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From fungi to pharmacy: Applied technologies in psilocybin production and its therapeutic applications

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Abstract

Psilocybin, a naturally occurring tryptamine alkaloid found in over 200 species of fungi, has emerged as a focal point in the modern revival of psychedelic science. Once relegated to the margins of psychopharmacology due to its association with counterculture and strict legal restrictions, psilocybin is now undergoing a scientific renaissance. This transformation is driven by its unique pharmacological profile and promising therapeutic potential across a range of psychiatric and neurodegenerative conditions. This review systematically summarizes the research progress on psilocybin, covering its natural biosynthetic pathways, production technologies, mechanisms of action, and clinical applications. We first introduced its four-enzyme synthesis pathway in Psilocybe fungi and explored how synthetic biology can revolutionize its production methods through microbial heterologous expression. Pharmacologically, psilocybin acts as a prodrug that is converted *in vivo* into its active metabolite, dephosphorylated psilocybin (psilocin), which functions as a partial agonist of the 5-HT_{2A} receptor. This activates neuroplasticity pathways such as BDNF and mTOR, thereby producing rapid and sustained antidepressant effects. Despite its therapeutic promise, significant challenges remain. These include methodological limitations such as functional unblinding in clinical trials, lack of diversity in study populations, and evolving regulatory frameworks. Looking forward, the integration of precision psychiatry, synthetic biology, and novel trial designs will be critical in translating psilocybin from a promising compound into a mainstream therapeutic agent. This review aims to provide a foundational understanding of psilocybin's scientific basis and its potential to reshape modern psychiatric care, we uniquely bridge the gap between upstream biosynthetic engineering and downstream clinical efficacy, providing a holistic roadmap for the drug's development from fungi to pharmacy.

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1. Introduction

Psilocybin, a naturally occurring tryptamine alkaloid found in over 200 species of fungi, particularly within the genus *Psilocybe*, has emerged as a focal point of contemporary neuroscience and psychiatric research. Historically revered by indigenous cultures in Mesoamerica as "teonanácatl", psilocybin-containing mushrooms have long been used in spiritual and healing rituals to facilitate introspection and transcendental experiences [1]. The modern scientific exploration of psilocybin began in the mid-20th century when Swiss chemist Albert Hofmann first isolated and synthesized the compound in 1958. Initially investigated for its psychopharmacological properties [2], psilocybin was soon swept into the broader countercultural movement, leading to its classification as a Schedule I controlled substance under the 1971 United Nations Convention on Psychotropic Substances. This legal status effectively halted clinical research for decades.

In recent years, however, a resurgence of interest - often termed the "psychedelic renaissance" - has brought psilocybin back into the scientific spotlight. This revival has been driven in large part by the limitations of existing

psychiatric treatments [3]. Up to 30% of patients with major depressive disorder (MDD) fail to respond to conventional therapies, a condition known as treatment - resistant depression (TRD). Traditional antidepressants often require chronic administration, have delayed onset, and are associated with significant side effects [4–10]. In stark contrast, psilocybin-assisted therapy represents a paradigm shift: it acts as a "neuroplasticity catalyst", demonstrating rapid, robust, and sustained therapeutic effects after only one or two administrations [11–13]. By activating the 5-HT_{2A} receptor (5-HT_{2A}R), psilocin promotes the activation of the brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signaling pathways, thereby enhancing neuronal connections and synaptic growth [14]. These neurobiological changes are believed to underlie the enduring therapeutic effects observed in patients, offering a mechanistic basis for psilocybin's potential to "reset" maladaptive neural circuits implicated in mood and anxiety disorders.

Multiple high-quality trials have confirmed the clinical potential of psilocybin in treating depression [15,16]. Notably, phase II [17] and III studies [18] have shown significant reductions in depressive symptoms, with some patients maintaining remission for up to 12 months or longer [19]. These findings have prompted the U.S. Food and Drug Administration (FDA) to grant psilocybin "Breakthrough Therapy" designation for both TRD and MDD, accelerating its clinical development. Parallel to advances in understanding its therapeutic potential, significant progress has been made in developing scalable production methods for psilocybin. While early efforts relied on extraction from fungal biomass or total chemical synthesis, these approaches are limited by variability, cost, and environmental concerns. More recently, synthetic biology has enabled the heterologous production of psilocybin in genetically engineered microorganisms such as *Escherichia coli* [20] and *Saccharomyces cerevisiae*, with yields exceeding 1.4 g L^{-1} [21]. These biotechnological advances not only offer a sustainable and cost-effective means of production but also raise novel regulatory challenges, particularly regarding the control of genetic resources (e.g., engineered microbial strains and plasmid DNA constructs) rather than the compound itself.

