatric disorders such as chronic pain, headache, and psychiatric distress at the end-stage of life [41]. However, clinical researchers stress the need for reliable research to define the neurobiological effects. The FDA's designation of "breakthrough therapy" to 4-PO-DMT for Treatment-Resistant Depression (TRD) in 2018 and Major Depressive Disorder (MDD) in 2019 has inspired the scientific community to undertake research studies on psychedelics more than ever [42, 43].

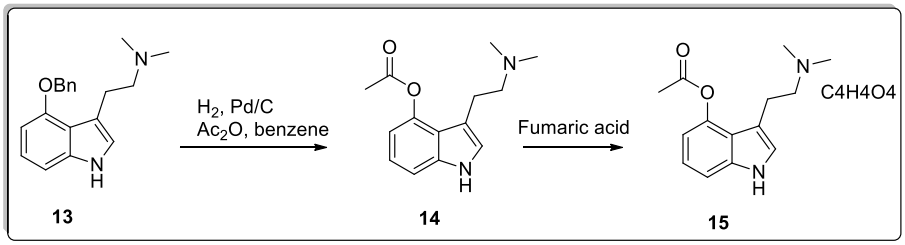
3. PSILOCYBIN CHEMISTRY

To conduct clinical trials and further enhance scientific research on 4-PO-DMT (1), it is essential to produce it in larger quantities (grams to kilograms). The demand for 4-PO-DMT has increased very rapidly, and several medicinal chemists, including well-known Sandoz chemist Albert Hofmann, have reported the synthetic methods for 4-PO-DMT. Recent medicinal chemistry efforts to improve yields and reduce synthetic steps for the total synthesis of 4-PO-DMT are very challenging. Medicinal chemistry researchers are now trying to develop a reliable kilo-scale synthetic procedure to meet the needs of modern clinical studies. The main challenges of large-scale synthesis of this important psychedelic include parameters such as temperature, appropriate solvent, and reagents in each step of the preparation. Additionally, minimizing the side products (impurities) in each step is also equally important because it allows simple purification processes such as trituration, filtration, and/or recrystallization in each step to get the pure product to proceed to the next. The following section will uncover several synthetic procedures and improvements made over the years to obtain pure 4-PO-DMT on a large scale.

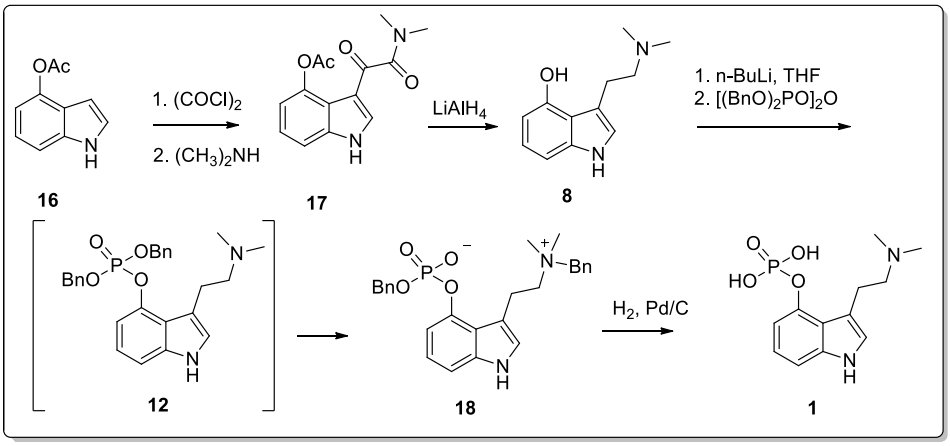
Several drugs have a core "tryptamine moiety", including 4-PO-DMT, and various synthetic methods are available in the literature to efficiently prepare this core moiety. The very first method Hoffman developed at Sandoz utilizes an electrophilic aromatic substitution reaction with oxalyl chloride, followed by amidation and reduction to obtain this core. 4-(benzyloxy)-1*H*-indole (**9**) was treated with oxalyl chloride, followed by dimethylamine to obtain 2-(4-(benzyloxy)-1*H*-indol-3-yl)-*N, N*-dimethyl-2-oxoacetamide (**10**). The reduction of carbonyl functionality was achieved by treating compound **10** with lithium aluminium hydride to obtain a tryptamine analog (**11**). The compound **11** was subjected to further reduction using hydrogen with palladium on carbon to get psilocin (**8**). Psilocybin (**1**) was obtained by phosphorylating a 4-hydroxy group of psilocin (**8**), followed by debenzylation (Scheme **1**) [28, 29, 44].



