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R. C. Van Court
Oregon State University

K. W. Meyer
Portland State University

M. S. Wiseman
Oregon State University

Daniel J. Ballhorn
Portland State University, ballhorn@pdx.edu

K. R. Amses
Oregon State University

See next page for additional authors

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Diversity, biology, and history of psilocybin-containing fungi: Suggestions for research and technological development

R.C. Van Court [a], M.S. Wiseman [b], K.W. Meyer [c], D.J. Ballhorn [d], K.R. Amses [b], J.C. Slot [e], B.T.M. Dentinger [f], R. Garibay-Orijel [g], J.K. Uehling [b, *]

[a] Department of Wood Science and Engineering, Oregon State University, Corvallis, OR, 97333, USA
[b] Department of Botany and Plant Pathology, Oregon State University, Corvallis, OR, 97333, USA
[c] Department of Chemistry, Portland State University, Portland, OR, 97201, USA
[d] Department of Biology, Portland State University, Portland, OR, 97201, USA
[e] Department of Plant Pathology, Ohio State University, Columbus, OH, 43210, USA
[f] Natural History Museum of Utah & School of Biological Sciences, University of Utah, Salt Lake City, UT, 84112, USA
[g] Instituto de Biología, Universidad Nacional Autónoma de México, Coyoacán, Mexico City, 04510, Mexico

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ABSTRACT

Therapeutic use of psilocybin has become a focus of recent international research, with preliminary data showing promise to address a range of treatment-resistant mental health conditions. However, use of psilocybin as a healing entheogen has a long history through traditional consumption of mushrooms from the genus *Psilocybe*. The forthcoming adoption of new psilocybin-assisted therapeutic practices necessitates identification of preferred sources of psilocybin; consequently, comprehensive understanding of psilocybin-containing fungi is fundamental to consumer safety. Here we examine psilocybin producing fungi, discuss their biology, diversity, and ethnomycological uses. We also review recent work focused on elucidation of psilocybin biosynthetic production pathways, especially those from the genus *Psilocybe*, and their evolutionary history. Current research on psilocybin therapies is discussed, and recommendations for necessary future mycological research are outlined.

1. Introduction

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) is an indole alkaloid originally derived from fungal species primarily in the genus *Psilocybe* (Fr.) Kumm. In the body psilocybin is dephosphorylated to form the bioactive agent psilocin. Psilocybin and psilocin are structurally analogous to the neurotransmitter serotonin (5-hydroxytryptamine). Serotonin and psilocin bind to 5-hydroxytryptamine (5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}) receptors disrupting serotonergic neurotransmission producing physiological effects (Tylš et al., 2014). Psilocin pharmacodynamics are reviewed thoroughly elsewhere (Tylš et al., 2014). Recent clinical trial data indicate psychedelics including psilocybin hold promise in treating patients with depression, anxiety, terminal illnesses, addiction, and other mental health conditions (e.g., Abbas et al., 2021; Anderson et al., 2020; Bogenschutz et al., 2015; Carhart-Harris et al., 2021; Davis et al., 2021; Jacobs 2020; Johnson et al., 2017).

2. Indigenous history and current traditional uses of psilocybin

The oldest evidence of the ritualistic consumption of *Psilocybe* species is in Mesoamerica and is recorded in the Codex "Yuta Tnoho" or "Vindobonensis Mexicanus I" (Hernández Santiago et al. 2016, 2017; Jansen et al., 1992). This codex, belonging to the Mixtec culture, was painted in the early 1500s CE (Hernández Santiago et al., 2017; Jansen et al., 1992) and depicts a sacred ceremony where diverse Mixtec deities consume sacred mushrooms prior to the first dawn. While ancient use outside of Mesoamerica has been speculated (Akers et al., 2011; Samorini 1992), and objects such as the "mushroom stones" in Guatemala may also suggest a long history of use (Lowy 1971), these paintings constitute unequivocal evidence of the importance of entheogenic fungi including *Psilocybe* species in the Mesoamerican worldview prior to the arrival of the Spanish (Hernández Santiago et al., 2017). Despite the

* Corresponding author.
E-mail address: jessie.uehling@oregonstate.edu (J.K. Uehling).

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prohibition of hallucinogenic mushroom consumption by the Spanish inquisition, the use of *Psilocybe* species continues to this day in Mexican ethnic groups such as the Chatins, Chinantecs, Matlazincs, Mazatecs, Mixes, Nahuatls, Purepechs, Totonacs, and Zapotecs (Guzmán 2008; Ramírez-Cruz et al., 2006). Fifty-seven hallucinogenic *Psilocybe* species have been described in Mexico (Ramírez-Cruz et al., 2006); from these, 35 species and 9 varieties have been reported to be used by ethnic groups and mestizos mainly in central and southern Mexico. According to modern species concepts, these 44 taxa correspond to 14 currently valid species (Cortés-Pérez et al., 2021; Guzmán 2008) (Table 1).

For many indigenous people of Mexico, these mushrooms are part of a sacred and ancient tradition (Guzmán 2003; Guzmán et al., 2009; Hernández Santiago et al. 2016, 2017). Curandera María Sabina was the first person to enable observation of ritualistic fungal practices by western scientists, despite hundreds of years of colonial efforts to eradicate these practices (Heim and Wasson 1958; Wasson 1957). Although María Sabina conditioned her knowledge sharing with an anonymity clause, and Wasson respected her request initially (Wasson 1957), he later published her actual identity in other works (Wasson 1959). Subsequently, up until her death in 1985 at the age of 91, María Sabina was inundated with requests from foreigners to partake in the mushroom ceremonies "out of curiosity" or to "find God," and observed that before Wasson the mushrooms had only been used to treat the sick (Echevarría 1979).

