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The evolution and ecology of psilocybin in nature

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ABSTRACT

Fungi produce diverse metabolites that can have antimicrobial, antifungal, antifeedant, or psychoactive properties. Among these metabolites are the tryptamine-derived compounds psilocybin, its precursors, and natural derivatives (collectively referred to as psiloids), which have played significant roles in human society and culture. The high allocation of nitrogen to psiloids in mushrooms, along with evidence of convergent evolution and horizontal transfer of psilocybin genes, suggest they provide a selective benefit to some fungi. However, no precise ecological roles of psilocybin have been experimentally determined. The structural and functional similarities of psiloids to serotonin, an essential neurotransmitter in animals, suggest that they may enhance the fitness of fungi through interference with serotonergic processes. However, other ecological mechanisms of psiloids have been proposed. Here, we review the literature pertinent to psilocybin ecology and propose potential adaptive advantages psiloids may confer to fungi.

1. Introduction

Psilocybin is a secondary/specialized metabolite in certain mushroom-forming and other fungal species that has potent effects on the nervous systems of humans and other animals. Psilocybin-producing fungi, commonly referred to as psychedelic/magic mushrooms, have a rich history of use by humans for medicinal and spiritual purposes (Van Court et al., 2022). These fungi are hypothesized to have influenced human cognitive evolution (Rodríguez Arce and Winkelman, 2021) and have shown promise as a supportive tool in treating psychological disorders in recent decades (Vollenweider and Preller, 2020). While knowledge of psilocybin's psychopharmacological effects on humans is advancing, its roles and origins in natural systems are still not well understood, despite recent speculation about the ecological interactions it may mediate (Boyce et al., 2019; Bradshaw et al., 2022; Lenz et al., 2021b; Reynolds et al., 2018). Psilocybin and its natural precursors and derivatives (collectively psiloids; Fig. 1A) primarily exert their potent psychoactive properties by interfering with serotonin signaling (Fig. 1B) (Vollenweider and Preller, 2020), but also act on other facets of the nervous system (Ray, 2010; Roth and Driscol, 2011).

Psiloids comprise eight tryptamine alkaloids derived from tryptophan via the psilocybin biosynthesis pathway (Fricke et al., 2017; Stijve, 1984). They are substituted on the tryptamine 4-position with either a compound-stabilizing phosphate group (4-OP) or a less stable hydroxyl group (4-OH). Psilocybin and the other phosphorylated psiloids are prodrugs (attenuated precursors) of their hydroxylated counterparts, some of which are considered the primary bioactive metabolites in animals (Klein et al., 2020; Madsen et al., 2019). Additionally, the terminal amine group can have zero (T), one (NMT), two (DMT), or three (TMT) separate carbon (methyl) groups attached. Norbaeocystin (4-OP-T) and 4-hydroxytryptamine (4-HT) have no methyl groups, baeocystin (4-OP-NMT) and norpsilocin (4-OH-NMT) have one, psilocybin (4-OP-DMT) and psilocin (4-OH-DMT) have two, and aeruginascin (4-OP-TMT) and 4-trimethylhydroxytryptamine (4-OH-TMT) have three. Psilocybin is the psiloid found in the highest concentrations in mushrooms, and the majority of bioactivity is attributed to its metabolite psilocin (Gotvaldová et al., 2021; Sherwood et al., 2020; Tsujikawa et al., 2003). However, psiloid mixtures may have unique effects (Gartz, 1989; Matsushima et al., 2009; Zhuk et al., 2015).

Psilocybin has been hypothesized to mediate interactions between fungi and other organisms (Reynolds et al., 2018). It is possible that, like many other fungal specialized metabolites, psilocybin evolved as a defense against antagonistic organisms such as fungivores and resource competitors (Spiteller, 2008). However, given its neuroactive properties, psilocybin may increase spore dispersal distance by altering the behavior of animals visiting the mushroom and expanding their travel

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radius. Alternatively, psilocybin has been proposed as a store or disposal product of excess nitrogen that might otherwise be toxic to the fungus itself (Schröder et al., 1999). However, its preferential production in mushrooms, which are not readily mined by the mycelium for later use, argues against this nitrogen storage hypothesis.

Although most attention to psilocybin derives from its spiritual-cultural history and potential therapeutic properties, its ecological functions likely preceded human use by tens of millions of years (Reynolds et al., 2018; Rodríguez Arce and Winkelman, 2021). Consequently, psilocybin's evolutionary history and ecological interactions probably do not entail a long-term role for our species. Nevertheless, studying the mechanisms and natural targets of psilocybin may shed new light on its effects and applications in humans. Moreover, exploring the dynamics of psilocybin ecology may also reveal how the animal nervous system has adapted to neurochemical interference and contributed to the evolution of consciousness.

In this review, we present and weigh the evidence for potential ecological role(s) of psilocybin by investigating the evolution, nutritional modes, and lifestyles of psilocybin-producing fungi. First, we consider the ecological contexts in which fungi produce psilocybin and how this relates to the diversification of psilocybin-producing species. We then present genomic evidence of selection for psilocybin production and identify ecological associations with genome evolution events related to its production. Finally, we use what is known about the neurological mechanisms of psilocybin activity to consider lineages of animals that may have been the targets of psilocybin throughout time.

2. The distribution, structure, and evolution of psilocybin bear evidence of natural selection

Psilocybin-producing fungi are globally distributed in a variety of biomes and on various substrates. The historical and ecological context of molecular evolution events, including the clustering of genes, convergent pathway evolution, and horizontal gene transfer, suggest selective pressures that have led to the psilocybin phenotype. Furthermore, the morphologies and ecological niches of these fungi highlight potential fitness advantages of psilocybin production. Psilocybin-producing mushrooms' various ecological roles and phylogenetic analyses reveal a complex evolutionary history of these fungi, showcasing the breadth of psilocybin's utility.

2.1. The distribution of psilocybin production raises hypotheses about its ecological function

Psilocybin-producing fungi represent a geographically and phylogenetically diverse group of species. While most known psilocybin producers are mushroom-forming fungi that inhabit dung and late-wood decay niches (Reynolds et al., 2018), some species are ectomycorrhizal (Matheny et al., 2019), and there is one report of psilocybin in an insect pathogen (Boyce et al., 2019). There is also an unconfirmed account of psilocybin in a lichen (Schmull et al., 2014) (Table 1). Psilocybin-producing fungi are documented on all continents except Antarctica and are found in diverse climates, from tropical rainforests to arid deserts, with the highest species concentrations and diversity found in the neotropics (Guzmán et al., n.d.). The most common factor among the various ecological niches of psilocybin-producing fungi appears to be their low-nitrogen substrates. For example, the late stages of wood and dung decay are nitrogen-poor environments (Chen et al., 2013; Cowling and Merrill, 1966; Hao et al., 2004; Hess et al., 2021; Petersen et al., 1998), and ectomycorrhizal species are effective nitrogen scavengers for their host plants (Hernández et al., 2002; Mbarki et al., 2008; Stamets, 1996). Yet, despite environmental limitations, a large portion of nitrogen is allocated to psiloids. For example, psilocybin can make up to 1.6% of a mushroom's total nitrogen content (Borner and Brenneisen, 1987; Braaksma and Schaap, 1996; Gartz, 1994; Kamata et al., 2005). This substantial nitrogen investment to psiloids is similar to that of other specialized metabolites important to the fitness of different fungi, such as amatoxins and ergot alkaloids (Aiken et al., 2009; Caradus et al., 2022; Kaya et al., 2015; Long et al., 2020; Newell et al., 1987). The high nitrogen allocation to psilocybin production suggests that its benefits outweigh any cost to nitrogen-limited growth and reproduction processes.

Most psilocybin-producing mushrooms have an agaricoid morphology (Table 1), which is characterized by an umbrella-like pileus

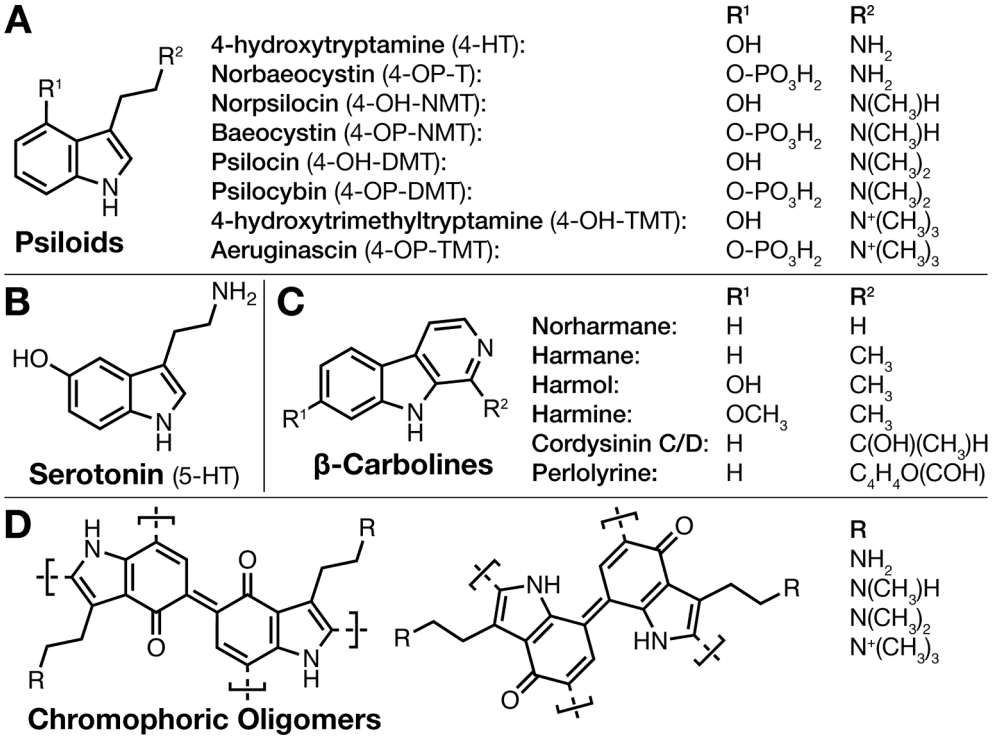

Fig. 1. Tryptophan-derived compounds in psychedelic/magic mushrooms (Gurevich, 1993; Lenz et al., 2021b). (A) Psiloids: the eight known natural 4-substituted tryptamine metabolites of the psilocybin biosynthesis pathway (Fricke et al., 2017; Stijve, 1984) found primarily in mushroom fruiting bodies (Blei et al., 2020). (B) Serotonin: a key signaling molecule found in all domains of life (Erland et al., 2019) and a key neurotransmitter in animals (Andrés et al., 2007). (C) β-carbolines: compounds with monoamine oxidase inhibitory (MAOI) and neuroactive properties found primarily in the mycelium of some psilocybin-producing fungi (Blei et al., 2020). (D) Chromophoric Oligomers: complexes of oxidatively-coupled psiloid dimers hypothesized to have tannin- and flavonoid-like properties (Lenz et al., 2020).