Scheme 2. Improved method of preparation of psilocybin by Nichols and Frescas.



Scheme 3. Synthesis of psilacetin and its fumarate salt by Nichols and Frescas.



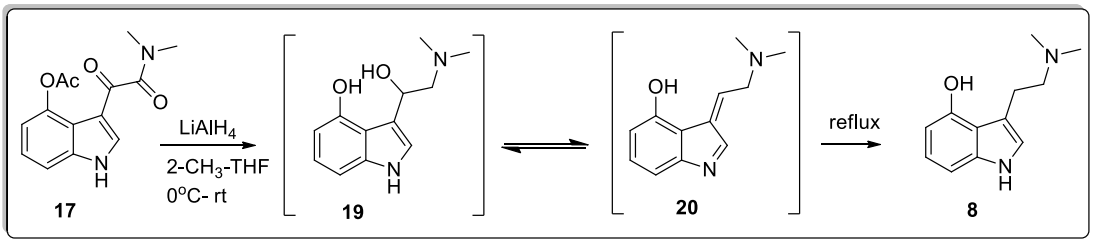
Scheme 4. Preparation of psilocybin by Shirota *et al.* [46].

Hoffmann's synthetic method has been improved by Nichols and Frescas [45]. They used different approaches for phosphorylation to improve the overall yield in key steps. Nichols and Frescas accomplished O-phosphorylation of psilocin (**8**) by reacting it with n-butyl lithium to obtain the O-lithium salt, followed by the treatment of this salt with the easy-to-handle crystalline compound tetra-O-benzylpyrophosphate to procure the precursor of psilocybin (**12**). Debenzylation was achieved by catalytic hydrogenation over palladium on carbon to procure the 4-PO-DMT (**1**), similar to Hoffman (Scheme **2**).

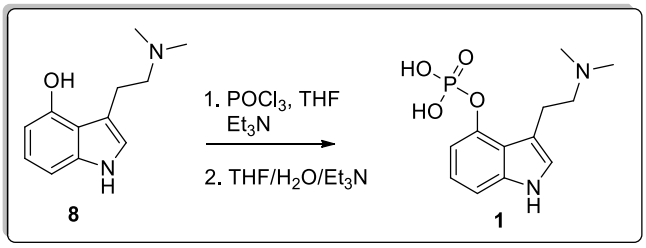
Due to problems faced in the preparation of 4-PO-DMT, particularly in phosphorylation and debenzylation, Nichols and Frescas [45] recommended the 4-acetoxy-*N*, *N*-dimethyltryptamine (**14**) as an alternative to 4-PO-DMT (**1**) for pharmacological activities. They prepared psilacetin (**14**) and its fumarate salt (**15**) by reacting 4-benzyloxy-*N*, *N*-dimethyltryptamine (**13**) with hydrogen over palladium on carbon, followed by the treatment of fumaric acid (Scheme **3**).

Using 4-acetyl indole, Shirota et al [46] developed a very concise gram-scale synthetic procedure for psilocin (**8**) and 4-PO-DMT (**1**) without chromatographic purification. Very interestingly, in their key step, conversion of the *O, O*-dibenzyl phosphate derivative (**12**) into the zwitterionic *N, O*-dibenzyl phosphate derivative (**18**) was accomplished by suspending the worked-up reaction mixture in dichloromethane (migration of benzyl group from O to N happened). The structure of zwitterionic *N, O*-dibenzyl phosphate derivative (**18**) was fully identified by employing 2D NMR analyses (Scheme **4**) [46].

To further improve the synthetic process of 4-PO-DMT, Sherwood et al [47] addressed the various important parameters, such as temperature and appropriate solvents for each



Scheme 5. Improved the synthetic process of key intermediate psilocin **8**.



