TMR Trends in Medical Research

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Historical Perspectives and Pharmacodynamic Actions of the Magic Mushroom (Psilocybin) for Future Global Healthcare

[1]Bennett Lange, [1]Luke Morgan, [1]Christopher Mattox, [1]Suhrud Pathak, [1]Keyi Liu, [1]Rishi Nadar, [2]Jeyaram Bharathi Jeyabalan, [3]Jun ren, [1]Timothy Moore and [1]Muralikrishnan Dhanasekaran

[1]Department of Drug Discovery and Development, Harrison College of Pharmacy, Auburn University, Auburn, 36849 AL, United States of America

[2]Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Nilgiris, Ooty, 643001 Tamil Nadu, India

[3]Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, 200032 Shanghai, China

ABSTRACT

Many medicines and treatments for varying levels of ailments were found through natural bioactives before complex separation techniques were available. Ironically, as medicine advances, drastically more people seem to be reverting to a desire for these natural bioactives. Due to this, it is important to discover and research the pharmacology of historically used plants and how exactly they can exert their effects. Magic mushrooms are a polyphyletic group of mushrooms that are characterized by the presence of a psychedelic compound (a drug classification that changes mental state and elicits hallucinations), Psilocybin. The PubMed (NIH) database was manually searched for published manuscripts up through the second week of April, 2024 for the current study using an advanced search feature. The keywords used for the search are given below. The search was done using the CDC, NIH and WHO databases. Journal articles, books and book chapters were manually searched under all languages without filter restrictions. Psilocybin has been found to exert a change in many different organ systems of the human body, including the central nervous system, ophthalmic system, cardiovascular system, respiratory system, digestive system, excretory system, endocrine system, immune system, integumentary system, auditory system, smooth muscles, skeletal muscles and spinal cord. This is possible through converting Psilocybin to Psilocin in the liver, which is a 5-HT2A agonist. This review profoundly analyzes magic mushrooms historical, current and future uses as they pertain to the human healthcare system. These uses contain nutraceutical, prophylactic and therapeutic pathways. It will also cover the toxicological effects on these organ systems and how dangerous these effects are.

KEYWORDS

Magic mushroom, psilocybin, pharmacodynamic actions, global healthcare, nutraceuticals

ISSN: 2151-6065 (Online)
ISSN: 1819-3587 (Print)
https://doi.org/10.3923/tmr.2024.245.273

Received: 15 Apr. 2024
Accepted: 27 Jun. 2024
Published: 28 Jun. 2024

INTRODUCTION

Magic mushrooms are a group of fungi that contain the chemical psilocybin, known for its psychoactive properties, which have fascinated cultures worldwide for centuries. When ingested, psilocybin is converted by the liver into psilocin, the active form of psilocybin. Psilocin then exerts its effects primarily by acting on the serotonin receptors in the brain, particularly the 5-HT2A receptor[1]. This interaction can lead to intense changes in perception, mood and thought processes[2]. The study of psilocybin and its potential therapeutic effects has gained momentum in recent years, underscoring the importance of reevaluating psilocybin's role in psychological and medicinal contexts.

The earliest known use of magic mushrooms is traced back to civilizations and cultures in Algeria and the Sahara. In these areas, using indirect evidence from rock paintings dated between 6000-4500 BCE, it was concluded that mushrooms were used for their psychoactive effects[3,4]. It is uncertain what exactly the intended results were from these uses, but it is believed that our ancestors were able to acquire some benefits from mushrooms that increased fitness and helped lead to the survival of our species. This theory has some evidence as there are several instances of psychoactive substances that affect human evolution[5]. More evidence stems from some of our closest relatives, the chimpanzees. Since humans have a lower tolerance to psychoactive drugs, it can be inferred that there is an evolutionary difference between the two species[6].

The historical consumption of mushrooms by hominins has also been established[7]. Although humans have used magic mushrooms as early as 6000-4500 BC, the first recorded instances of them being used medicinally and ritualistically are in Mesoamerica in the 1500s CE[8,9]. These societies, particularly the Aztecs, viewed mushrooms as sacred, which is highlighted by the fact that the fruiting bodies of mushrooms were seen as "the flesh of the gods"[10,11]. The Aztecs even had a sculpture of the god of flowers that incorporated hallucinogenic mushrooms, one of which was *Psilocybe aztecorum*, which was limited to the region of the Aztecs. One use of these magic mushrooms was for the treatment of fevers and gout. In these cases, priests would give mushrooms to patients to discover the cause of the diseases as well as how to treat it[12]. Using the visions that the patients reported, they were able to gather the medicinal information to help treat themselves[10,12].

Another influential Mesoamerican civilization with extensive medicinal and ritualistic use of magic mushrooms was the Mazatecs. The Mazatecs employed primarily women specialists to work with magic mushrooms. This group was called "curanderas" or "curanderos." These names translate to "healers" in English and are divided into three distinct categories. The first category was the most subordinate of the specialists and could be evil and spiritually turn themselves into animals. The second specialist was in the middle of the hierarchy and would use their own sacred language. This specialist also used massages and other potions to exert effects.

Finally, at the top of the hierarchy, the specialist relied on the power to eat and communicate with the mushrooms. This process of 'communication' was understood as a form of divination or knowledge-gathering, wherein the mushrooms served as a medium for obtaining insights beyond the reach of ordinary means. This specialist, distinguished by their elevated status, refrained from employing potions or engaging in malevolent activities. Revered as "saint children", this title highlighted their esteemed role. These experts sought to regulate mushroom use, with a focus primarily on healing illnesses. Their goals also included identifying stolen goods and attempting to forecast the future[13].

Magic mushrooms, found globally across nearly every region, facilitated another group's use of these fungi: The Shamans in Siberia[4]. Unlike some of the mushrooms used in Mesoamerica, the mushroom used in Siberia was the *Amanita muscaria*, more commonly known as the Red Fly Agaric. This mushroom is also

found in North and South America, but its use there was much more limited or nonexistent. These magic mushrooms contained the same active ingredient that induced visions or hallucinations. However, they also possessed poisonous compounds, which significantly limited their use in the Americas. These compounds, along with the effects of the psilocybin in magic mushrooms, would cause the Siberians to lose muscle coordination and hallucinate. The documented uses of *Amanita muscaria* involved both religious and recreational uses. A primary reason for the use of mushrooms in both recreational and religious contexts was their status as the first intoxicating agent available in the area. This is different from the usage of magic mushrooms in Mesoamerica as the usage there was solely for rituals and not recreational use. The Siberian usage dates to the 17th century. The individuals whose aim was to explore a different state of mind were called shamans. In Siberia, becoming a shaman was a selective process, open to both men and women, yet often reserved for those believed to possess a unique "inner nature". These shamans underwent rigorous preparations, including fasting and isolation, complemented by ritual attire and music, to achieve altered states of consciousness. In these states, they communicated with spirits, receiving visions and guidance, with practices and experiences varying across cultures. The reason shamans consumed these mushrooms also varied through each specific culture, but the general reasons included: Communication with spirits to gain information, treatment for illnesses, creativity for ideas and music, predicting the future and to change one's character[13]. Although the earliest documented evidence of magic mushrooms in rituals is in 1500s CE, mushroom stones dated from 1000-500 BCE were identified in modern day Guatemala which was, at the time, the location of the Mayans. This collection of stones featured simplistic humanoid shapes; some mimicked mushrooms with prominent caps, while others wore mushroom-like hats[14]. These mushroom stones are surrounded by some controversy, as some interpretations have stated they were used for pottery molds. However, the overwhelming opinion is they were associated with the use of magic mushrooms. These mushrooms were not only found throughout Guatemala but in certain Mexican regions[15].

The current and modern use of magic mushrooms has been hindered in most of the world due to the legal restrictions on psilocybin use. This banning of usage is not a recent development and comes from the Spanish during the Spanish Inquisition[9]. After Hernando Cortes reported the ritualistic usage of mushrooms in the 1500s, Catholic missionaries carried out a suppression campaign against the rituals of the Aztecs[16]. This discrimination forced them to perform their rituals involving magic mushrooms in secret[17]. Not only did the Spanish restrict the rituals, but they also participated in extensive book burning. This effectively erased most records of the use of magic mushrooms in Mesoamerica. This negative stigma around magic mushrooms, which began in the 1500s, created a precedent still felt today. Spain, for example, has laws that make the possession of psilocybin illegal, thereby making magic mushrooms illegal as well[18].

Despite the precedent of legality set in the 1500s, the United States did not enact laws until the 1960s[19]. This, along with some 21st century clinical trials, allowed for the discovery of medicinal uses of psilocybin. The results of these trials have shown a reduction in depression and anxiety when compared with placebo. Other results also showed that psilocybin may be beneficial for breaking addictions[20]. More clinical and longitudinal studies are needed to test the efficacy and safety of magic mushrooms. Because many countries are undecided about the potential benefits against the adverse effects, most countries have outlawed the use of psilocybin. Figure 1 shows the countries that legalized psilocybin use and hopefully, this number will increase soon.

Pharmacodynamic actions of the magic mushroom-psilocybin: Effect on the human organ systems (Fig. 2, Table 1).

