Review

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Review

Psilocybin in Older Adults: Therapeutic Opportunities in Inflammation-Driven Disorders of Aging—From Depression to Neurodegeneration

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Abstract

Aging is associated with chronic, low-grade inflammation ("inflammaging"), which contributes to neuropsychiatric and neurodegenerative disorders such as depression, Alzheimer's disease, and Parkinson's disease. Conventional pharmacotherapies often provide limited benefit in older adults and are further complicated by polypharmacy and drug-drug interactions. Psilocybin, a serotonergic psychedelic acting primarily as a 5-HT_2A receptor agonist and currently undergoing accelerated clinical development, has emerged as a potential multimodal therapeutic agent addressing these challenges. Acting via its active metabolite psilocin, 5-HT_2A-mediated signaling biases cortical glutamatergic transmission, enhances TrkB/BDNF pathways, and modulates neuroimmune cascades (including NF-κB), with convergent systems-level effects such as reorganization of the default mode network. Human studies report acute reductions in TNF-α with variable effects on IL-6 and CRP, consistent with an immunomodulatory profile. Pharmacokinetically, psilocybin shows properties advantageous in geriatric care: rapid onset, short half-life, and predominant phase-II glucuronidation, reducing interaction risk. Controlled studies demonstrate rapid antidepressant and anxiolytic effects in major depressive disorder, treatment-resistant depression, and existential distress, with emerging feasibility signals in neurodegeneration. Together, these findings support the hypothesis that a time-limited, mechanism-based intervention may improve mood and cognition while attenuating inflammation. This review integrates current evidence on psilocybin's neuroimmune and pharmacokinetic mechanisms relevant to aging, outlining its potential role in inflammation-related disorders and highlighting the need for targeted studies in older adults, who remain underrepresented in psychedelic research.

Keywords: psilocybin; inflammation; aged; 5-HT2A; receptor; serotonin; neuronal plasticity; depression; neurodegenerative diseases

1. Introduction

According to the World Health Organization (WHO), the proportion of the global population aged 65 and over is projected to nearly double - from 12% in 2015 to 22% by 2050. More than 20% of older adults suffer from either a mental or neurological disorder, with depression and dementia being among the most prevalent neuropsychiatric conditions in this age group [1,2].

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Aging is increasingly recognized as a state of chronic, low-grade systemic inflammation - a phenomenon often referred to as inflammaging - characterized by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) in the absence of active infection. This immunosenescent state contributes to the pathogenesis of numerous age-related conditions, including cardiovascular disease, sarcopenia, frailty, and neuropsychiatric disorders [3–5].

Neuroinflammation, in particular, plays a central role in the progression of various neurodegenerative and psychiatric disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and major depressive disorder (MDD) [6,7]. These conditions are marked by chronic activation of microglia, blood-brain barrier (BBB) disruption, oxidative stress, and dysregulated cytokine production, which together contribute to neuronal injury, demyelination, and synaptic dysfunction [8,9].

In AD, pro-inflammatory cytokines and microglial activation facilitate amyloid-β aggregation and tau hyperphosphorylation, exacerbating cognitive decline [10]. In PD, neuroinflammation contributes to dopaminergic neuron degeneration in the substantia nigra [11]. In MS, immune-mediated demyelination and glial activation lead to lesion formation and progressive disability [12], while in ALS, inflammatory responses correlate with motor neuron loss and disease progression [13]. Similarly, following traumatic brain injury (TBI) or stroke, neuroinflammation sustains secondary neuronal damage and impairs long-term recovery [14,15].

Moreover, elevated concentrations and activity of immune cells, along with increased levels of pro-inflammatory cytokines, have been observed in a subset of patients with depression - especially those with treatment-resistant depression (TRD) and suicidal behaviour [16,17]. Depression itself has been associated with an increased risk of subsequent dementia, suggesting a bidirectional and biologically intertwined relationship between affective and neurodegenerative pathology [18]. In older adults, this inflammatory burden is further amplified by elevated levels of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and gut microbiota disturbances [19].

Given the limitations of conventional therapies, which have shown limited long-term efficacy in managing chronic neuroinflammation, especially in older populations, there is an urgent need for novel interventions that can precisely modulate inflammatory pathways while simultaneously improving mood, cognition, and functional status.

Rapid-acting agents with antidepressant properties, including serotonergic psychedelics such as psilocybin - have attracted attention as candidate multimodal therapeutics. In clinical studies, psilocybin has shown promise for major depressive disorder (MDD), TRD, anxiety, and existential distress associated with life-threatening illness, with benefits that can persist for months after a single administration [20,21]. These compounds exert multimodal effects by modulating neuroplasticity, serotonergic and glutamatergic signaling, and immune activity. Psychedelics have demonstrated the ability to reduce the expression of pro-inflammatory cytokines, regulate microglial activation, and promote synaptogenesis, making them attractive therapeutic tools in inflammation-driven psychiatric and neurodegenerative conditions [22].

Because inflammaging and multimorbidity frequently co-occur in older adults, the rationale for interventions that act on immune and neural targets simultaneously is compelling. Polypharmacy-prevalent in this population - is associated with increased risks of cognitive impairment, drug–drug interactions, and poor adherence (Maia et al., 2025). In geriatric care, the priority is often to simplify pharmacological regimens rather than to add new medications. Therefore, therapeutic agents that offer multimodal benefits - anti-inflammatory, neuroplastic, and mood-stabilizing effects - within a single compound are of particular interest in this population.