Contemporary syncretic rituals and ceremonies combining Mesoamerican and Catholic elements are based in *Psilocybe* species consumption and used to treat both spiritual and physical illness (Guzmán et al., 2009). *Psilocybe* mushrooms induce hallucinations and synesthesia resulting in a trance-like experience that is thought to allow dissociation of the soul from the body. As a result, bodily ailment diagnoses, introspection, self-healing, and revelation of lost persons' locations can be facilitated by traditional doctors or shamans. While practices vary between indigenous groups (Guzmán 2008; Herrera 2007), in general ceremonies are always done with care at night in a quiet place guided by an elder or shaman, no meals, alcohol, medicine or drugs are taken in advance, and travel is discouraged for a week after (Guzmán 2003, 2008). In addition to these metaphysical applications, *Psilocybe* mushrooms are traditionally used by indigenous communities to treat anxiety, rheumatism, and as analgesics to relieve toothaches and stomach pain (Bautista-González and Moreno-Fuentes 2014; Guzmán et al., 2009) (Table 1).

Given the ethnic groups that use *Psilocybe* mushrooms, their geographic spread, and their applications, the most culturally important hallucinogenic species of *Psilocybe* are *Psilocybe aztecorum*, *Psilocybe caerulescens*, *Psilocybe cubensis*, *Psilocybe mexicana*, and *Psilocybe zapotecorum* (Bautista-González and Moreno-Fuentes 2014; Cortés-Pérez et al., 2021; Guzmán 2008; Ramírez-Cruz et al., 2006). In addition, endemic species from Mexico with locally restricted use include *Psilocybe candidipes*, *Psilocybe cordispora*, *Psilocybe fagicola*, *Psilocybehoogshagen*ii, *Psilocybe muliercula*, *Psilocybe sanctoru*m, and *Psilocybe subcubensis* (Table 1). These genetic resources, their traditional uses and surrounding culture constitute a biocultural heritage of Mexican indigenous groups protected by the Nagoya Protocol. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization is a supplementary agreement to the Convention on Biological Diversity to which Mexico is signatory (Secretariat of the Convention on Biological Diversity, 2011). Consequently, and to avoid international prosecution, careful consideration including national origin evaluation should be used to identify strains for commercial development.

Psilocybin usage differs by region and includes a long history of whole mushroom consumption in Mesoamerica as detailed above. There has been a more recent history of mushroom and sclerotia ('truffels') consumption in Jamaica (Lowe et al., 2021) and the Netherlands (van Amsterdam et al., 2011). The consumption of 'truffles' from *Psilocybe mexicana* and *Psilocybe tampanensis,* species originally described in peer-reviewed literature from Oaxaca, Mexico (Heim 1957) and Florida, USA (Guzmán and Pollock 1978), surged in popularity following the 2008 ban of fresh mushroom sales in the Netherlands (Illana-Estebad 2011)**.** Preliminary evidence indicates that the majority of cultivated psilocybin-producing fungi are *Psilocybe cubensis* isolates, though substantial morphological variety between cultures exists, as demonstrated in a recent analysis of 76 separate *P. cubensis* strains (McKernan et al., 2021b).

2.1. Global diversity of psilocybin producing fungi

Psilocybin and psilocin biosynthetic production has been documented in a polyphyletic assemblage of species of the mushroom genera *Conocybe* Fayod, *Galerina* Earle, *Gymnopilus* P. Karst., *Inocybe* (Fr.) Fr., *Panaeolus* (Fr.) Quél., *Pholiotina* Fayod, *Pluteus* Fr., and *Psilocybe* (Fr.) Kumm (Halama et al., 2014; Reingardiene et al., 2005; Reynolds et al., 2018). Psilocybin has also been reported in *Massospora platypediae* R.S. Soper and *M. levispora* R.S. Soper, though their genomes lack *Psi* genes found in the characterized biosynthetic pathway of (Fricke et al. 2017; Boyce et al., 2019). In total, there are species from at least eight currently recognized genera of fungi that produce psilocybin and psilocin (Guzmán 2009; Lincoff and Mitchel 1977; Stamets 1996).

The majority of known psilocybin-producing fungi belong to the genus *Psilocybe* sensu stricto (s.s.), from which psilocybin and psilocin were first isolated (Hofmann et al., 1958). The genus *Psilocybe* sensu lato (s.l.) is paraphyletic, with the psilocybin-producing species and the psilocybin-deficient species forming two non-sister monophyletic clades (Moncalvo et al., 2002). The latter group was segregated from *Psilocybe* into the resurrected genus *Deconica* (W.G. Sm.) P. Karst (Redhead et al., 2007), although the assignment of the known species of *Psilocybe* s.l. to the newly defined genera remains incomplete. The most comprehensive and recent study of the phylogenetic relationships in *Psilocybe s.s.* was conducted by Ramírez-Cruz et al. (2013). In this work, three gene regions (5.8S, LSU, and *rpb1)* were employed to resolve many, but not all, of the relationships among the species sampled. Later phylogenetic and biochemical work has shown that appropriately designated *Psilocybe fuscofulva* (= *Psilocybe atrobrunnea*) does not produce psilocybin (Borovička et al., 2015), suggesting potential loss of production in select lineages.

The genus *Psilocybe* is now estimated to contain over 300 species and is distributed worldwide (Guzmán 2005; He et al., 2019a). Systematic surveys for *Psilocybe* are entirely lacking for many regions of the world. All described species, except the enigmatic secotioid *Psilocybe weraroa*, from New Zealand (Borovička et al., 2011), are fungi which produce pileate-stipitate, agaricoid basidiomata (Fig. 1). Salient macromorphological features for the majority of *Psilocybe* species include dark purple-brown basidiospores, the presence of an annulus that can be senescent, and blue bruising on the stipe, pileus, and mycelium upon contact. All currently described *Psilocybe* species are assumed to be saprotrophic and found on a diversity of substrates including herbivore dung, grasses, roots, wood, and soil (Singer 1958; Stamets 1996).

Table 1
Species of *Psilocybe* used in ceremonies and traditional medicine in Mexico.