Scheme 6. Direct phosphorylation of psilocin **8** to psilocybin **1**.

synthetic step. They produced multigram 4-PO-DMT in five steps with an overall 23% yield without chromatography or aqueous workup. Mostly, they followed the previously reported general synthetic process for the preparation of 4-PO-DMT. Strikingly, they detected intermediates **19** and **20** utilizing spectroscopic analysis in producing the key intermediate psilocin (**8**) from 3-(2-(dimethylamino)-2-oxoacetyl)-1H-indol-4-yl acetate (**17**) (Scheme **5**). This more reliable preparation of critical intermediate **8** will pave the way to an attractive combination of synthetic/biocatalysis of enzymatic phosphorylation of psilocin (**8**) to 4-PO-DMT (**1**).

Clinical research of 4-PO-DMT gained momentum after the FDA's breakthrough therapy designation in 2018. Currently, demand for obtaining 4-PO-DMT on a kilogram scale is growing to conduct clinical studies. To improve the production of 4-PO-DMT, the Kargbo lab [48] developed the second-generation synthesis of 4-PO-DMT. The authors expected that direct phosphorylation of vital intermediate psilocin **8** to 4-PO-DMT **1** could potentially avoid problems associated with phosphorylation using tetra-*O*-benzylpyrophosphate (TBPP) and debenzylation. Subsequently, they accomplished the direct phosphorylation of psilocin **8** to 4-PO-DMT **1** (Scheme **6**) and produced the kilogram-scale 4-PO-DMT.

To discover new 4-PO-DMT-based analogs, medicinal chemistry researchers are trying to develop Structure-Activity Relationship (SAR) studies around 4-PO-DMT. For several decades, medicinal chemistry has recognized 4-PO-DMT as a valuable source for the discovery of new psychedelics. Several research groups (Sard *et al* and Klein *et al.*) [49, 50] have investigated the SAR studies of 4-PO-DMT analogs. They conducted studies mainly varying the *N, N*-dialkyl (symmetrical and/or nonsymmetrical) group of ethylamine side chain, along with changing substituents at C-4 and N-1 position on the indole moiety. Sard et al and Klein et al [49, 50] concluded that their SAR studies (Fig. **3**) have displayed 4-PO-DMT-like pharmacological activities [49].

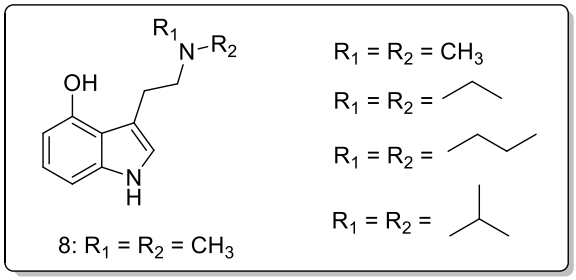


Fig. (3). SAR of 4-Hydroxy-*N, N*-dialkyltryptamines [49].

4. MAIN THERAPEUTIC USES OF PSILOCYBIN: A FOCUS ON DEPRESSION

In recent years, we have noticed a renewed interest in 4-PO-DMT as a potential treatment option for a wide range of mental disorders, such as depression or MDD, TRD, post-traumatic stress disorders, alcohol use disorder, tobacco addiction, and obsessive-compulsive disorder. MDD has been ranked as the third leading cause of disease burden globally, and nearly 10% of the adult population is diagnosed with MDD in the USA, creating an urgent need for novel therapies [51]. The renewed interest in psilocybin and other psychedelics is in part due to a lack of successful therapeutics in the mental health field. Because the incidence of depression has risen globally in recent years, MDD has become a major public health concern, especially in adults. MDD is characterized by persistent feelings of sadness, loss of interest, sleep disturbance, loss of appetite, and energy levels [52].

Mechanistically, depression is complex and involves dysregulated stress responses, neuroinflammation, changes in brain function and structure, and disruptions in neurotransmitter function [53]. This makes psilocybin a prime drug candidate because, unlike current antidepressant daily medication like Selective Serotonin Reuptake Inhibitors (SSRIs), psilocybin preclinically increases neuroplasticity, rewires brain circuits, and reduces inflammation, and clinically can be administered in one or two supervised sessions to work rapidly [54]. 4-PO-DMT produces these therapeutic effects primarily *via* 5-HT2A receptors.