In this narrative review, we focus on psilocybin, a serotonergic psychedelic acting primarily as a 5-HT_2A receptor agonist, with the most advanced clinical evidence among psychedelic compounds. As the field of psychedelic-assisted therapy evolves, it is essential to critically assess existing data regarding its efficacy, safety, and underlying mechanisms - particularly in the context of older adults,

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who are often burdened with complex comorbidities such as depression, anxiety, existential distress, chronic pain, and neurodegenerative conditions.

The aim of this review is to evaluate the therapeutic potential of psilocybin in geriatric neuropsychiatry by examining its pharmacokinetics, mechanisms of action, clinical efficacy, and safety, with a focus on inflammation-related disorders of aging. More importantly, we seek to highlight the critical need for greater inclusion of older adults in clinical trials with psychedelics - a group that remains severely underrepresented despite potentially benefiting the most from such interventions (Figure 1).

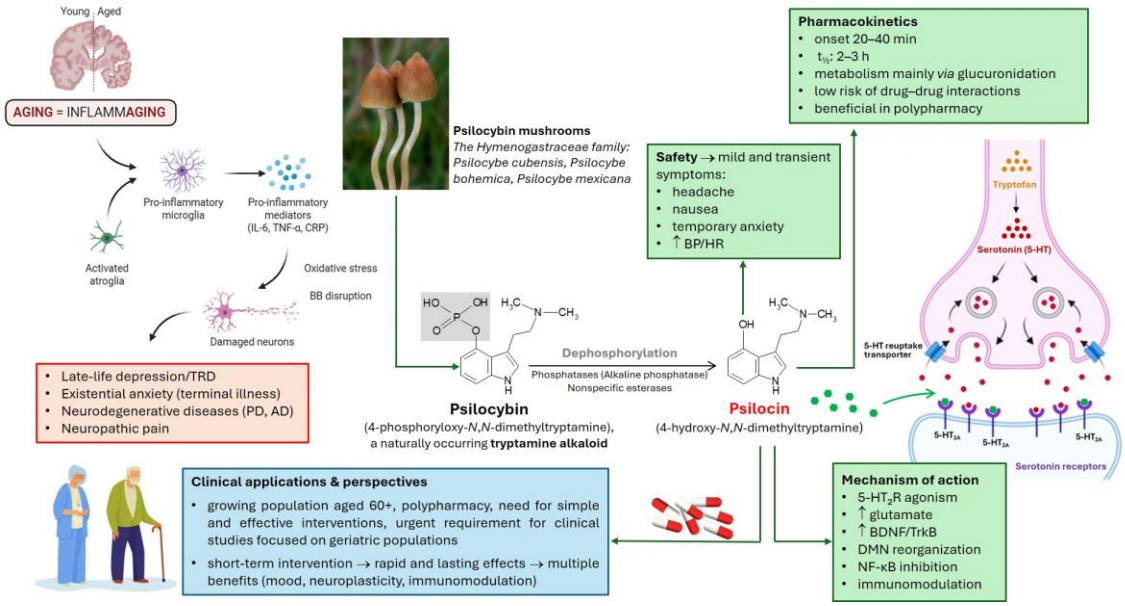

Figure 1. Overview of psilocybin in elderly: from natural origin to synaptic action. Created with BioRender.com and MDL ISIS Draw version 2.3.

2. Psilocybin

Psilocybin has emerged as a compound of growing scientific interest due to its unique ability to modulate consciousness, cognition, and emotional states. It is a naturally occurring tryptamine-derived psychedelic compound found in certain species of mushrooms, such as *Psilocybe cubensis* and *Psilocybe Mexicana*. These so-called "magic mushrooms" have a long history of ritual and therapeutic use in indigenous cultures of Central and South America. Archaeological findings, including ceremonial "mushroom stones," suggest that psilocybin-containing mushrooms were used as early as 3000 years ago. The Aztecs referred to them as *teonanacatl* "the flesh of the gods" and considered them sacred tools for spiritual insight and healing [23].

Modern scientific interest in psilocybin began in the late 1950s when Swiss chemist Albert Hofmann first isolated and synthesized the compound. In the 1960s, psilocybin gained broader attention in psychiatric research, notably through studies conducted by Walter Pahnke and Timothy Leary, which explored its impact on consciousness, behaviour, and mental health [24].

However, widespread recreational use and the countercultural movement of that era led to increasing concerns over public safety and misuse. As a result, in 1963, the United States imposed strict legal restrictions on the production, distribution, and use of serotonergic psychedelics, including psilocybin and lysergic acid diethylamide (LSD). Psilocybin was subsequently classified as a Schedule I substance under the Controlled Substances Act - defined as having a high potential for abuse and no accepted medical use. Similar restrictions were adopted in many other countries, effectively halting research for decades [25].

In recent years, rising interest in psychedelic-assisted therapies has renewed attention to psilocybin's clinical potential. Several preclinical and clinical studies have demonstrated its possible

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efficacy in treating a range of psychiatric conditions, including depression, anxiety, and substance use disorders. In recognition of these findings, the U.S. Food and Drug Administration (FDA) granted psilocybin "Breakthrough Therapy" designation in 2018 for its use in TRD, facilitating accelerated clinical evaluation and regulatory support [26].

While regulatory progress has been most notable in the United States, European frameworks have been slower to adapt [27]. Given the rising global burden of mental illness and the specific needs of aging populations - including military veterans exposed to chronic psychological stress - there is growing momentum to accelerate clinical research and policy reform. Recent geopolitical events, including large-scale armed conflicts, may further catalyse interest in novel therapies capable of addressing trauma, depression, and existential distress in affected populations.

