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The Action on Psilocybin in Neural Plasticity, Brain Reorganization and Cognitive Enhancement

Carlos Henrique Marchiori[1*], Marco Vinícios de Oliveira Santana[1], Klebert de Paula Malheiros[1]
[1]Professor and Researcher, Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil

Abstract: Psilocybin and psilocin do not cause addiction or dependence, as they do not interact with the dopaminergic reward system. New pharmacological treatment strategies for substance abuse disorders have targeted craving, which is characterized, in a simplified way, by an intense desire to use the substance. Psilocybin is an indole alkaloid of the hallucinogenic tryptamine group whose molecular structure resembles that of the neurotransmitter serotonin, which you may know as psilocin, especially in its dephosphorylated form. In Brazil, it is authorized by Anvisa through Ordinance 344 of 1998, provided that special authorization is obtained from the Health Surveillance Secretariat of the Ministry of Health. The manuscript aims to verify the Action of psilocybin in neural plasticity, brain reorganization, and cognitive enhancement. This paper is a narrative review of the literature, which is designed to explain and discuss a certain subject from a theoretical or contextual perspective, to allow the reader to acquire or update knowledge on a specific topic. The search for scientific articles that comprised this review was carried out in Academic.edu, Biological Abstract, Google Scholar, HAL, Qeios, ResearchGate, Scielo, and SSRN. The inclusion criteria were original articles and reviews, published nationally and internationally in full, available electronically, and published in Portuguese, English, and Spanish. There is also a growing popularity of psilocybin and other psychedelics for health purposes. Mushrooms can be important for improving various conditions and symptoms of disorders. People report that this type of mushroom specifically works against fatigue, discouragement, depression, anxiety, and cognition, and helps to deal with withdrawal symptoms from some addiction. Increased concentration can be observed, with improved brain activity.

Keywords: Brain, Fungi, Psychedelics, Therapeutics, Treatment.

REVIEW PAPER

***Corresponding Author:**
Carlos Henrique Marchiori
Professor and Researcher, Department of Biology and Medicine do Instituto Marco Santana, Goiânia, Goiás, Brazil

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1. INTRODUCTION

1.1. Fungi with Emphasis on Mushrooms ("Magic Mushrooms")

Fungi are eukaryotic organisms with individualized cells that are heterotrophic and cannot produce their food. The cells of these living beings are distinguished by the presence of a chitin cell wall and the absence of photosynthetic pigments and plastids. Their main reserve substance is glycogen. About the body structure, the most common forms are isolated cells and multicellular filaments. The body of multicellular fungi is made up of a network of thin filaments known as hyphae (Figure 1) (Shoji, 2006; Davison *et al.*, 2015; Dunthorn *et al.*, 2017; MundoEcologia, 2019: Naranjo-Ortiz and Gabald´on, 2019; Santos, 2024).

Fungi are essential organisms for the balance of the ecosystem. These living beings act as primary decomposers of organic matter, ensuring the recycling of nutrients and also the cleaning of the environment. By promoting the recycling of nutrients, fungi, together with bacteria, allow nutrients to be used by other living beings, ensuring the maintenance and balance of the ecosystem. We cannot fail to mention, however, that although fungi are very important for carrying out decomposition, this same process can cause harm to human beings. This is because fungi can, for example, cause damage to food and wood (Shoji, 2006; Davison *et al.*, 2015; Dunthorn *et al.*, 2017; MundoEcologia, 2019; Naranjo-Ortiz and Gabald´on, 2019; Santos, 2024).

In addition to decomposition, fungi can interact with other living beings in ecosystems, establishing important ecological relationships. One of these relationships occurs between fungi and plant roots, forming the so-called mycorrhizae. Lichens are also ecological relationships established between fungi and algae or fungi and cyanobacteria. Fungi also stands out

for being very important economically, as it is used in the manufacture of different foods. Fungi, because they carry out fermentation, are used in baking. They are also used in the production of wine, beer, and cheese. Some fungi can also be consumed without any processing, such as mushrooms (Figure 1-2) (Shoji, 2006; Davison *et al.*, 2015; Dunthorn *et al.*, 2017; Naranjo-Ortiz and Gabald´on, 2019; Santos, 2024).

Figure 1: Diversity of fungal species
Source: https://www.rciscience.ca/blog/fantastic-fungi

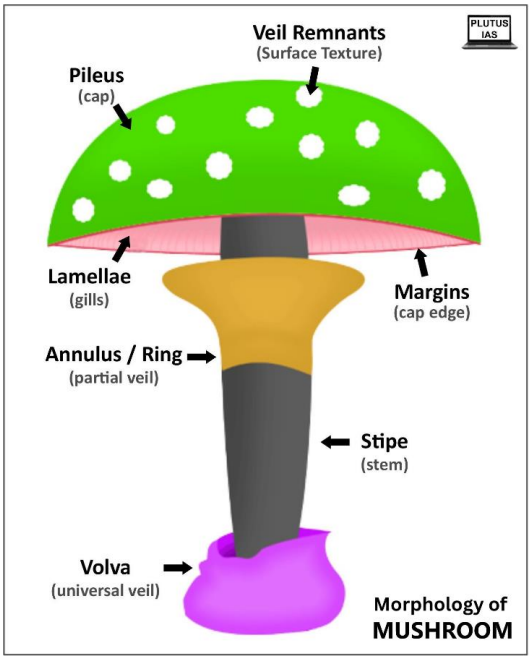

Figure 2: The standard mushroom morphology includes a stem (stipe), a cap (pileus), and gills (lamellae) on the underside of the cap. These gills produce microscopic spores, aiding the fungus's spread across the ground or surrounding surface
Source: https://plutusias.com/mushrooms/

Fungi can also be used as raw material for the production of medicines. Among the medications produced with fungi, we can mention penicillin, an important antibiotic, and cyclosporine, which is used in transplant patients to suppress the immune system. Fungi can be responsible for causing diseases in other living beings, including plants, humans, and other animals. In the case of humans, we can highlight diseases such as candidiasis, aspergillosis, fungal meningitis, rhinosinusitis, onychomycosis, and others. Diseases caused by fungi are known as mycoses (Figure 3) (Shoji, 2006; Davison *et al.*, 2015; Dunthorn *et al.*, 2017; MundoEcologia, 2019; Naranjo-Ortiz and Gabald´on, 2019; Santos, 2024).

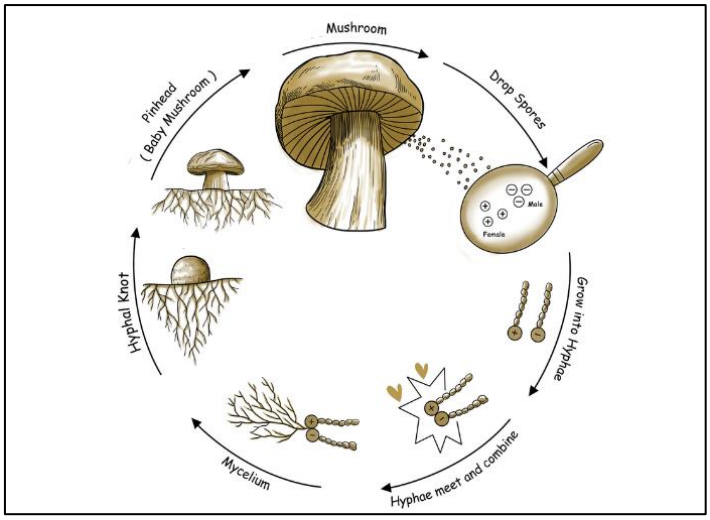

Figure 3: The mushroom life cycle is truly fascinating! Whether observing the growth of small mushrooms, which can sprout in just a day or marveling at the development of larger mushrooms over 3 to 4 days, something is mesmerizing about watching these fungi (mushrooms) thrive. But for mushrooms to reach their full potential, the environment must be conducive to their growth. Steady moisture is key for the mushroom life cycle to unfold
Source: https://forestorigins.com/blogs/blog/the-mushroom-life-cycle