The canonical signaling of 5-HT2A receptors involves $G_{\alpha q/11}$ protein activation, leading to activation of phospholipase C, which produces inositol phosphate (IP_3) and diacylglycerol (DAG). Intracellular calcium is increased, activating protein kinase C to produce specific cellular responses [55]. Non-canonical pathways can include arrestin-dependent signaling (desensitization and internalization of the receptor from the cell surface) [55], signaling through $G_{\alpha i/o}$ proteins, and ARF (ADP-ribosylation factor)/PLD (phospholipase D) signaling cascade independent of G-proteins [56]. Additionally, the 5-HT2A receptor can directly interact with proteins such as PSD-95, thereby enhancing receptor signaling and influencing activity [57]. Psilocybin has also been shown to increase extracellular concentrations of glutamate, serotonin, dopamine, and GABA in the frontal cortex, which could facilitate neuroplastic adaptations to treat affective disorders [58].

More than 100 active and recruiting psilocybin studies are registered on ClinicalTrials.gov, fueled by the growing evidence that psychedelics could offer rapid and sustained therapeutic benefits in an area that has proven difficult to treat using conventional pharmacological approaches. Among the therapeutic indications, MDD has been the primary focus. In fact, phase 2 double-blind randomized control trials involving psilocybin have now progressed into phase 3 (NCT05624268), determining efficacy, safety, and tolerability in participants for TRD. However, it is important to note that the mechanisms underlying these clinical effects still remain unclear, and more comparative mechanistic studies are needed to enable safe and scalable implementation [59]. In a comparative clinical application, 4-PO-DMT and escitalopram, the current treatment for MDD, both successfully reduced depressive symptoms, but the secondary outcomes favored psilocybin [52]. In a more recent comparative study with escitalopram, the psilocybin treated group had a greater degree of improvement on psychosocial functioning, meaning in life, and connectedness, but both treatments were associated with long-term improvements in depressive symptom severity [60]. However, these studies are limited in power to detect small meaningful differences between treatments and rely on self-report measures.

The Beckley Foundation and Imperial College London initiated the early clinical trials using psilocybin for TRD, demonstrating safety in patients receiving two oral doses of 4-PO-DMT (10 mg -safety dose and 25 mg -treatment dose). Additionally, depressive symptoms were markedly reduced 1 week and 3 months after high-dose treatment [61]. This study provided the preliminary support needed to motivate larger and more rigorous trials. In tandem, Johns Hopkins University was leading the charge in reviving psilocybin research, especially for addiction in longtime smokers [62]. From there, they showed psilocybin eased anxiety in people with cancer and helped with alcohol addiction [31, 62, 63-67]. More recently, 4-PO-DMT- assisted therapy for MDD, along with 11 hours of supportive psychotherapy, produced large, rapid, and sustained antidepressant effects in MDD subjects [68]. These sustained effects also appear to be safe and efficacious through 12 months in patients with moderate to severe MDD [69]. In more complex patients with MDD and bipolar II disorder, repeated dosing of psilocybin is also well tolerated and associated with greater antidepressant effects [70]. The perception and acceptability of psilocybin treatment are also important for its integration and use in the clinic. In patients with cancer and depression, the acceptability of psilocybin-assisted group therapy was explored. Participants described generally positive experiences in terms of safety and fear. They also felt more connected to the group, which enhanced their willingness to engage in therapy [71]. Among palliative care patients, 51.6% of participants expressed interest in future psilocybin treatment, noting its benefits for stress and anxiety [72]. However, concerns included risk of psychosis, lack of trained providers, and potential for exploitation.

Although psilocybin treatment for depression is showing promise, it is important to note the challenges with trust-building and expectation management, navigating the experience, and the need for more comprehensive treatment [73]. Additional studies are needed to establish the real-life potential of 4-PO-DMT therapy for treatment-resistant depression patients, as many clinical trials suffer from small sample sizes and limited follow-up. Additionally, other side effects such as transient anxiety, nausea, headaches, fluctuations in blood pressure, and confusion are common with psilocybin treatment, with some patients exhibiting acute psychological distress [74]. In real-world conditions, Hallucinogen Persisting Perception Disorder (HPPD), the recurrence of psychedelic effects, is seen in 32.1% of participants, confirming the necessity of assessing such side effects in post-session follow-up [75]. However, no cases of HPPD have been reported in participants of clinical trials as of November 2025.