Current name	Synonyms	Traditionally used by	Traditional use	Distribution
Psilocybe aztecorum R. Heim	*Psilocybe aztecorum* var. *bonetii* (Guzmán) Guzmán *Psilocybe bonetii* Guzmán *Psilocybe quebecensis* Ola'h & R. Heim	Nahuatls, central Mexico	Analgesic, soul healing, divinatory and diagnostic, antirheumatic	Canada to central Mexico
Psilocybe caerulescens Murrill	*Psilocybe bispora* Guzmán, Franco-Mol. & Ram.-Guill. *Psilocybe caerulescens* var. *albida* R. Heim *Psilocybe caerulescens* var. *mazatecorum* R. Heim *Psilocybe caerulescens* var. *nigripes* R. Heim *Psilocybe caerulescens* var. *ombrophila* R. Heim *Psilocybe caribaea* Guzmán, T.J. Baroni & F. Tapia *Psilocybe heliconiae* Guzmán *Psilocybe mazatecorum* R. Heim *Psilocybe mixaeensis* R. Heim *Psilocybe subannulata* E. Horak & Guzmán *Psilocybe villarrealiae* Guzmán *Psilocybe weilii* Guzmán, Stamets & F. Tapia *Psilocybe wrightii* Guzmán	Chatins, Mazatecs, Mixes, Nahuatls, Purépecha, Totonacs, Zapotecs, central and southern Mexico	Analgesic, soul healing, divinatory and diagnostic	USA, Mexico, Ecuador, Venezuela, Argentina, Brazil, and the Caribbean
Psilocybe candidipes Singer & A.H. Sm.		Mazatecs, southern Mexico	Soul healing, divinatory and diagnostic	Mexico
Psilocybe cordispora R. Heim		Mazatecs, Mixes, Totonacs, southern Mexico	Soul healing, divinatory and diagnostic	Mexico
Psilocybe cubensis (Earle) Singer	*Psilocybe cubensis* var. *caerulescens* (Pat.) Singer & A.H. Sm. *Psilocybe cubensis* var. *cyanescens* (Murrill) Singer & A.H. Sm. *Stropharia cubensis* Earle	Chatins, Mazatecs, Mixes, Nahuatls, Zapotecs, central and southern Mexico	Analgesic, soul healing, divinatory and diagnostic	America, from Canada to Argentina, Europe, Asia, and Australia
Psilocybe fagicola R. Heim emend. Guzmán	*Psilocybe fagicola* var. *Mesocystidiata* Guzmán *Psilocybe wassoniorum* Guzmán & Pollock	Nahuatls, Totonacs, Central and southern Mexico	Soul healing, divinatory and diagnostic	Mexico
Psilocybe hoogshagenii R. Heim ex Guzmán & A. Cortés-Pérez	*Psilocybe hoogshagenii* R. Heim	Chinantecs, Mazatecs, Mixes, Zapotecs, southern Mexico	Anxiolytic, analgesic, soul healing,	Mexico, Colombia
Psilocybe mexicana R. Heim	*Psilocybe armandii* Guzmán & S.H. Pollock *Psilocybe galindoi* Guzmán *Psilocybe pileocystidiata* Guzmán & Ram.-Guill. *Psilocybe subacutipilea* Guzmán, Saldarr., Pineda, G. García & L.-F. Velázquez	Chatins, Chinantecs, Mazatecs, Mixes, Nahuatls, Zapotecs, central and southern Mexico	Soul healing	Mexico, Guatemala, Costa Rica
Psilocybe muliercula Singer & A.H. Sm.	*Psilocybe angustipleurocystidiata* Guzmán *Psilocybe mexicana* var. *brevispora* Heim *Psilocybe wassonii* R. Heim	Nahuatls, Matlazincs, central Mexico	Anxiolytic, analgesic, soul healing, divinatory and diagnostic	Mexico
Psilocybe sanctorum Guzmán		Matlazincs, central Mexico	Anxiolytic, analgesic, soul healing	Mexico
Psilocybe subcubensis Guzmán		Chatins, Mazatecs, Mixes, Nahuatls, central and southern Mexico	Analgesic, soul healing, divinatory and diagnostic	Mexico
Psilocybe yungensis Singer & A.H. Sm.	*Psilocybe acutissima* R. Heim *Psilocybe chiapanensis* Guzmán *Psilocybe isauroi* Singer *Psilocybe subyungensis* Guzmán *Psilocybe yungensis* var. *diconica* Singer & A.H. Sm.	Mazatecs, southern Mexico	Analgesic, soul healing, divinatory and diagnostic	Mexico, Costa Rica, Colombia, Argentina, and Brazil
Psilocybe zapotecorum R. Heim emend. Guzmán	*Psilocybe aggericola* Singer & A.H. Sm. *Psilocybe aggericola* var. *alvaradoi* Singer *Psilocybe barrerae* Cifuentes & Guzmán *Psilocybe barrerae* Cifuentes & Guzmán emend. Guzmán	Chatins, Mazatecs, Totonacs, Zapotecs, southern Mexico	Analgesic, soul healing, divinatory and diagnostic	USA, Mexico, Costa Rica, Colombia, Argentina, and Brazil

Table 1 (*continued*)

Current name	Synonyms	Traditionally used by	Traditional use	Distribution
	Psilocybe bolivarii Guzmán *Psilocybe candidipes* Singer & A.H. Sm. *Psilocybe chaconii* Guzmán *Psilocybe microcystidiata* Guzmán & Bononi *Psilocybe pseudozapotecorum* Guzmán *Psilocybe sanctorum* Guzmán *Psilocybe subzapotecorum* Guzmán *Psilocybe zapotecorum* f. *elongata* R. Heim *Psilocybe zapotecorum* R. Heim *Psilocybe zapotecorum* var. *ramulosum* Guzmán & Bononi			

Data from: Ramírez-Cruz et al. (2006), Guzmán (2008), Bautista-González and Moreno-Fuentes (2014), Cortés-Pérez et al. (2021), Index Fungorum (http://www.indexfungorum.org/names/names.asp), and Mycobank (https://www.mycobank.org/) repositories.

3. Psilocybin production mechanisms

Psilocybin is a natural secondary metabolite produced by several fungal species. Traditional ceremonial utilization includes consumption of whole fresh or dried mushrooms. However, fungi can be cultivated in numerous ways, and modern efforts to produce psilocybin vary. Potential sources for obtaining psilocybin products include (1) *in vitro* enzymatic biosynthesis (Fricke et al. 2019a, 2020); (2) hemi-/semisynthetic or total synthesis (Kargbo et al., 2020; Shirota et al., 2003); (3) artificial production of psilocybin in cell culture using biotechnologically modified genetic model organisms (Adams et al., 2019; Milne et al., 2020); or (4) cultivation of fungal tissues such as hyphae, mushrooms, and sclerotia, also known as 'truffles' (Rosero Yépez et al., 2018; van Amsterdam et al., 2011).

