

**Psychological Mechanisms Underlying the Effect of Psilocybin in the Treatment of  
Depression, Anxiety and Substance Use Disorder: A Mixed Methods Systematic  
Literature Review**

Master Thesis

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## Abstract

**Introduction.** In the last decades psychedelic substances, such as psilocybin, have shown promising effects in treating mental disorders. However, how psilocybin works on a psychological level is still not well understood. Identifying psychological mechanisms that underly its mode of working is important in order to develop therapy methods that maximise the benefits for the patients. In this context, the combination of positive psychological treatment approaches with psilocybin is valuable to investigate as well. The present literature review provides an overview of the current literature on potential psychological mechanisms of psilocybin-assisted therapy.

**Methods.** A mixed methods systematic literature review following the PRISMA guidelines was conducted. Peer-reviewed articles about psilocybin treatment and its underlying psychological mechanisms and mediators were searched in the databases Scopus and PubMed. 13 studies were included in the review.

**Results.** Nine potential (groups of) potential mechanisms underlying the treatment with psilocybin were found. These were categorised into three groups. Mystical experience could be identified as a mediator with strong statistical evidence. Rumination, psychological flexibility, thought suppression, and self-compassion were identified as mediators with weak statistical evidence. Lastly, social connectedness and prosocial behaviour, self-efficacy and motivation, psychological insight, and complex emotional experiences were categorised as mediators with no direct statistical evidence.

**Discussion.** Although statistical evidence of longitudinal high-quality studies is scarce, the present review provides a first base for future research on underlying mechanisms and mediators of psilocybin-assisted psychotherapy. Furthermore, the review showed that possible mechanisms of psilocybin have similarities to frameworks of positive psychology. Therefore, it was recommended to research the inclusion of positive psychological methods such as ACT, mindfulness, or self-compassion exercises in the development of protocols for conducting psilocybin-assisted psychotherapy.

## Introduction

### Problem Statement

Mental health conditions are highly prevalent on a global level. Approximately every eighth person is experiencing a mental disorder (WHO, 2022). Mental illnesses impair people's functioning, well-being, quality of life, and social interactions and, in the worst case, can lead to suicide (WHO, 2022). In the Netherlands, the third most common cause of death in 2021 was mental disorders (Statista, 2022). The available treatment options and effectiveness of mental health care have increased immensely in the last century, particularly the prescription of psychopharmacology (Braslow & Marder, 2019). For instance, antidepressants such as SSRIs seemed to be a successful and easy option to treat depression when released (Braslow & Marder, 2019). However, current research questions its effectiveness compared to placebos and stresses the negative influence due to side effects related to their intake (Moncrieff & Kirsch, 2005; Pigott et al., 2010; Andrews et al., 2012). Recent trials showed that approximately two-thirds of individuals suffering from depression do not experience recovery after trying one type of antidepressant treatment, and about one-third of them do not achieve remission even after trying multiple consecutive treatments (Ionescu et al., 2022).

Considering the questioned effectiveness of current psychopharmacological treatments and their negative side effects, it is needed to develop new treatment options in mental health care. A reappearing field of research that has received increasing attention in the last few years is the use of classical psychedelics, such as psilocybin (magic mushrooms), lysergic acid diethylamide (LSD), Ayahuasca, or DMT (Dimethyltryptamine) in the treatment of mental disorders (Nichols, 2016). Psychedelics provide a unique and novel approach to mental health care. Traditional psychopharmacology primarily focuses on symptom management through the modulation of neurotransmitters. Contrary, psychedelics have the potential to go beyond symptom management and provide a deeper exploration of underlying psychological and emotional issues (Yaden & Griffiths, 2020). They can facilitate profound introspection, emotional processing, and personal growth (Nichols, 2016). This aspect of psychedelic therapy may contribute to long-term healing.

### Psychedelics

Psychedelics are a category of psychoactive substances that can alter one's perception, mood, and cognitive processes (Johnson et al., 2019). A distinction is made between classical psychedelics which includes LSD, psilocybin, mescaline or DMT, and non-classical psychedelics, such as ketamine or MDMA. The difference lies in their chemical structure and

mechanism of action in the brain (Dai et al., 2023). While both types of psychedelics can induce altered states of consciousness and profound experiences, they have different pharmacological properties and effects. Classical psychedelics have distinct chemical structures and are derived from natural or synthetic sources. Non-classical psychedelics encompass a broader range of substances that may not necessarily fit the traditional definition of psychedelics (Dai et al., 2023).