Fig. 1: Countries where possession of psilocybin is legal

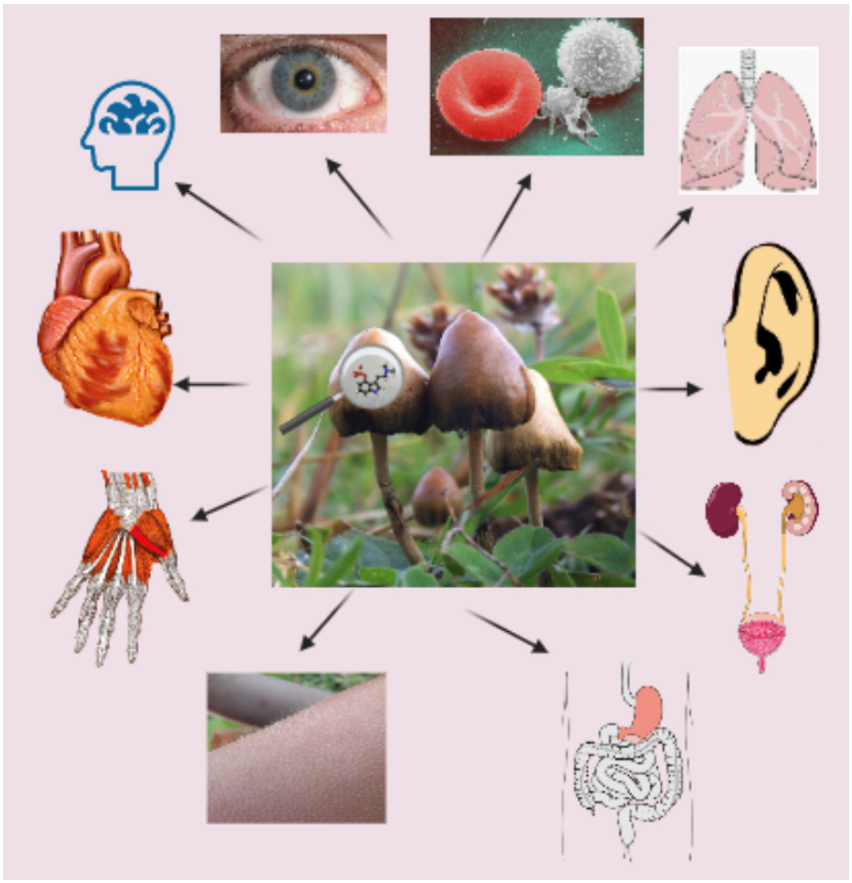

Fig. 2: Effects of magic mushrooms on the human organ system

Central nervous system: In the human body, no group of organs are more important than the Central Nervous System (CNS). The CNS consists of the body's brain and spinal cord and has a wide array of distinct functions in controlling the body. The forebrain is the superficial part of the brain that controls movement, the senses, the sleep cycle and emotions[21]. This part of the brain is made up of the outer cerebrum as well as most of the limbic system[22] (the part of the brain responsible for the emotional regulation of the human body) and is rich in 5-HT type receptors. These receptors bind serotonin (serotonergic) and have seven different subtypes, each with further groupings beneath them[23]. Psilocybin is a prodrug that is readily converted to psilocin in the body. Psilocin is a bioactive which targets 5-HT2A receptors in the body, which are very abundant in the CNS. The hippocampus, the part of the brain

Table 1: Effects and toxicology of psilocybin

Organ system	Pharmacodynamic actions of magic mushroom	Toxicological effects of magic mushroom
Central nervous system	5-HT2A agonist, increases neurogenesis Assist neuronal proliferation, differentiation and neuroplasticity Increased paraventricular nuclei density	Hallucinatory effect Anxiety Adverse effect to perception of risk and reality Higher risk to have prolonged psychosis (patients have a history of mental health issues)
Ophthalmic system	Temporary improve color deficiency as serotonergic hallucinogens	Hallucinogen persisting perception disorder and permanently dilated pupils Hallucinogen Persisting Perception Disorder (HPPD)
Cardiovascular system	Affect blood pressure by serotonergic system effect and potential sympathomimetic effects Vasoconstrictive effects	Systolic dysfunction and takotsubo Cardiomyopathy, increase the risk of heart valve disease Acute increase in blood pressure Cardiomyocyte mitochondria degeneration induced tachycardia, myocardial ischemia and aberrant intraventricular conduction
Respiratory system	Increase the blood flow and decrease Nitrous Oxide (N_2O), which increases blood pressure, heart rate and blood volume Increase the antigens response induced anti-inflammatory responses	Anxiety induced psychogenic dyspnea and hyperventilation
Digestive system	Activate metabolism of psilocybin Control (or at least assist in) smooth muscle contraction	Slower bowel movements, increased pancreatic Secretions, abdominal pain and discomfort, nausea and vomiting Adverse drug reactions
Excretory system	Increase lipid metabolism in liver Increase immune response in liver Increase the mitochondrial biogenesis in kidney Activate JAK1 and 2 immune pathway	Kidney damage caused by psilocybin metabolism Acute Kidney Injury (AKI) Kidney induced hypertension
Endocrine system	Relief the leptin and insulin hormones induced neurobiology of eating disorders by affect the cognitive barriers Activated the orexins that participate in appetite regulation and sleep	Upregulate the nervous signals within the sympathetic nervous system and the Hypothalamic-Pituitary-Adrenal (HPA) axis, Induced epinephrine and norepinephrine increase
Immune system	Activate neuronal survival mechanisms, promote cortical neuron growth and modulate the immune system Strong anti-inflammatory effects in peripheral immune system Inhibit nitric oxide synthase activity within the C6 glioma cells Presumably reduce peripheral TNF-alpha-induced inflammatory signal Presumably anti-neuroinflammatory	Cellular damage during acute tissue injury or chronic disease IL-1β-dependent inflammatory response Higher risk of autoimmune diseases
Integumentary system	Aid in skin, hair and nail inflammation	
Auditory system		Auditory hallucinations by auditory complex dysfunction Disrupted gamma oscillations Difficulties differentiating and pronouncing similar sounds Interference to 40 Hz Auditory Steady-State Responses (ASSR) amplitude
Smooth muscles	Elicit a response in the 5-HT1 receptor Mediate a contractile response	
Skeletal muscles	Presumably activate the JAK/STAT pathways in cell division and growth	
Spinal cord	Easing chronic pain	Muscle spasms

responsible for transferring short-term memories to long-term memories, is especially rich in this receptor. In a study by Klempin *et al.*[24], it has been found that psilocybin increases neurogenesis, or new cell growth, *in vivo*, however, the exact mechanism is unknown. Furthermore, 5-HT2A receptors were found *in vitro* to assist in neuronal proliferation and differentiation[25]. Alongside neurogenesis, psilocybin-as well as many other psychedelics-were found to have a profound increase in neuroplasticity[26]. Neuroplasticity is the brain's redirection of neuronal connections. It is the brain's way to hardwire itself to improve learning. The way that psilocybin is able to increase neuroplasticity is not currently understood[26]. Though neurogenesis and neuroplasticity have both been found to affect depression.

In a study looking at brain volume against Major Depressive Disorder (MDD), it was found that adult patients with MDD possessed a statistically significant decrease in brain matter, especially in the forebrain[27]. Alongside this, patients were found to have higher microglial activity which might decrease neuroplasticity[27], which highlights the need for newer neuronal connections. Although a lack of neurogenesis and neuroplasticity have not been proven to be the direct etiology of MDD since the cause of MDD is still debated, it is a common occurrence that patients with MDD have a decrease in both areas and reversing these adverse side effects with psilocybin might be able to play a role in treating MDD. In fact, a meta-analysis showed the efficacy of multiple studies in using psilocybin to treat depressive orders[28]. One thing to note about psilocybin and the CNS: One of psilocybin's most notorious and arguably infamous due to its classification as a Schedule I drug, effects of the CNS and forebrain is its hallucinatory effect that it has on humans. This will be discussed in a later section, though it should be noted that ultimately the Ophthalmic System's processing falls under the CNS's umbrella.

The midbrain is the deeper part of the brain that includes the hypothalamus, the thalamus, the subthalamus and the epithalamus. This system helps relay sensory stimuli to the processing part of the brain and three of the regions[29] (hypothalamus, thalamus and subthalamus) have been found to possess the 5-HT2A receptor, which means that psilocybin is able to exert an effect on the midbrain. The amount of research done on the midbrain and psilocybin is smaller compared to the amount done on the forebrain, although there are still studies done that investigate psilocybin's effects.

In one study, it was found that repeated low doses of psilocybin increased paraventricular nuclei density[30] in the hypothalamus which can help regulate blood pressure and its changes. It was also found in this same study to decrease stress in response to negative stimuli. As stated before, the exact mechanism is unknown and further research needs to be done to further understand the role of 5-HT2A receptors in physiological functions. That said, psilocybin can affect the midbrain. The final part of the CNS is the hindbrain which consists of the cerebellum, medulla oblongata and the pons. This part of the human body is important and regulates many subconscious roles of the brain including breathing, balance and assisting in the sleep cycle.

In multiple studies, the cerebellum has been found to have no binding (and thus likely an absence) of the 5-HT2A receptors, but 5-HT2A binding has been found in both the medulla oblongata and the pons. With that being said, the pons has little research (regarding psilocybin at least) in academic journals. In a study by Barnett *et al.*[31], it was found that psilocybin can directly affect the sleep-wake cycle (the job of the pons), however, no mention of the pons was described in the paper. Similarly, few mentions of the medulla and psilocybin exist. The medulla oblongata plays roles in communication of subconscious activities like breathing and heart rate, though no true studies have been done to test psilocybin's effect on this part of the brain. This may be one of the areas of research in the future, although the exact mechanism of the 5-HT2A receptor and the exact roles of psilocybin seem to be unknown.