Table 1
Basic taxonomic, ecological, and morphological information of genera with psilocybin-producing species (Banerjee, 1994; Boyce et al., 2019; Gartz, 1986a, 1995; Guzmán et al., n.d.; Justo et al., 2011; Kalichman et al., 2020; Smith et al., 2015; Stamets, 1996).

Genus	Family	PS + Spp.*	Lifestyle	Morphology	Sclerotia†
Conocybe	Bolbitiaceae	2	Saprobic	Agaricoid	No
Panaeolus	Bolbitiaceae	18	Saprobic	Agaricoid, Secotioid	Yes
Pholiotina	Bolbitiaceae	2	Saprobic	Agaricoid	No
Gymnopilus	Hymenogastraceae	17	Saprobic	Agaricoid	No
Psilocybe	Hymenogastraceae	137	Saprobic	Agaricoid, Secotioid	Yes
Pluteus	Pluteaceae	9	Saprobic	Agaricoid	Yes
Inocybe	Inocybaceae	8	Ectomycorrhizal	Agaricoid	Yes
Massospora	Entomophthoraceae	1	Insect Pathogenic	Abdominal Spore Mass	No

* Estimated number of described psilocybin-producing species.
† Yes = at least one known species produces sclerotia, No = no known species produce sclerotia.

(cap) with lamellae (gills) on its underside and elevated by a stipe (stem). Some species also have a secotioid morphology, in which the hymenophore of the mushroom is either partially enclosed or remains almost entirely enclosed at maturity, leaving them dependent on passive or animal dispersal. The secotioid morphology has arisen convergently in psilocybin-producing species of the mostly agaricoid genera *Psilocybe* and *Panaeolus* (Borovička et al., 2011). Some species additionally produce sclerotia, colloquially referred to as "truffles," that produce psilocybin and other neuroactive compounds (i.e., β-carbolines) but lack a spore-producing hymenophore. Most psilocybin-producing mushrooms have firm-to-tender flesh, making them potential targets for fungivores. Mycophagy pressures have likely driven the evolution of multiple defensive strategies, such as the production of toxic metabolites (Spiteller, 2015), including psilocybin.

Psilocybin production has been confirmed in species from several distantly related families in the mushroom-forming order Agaricales (Basidiomycota), including Bolbitiaceae, Inocybaceae, Hymenogastraceae, and Pluteaceae (Dinis-Oliveira, 2017; Stamets, 1996; Wurst et al., 2002). It has also been reported outside of Basidiomycota in the insect pathogen *Massospora levispora/platypediae*, in the family Entomophthoraceae (Entomophthoromycota) (Boyce et al., 2019). Here, we discuss the range of ecologies and phylogenetic diversity of psilocybin-producing fungi to identify patterns in their distribution.

Grasslands are home to diverse psilocybin-producing taxa. The genus *Panaeolus* (Bolbitiaceae) contains approximately 100 species and is found in grassy regions worldwide, often associated with herbivore dung (Stamets, 1996; Strauss et al., 2022). At least 18 of these species produce psilocybin. The presence of psilocybin in *Panaeolus* is sporadic and found in the most distantly related clades of the genus (Hu et al., 2020). All species from the *Copelandia* clade (a genus name describing a clade sister to the clade containing all other *Panaeolus* species) produce psilocybin, and other *Panaeolus* clades contain psilocybin-producing species (Hu et al., 2020). Consequently, psilocybin production may be ancestral in *Panaeolus*, with some combination of subsequent losses and a potential re-acquisition. Alternatively, the distribution could be the result of several independent acquisitions. The history of psilocybin in *Panaeolus,* like other lineages below, will be better resolved when genetic data are available.

Other psilocybin-producing species inhabit grasslands and meadows just outside forest tree lines. *Pholiotina* is a paraphyletic genus in which the genus *Conocybe* (Bolbitiaceae) is derived. These genera are distributed globally and found in various substrates such as grass, wood chips, and other organic matter (Stamets, 1996). Out of approximately 300 combined species, only two in each genus are known to produce psilocybin. In all instances, the psilocybin-producing species are distantly related in recently-formed clades (Tóth et al., 2013). The distant relationship between psilocybin-producing species in multiple clades suggests multiple, recent, independent acquisitions as the most parsimonious hypothesis for its origin in these genera, and the placement of currently unsequenced psilocybin-producing species (e.g., *C. siligineoides*) in molecular phylogenies will improve our ability to infer psilocybin evolutionary events.

Psilocybin-producing mushrooms are also found in forest habitats. Indeed, it can be inferred that the first origin of the psilocybin pathway was in the late-stage wood decay niche in the common ancestor of *Psilocybe* and *Gymnopilus.* An alternative, perhaps more parsimonious, hypothesis of independent origins in these two genera would still imply multiple origins in late-stage wood decay. *Gymnopilus* (Hymenogastraceae *s.l.*) is a global and diverse genus of white-rot wood-decay fungi. The genus contains over 250 species, with a small portion (i.e., 17 species) known or presumed to produce psilocybin due to blue staining (Stamets, 1996; Strauss et al., 2022). Psilocybin production is found across the major clades of *Gymnopilus* (Guzmán-Dávalos et al., 2003; Khan et al., 2017; Reynolds et al., 2018). Furthermore, the psilocybin pathway has been detected in the genome of a species not previously known to be psychedelic (e.g., *G. chrysopellus*) (Reynolds et al., 2018), suggesting psilocybin is more widespread in *Gymnopilus* than reported. In the *G. spectabilis/G. junonius* species complex, some populations produce psilocybin while others do not (Hatfield and Valdes, 1978; Kusano et al., 1986). In this species complex, inactive remnants of the psilocybin metabolic pathway persist in the genome, suggesting dynamic evolution on recent timescales (Ruiz-Dueñas et al., 2021). Cumulatively, the evidence for any particular hypothesis of the history of psilocybin production within *Gymnopilus* is ambiguous. Psilocybin production may be the ancestral trait in *Gymnopilus* with several subsequent losses, but without further genetic evidence, the possibility of multiple acquisitions exists.

Another forest-inhabiting genus, *Pluteus* (Pluteaceae), is globally distributed and primarily contains species that grow on wood. Of the over 500 species, only nine are known to produce psilocybin (Stamets, 1996; Strauss et al., 2022). Psilocybin-producing species of *Pluteus* are only found in the small salicinus clade (Justo et al., 2014; Menolli et al., 2014). While most species within the salicinus clade produce psilocybin, those that do not are polyphyletic (Justo et al., 2014; Menolli et al., 2014), consistent with subsequent losses. The salicinus clade has also arisen recently, suggesting psilocybin production is not the ancestral state of *Pluteus* (Justo et al., 2014; Menolli et al., 2014). The current phylogeny is consistent with either two independent acquisitions or one acquisition with two subsequent losses in the salicinus clade as the most parsimonious explanation for the distribution of psilocybin in *Pluteus*, and the best of these models may emerge when more genetic data is available (Justo et al., 2014; Menolli et al., 2014).

An important ecological function of many mushroom-forming fungi in forests is forming ectomycorrhizal nutritional mutualisms with tree roots. The only ectomycorrhizal psilocybin-producing genus, *Inocybe* (Inocybaceae), is globally distributed but concentrated in temperate and tropical forests of the Northern Hemisphere. The genus contains over 800 species, of which only eight are known to produce psilocybin (Kosentka et al., 2013; Stamets, 1996). Psilocybin is inferred to have originated twice in recently-derived clades within *Inocybe* (Kosentka et al., 2013). *Inocybe* produces the trimethylated psiloid aeruginascin in higher concentrations than other psilocybin-producing fungi (Gartz,

1989). The presence of aeruginascin (and psiloids in general) in an ectomycorrhizal species raises the idea that it may play a role in plant-fungal communication, given the structural similarity with auxin plant hormones. Auxins produced by other mycorrhizal fungi are known to facilitate interactions with their hosts (Strzelczyk and Pokojska-Burdziej, 1984). For example, hypaphorine (N,N,N-trimethyl-tryptophan), which is structurally similar to aeruginascin, manipulates root morphology in *Pisolithus-Eucalyptus* mycorrhizal interactions through auxin interference (Ditengou et al., 2003). It is possible that *Inocybe* species also produce hypaphorine, as other psilocybin-producing species contain an additional non-PsiM methyltransferase (TrpM) that allows for methylation of tryptophan's terminal amine group directly (Blei et al., 2018), but the presence of this gene or compound has not yet been explored in *Inocybe*.