Despite this progress, the field faces significant hurdles. The intense subjective effects of psilocybin complicate the blinding of clinical trials, leading to potential bias through functional unblinding and expectancy effects [22]. Moreover, the generalizability of findings is limited by the predominance of participants from Western, educated, industrialized, rich, and democratic (WEIRD) populations. Legally, psilocybin remains a Schedule I substance at the federal level in the United States, although states such as Oregon and Colorado have begun to implement regulated therapeutic frameworks [23].

In summary, psilocybin stands at a critical juncture in its journey from ancient sacrament to modern medicine. Its unique pharmacology, compelling clinical efficacy, and evolving production technologies position it as a potential game-changer in psychiatric care [24,25]. However, realizing its full therapeutic potential will require overcoming methodological, regulatory, and ethical challenges. As research continues to unfold, psilocybin may not only offer new hope for millions suffering from mental illness but also deepen our understanding of consciousness, neuroplasticity, and the nature of healing itself.

2. The Natural Biosynthesis of Psilocybin: An Elegant Enzymatic Cascade

In nature, the biosynthesis of psilocybin is a four-step enzymatic cascade that begins with the universal amino acid L-tryptophan [26,27]. This pathway (Fig. 1), elegantly clustered in the *psi* operon of psilocybin-producing mushrooms, represents a striking example of metabolic refinement aimed at producing a stable, storable prodrug. Each enzyme in the sequence - PsiD, PsiH, PsiK, and PsiM - plays a distinct and finely tuned role, ensuring metabolic fidelity and the stability of intermediates throughout the biosynthetic flux. [28–30] .

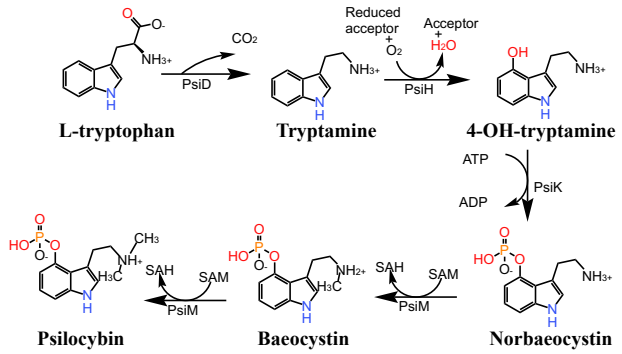

Fig. 1 Biosynthesis pathway of psilocybin from L-tryptophan by PsiD, PsiH, PsiK and PsiM.

The first committed step is catalyzed by PsiD, a non-canonical decarboxylase that converts L-tryptophan into tryptamine. Its catalytic efficiency is respectable but constrained by its unique mechanism, as detailed in Table 1. Unlike typical PLP-dependent decarboxylases, PsiD uses a self-generated pyruvoyl cofactor formed *via* an autocatalytic cleavage event. This unusual mechanism not only underscores the enzyme's evolutionary uniqueness but also presents an engineering challenge: its N-terminal peptide acts as a self-inhibitory lid, reducing catalytic throughput. Truncation or mutagenesis of this region has been shown to enhance activity, making PsiD a prime target for synthetic biology optimization.

Next, PsiH, a cytochrome P450 monooxygenase, regioselectively hydroxylates tryptamine at the 4-position of the indole ring. This step is biologically critical for installing the phenolic moiety required for subsequent phosphorylation; however, it also yields intermediates that are prone to oxidative oligomerization, a process chemically manifesting as the characteristic "blueing

reaction" [31]. PsiH is membrane-anchored and requires a dedicated cytochrome P450 reductase (CPR) for electron transfer. This eukaryotic-specific redox partnership has made functional expression in *E. coli* notoriously difficult, representing a major bottleneck for *de novo* microbial synthesis. Recent advances in yeast and filamentous fungal systems have circumvented this issue by leveraging endogenous CPRs, enabling higher flux through the pathway.