3. Mechanism of Action of Psilocybin: Implications for the Aging Brain

Psilocybin is a prodrug rapidly metabolized into psilocin, its pharmacologically active form. Psilocin is a tryptamine compound structurally analogous to serotonin (5-HT) and acts primarily as a partial agonist at the 5-HT_2A receptor subtype. These receptors are highly expressed in brain regions involved in cognition, emotion regulation, and perception - including the prefrontal cortex, anterior cingulate cortex, and visual cortex [23,28].

The psychedelic effects of psilocin, understood as alterations in perception, cognition, and self-referential processing, are largely mediated by biased agonism at 5-HT_2A receptors, resulting in distinct intracellular signalling patterns relative to endogenous serotonin. This leads to increased glutamate release in cortical microcircuits and subsequent activation of neuroplasticity-related cascades, including the upregulation of brain-derived neurotrophic factor (BDNF) and engagement of tropomyosin receptor kinase B (TrkB) signalling [29,30]. Notably, recent data suggest that psilocin may also act as an allosteric modulator of TrkB, enhancing BDNF-driven neuroplasticity independently of serotonergic pathways [30].

These mechanisms are particularly relevant in the context of aging, as neuroplasticity and BDNF signalling decline with age and are further impaired in neuropsychiatric and neurodegenerative disorders [31]. By modulating plasticity-related signalling, psilocybin may counteract age-related synaptic rigidity and support adaptive emotional and cognitive functioning in older adults.

Psilocybin also modulates large-scale brain networks. Functional neuroimaging studies have consistently shown reduced activity and connectivity within the default mode network (DMN) - a system implicated in self-referential thought, rumination, and affect regulation - which is often hyperactive in depression and functionally disrupted in aging and dementia [32–34]. In older adults, age-associated changes in DMN integrity may influence both the subjective and therapeutic effects of psilocybin, possibly shifting the mechanism of benefit from intensely perceptual experiences toward improved emotional regulation and psychological flexibility.

At the cellular level, psilocybin induces rapid structural plasticity, including increased dendritic spine density and synaptogenesis in key regions such as the medial prefrontal cortex and hippocampus - areas known to atrophy with aging and neuroinflammation [5,29,35]. These neuroadaptive effects may underlie the sustained improvements in mood and anxiety observed even after a single administration, offering a potential therapeutic avenue for older adults with depression or neurodegenerative conditions.

Although 5-HT_2A receptor activation is central to psilocybin's mechanism of action, psilocin also binds with lower affinity to other serotonergic subtypes (5-HT_1A, 5-HT_2C, 5-HT_1D), and modulates glutamatergic and dopaminergic systems [23,28]. Consistent with this, increased extracellular dopamine has been observed in the nucleus accumbens and frontal cortex following psilocybin administration, potentially enhancing reward processing and motivational drive, which may be blunted in late-life depression [24,36,37].

In sum, psilocybin engages a network of molecular and systems-level mechanisms - serotonergic signalling, glutamate transmission, neurotrophic modulation, and DMN reorganization - that may

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be particularly suited to addressing the multifactorial neurobiology of mood and cognitive disorders in older adults. Its ability to influence synaptic remodeling, emotional processing, and inflammation pathways sets it apart from typical monoaminergic drugs and highlights its potential for geriatric neuropsychiatry (Table 1).

Table 1. Mechanisms of action of psilocybin/psilocin and their relevance to aging. Summary of receptor-level, synaptic, intracellular, neuroimmune, and network-level processes potentially engaged by psilocybin/psilocin, with concise aging relevance statements (right column).

Level	Mechanism / target	Core effect	Aging relevance
Receptor	Partial, biased agonism at 5-HT_2A (plus lower-affinity 5-HT_1A/5-HT_2C/5-HT_1D)	Distinct intracellular signaling vs endogenous 5-HT; drives psychedelic state	Preserved post-synaptic 5-HT_2A signaling may bypass age-related declines in presynaptic 5-HT tone
Synaptic signaling	Cortical glutamate surge downstream of 5-HT_2A	Triggers plasticity cascades (activity-dependent)	Counters age-related synaptic rigidity
Neurotrophic pathways	BDNF ↑; TrkB engagement (allosteric modulation by psilocin)	Enhances synaptogenesis and spine formation	Restores plasticity pathways that decline with age
Intracellular cascades	MAPK/ERK, PI3K/Akt, mTOR	Gene programs for growth, survival, remodeling	Supports repair/adaptation in vulnerable aging circuits
Network-level	Default Mode Network (DMN) activity/connectivity ↓; network reorganization	Reduces rumination/self-referential rigidity; increases cognitive flexibility	DMN is altered in aging/dementia; normalization may aid mood/cognition
Limbic processing	Amygdala responsivity recalibration	Improves processing of emotional salience	Targets affective dysregulation common in late-life depression/anxiety
Dopaminergic interplay	Striatal extracellular dopamine ↑ (indirect)	Boosts reward/motivation	May mitigate anergia/anhedonia in older adults with depression
Neuroimmune (central)	5-HT_2A-linked NF-κB inhibition; microglial modulation (TLR4↓, morphology shift)	↓TNF-α/IL-1β/IL-6; reduced pro-inflammatory transcription	Addresses inflammaging and microglial priming
Neuroimmune (systemic)	Acute TNF-α ↓; sustained IL-6/CRP ↓ at ~7 days (dose/time dependent)	Systemic anti-inflammatory signature after single dose	Potentially greater benefit in older adults with elevated baseline inflammation
Tryptophan metabolism	5-HT_2A-linked shift in kynurenine pathway (↓ quinolinic acid / ↑ kynurenic acid)	Lowers neurotoxic load; supports neuroprotection	Relevant to late-life depression/AD with kynurenine dysregulation
Glutamate–excitotoxicity	Modulation of glutamatergic tone	Reduces excitotoxic stress contributing to neuroinflammation	Aging brains are more susceptible to excitotoxic injury

4. Anti-Inflammatory Action of Psilocybin

Psilocybin's potential anti-inflammatory action is believed to occur primarily through agonism at serotonin 5-HT2A receptors, which are expressed not only in the brain but also in peripheral and central immune cells. In vitro studies have shown that psilocybin reduces the immune response triggered by bacterial lipopolysaccharides (LPS), specifically by suppressing pro-inflammatory cytokines such as IL-1β and TNF-α [29,38]. In healthy human participants, a single dose of psilocybin has been shown to acutely lower TNF-α and, more persistently, reduce circulating levels of IL-6 and CRP for up to seven days post-administration [39]. These reductions were associated with improvements in mood and attenuation of stress-induced cortisol reactivity.