The globally distributed genus *Psilocybe* (Hymenogastraceae *s.l.*) contains the majority of all psilocybin-producing species. *Psilocybe* has diversified in various habitats and substrates, including grassy and forest humus soils, with a few species growing on herbivore dung (e.g., *Ps. cubensis* and *Ps. subcubensis*) (Stamets, 1996; Strauss et al., 2022). *Psilocybe* is also the only known genus of psilocybin-producing fungi where the pathway has been transmitted through multiple ecological transitions (e.g., wood decay to dung decay). Most *Psilocybe* mushrooms are small to medium in size, with a brown to yellow–brown colored hygrophanous pileus that leaves a spore print ranging from lilac-brown to dark purple-brown in color. They are commonly found in the neotropics, particularly in Mesoamerica, Brazil, and Chile, as well as in temperate regions such as mulched landscaped areas. For decades, psilocybin production was considered a variable trait in *Psilocybe*. However, the removal of several species now placed in *Deconica* based on molecular systematics has resulted in all but one of the over 100 *Psilocybe* species, *Ps. fuscofulva*, producing psilocybin (Borovička et al., 2015; Guzmán, 2005; Ramirez-Cruz et al., 2013; Redhead et al., 2007). The nearly universal presence of psilocybin in *Psilocybe* suggests that psilocybin is a shared-derived trait for species in the genus.

Multiple species of *Psilocybe* found in the wet montane forests of central Mexico (e.g., *Ps. zapotecorum*, *Ps. hoogshagenii*, *Ps. caerulescens*, *Ps. barrerae*, *Ps. muliercula*) are commonly referred to as "derrumbes" (landslides) mushrooms by indigenous peoples. These mushrooms typically emerge from vertical walls and scars created by landslides at high elevations (Guzmán, 2012), where accumulated buried organic material provides a carbon source. Anecdotally, Derrumbes exhibit longer-lasting basidiocarps compared to other *Psilocybe* species (Alan Rockefeller, personal communication; Derrumbes & Landslide Mushrooms of the Trans-Mexican Volcanic Belt, 2022), allowing them to sporulate over an extended period. This characteristic may provide an adaptive advantage by increasing the likelihood of landing on pockets of organic matter within the surrounding rubble. However, the limited nitrogen in these zones (Dalling and Tanner, 1995; Guariguata, 1990) may attract fungivorous animals to the mushrooms and lead to selection for chemical defenses. Fungi are effective nitrogen scavengers (Behie et al., 2012; Gadd, 2006; Hodge and Fitter, 2010; Lee et al., 2013; Ray et al., 2019) and may represent a significant source of available nitrogen in this environment. Derrumbes mushrooms are rumored to have high potency, with dried *Ps. zapotecorum* specimens reportedly containing 2.6% or more psilocybin (Jordan Jacobs, personal communication). Nitrogen scarcity for animals may underpin the tendency for psilocybin-producing mushrooms to be associated with nitrogen-limited environments.

2.2. The molecular evolution of the psilocybin gene cluster gives clues about selective pressures

The molecular evolution of psilocybin production offers insights into its chemical ecology. For example, specific molecular evolution events can indicate that ecological selection has impacted the psilocybin pathway. The psilocybin biosynthetic pathway consists of a tryptophan decarboxylase (PsiD), a P_{450} monooxygenase (PsiH), a methylthioribose family small-molecule kinase (PsiK), an S-adenosylmethionine-dependent methyltransferase (PsiM), and a major-facilitator-type transporter (PsiT), which enable the transformation of tryptophan into psilocybin (Fricke et al., 2017; Stijve, 1984). The presence of the pathway across multiple lineages and its organization into a gene cluster suggest a selective pressure on the end product, likely driven by its ecological function as a chemical defense or for interaction with other organisms. Selection on the psilocybin pathway is further supported by its convergent evolution in multiple lineages and multiple horizontal transfers of the psilocybin gene cluster (Awan et al., 2018; Reynolds et al., 2018).

The organization of the psilocybin biosynthetic pathway genes into a metabolic gene cluster is *de facto* evidence of natural selection for the production of psilocybin printed in the genome architecture (Slot and Gluck-Thaler, 2019). Metabolic gene clusters are loci containing genes (usually from diverse gene families) that participate in the same metabolic pathway, such as the psilocybin biosynthesis pathway. The assembly of the psilocybin pathway from various genes, from different gene families, and originating from multiple genome locations is improbable without selection. The clustering of this biosynthesis pathway may result from the selection of an optimal metabolic phenotype (Lawrence and Roth, 1996; McGary et al., 2013; Mylona et al., 2008; Xu et al., 2019a; Zinani et al., 2022) through mechanisms such as co-inheritance, co-adapted alleles, and coordinated gene expression (Lawrence, 1999; Schwander et al., 2014; Walton, 2000; Zinani et al., 2022). The resulting cluster may be optimized to reduce autotoxic psilocybin intermediates and for the metabolic efficiency of end-product production. For example, if the phosphorylating gene (PsiK) were lost or poorly coordinated with its substrate production, unstable hydroxylated psiloids might form potentially autotoxic tannin-like structures (Anttila et al., 2013; Jin, 2019; Lenz et al., 2021a, 2020).

The convergent evolution of the psilocybin gene cluster is further evidence of selection for psilocybin production. Psilocybin gene clusters have arisen independently at least twice in the Agaricales order, resulting from different genes converging on similar functions (Awan et al., 2018). Furthermore, the absence of homologs of known psilocybin genes in Entomophthoromycota is consistent with another convergent origin of the pathway (Boyce et al., 2019). The convergent psilocybin clusters within Agaricales appear to have near-identical pathways in terms of gene functionality (i.e., monooxygenase, kinase, methyltransferase, and transporter) but evolved from different gene families (Awan et al., 2018; Fricke et al., 2017). Yet despite convergent evolution in multiple mushroom-forming fungi and an insect pathogen, and its relatively simple biosynthesis compared to other specialized metabolites, psilocybin has not been found in filamentous Ascomycota or yeasts.

The horizontal transfer of the psilocybin gene cluster is still further evidence of selection for psilocybin production, pointing to precise ecological niches where this selection may occur. The psilocybin gene cluster is inferred to have undergone multiple horizontal transfers (Fig. 2A) across divergent genera (Awan et al., 2018; Reynolds et al., 2018). This is noteworthy due to the various obstacles preventing such transfers in eukaryotes, such as genetic material traversing the boundaries of the cell wall and nuclear envelope (Jaramillo et al., 2015; Jensen, 2016). Given the odds against the retention of randomly acquired DNA, a selective benefit of producing psilocybin in the recipient fungi can easily be inferred (Gogarten and Townsend, 2005; Kimura, 1977; Kurland, 2005). Furthermore, the psilocybin cluster is a rare example of horizontal transfer of a biosynthetic gene cluster in mushrooms (Luo et al., 2018; Reynolds et al., 2018; Slot and Gluck-Thaler, 2019; Walton, 2018; Wisecaver et al., 2014). This is noteworthy, as morphologically complex fungi like mushrooms are generally considered to have less-clustered genomes than those with simpler development, suggesting that its benefit might outweigh any elevated costs of HGT in these fungi (Marcet-Houben and Gabaldón, 2019; Slot and Gluck-Thaler, 2019). The evolution of psilocybin clusters is reminiscent of "selfish clusters," whose individual genes are weakly selected, but their collective fitness