Four majorphyla were defined within the true fungi, based on their morphological and reproductive traits: Chytridiomycota, Zygomycota, Ascomycota, and Basidiomycota. Later, molecular phylogenies proved the paraphyly of Zygomycota and Chytridiomycota. The Chytridiomycota division has representatives with cells that have flagella in at least one stage of the life cycle. The Zygomycota division presents, in most of its representatives, coenocytic hyphae. The Ascomycota division is the largest group of fungi, has septate hyphae and forms a structure called ascus where spores are formed. The Basidiomycota division represents the majority of macroscopic fungi such as mushrooms and stands out for the production of basidium, a spore-producing structure, in addition to having septate hyphae (Shoji, 2006; Davison *et al.*, 2015; Dunthorn *et al.*, 2017; MundoEcologia, 2019; Naranjo-Ortiz and Gabald´on, 2019; Santos, 2024).

Psilocybe Kummer., (Agaricaceae) is a genus of psychedelic mushrooms that is found worldwide. These are just a few of the species in the *Psilocybe*, and they are the best known of the approximately 378 species that are distributed worldwide (Schoch *et al.,* 2020). Some species: *Psilocybe azurescens* is a highly potent species native to the U.S.A. states of Washington and Oregon. *Psilocybe cyanescens* Wakef, 1946, native to the Pacific, Northwest of North America, but also found in western Europe. The species *Psilocybe mexicana* Heim, 1957 commonly grows in flooded lands in the region of Mexico. *Psilocybe natalensis* Gartz *et al.,* 1995, is found in South Africa. *Psilocybe semilanceata* (Fr.) Kum (1871), found in northern temperate climates. *Psilocybe silvatica* (Peck) Singer & A.H. Sm., 1958, was discovered in the northeastern region of the United States and is also present in the northwestern region bathed by the Pacific Ocean (Bresinsky and Besl, 1989; Alexopoulos *et al.*, 1996; Gandy, 2024).

Psilocybe cubensis (Berk & Broome) Singer, 1951, is a species of entheogenic mushroom, known worldwide as magic mushroom or sacred mushroom, whose main active ingredients are psilocybin and psilocin, which act on the brain in a similar way to the neurotransmitter serotonin. However, it contains other alkaloids in small quantities, such as norbeocystine or beocystine, whose action on the human nervous system is little known. They are small mushrooms, usually with characteristics that make them easily recognizable (Figure 4) (Stephen *et al.*, 2003; Pollan, 2018a; FDA, 2019). In Brazil, in addition to mushrooms of the genus *Psilocybe*, species belonging to other genera such as *Panaeolus* (Fr.) Quél, 1872, *Pholiotina* Fayod, 1889, and *Pluteus* Fr. 1836 can also be found (Memed, 2023).

Figure 4: *Psilocybe cubensis* (Berk. & Broome) Singer, 1951 (Basidiomycota: Strophariaceae)
Source:
https://pt.wikipedia.org/wiki/Psilocybe_cubensis

Psilocybin is an indole alkaloid of the hallucinogenic tryptamine group whose molecular structure resembles that of the neurotransmitter serotonin, which you may know as psilocin, especially in its dephosphorylated form. In Brazil, it is authorized by Anvisa through Ordinance 344 of 1998, provided that special authorization is obtained from the Health Surveillance Secretariat of the Ministry of Health (Figure 5) (Carhart-Harris *et al.*, 2012; Stahl, 2017; Geiger *et al.*, 2018, Memed, 2023).

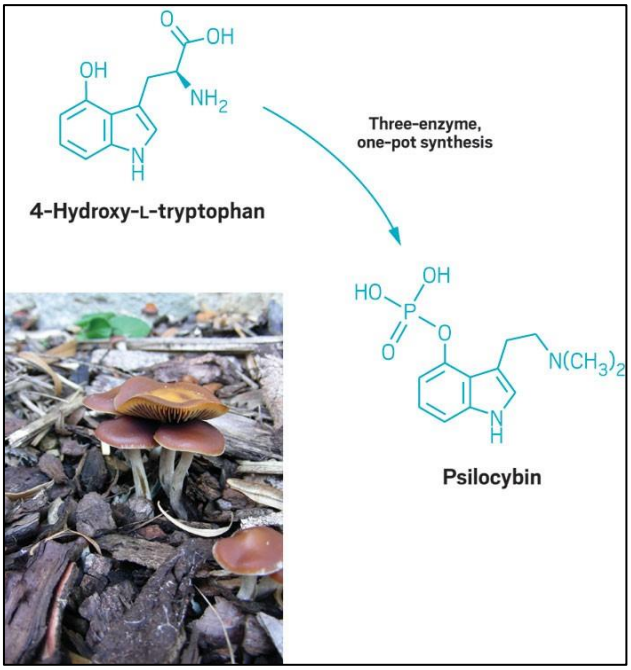

Figure 5: Researchers deciphered the biosynthetic route in genus *Psilocybe* "magic mushrooms" shown that makes the psychoactive natural product psilocybin and then used the key enzymes in a one-pot enzymatic synthesis starting from 4-hydroxy-L-tryptophan
Source: Dirk Hoffmeister (mushrooms)

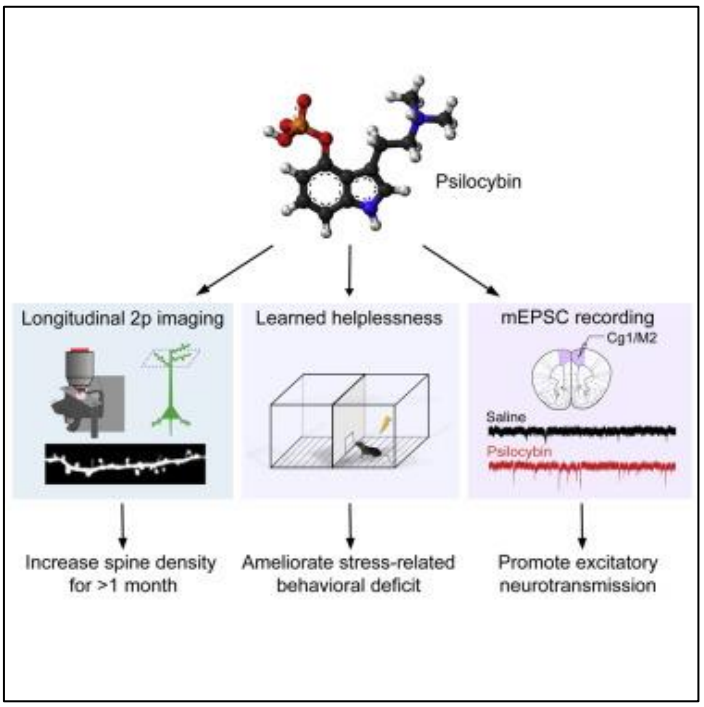

Figure 6: 1. Psilocybin improves stress-related behavioral deficits in mice. 2. Psilocybin increases spine density and size in the frontal cortical pyramidal cells. 3. Psilocybin-evoked structural remodeling is persistent for at least 1 month. 4. The dendritic rewiring is accompanied by elevated excitatory neurotransmission
Source: Doi: org/10.1016/j.neuron.2021.06.008

The clinical application of this psilocybin is quite common in the treatment of psychiatric disorders and disorders related to personality, mood, schizophrenia, anxiety, chronic migraine, depression and Obsessive Compulsive Disorder (OCD) can also obtain improvements in the clinical picture with the use of psilocybin (Memed, 2023). Some characteristics related to the user can determine the effects that will be observed when using this substance. Therefore, mentally unstable or anxious patients tend to experience the impacts considered bad. Among the most reported general effects are: Visual changes, especially in colors; Confusion and derealization; Feelings of joy (euphoria); Tranquility; Synesthesia; Dizziness and drowsiness; Dilation of the pupils (mydriasis); Gastrointestinal changes (nausea and vomiting) (Carhart-Harris *et al.*, 2012; Stahl, 2017; Geiger *et al.*, 2018; Pollan, 2018b; Aday *et al.*, 2019; Dupui, 2022).