Ophthalmic system: The ophthalmic system includes some of the anatomical and physiological components that enable vision. This system encompasses the eye and its surrounding associated structures. This includes the eyelids, tear ducts and eyelashes. The ophthalmic system allows electromagnetic waves in the visible light spectrum to be converted to electrical signals that can be transformed into images in our brain. This is not only essential for vision but also interacting with other senses and processes in the human body such as: Balance, spatial orientation and interacting with the environment. Since the proper functioning of the ophthalmic system is important in day-to-day life, it is important to understand the effects magic mushrooms have on this system. One of the possible positive effects of psilocybin is the improvement of color deficiency. This improvement was found in a case study of a subject with red-green deficiency who saw improvement with color deficiency for at least 16 days after treatment[32]. This can possibly be explained by serotonergic hallucinogens, particularly their interaction with the 5-HT2A receptors, causing an increase in contrast and brightness[1,33]. Although this was a temporary improvement, small doses over a long period of time could yield a significant quality of life change for users with color deficiency.

Involuntary eye movements, known as saccades, can increase after consumption, particularly when fixating on a small point. This can lead to a change in the point of fixation[34]. Visual hallucinations can also occur after taking psilocybin. These hallucinations can cause but are not limited to texture, color, motion, shape and proportion changes[35]. These visual changes can also cause the user to have a contracted visual space and a unique change to handwriting size[36]. These hallucinations may persist after the consumption of psilocybin for 5 or more years in a condition called hallucinogen persisting perception disorder[37]. One visible change that occurs to the ophthalmic system is mydriasis or dilation of the pupil[38]. These pupillary changes seem to correspond to the intensity of the drug experience[34]. However, these pupillary changes can cause possible permanent pupillary changes. In a case study an individual who began to use psilocybin containing mushrooms at age eleven reported permanently dilated pupils. This caused the patient discomfort and an occasional burning sensation within sunlight[39]. Although several physical changes occur in the eye it is believed that the exact cause of the visual changes occur due to changes in brain activity through the activation of the 5-HT2A receptor in visual areas of the brain[40].

Cardiovascular system: The cardiovascular system is made up of the heart that contracts to move blood and a branching vasculature that includes arteries, veins and capillaries[41]. The primary function of this system is to maintain adequate perfusion to all the body's systemic tissues as well as remove any Carbon Dioxide (CO_2) and other wastes produced by normal cellular function[42]. Due to the recent increased interest within the scientific community in the potential therapeutic effects of psychedelics for a variety of medical conditions, it is imperative to assess their overall safety and risks associated with the cardiovascular system. The effects of psilocybin can best be described by their impact on the serotonergic system within the heart as well as their potential sympathomimetic effects[43].

As the serotonin (5-HT) neurotransmitters bind to the many types of serotonin receptors located within the vascular endothelium and smooth muscle tissues, they can produce either pressor or depressor effects depending on the location of the serotonergic receptor site, the signaling mechanisms activated during their transmission and the overall concentration of the neurotransmitters themselves[43]. Studies have shown that psychedelic substances such as psilocybin-containing "magic mushrooms" produce vasoconstrictive effects on the body's vasculature due to their role as serotonergic receptor agonists, meaning that they exhibit pressor effects, or increase overall blood pressure within the vasculature[43]. The effects of psilocybin on the cardiovascular system's function are still largely unknown due to inconsistencies within the experimental studies that have already been conducted. Fujita *et al.*[44] discovered that psilocybin intoxication of Wistar rats through intraperitoneal injection induced systolic dysfunction and takotsubo cardiomyopathy potentially caused by its interaction with the adrenergic, dopaminergic

and serotonergic receptors, as well as its toxic effect on the cardiomyocytes and its strong sympathomimetic effect. Another study discovered that psychedelics may increase the risk of heart valve disease by binding to the 5-HT2B serotonergic receptors[44]. However, the only experimental studies that have been conducted that included a histological examination of the heart were conducted with ayahuasca, another psychedelic 5-HT2A receptor agonist, not the psilocybin compound.

Respiratory system: The respiratory system (RS) is a system of organs that include the mouth, lungs, trachea, pharynx and other organs necessary to perform the act of breathing and gas exchange. Psilocybin is very active in the RS system mainly because of the role of the prominent 5-HT2A receptor. As mentioned earlier, psilocybin is an agonist for the 5-HT2A receptors located primarily in the CNS. Although the 5-HT2A receptors can play a role in hallucinations and many other jobs, one of the primary roles of the 5-HT2A receptor is to control the constriction of different blood vessels and allow for a higher blood flow[45]. Because of this, it is important to have the 5-HT2A receptors in both the lungs and the blood vessels. Both the lungs[46] and blood vessels/bloodstream (mainly in platelets)[47] have been proven to contain the 5-HT2A receptors. Although the exact pathway of how the 5-HT2A receptor is able to increase blood flow is unknown, it has been found to decrease Nitrous Oxide (N_2O)[47] which increases blood pressure, heart rate and blood volume[48]. In another experiment by Segura *et al.*[49], it was found that lungs involved with high frequencies of smoking corresponded to a higher number of 5-HT2A receptors. This might suggest that 5-HT2A receptors can decrease inflammation or increase immune cells in the lungs in areas of higher stress, but this has not been proven. This can be crossed with another experiment where antagonists of the 5-HT2A receptor were evaluated on their role in lung cells[50]. It was found that antagonists of the 5-HT2A receptors resulted in hyporesponsiveness of the lungs, meaning that agonists (such as psilocybin) might result in a higher level of lung response to antigens. The future of psilocybin research and the RS will likely be to further define the exact biochemical pathway in the lungs and further define the exact role of psilocybin in RS diseases. For example: One study found that psilocybin was able to have anti-inflammatory responses in the lungs[51], but how does that affect asthma or COPD etc.?

Digestive system: The digestive system (DS) is comprised of the mouth, esophagus, stomach, small and large intestine, liver, gallbladder, pancreas and anus. This system's job used to be thought of as being limited to providing nutrients from food/drinks. However, the more research on this system is performed, the more important it seems to become. Many studies now connect the microbiome and receptors in the gut to the CNS through the gut-brain axis (GBA)[52]. The first way that the gut can interact with psilocybin is that the liver and stomach are the sites of psilocybin to psilocin dephosphorylation by alkaline phosphatase[53]. This means that without the gut, psilocybin would never even become a biologically active compound. Secondly, 5-HT2A receptors have been found in the stomach, colon and small intestines[54]. The 5-HT2A receptors have been found to control (or at least assist in) smooth muscle contraction, although this will be addressed in depth in a later section. This means that the main role of the DS, though, with psilocybin seems to be the metabolism of, as well as potential communication with the CNS. Regarding future research, one of the major areas that should be investigated is how exactly psilocybin can interact with the gut microbiome since this has apparent effects on mental health, physical health and signaling between systems[55].

Excretory system: The excretory system (EXS) is a system comprised of the skin, liver, large intestine, lungs and kidneys. The role of this organ system is to filter and dispose of liquid waste from the bloodstream. Of the organs making up the EXS, mainly the liver and kidneys, both of which have been found to express the 5-HT2A receptors[56, 57], will be focused on since the other organs are the major organs of larger, more well-known organ systems. The liver has a high presence of 5-HT2A receptors and this receptor seems to play a role in many different functions regarding psilocybin. In one study, it is

mentioned that the activation of 5-HT2A receptors leads to an increase in liver lipid metabolism[58], while another investigated the results of 5-HT2A receptor antagonists. These molecules decrease immune response and inflammation in the liver (a benefit in cirrhosis cases), although this may suggest that psilocybin can lead to an increase in immune response in the liver, which may be beneficial in certain instances[59]. The 5-HT2A receptors also play a large role in the kidneys.

First, the activation of the 5-HT2A receptor leads to mitochondrial biogenesis in kidneys[60], meaning that psilocybin might be able to produce higher numbers of mitochondria in the renal system. This would lead to a higher cellular respiration rate and in turn more energy for renal cells. Similarly, the activation of the 5-HT2A receptors in kidney cells leads to the activation of different immune response pathways (JAK1 and 2)[61]. All of this suggests that psilocybin could play a major role in the immune responses of the EXS through the activation of 5-HT2A receptors. One thing to note: almost all of these studies discuss the role of either agonists/antagonists and their role on 5-HT2A receptors in either the liver or kidneys. However, psilocybin is not mentioned specifically in these. That said, since psilocybin is an agonist or activator, of the 5-HT2A receptors, it can be reasonably predicted what effect this prodrug would have on them. Of course, future research should be done that focuses on the kidney and liver regarding psilocybin specifically, especially since psilocybin is metabolized in the liver (discussed earlier) and can cause kidney damage (to be discussed later)[62].

Endocrine system: The human endocrine system's main function is to utilize hormones to control the body's growth and development, metabolism, reproductive processes, mood and responses to physical injuries and stressors[63]. The endocrine system is made up of several organs, including the pancreas, hypothalamus, thyroid gland, thymus, pineal gland, adrenal glands and parathyroid glands[64]. Recent experimental studies conducted on animals have revealed that disruptions in the integration of homeostatic signaling within the endocrine system are correlated with abnormal eating behaviors and can shape the neural processing of food reward and stress. This is because substantial weight gain influences the levels of the leptin and insulin hormones within the blood plasma, with increased insulin levels potentially causing an increase of dopamine release within the dorsal striatum portion of the brain, which research has shown can be targeted by the psilocybin compound[65]. Research has suggested that these neuroendocrine alterations can differ based on the severity of the patient's stage of mental illness, but it is currently still unclear which specific alteration leads to the onset of eating disorders.