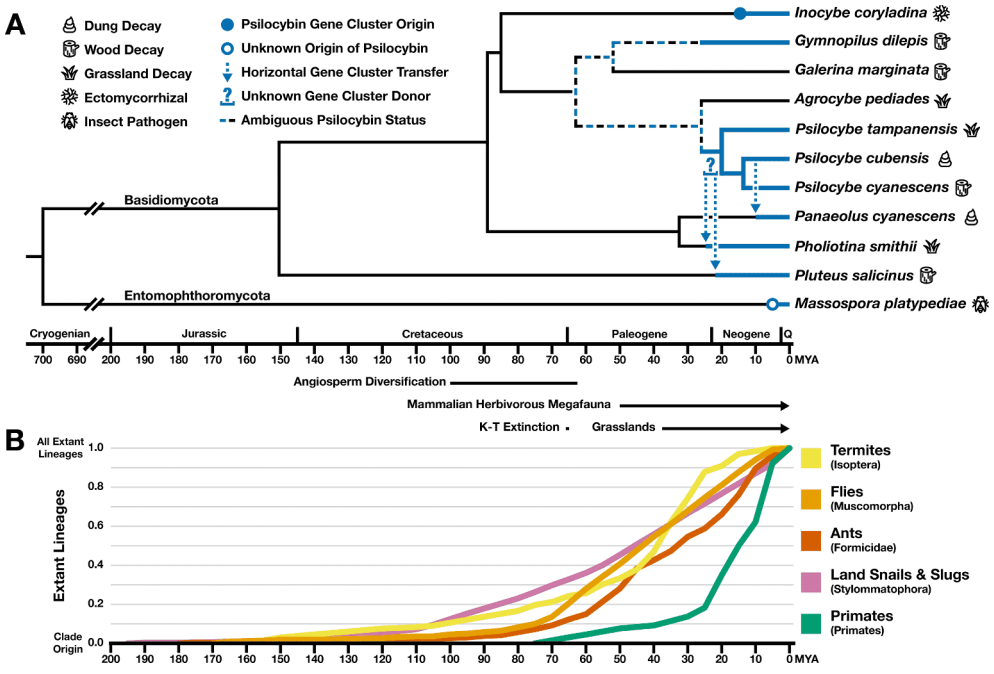

Fig. 2. Evolution of psilocybin-producing fungi and potential interacting animals. (A) Phylogeny of select psilocybin-producing lineages inferring key evolutionary events in the acquisition of psilocybin production (Awan et al., 2018; Boyce et al., 2019; Kosentka et al., 2013; Reynolds et al., 2018) alongside lineages' lifestyles and relevant major Earth geological and ecological events (Floudas et al., 2012; MacFadden, 2000; Ramirez-Cruz et al., 2013; Retallack, 2001; Tóth et al., 2013). Branching order was derived from Reynolds et al. (2018) and Sánchez-García et al. (2020), and divergence dates from Ruiz-Dueñas et al. (2021), with exception of the divergence date of *Agrocybe* and *Psilocybe,* which is conjecture. (B) Increase of extant lineages of animal clades that are hypothesized to have driven the selection of psilocybin: primates (Springer et al., 2012), flies (Wiegmann et al., 2011), termites (Bourguignon et al., 2015), ants (Chomicki and Renner, 2017), and terrestrial gastropods (Ayyagari and Sreerama, 2020). Lineages were selected due to hypotheses discussed in this review rather than a comprehensive survey of potential drivers. Based on chronograms, lineage counts within defined clades were assessed every 5 million years. A proportional value (0–1) was obtained by dividing the lineage count at a specific time point by the total lineages at 0MYA, normalizing the data and enabling the comparison of clades with varying extant lineages on a single axis. Given that these dates are generated by different methods, each plot should be considered independently. This metric does not account for the role of extinction rates in observed diversity.

increases through HGT of the complete selectable function of the pathway in a clustered state (Lawrence and Roth, 1996; Walton, 2000). Like selfish clusters, acquiring the psilocybin cluster likely provides a strong but temporary benefit to its hosts due to chemical arms races with organisms targeted by psilocybin (Hatfield and Valdes, 1978; Kusano et al., 1986; Ruiz-Dueñas et al., 2021). Indeed, the psilocybin cluster has been lost in at least one and probably many instances, given the evidence of a degenerate cluster in *G. junonius* (Ruiz-Dueñas et al., 2021) and its patchy distribution in multiple genera (Guzmán-Dávalos et al., 2003; Hu et al., 2020; Justo et al., 2014; Khan et al., 2017; Kosentka et al., 2013; Menolli et al., 2014; Tóth et al., 2013).

Evolutionary genomics is a powerful tool that can provide insights into the ecological role of psilocybin production. By studying rare molecular evolutionary events surrounding psilocybin's biosynthetic pathway (i.e., gene clustering, convergent evolution, HGT), we are given clues as to how these species have adapted to their environments. Two convergent origins of the psilocybin gene cluster in Agaricales have been inferred in wood-decay (a nutritional mode shared by *Gymnopilus* and *Psilocybe*) and in the ectomycorrhizal *Inocybe*, with another possible convergence in Entomophthoromycota (Awan et al., 2018; Boyce et al., 2019; Reynolds et al., 2018). Most other known psilocybin producers are saprobes and likely acquired the wood-decay-associated cluster through HGT (Fig. 2A) (Reynolds et al., 2018). This suggests that psilocybin may have different functions in different ecological niches but is most useful in decay niches. The ancestral ecologies of the cluster donor species were likely similar saprobic niches to their recipients, leading to physical contact between them and increasing the chances of HGT (Gluck-Thaler and Slot, 2015; Reynolds et al., 2018). Horizontal acquisition of psilocybin production may also facilitate expansion into new ecological niches (Slot, 2017). For instance, the HGT between the *Ps. cubensis* and *Pa. cyanescens* lineages likely occurred in their shared dung decay niche (Reynolds et al., 2018), suggesting both species faced similar pressures that psilocybin may have at least partially alleviated. Psilocybin production may defend against cohabiting animals, especially insects, that compete for resources or consume the fungus. An ecological association with insects is further supported by the likely convergent origin of psilocybin in *Massospora levispora/platypedia*, a fungus that is directly antagonistic to an insect.

Fungal specialized metabolite pathways are generally subject to rapid diversification, likely due to an ever-changing competitive landscape (Bradshaw et al., 2013; Raguso et al., 2015). Changes in these pathways can occur through modifications, gains, losses, and duplications of genes in the gene cluster, or through recombination with other pathways (Lind et al., 2017). Different enzyme activities may be responsible for the observed differences in psiloid proportions among species. For instance, *Pa. cinctulus* appears to have a relatively high concentration of baeocystin (Gotvaldová et al., 2022), and *I. aeruginascens* has a higher concentration of aeruginascin (Gartz, 1989). However, the composition of the psilocybin cluster is remarkably stable, with the notable exceptions of monooxygenase (PsiH) and transporter (PsiT) genes of unknown function, which can vary in copy number among different species (McTaggart et al., 2022; Reynolds et al., 2018). These duplications may increase the production of known psiloids or create new, yet-to-be-discovered products of the psilocybin pathway. Although much remains to be learned about the diversification of psiloid chemistry, there is certainly the potential to discover differently adaptive chemodiversity among the various psilocybin pathways.

3. Organismal interactions may have selected for psilocybin production

The study of chemical ecology aims to understand how specialized metabolites mediate the interactions between organisms and an ecosystem's physical environment. Like plants and bacteria, fungi produce metabolites that can serve communicative, attractive, defensive, dispersive, behavior-manipulative, and symbiosis-facilitative ecological functions through antibiotic, antifeedant, bioluminescent, or nutrient-mining properties (Quin et al., 2014; Spiteller, 2008; Ülger et al.,

2020). The concentration of these metabolites is typically higher in fruiting bodies (i.e., mushrooms) than vegetative mycelium (Spiteller, 2008; Stadler and Sterner, 1998), and this difference in expression may indicate the pressures each structure faces and, in turn, the ecological role of the compounds. No ecological roles have been definitively demonstrated for psilocybin, but we present some current compelling hypotheses here.

3.1. Psilocybin may impact ecological interactions like mycophagy and spore dispersal

The primary function of mushrooms is reproduction via sexual spore dispersal, which can be supported by specialized metabolites, including psilocybin (Splivallo et al., 2011). While the agaricoid morphology is thought to facilitate wind dispersal (Fischer and Money, 2010; Halbwachs, 2015), where investigated, only about 2% of wind-dispersed spores travel greater than 5 m, and only about 5% travel more than 1 m (Galante et al., 2011; Li, 2005). Animals can facilitate long-distance dispersal by transporting spores on their exteriors (e.g., exoskeletons, scales, feathers, skin, fur, etc.) or by transporting the whole spore-bearing basidiocarp (Elliott et al., 2022). Furthermore, spores are usually viable after passing through animal digestive tracts and even after secondary consumption by carnivores (Buller, 1909; Elliott et al., 2023; Halbwachs, 2015; Koch and Aime, 2018; Lloyd, 2001; O'Malley et al., 2013).

Psilocybin-producing mushrooms, like most mushrooms, are a potentially valuable food source for many animals. They contain high nutritional value (e.g., protein, amino acids, selenium, etc.), require little processing (e.g., husking, peeling, extracting, etc.), and are a source of hydration in low-moisture environments (Elliott et al., 2022; Getz, 1968; Khaund and Joshi, 2015; Obodai and Apetorgbor, 2008). Larger animals typically eat the whole mushroom, while smaller animals generally prefer to graze on the lamellae (Buller, 1909; Castillo-Guevara et al., 2012; Elliott et al., 2022; Sharma and Gautam, 2015; Walton, 1903). Anecdotal reports of animals consuming psilocybin-producing mushrooms primarily describe partial (rather than whole) mushroom consumption, which is possibly explained by some level of deterrence or behavior modification. The lamellae of poisonous mushrooms frequently have lower toxin concentrations than other mushroom tissues, which may guide fungivorous animals to the spore-bearing gills (Eilers and Nelson, 1974). Indeed, the spores of psilocybin-producing mushrooms lack psilocybin (Gotvaldová et al., 2021), making it likely that the spore-producing gills would also have considerably lower psilocybin concentrations than the surrounding tissues.

Another hypothesis may be that psiloids prevent the consumption of immature mushrooms before spore maturation. Broadly, repellents and toxins are more concentrated in the early stages of mushroom growth before the spores have fully developed (Ávila and Guevara-Pulido, 2020; Luo et al., 2010; Taskirawati and Tuno, 2016). A lack of appeal to fungivores during early growth could help ensure spores mature and disperse before the mushroom is consumed. While the psilocybin gene cluster is also expressed most highly in the early stages of mushroom development, the concentration of psilocybin appears to remain constant from the early stages of development to maturity (Demmler et al., 2020), suggesting that any potential repellent effect would not be limited to the early stages of development. Furthermore, the presence of psilocybin in vegetative mycelium, although in lower concentrations than the basidiocarps (Blei et al., 2020), also suggests it has some utility beyond the defense of its reproductive structures.