Psilocybin is an agonist at 5-HT2A (5-hydroxytryptamine receptor 2A receptors), but it also has an affinity for other types of 5-HT receptors (5-hidroxitriptamina). Psilocybin is structurally very similar to serotonin, so it is not surprising that psilocybin binds with high affinity to 5-HT receptors and that the neuropharmacological action of psilocybin is dependent on the distribution of 5-HT receptors in different cell types (Figures 7-8) (Carhart-Harris *et al.*, 2012; Stahl, 2017; Geiger *et al.*, 2018; Aday *et al.*, 2019; Zieba *et al.*, 2022).

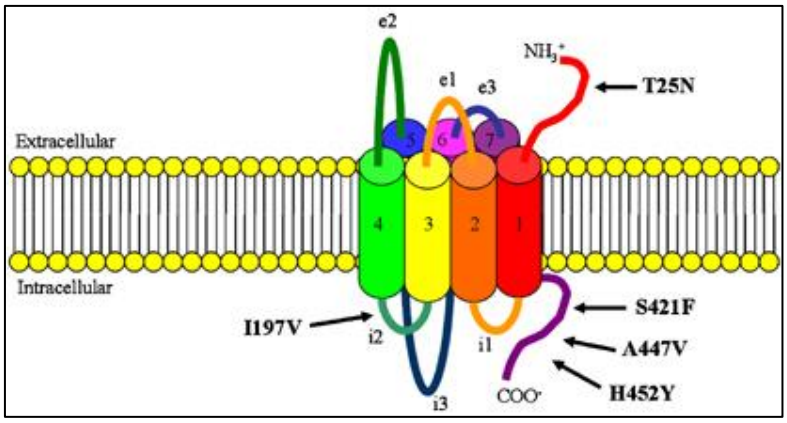

Figure 7: Schematic representation of the 5-HT2A receptor showing the location of the five SNPs relative to the helices (numbered 1–7), loops (e1–3, i1–3), and tails (NH3+ and COO-)

Source: https://www.researchgate.net/figure/Schematic-representation-of-the-5-HT2A-receptor-showing-the-location-of-the-five-SNPs_fig3_7453889

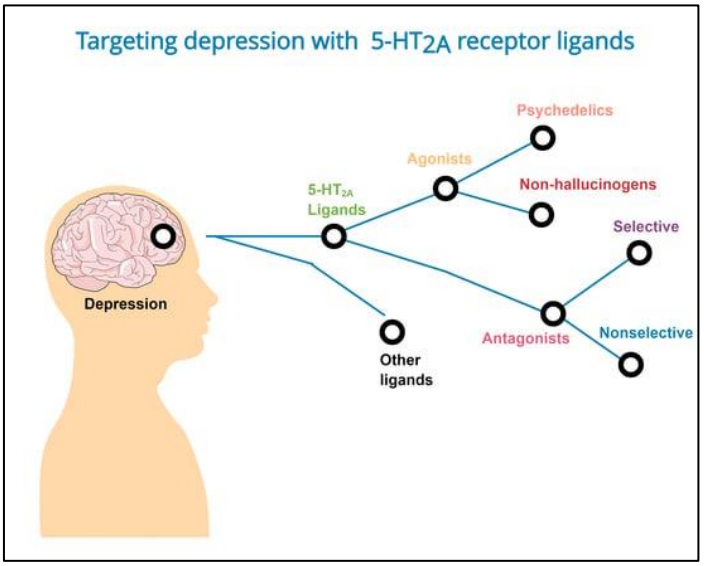

Figure 8: Depression is a multifactorial disorder that affects millions of people worldwide, and none of the currently available therapeutics can completely cure it. Thus, there is a need for developing novel, potent, and safer agents. Recent medicinal chemistry findings on the structure and function of the serotonin 2A (5-HT2A) receptor facilitated the design and discovery of novel compounds with antidepressant action. Eligible papers highlighting the importance of 5-HT2A receptors in the pathomechanism of the disorder were identified in the content screening performed on the popular databases

Source: Doi.org/10.3390/ijms23010010

In terms of classification, psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine), and psilocin in its dephosphorylated form (4-hydroxy-N, N-dimethyltryptamine) (4-OH-DMT). Fall into the group of classic hallucinogens, also known as serotonergics. According to this classification, there is also the group of dissociative hallucinogens, ketamine, and the delirious atropines. The group of serotonergic hallucinogens is divided into subgroups: The indoleamine class, which includes psilocybin and psilocin, and other substances such as dimethyltryptamine (DMT) found in ayahuasca, semisynthetic ergolines or lysergamides (LSD) and iboga alkaloids (ibogaine), and the phenylalkylamine class, which includes mescaline (Figure 9) (Carhart-Harris *et al.*, 2012; Geiger *et al.*, 2018; Aday *et al.*, 2019; Shao *et al*., 2021; Reichert *et al.*, 2022; Reis, 2024).

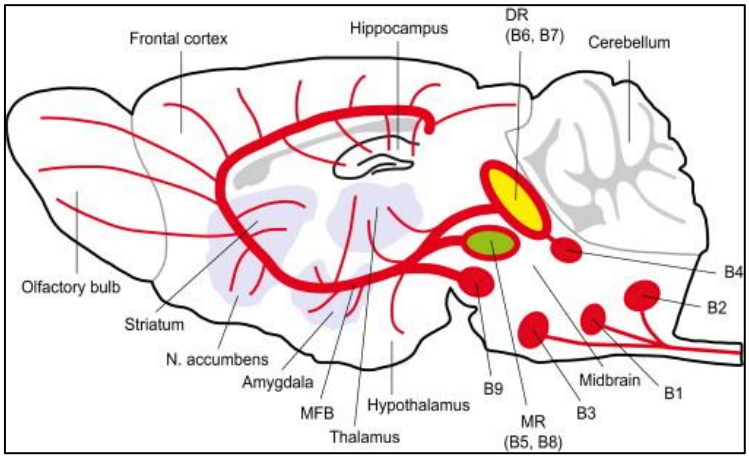

Figure 9: Schematic drawing depicting the serotonergic pathways in the brain. Psilocybin falls into the group of classic hallucinogens, also known as serotonergic. It has been reported that over 90% of 5-HT in the whole body is synthesized in the gastrointestinal tract. However, 5-HT cannot permeate the blood-brain barrier, it has to be synthesized in the brain. In humans as well as most animal species, the initial step in the synthesis of 5-HT is the facilitated transport of the amino acid l-tryptophan from blood into the brain. As the precursor to 5-HT, tryptophan is then transformed into 5-HT mainly by tryptophan hydroxylase (TPH) in the brain. Although 5-HT is synthesized in a limited number of neurons in the CNS nuclei B1 to B9 in the brainstem, its action is widespread in all the CNS

Source: https://www.creative-diagnostics.com/serotonergic-synapse-pathway.htm

Being a prodrug, when ingested by humans, psilocybin is dephosphorylated by hepatic metabolism into psilocin, the actual psychotropic active principle, and significant amounts of psilocybin can be found in blood plasma between 20 and 40 minutes after consumption, on an empty stomach (Figure 6) (Stahl, 2017; Aday *et al.*, 2019; Gomes-Medeiros *et al.*, 2019; Shao *et al.*, 2021; Coelho, 2024).