In addition to being important for controlling homeostatic bodily functions like appetite control and sleep, orexins are a type of neuron that is primarily found in the lateral portion of the hypothalamus. These neurons are also known to increase food cravings and are activated by the hormone ghrelin, which stimulates hunger and inhibited by the hormone leptin, which regulates satiety[65]. Research has shown that these neurons are activated via the 5-HT2A receptors by psychedelic substances including psilocybin[66]. Upon activation of these neurons, the cholinergic neurons located within the basal forebrain are upregulated, which scientists suspect is involved in both stress and arousal[67]. The dorsal striatum and the central nucleus of the amygdala are the two brain areas that contain the two kinds of orexin receptors, orexin-R1 and orexin-R2. These regions are important in controlling motivation[65]. These areas that work to regulate human motivation can also be targeted by the psychedelic psilocybin, which serves as an agonist of the 5-HT2A receptor and leads to an increase in neuroplasticity which is related to brain-derived neurotrophic factor[65]. Studies have shown that when these serotonergic receptors are stimulated by psilocybin, the activity of the default mode network in the brain is significantly altered; hyperactivity of this network has been linked to both cognitive rigidity and rumination, which are two of the main cognitive barriers that patients face when undergoing psychotherapeutic treatments for their eating disorders[65]. Scientists should continue to examine the effects of the psilocybin bioactive on neural network integration and how that correlates with the hallmark symptoms of eating disorders.

Immune system: The complex structure of tissues, organs and cells that make up the human immune system functions to defend the body against the entry of infections and other substances that might cause disease[68]. There are two main components to the immune system: The innate immune system and the acquired immune system[69]. The innate immune system includes the skin, the cornea of the eye and the mucous membrane that lines the gastrointestinal, genitourinary and respiratory tracts within the body; they all serve as a physical barrier against infection[70].

The acquired immune system includes the spleen, thymus, tonsils, adenoids, bone marrow, lymph nodes and lymph vessels; these structures produce antibody proteins to aid the body's defense against specific pathogens[71]. Neurodegenerative diseases such as Alzheimer's disease and dementia are marked by a loss of dendritic spines, a reduction in synapse density, neuroinflammation and atrophy within the dendritic structures themselves[72]. In recent years, scientific studies have shown that psychedelic substances such as psilocybin agonize the 5-HT2A serotonergic receptors to activate neuronal survival mechanisms, promote cortical neuron growth and modulate the immune system[72]. It has also been discovered that psychedelics can cause strong anti-inflammatory effects through binding to the 5-HT2A receptors on the immune cells located within the peripheral immune system. Miller *et al.*[71] found that, when psychedelics such as psilocybin activate the 5-HT2A serotonergic receptors, they inhibit nitric oxide synthase activity within the C6 glioma cells. Mackowiak *et al.*[72] expanded upon this finding when studying 2,5-dimethoxy-4-iodoamphetamine, a psychedelic drug more commonly known as DOI. The DOI is a serotonin 5-HT2A receptor agonist and produces similar effects to psilocybin[72]. It has been shown to significantly reduce peripheral TNF-alpha-induced inflammatory signaling within *in vivo* studies only[72]. Their research found that DOI can strongly prohibit pro-inflammatory gene expression *in vivo* in response to tumor necrosis factor-alpha and serve as a potential prophylactic treatment for symptoms of allergic asthma[72].

Most of the studies concerning the anti-inflammatory potential of psychedelics have been focused on its activity in the peripheral immune system and primarily *in vitro* studies. Research has shown that oligomeric amyloid-beta species initiate the triggering of glial pattern recognition which then activates the receptors expressed on myeloid cells, α6β1 integrin, CD14, CD47 and scavenger receptors like CD36[72]. When the amyloid beta species bind to these specific receptors, pro-inflammatory cytokines (such as TNF-α and IL-1β), reactive nitrogen and oxygen species and chemokines are released, which leads to an increased amount of phagocytic activity[72]. All these things lead to decreased functional performance within the microglia and astrocytes. However, due to the presence of serotonergic receptors on the surface of glial cells, there is a possibility that 5-HT2A receptor agonists such as psilocybin could lead to a significant reduction in neuroinflammation[72]. Due to limited research, scientists should examine whether similar anti-neuroinflammatory effects can be applied to the CNS.

Integumentary system: The integumentary system is made up of the skin, hair, nails and associated glands[73]. This system is the main barrier the human body uses to protect against the external environment. This protects the inner organs from pathogens, abrasions and ultraviolet radiation. The integumentary system also plays a key role in kinetic progression, temperature and pain. It is vital not only for the physical aspects but also for mental aspects as it also contributes to overall self-image and appearance, which is why it is important to monitor the health of it. Psilocybin, which is converted to psilocin in the human body, is detected in hair after usage[74]. Magic mushrooms may help decrease inflammation in the human body. This is through the decrease in lipopolysaccharide production of proinflammatory proteins TNF-α and IL-1β[51]. The TNF-α is an inflammatory cytokine that is produced during mild inflammation and can lead to necrosis or apoptosis[75]. The IL-1βh is another key mediator in inflammatory responses and worsens

damage done during chronic disease and tissue injury[76]. Significant decreases in IL-6 and COX-2 may also contribute to a decrease in inflammation which is another pro-inflammatory cytokine and an enzyme that promotes inflammation respectively[77,78]. Serotonin receptor agonists like psilocybin may also contribute to the anti-inflammatory effects of magic mushrooms[79]. Together these anti-inflammatory properties help aid in conditions characterized by inflammation of the skin, hair and nails. More research is needed to determine the efficacy of the treatment of psilocybin, but it is a promising avenue.

Auditory system: The auditory system is one of the most important systems for humans in their ability to gather stimuli around them. The auditory system (AS) comprises the outer, inner and middle ear. It also contains cochlear nuclei, lateral lemniscus, inferior colliculus and the auditory cortex[80]. Of these structures, unsurprisingly, the processing (brain) portion seems to dominate in possible psilocybin connections. First, the auditory cortex has been found to possess 5-HT2A receptors[31]. In the auditory cortex the 5-HT2A receptors play a role in allowing the ear to differentiate between different pitches and timbres[81], essentially allowing us to tell the difference in different sounds. This could explain why psilocybin can produce auditory hallucinations in many instances. One thing that is important to note about the 5-HT2A receptor and the auditory complex: In many cases, a lower-than-normal number of 5-HT2A receptors are typically found in the auditory cortex for patients with schizophrenia. Taking psilocybin (or any 5-HT2A receptor) results in the downregulation of 5-HT2A receptors in the body[82] which might lead to a possible etiology for people who develop schizophrenia after taking psychedelics, although this is purely hypothetical. Another structure that has been found to contain 5-HT2A receptors in the AS is dorsal cochlear nuclei[83]. These nerves are responsible for transmitting pitch and timbre. *In vivo* studies have shown that the 5-HT2A receptor is responsible for modulating excitability in the neurons, with the activation leading to increased excitability in the nerves[83]. Again, this could show a hypothetical reason for auditory hallucinations after taking psilocybin. That said, future research in the AS should focus on (1) Differences and possible reasons for different mental health diseases and their ties to the 5-HT2A receptor in the auditory cortex and (2) Possible reasons for auditory hallucinations.

Smooth muscles: Smooth muscles are a set of muscle cells that are involuntary and lack striations when viewed (when compared to skeletal or cardiac muscle cells). These muscles line the organs of the human body and are present in the GI tract, eyeballs, kidneys, etc. The 5-HT2A receptor can mediate a response in many smooth muscles and primarily the cardiac smooth muscles like the lining of blood vessels. The main role of the 5-HT2A receptor in these muscles is to mediate a contractile response[84]. This can lead to a variety of bodily responses. Very little research has been done on the effect of psilocybin and smooth muscles. The LSD, another 5-HT2A agonist, has been found to increase smooth muscle tone in guinea pigs via the 5-HT1 receptor[85]. Psilocybin has been found to elicit a response in the 5-HT1 receptor, although it is very minimal[86] and most likely will not have a crucial role in smooth muscle tone.

Skeletal muscles: Skeletal muscles are a set of muscles that contribute to voluntary movement. They are striated and allow people to move around their surroundings. These muscles have little research done on them when focusing on psilocybin, admittedly. However, there has been research done that has shown the presence of 5-HT2A receptors in skeletal muscle cells[87]. These receptors help activate the JAK/STAT pathways, which are useful in cell division and growth[61]. That said, there have not been many studies that show that psilocybin will meaningfully affect these pathways in humans. Similarly, few, if any, studies have focused on the effects of other 5-HT2A receptor agonists (like LSD or DMT) (Fig. 3) on skeletal muscle cells. Because of this, psilocybin and skeletal muscles should be viewed in a "future studies" lens. However, since psilocybin already has a limited understanding of it, skeletal muscles are probably far down on the priority list.