The use of psychedelic substances has been documented throughout human history, with evidence of their use dating back thousands of years in various cultures worldwide (Garcia-Romeu & Richards, 2018). Till today, naturally occurring psychedelic substances, such as psilocybin mushrooms, peyote, or ayahuasca, play an essential role in many indigenous populations and are part of medicinal, spiritual, and religious purposes. In the 1950s and 1960s, psychiatric and neuroscience researchers conducted studies on the use of LSD and other psychedelics in the treatment of various mental health conditions (Nichols & Walter, 2021). However, the widespread use of psychedelics in the counterculture of the 1960s and their association with social unrest and perceived threats to public safety led to increased government scrutiny and regulation of these substances (Johnson et al., 2019). Not until the 21st century, renewed scientific interest and relaxation of regulations led to a resurgence of research into the therapeutic effects of psychedelics (Garcia-Romeu & Richards, 2018). The classical psychedelic substance that is assumed to be most effective, mostly tolerated, and safe for therapeutic use is psilocybin (Lowe et al., 2021). Therefore, the present review focuses on the psychedelic substance psilocybin.

### **Psilocybin**

Clinical research has suggested that psilocybin may have therapeutic potential in treating several mental health conditions, including depression, anxiety, and addiction (Nichols, 2020). These effects may be due to the compound's ability to induce profound changes in subjective experience, leading to shifts in mood, cognition, and behaviour. The substance psilocybin is a tryptamine alkaloid that can be found in over 100 species of mushrooms, commonly also known as “magic mushrooms” (Nichols, 2020). Psilocybin has been shown to have low physiological toxicity and does not cause physical addiction or major physiological disturbances (Johnson & Griffiths, 2017). The substance starts operating approximately 30 to 60 minutes after ingestion (Lowe et al., 2021). The psychedelic state, also called "psychedelic trip, " usually lasts around three to six hours (Lowe et al., 2021).

The biological mechanism of action of psilocybin involves its conversion to psilocin, which acts primarily as a partial agonist at serotonin 2A (5-HT<sub>2A</sub>) receptors (Tylš et al.,

2014). Activation of 5-HT<sub>2A</sub> receptors leads to a cascade of downstream effects, including increased neuronal excitability, altered neurotransmitter release, and changes in brain activity and connectivity. These changes are thought to underlie the characteristic subjective effects of psilocybin, including alterations in perception, mood, and cognition (Tylš et al., 2014). According to Lowe et al. (2021), psilocybin's effects occur due to its action on several neurotransmitter systems. In addition to its effects on 5-HT<sub>2A</sub> receptors, psilocybin also interacts with other serotonin receptor subtypes, as well as with dopamine and norepinephrine receptors. These interactions are thought to modulate the balance of excitatory and inhibitory neurotransmission in the brain, leading to the characteristic effects of psilocybin (Lowe et al., 2021).

Since psilocybin-assisted psychotherapy is still being researched, its components, structure, and execution varies among the existing trials. However, some aspects have shown to be essential in its implementation. In most studies, the patients received two to three psilocybin sessions (Rucker et al., 2021). Psilocybin is typically administered orally in the form of capsules. The dosage is carefully determined based on factors such as the individual's weight, previous experience, and therapeutic goals (Rucker et al., 2021). Before the session, the therapist works with the patient to establish rapport, build trust, and create a safe and supportive environment (Horton et al., 2021). This includes providing information about the therapeutic process, discussing goals and intentions, and addressing any concerns or questions (Horton et al., 2021). The session takes place in a comfortable, quiet, and controlled setting. During the session, the patient is encouraged to lay down, wear an eye mask, and listen to a carefully curated music playlist to facilitate introspection and the inward journey (Rucker et al., 2021). Since the patient may encounter various thoughts, emotions, memories, and insights, one or two therapists remain present and offer emotional support, reassurance, and guidance throughout the experience (Thomas et al., 2017). After the acute psilocybin experiences, posttreatment is an essential part of the therapy. Integration sessions provide an opportunity to process and make sense of the experiences, explore insights gained during the session, and integrate them into daily life. Integration may involve verbal processing, creative expression, journaling, or other forms of self-reflection (Thomas et al., 2017).

### **Mechanisms of Psilocybin-assisted Psychotherapy**

Several systematic reviews and meta-analyses have evaluated the effectiveness of psilocybin on mental illnesses (van Amsterdam & van den Brink, 2022; Van Der Meer et al., 2023; Vargas et al., 2020). They came to the conclusion that psilocybin-assisted

psychotherapy is a promising option for treating mental illnesses. However, they stressed that larger, longitudinal, and high-quality studies are needed to prove their safety and effectiveness. Nevertheless, how psilocybin works on a psychological level, in particular its underlying psychological mechanisms, is not known yet (van Elk & Yaden, 2022). A mechanism can be defined as a process or event that causes a specific change (Kazdin, 2007). Mechanisms serve to understand the underlying processes or pathways of a phenomenon, by explaining how it occurs (Kazdin, 2007). Gaining a comprehensive understanding of the psychological mechanisms of psilocybin is vital in order to create specific therapeutic approaches within psilocybin-assisted psychotherapy (van Elk & Yaden, 2022). The approaches should be tailored to the individual patient and focus on amplifying factors within the therapy process that have the potential to maximize their benefits.