Upon binding to 5-HT2A receptors, psilocin initiates a complex intracellular cascade involving Gq-protein coupling, activation of phospholipase C (PLC), and downstream messengers such as inositol trisphosphate (IP3) and diacylglycerol (DAG). These second messengers stimulate protein kinase C (PKC) and release calcium from intracellular stores, which in turn activate transcription factors such as c-Fos and EGR1. These transcriptional changes are associated with neuroplasticity, cellular resilience, and immune regulation [24,40]. Other signalling pathways modulated by

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psilocybin include MAPK/ERK, PI3K/Akt, and the mammalian target of rapamycin (mTOR), all of which are implicated in inflammation resolution and neurogenesis [41,42].

A key mechanism by which psilocybin may exert anti-inflammatory effects involves inhibition of the nuclear factor-kappa B (NF-κB) pathway - a central regulator of immune response. Activation of 5-HT_2A receptors interferes with NF-κB signalling by preventing the degradation of IκB, thereby keeping NF-κB sequestered in the cytoplasm and limiting transcription of pro-inflammatory genes [43]. Psilocin has also been shown to affect microglial morphology and function, decreasing Toll-like receptor 4 (TLR4) expression and reducing NF-κB activation in LPS-stimulated mouse microglia [38].

Psilocybin may also influence inflammatory status through serotonergic regulation of the kynurenine pathway. Activation of 5-HT_2A receptors shifts tryptophan metabolism away from the neurotoxic metabolite quinolinic acid toward kynurenic acid, a compound with known neuroprotective and anti-inflammatory effects [23,44]. Additionally, psilocybin modulates glutamate release in cortical and hippocampal circuits, potentially reducing excitotoxicity - a known contributor to neuroinflammation [45].

Unlike NSAIDs and corticosteroids, which target broad peripheral inflammatory pathways, psychedelics selectively modulate central neuroimmune interactions. By acting on specific signalling cascades such as PI3K/Akt, mTOR, and NF-κB, psychedelics exert cell-type-specific and regionally targeted effects in the brain. Importantly, they promote neuroplasticity while simultaneously reducing microglial activation and pro-inflammatory cytokine expression - a dual action not typically achieved by conventional anti-inflammatory drugs [46,47] (Table 1).

While these mechanisms are supported by robust in vitro and preclinical evidence, findings in human populations remain preliminary. Studies using psilocybin in healthy volunteers have produced mixed results, possibly due to differences in dosing, timing of biomarker assessment, and baseline immune status [48]. Inflammation-related benefits may be more pronounced in individuals with elevated inflammatory markers or dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, which is common in older adults with depression and neurodegenerative conditions. In light of psilocybin's anti-inflammatory, neuroplastic, and neuroimmune effects, we next summarize clinical outcomes in inflammation-linked conditions, in which it may offer a new therapeutic approach.

5. Clinical Applications in Inflammation-Linked Conditions

5.1. Depression and Anxiety

Psilocybin has demonstrated clinically meaningful antidepressant and anxiolytic effects across randomized and open-label clinical studies in MDD and TRD populations. Symptom reduction typically occurs within days and, when embedded within structured psychotherapeutic support, may persist for weeks to months.

MDD/TRD. In MDD, a randomized, waiting-list–controlled study with two supported psilocybin dosing sessions (20 mg/70 kg followed by 30 mg/70 kg; mean interval of ~1.6 weeks) reported a 71% response rate and a 54% remission rate at 4 weeks, with sustained benefit in a substantial subset at 12 months [49,50]. In a head-to-head phase-2 trial, two 25-mg psilocybin sessions (3 weeks apart) outperformed escitalopram on multiple secondary outcomes, including changes in the Beck Depression Inventory (BDI-1A), Hamilton Depression Rating Scale (HAM-D-17), Montgomery–Åsberg Depression Rating Scale (MADRS), State–Trait Anxiety Inventory (STAI), and measures of well-being and functional impairment, with higher response (70% vs. 48%) and remission (57% vs. 28%) rates at week 6 [51]. In TRD, open-label protocols that administered psilocybin as 10 mg followed by 25 mg seven days later produced marked short-term improvements with persistence in a subset at 3–6 months [52]. A larger phase 2b study found that a single 25-mg session produced the greatest short-term improvement at week 3, with between-group differences narrowing by week 12 - useful context when setting expectations for durability after one dose [53]. Complementing SSRI-washout paradigms, an exploratory open-label study in which a single 25-mg

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psilocybin session was added to ongoing SSRI therapy achieved week 3 response and remission rates of 42% each, indicating that efficacy signals can emerge without suspending background antidepressants [54].

Beyond symptomatic improvement, increasing attention has been directed toward the role of inflammation in depression. Treatment-resistant and late-life depression are frequently associated with elevated inflammatory markers, and evidence suggests that patients with higher baseline inflammation may derive greater benefit from immunomodulatory interventions [17]. Although psilocybin has been proposed to interact with neuroimmune pathways, clinical evidence supporting its anti-inflammatory effects in patient populations remains limited.