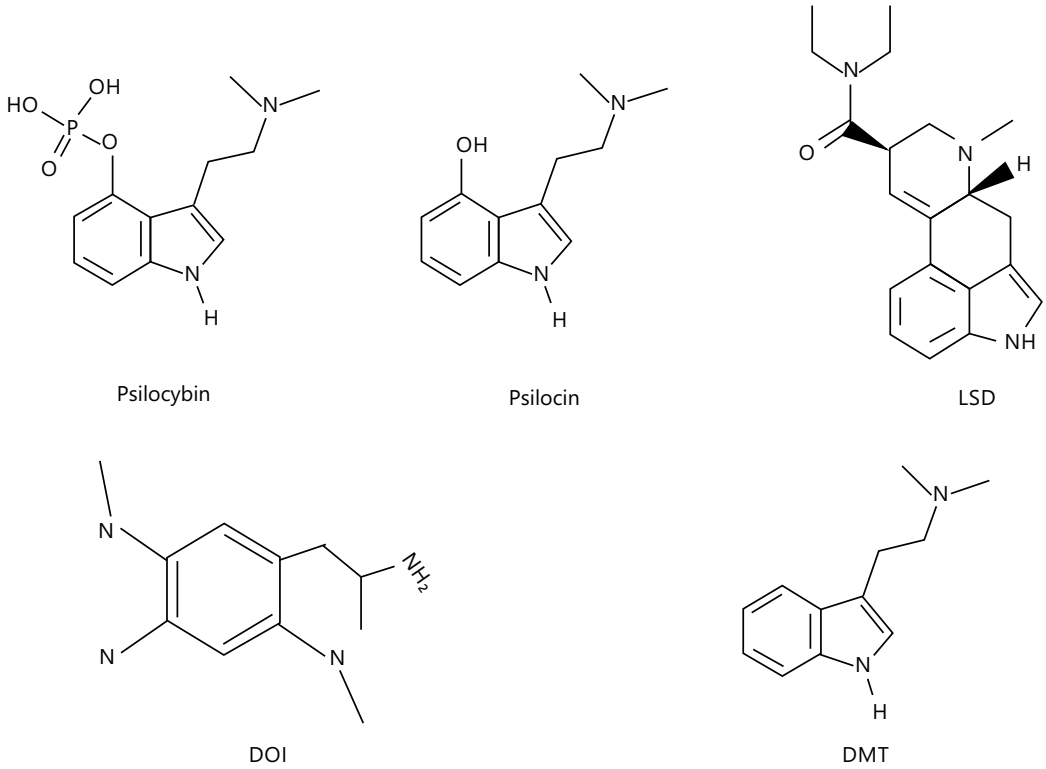

Fig. 3: Bond line structures of common 5-HT2A agonists

Spinal cord: A group of bones and nerves called the spinal cord transmits information from the body to the brain or the brain to the body. The spinal cord is key in the communication of stimuli signals and damage to it can lead to paralysis, death, or chronic pain. The 5-HT2A receptor seems to play a vital role in the spinal cord's ability to communicate using serotonin[88]. In most studies, including those on both psilocybin and the spinal cord, the focus tends to be on easing chronic pain. An example of this is patients with Lupus, an autoimmune disease that causes pain in the joints and muscles. It has been found in one study by Kandel and Mandiga[89], that psilocybin was able to help with chronic pain. In this study and many other studies, it is believed that psilocybin can help with chronic pain by rerouting neural connections-neuroplasticity in the spinal cord. It should be noted, though, that almost every study that proposes this is not completely sure that neuroplasticity is the main proponent towards fixing chronic pain. Because of the spinal cord's role in the human body, as well as its high density in 5-HT2A receptors, the role of psilocybin in the spinal cord needs to be studied more. Its role and pathways should be well documented to help patients with chronic pain, spinal cord injuries and mental health disorders.

Current uses of the magic mushroom (psilocybin)

Prophylactic use: Cluster headaches are a common form of autonomic cephalalgia in which a patient experiences an excruciating unilateral headache at specific times throughout the day[90]. These attacks can last for hours with a single cluster cycle potentially extending for up to several months[91]. If the cluster cycles continue for over a year without a period of patient remission lasting for more than three months, then the condition may be labeled as chronic[92]. Currently, the exact etiology of this condition is unknown; however, studies have revealed that the cranial autonomic symptoms that accompany a cluster headache attack are the result of stimulation of the trigeminal-autonomic reflex pathway, causing additional symptoms such as nasal congestion, conjunctival injection and excessive lacrimation[91].

Due to the manifestation of these additional symptoms as well as current research, scientists suspect certain pathophysiological mechanisms to be involved as well as specific regions of the central nervous system, including the posterior portion of the hypothalamus[93]. Research has shown that this portion of

the hypothalamus aids in the generation of a "permissive state" that allows the cluster headache period to begin[94]. Current forms of acute treatment include drugs within the triptan grouping administered intranasally or subcutaneously as well as high-flow oxygen inhalations through a special non-rebreather mask[93]. Studies concerning potential prophylactic pharmacological treatments for cluster headache disorder have offered little clinical evidence, but the main recommendation for prophylactic treatment is verapamil followed by lithium[93]. Drugs including gabapentin, melatonin, divalproex sodium and topiramate are also suspected to be effective in the treatment of this condition but are not prescribed often due to their unknown efficacy[95]. In addition to physician-prescribed treatment, it is estimated that one-third of patients with cluster headache disorder use adjuvant or alternative forms of treatment including acupuncture, relaxation techniques, physical therapy and herbal medicine, most of which have not been clinically studied as potential treatments for cluster headaches[93].

In an examination of 8 survey studies conducted by Rusanen *et al.*[92], psilocybin-containing mushrooms demonstrated a higher correlation to self-reported treatment efficacy when all the data was compiled into a hierarchical formation that demonstrated the linkage between prophylactic effects and patient-reported efficacy.

It is reported that all the serotonergic substances examined in their survey study were more effective than the traditional pharmacological treatments verapamil and corticosteroids, shown in Fig. 4. In addition, they also reported that serotonergic substances such as LSD and psilocybin mushrooms were able to stimulate a prolonged reduction or complete cessation of cluster headache symptoms with one dose when compared to the more conventional treatments[93]. Scientists suspect that psilocybin's structural similarity to triptans is what allows it to serve as an abortive treatment for cluster headaches by eliminating cluster periods and prolonging periods of remission in patients[96]. However, the exact mechanism by which the bioactive achieves symptom reduction has not yet been deduced and should therefore be examined further. Although the exact pharmacological mechanism of psilocybin has yet to be elucidated, its structural similarity to traditional drug treatments as well as its significant reduction in headache symptoms warrants further research into its prophylactic potential for the prevention of cluster headaches. In patients diagnosed with major depressive disorder, a histopathological examination revealed that these individuals can exhibit signs of neurodegeneration: Post-mortem brain studies revealed atrophy and neuronal loss in both the hippocampus and the prefrontal cortex regions[97]. Studies have shown that psychedelic substances including psilocybin can induce neuronal protective mechanisms including neurogenesis, neuroplasticity and neuroprotection[97]. Neurodegeneration within the brain can be caused by oxidative cell damage, which can be caused by an imbalance in free radicals including reactive oxygen species and reactive nitrogen species, as well as the presence of antioxidant and antioxidative proteins including thioredoxin peroxidases, glutathione peroxidases and superoxide dismutase[97]. This imbalance is caused by an increased number of free radicals and a reduced number of antioxidants, which led to the neurodegeneration observed in these patients[98]. When these molecules are present in excess inside the cell, they can cause damage to the plasma membranes, the mitochondria and the DNA and over time can lead to degeneration in the body's organs and tissues[97]. Studies have shown that psilocybin can exhibit anti-oxidative effects through activation of the 5-HT2A receptor activation[99]. The 5-HT2A receptor agonist 8-OH-DPAT stimulates the release of the anti-oxidative factors metallothionein-1/-2 and Nfr2[97,99]. It then reduces the amount of damage caused by the oxidative agent paraquat through the stimulation of superoxide dismutase 1 and 2, NADPH: Quinone acceptor oxidoreductase 1, heme oxygenase 1 and the expression of catalase mRNA[97]. By reducing the number of free radicals located within the CNS, the onset of neurodegenerative diseases including Alzheimer's disease is decreased as well, meaning that psilocybin could potentially serve as a prophylactic treatment for neurodegeneration[100].

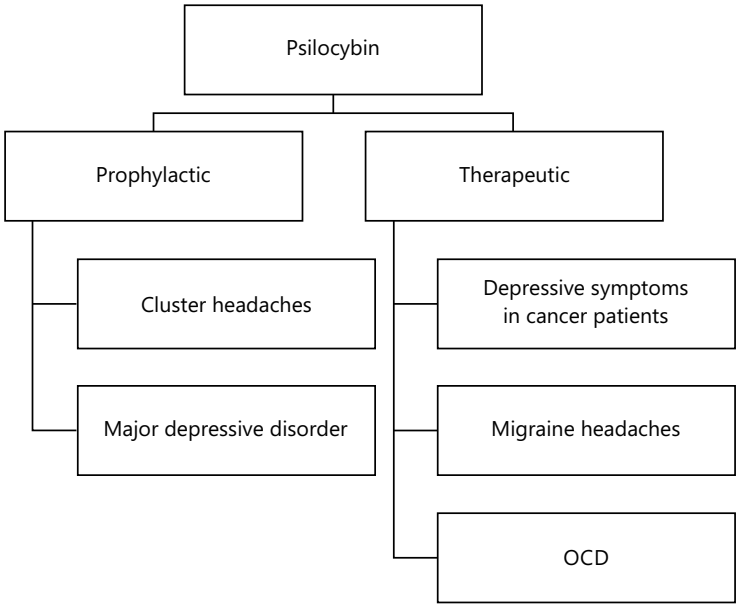

Fig. 4: Current uses of psilocybin

Therapeutic uses: Migraine headaches are a type of headache disorder that is very common, with about 15% of the global population suffering from this condition[101]. Currently, the range of pharmacological treatments for this condition offers limited efficacy and some adverse drug reactions that may impair their long-term success. Recent studies have shown that agonists of certain 5-HT2A receptors, including psilocybin and Lysergic Acid Diethylamide (LSD), have similar chemical structures and pharmacological effects when compared to conventional drug treatments for migraine headaches such as methysergide and dihydroergotamine and they have been reported to produce reductions in headache symptoms for extended periods of time after only a single or a few doses[101]. An exploratory study was conducted to investigate the impact of psilocybin on migraine headache symptoms and upon conclusion of the experiment and analysis of the data, researchers observed that the number of weekly migraine days was significantly reduced after the participants ingested the psilocybin capsule when compared to the placebo[101]. In addition, a significant reduction from the baseline was observed after the participants took psilocybin in the number of weekly migraine abortive days, weekly migraine attacks, level of pain severity and level of functional impairment[101]. Although the exact pathological mechanism of migraine headaches remains unclear, the brain's serotonergic system is suspected to play a key role in the development of the disorder[102]. Serotonin causes vasoconstriction within the nerve endings and blood vessels within the brain and low serotonin levels have been shown to cause vasodilation and the initiation of migraine symptoms[103]. Because of its agonistic effects on serotonin receptors, psilocybin can act as a potential natural treatment for migraine headaches.