Psilocybin, when ingested and absorbed by the intestine psilocin acts on brain receptors, inducing psychedelic effects. It activates serotonin receptors mainly in the prefrontal cortex. This part of the brain affects mood, cognition, and perception. Thus, psilocybin can distort the way some people who ingest it perceive objects and people. Psilocybin is a prodrug that is subject to dephosphorylation by alkaline phosphatase in the liver and intestine, producing psilocin, which is responsible for the psychedelic effects (Barrett *et al.*, 2017; Geiger *et al.*, 2018; Aday *et al.*, 2019).

Psilocybin and psilocin do not cause addiction or dependence, as they do not interact with the dopaminergic reward system. New pharmacological treatment strategies for substance abuse disorders have targeted craving, which is characterized, in a simplified way, by an intense desire to use the substance. The group of hallucinogenic psychedelics, such as psilocin can have an anti-craving effect and has been shown to have the ability to alleviate symptoms of alcohol, tobacco, and crack in the treatment of drug addiction. Psilocin can generate a certain tolerance, and there is also cross-tolerance between LSD and psilocin (Chapman *et al.*, 1972; Bogenschutz, 2013; Bogenschutz, 2017; Geiger *et al.*, 2018; Aday *et al.*, 2019; Oliveira and Nunes, 2021).

In turn, psilocin is subject to phase I reactions such as demethylation and oxidation, by MAO or aldehyde dehydrogenase, to an intermediate metabolite that subsequently undergoes oxidation or reduction. Phase II reactions correspond to glucuronidation by the action of UGT1A10 in the small intestine and UGT1A9 in the liver. Psilocybin has a half-life of 160 minutes while psilocin has a half-life of 50 minutes. Psilocybin is eliminated mainly in the urine, 65% in the form of glucuronide metabolite. After an average of 20 to 30 minutes after ingestion, its effects begin to appear, which may include hallucinations, visual and auditory distortions, tactile perceptions such as tingling or heat, and synesthesia (Figure 10) (Barrett *et al.*, 2017; Geiger *et al.*, 2018; Aday *et al.*, 2019; Jann and PharmD, 2021).

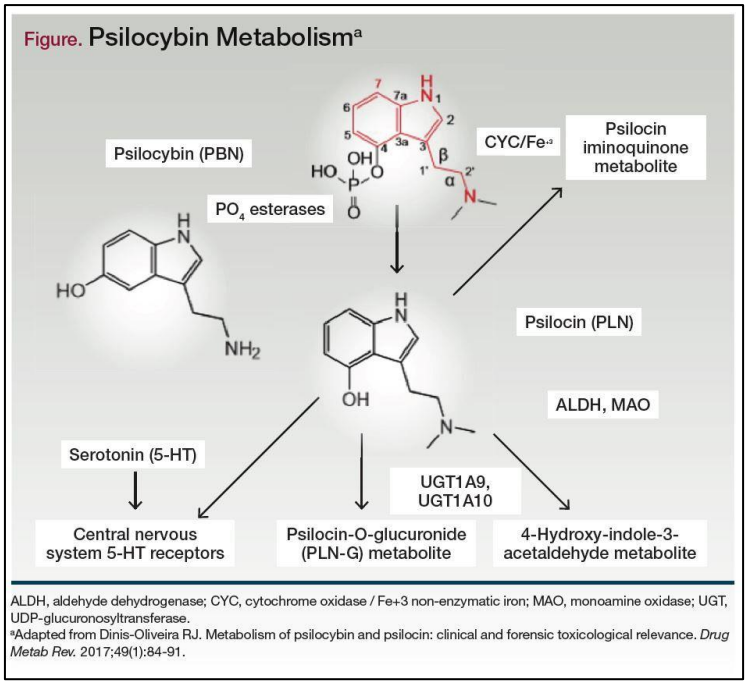

Figure 10: Psilocybin metabolism

Source: https://www.psychiatrictimes.com/view/psilocybin-revisited-science-behind-drug-surprising-therapeutic-potential

More notable than the growth in the number of publications are some results of studies on the medicinal applications of substances such as psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and lysergic acid diethylamide (LSD). The effectiveness of psychedelic therapies for psychiatric disorders such as depression and severe trauma has been shown, in many cases, to be superior to that of currently adopted methods and drugs. With additional advantages, for psychedelics, faster symptom relief and chemical treatment limited to a few doses administered during treatment protocols lasting between a few weeks and a few months (Figure 11) (Carhart-Harris *et al.*, 2012; Almeida, 2017; Caetano, 2018; Schenberg, 2018; Aday *et al.*, 2019; Kuyperset *et al.*, 2019; Zeiss *et al.*, 2021; Dupui, 2022).

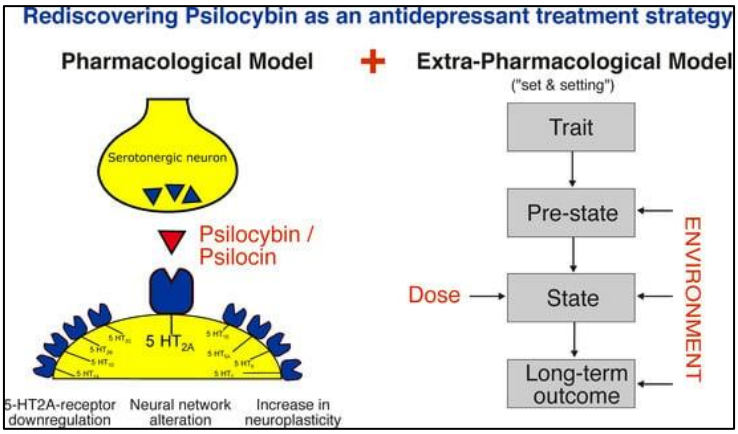

Figure 11: Mechanisms of action of psilocybin: A pharmacological and extra-pharmacological model. Extra-pharmacological model reprinted from ref. Psilocybin is an effective psychedelic therapy for psychiatric disorders such as depression (ref. 10.1177/0269881119857204)

Source: Doi: 10.1177/0269881119857204)

Along with a more realistic assessment of risks, advances in research have shown promising results in the use of these substances to address highly prevalent disorders that have a major impact on individuals, communities, and societies, such as depression, anxiety, persistent trauma, alcoholism, smoking and other forms of chemical dependency, addiction, and compulsive behavior. These are conditions for which the pharmacological and therapeutic responses prescribed and adopted today have proven to be largely insufficient or even inadequate (Bogenschutz, 2013; Bogenschutz *et*

al., 2015; Barrett *et al.*, 2017; Bogenschutz, 2017; Schenberg, 2018; Aday *et al.*, 2019).

In a generic and simplified summary, we can say that the therapeutic potential of psychedelics derives from their ability to generate neural, emotional, and cognitive states and processes that allow patients to change stagnant patterns of processing ideas and memories, perceptions, beliefs, and imprisoning and painful narratives about themselves and life. When successful, this mental and emotional renewal is associated with the flexibility of rigid behaviors, providing profound and lasting changes (Bogenschutz, 2013; Bogenschutz *et al.*, 2015; Barrett *et al.*, 2017; Bogenschutz, 2017; Schenberg, 2018).

1.2. OBJECTIVE

The manuscript aims to verify the action of psilocybin in neural plasticity, brain reorganization, cognitive enhancement, and other psychedelics.