The third enzyme, PsiK, is a kinase that phosphorylates 4-hydroxytryptamine to form norbaeocystin [28]. PsiK is not merely a biosynthetic catalyst - it is a quality-control enzyme. Kinetic analysis reveals a remarkable dual function: while PsiK catalyzes the biosynthetic forward reaction, it exhibits an over threefold higher efficiency for re-phosphorylating the oxidatively unstable metabolite psilocin back into psilocybin (see Table 1 for kinetic parameters). This "repair" function reveals an evolutionary strategy to ensure that the final product remains in its stable, prodrug form. From a biotechnological standpoint, PsiK's dual role makes it a key node for pathway optimization, especially in fed-batch fermentation where psilocin accumulation can reduce yield.

Finally, PsiM catalyzes two successive N-methylations using S-adenosylmethionine (SAM), converting norbaeocystin first to baeocystin and then to psilocybin [32]. Structurally, PsiM is a derivative of the METTL 16 RNA methyltransferase family - an intriguing example of enzyme exaptation from RNA metabolism to secondary metabolite biosynthesis. Its iterative methylation mechanism is efficient but rate-limiting under high-flux conditions, making the selection of a highly active PsiM variant, such as that from *Gymnopilus dilepis*, a key strategy for improving titers (Table 2). Together, these four enzymes form a tightly regulated, high-fidelity assembly line that prioritizes product stability over immediate bioactivity. The endpoint is not psilocin - the psychoactive agent - but psilocybin, a phosphorylated prodrug that resists oxidation and degradation. This design is not accidental; it is a biological solution to the problem of storage and delivery, ensuring that the active compound is only released upon ingestion and dephosphorylation in the human body.

In sum, psilocybin biosynthesis is not just a metabolic pathway - it is a masterclass in biochemical logic, where each enzyme is both a specialist and a failsafe. Understanding this cascade at atomic resolution has not only illuminated the ingenuity of fungal metabolism but also provided a modular toolkit for synthetic biology. By reconstituting this pathway in heterologous hosts, we can now produce psilocybin at scale, offering a renewable alternative to chemical synthesis and a glimpse into the evolutionary elegance of nature's own pharmacology.

3. Production Methodologies: A Comparative Analysis and Technological Succession

As psilocybin transitions from a controlled substance to a promising therapeutic agent, the development of efficient, scalable, and compliant production methods has become a central focus. Currently, three primary production strategies exist: natural extraction from fungal biomass, total chemical synthesis, and microbial heterologous biosynthesis. Each method presents distinct advantages and limitations, and their evolution reflects a clear trajectory from traditional extraction to advanced synthetic biology.

Natural Extraction: Tradition Meets Limitation

Natural extraction from psilocybin-containing mushrooms is the oldest method. Although techniques such as ultrasound-assisted extraction (UAE) using methanol have been identified as highly efficient in a recent systematic review [33,34], this approach still faces significant hurdles for pharmaceutical-grade production. Extraction yields vary substantially by species and protocol; while typical yields for *Psilocybe cubensis* range from 0.5% to 1.3%, optimized protocols have achieved exceptionally high yields of up to 3.42% in potent species like *Psilocybe cyanescens*. However, obtaining high-purity (>99%) final products is chemically difficult due to the co-extraction of proteins and structurally similar tryptamine alkaloids (e.g., baeocystin), necessitating expensive chromatographic purification [35]. Additionally, ecological concerns and the risk of contamination with toxic mushroom species further limit its industrial viability[36].

Chemical Synthesis: High Purity at a High Cost

Total chemical synthesis offers a route to high-purity psilocybin independent of biological sources. The most commonly used route begins with 4-acetoxyindole and proceeds through acylation, amination, and phosphorylation steps [26]. However, the conversion of psilocin to psilocybin remains a technical bottleneck. According to Eklund *et al*. [35], this critical phosphorylation step is often yield-limiting (typically ~47%), and alternative simplified methods struggle with reproducibility. Consequently, the total yield of the multistep synthesis is generally moderate (approx. 40–50%). This limitation, combined with the use of expensive reagents, keeps production costs high - estimated at approximately $2 USD per milligram for pharmaceutical-grade material [37] - thereby limiting scalability.