Serious illness and death anxiety. Two double-blind, cross-over RCTs in patients with life-threatening cancer demonstrated rapid and sustained reductions in anxiety and depressive symptoms following a single moderate-to-high psilocybin dose, with approximately 60–80% of participants maintaining clinically significant improvements at 6 months [55,56]. Reductions in death anxiety and changes in perceptions of mortality were assessed using validated instruments, including the Death Transcendence Scale. Patients frequently reported profound shifts in perspectives on life and death, and the intensity of "mystical-type" experiences statistically mediated clinical benefit - phenomena particularly relevant to existential distress in later life [55,57].

5.2. Neurodegenerative Disorders

Across neurodegenerative diseases, neuroinflammation, synaptic vulnerability, and impaired neuroplasticity create a convergent therapeutic target profile for serotonergic psychedelics. Mechanistically, 5-HT_2A–biased signalling has been shown to attenuate NF-κB–dependent transcription and peripheral cytokine production, with complementary effects on microglial states and mTOR/BDNF-linked structural plasticity - an immune-neuroplastic "double hit" particularly relevant to diseases such as PD and AD [58,59]. Recent preclinical evidence further supports a potential role of psilocybin in modulating biological aging processes. In a murine model, psilocybin administration increased survival in aged animals and extended cellular lifespan, effects associated with reduced oxidative stress, preservation of telomere length, and upregulation of longevity-related pathways such as SIRT1 signalling [60].

Parkinson's disease. First-in-disease clinical data now indicate that psilocybin therapy is feasible in PD and may benefit domains beyond mood. In an open-label pilot (NCT04932434), 12 adults with mild–moderate PD and comorbid depression and/or anxiety received two supported doses (10 mg then 25 mg) with structured psychotherapy. The intervention was well tolerated with no serious adverse events or psychosis exacerbation. Clinically, non-motor symptoms and activities of daily living improved substantially, with smaller but significant gains on standardized motor assessments, and better performance on selected cognitive tasks in domains of memory and executive function. Depressive and anxiety symptoms decreased and remained lower at 3 months in exploratory follow-up. Notably, nine participants continued stable carbidopa–levodopa without apparent interaction signals [61]. Complementing these pilot data, a detailed case report described a 43-year-old person with PD without depression who underwent four high-dose psilocybin-assisted psychotherapy sessions over one year. Treatment was well tolerated and associated with durable reductions in anxious ruminations, improved dispositional optimism and disease acceptance, and stable motor status - underscoring potential quality-of-life benefits even when mood disorder is subthreshold [62]. Together, these signals justify controlled trials to disambiguate specific effects on mood, non-motor burden, motor function, and cognition in PD.

Alzheimer's disease. Initial clinical trials are underway: an open-label pilot at Johns Hopkins is testing two psilocybin sessions at weeks 4 and 6, embedded within eight weeks of weekly psychological support, to alleviate depressive symptoms in people with MCI or early AD, with outcomes tracked up to ~6 months (NCT04123314).

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Neuropathic pain. Early evidence suggests that psilocybin may deliver clinically meaningful analgesia in neuropathic pain. Case reports and small series in conditions such as complex regional pain syndrome and phantom-limb pain describe marked reductions in pain intensity and interference, sometimes accompanied by reduced analgesic use, after one or a few supported dosing sessions [63,64]. Preclinical data align with these observations: a single psilocybin dose produces persistent antinociception in neuropathic models and engages 5-HT$_2$A-linked plasticity mechanisms relevant to central sensitization [64,65]. Trial readiness also appears high - most patients (~77%) in the PEACE-PAIN prospective assessment indicated willingness to enroll in an RCT, citing the importance of credible controls and structured psychological support [66].

5.3. Pharmacokinetics of Psilocybin

As noted above, psilocybin is a prodrug whose pleiotropic effects are mediated by its pharmacologically active metabolite, psilocin, formed rapidly via dephosphorylation by alkaline phosphatases and non-specific esterases during first-pass metabolism. Following oral administration, plasma psilocin reaches its maximum at ~ 2 hours (C_max 15 - 20 ng/mL), whereas subjective effects begin 20 - 40 minutes after dosing, peak at 60 - 90 minutes, and last 4–6 hours. The elimination half-life is 2 - 3 hours. These pharmacokinetic parameters have been reported in trials using both fixed oral dosing (e.g., 25 mg) and weight-adjusted regimens (typically 0.2–0.3 mg/kg) [55,57,67].

Approximately 80% of psilocin is metabolized via phase II conjugation, primarily through glucuronidation by the isoenzymes UGT1A10 (intestinal) and UGT1A9 (hepatic) (Figure 2). The resulting metabolite, psilocin-O-glucuronide, is pharmacologically inactive and is excreted predominantly in urine, with elimination essentially complete within 24 hours. Only about 1.5% of the administered psilocybin dose is excreted unchanged as free psilocin [68].

The remaining fraction of psilocin is cleared via minor metabolic pathways, including monoamine oxidase (MAO) and aldehyde dehydrogenase (ALDH), leading to the formation of 4-hydroxyindole-3-acetaldehyde (4-HIA). This intermediate is further metabolized either to 4-hydroxyindole-3-acetic acid (4-HIAA) - a major urinary metabolite - or to 4-hydroxytryptophol (4-HTP), likely via alcohol dehydrogenase (ADH) [69].