When utilizing *in vivo* whole organism-based psilocybin production, it becomes essential to sequence genomic loci considered to be species-level barcodes to accurately identify fungi. The Internal Transcribed Spacer (ITS) region of ribosomal DNA (rDNA) is the current gold standard for genetic species-level barcoding, but its ability to resolve species still bears limitations (Tremble et al., 2020; Yahr et al., 2016). ITS sequences for many *Psilocybe* species and other fungi that produce psilocybin are available in public data repositories such as GenBank, the DNA sequence repository operated by the National Center for Biotechnology Information (NCBI). However, accurate species-level identification of GenBank DNA sequence data accessions can be variable, uncertain, and misleading due to several factors. Generating sequences from misidentified specimens, mislabeled sequence data accessions, and the scarcity of authority-curated, type-specimen-based authenticated sequence deposition contribute to the stratification of GenBank data quality (Hofstetter et al., 2019). Accurate identification of fungal species is therefore reliant on sometimes subtle macro- and micromorphological features and genetic comparison to databased reference sequences of varying quality.

There is notable variability in psilocybin content from species to species and even between mushrooms in the same fruiting flush (Andersson et al., 2008; Kamata et al., 2005; Stríbrný et al., 2003; van Amsterdam et al., 2011). *Psilocybe* species can vary in psilocybin content from 0.01 to 2.40% by dry weight (Beug and Bigwood 1982; Kamata et al., 2005). This natural variation across mushroom species, tissues, and fruitings (Beug and Bigwood 1982) coupled with a historical focus on dry mushroom weight based dosing (Guzmán 2009) has led to challenges in comparing mushroom consumption experiences and clinical trial data.

3.1. Biosynthesis & biochemistry of psilocybin

Psilocybin is synthesized by four spatially clustered genes coding enzymes that catalyze reactions for the conversion of tryptophan to psilocybin (Fig. 2) (Fricke et al., 2017; Reynolds et al., 2018). The genes involved in psilocybin biosynthesis, or the *Psi* genes, occupy an ~11–22 kilobase genomic region that includes four genes encoding the biosynthetic enzymes (*PsiD, PsiK, PsiM, PsiH*) and one gene that encodes a putative solute transporter (*PsiT*) of unknown function (Blei et al., 2018; Demmler et al., 2020; Fricke et al. 2017, 2019b, 2020; Lenz et al., 2021; Torrens-Spence et al., 2018) that is co-inherited with the cluster (Reynolds et al., 2018). According to Fricke et al. (2017), psilocybin biosynthesis begins when tryptophan is decarboxylated by *PsiD* to form tryptamine. Tryptamine is then hydroxylated on the 4-position of the indole backbone by the cytochrome P-450 monooxygenase, *PsiH,* to form 4-hydroxytryptamine. The hydroxyl group of 4-hydroxytryptamine is next phosphorylated by *PsiK* to form norbaeocystin. Iterative methylation of the amine by *PsiM* then forms baeocystin, and then psilocybin. Psilocin is derived from the spontaneous dephosphorylation of psilocybin and can be converted back to psilocybin by *PsiK*.

The psilocybin biosynthetic pathway produces intermediates including the tryptamines baeocystin and norbaeocystin (Fig. 2) (Fricke et al., 2017). In addition to psilocybin and related tryptamines, some *Psilocybe* species also biosynthesize β-carbolines (e.g., harmane, harmine, norharmane), which inhibit the monoamine oxidase (MAO) family of enzymes responsible for degradation of serotonin, psilocybin, and related chemicals (Blei et al., 2020; Lenz et al., 2021). The simultaneous production of β-carboline compounds in some *Psilocybe* species has been noted to differ between mycelia and mushrooms tissues (Blei et al., 2020).

3.2. Genomic resources & evolutionary history of Psi gene cluster

Genomic resources, including assembled genomic contigs, unassembled whole genome sequencing data, and transcriptome data, are available in NCBI GenBank and the Sequence Read Archive (SRA). Other sources of genomic data for psilocybin-producing fungi are available through MycoCosm (Grigoriev et al., 2014) developed by the Joint Genome Institute, or as supplemental data associated with publications (e.g. Awan et al., 2018). A high-quality draft assembly of a strain of *P. cubensis* (McKernan et al., 2021a) is also available for comparative genomic analyses through CoGe

Fig. 1. *Psilocybe* species diversity. Basidiomata of **(A)** *Psilocybe serbica* (jonagruska, CC-BY-SA 3.0), **(B)** *P. mescalenroensis* (Alan Rockefeller, CC BY-SA 4.0), **(C)** *P. cubensis* (Ricardo Arredondo, CC BY-NC), **(D)** *P. ovoideocystidiata* (Shroomydan, CC-BY-SA 3.0), **(E)** *P. allenii* (Alan Rockefeller, CC-BY-SA 3.0), **(F)** *P. azurescens* (Shroom360, CC BY-SA 3.0), **(G)** *P. cyanescens* (Alan Rockefeller, CC BY-SA 3.0), **(H)** *P. subaeruginosa* (ericos_bob, CC BY-SA 3.0), **(I)** *P. angulospora* (Inski, CC BY-NC-SA), **(J)** *P. baeocystis* (Caleb Brown, CC-BY-SA 3.0), **(K)** *P. pelliculosa* (Scottdarbey, CC-BY-SA 3.0), **(L)** *P. semilanceata* (Alan Rockefeller, CC-BY-SA 3.0), **(M)** *P. hoogshagenii* (Brayan Coral Jaramillo, CC BY-SA 3.0), **(N)** *P. mexicana* (Alan Rockefeller, CC BY-SA 4.0), **(O)** *P. neoxalapensis* (David Morales, CC-BY-NC 4.0), **(P)** *P. zapotecorum* (Alan Rockefeller, CC-BY-SA 3.0). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Lyons and Freeling 2008). ITS sequences are available for over 60 valid *Psilocybe* species. In total, genomic data is available for seven psilocybin containing species, with hyphae and basidiomata transcriptomes available for two of these (Supplemental Table 1). These data have enabled insights into the evolutionary history of the *Psi* genes and fungi which contain them (Reynolds et al., 2018).