Microbial Heterologous Production: The Synthetic Biology Revolution

Reconstructing the psilocybin biosynthetic pathway in genetically engineered microbes represents the most promising direction for industrial-scale production. *Escherichia coli* and *Saccharomyces cerevisiae* have emerged as leading host organisms due to their genetic tractability and fermentation scalability.

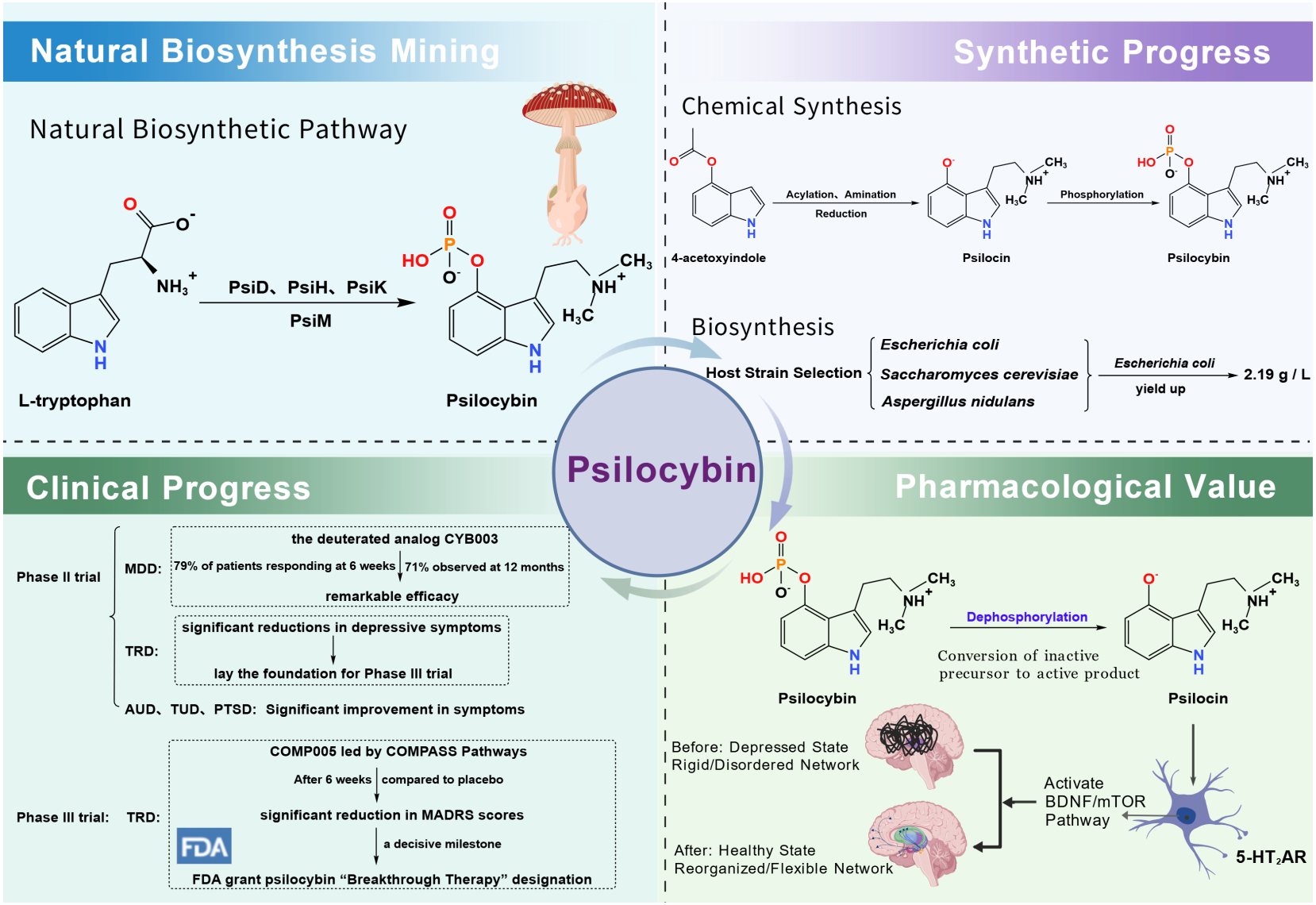

Fig. 2 Integrated landscape of psilocybin development technologies and therapeutic applications. (1) Natural Biosynthesis: The native enzymatic pathway from L-tryptophan. (2) Synthetic Progress: The evolution from chemical synthesis to high-yield microbial biosynthesis. (3) Pharmacological Value: The conversion of psilocybin to psilocin activates 5-HT_{2A} receptors and downstream BDNF/mTOR signaling, facilitating brain network reorganization. (4) Clinical Progress: Key advancements in clinical trials for depression (MDD/TRD) and other disorders, including the development of analogs like CYB003 and FDA regulatory milestones.

Table 1 Kinetic parameters and structural characteristics of key enzymes in psilocybin biosynthesis.

enzymes	substrate	K_M/K_0.5 (μM)	k_cat (s^{-1})	Catalytic efficiency (k_cat/K_M) ($M^{-1}s^{-1}$)	Key structural/mechanistic features	Challenges and engineering implications
PsiD	L-tryptophan	100	1.74	1.74×10^{4}	PLP is non-dependent, self-catalyzed cleavage, and has an N-terminal self-inhibitory structure	Catalytic activity can be improved by removing self-inhibiting regions.
PsiH	Tryptamine	Not quantified	Not quantified	Not quantified	Eukaryotic P450, membrane-bound, requires CPR electronic donor	Functional expression is difficult in prokaryotic hosts, which is a bottleneck in biosynthesis.