3.2. Psiloids mimic serotonin molecules involved in various physiological processes

Psiloids structurally resemble serotonin (5-hydroxytryptamine, 5-HT; Fig. 1B), an important molecule across the tree of life involved in intercellular signaling, growth, development, and responses to external stimuli (Erland et al., 2019; Roshchina, 2016). Two main differences exist between serotonin and psiloids. First, serotonin is hydroxylated on the 5-position of the tryptamine backbone, while psiloids are hydroxylated (and subsequently phosphorylated) on the 4-position (Passie et al., 2002). Second, psiloids can have up to three methylations on the terminal amine, while serotonin has none. The position of the hydroxyl group and the number of terminal amine methylations can affect the psychoactive and physiological characteristics of tryptamines in mammals by altering receptor-binding affinities (Glatfelter et al., 2022a, 2022b; Pottie and Stove, 2022; Shulgin and Shulgin, 2002; Zamberlan et al., 2018) (Table 2). This is exemplified by the fact that some neuroactive tryptamines (e.g., 4-OH-MET) have a high affinity for the 5-HT_{2A} receptor, while others (e.g., 4-OH-DiPT) have a low affinity for the same receptor (Kozell et al., 2023).

3.3. Animal nervous systems are likely targets for psiloids in nature

It is easy to surmise that animals are the target of psiloids due to their structural similarity to serotonin and binding specificity to its receptors. Many specialized metabolites mediate interactions by targeting the animal serotonin system (Spiteller, 2008). The physiological effects of psilocybin on animals could also benefit fungi through several mechanisms. For example, in humans, serotonin influences functions like gastrointestinal, cardiovascular, and neurological processes, as well as behavior and personality (Andrés et al., 2007). More broadly, serotonin affects crucial physiological processes in animals, making this compound an effective point of interference during interactions with animals (Spiteller, 2008). Psiloids bind to serotonin receptors with varying specificity, and their effects on animals can vary depending on the diversity and distribution of differently adapted receptors among species. The wide range of receptor subtypes among different species, along with different psiloids' varying binding affinities, suggest that the ecological and evolutionary pressures that these compounds may mediate are likely diverse and complex.

An ancestral 5-HT receptor is believed to have diversified into most major classes, 5-$HT_{1,2,4\text{-}7}$, approximately 650 to 700 million years ago, before the split of protostomes and deuterostomes (Ayala et al., 1998). This early diversification resulted in the sharing of the major serotonergic receptor classes between vertebrates and invertebrates (Hauser et al., 2006; Peroutka and Howell, 1994). In animals, serotonin serves as a classical neurotransmitter (fast-acting; involved in memory, learning, and coordination), a neuromodulator (slow-acting; involved in arousal, hormone release), or a neurohormone (slow-acting; involved in metabolism, growth, development, reproduction), and it is involved in

Table 2
Hydroxylated psiloids' serotonin receptor binding affinities as compared to serotonin (Chadeayne et al., 2020; Glatfelter et al., 2022b; Ray, 2010; Roth and Driscol, 2011).

Receptor	*4-OH-TMT*	*Psilocin*	*Norpsilocin*	*4-HT*	*Serotonin*
5-HT_{1A}	4,400* (H†)	164 (H)	86 (H)	95.5 (P†)	3.2 (H)
5-HT_{1B}	–	580 (H)	99 (H)	1,050 (R§)	4.3 (H)
5-HT_{1D}	–	130 (H)	194 (H)	–	5.0 (H)
5-HT_{1E}	–	155 (H)	161 (H)	–	7.5 (H)
5-HT_{1F}	–	–	–	–	10 (H)
5-HT_{2A}	670 (H)	180 (H)	391 (H)	724 (R)	11.6 (H)
5-HT_{2B}	120 (H)	8 (H)	57 (H)	–	8.7 (H)
5-HT_{2C}	–	175 (H)	243 (H)	40.7 (P)	5.0 (H)
5-HT_3	>10,000 (H)	>10,000 (H)	–	–	593 (H)
5-HT_4	–	–	–	–	126 (H)
5-HT_{5a}	–	116 (H)	365 (H)	–	251 (H)
5-HT_6	2,267 (H)	38 (H)	54 (H)	–	98.4 (H)
5-HT_7	–	75 (H)	68 (H)	–	8.1 (H)

* K_i given as nM. Higher K_i values indicate lower receptor binding affinity.
† Human receptor.
‡ Pig receptor.
§ Rat receptor.

multiple physiological and behavioral processes (Weiger, 1997). As a component of complex neurochemical pathways, serotonin influences a wide range of processes, including swimming contractions in cnidarians, reproductive behavior in platyhelminths, feeding and learning in mollusks, swimming and feeding in annelids, aggression in crustaceans, locomotion in jawless fish, and sleep, appetite, and mood in mammals (Mohammad-Zadeh et al., 2008). Consequently, the physiological effects of psiloids may vary among species. For example, psilocybin increases motor activity in fruit flies but decreases activity in rats (Chen et al., 2023; Hibicke and Nichols, 2022; Jefsen et al., 2019).

Psiloids are agonists or partial agonists of several serotonin receptors (Halberstadt and Geyer, 2011). Psilocybin, the primary serotonergic compound in psychedelic mushrooms (Tsujikawa et al., 2003), is quickly dephosphorylated into its neuroactive metabolite psilocin when ingested (Passie et al., 2002). Psilocin's psychedelic properties in humans are believed to result from its binding affinity for the 5-HT_{2A} receptor, but it also has high affinities for other 5-HT receptors (Table 2) (Tylš et al., 2014). Other free-hydroxyl psiloids also have activities on 5-HT receptors.

Given the diverse roles of receptor subtypes in animals (Bubak et al., 2020; Sharp and Barnes, 2020; Tierney, 2018), psiloids likely have a broad range of effects across and within different animal phyla. Additionally, small changes in the amino-acid sequence of serotonin receptors can significantly alter the binding affinity of psiloids and, consequently, their effects (Schmitz et al., 2022). The binding affinity and pharmacological action across species are further complicated by 5-HT receptors forming complexes with other receptors, modifying their functions (Ibi, 2022). And although the 5-HT_{2A} receptor is often the focus of research due to its prominent psychedelic effects in humans (Dodd et al., 2022; Ling et al., 2022; Vollenweider et al., 2007), there is no clear evidence that any specific receptor or subtype is an ecological target.

In addition to the strong effects on specific serotonin receptors, psilocin also binds to other neurotransmitter receptors (Table 3) (Ray, 2010). For example, psilocin has a much stronger binding affinity to dopamine receptors D_1 and D_3 than to 5-HT_{2A}. In fact, its affinity to D_1 is significantly higher than that of serotonin or even dopamine itself, and it is comparable to dopamine's binding affinity to D_3 (Janowsky et al., 2014). This high binding affinity of psilocin to D_1, which plays a significant role in regulating mood, motivation, and reward (Nieoullon and Coquerel, 2003), may contribute to its neuroactive effects in mammals (Grandjean et al., 2021). Relatedly, some research also suggests that psychoactive tryptamines like psiloids may be enzymatically converted to dopamine or other catecholamines *in vivo*, increasing their impact on the dopamine system (Fitzgerald, 2021). Dopamine receptors are present in both invertebrates and vertebrates, playing important roles in regulating behavior, movement, and other neurological processes (Gallo et al., 2016; Nieoullon and Coquerel, 2003; Stefano and Kream, 2010; Yamamoto and Vernier, 2011). This suggests that psiloids may impact most animal phyla through both the dopamine and serotonin systems.

The imidazoline receptor I_1 is also a binding target of psilocin in humans (Table 3). Little is known about the function of imidazoline receptors, but I_1 seems to influence cellular processes such as apoptosis, viability, growth, and proliferation in humans (Bousquet et al., 2020). In addition, psilocin weakly binds to the alpha-2 adrenergic receptors α_{2A}, α_{2B}, and α_{2C}. Broadly, α_2 receptors affect the human central nervous system and influence sedation, muscle relaxation, analgesia, and body temperature by modulating the effects of endogenous epinephrine and norepinephrine (Philipp et al., 2002). Psilocin also has an appreciable binding affinity to the trace amine-associated receptor 1 ($TAAR_1$), which broadly regulates processes such as feeding, mating, and olfactory responses through the modulation of the dopamine and serotonin systems (Borowsky et al., 2001; Grandy et al., 2016; Miller, 2011). $TAAR_1$ agonism may also reduce the stimulant properties of psiloids, as it does for other monoamines (Cara et al., 2011). Finally, psilocin binds to the serotonin transporter SERT, suggesting it may reduce serotonin reuptake, similar to the mechanism of drugs like SSRIs, SNRIs, and tricyclic antidepressants (David and Gardier, 2016). However, psilocin's binding affinity to SERT is considerably lower than most antidepressants or serotonin itself, making its effects likely minimal (Owens et al., 2001). Together, the diversity of potential targets in animal signaling pathways draws attention to the lack of conclusive evidence that 5-HT_{2A} is the primary receptor of ecological significance, despite its importance in human phenomenology.

The physiological effects of psilocybin have primarily been studied in mammalian models, and it is often shown to have strong neurological effects (Andrés et al., 2007). In humans, psilocybin ingestion has been found to alter sensory perception, mood, and states of consciousness (Jo et al., 2014). A growing body of research suggests that psilocybin may be useful in treating neurological disorders, including depression and anxiety, due to its ability to decrease activity in the amygdala and default mode network and increase neuroplasticity (Ling et al., 2022; Smausz et al., 2022). However, additional investigation is needed to develop a comprehensive model of the neuromodulatory effects of psilocybin to fully explain its mechanisms and the connected subjective psychedelic experience. While psilocybin may rarely cause adverse effects such as increased heart rate, nausea, and anxiety, clinical trials have demonstrated its general safety and efficacy (Jo et al., 2014).