2.0. METHODS

This paper is a narrative review of the literature, which is designed to explain and discuss a certain subject from a theoretical or contextual perspective, to allow the reader to acquire or update knowledge on a specific topic. The search for scientific articles that comprised this review was carried out in Google Scholar, Biological Abstract, HAL, Qeios, ResearchGate, Scielo, and SSRN. The inclusion criteria were original articles and reviews, published nationally and internationally in full, available electronically, and published in Portuguese, English, and Spanish.

3. STUDIES PERFORMED

Although psychedelics continue to be used for a variety of purposes, the consumption of psychedelic substances in sub-hallucinogenic doses microdosing, that is, doses that are not capable of causing hallucinations or perceptual distortions, has become popular in the treatment of psychiatric disorders and to improve cognitive functions. Even though the use of microdosing is not yet officially recognized as a treatment, it is possible to find a schedule for the practice on online platforms, obtain it through recommendations from acquaintances, or even be defined by the individual himself (Carhart-Harris *et al.*, 2012; Barrett *et al.*, 2017; Stahl, 2017; Geiger *et al.*, 2018; Dupui, 2022).

Microdosing involves taking approximately one-tenth to one-twentieth of the regular/recreational dose (5) orally on a specific and intermittent schedule (6). However, due to the scarcity of studies to date, the use of microdosing for therapeutic purposes does not yet have an adjusted dosage. Since some reports show that microdosing has an effect for two days, most schedules are based on a cycle: microdosing one day and stopping the use of the substance on the following two days. Typically, the cycles are repeated for a month or more. Among the various substances that can be consumed, LSD and psilocybin stand out (Figure 12) (Barrett *et al.*, 2017; Stahl, 2017; Psychedelic-Assisted Psychotherapy, 2024).

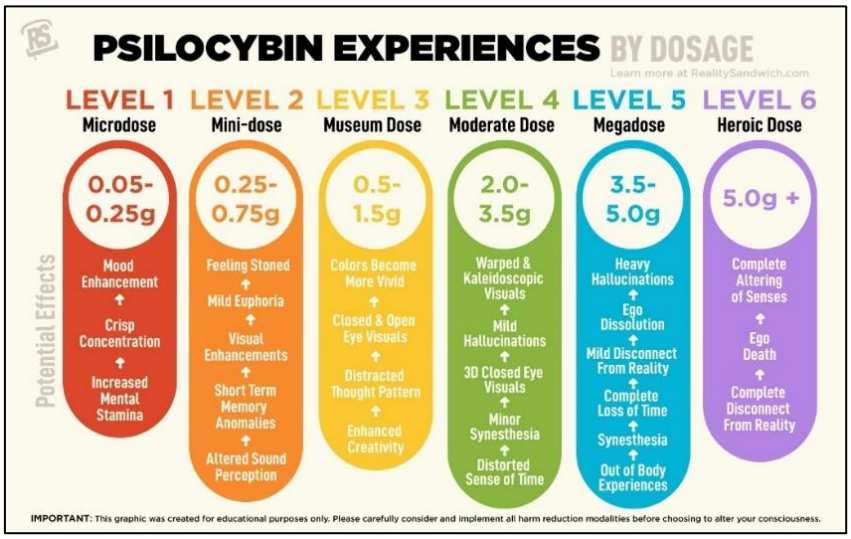

Figure 12: The psychedelic community has developed a way to communicate the effects of psilocybin at different doses using a 5-tier system: Level 1 refers to a mild dose that is just above the threshold. It involves a mild "stoned" effect (noticeable psychoactive effect), visual enhancements, short-term memory abnormalities, and an altered perception of music that makes it sound larger. Level 2 involves bright colors, soft visuals with eyes closed and open, a distracted thought pattern, and enhanced creativity. Level 3 includes visuals with distorted kaleidoscope-like patterns, mild hallucinations, three-dimensional visuals with eyes closed, minor synesthesia, and a distorted sense of time. Level 4 includes effects such as severe hallucinations, split ego, mild loss of reality, complete loss of time, synesthesia, and out-of-body experiences. Level 5 involves a heavy dose that will cause effects such as complete loss of regular senses, complete loss of ego, and complete loss of reality. At this level, a common description is that the universe ceases to exist for a person, making it difficult to put into words

Source: From https://psicodelix.com/microdose-de-cogumelos-magicos/

For recreational use, psilocybin consumes 4 to 8 g of the substance to produce the hallucinogenic effect, with the intensity being dose-dependent. That is, using approximately 4 g results in mild effects such as relaxation and some bodily sensations, while higher doses cause changes in perception. In microdosing, doses ranging from 0.1 to 0.4 g are used (Reiner *et al.*, 2017; Yanakieva *et al.*, 2018; Fadiman and Korb, 2019; Hutten *et al.*, 2019; Mohamed, 2014). Motivation for microdosing ranges from personal development; improved mental health, psychological well-being, and mood; increased cognitive performance, and reduced symptoms of anxiety and depression to treatment of post-traumatic stress disorder and attention deficit hyperactivity disorder (Barrett *et al.*, 2017; Geiger *et al.*, 2018; Lea *et al*., 2020; Reichert *et al.*, 2022).

Common doses from clinical research: The journal Mental Health Clinic conducted a meta-analysis of all psilocybin studies from 1999 to 2008. This meta-analysis found that clinical doses ranged from 25 micrograms per kilogram to 420 micrograms per kilogram. For an average adult weighing 70 kilograms, or about 150 pounds, this would be a dose between 1.75 milligrams to 29.4 milligrams. Considering an average amount of psilocybin contained in dried *P. cubensis* of 0.60%, this would be 0.3 grams to 4.9 grams of dried mushrooms (Psychedelic-Assisted Psychotherapy, 2024). Microdosing magic mushrooms every day is not recommended because psychedelics can build up a tolerance, even with microdosing, so you may see diminishing returns after a few days. Also, the fact that the benefits can still be felt in the following days is a good reason to space out your doses (Psychedelic-Assisted Psychotherapy, 2024).

A new study has shown that psilocybin, derived from mushrooms, works in the treatment of anorexia nervosa. According to the researchers, during the experiments the substance managed to improve the maintenance of body weight and facilitate cognitive flexibility in laboratory rats with the disease. The scientific journal published an article on "Molecular Psychiatry", a specific mechanism was discovered within the brain by which psilocybin acts to make “anorexic thinking” more flexible, paving the way for targeted therapies. “Cognitive inflexibility is a hallmark of the condition that usually emerges before symptoms of anorexia nervosa are obvious and persist after weight regain, making this symptom a prime target for therapeutic intervention” [Claire Foldi] (Figure 13) (Barrett *et al.*, 2017; Bogenschutz, 2017; Geiger *et al.*, 2018; Dupui, 2022; Zheng *et al.*, 2024).