PsiK	4-hydroxytryptamine	67	4.5	6.67×10^{4}	Monomer activity, S-type kinetics, and efficient repair of dephosphate psilocybin	Ensures product stability and can be used for prodrug production optimization.
PsiK	Psilocybin dephosphate	72	16.1	2.24×10^{5}	The repair efficiency was significantly higher than that of the main pathway, and evolutionary priority was given to stabilizing products	
PsiM	Denathylene psilocybin	Not quantified	Not quantified	Not quantified	SAM-dependent iterative methyl transfer, derived from RNA-modifying enzymes	Methylation efficiency is a bottleneck that optimizes the enzyme source to increase yield.

Table 2 Comparison of titers and key breakthroughs in the production of psilocybin by genetically engineered microorganisms.

Host microbes	Production strategy	Highest reported titer ($g\ L^{-1}$)	Key engineering breakthroughs	Main references
Escherichia coli	Precursor feeding	2.19	Optimize the PsiM enzyme source（*Gymnopilus dilepis*）; The feed is fermented in batches	Adams *et al.* [20] and Keller *et al.* [21]
Escherichia coli	*de novo*	0.0794	PsiH protein engineering (N-terminal truncation/SUMO fusion); Optimization of the electronic delivery chain	Huang et al. [39]
Saccharomyces cerevisiae	*de novo*	0.627	expressing homologous CPR; Optimizing precursor supply (shikimic acid pathway regulation)	Milne *et al.* [30]
Aspergillus nidulans	*de novo*	0.267	Inhibition of L-tryptophan catabolism (ARO8/ARO9/BNA2 deletion)	Janevska *et al.* [29]

Table 3 Summary of key clinical trials for psilocybin therapy.