Initial phylogenetic analyses of the *Psi* gene cluster suggested it originated in a common ancestor of *Psilocybe* and *Gymnopilus* (Reynolds et al., 2018). Outside of the mentioned mushroom lineages, close homologs of all psilocybin genes are only currently known in the crust-forming fungal family, *Atheliaceae*, but the genes are not clustered, and psilocybin has not been detected in this family (Konkel et al., 2021; Reynolds et al., 2018). At least two instances of convergent evolution of a psilocybin pathway and/or gene cluster have since been documented (Boyce et al., 2019). The presence of psilocybin in cicadas parasitized by *Massospora* spp. that lack the canonical biosynthetic gene cluster (Boyce et al., 2019) suggests the possibility multiple independent origins of psilocybin biosynthesis. Similarly, in a publication pre-print (Awan et al., 2018) reported there is no evidence in *Inocybe corydalina* for orthologs of the core psilocybin biosynthesis genes of the characterized psilocybin biosynthetic gene cluster. Instead, it was suggested that a different cluster of genes predicted to encode enzymes, each with catalytic activity similar to a psilocybin biosynthetic steps evolved convergently (Awan et al., 2018).

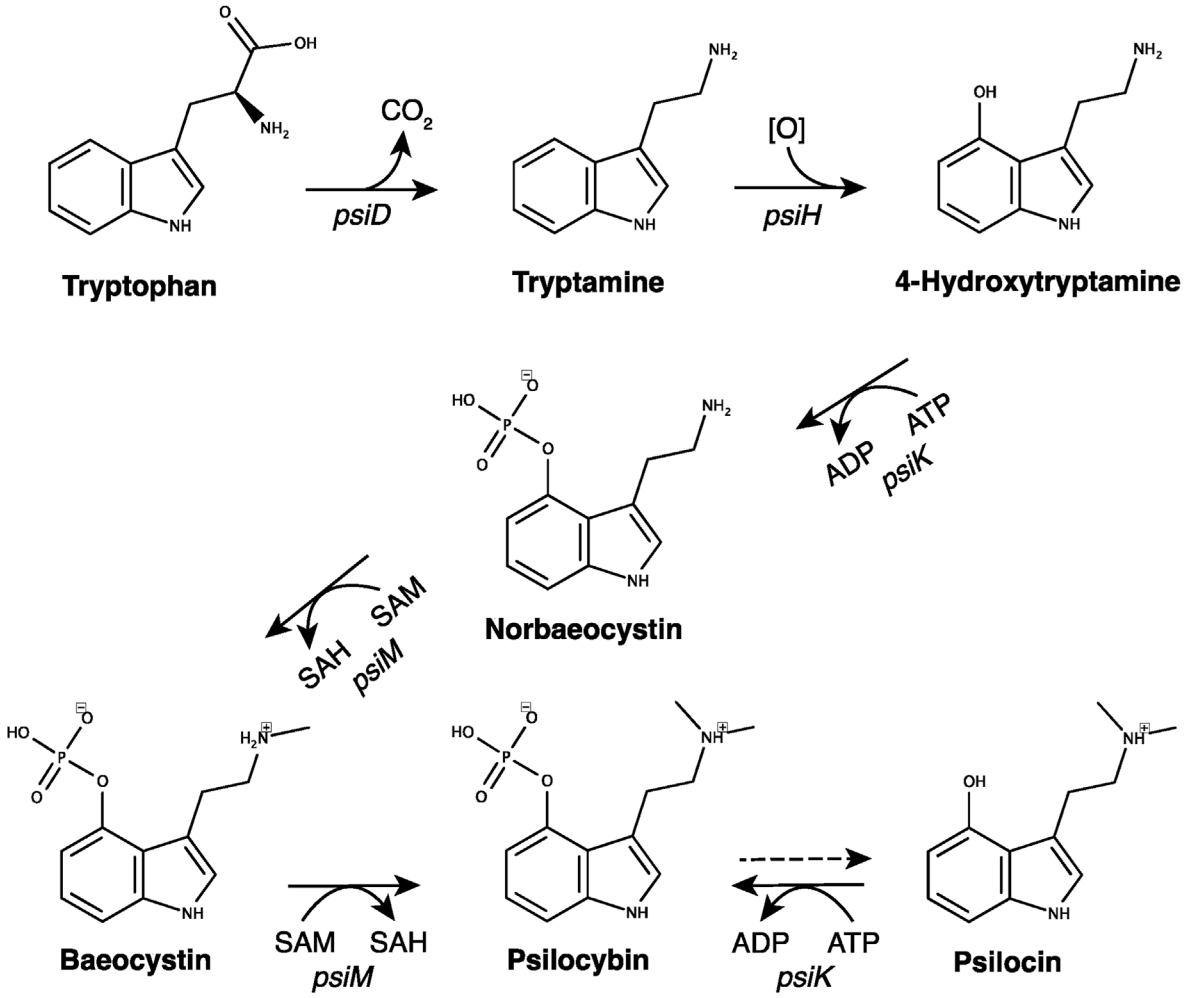

Fig. 2. Enzymatic biosynthesis pathway of psilocybin and psilocin from tryptophan as elucidated and confirmed by *in vitro* assays by Fricke et al. (2017).

Phylogenetic evidence suggests the presence of the psilocybin gene cluster in some distantly related mushroom genera such as *Conocybe*, *Panaeolus*, and *Pluteus* was the result of horizontal gene transfer (HGT) (Awan et al., 2018; Reynolds et al., 2018). Species with the most similar clusters shared ecological habits (e.g., dung-decaying, wood-decaying), and this taken together with the conflict with expected species relationships, may suggest spatial proximity is a facilitating factor in HGT. However, further taxon sampling and genomic analyses are needed to unequivocally evaluate this hypothesis, and the mechanism(s) of HGT between mushroom-forming fungi are not known. Some genes in the *Psi* gene cluster vary in copy number, suggesting differential evolutionary pressures may act on parts of the psilocybin biosynthetic pathway (Reynolds et al., 2018).