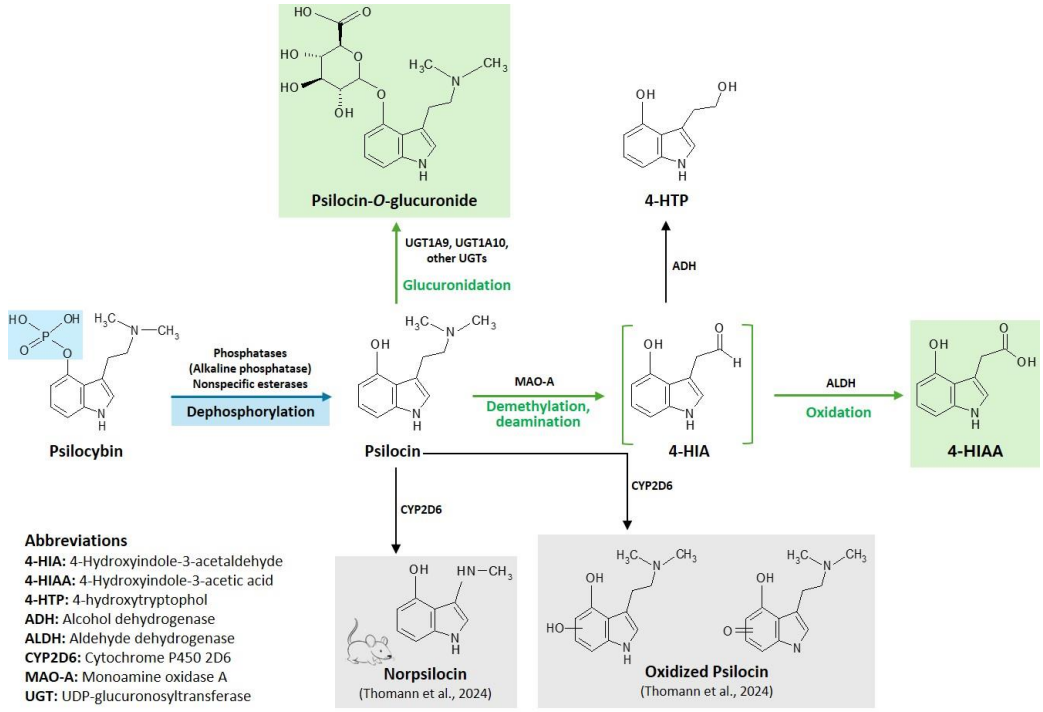

Figure 2. Synthesis and metabolic pathways of psilocin. Created with MDL ISIS Draw version 2.3. The primary active metabolites (highlighted in green) include: psilocin-O-glucuronide (the most abundant) and 4

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Hydroxyindole-3-acetic acid (4-HIAA). The intermediate metabolite (4-HIA, 4-Hydroxyindole-3-acetaldehyde) is shown in green brackets, while potential or not structurally confirmed metabolites are displayed on a grey background.

From a clinical standpoint, this metabolic profile offers distinct advantages in older adults. The reliance on phase II metabolism, which remains largely preserved with age, and minimal involvement of CYP450-mediated pathways - unlike other tryptamines such as N,N-dimethyltryptamine (DMT) or LSD - suggest a lower risk for pharmacokinetic drug–drug interactions [67]. This is particularly relevant in geriatric patients frequently affected by polypharmacy. Over the studied range, psilocin displays linear pharmacokinetics, and interindividual variability is not explained by body weight [28]. Additionally, the short half-life of psilocin (2–3 hours) contributes to a favourable safety profile, minimizing the risk of drug accumulation and allowing for time-limited therapeutic windows. Compared to commonly prescribed psychotropic agents - such as benzodiazepines, which often have long half-lives and are associated with sedation, falls, and cognitive decline, or antipsychotics, which carry significant extrapyramidal and metabolic risks - psilocybin may represent a safer and more manageable pharmacological option, particularly in older adults, when administered within controlled clinical settings.

5.4. Effectiveness of Psilocybin in Older Adults

5.4.1. Neurobiological Considerations

Taking into account the favourable pharmacokinetic profile of psilocybin in older adults - including preserved phase II metabolism, low CYP450 interaction risk, and short half-life - an important question arises: can psilocybin be equally effective in this population, whose neurobiology may differ significantly from that of younger patients? The effectiveness of psilocybin in this population may be modulated by age-related alterations within the serotonergic system. While serotonergic neuron firing rates and central serotonin synthesis are known to decline with age, this may not necessarily impair the pharmacodynamic response to psilocybin [70]. Unlike selective serotonin reuptake inhibitors (SSRIs), psilocybin acts as a direct agonist at 5-HT_2A receptors, bypassing the need for elevated endogenous serotonin levels.

Moreover, recent meta-analytic data indicate that serotonin transporter (SERT) availability decreases moderately with age, potentially prolonging synaptic serotonin activity by slowing reuptake [71]. This compensatory mechanism could mitigate the impact of reduced presynaptic activity and support sufficient receptor engagement. Importantly, vesicular monoamine transporter 2 (VMAT2) - which packages serotonin into presynaptic vesicles - appears to remain largely stable across the adult lifespan, suggesting that vesicular 5-HT content is preserved in the aging brain [72]. However, the density and functional sensitivity of 5-HT_2A receptors - which mediate the psychedelic effects of psilocybin - may also decline with age, particularly in cortical regions involved in mood and cognition [73]. Whether this results in diminished, preserved, or even heightened sensitivity to psilocybin remains unclear and likely varies between individuals depending on their receptor expression patterns, inflammatory status, and cortical plasticity.