Test identification/ first author	Indications	Psilocybin dosage	Control group	N	Primary endpoint	Key efficacy outcomes	Longest follow-up data
Davis *et al.* [60] Gukasyan *et al.* [19]	MDD	20 mg/70 kg, 30 mg/70 kg (2 doses)	Waiting list	24	GRID-HAMD	71% response rate and 54% response rate at 4 weeks	Response rate 58% at 12 months
Carhart-Harris *et al.* [10]	MDD	25 mg (2 doses)	Escitalopram	59	QIDS-SR-16	There was no significant difference between depression scores and SSRIs at 6 weeks	At 6 months, it is better than SSRIs in many aspects such as life function
Goodwin *et al.* (2022) [6]	TRD	1 mg, 10 mg, 25 mg (1 dose)	1 mg dose	233	MADRS	37% response rate in the 25 mg group at 3 weeks	20% sustained response rate in the 25 mg group at 12 weeks
COMPASS, 2025	TRD	25 mg (1 dose)	placebo	258	MADRS	The mean difference in MADRS score at 6 weeks compared to placebo was -3.6 ($p<0.001$)	To be announced
Cybin, 2024	MDD	12 mg, 16 mg (2 doses)	placebo	N/A	MADRS	79% of patients responded at 6 weeks	71% response rate in the 16 mg group at 12 months
Bradley *et al.* [61]	Parkinson's disease mood disorder	10 mg, 25 mg (2 doses)	Open label	12	MADRS, HAM-A, MDS-UPDRS	Mood, cognition, and movement improved significantly at 1 week and 1 month after treatment	Mood improvement is still significant after 3 months
Agin-Liebes *et al.* [62]	Alcohol Use Disorder (AUD)	25–40 mg/70 kg	placebo	13	PHDD, MEQ	Significantly reduce the number of heavy drinking days and improve self-awareness	Good long-term results
Heinzerling *et al.* [63]	Alcohol Use Disorder (AUD)	25 mg (2 doses)	Nature-themed video intervention control	20	PROMIS Alcohol Use, BP	Alcohol consumption was significantly reduced, and blood pressure increased less in the video intervention group	Good long-term results
Johnson *et al.* [64] Johnson *et al*. [65]	Tobacco Use Disorder (TUD)	20 mg/70 kg, 30 mg/70 kg (3 doses)	Cognitive behavioral therapy	15	7-day smoking cessation success rate	80% success rate for quitting smoking at 6 months and 67% at 12 months	30 months 60%

In *E. coli*, two main strategies have been pursued. The "precursor-feeding" approach bypasses the expression of the difficult-to-express fungal P450 enzyme PsiH by supplying 4-hydroxyindole exogenously. This method has achieved the highest reported titers, reaching 2.19 g L^{-1} in fed-batch fermenters by optimizing the PsiM enzyme source (Table 2). Alternatively, the "*de novo*" strategy aims for complete biosynthesis from simple carbon sources, with current yields reaching 79.4 mg L^{-1} in shake-flask cultures [38,39]. This approach, though currently lower in yield, offers long-term advantages in cost and sustainability.

S. cerevisiae, as a eukaryotic host, provides a more suitable environment for expressing complex enzymes like PsiH. Through metabolic engineering, including the suppression of L-tryptophan catabolism and optimization of the shikimate pathway, researchers have achieved *de novo* psilocybin production titers of up to 627 mg L^{-1} in fed-batch fermentation [30]. Other fungal hosts are also being explored; for instance, engineered *Aspergillus nidulans* has produced 0.267 g L^{-1} of psilocybin by deleting genes involved in L-tryptophan catabolism as showed in Table 2 [29].

The analysis of these different production methods reveals the rise of biosynthesis. Within the biosynthesis field, the precursor-feeding route in *E. coli* and the "*de novo*" synthesis route in yeast represent different engineering philosophies and strategic trade-offs - the former targeting maximum short-term yield, the latter aiming for a more economically and environmentally superior fully biological system. However, the success of these biosynthesis techniques also introduces a novel and complex regulatory challenge. Studies have shown that a considerable amount of psilocybin can be produced using simple, "homebrew"-style equipment, shifting the object of control from physical substances to the genetic resources (e.g., engineered microbial strains and plasmid DNA constructs) rather than the compound itself, posing an unprecedented challenge to existing drug control regulations [40,41].

4. Pharmacology and Therapeutic Applications

Psilocybin's therapeutic potential is rooted in its unique pharmacology, which profoundly influences brain function, particularly by modulating neuroplasticity to remodel neural circuits associated with mood and cognition [42]. Its mechanism of action is fundamentally different from that of traditional psychiatric drugs, acting more as a "catalyst" than a chronic "suppressant" of symptoms.

Molecular Mechanism of Action and Neuroplasticity

Psilocybin is a naturally occurring tryptamine alkaloid that is widely present in over 200 types of fungi. Psilocybin itself is a prodrug. After oral ingestion, it is rapidly dephosphorylated in the gut and liver into its primary pharmacologically active metabolite, psilocin [16,43,44]. The core pharmacological effect of psilocin is mediated through its action as a potent partial agonist of the 5-HT_{2A}R [45]. Positron emission tomography (PET) studies in humans have confirmed a strong positive correlation between the intensity of subjective psychedelic effects and the degree of the 5-HT_{2A}R occupancy in the brain, providing direct evidence that this receptor is the key molecular target [46].