Due to their condition, it is common for cancer patients to develop severe symptoms indicative of declining mental health, including depression, anxiety and an overall reduced quality of life: These symptoms are associated with a decrease in patient treatment adherence, a decreased quality of life, prolonged periods of hospitalization, as well as an increase in suicidal thoughts and/or actions[104]. Benzodiazepine drugs are the most common form of pharmacological intervention that attempts to treat depression and anxiety in cancer patients, but they have a limited efficacy and are usually only recommended to be taken for a small amount of time due to adverse effects and possible symptoms of withdrawal[104]. Psychedelic substances such as LSD and psilocybin were studied throughout the 1960s and 1970s because they were suspected to be effective treatments for mental health disorders in cancer patients, but the topic was abandoned due to safety concerns as well as an increased spike in the

recreational use of hallucinogenic substances during that time[104]. A double-blind experimental study was conducted to examine the effects of high-and-low doses of psilocybin on the symptoms of depression, anxiety and overall quality of life as well as short-and-long term changes in behavior and attitude in cancer patients. The study revealed a 78 and 83% rate of clinical response in two groups at 6 months and a 65 and 57% rate of symptom remission after ingesting psilocybin[104].

Due to the significant clinical response of the psilocybin bioactive, further research should be conducted on a larger number of patients to deduce the overall risk and long-term effects of psilocybin treatment on the mental health distress of cancer patients. In addition, because of recent research showing that fluctuations in the transmission and function of serotonin are involved in the development of depression and anxiety, psilocybin can potentially serve as a therapeutic treatment for cancer patients suffering from depression and anxiety due to its agonistic roles in 5-HT2A receptors. Research has also shown that psychedelic substances including psilocybin mushrooms may also serve as a potential treatment for the symptoms of obsessive-compulsive disorder[105]. A 2004 study of nine patients that were diagnosed with DSM-IV-defined obsessive-compulsive disorder revealed a significant decrease in the severity of the patient's OCD symptoms during at least 1 of the testing sessions as well as a 23-100% decrease in the YBOCS score after receiving varying doses of psilocybin[105].

Nutraceutical uses: The term nutraceutical is defined as "a food or a part of food, such as a dietary supplement that has a medical or health benefit, including the prevention and treatment of disease"[106]. In a research study conducted in 2006 that involved 53 patients that suffered from cluster headache disorder who also used one of the hallucinogenic substances Lysergic Acid Diethylamide (LSD) or psilocybin, it was observed that 22 of 26 psilocybin users stated that the psychedelic drug prevented headache attacks and 25 of 48 psilocybin users stating that the drug terminated their period of cluster headache symptoms[107]. In addition, 18 out of 19 psilocybin users stated that the drug successfully delayed or prevented their next cluster period, something that none of the traditional pharmacological treatments for the condition have been able to accomplish[107]. Further research should be conducted due to the promising results of this study.

Toxicological effects of the magic mushroom (psilocybin)

Central nervous system: The Central Nervous System (CNS) controls many functions essential for cognition, sensation and motor responses. Encompassing the brain and spinal cord, the CNS acts as the command center for the body, responding to changing internal and external stimuli. Understanding the toxicological effects of psilocybin on this complex system is important, as some effects can significantly alter neural communication, possibly leading to mental health changes and other neurological functions. This exploration is not only crucial for understanding the psychological impact but also for evaluating the potential therapeutic uses. One possible psychiatric symptom that may occur after ingesting magic mushrooms is attacks of anxiety during and after intoxication. For instance, a case report detailed a 24 years old man who sought outpatient care for anxiety episodes occurring 2 weeks after consumption[108]. Similarly, during intoxication, users also report episodes of anxiety[109]. Furthermore, research focusing on the epidemiology of hallucinogen use, found that use was significantly associated with anxiety disorders, but it remains unclear whether magic mushroom use directly causes these conditions. Additionally, the occurrence of anxiety-related reactions is influenced by the user's setting, with "aesthetically pleasing environments" potentially reducing distress, while a "clinical" look may increase it[110,111].

Adverse effects on decision-making can occur in individuals intoxicated by magic mushrooms, primarily due to psilocybin-induced altered states of consciousness. These changes in emotion and thought may challenge the users' perception of risk and reality[110,112]. This may result in behaviors that pose a risk of

physical harm to the user or others. One study found that 10.7% of users reported that while intoxicated with psilocybin, they made decisions that led to a risk of physical damage to themselves or others. Among the most severe outcomes of such impaired judgment are tragic instances where individuals have lost their lives by jumping from buildings[113]. These decisions can be influenced by the fact that bad trips and episodes of negative experiences during intoxication, can cause cognitive disarray, intense unease, severe distress, terror and psychotic episodes including odd and scary visions, deep paranoia and a breakdown in the perception of reality[110]. While immediate psychological effects like anxiety and impaired decision-making are concerning, psilocybin can also lead to more severe long-term consequences such as prolonged psychosis[114]. If certain precautions are taken, the occurrence rate of these episodes is rare. Although establishing a direct cause-and-effect relationship is challenging, there's evidence suggesting that individuals who exhibit adverse psychological reactions to hallucinogens often have a history of mental health issues prior to their use of these substances. In a survey of researchers who administered hallucinogens, out of 1200 participants, only one case had a psychotic reaction that lasted over 2 days. However, this participant was an identical twin of a schizophrenic patient and should have been screened out from participation[110].

Ophthalmic system: The ophthalmic system, which turns visible light into electrical signals for image processing done in the brain, consists of the eyes and its associated structures. Besides just vision, this system plays a role in balance and spatial orientation. Understanding the toxicology in this system is crucial for daily functioning. Hallucinogen Persisting Perception Disorder (HPPD) is a possible effect after using psilocybin[115]. The HPPD is a condition that causes users to experience perceptual effects like those felt during intoxication. This disorder can cause distress and/or impair functioning and may last five or more years[116]. Not much is known about what triggers HPPD so more research on the subject is needed. Another adverse effect is permanent pupillary changes. In a case study, an individual who began to use psilocybin containing mushrooms at age eleven reported permanently dilated pupils. This caused the patient discomfort and an occasional burning sensation within sunlight[39].

Cardiovascular system: The cardiovascular system is a vital system composed of the heart, blood and blood vessels. This network plays a key role in maintaining homeostasis by ensuring the continuous circulation of blood throughout the entire body. Understanding the impact of magic mushrooms on the cardiovascular system (Fig. 5) is essential, as deviations can cause significant changes throughout the body. One negative effect is an increase in blood pressure. A study found that ingesting psilocybin caused significant acute increases in blood pressure. Although no severe hypertension was observed, individuals with pre-existing hypertension should exercise caution, as the increase in blood pressure could pose additional health risks[117].

One study conducted on rats identified cardiotoxic effects after several weeks of exposure. In this experimental study, rats received psilocin every other day for 12 weeks. An ECG performed afterward revealed abnormalities such as "tachycardia, myocardial ischemia and aberrant intraventricular conduction"[118]. Tachycardia, which is characterized by excessively fast heartbeats, can cause loss of consciousness, lightheadedness, shortness of breath and palpitations[119]. Myocardial ischemia, which was also found to have been caused by psilocin, can be described as a reduction of blood flow to the heart muscle. Chest discomfort is a major symptom of myocardial ischemia and can serve as a potential predictive indicator for coronary heart disease[120]. Finally, aberrant ventricular conduction occurs when the heart conducts electrical impulses abnormally. This can lead to tachycardia and cause its associated symptoms[121]. These symptoms are possibly caused by degenerative changes in cardiomyocyte mitochondria[118].

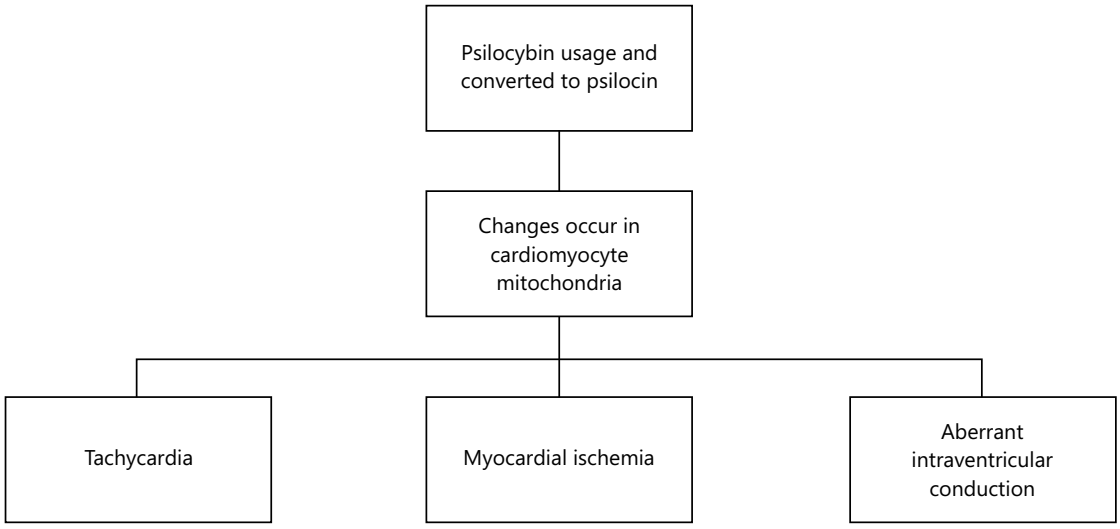

Fig. 5: Possible mechanism of psilocybin's impact on cardiovascular function

Respiratory system: The respiratory system is an essential network comprising the lungs, airways and respiratory muscles. This system facilitates gas exchange between blood and atmospheric air, allowing the body to remove carbon dioxide from the bloodstream while replenishing oxygen. It is crucial for maintaining metabolic balance and overall health. Understanding the impact of magic mushrooms on the respiratory system is critical, as significant changes could lead to permanent damage or even death. One possible negative effect on the respiratory system stems from the intense anxiety experienced during intoxication. Anxiety can induce psychogenic dyspnea, which is a psychologically uncomfortable awareness of one's own breathing. This sensation can lead to the user feeling short of breath, despite the absence of any underlying pathophysiological cause[122]. Anxiety can also cause hyperventilation, characterized by an increase in respiratory rate[123]. Given these possible side effects, it is imperative that more comprehensive research is conducted on the effects on the respiratory system. This will allow for a better understanding and management of potential health risks associated with magic mushroom use.