The 4-substituted nature of psiloids offers further clues that they may be targeted to animal central nervous systems. After spontaneous or enzymatic dephosphorylation, psilocin can form a pseudo-ring structure due to the hydroxyl group on its 4-position (Bhadoria and Ramanathan, 2023; Lenz et al., 2022), which reduces its polarity and allows it to more easily cross the lipophilic membrane of the blood–brain barrier. The pseudo-ring structure also slows its degradation by endogenous monoamine oxidase (MAO) (Lenz et al., 2022). In comparison, 5-hydroxylated tryptamines (e.g., bufotenine) are too polar to readily cross the blood–brain barrier (McBride, 2000; Migliaccio et al., 1981; Zohairi et al., 2023), and non-hydroxylated tryptamines (e.g., DMT) are too quickly degraded by MAO to reach the blood–brain barrier (Barker et al., 1980). Many animal lineages (including invertebrates) have a lipid-based central nervous system diffusion barrier similar to that of the human blood–brain barrier (Dunton et al., 2021) and produce MAO (Sloley, 2004). Therefore, psiloids' pharmacodynamics may be similar among other animal phyla, consistent with the hypothesis that they are targeted broadly to the central nervous system.

3.4. Psilocybin may act in synergy with other tryptamines

The psiloids produced by psychedelic mushrooms exhibit different properties. For example, pure baeocystin and norbaeocystin do not produce any psychoactive effects on their own *in vivo* (Adams et al., 2022; Sherwood et al., 2020). Although psilocybin is the psiloid

Table 3
Psilocin, serotonin, and dopamine binding affinities (<10,000 nM) on non-serotonin receptors and transporters (Janowsky et al., 2014; Ray, 2010; Rickli et al., 2016; Roth and Driscol, 2011).

Receptor/Transporter	*Psilocin*	*Serotonin*	*Dopamine*
D_1	20* (H†)	9,690 (H)	4,300 (H)
D_2	3,700 (H)	>10,000 (H)	1,710 (H)
D_3	101 (H)	–	61 (H)
α_{1A}	6,700 (H)	>10,000 (R‡)	–
α_{2A}	2,044 (H)	>10,000 (R)	>10,000 (R)
α_{2B}	1,271 (H)	>10,000 (R)	>10,000 (R)
α_{2C}	4,404 (H)	>10,000 (R)	–
I_1	792 (H)	–	–
H_1	1,600 (H)	–	–
$TAAR_1$	1,400 (R)	6,000 (H)	422 (H)
SERT	852 (H)	44 (R)	6,489 (R)

* K_i given as nM. Higher K_i values indicate lower receptor binding affinity.
† Human receptor.
‡ Rat receptor.

produced in the highest quantities within the mushrooms, whole-mushroom extracts have been shown to produce more potent physiological effects on mammals than pure synthetic psilocybin, even at one-tenth of the concentration (Zhuk et al., 2015). This is consistent with the "entourage effect" hypothesis, which posits that psiloids and/or other fungal compounds act synergistically in animals (Dörner et al., 2022).

Relatedly, some psiloid-producing fungi synthesize β-carbolines (Fig. 1C), such as harmane, norharmane, and harmine, at varying levels and combinations across species (Blei et al., 2020). Like psiloids, β-carbolines also have binding affinities to serotonin and dopamine receptors and can produce moderate psychoactive stimulant effects on their own (Glennon et al., 2000; Grella et al., 1998). Additionally, β-carbolines can potentiate the effects of psiloids by acting as monoamine oxidase inhibitors (MAOIs) (Estrella-Parra et al., 2019; McKenna et al., 1984), which prevent the metabolic elimination of psiloids by monoamine oxidase A (MAO-A) (Dinis-Oliveira, 2017; Gessner et al., 1960). Thus, the MAOI activity of the fungal β-carbolines is expected to potentiate and prolong the bioactivity of psiloids. The fungal β-carbolines are expressed in higher concentrations in the mycelium (21 μg/g dry mass) than in the mushrooms (0.2 μg/g dry mass) or sclerotia (1.5 μg/g dry mass) if present (Blei et al., 2020). This means that if an animal consumes the mycelium, the higher concentration of β-carbolines may enhance the action of the psiloids despite their minute concentrations. Conversely, the minute quantities of β-carbolines in the mushroom may enhance the effect of psilocybin or cause other psiloids to become psychoactive.

The presence of serotonin in several species of the psiloid-producing genus *Panaeolus* raises the possibility of synergy between compounds that act on similar physiological systems (Gurevich, 1993; Stijve, 1992; Tyler, 1958; Wier and Tyler, 1963). Compared to other genera, *Panaeolus* only recently acquired the psilocybin gene cluster (Reynolds et al., 2018). One hypothesis is that serotonin itself can also, at least partially, perform a similar ecological role to psiloids. And while serotonin cannot cross the blood–brain barrier directly, it may be brought across via 5-HT transporters or act on peripheral serotonin receptors (Jonnakuty and Gragnoli, 2008). Indeed, plants utilize serotonin for anti-herbivory purposes (Chen et al., 2022; Ishihara et al., 2008). However, psiloids may be more effective than serotonin at this role, which may explain why other psiloid-producing fungi have not been found to produce serotonin.

3.5. Psilocin oligomers may have ecological functions

A recent hypothesis states that the primary ecologically active products of the psilocybin cluster may not be psilocin, but rather its oligomers. Psiloid-producing fungi turn blue when damaged, caused by a rapid conversion of phosphorylated psiloids into their hydroxylated counterparts, followed by oxidative coupling that forms blue oligomers (Fig. 1D) (Lenz et al., 2020). This transformation is enzymatically mediated by a phosphatase (PsiP) and a laccase (PsiL). The oligomers contain between three and thirteen subunits and are preferentially coupled at the 5 and 7 positions within their indole ring, with 7,7′-dimeric coupling contributing most to the blue coloration (Lenz et al., 2021a). This production of chromophoric oligomers appears to be a unique property of 4-substituted psiloids and does not naturally occur in other bioactive tryptamines, such as serotonin and bufotenine, despite their structural similarities (Gilmour and O'Brien, 1967; Lenz et al., 2021a), and may play a role in their organisms' ecology beyond its psychoactive properties.

Chromophoric oligomers may serve a defensive ecological function due to their similar polyphenolic and aryl-coupling properties to tannins, melanins, and oligomeric polypyrroloindolines (Jamison et al., 2017; Leopoldini et al., 2004a, 2004b). When ingested, these compounds generate reactive oxygen species, causing intestinal lesions in insects (Barbehenn and Peter Constabel, 2011; Salminen and Karonen, 2011). Additionally, gastropods also experience adverse health effects such as lethargy, shell reclusion, hemolymph release, growth disruption, detoxification inhibition, appetite reduction, and death when exposed to tannins and flavonoids (Noorshilawati et al., 2020; Silva et al. 2020; Singaba et al., 2006). Furthermore, tannins can cause disorientation, decrease egg-laying rates, and increase mortality in nematodes, likely through external cuticular damage and enzyme-inhibiting activities (Hoste et al., 2006; Maistrello et al., 2010). While some tannins have positive health effects in vertebrates, some can cause digestive, liver, and kidney pathologies (Mueller-Harvey, 2006). By analogy, psiloids may serve as inactive monomers that only become toxic when the mushroom is damaged by predators, functioning as an on-demand defense against fungivory (Lenz et al., 2020).

It is unlikely that the formation of tannin-like psilocin oligomers is the only mechanism involved in psilocybin ecology. Although most species of psilocybin-producing mushrooms bruise blue easily, indicating the catalyzed oligomerization reaction, some species require excessive mechanical tissue destruction for this to occur (Borovička et al., 2015; Gartz, 1986b). In these species, catalyzed oligomerization is likely insufficient for ecological activity. If the chromophoric oligomers were the sole active product, all psilocybin-producing species might be expected to bruise blue when macroscopically damaged. Furthermore, the genes responsible for the oligomerization reaction (i.e., PsiP, PsiL) are not found in the psilocybin gene cluster (Lenz et al., 2020), which suggests that psilocybin production and oligomerization are not inherited together during horizontal gene transfers. However, these genes are highly conserved in Agaricales, so they may be readily utilized for this function following the acquisition of psilocybin synthesis due to their nonspecific activity (Lenz et al., 2020). Collectively, both psiloid monomer neuroactivity and their oligomers' toxicity appear to be strong hypotheses.

3.6. Diversification of other neuroactive compounds alongside psilocybin suggests coevolution with animals

In some genera of psilocybin-producing mushrooms, alternative neuroactive compounds are present in species that do not produce psiloids. For example, many species in the genus *Inocybe* produce the parasympathetic nervous system toxin muscarine, while few species instead produce psilocybin (Kosentka et al., 2013). Muscarine mimics the neurotransmitter acetylcholine and binds to muscarinic acetylcholine receptors, in contrast to psilocybin's affinity for serotonin receptors. The production of muscarine is thought to be the ancestral state of these lineages, which was lost coincident with multiple convergent origins of psilocybin (Kosentka et al., 2013). Similarly, the genus *Gymnopilus* has many species that produce psilocybin and others that produce nicotinic acetylcholine receptor agonists called gymnopilins (Hatfield and Valdes, 1978; Kayano et al., 2014; Kusano et al., 1986). The production of gymnopilins is most likely the ancestral trait, with a later gain and loss of psilocybin (Caldas et al., 2022; Guzmán-Dávalos et al., 2003; Hatfield and Valdes, 1978). Although psilocybin and gymnopilins have not been recorded as appearing in the same specimen to date, more systematic studies are required to verify this condition. Furthermore, different entomopathogenic *Massospora* species produce either psilocybin or the amphetamine cathinone (*M. levispora/platypediae* and *M. cicadina*, respectively), with both species seemingly producing behavior-manipulating effects in their cicada hosts (Boyce et al., 2019). The possibility that psilocybin and other neuroactive compounds are interchangeable could suggest that they serve similar ecological functions but may be adapted to different predators or predator populations with more recently evolved toxin resistance.