However, the lasting therapeutic effects of psilocybin are not attributed to the acute presence of the drug but to the enduring neurobiological changes it initiates - namely, neuroplasticity. Psilocin's binding to the 5-HT_{2A}R activates downstream intracellular signaling cascades, with the BDNF and mTOR pathways being critical mediators. These pathways are central to neuronal growth and synapse formation. In animal models, a single dose of psilocybin induces a rapid and persistent increase in the density and size of dendritic spines on pyramidal neurons in the prefrontal cortex [47–49]. These microscopic structural changes are believed to underlie macroscopic brain network reorganization [50,51]. In disorders like depression, the default mode network (DMN), which is associated with rumination, exhibits hyperactivity and rigid connectivity patterns. By promoting neuroplasticity, psilocybin may provide a "reset" mechanism for these dysfunctional circuits, thereby enhancing cognitive flexibility and improving mood regulation [52]. This mode of action represents a fundamental shift from chronic symptom management to a potentially curative therapeutic paradigm.

Clinical Trial Evidence

A series of well-designed randomized controlled trials (RCTs) has provided strong evidence for psilocybin's clinical utility, particularly for depression. Landmark trials have demonstrated that one or two moderate-to-high doses of psilocybin can produce rapid and significant antidepressant effects, with high response and remission rates [6]. For example, in one study on MDD, 71% of participants responded and 54% were in remission four weeks after treatment. Even more compelling is the durability of these effects; multiple studies have shown that significant antidepressant effects can last for up to 12 months or even longer in a substantial portion of patients [6]. The success of the large-scale Phase III trial (COMP005) for TRD, led by COMPASS Pathways, is a decisive milestone on the path to regulatory approval, showing a statistically significant reduction in MADRS scores at week 6 compared to placebo.

Despite its high efficacy, psilocybin treatment is not without risks. Adverse effects, including nausea, headache, and transient anxiety, are generally dose-dependent, with higher doses (e.g., 25 mg vs. 10 mg) significantly increasing the incidence of acute physical and psychological discomfort [53]. In clinical settings, physiological toxicity is low; therefore, the primary approach to minimizing drug "toxicity" (adverse psychological reactions) is the rigorous "set and setting" protocol. This involves optimizing the physical environment and providing professional psychological support before, during, and after dosing. Furthermore,

therapeutic outcomes vary among individuals. Recent research suggests that resistance or variability in treatment response may be attributed to genetic polymorphisms in the *HTR2A* gene (which encodes the 5-HT_{2A} receptor) affecting receptor density or binding affinity, as well as baseline personality traits such as "absorption" (openness to experience) [54].

Beyond depression, psilocybin has also shown promise in treating anxiety in patients with life-threatening cancer [55,56], post-traumatic stress disorder (PTSD), and substance use disorders [57]. For example, in a pilot study for Tobacco Use Disorder, psilocybin-assisted therapy resulted in an 80% smoking cessation rate at a 6-month follow-up [58]. Similarly, trials in Alcohol Use Disorder have shown significant reductions in the number of heavy drinking days. Emerging evidence also points to its potential for treating mood disorders in neurodegenerative conditions, with an open-label trial in Parkinson's disease patients showing significant improvements in mood scores that were sustained for three months (Table 3).

Meanwhile, the pharmaceutical industry's dynamics are noteworthy. Because psilocybin is a natural molecule with limited patent protection, companies like Cybin are actively developing "second-generation" psychedelics with proprietary intellectual property, such as the deuterated analog CYB003. By making minor chemical modifications to alter its pharmacokinetic properties, a new chemical entity can be created, thus securing strong patent protection. Phase II clinical data for CYB003 has shown remarkable efficacy in MDD, with 79% of patients responding at 6 weeks and a durable remission rate of 71% observed at 12 months, reflecting a key business strategy in the field: establishing intellectual property barriers through technological innovation (Table 3).