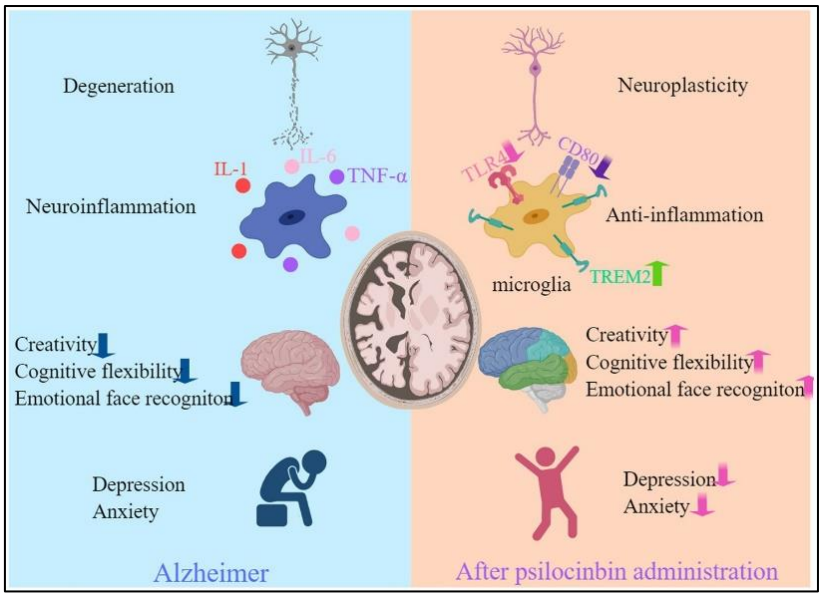

Figure 13: Psilocybin may potentially benefit individuals with AD. Psilocybin has shown benefits for AD in terms of enhancing neuroplasticity, reducing inflammation, neurocognitive improvement, and alleviating anxiety and depression

Sources: Created with MedPeer (www.medpeer.cn) and Doi: 10.3389/fnins.2024.1420601

The study looked at the effect of psilocybin on the 5HT2A molecule, a specific “receptor” that neurons use to process the neurotransmitter serotonin. Using genetically modified animals, she showed that this protein is a pathway for psilocybin to act in treating addiction. In the study, the animals also showed clinical signs of improvement. “Psilocybin reversed the bodily signs of nicotine withdrawal in mice. Our study suggests that classic psychedelics like psilocybin may be an effective treatment for smoking cessation” [Belle Buzzi, da Universidade Commonwealth da Virgínia EUA] (Carhart-Harris *et al.*, 2012; Stahl, 2017; Geiger *et al.*, 2018; Coelho, 2024; Queiroz, 2024). "Xavier highlights that the proof of 5HT2A as a serotonin receptor affected by psilocybin opens up a different action potential than that of another receptor, 5HT1A, targeted by

conventional antidepressants" [Psychiatrist Dartiu Xavier, Federal University of São Paulo (Unifesp)] (Queiroz, 2024).

Recently, modern science has begun to unravel the mechanisms by which psilocybin acts on our brains. When ingested, psilocybin is converted to psilocin, which interacts with serotonin (5-HT2A) receptors in the brain. This interaction causes changes in perception, mood, and cognition, facilitating deep introspection and greater openness to new ideas (Bogenschutz, 2017; Geiger *et al.,* 2018; Aday *et al.,* 2019).

"It has been shown that LSD has a unique binding pattern inside the receptor, which forms a kind of 'lid' that traps it inside thus, it remains bound to the receptor for many hours, something extremely unusual in the interactions between drugs and receptors in the central nervous system", he states. "On a systemic scale", continues the researcher, "we observed that LSD, like psilocybin, temporarily desynchronizes the cerebral cortex and, in doing so, allows areas of the brain that normally operate separately as if they were radio stations transmitting at different frequencies to start communicating. This allows for greater cognitive, emotional and behavioral fluidity, and is related to several of the therapeutic benefits" [Schenberg, who is a founding member of the International Society for Psychedelic Research] (Figure 14) (Carhart-Harris *et al.,* 2012; Geiger *et al.,* 2018; Dupui, 2022; Chaphalkar, 2024).

In a study of 7 healthy volunteers, each participant had their brain scanned an average of 18 times. Healthy adults were tracked before, during, and for 3 weeks after high-dose psilocybin (25 mg) and methylphenidate (40 mg) and brought back for an additional psilocybin dose 6–12 months later. The scans using functional magnetic resonance imaging (fMRI), which measures changes in blood flow in the brain, revealed that connections within established brain networks were disrupted, while communication between networks increased. The unpredictability of normal information processing in the brain was found to be increased by psilocybin [researchers at Washington University School of Medicine in St. Louis] (Siegel *et al*., 2024; van Elk, 2024).

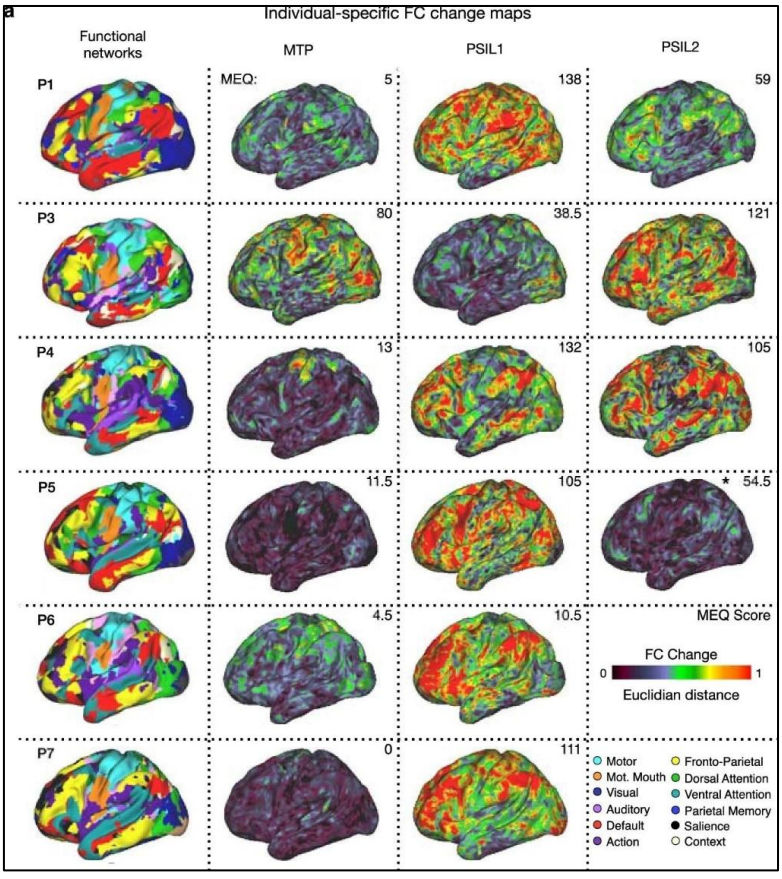

Figure 14: Individual participant methylphenidate (MTP) and psilocybin (PSIL) FC change maps. The Most column shows individuals' functional networks. The right 3 columns show FC change maps, generated by calculating Euclidean distance from baseline seed maps for each vertex. For each session, the total score on the Mystical Experience Questionnaire (MEQ30: out of a maximum of 150) is given in the upper right corner. P5 had an episode of emesis 30 minutes after drug ingestion during PSIL2. Study: Psilocybin desynchronizes the human brain

Source: from https://www.news-medical.net/news/20240718/Psilocybin-reconfigures-brain-networks-showing-potential-for-lasting-therapeutic-effects.aspx

Cognitive enhancement (CE) is a recent topic in the field of neuroethics, which studies the ethics of neuroscience and the neuroscience of ethics. The definition of CE is not fully established, and it is not clear whether enhancement and treatment can be distinguished. CE corresponds to the extension or amplification of basic cognitive capacities through the improvement of information processing systems by mechanisms internal or external to the individual. Considering the aforementioned definitions, CE can be assumed to be the use of drugs by healthy individuals to increase certain cognitive capacities without there being a medical need (Nutt *et al.,* 2010; Glannon, 2011; Figlie *et al.,* 2015; Hartogsohn, 2017; Stahl, 2017; Lobo, 2021; Dupui, 2022).