3.7. Above- versus below-surface pressures may have driven differential psilocybin expression

The differing concentrations of psiloids in the mushroom, mycelium, and sclerotia of psilocybin-producing fungi may reflect the distinct

environmental selective pressures they face inside and outside the substrate. Mushrooms, which produce more psiloids than β-carbolines (67,500:1 psilocybin to harmane) (Blei et al., 2020; Gotvaldová et al., 2021), are generally exposed to larger predators (e.g., macro-insects, vertebrates) because they grow above ground. In contrast, the mycelium, which is harder to separate from its substrate, is more likely to be targeted by smaller predators (e.g., microarthropods and nematodes) and generally produce more β-carbolines (70:1 psilocybin to harmane) (Blei et al., 2020; Gotvaldová et al., 2021). Sclerotia are a potential target of digging animals and smaller animals living in the substrate, as their larger structure makes for a more substantial source of nutrients that can be more easily separated from the substrate. It is possible that the ratio of psiloids to β-carbolines reflects these dual environmental pressures (i.e., macro and micro predators), as concentrations measured in the sclerotia fall between those found in mushrooms and mycelium (1,750:1 psilocybin to harmane) (Blei et al., 2020; Gartz, 1995). Considering these patterns of expression, it can be speculated that psiloids are specialized for above-surface pressures (e.g., mediating interactions with larger animals), while β-carbolines are specialized for below-surface pressures (e.g., smaller substrate-dwelling and larger animals that dig).

4. Specific animal phyla may have provided initial selective pressures on psilocybin-producing fungi

Psiloids may act as neurotransmitter analogs and interfere with fungivorous and competitor animals. The emergence of lignified tissues approximately 380MYA (Floudas et al., 2012) created the new wood-decay niche that would be filled by many ancestral fungal lineages later known to produce psilocybin. Following this, psilocybin production is estimated to have horizontally dispersed and independently emerged alongside the expansion of grasslands and the emergence of dung-producing mammalian herbivorous megafauna 50-40MYA (MacFadden, 2000; Ramirez-Cruz et al., 2013; Retallack, 2001; Tóth et al., 2013), creating additional ecological niches to be filled such as grass and dung decay. Many diverse animals also inhabit these niches, but invertebrates likely exert stronger selective pressures on mushrooms in these niches than most vertebrates due to their greater numbers (Walton, 2018). Four taxonomic groups, Arthropoda, Gastropoda, Nematoda, and Primates, are compelling candidates as the drivers of selection for psilocybin production in fungi. These animal clades are commonly fungivorous or compete with fungi for resources, are in close physical contact with fungi in shared ecologies, and have overlapping evolutionary diversification times.

4.1. Arthropods and psilocybin producers cohabitate in ecological niches

Arthropods, especially insects, have the most substantial evidence of co-diversification alongside and likely in shared niches with psilocybin-producing fungi. Psilocybin-producing fungi commonly occupy late-stage dung- and wood-decay ecological niches, directly competing with mycophagous and wood/dung-eating insects (Reynolds et al., 2018). Indeed, terrestrial isopods have been observed feeding on wood-decaying *Ps. cyanescens* psilocybin-producing mushrooms (Gießler, 2018). Decay niches, like those occupied by psilocybin-producing fungi, are also highly competitive environments among fungi. The ability of fungi to tolerate damage from arthropods during the final stages of decay might confer a greater competitive advantage than direct fungus-fungus combative ability (A'Bear et al., 2013; A'Bear et al., 2013; Crowther et al., 2011, 2011; Jacobsen et al., 2015), providing yet another pressure for psilocybin-producing fungi to mediate interactions with insects.

The means by which psilocybin might have coevolved with arthropods is through the regulation of a wide range of serotonin-controlled physiological processes, including sleep, memory, vision, swarming, aggression, muscular contractions, heart rate, olfaction, mating, reproduction, appetite, and digestion (Anstey et al., 2009; Dacks et al., 2003; Dierick and Greenspan, 2007; Evans and Myers, 1986; French et al., 2014; Lee et al., 2001; Neckameyer, 2010; Python and Stocker, 2002; Sitaraman et al., 2012, 2008; Thamm et al., 2010; Yuan et al., 2006, 2005; Zornik et al., 1999). As a prime example, the entomopathogenic *M. levispora/platypediae* produces psilocybin, which is posited to contribute to the behavior manipulation of its host cicadas, increasing sexual behavior and increasing spore dispersal (Boyce et al., 2019). Additionally, *Drosophila* flies fed psilocybin (0.03 mM) for five consecutive days exhibited increased motor activity (Hibicke and Nichols, 2022). Furthermore, one documented instance showed a single dark-winged fungus gnat (*Sciaridae* sp.) larva completing development (i.e., egg to adult) inside a psiloid-producing mushroom (*Ps. cyanescens*) (Awan et al., 2018). While this shows that some insects can develop while consuming psilocybin-containing tissue, it is notable that only a single fly emerged in this experiment, considering that a single fly can lay dozens of eggs on a single mushroom (Erler et al., 2011, 2009). This may imply that there was some factor inhibiting larval development (e.g., psiloids) because most eggs complete development and emerge in the absence of toxins (or with coevolved tolerance to said toxins) (Erler et al., 2011, 2009; Scott Chialvo and Werner, 2018).

4.2. Gastropods are voracious fungivores

Terrestrial gastropods (i.e., snails and slugs) pose a threat to psilocybin-producing fungi due to their generalist feeding behavior on both mushrooms and hyphae (Barker and Efford, 2004; Butler, 1922; Elliott, 1922; Keller and Snell, 2002; White-Mclean and Capinera, 2014; Wolf and Wolf, 1939). Snails and slugs have been specifically observed grazing on psilocybin-producing *Ps. cyanescens*, preferentially feeding on the gills (Gießler, 2018). Additionally, fungivorous gastropods are well-established dispersal agents of fungal spores via excretion within their nutrient-rich feces (Kitabayashi et al., 2022), providing an incentive to manipulate their feeding and travel behaviors. Although terrestrial gastropods (order Stylommatophora) began to rapidly diversify starting around 110MYA (Fig. 2B), this diversification continued through the evolution of psilocybin-producing fungi (~40MYA) without plateauing (Ayyagari and Sreerama, 2020). Serotonin plays a crucial role in gastropods, regulating processes such as locomotion, olfactory perception, reproduction, and development (Audesirk et al., 1979; Croll, 2009; Croll et al., 1991; Muschamp and Fong, 2001, p. 2001; Pavlova, 2001; Roshchin and Balaban, 2012; Sugamori et al., 1993), providing a wide variety of targets for psilocybin to influence. Because terrestrial gastropods can be both antagonists and mutualists of mushroom-forming fungi, psilocybin may act both as a deterrent and as a beneficial behavior manipulator depending on the species interaction.

4.3. Nematodes are strong resource competitors and predators of psilocybin producers

Nematodes are potential drivers of fungal psilocybin production, as both nematodes and fungi are among the most prevalent eukaryotes in decay ecosystems and frequently interact antagonistically (Zhang et al., 2020). Nematodes (order Tylenchida) inhabit and consume mushrooms (Zhang et al., 2020) and are known to consume half of the fungal biomass in soil (Spiteller and Spiteller, 2008), presenting a strong selection on fungi for defense against these organisms. Additionally, numerous non-psilocybin-producing wood decay fungi generate compounds toxic to wood-dwelling nematodes (Futai, 2013; Lee et al., 2023; Pimenta et al., 2017), suggesting psilocybin may also have been selected to combat nematodes. A nematode's muscular system, carbohydrate metabolism, and adenylate cyclase regulation are all influenced by serotonin (Mansour, 1979), and nematodes are vulnerable to compounds that interfere with serotonin receptors (Levin and York, 1978; Mansour, 1979; Rodriguez et al., 1982). It is, therefore, plausible that nematodes may be a target of psilocybin. Many nematodes also inhabit dung- and

wood-decay niches, suggesting fungi may have evolved the ability to produce psilocybin as a way to combat fungivorous and resource-competitor nematodes.

4.4. Primate diversification coincided with psilocybin-producing mushroom diversification

The majority of psilocybin-producing mushrooms arose following the K/T extinction, which also marks the beginning of the age of mammals (Springer et al., 2019). Many mammals are known to browse on mushrooms and could have imposed predation pressure that favored psilocybin's diversification. For example, primates may be an early target of psilocybin due to the alignment of their diversification timeframes with psilocybin-producing fungi. Although there is conflicting evidence on the exact origin date of the primate clade (Heads, 2010), major studies agree that primates originated earlier than the diversification of most psilocybin-producing species (approximately 40MYA) (Janečka et al., 2007; Reynolds et al., 2018; Ruiz-Dueñas et al., 2021). Regardless of the exact origin date, extant lineages of primates began to rapidly increase in number, approximately 25MYA (Springer et al., 2012), in alignment with the diversification of psilocybin-producing species of fungi (Fig. 2B). Although the apes (superfamily Hominoidea) also originated around this time period (approximately 28MYA), humans were likely not a selective force for the initial evolution of fungal psilocybin production, as the genus *Homo* only evolved approximately 2.8MYA (Spoor et al., 2015).