5. Key Challenges and Future Directions

Despite impressive progress, psilocybin is at a critical methodological crossroads. A series of significant scientific, methodological, and regulatory hurdles must be overcome before it can become a mainstream clinical treatment.The most central and intractable problem in clinical psychedelic research is a methodological one. The "gold standard" for clinical trials - the randomized, double-blind, placebo-controlled trial (RCT) - is fundamentally compromised. The intense and unique subjective effects of a moderate-to-high dose of psilocybin make it nearly impossible for participants and researchers to remain blind to the treatment allocation, a phenomenon known as "functional unblinding". This unblinding dramatically amplifies expectancy and placebo effects. Given the widespread positive media coverage, participants often have high expectations, which can themselves produce a powerful therapeutic effect, thereby overestimating the drug's true efficacy. To address this, researchers are exploring various strategies, such as using active placebos, though their effectiveness remains limited. Another major limitation is the homogeneity of study populations, who are predominantly from WEIRD societies, which severely limits the external validity of the findings.

Furthermore, psilocybin's future is inextricably linked to the evolving legal and regulatory landscape. It remains a Schedule I substance under U.S. federal law. Although the FDA has granted psilocybin "Breakthrough Therapy" designation multiple times, the recent rejection of the MDMA-assisted therapy application for PTSD by an FDA advisory committee has sent a clear message to the field: regulatory agencies demand methodological rigor. In stark contrast to federal stagnation, several U.S. states, such as Oregon and Colorado, are pioneering change by legalizing supervised psilocybin-assisted therapy [59]. These state-level "experiments" are providing invaluable real-world data on regulation and implementation. This dynamic interplay between science, public opinion, and policy is driving the field forward at an unprecedented pace.

6. Conclusion and Outlook

This review reveals the rapid advances in psilocybin research. Its core findings include: the maturation of biosynthetic technology, with microbial heterologous production achieving gram-scale yields that lay the groundwork for commercial manufacturing; an in-depth elucidation of its pharmacological mechanism, now resolved at the level of specific cell types and neural circuits, suggesting how long-lasting therapeutic effects might be dissociated from consciousness-altering actions; and broad clinical efficacy, demonstrating psilocybin’s considerable potential in MDD, TRD, anxiety disorders, SUDs, Parkinson’s disease, and the emerging field of healthy aging. However, deeper research has also exposed severe challenges. Functional unblinding and strong expectancy effects seriously interfere with the interpretation of clinical trial results, testing the limits of the traditional evidence-based medicine framework. To visualize the comprehensive journey of this compound, Fig. 2 summarizes the translational roadmap of psilocybin research, integrating upstream natural discovery, midstream production optimization, and downstream clinical application.

Looking ahead, the journey of psilocybin from a promising research compound to a widely accepted clinical tool will depend on progress in several key areas. First, solving the methodological dilemma is the most urgent task. The scientific community needs to collaborate closely with regulatory agencies to explore and validate innovative clinical trial designs that can effectively control for bias. Second, research boundaries must be expanded to include more diverse populations and to explore its efficacy in a wider range of disease indications. At the same time, the therapeutic paradigm needs to be optimized by refining the integration of the drug with psychotherapy, including standardizing therapist training and exploring synergistic effects with different therapeutic models. Finally, the accumulation of scientific evidence will continue to drive regulatory reform. Successful Phase III trials will provide

strong justification for the FDA to re-evaluate its drug scheduling classification.

In conclusion, psilocybin research stands at a pivotal juncture filled with both hope and challenges. It may not only offer a new treatment option for millions suffering from mental illness but also profoundly change our understanding of consciousness, psychopathology, and healing itself. While the path forward is complex, a commitment to scientific rigor, innovative thinking, and patient well-being will be essential to guide this transformative therapy from the laboratory to the clinic for the benefit of human health.

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9. CRediT author statement

Qinqing Chen: Conceptualization; Methodology; Writing - Original draft preparation.

Peiyuan Chen: Software; Data curation; Writing - Original draft preparation.

Tao Wei: Software; Validation; Reviewing and Editing.

Sunita Chamyuang: Validation; Investigation.

Bai-Xiong Chen: Supervision; Writing - Reviewing and Editing.

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11. Ethics Approval and Consent to Participate

Not applicable.

12. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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