Amphetamine-dextroamphetamine increases dopamine release and is also used in Attention Deficit Hyperactivity Disorder (ADHD). Modafinil, on the other hand, is used in the treatment of narcolepsy and sleep disorders and is a drug with multiple mechanisms of action, galantamine, donepezil, galantamine rivastigmine, and β-blockers. All of these drugs, due to their use as potential cognition enhancers in healthy individuals, can also be referred to as nootropics (Carhart-Harris *et al.,* 2016; Barrett *et al.,* 2017; Stahl, 2017; Geiger *et al.,* 2018; Lobo, 2021). What psychedelics promise is not the daily consumption of a pill, but the occasional use, in low doses, of very powerful substances that can increase neural plasticity and allow the brain to reorganize itself and find a way of functioning with more mental health and improved cognition. I am a reality of transformation in Psychiatry and Neurology (Figure 15) (Schenberg, 2018; Aday *et al.,* 2019; Lobo, 2021; Vorobyeva and Kozlova, 2022).

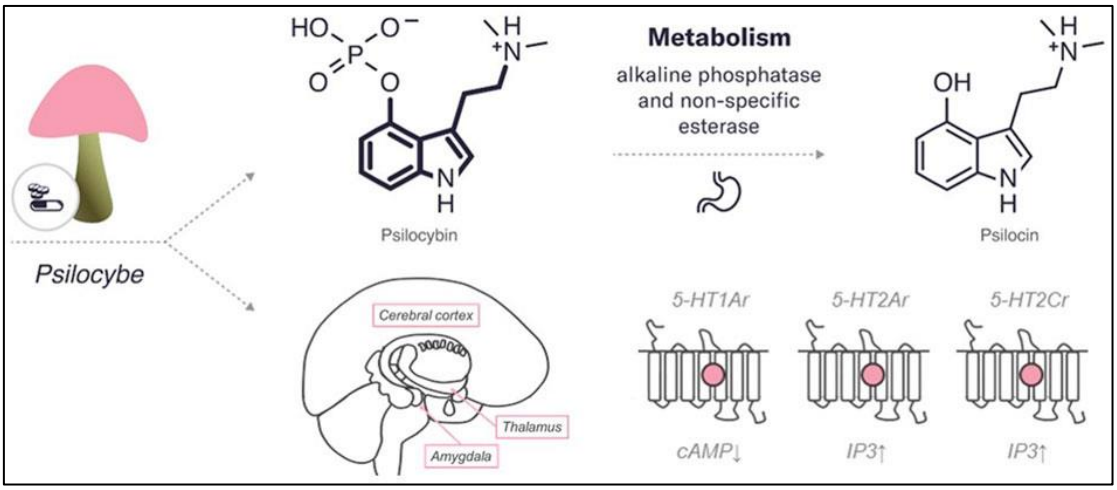

Figure 15: The bold lines indicate similarities in the chemical structure between this psychedelic and serotonin. In addition, the enzymes and major organs involved in the metabolism and excretion of psilocybin are indicated. The mechanism of action represents the targets of the psychedelic, both the region of the brain affected by the psychedelic and the receptors with which it interacts (pink circle for agonist). 5HT—serotonin receptors (2Ar, 1Ar, 2Cr, – subtypes). IP3, inositol-3-phosphate; cAMP, cyclic adenosine monophosphate
Source: Doi: 10.3389/fphar.2022.927984

Because the next frontier is the plan to test them against neural trauma, stroke, concussion, and other neurological problems (Sidarta Ribeiro, director of the Brain Institute at the Federal University of Rio Grande do Norte) (Aday *et al.,* 2019; Leite, 2021).

Many entrepreneurs have reported transformative experiences after using magic mushrooms. Apple co-founder Steve Jobs is a famous example of someone who used psychedelics to expand his mind and find inspiration. Contemporary user reports suggest that psilocybin can help break down mental barriers, allowing individuals to see beyond conventional limitations and explore new business possibilities. These experiences often result in greater clarity of purpose and renewed motivation to pursue innovative ideas. The introspection facilitated by psilocybin can help entrepreneurs align their values with their professional goals, fostering a deeper sense of mission and commitment (Carhart-Harris *et al.,* 2012; Geiger *et al.,* 2018; Aday *et al.,* 2019; Leite, 2021; Dupui, 2022).

4. CONCLUSION

There is also a growing popularity of psilocybin for health purposes. Mushrooms can be important for improving various conditions and symptoms of disorders. People report that this type of mushroom specifically works against fatigue, discouragement, depression, anxiety, and cognition, and helps to deal with withdrawal symptoms from some addiction. Increased concentration can be observed, with improved brain activity.

REFERENCE

- Aday, J. S., Bloesch, E. K., & Davoli, C. C. (2019). A year of expansion in psychedelic research,

industry, and deregulation, *Drug Science, Policy and Law*, *2020*, 6.

- Alexopoulos, C. J., Mims, C. W., & Blackwell, M. (1996). Introductory Mycology. Nova Jersey: John Wiley and Sons.
- Almeida, G. (2017). Were mushrooms the driving force behind human evolution? Com Ciência-Revista Científica de Jornalismo Científico. Retrieved Sep, 12, 2024, from https://www.comciencia.br/foram-os-cogumelos-motores-da-evolucao-humana/
- Barrett, F. S., Robbins, H., Smooke, D., Brown, J. L., & Griffiths, R. R. (2017). Qualitative and quantitative features of music reported to support peak mystical experiences during psychedelic therapy sessions. *Frontiers Psychology*, *8*, 1238.
- Bresinsky, A. S., & Besl, H. (1989). A colour atlas of poisonous fungi: a handbook for Pharmacists, Doctors, and Biologists. London: Manson Publishing Ltd.
- Bogenschutz, M. P. (2017). It's time to take psilocybin seriously as a possible treatment for substance use disorders. *American Journal Drug Alcohol Abuse*, *43*(1), 4–6.
- Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P. C., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *Journal of psychopharmacology*, *29*(3), 289-299.
- Bogenschutz, M. P. (2013). Studying the effects of classic hallucinogens in the treatment of alcoholism: rationale, methodology, and current research with psilocybin. *Current Drug Abuse Reviews*, *6*(1), 17–29.
- Caetano, B. (2018). LSD: What it is, effects, and risks for the body. Retrieved Sep, 15, 2024, from https://www.minhavida.com.br/materias/materia-18013
- Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., ... & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619-627.
- Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., ... & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences*, *109*(6), 2138-2143.
- Chaphalkar, S. R. (2024). Psilocybin reconfigures brain networks, showing potential for lasting therapeutic effects. Retrieved Sep, 14, 2024, from https://www.news-medical.net/news/20240718/Psilocybin-reconfigures-brain-networks-showing-potential-for-lasting-therapeutic-effects.aspx
- Chapman, N. B., Scrowston, R. M., & Sutton, T. M. (1972). Synthesis of the sulphur analogue of psilocin and some related compounds. *Journal of the Chemical Society Perkin Transactions*, *1*, 3011–3015.
- Coelho, J. (2024). Psilocybin: the substance in magic mushrooms. Lab Global. Retrieved Sep, 12, 2024, from https://www.ecycle.com.br/psilocibina/
- Davison, J., Moora, M., Öpik, M., Adholeya, A., Ainsaar, L., Bâ, A., ... & Zobel, M. (2015). Global assessment of arbuscular mycorrhizal fungus diversity reveals very low endemism. *Science*, *349*(6251), 970-973.
- Dunthorn, M., Kauserud, H., Bass, D., Mayor, J. & Mah´e, F., (2017). Yeasts dominate soil fungal communities in three lowland Neotropical rainforests. *Environmental Microbiology Reports*, *9*, 668–675.
- Dupui, D. (2022). The socialization of hallucinations: Cultural priors, social interactions, and contextual factors in the use of psychedelics. *Transcultural Psychiatry*, *5*, 625-637.
- Fadiman, J., & Korb, S. (2019). Might microdosing psychedelics be safe and beneficial? An initial exploration. *Journal of Psychoactive Drugs*, *51*(2), 118-122.
- FDA. (2019). Breakthrough therapy designation to Usona Institute's psilocybin program for major depressive disorder. Retrieved Sep, 13, 2024, from https://www.businesswire.com
- Figlie, N. B., Bordin, S., & Laranjeira, R. (2015). Addiction Counseling. Rio de Janeiro: Guanabara Koogan.
- Gandy, S. (2024). An enthusiast's guide to *Psilocybe natalensis*. DoubleBlind Mag. Retrieved, Sep, 15, 2024, from https://doubleblindmag.com/psilocybe-natalensis/
- Geiger, H. A., Wurst, M. G., & Daniels, R. (2018). DARK Classics in Chemical Neuroscience: Psilocybin. *ACS Chemical Neuroscience*, *10*, 2438–2447.
- Glannon, W. (2011). Brain, body, and mind: neuroethics with a human face. Oxford: Oxford University Press.
- Gomes-Medeiros, D., Faria, P. H., Campos, G. W. S., & Tófoli, L. F. (2019). Drug policy and public health: Necessary dialogues. *Cadernos de Saúde Pública*, *35*(7), e00242618.
- Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science Policy and Law*, *3*, 1-7.
- Hutten, N. R., Mason, N. L., Dolder, P. C., & Kuypers, K. P. (2019). Motives and side-effects of microdosing with psychedelics among users. *International Journal of Neuropsychopharmacology*, *22*(7), 426-434.
- Jann, M. W., & PharmD, F. C. P. (2021). Psilocybin revisited: The science behind the drug and its surprising therapeutic potential. *Psychiatric Times*, *38*(3), 03.
- Kuypers, K. P., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., ... & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for