The ecological function(s) of psilocybin/psilocin remains uncertain. The neuroactive properties of these chemicals have led to speculation about their potential role as antifeedants or defenses targeting mycophagous insects and invertebrates (Reynolds et al., 2018), although empirical evidence is still lacking. However, psilocybin or psilocin may not be the primary compound for a hypothetical defense mechanism. Lenz et al. (2020) recently found that the chemical structure corresponding to the blue pigment characteristic of some *Psilocybe* species results from damaged and senescent cells. This pigment is derived from linkage of psilocin monomers, generated by a dephosphorylase, into short chains by the release of a laccase enzyme (Lenz et al., 2020). The ecological function of psilocybin may be due to the potentially toxicity of the oligomers that are produced upon injury, while the psychoactive properties of psilocybin/psilocin in humans may be secondary or incidental.

4. Extraction and quantification of psilocybin

The first extractions of psilocybin were completed in the 1950s utilizing polar solvents including methanol, chloroform, and water-alcohol mixtures (Heim and Wasson 1958; Hofmann et al., 1958, 1959). Albert Hoffman and his research team isolated psilocybin and psilocin from dried, powdered tissues of *P. cubensis* and *P. mexicana* (Heim and Wasson 1958; Hofmann et al., 1958, 1959). After redissolving dried residues in a butanol-water mixture and chromatographic separation on a cellulose column, they crystalized psilocybin and elucidated the structure by employing a range of spectroscopic analyses. Later, these structural analyses were confirmed through the first psilocybin synthesis by Hofmann's team in Troxler et al. (1959).

Purification of psilocybin has been carried out using a range of methodologies (Andersson et al., 2008). Psilocybin can be isolated from fungal tissues using solid phase extraction (SPE) column chromatography, in which molecules are separated based on polarity using cartridges packed with a solid stationary phase and solvents with variable polarity. Due to the high relative polarity of both psilocybin and psilocin, reverse-phase chromatography

columns (non-polar stationary phase and polar mobile phase) can be used to promote psilocybin and psilocin column migration and simultaneous separation of nonpolar contaminants (Stebelska 2016). Altering column length and size, types of SPE columns, and polarity of phases have been used to optimize chromatographic separation of psilocybin, psilocin, and other compounds (Gotvaldová et al., 2021; Nagy and Veress 2016; Rácz et al., 2019; Veress et al., 2019).

Quantitative psilocybin and psilocin detection methods involve gas chromatography, high-performance liquid chromatography, or ultra-high performance liquid chromatography methods and can be combined with mass spectrometers (Stebelska 2016). Molecules of interest are ionized (become charged), then are separated via a magnetic field based on their mass-to-charge ratios (m/z) and the resulting mass signal intensities can be used to precisely identify psilocybin, psilocin, and potential contaminants in each sample. Quantification of psilocybin and related compounds is achieved by comparing experimental values to a known concentration range of pure analytes as reference standards or internal standards, sometimes with isotopic substitutions for unique distinction from the mass of interest (e.g., psilocybin-D6, with six deuterium isotope substitutions). Other methods of analytical detection and qualitative, semi-quantitative, or quantitative analysis include: spectroscopic techniques (UV—Vis, IR), thin-layer chromatography, and ion mobility spectrometry (Stebelska 2016). These technologies can be readily adapted for detection of contaminants in fungal products and or extracts including residual solvents from extractions, microbial contaminants, and disinfectants from cultivation (Chang et al., 2014; Du et al., 2018; Gałgowska and Pietrzak-Fiećko 2017; Lambert 1938; Moore 2005; Stamets and Chilton 1983; Tian et al., 2020).

5. Therapeutic psilocybin usage

Indigenous practices have pioneered and established the notion of individual and group psilocybin therapies (Echevarría 1979; Heim and Wasson 1958; Wasson 1957). Various Mesoamerican cultures, in particularly the Mazatec people, have employed ritualistic elements and guidance facilitated by curandero(a)s to prepare individuals for the sacrament of taking psilocybin mushrooms. These rituals were and are undertaken to provide new perspectives on mental and emotional health, conflicts, and to resolve social dysfunction, trials, and tribulations (Echevarría 1979; Heim and Wasson 1958; Wasson 1957). To provide a positive experience, a mainstay practice for generations of indigenous people has been to place emphasis on competent, experienced, and genuine guides. These guides can ensure that environmental and personal factors, or what is currently described as set and setting, are favorably aligned.

The indigenous knowledge that psilocybin experiences have high therapeutic potential has been mirrored in recent, western, medicalized psilocybin clinical trials, which have confirmed the importance of preparation, set and setting (e.g.,Carhart-Harris et al., 2018; Horton et al., 2021; Roseman et al., 2018). In addition, the benefits of group-based therapies (Anderson et al., 2020) and having a guiding therapist performing a curandero(a)-like role have been quantified (Horton et al., 2021).

There are currently over 60 ongoing psilocybin clinical trials overseen by the United States National Institute of Health. Given that many psilocybin clinical trials are in early phases, explicit long-term medical effectiveness in treating mental health conditions are yet to be determined in the western framework. Even so, preliminary data suggest psilocybin therapies are effective in treating depression (e.g. Carhart-Harris et al., 2017; Goldberg et al., 2020; Griffiths et al., 2016; Grob et al., 2011), obsessive-compulsive disorder (Jacobs 2020; Moreno et al., 2006), smoking cessation (Garcia-Romeu et al., 2014; Johnson et al. 2014, 2017), and alcoholism (Bogenschutz et al., 2015). In addition, a clinically meaningful change was seen in psilocybin-assisted group therapy for demoralization in older long term AIDS survivors (Anderson et al., 2020).