Digestive system: The main components of the human digestive system include the alimentary canal and all its accessory digestive organs which include the liver, gallbladder and pancreas[124]. Research has shown that there are a wide variety of serotonergic receptors located throughout the alimentary canal's epithelium and lamina propria layers, including the 5-HT2A receptors that the psilocybin molecules can target. Stimulation of these receptors can influence key gastrointestinal functions and lead to symptoms such as slower bowel movements, increased pancreatic secretions, abdominal pain and discomfort, nausea and vomiting[125]. Although there is limited research involving psilocybin's effects on this organ system, the work that has been done suggests that it can cause several adverse drug reactions in patients, including vomiting, nausea, diarrhea and abdominal pain[126]. The exact mechanisms by which psilocybin causes these symptoms have not yet been elucidated, so further research should be conducted to further understand them.

Excretory system: The human excretory system is essential for removing excess materials and waste products from the body with the goal of maintaining homeostasis[127]. Organs such as the kidneys, ureters, bladder and urethra are included in this system and release waste in the form of urine, feces and sweat[127]. Although research has shown there to be relatively few adverse effects that accompany psilocybin use, a 2019 case involving a 15 years old male suggests that consumption of this drug may induce nephrotoxicity. After two days in the hospital, the patient's creatinine concentration was 444 micromoles/L, far outside the normal range of 65-121 micromoles/L[62]. This abnormal, extremely heightened concentration of the creatinine molecule indicates that normal kidney function has been significantly

impaired, which can lead to continual decline in functionality as well as Acute Kidney Injury (AKI)[128]. The patient was confirmed to have ingested *Psilocybe cubensis* which caused him to experience symptoms such as nausea, hypertension and abdominal pain[62]. This is the first reported case of AKI caused by psilocybin-containing mushrooms, so further research should be conducted to uncover the full nephrotoxic potential of this drug.

A similar case was reported in 1992 where a 20 years old woman was admitted to the hospital with symptoms of nausea, vomiting, diarrhea, flatulence and abdominal pain after ingesting magic mushrooms that contained the psilocybin compound approximately a week prior. Upon further examination and diagnostic testing, physicians observed mild proteinuria, pyuria and hematuria and a systemic blood pressure of 160/100 mmHg, indicating hypertension[129]. Urinary cytopathology revealed mild ischemic necrosis of the convoluted tubules located within the renal cortices, however no glomerular damage was observed[129]. Studies have shown that necrosis of these convoluted tubules within the kidneys can decrease the filtration of wastes within the nephrons and therefore decrease its excretion from the body via urine, ultimately causing harmful accumulation of these waste products[130]. Based on the symptoms, the absence of the so-called "high" that hallucinogenic substances typically provide and the absence of other causative factors, physicians determined that the patient's severe acute renal failure was a result of magic mushroom ingestion[129]. Due to the scarcity of other cases involving nephrotoxicity caused by psilocybin consumption and the lack of knowledge about the exact mechanisms by which it is induced, further research should be conducted.

Endocrine system: The main goal of the human endocrine system is to synthesize and secrete hormones that maintain homeostasis within the body[69]. Recent research suggests that a variety of drugs, including psilocybin-containing mushrooms, may upregulate the nervous signals within the sympathetic nervous system and the Hypothalamic Pituitary Adrenal (HPA) axis, the primary location where hormones like epinephrine and norepinephrine are synthesized[131]. These molecules are involved in regulating homeostasis within the body by increasing heart rate, blood pressure, respiratory rate, mental alertness and muscle strength as needed[132]. In addition, scientists have discovered that DMT, a common psychedelic drug similar to psilocybin, may be converted into several catecholamines including dopamine, epinephrine and norepinephrine through a series of chemical reactions; this conversion can cause increased levels of these molecules within the brain and lead to symptoms that include bradycardia, hypertension, increased perspiration and tachypnea[131]. Research has demonstrated that psilocybin is structurally like DMT and that it has potential to undergo similar chemical reactions to form the catecholamines, ultimately leading to the same symptoms[131]. Further research should be conducted on the influence of psilocybin on the synthesis of hormones within the endocrine organs.

Immune system: The main goal of the human immune system is to fight off pathogens like fungi, bacteria, viruses and parasites that enter the body to prevent infection[133]. This protective mechanism is aided by a vast number of mediator molecules that are released to combat any inflammation caused by these pathogenic substances[134]. Research has shown that a single dose of psilocybin can cause increased amounts of pro-inflammatory cytokines such as IL-1β and TNF-α, leading to increased inflammation within specific areas of the body in the event of infection[135]. The IL-1β (interleukin-1β) is a key cytokine that is involved in the body's response to inflammation, but research has shown that it can lead to further cellular damage during cases of acute tissue injury or chronic disease[76]. In these cases, various neutrophil-derived proteases cleave pre-formed IL-1β into biologically active molecules that can result in an IL-1β-dependent inflammatory response[76]. The TNF-α (tumor necrosis factor alpha) is a cytokine known to play a major role in the regulation of the body's response to inflammation, but if present in excess, research has shown that it can contribute to the pathogenesis of several autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis and psoriasis[136]. Extensive research should be conducted to further understand the mechanisms by which psilocybin increases TNF-α synthesis within the body, as they remain relatively unknown.

Integumentary system: The integumentary system, comprising the skin, hair, nails and associated glands, serves as the primary barrier protecting the human body from the external environment. It safeguards against pathogens, physical abrasions and ultraviolet rays. Additionally, the integumentary system is crucial for sensing temperature, pain and touch. This diversity of functions underscores the importance of understanding the toxicological effects psilocybin may have on this system. Currently, research does not identify any known adverse side effects on the integumentary system. More specialized research is required to determine if any adverse effects exist.

Auditory system: The main goal of the auditory system is to take in sound waves through the ears and convert them into sensory signals to help guide human behavior when combined with other sensory information[137]. A research study investigated the effects of psilocybin on 40-Hz Auditory Steady State Responses (ASSR) and found that during the "high" that users experience when using the drug, it also decreased the amplitude of the 40 Hz ASSR, which then leads to disrupted gamma oscillations within the CNS[138]. When they remain within a normal range, these gamma oscillations are key in performing tasks such as perception (including auditory perception), movement, memory and emotion. Disruptions in these oscillations can lead to difficulties in differentiating and pronouncing similar sounds and words[139]. Furthermore, studies have demonstrated that abnormal 40 Hz gamma oscillations are found in schizophrenia patients because they disrupt the normal functioning of the interaction between parvalbumin-positive GABAergic neurons and pyramidal neurons in the prefrontal cortex region of the brain, resulting in the typical sensory deficits associated with schizophrenia[140]. These neurons are crucial for taking in sensory information and relaying it to specific regions of the central nervous system and when impaired, result in the perceptive difficulties seen in these patients[140]. Due to the possible interference of the psilocybin compound on the 40 Hz ASSR amplitude and therefore the patient's ability to effectively perceive their surroundings, it is important to continue research on the effects of the drug on auditory perception.

Smooth muscles: Smooth muscles are an important part of the muscular system, located on the walls of blood vessels and internal organs. These muscles are involuntary and are regulated by the autonomic nervous system. Smooth muscles play a wide role in the body, including regulating blood flow, controlling the movement of food and fluids through the digestive tract, facilitating childbirth and adjusting the diameter of airways. Given the importance of this system, it is essential to acknowledge the lack of research on the effects of magic mushrooms. With no known adverse side effects identified, further investigation into their effects on smooth muscles is imperative.

Skeletal muscles: Skeletal muscles are an important part of the human body. They are important in the process of regulation of movement, heat, posture, balance and breathing. These are made of repeating units of myofibrils and repeating, multinucleated cells. As of now, psilocybin does not seem to have an adverse side effect on skeletal muscles. There is not a comprehensive review on toxicological effects on different organs, so psilocybin should be investigated to see if it is able to exert a negative effect like cramping or spasms.

Spinal cord: Although limited, the research that has been conducted suggests that administering psilocybin to patients with severe spinal cord injuries can both reduce their muscle-related symptoms as well as effectively manage their chronic pain, but not without some side effects[141]. An observational study of a 37 years old man who suffered a cervical spinal cord injury due to a rollover vehicle accident was conducted; the patient has no motor function below the T4 vertebrae, which causes him to suffer from neuropathic pain below this point[142]. He describes this pain as "radiating through the abdomen and bilaterally down both legs" and as a "searing sensation with an electric shock-like quality"[142]. After the patient ingested 250 mg of psilocybin-containing mushroom powder, he experienced near-total relief of

his neuropathic pain for up to 8 hrs; however, the patient also reported a rather unexpected side effect of muscle spasms in his paralyzed limbs[142]. Although the patient reports that these spasms were soothing to his paralyzed muscles, this may not be the case for all patients suffering from a spinal cord injury and the full range of potential side effects of the drug on this demographic should be determined[142].