5.4.2. Emerging Clinical Evidence

Although older adults remain severely underrepresented in clinical trials involving psychedelic compounds - with only 1.4% of participants aged 65 or older enrolled in such studies since 1965 - a recent systematic review underscores the urgent need for age-inclusive research in this field [20]. In one of the first prospective observational studies focused specifically on this population, Kettner and colleagues (2024) followed 62 individuals aged 60 and above who voluntarily participated in group-based psilocybin ceremonies [74]. The study found statistically significant improvements in psychological well-being, as measured by the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), particularly two and four weeks after the session. Notably, these effects were most

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pronounced among participants with a history of mental health diagnoses, suggesting that psilocybin may provide particular benefit for older adults with longstanding psychological distress.

Interestingly, while older adults reported lower intensity of classic psychedelic experiences - such as ego dissolution or mystical-type states - compared to younger controls, their improvements in well-being were comparable. This suggests that therapeutic efficacy in older adults may be mediated by distinct mechanisms. Indeed, in this age group, the strongest predictor of improved outcomes was the degree of *communitas* - a sense of emotional connectedness and belonging experienced during the group session. These findings indicate that relational and contextual factors may be especially therapeutic for older individuals, potentially compensating for age-related reductions in serotonergic plasticity or altered subjective responsiveness to psychedelics.

6. Adverse Effects and Safety Considerations of Psilocybin

Psilocybin was classified as a Schedule I substance, in part due to concerns over its potential to trigger persistent psychiatric conditions such as psychosis [75]. However, subsequent analyses have shown that these risks are substantially elevated only in individuals with a personal or family history of psychotic disorders. For example, a recent case series examining long-term psychological consequences of psychedelic use found that all participants who received a psychiatric diagnosis following a psychedelic experience had underlying preexisting mental illness [76].

Psilocybin-assisted therapy has consistently demonstrated a favourable safety profile when administered in controlled clinical environments with appropriate psychological support. Across multiple trials, most reported adverse events have been transient, mild to moderate in intensity, and typically confined to the acute drug-effect window. The most frequently observed somatic symptoms include headache, nausea, and dizziness, all of which generally resolve spontaneously and without medical intervention [77]. Transient psychological discomfort, such as anxiety or emotional unease, has also been noted but was rarely associated with lasting consequences when managed by trained therapists [52].

Importantly, extensive participant screening has played a critical role in minimizing the incidence of serious adverse events. Most clinical protocols excluded individuals with a personal or family history of psychosis or bipolar disorder - conditions considered relative contraindications for psychedelic therapy. When such precautions are taken, the risk of severe psychiatric sequelae appears minimal. A 12-month follow-up study reported no evidence of persistent perceptual disturbances, emergent psychosis, or signs of dependence following psilocybin treatment [49].

A recent comprehensive safety review of 214 studies (including more than 3,500 participants) reported delayed serious adverse events in 3.9% (23/584) of outpatients participating in high-dose psilocybin trials, predominantly among individuals with preexisting neuropsychiatric disorders. These events included transient suicidality, worsening depression, and isolated episodes of psychosis or convulsions. Notably, no serious adverse events were observed in healthy individuals [78]. However, the analysis highlighted considerable heterogeneity in how adverse events were monitored and reported - only 23.5% of studies used systematic pharmacovigilance protocols - indicating a need for greater consistency in future research.

Although generally well tolerated, psilocybin may produce transient increases in blood pressure and heart rate, which could pose a risk in older adults with poorly controlled cardiovascular disease [79] (Table 2). Nevertheless, when compared to conventional psychotropic agents commonly prescribed in geriatric populations - such as benzodiazepines or antipsychotics - psilocybin appears to present a lower risk of cognitive impairment, sedation, falls, and extrapyramidal symptoms [51].

Table 2. Adverse effects of psilocybin in older adult patients (≥65 years).

AE category	Typical events reported in older adults
Cardiovascular	Transient increases in blood pressure and heart rate during dosing; occasional SBP >140–180 mmHg

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Gastrointestinal	Nausea, GI upset; occasional vomiting
Neurologic / somatic	Headache (including "next-day headache"), dizziness, fatigue
Psychological (acute)	Transient anxiety, emotional discomfort, brief confusion; rare session-limited paranoid/psychotic-like content
Serious adverse events (SAEs)	None observed; no HPPD or persistent psychosis
Drug–drug interactions	SSRIs/MAOIs/TCAs may blunt or alter acute effects; serotonin toxicity risk theoretical in trials. Psilocin primarily glucuronidated via UGT1A9/UGT1A10; inducers (e.g., rifampicin) may lower exposure; inhibitors (e.g., probenecid, diclofenac) may raise exposure

Abbreviations: AE - adverse event; SAE - serious adverse event; GI - gastrointestinal; SBP - systolic blood pressure; HPPD - hallucinogen-persisting perception disorder; SSRI - selective serotonin reuptake inhibitor; MAOI - monoamine oxidase inhibitor; TCA - tricyclic antidepressant; UGT - uridine diphosphate-glucuronosyltransferase. [20,28,55,62,74,86,87].

While the overall safety profile of psilocybin is reassuring, data on adverse effects specifically in older adults remain sparse. In a recent systematic review, detailed safety data were available for only 10 older participants (≥ 60 years) who received psilocybin-assisted therapy in the context of serious illness [20]. Among them, four individuals reported mild-to-moderate, transient psychiatric adverse events - primarily anxiety, paranoid ideation, or thought disturbance - all of which were successfully managed by study therapists without the need for pharmacological intervention or psychiatric hospitalization. No cases of persistent psychosis or hallucinogen-persisting perceptual disorder were observed. Transient episodes of hypertension were observed during dosing, with the highest recorded systolic pressure at 186 mmHg, but none required medical treatment or resulted in long-term sequelae. Additionally, time-limited headaches and mild gastrointestinal symptoms were reported in a small subset [56,80]. These findings suggest that psilocybin, when administered in controlled clinical environments, may be well tolerated even in older adults. However, the small sample size and lack of systematic age-stratified reporting across most trials highlight the urgent need for dedicated safety studies in geriatric populations.