future research. *Journal of Psychopharmacology*, *33*(9), 1039-1057.
- Lea, T., Amada, N., Jungaberle, H., Schecke, H., & Klein, M. (2020). Microdosing psychedelics: Motivations, subjective effects, and harm reduction. *International Journal of Drug Policy*, *75*, 102600.
- Leite, M. (2021). Psychonauts: Journeys with Brazilian psychedelic science. São Paulo: Fósforo Editora.
- Lobo, F. (2021). Will psychedelics revolutionize Psychiatry? Retrieved Sep, 12, 2024, from https://www.ipea.gov.br/cts/pt/central-deconteudo/artigos/artigos/291-o
- Memed. (2023). Psilocybin: what it is and how it can be used in clinical treatments. Retrieved, Sep, 16, 2024, from https://blog.memed.com.br/psilocibina-o-que-e/
- Mohamed, A. D. (2014). Neuroethical issues in pharmacological cognitive enhancement. *Wiley Interdisciplinary Reviews Cognitive Science*, *5*(5), 533-549.
- MundoEcologia. (2019). Types of mushrooms: Species with names, benefits, and photos. Retrieved Sep, 13, 2024, from https://www.mundoecologia.com.br/plantas/tipos-de-cogumelos-especies-com-nomes-beneficios-e-fotos/#google_vignette
- Naranjo-Ortiz, M. A., & Gabald´on, T. (2019). Fungal evolution: diversity, taxonomy, and phylogeny of the Fungi. *Biological*, *94*, 2101–2137.
- Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: a multicriteria decision analysis. *Lancet*, *376*(9752), 1558-1565.
- Oliveira, R. C., & Nunes, R. (2021). Pharmacological cognitive enhancement: A promising future? Or an inevitable future? *Bioethics Journal*, *29*, 1.
- Pollan, M. (2018a). How to change your mind: What the new science of psychedelics can teach us about consciousness, death, addiction, depression, and transcendence. São Paulo: Editora Intrínseca.
- Pollan, M. (2018b). The new science of psychedelics. The Wall Street Journal. Retrieved Sep, 13, 2024, from https://www.wsj.com/articles/the-new-science-of-psychedelics-1525360091
- Psychedelic-Assisted Psychotherapy (2024). What is microdosing of *Psilocybe cubensis* (Berk. & Broome) Singer, 1951 (Basidiomycota: Strophariaceae). Retrieved Sept, 14, 2024, from https://psicodelix.com/microdose-de-cogumelos-magicos/
- Queiroz, T. (2024). Magic mushrooms: science explains the clinical effects of psilocybin. Retrieved Sep, 17, 2024, from https://brotandoconsciencia.com.br/cogumelos-magicos-ciencia-explica-os-efeitos-clinicos-da-psilocibina/
- Reichert, N. L., Suyenaga, E. S., Sfair, L. L., & Sgaravatti, A. M. (2022). Effects of microdosing LSD and psilocybin: A literature review. *Brazilian Journal of Neurology and Psychiatry*, *26*(1), 32-48.
- Reis, M. (2024). Ayahuasca: what it is, effects on the body, possible benefits and risks. Logo Rede D'or. Retrieved Sep 15, 2024, from https://www.tuasaude.com/ayahuasca/
- Reiner, M., Gruzelier, J., & Bamidis, P. D. (2017). Cognitive enhancement: a system view. *International Journal of Psychophysiology*, *122*, 1-5.
- Santos, V. S. Fungi. (2024). World education. Retrieved, Sep, 13, 2024, from https://mundoeducacao.uol.com.br/biologia/os-fungos.htm
- Schenberg, E. E. (2018). Psychedelic-assisted psychotherapy: A paradigm shifts in psychiatric research and development. *Frontiers Pharmacology*, *9*, 733.
- Schoch, C. L., Ciufo, S., Domrachev, M., Hotton, C. L., Kannan, S., Khovanskaya, R., ... & Karsch-Mizrachi, I. (2020). NCBI Taxonomy: a comprehensive update on curation, resources and tools. *Database*, *2020*, baaa062.
- Shao, L. X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*, *109*(16), 2535-2544.
- Shoji, J. Y., Arioka, M., & Kitamoto K. (2006). Possible involvement of pleiomorphic vacuolar networks in nutrient recycling in filamentous fungi. *Autophagy*, *2*(3), 226–227.
- Siegel, J. S., Subramanian, S., Perry, D., Kay, B. P., Gordon, E. M., Laumann, T. O., ... & Dosenbach, N. U. (2024). Psilocybin desynchronizes the human brain. *Nature*, 1-8.
- Stahl, S. (2017). Psychopharmacology: Neuroscientific bases and practical applications. Porto Alegre: Ganabara Koogan.
- Tsujikawa, K., Kanamori, T., Iwata, Y., Ohmae, Y., Sugita, R., Inoue, H., & Kishi, T. (2003). Morphological and chemical analysis of magic mushrooms in Japan. *Forensic science international*, *138*(1-3), 85-90.
- van Elk, M. (2024). What Knowing About the Effect of Psilocybin on the Brain Can Tell You About Its Therapeutic Potential. Retrieved Sep, 17, 2024, from https://theconversation.com/what-knowing-about-the-effect-of-psilocybin-on-the-brain-can-tell-you-about-its-therapeutic-potential-235857.
- Vorobyeva, N., & Kozlova, A. A. (2022). Three naturally-occurring psychedelics and their significance in the treatment of mental health disorders. *Frontiers Pharmacology*, *13*, 927984.
- Yanakieva, S. (2018). The effects of microdose LSD on time perception: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology*, *236*, 1159–1170.

- Zeiss, R., Gahr, M., & Graf, H. (2021). Rediscovering psilocybin as an antidepressive treatment strategy. *Pharmaceuticals, 14*, 985.
- Zheng, S., Ma, R., Yang, Y., & Li, G. (2024). Psilocybin for the treatment of Alzheimer's disease. *Frontiers Neuroscience, 18*,1420601.
- Zieba, A., Stepnicki, P., Matosiuk, D., & Kaczor, A. A. (2022). Overcoming depression with 5-HT_{2A}. Receptor Ligands. *Journal of Molecular Sciences, 23*, 10.