Major Depressive Disorder symptoms decreased following psilocybin administration coupled with psychological support in a phase 2 controlled trial that compared psilocybin with the selective serotonin reuptake inhibitor (SSRI) escitalopram utilizing the Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR-16) (Carhart-Harris et al., 2021). This group found that the primary outcome, defined as mean (±SE) change from baseline QIDS-SR-16 score did not significantly differ between groups, and that psilocybin therapies had similar effectiveness in lowering MDD symptoms. A second study found that MDD symptoms decreased following psilocybin and supportive psychotherapy as measured by GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores in a randomized clinical trial (Davis et al., 2021). Obsessive Compulsive Disorder symptoms also were seen to decrease following psilocybin assisted therapies measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS) in a modified double-blind dose escalation study (Moreno et al., 2006). Cancer-related depression and anxiety symptoms decreased after psilocybin assisted therapy as measured by the Beck Depression Inventory, Hospital Anxiety and Depression Scale, State-Trait Anxiety Inventory metrics in a double-blind, placebo-controlled clinical trial (Ross et al., 2016). Further, decreases in psychological distress and anxiety about cancer related death post psilocybin assisted therapy were observed in a randomized, double-blind, cross-over trial utilizing a 17-item GRID-Hamilton Depression Rating Scale (GRIDHAM-D-17) and Hamilton Anxiety Rating Scale (HAM-A) (Griffiths et al., 2016).

Results of psilocybin ingestion outside of clinical trials have also been described throughout the literature. These include increased connection to nature, enhanced creativity and greater enjoyment of music (Riley and Blackman 2008). Psilocybin ingestion increased positive mood, attenuated recognition of negative facial expressions, increased goal-directed behavior toward positive cues, and facilitated positive emotional effects in a randomized double-blind study (Kometer et al., 2012). In an additional study psilocybin consumption induced decreases in amygdala activity correlated with positive mood (Kraehenmann et al., 2015).

The effects of psilocybin consumption has also been found to alter temporal processing (Wittmann et al., 2006), and brain region connectivity via blood flow patterns (Carhart-Harris et al., 2017; Johnson et al., 2019; Lebedev et al., 2015; Tagliazucchi et al., 2014). Psilocybin has been found to alter activation of different areas of the brain when participants were asked to recall memories (Carhart-Harris et al., 2012b), and to be associated with decreases in cerebral blood flow and blood oxygen level dependent signaling (Carhart-Harris et al., 2012a). This led authors to suggest psychoactive effects may be due to decreased activity and connectivity of some brain regions (Carhart-Harris et al., 2012a). Cerebral blood flow also showed post-treatment decrease in the temporal cortex including the amygdala in patients with treatment -resistant depression, which was correlated with reduced depressive symptoms (Carhart-Harris et al., 2017). Further studies showed that plasma psilocybin level is correlated with functional connectivity reflected in network integrity and network segregation (Madsen et al., 2021). An association between “ego-dissolution” and decreased interhemispheric communication has also been reported (Lebedev et al., 2015). It has been postulated that neuroplasticity may be responsible for psilocybin's therapeutic effects (Banks et al., 2021).

6. Potential risks of psilocybin usage

While potential benefits of psilocybin are striking, adverse physiological and psychological reactions to consuming psilocybin mushrooms have been documented and reviewed (Andersson et al., 2008; Johnson et al., 2019; Oregon Psilocybin Evidence Review 2021). In a recent large scale clinical trial of 233 patients, 179 reported headache, nausea, fatigue, or insomnia, and concerningly 12 patients showed suicidal behavior, intentional self-injury, and suicidal ideation (COMPASS Pathways 2021). Other studies have reported potential risks of ingesting psilocybin containing-mushrooms to include short lived panic, anxiety, and paranoia (Hasler et al., 2004; Musha et al., 1986; Riley and Blackman 2008), hypertension, tachycardia, hyperreflexia, mydriasis, paresthesia, and feelings of depersonalization (Peden et al., 1982), renal and gastrointestinal complications (Austin et al., 2019), and hallucinatory sensations (Satora et al., 2005). In clinical settings, safety guidelines have been instated to manage adverse reactions (Johnson et al., 2008). It is unclear to what extent side effects reported when mushrooms were consumed are due to the presence of other co-occurring compounds. For example, phenylethylamine, which is associated with tachycardia, nausea, and anxiety, has been reported in *Psilocybe semilanceata* (Beck et al., 1998). The presence of other bioactive compounds including psilocybin biosynthetic pathway intermediates (Beug and Bigwood 1982; Fricke et al., 2019b; Sherwood et al., 2020; van Amsterdam et al., 2011) may also be associated with some of these effects.

In addition, unknown bioactive compounds in *Psilocybe* species may pose a risk for consumers. Some species (*Psilocybe azurescens, Psilocybe subaeruginosa,* and other species that grow on decaying wood) are believed to be capable of inducing a temporary paralytic state, colloquially known as “wood lovers’ paralysis”. This phenomenon has been mentioned anecdotally in formal literature (Sherwood et al., 2020), and may have been described in a report of temporary paralysis and hallucination in Japan (Imai 1932). While this phenomenon is not yet documented in the primary literature, extreme care should be taken to avoid adverse reactions by consumption of these species.

Combining psilocybin with other substances can also cause striking adverse reactions in some individuals. Fatalities reported in connection with the consumers of psilocybin mushrooms often involve alcohol and other drugs (Andersson et al., 2008; van Amsterdam et al., 2011). Hallucinogen persisting perception disorder has also been reported in a case study where *Psilocybe* mushrooms were consumed with alcohol and cannabis (Skryabin et al., 2018). Ingestion of mushrooms may also be associated with exacerbation of some underlying mental health conditions (Johnson et al., 2019; Nielen et al., 2004). Other risks of consuming fungal products, in general, include allergic reactions or potential gastrointestinal distress for sensitive consumers.

Consuming misidentified fungi can cause severe adverse reactions for consumers, including death. The majority of psilocybin and psilocin producing mushrooms have a similar appearance to mushrooms that produce potent toxins, and misidentification can lead to fatalities (Lincoff and Mitchel 1977). Notably, several species of *Galerina* produce cyclopeptides including amatoxins that permeate the liver and kidneys and inhibit DNA-dependent RNA polymerase B. By disrupting mRNA transcription, amatoxins cease protein synthesis, resulting in cell necrosis (Horowitz and Moss 2021; Wieland et al., 1981). Potential harms of ingesting misidentified fungi include acute or delayed gastrointestinal distress, hypotension, tachycardia, coagulopathy, liver and kidney damage, autonomic and central nervous system malfunction, and/or death (Franz et al., 1996; Lincoff and Mitchel 1977). Accurate identification of fungi to species often requires DNA sequencing combined with expert evaluation of salient micro- and macromorphological features and is paramount to safe use of mushrooms and products thereof.