Future use

Preventative uses: As magic mushrooms are currently illegal in most countries, the future use of them is an interesting topic. First, to even have a future use, countries must decriminalize or make them legal. This is similar to the current use of marijuana, where more and more countries are starting to see the potential benefits of this plant and making it, at least for medicinal uses, legal. Although the recreational use of magic mushrooms in the immediate future is doubtful, as research continues to improve on this subject, it becomes increasingly likely that this decriminalization is possible and likely. The second thing that is important to mention is the definition of "future". As mentioned earlier, the present use of magic mushrooms is illegal. Because of this, many current uses can be listed under this category, since the current use is only under lab or government allowance. This puts a damper on the term "future use" since almost all use will be future. However, for this paper, "future use" will be direct research that does not have substantial amounts of work behind it (Fig. 6).

Essentially, this paper assumes that topics with more research will be quickly implemented should magic mushrooms become legal tomorrow. Conversely, the "future use" would be for topics with less concrete studies and research done, which would be implemented later than the former. Because of this, the true future use of psilocybin is going to be primarily focused on research so that it can be better understood. First, the hallucinogenic effects should be studied. By doing this, the government could be better informed in their decision to possibly legalize psilocybin. Conversely, if the government decided to not legalize it, these studies might be able to diminish the hallucinations caused by psilocybin, which could encourage the legalization of it. Next, its effects on mental health should be studied further. These seem to be the most promising of the therapeutic effects (will be discussed later). Next, anti-cancer and antioxidant effects should be further investigated.

Finally, research focusing on the prophylactic uses for magic mushrooms is slim. Since magic mushrooms are illegal, it is hard to get the government to sign off on a longitudinal study that would be expensive and over a long period of time. Similarly, research on magic mushrooms is not very dense. It is more important, then, to focus on what magic mushrooms can do immediately than how they affect the body months after administration. This is because how psilocybin in the mushrooms affects the body is important to understand how it will affect the body over long periods of time. With these ideas being

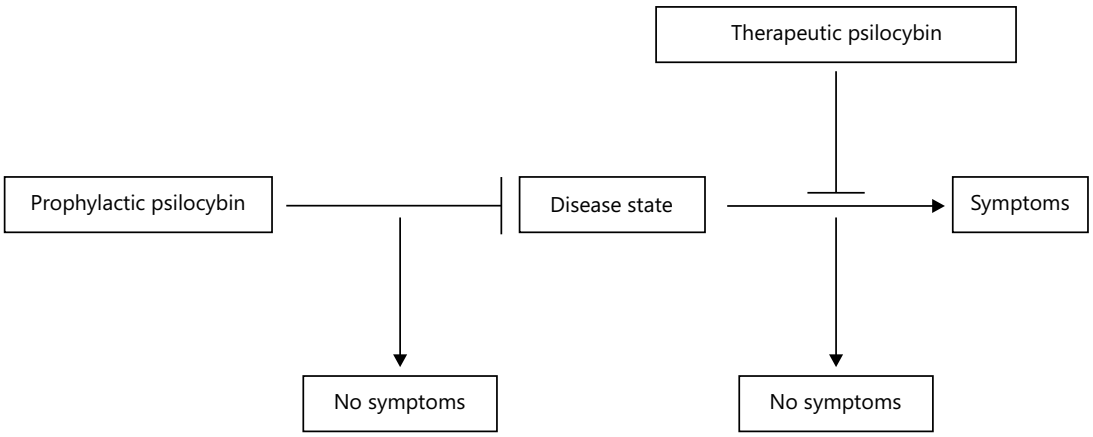

Fig. 6: Uses of psilocybin as a flowchart

established, the primary research on prophylactic use of magic mushrooms has been centered around preventing migraines. In many instances, psilocybin has been found to decrease the number of weekly migraines as compared to a placebo[102]. This is very interesting because the 5-HT2A receptor has been found to not play a part in migraine pathophysiology[102], yet migraines are still influenced by psilocybin. This could be for multiple reasons. First, psilocybin can influence many other 5-HT receptors and these may play a role in dictating the response. Also, many researchers are starting to look towards the rewiring of the brain by psychedelics. They want to see if common psychedelics can exert effects on the whole body or brain outside of their single receptors.

Therapeutic: With these ideas being established, the primary research on prophylactic use of magic mushrooms has been centered around the idea of "microdosing". As mentioned earlier, psilocybin is a psychoactive compound and can produce a euphoric feeling and visual and auditory changes. Although this is its intended purpose for recreational use, it is less than ideal for medicinal uses. Microdosing prevents this. By taking very small doses of psilocybin, in certain cases, it is possible to elicit many of the positive side effects without obtaining the hallucinogenic ones[142]. This will allow for everyday use of psilocybin and can prevent it from interfering with people's work or social lives. One reason that microdosing is not well-researched is because of the impreciseness. Many people respond to different doses and a well-defined range of psilocybin is not well defined. Similarly, since microdosing is generally with illegal substances, it is hard to get firsthand or, more importantly, reliable, unbiased responses to possible microdosing ranges. However, a general, although unscientific, range of ten to twenty percent of the active doses can be used. The biggest use of microdosing, with psilocybin specifically, is to prevent depression. In fact, a study decided to evaluate the possible effects of microdosing on anxiety and depression. In this study (n = 8,703), a DASS-21 score was used to evaluate these mental health disorders. They reported a significant decrease in these scores for the microdosing group[142]. Once again, these effects are possibly due to allowing psilocybin to exercise its positive effects while being at a low enough dose to prevent hallucinations, however, until more research is done it is impossible to know for sure.

Similarly to mental health, microdosing is starting to be evaluated for possible treatments for other disease states. For example, although microdosing for acne has not been evaluated expressly in academic journals, it does have some merit. In one study, it was shown that fungi, as well as magic mushrooms, have possible cosmetic effects which could affect acne[140]. Alongside this other academic journals supporting possible psilocybin effects in cosmetics, should steer future research and possible future treatment.

CONCLUSION

Magic mushrooms are a subset of mushrooms that possess the compound psilocybin. Psilocybin seems to be a strong natural bioactive, with effects in most organ systems in humans. Similar to the promising effects of psilocybin, it also contains minor adverse effects. These pharmacodynamic actions, though, must be studied more in-depth. Currently, psilocybin is illegal both recreationally and medicinally in almost all countries, which makes further research difficult. The current work depicted delves into the historical, current and potential future prophylactic and therapeutic applications of Psilocybin, a psychedelic compound commonly found in magic mushrooms, on various organ systems. As mankind progressively gravitates towards natural bioactives in healthcare, understanding the pharmacology of historically used plants becomes paramount. Magic mushrooms, with their psychedelic properties mediated by psilocybin, offer a rich tapestry of therapeutic potential across various physiological realms. It is evident that the conversion of psilocybin to psilocin in the liver initiates a cascade of pharmacological effects on multiple organ systems as the compound possess an agonist activity towards the 5-HT2A receptors that are extensively located in the central nervous system, particularly in brain regions essential for learning and memory. Numerous studies have elucidated psilocybin's ability to induce profound alterations in consciousness, which can be harnessed for therapeutic purposes, particularly in the management of

neuropsychiatric disorders such as depression, anxiety and substance use disorders. Moreover, emerging research suggests its neurogenic and neuroplastic properties, suggesting a possible, potential, prophylactic and therapeutic benefit in various neurodegenerative diseases and disorders. Further, investigations into the cardiovascular and respiratory systems indicate a promising therapeutic pharmacological profile of the natural bioactive, with minimal acute toxicity observed even at higher doses. Preliminary evidence also suggests modulations of inflammatory pathways by psilocybin, offering potential therapeutic avenues in conditions such as inflammatory bowel disease and autoimmune disorders. In recent times, the resurgence of interest in natural bioactives underscores a paradigm shift towards holistic approaches to healthcare. Magic mushrooms, with their multifaceted therapeutic properties, epitomize this trend, offering not only symptomatic relief but also avenues for profound healing and personal growth. As research into magic mushrooms continues to evolve, it becomes crucial in navigating the complexities of therapeutic innovation while upholding standards of safety and efficacy.

The integration of magic mushrooms into mainstream medicine holds the promise of ushering in a new era of holistic healthcare, grounded in the wisdom of nature and propelled by scientific inquiry. Looking ahead, the future of psilocybin as a therapeutic agent appears promising, albeit with several caveats. Establishing standardized dosing regimens and refining administration protocols are imperative to maximize efficacy and minimize adverse effects. Additionally, robust safety measures, including screening protocols and patient monitoring, should be implemented to mitigate potential risks, especially concerning psychological distress and exacerbation of underlying psychiatric conditions. In conclusion, while psilocybin holds immense therapeutic promise across various human organ systems, its widespread adoption necessitates a balance between its therapeutic potency and safety. Through continued and rigorous research and regulatory oversight, the integration of psilocybin into the mainstream of medicine may herald a transformative paradigm shift in the evolving healthcare, offering new therapeutic strategies for various diseases and disorders involving various organ systems.

SIGNIFICANCE STATEMENT

Natural bioactives were the source of several medications and therapies for a wide range of illnesses until efficient separation methods were developed. Strangely, a growing number of individuals appear to be returning to a need for these natural bioactives as medicine progresses. Because of this, it's critical to learn about the pharmacology of historically utilized herbs and how they specifically work. Enchantment a polyphyletic genus of plants known as mushrooms is distinguished by the presence of psilocybin, a hallucinogenic ingredient that induces hallucinations and alters mental state. The historical, contemporary and potential applications of magic mushrooms to the human healthcare system are thoroughly examined in this paper. These applications include nutritional, prophylactic and therapeutic approaches.

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