In contrast to controlled clinical settings, a recent case report described prolonged and clinically significant adverse effects following repeated high-dose psilocybin use in an unregulated training environment in a 71-year-old participant, ultimately requiring electroconvulsive therapy [81]. Although this case does not reflect the safety profile observed in regulated clinical trials, it underscores the importance of careful screening, dose control, and structured clinical oversight, particularly in older adults.

7. Perspectives

As the global population ages, the prevalence of chronic neuroinflammatory and neuropsychiatric disorders - including treatment-resistant depression, anxiety, neurodegeneration, and multimorbidity - continues to rise. Older adults frequently require multiple medications to manage these conditions, which increases the risk of polypharmacy, adverse drug interactions, and treatment nonadherence. Psychedelic-assisted therapy, particularly with psilocybin, offers the possibility of addressing multiple age-related pathologies through a single pharmacological intervention that modulates both immune and neural pathways [82].

Given its anti-inflammatory, neuroplastic, and affective regulatory properties, psilocybin may serve as a multimodal therapeutic agent in this population. However, this potential can only be realized through rigorous clinical investigation that includes older adults, who have thus far been routinely excluded from psychedelic trials. Importantly, this gap is now being addressed by large-scale initiatives such as the NIH-funded INSPIRE Network (1UG3AG094957-01), which aims to establish a geriatric psychedelic research consortium to evaluate the safety of psilocybin and LSD in

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older adults, followed by clinical trials targeting pain-related conditions. Carefully designed studies must consider the unique physiological and psychological characteristics of aging, including altered serotonin signalling, cardiovascular vulnerability, and emotional processing in later life. Equally important is ensuring that participants are cognitively intact and able to comprehend and integrate the psychedelic experience [9].

In parallel, regulatory reconsideration of psilocybin's legal status may be warranted. In many jurisdictions psilocybin remains in the most restrictive schedule (e.g., Schedule I), a designation that materially hinders clinical trials and regulated supply. Reclassification from prohibition-only schedules to research-permissive categories (e.g., Schedule II/III, depending on jurisdiction) would lower administrative barriers, enable standardized manufacturing and controlled access for studies, and allow an evidence-based evaluation of benefit–risk while maintaining strict safeguards.

Despite growing enthusiasm, the integration of psychedelics into mainstream medicine faces ethical, logistical, and societal challenges. Public perception remains clouded by decades of stigma associated with recreational use, and concerns persist regarding variability in response, risk of abuse, and long-term safety [83]. Ethical concerns in clinical research are especially pronounced in psychedelic therapy: informed consent must be robust, protocols must be trauma-informed, and long-term psychological support should be guaranteed [84,85]. The success of clinical interventions depends heavily on access to trained psychedelic therapists - currently a limited resource - and on the infrastructure to deliver preparation and integration, which can be resource-intensive and cost-prohibitive.

Addressing these barriers will require multi-level efforts: standardized training programs, development of clinical guidelines, public education, and progressive regulatory reform. Moreover, interdisciplinary research combining neuroimaging, immunology, aging science, and psychotherapy is needed to optimize treatment protocols and ensure safety in vulnerable populations such as older adults. The therapeutic promise of psilocybin is real, but its realization depends on the integrity, inclusivity, and sustainability of the systems we build around it.

8. Summary

Psilocybin has emerged as a promising multimodal therapeutic agent for inflammation-linked neuropsychiatric and neurodegenerative disorders in older adults. These effects are thought to be mediated, in part, by modulation of neuroplasticity, neurotransmission, and immune signalling via 5-HT_2A receptor activation. From a pharmacological perspective, psilocybin offers several advantages in geriatric care: it has a rapid onset, a short half-life, and can exert long-lasting effects after a single administration. Its metabolic profile - relying predominantly on phase II glucuronidation rather than CYP450 enzymes - suggests a low risk of drug–drug interactions, which is particularly important in populations affected by polypharmacy. Despite these advantages, older adults remain significantly underrepresented in clinical trials with psychedelics. This review highlights the mechanistic rationale, safety profile, and preliminary clinical data supporting psilocybin's use in this population with multimorbidity and underscores the urgent need for age-inclusive research to fully assess its therapeutic potential in geriatric neuropsychiatry.

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Abbreviations

The following abbreviations are used in this manuscript:

AD – Alzheimer's disease
ALS – amyotrophic lateral sclerosis
BBB – blood-brain barrier
BDNF – brain-derived neurotrophic factor
CRP – C-reactive protein
DMN – default mode network
FDA – Food and Drug Administration
HPA – hypothalamic–pituitary–adrenal
IL-1β – interleukin-1 beta
IL-6 – interleukin-6
LPS – lipopolysaccharide
LSD – lysergic acid diethylamide
MCI – mild cognitive impairment
MDD – major depressive disorder
MS – multiple sclerosis
mTOR – mammalian target of rapamycin
NF-κB – nuclear factor-kappa B
NSAIDs – nonsteroidal anti-inflammatory drugs
PD – Parkinson's disease
SSRI – selective serotonin reuptake inhibitor
TBI – traumatic brain injury
TNF-α – tumor necrosis factor-alpha
TRD – treatment-resistant depression
TrkB – tropomyosin receptor kinase B
WHO – World Health Organization
5-HT – serotonin
5-HT_2A – serotonin 2A receptor

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