7. Currently available diagnostics

Diagnostics have been developed for detection psilocybin and psilocybin. In the body these include analysis of psilocybin content in hair (Pichini et al., 2014), urine (Bambauer et al., 2021; Kamata et al., 2005; Poliwoda et al., 2020; Shoda et al., 2011), or in blood plasma (Sticht and Käferstein 2000). Procedures to identify *Psilocybe* mushrooms and products have also been developed (Gambaro et al. 2015, 2016). Methods for detection include enzyme-linked immunosorbent assays (ELISAs) via monoclonal antibodies that bind psilocybin or psilocin (Morita et al., 2020), liquid or gas chromatography (Kamata et al., 2005; Rácz et al., 2019; Saito et al., 2005), and mass spectrometry (Pichini et al., 2014). It is possible to differentiate between psilocybin, psilocin, and related molecules using hydrophilic interaction liquid chromatography (Gotvaldová et al., 2021; Rácz et al., 2019).

There are also field-based mushroom diagnostic kits that enable affordable, rapid, sensitive, and accurate detection of fungal substances and identities (Gao et al., 2021; He et al., 2019b; St John and Price 2014; Wang et al., 2021). These kits employ a range of technologies including nucleic acid amplification, antibody detection via immunoassay, and chemical detection via chromatography (Bever et al., 2020; St John and Price 2014). Non-laboratory-based assays are critical to harm reduction as they enable species identification verification and dosage determination. Currently, there are field based kits available for quantification of psilocybin (Miraculix, Jena, Germany) and detection of amatoxin, the cyclopeptide toxin found in many deadly mushrooms including *Galerina marginata* (Bever et al., 2020) which is morphologically similar to several *Psilocybe* species, such as *Psilocybe allenii* and *Psilocybe cyanescens*.

8. Necessary research and technological advancements

Genetic and genomic data are essential tools necessary to identify, study, and utilize fungi in applied efforts, and as such the need for research on fungal genomics and biology cannot be underscored enough. Utilizing modern DNA sequencing-based approaches will enable an understanding of population-level diversity and its conservation. Further, the generation of genome sequences will facilitate evaluation of how evolutionary and potentially anthropogenic selective pressures have affected psilocybin biosynthetic gene clusters including sequence and copy number variation, gene orientation, and elucidation of novel function. Last, such resources will allow a better understanding of the species diversity in *Psilocybe* and other psilocybin producing fungi.

Diagnostic development is crucial for safe and effective applied fungal biological efforts. While current diagnostic kits described above allow for identification of psilocybin and amatoxins, only the Miraculix kit, which confirms the presence and quantity of psilocybin, is available to consumers. Preliminary research has shown psilocybin containing species from *Inocybe* (Kosentka et al., 2013) and *Galerina* (Gartz 1995) that have been analyzed so far do not contain the same toxins as their close relatives. However, given the repercussions of fungal toxin poisoning and wide diversity of uncharacterized fungal species, a robust multiplex assay that can differentiate psilocybin-containing genera is desired. While presence of psilocybin is a good indicator that the tested sample is not a misidentified toxic mushroom, there is a need for field-deployable identification kits that compare toxin presence as well.

Understanding the molecular basis for adverse reactions to fungal consumption including “wood lover's paralysis” (WLP) is

high research priority. While no references are currently available in the research literature, numerous anecdotal reports describe short term (less than 24 h) paralysis and other WLP symptoms 4–6 h post ingestion of *P. azurescens*, *P. cyanescens*, and *P. subaeruginosa,* amongst others. Temporary paralysis carries situational hazards such as hypothermia, heat-stroke, drowning, and trauma. There have been very few documented deaths in the peer-reviewed literature associated with the consumption of psilocybin-containing mushrooms including the wood lovers, and in all references, confounding factors are noted (van Amsterdam et al., 2011). Gaining insight into the origins and molecular mechanisms of WLP will guide safe and effective interfacing between the public and fungi.

At present, there is a limited understanding of fungal biology including psilocybin-producing fungal species in the public, and an accompanying under representation of diverse peoples and knowledge in both applied and academic mycology. Education and outreach efforts are central to diversifying mycological communities and encouraging citizen scientists' contributions to mycological progress. Promoting awareness of fungal biology and ecology promotes public health by equipping populations to identify and avoid consumption of toxic or poisonous fungi, and to utilize fungi in novel application development.

The goal to increase fungal biological knowledge in all communities can be pursued by creating modernized educational materials and utilizing digital resources such as iNaturalist. Engaging the public with citizen science efforts such as documenting fungal diversity results in large and powerful datasets. For example, because only a fraction of fungal species diversity is currently described (Hawksworth and Lücking 2017; James et al., 2020) tools such as iNaturalist harness the power of citizen science to better understand fungal biology and distributions. This knowledge in turn better informs science-based policy development.

We can begin to address the lack of diversity in mycology through the integration of fungal biology modules into childhood and K-12 curricula, as well as diversifying equitable educational materials such as open access publications, audio and video recordings, and visual digital platforms. Increasing the diversity of peoples involved in all aspects of mycology ensure equitable and just adoption of psilocybin use. Development of therapeutic practices must be tested across a range of participants, including those from traditionally marginalized groups.

Lastly, financial gain from psilocybin therapies must be examined and knowledge keepers compensated. After Gordon Wasson introduced psilocybin mushrooms to the wider world, and violated his commitment to secrecy by exposing the identity of María Sabina, multiple patents were put forward based on compounds from *Psilocybe* mushrooms without any planned compensation for indigenous communities (Gerber et al., 2021). Protection of indigenous intellectual property rights and just compensation are needed as psilocybin products are developed, to not continue the history of large pharmaceutical companies profiting off indigenous knowledge without adequate compensation (McGonigle 2016).

Declaration of competing interest

JCS is a paid scientific advisor to Back of the Yards Algae Sciences and served on the board of the Entheome Foundation. All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.funbio.2022.01.003.

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