Along with depression, the other significant therapeutic uses of 4-PO-DMT include addiction, cancer-related depression and anxiety [66, 67, 76], mystical experiences [77-82], and extension of lifespan and cognition in preclinical studies [83, 84]. These other beneficial uses are most likely due to 4-PO-DMT's ability to promote cognitive flexibility, enhance neurogenesis, and reduce levels of proinflammatory markers and cytokines. However, evidence for the clinical benefits of neuroplasticity and longevity remains hypothetical, requiring molecular and imaging biomarkers and functional connectivity measures to establish translational relevance. The authors will explore these noteworthy indications in separate topic review articles, as covering them will be beyond the scope of this mini-review article. Additionally, medicinal chemistry readers and scientists working in the 4-PO-DMT research area are encouraged to read the recent articles to gain further insights [41, 85-88].

4-PO-DMT has emerged as a promising drug for the treatment of mental health conditions such as depression,

anxiety, and addiction. When it is administered in controlled settings with psychological support, it can produce profound psychological understandings. The presence of skilled therapists is critical in ensuring the safety and efficacy of the therapy. Therapists must adopt strict ethical guidelines, such as informed consent, preventing misuse, and managing potential adverse effects, to protect patients from potential harm. The US government legislation and policy imply that access to this psychedelic remains illegal on the federal level in spite of several attempts to decriminalize it at the state level, which will be extended to enable further research into its treatment. How it will be controlled and who will have the right to use it for the treatment will raise legal and ethical questions that psychiatrists should study (Fig. **4**).

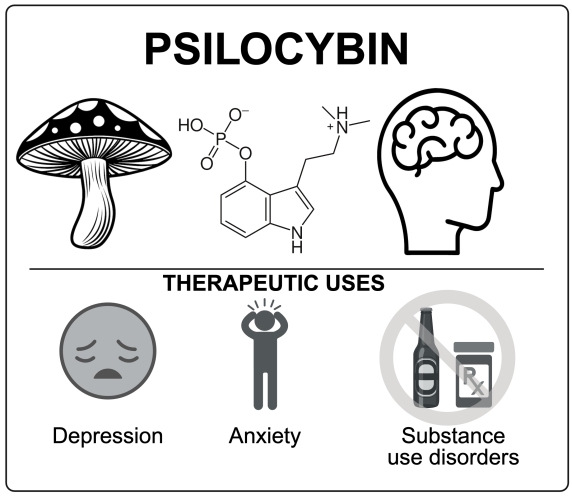


Fig. (4). Therapeutic uses of psilocybin.

CONCLUSION AND FUTURE PERSPECTIVE

In this mini review, we summarize the chemistry research efforts aimed at improving the production of 4-PO-DMT, along with its brief history and pharmacology.

From a synthetic chemistry perspective, several research groups have worked to overcome the synthetic challenges associated with the original Hoffman method. The main synthetic issues, such as phosphorylation and debenzylation steps, created problems in obtaining pure 4-PO-DMT. Scientists have recently achieved success in producing this vital psychedelic at the kilogram level by the direct phosphorylation process. We hope that future medicinal chemistry research efforts will work towards developing more detailed SAR around 4-PO-DMT to produce cost-effective and easily made pure drug(s) with enhanced potency for therapeutic use. The use of 4-PO-DMT for overall better brain health is of utmost importance, given its long-lasting therapeutic effect on depressive disorders and potential to treat age-related diseases. Future research should be aimed at elucidating the mechanisms of 4-PO-DMT and synthesizing novel drugs from these molecules without the hallucinogenic side effects. It will be important to understand if the "psychedelic trip" is necessary for the beneficial impacts and whether 4-PO-DMT produces the same effects in more diverse clinical trial studies.

AUTHORS' CONTRIBUTION

SAP and HCH both contributed to the literature search and design of the review. Specifically, SAP wrote the chemistry sections, and HCH wrote the therapeutic and biology sections.

LIST OF ABBREVIATIONS

4-PO-DMT	=	Psilocybin
5-HT2A	=	5-hydroxytryptamine 2A
ADP	=	ADP-ribosylation Factor
DAG	=	Diacylglycerol
FDA	=	Food and Drug Administration
HPPD	=	Hallucinogen Persisting Perception Disorder
IP_3	=	Inositol phosphate
kg	=	Kilogram
Ki	=	Inhibition constant
LSD	=	Lysergic acid diethylamide
MDD	=	Major Depressive Disorder
mg	=	Milligram
PLD	=	Phospholipase D
PSD-95	=	Postsynaptic Density Protein 95
SAR	=	Structure-Activity Relationship
TRD	=	Treatment-Resistant Depression

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, financial or otherwise.

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Declared none.

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