Shared geographic ranges and ecologies between ancestral non-human primates and psilocybin-producing mushrooms also allow for the possibility of evolutionarily significant interactions. Extant primate species typically reside in tropical zones throughout the globe, though some species also occupy temperate and arid biomes (Reed and Fleagle, 1995). Psilocybin-producing mushrooms have a broad range, but the highest concentration and diversity also occur in the tropics (Guzmán et al., n.d.). Most primate diets are dominated by fruit and insects (Hohmann, 2009; Redford et al., 1984), but fungi are also consistently eaten by many species (Hanson et al., 2003; Sawada, 2014). Mycophagous primates typically consume the above-ground fruiting bodies, but some also seek out below-ground sclerotia. The ancestral ecology of psilocybin-producing fungi is hypothesized to be wood decay (Reynolds et al., 2018), and these niches are also heavily populated with wood-eating termites (Bignell et al., 2010). Specifically, termites are a staple of many primate diets (Adams et al., 2017; Davies and Baillie, 1988; De Moraes et al., 2014; Hamad et al., 2014; Julliot and Sabatier, 1993; Matsuda et al., 2009), and it is possible that while consuming termite-inhabited tree bark or termite fishing (Falotico, 2011; McGrew, 2014), these primates may have consumed the psilocybin-containing mushrooms fruiting from the same decaying wood. Such chance consumption could have instigated effects that deterred further feeding or altered primate behavior in a way that increased spore dispersal. Since primates have behaviors and even simple technologies that are transmitted socially, it could be speculated that they have periodically experienced creative advances that resulted in novel selective forces within their populations (Rodríguez Arce and Winkelman, 2021). However, any such creative effects on primates are not likely to have favored psilocybin-producing species until the sociocultural implementation by modern humans increased their dispersal through trade (Merino, 2022; de Teresa, 2022).

5. Psilocybin-mediated interactions with animals may entail a variety of mechanisms

5.1. Psilocybin may cause direct toxicity

Perhaps the most straightforward hypothesis for psilocybin's ecological role is as a form of direct toxicity upon ingestion by fungivorous species, as is the case for many fungal specialized compounds (Spiteller, 2008). In mouse models, relatively high doses (LD_{50} = 293 mg/kg) of psilocin have been fatal (Zhuk et al., 2015). Furthermore, at considerably lower doses (10 mg/kg), psilocin can cause oxidative DNA damage to the frontal cortex and hippocampus of rats (Wojtas et al., 2022). Additionally, extracts of psilocybin-producing fungi are highly lethal to the arthropod model, brine shrimp (*Artemia* spp.) (Meyer, 2017). While not extensively tested on invertebrates, the potential for psiloids to produce oxidative damage could be lethal, as other defensive specialized metabolites act via this mechanism (Choquer et al., 2007; Kensler et al., 2011; Wu et al., 2014). As discussed earlier, it is also possible that the psiloid oligomers may also be directly toxic to animals that have ingested them. They may generate reactive oxygen species when ingested, leading to deleterious effects that decrease fitness in a variety of phyla.

5.2. Psilocybin may modulate gut microbiomes with varied effects

Many plants produce compounds that downregulate the appetite of herbivorous insect species, resulting in reduced overall herbivory (Lev-Yadun and Mirsky, 2007; Saha et al., 2017). Psilocybin may also reduce feeding in fungivorous species, as 5-HT agonism has been demonstrated to be an appetite suppressant (Dacks et al., 2003; Falibene et al., 2012; French et al., 2014). The mechanism of action may be related to the ability of serotonin to regulate insect gut microbiome levels via *Duox* expression (Zeng et al., 2022), and gut microbiome levels can affect appetite (Fetissov, 2017). Furthermore, excess serotonin can increase mortality (Zeng et al., 2022), likely again related to microbiome dysbiosis (Raymann et al., 2017; Wei et al., 2017; Xu et al., 2019b).

5.3. Psilocybin may cause immune system depression and select against mushroom consumption

Psilocybin may also act as an indirect defense by impairing insects' immune systems, creating higher susceptibility to pathogen infection. In human microglia, psilocin downregulates pro-inflammatory factors (TLR4, p65, and CD80) and upregulates TREM2 (Kozłowska et al., 2021). These immunomodulatory factors are also crucial for defense against bacterial infections in *Drosophila* (Patrick et al., 2019; Tauszig et al., 2000), and the serotonin system influences insect immunity (Hasan et al., 2019; Milutinović and Schmitt, 2022). If psilocin's immunomodulatory effects also weaken insects' immune systems, they would become more susceptible to infections in the bacteria-rich decay niches psiloid-producing fungi often inhabit.

5.4. Social behavior may be disrupted by psilocybin ingestion

Because serotonin can modify social behaviors in insects, psilocybin disrupting prosocial behaviors among mycophagous eusocial species may be advantageous. The primary consumers of herbivore dung worldwide are termites (Khan et al., 2018), likely putting them in contact with coprophilous psilocybin-producing fungi. Like ants, termites function as a superorganism and rely on prosocial behaviors for ecological success (Nalepa, 2015). *Xylaria nigripes* is a fungus that colonizes abandoned termite nests and the termite gut (Fricke et al., 2023; Rogers et al., 2005; Sreerama and Veerabhadrappa, 1993). *X. nigripes* also produces ergot alkaloids under specific conditions (Hu and Li, 2017), posing the possibility that the serotonergic compounds may disrupt colony cooperation. For example, LSD has been shown to produce asocial behaviors within ants, such as decreased group formation, food sharing, and nest return rates of foragers (Frischknecht and Waser, 1980). Consequently, the available food for the colony decreases, and nursing ants are recruited as foragers, restricting the colony's growth. By analogy, psilocybin may affect similar behaviors in termites, selecting for avoidant behavior toward psiloid-producing fungi.

5.5. Psilocybin may promote dispersal through animal behavior manipulation

A complementary hypothesis to defense is that psilocybin facilitates interactions with animal vectors. Mycophagous animals evolve to overcome the chemical defenses of different fungal genera, altering the composition of animal communities (Yamashita and Hijii, 2013). Fungal toxins may create an environment suitable for animals that are less harmful to the host fungus than non-adapted insects, or the compounds may facilitate mutualistic relationships where the animals disperse the spores of the mushroom (Tuno et al., 2010). For example, fruit flies travel more after ingesting psilocybin (Hibicke and Nichols, 2022), which in a naturalistic setting, could potentially facilitate further spore dispersal than flies having consumed fungal tissues without psilocybin. In fact, spores of some mushroom-forming Basidiomycota species see improved germination from passage through insect digestive tracts and, therefore, incentivize visitation (Kobayashi et al., 2017; Page et al., 2017; Tuno, 1998).

Alternatively, if animals can detect and avoid psilocybin, this may deter them from the mushroom flesh while guiding them to the non-psilocybin-containing spores (Gross, 2000), potentially helping to distribute the spores. This phenomenon is seen in gastropods, as some snails prefer the spore-containing lamellae of *Ps. cyanescens*, avoiding the psilocybin-containing pileus and stipe (Gießler, 2018).

Psilocybin's effects on behavior may also include making fungivores more visible to predators, potentially increasing the likelihood of their predation. For example, other psiloid-like serotonergic agents can induce writhing and undulation behavior in gastropods, which may attract their predators (Abramson and Jarvik, 1955; Aguiar and Wink, 2005; Sakharov and Salánki, 1982), in a manner similar to how other gastropod-manipulating organisms attract birds (Wesołowska and Wesołowski, 2014). Fungal tissues (e.g., mycelium, mushrooms, spores) are viable not only after passage through slug stomachs but also through the digestive tracts of toads that have consumed slugs containing fungal tissues (Vogilino, 1895). If the fungal tissues of psilocybin-producing fungi are also viable after secondary consumption by birds, the dispersal radius would be greatly enhanced through bird droppings.

Some psilocybin-producing fungi may also rely on vertebrates as their primary dispersal agents. The fact that some psilocybin-producing species have convergently evolved the secotioid morphology and retained their ability to produce psilocybin (Borovička et al., 2011) further suggests that psilocybin may not deter all animals, as secotioid mushrooms rely heavily on mammalian consumption for spore dispersal (Albee-Scott, 2007; Thiers, 1984). Because larger mammalian fungivores typically consume the whole mushroom (Elliott et al., 2022), they would likely ingest a neuroactive dose of psilocybin. However, the possible beneficial effects of psilocybin for the mushroom in terms of behavior manipulation in these scenarios remain to be seen.

6. Conclusions

Psilocybin may offer a small window into the vast array of neuroactive metabolites produced by fungi and plants in dynamic competitive environments. The specific evolutionary trajectories and unique properties of psilocybin production suggest the existence of yet-to-be-described ecological relationships between psilocybin-producing fungi and animals. Evidence of selection for psilocybin can be found in the genome of species that produce it, such as gene clustering, horizontal gene transfer, and convergent evolution of the psilocybin biosynthetic pathway. Specific animals that prey on and compete with psilocybin-producing fungi likely exert pressures that are partially mitigated by psilocybin. Existing evidence suggests invertebrates are likely to have driven the emergence and dispersal of the psilocybin pathway, although it is possible that primates also played a role at more recent timescales. The alternate production of psilocybin and other neuroactive metabolites in fungi further suggests psilocybin is targeted to animals, and also that its benefits may be temporary and interchangeable with other neuroactive compounds in the ongoing animal-fungal chemical arms race. Psiloids' chemical properties give them a unique relationship with animal physiology, allowing them to avoid digestive degradation and access the central nervous system in ways other tryptamines cannot. Psilocybin has a particular affinity for serotonin receptors, but also dopamine and other receptor types, potentially having wide-ranging neuroactive effects across different animal phyla. Psiloids may also function through mechanisms beyond neuroactivity, including as precursors to complex chemical structures with potential anti-fungivory properties via digestive and nutritional interference. The fitness benefits of psilocybin to fungi may come in the form of reduced predation or improved spore dispersal, and different mechanisms may be at play in different circumstances. These questions will be addressed by direct experimentation that we expect will lead to novel insights into the genetics, chemistry, and ecology of fungal psychedelics.

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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