The theoretical paper by van Elk and Yaden (2022) already explored potential psychological, pharmacological, and neural mechanisms underlying psychedelics. They suggested five potential psychological mechanisms of psychedelics. Firstly, they determined altered states of consciousness often caused by so-called mystical experiences as a potential mechanism. Mystical experience is a common and frequently mentioned construct in psychedelic research (van Elk & Yaden, 2022). However, it is also a very complex and versatile one. These experiences can occur spontaneously or be induced through meditation, prayer, other spiritual practices, and psychedelic experiences (Wulff, 2014). Some common features of mystical experiences include the unity consciousness, a sense of oneness with everything around someone, or experiencing timelessness. Furthermore, people who had a mystical experience frequently reported a transcendence of the self, which describes a feeling of ego dissolution, where the individual no longer feels like a separate self, but part of a larger whole (Barrett & Griffiths, 2018). Moreover, individuals often experience strong positive emotions, such as awe, peace, or joy. Furthermore, many people describe it as ineffable and have difficulties expressing the experience in words, as it often transcends language and concepts (Barrett & Griffiths, 2018). Mystical experiences have been reported across cultures and throughout history and are often associated with spiritual or religious practices (Johnson et al., 2019). They can have a profound impact on the individual's worldview or sense of self and are sometimes described as life-changing experiences (Wulff, 2014). It is assumed that they contribute positively to mental health by opening new perspectives on people's lives, enhancing meaning and purpose, and providing a sense of common humanity (Kangaslampi, 2023).

Secondly, they found that enhanced cognitive and psychological flexibility might be an underlying mechanism of psychedelics (van Elk and Yaden, 2022). Cognitive flexibility is the ability to switch between different tasks or thought patterns, solve problems creatively, and think abstractly (Hartkamp & Thornton, 2017). It involves being able to see things from different perspectives and change one's thinking based on new information or feedback. Psychological flexibility is the ability to adapt to changing emotional and situational demands, remain open to experiences, and act in accordance with one's values and goals (Kashdan & Rottenberg, 2010). It involves being able to accept and tolerate uncomfortable emotions, and still make choices that are in line with one's values. Both are important for personal growth, resilience, and well-being.

Furthermore, van Elk and Yaden (2022) identified social connectedness as a potential mechanism. Social connectedness refers to the sense of belonging, emotional closeness, and meaningful relationships individuals experience with others (Haslam et al., 2015). It encompasses the quality and quantity of social interactions, the feeling of being supported and understood, and the extent to which one feels connected to a community. Research has shown that social connectedness is crucial for overall well-being, as it promotes feelings of inclusion, validation, and social support, which can positively impact mental health (Haslam et al., 2015).

Moreover, changes in beliefs and worldviews have been shown to be a relevant aspect of psychedelic treatments (van Elk and Yaden, 2022). Beliefs and worldviews influence our thoughts and interpretations of events (Poulin & Cohen Silver, 2008). When individuals hold rigid or maladaptive beliefs, such as extreme self-criticism, it can contribute to mental health problems like anxiety and depression (Boden et al., 2012). When having an experience that challenges these beliefs, individuals might gain more balanced, realistic, and positive ones. Moreover, changed beliefs can lead to a broader perspective and increased acceptance of oneself and others (Boden et al., 2012). Furthermore, they provide a framework for understanding the world and finding meaning in life (Poulin & Cohen Silver, 2008). Changing negative beliefs is also part of evidence-based therapeutical approaches such as cognitive behavioural therapy (CBT) (Boden et al., 2012; Poulin & Cohen Silver, 2008).

Lastly, the review by van Elk and Yaden (2022) identified positive change in behaviour as a potential psychological mechanism. Similarly, to changes in beliefs, changing behaviour is also an important aspect of CBT. It can be defined as modifying patterns of behaviour that may contribute to or exacerbate mental health challenges (Teixeira et al., 2022).

In their theoretical paper van Elk and Yaden (2022) explored potential psychological mechanisms underlying psychedelic-assisted psychotherapy that are important to consider in future research. The present review builds on this and aims to identify mechanisms in a more systematic way by identifying to what extent there is statistical evidence to support the mechanisms they already identified.

### **Psychedelics and Positive Psychology**

Looking at the effects of psilocybin-assisted psychotherapy and the potential mechanisms identified by van Elk and Yaden (2022), similarities to the positive psychological approach can be found. For instance, Acceptance and Commitment Therapy (ACT), focuses on psychological flexibility to support individuals in managing difficult emotions, thoughts, and situations (Scott & McCracken, 2015). Furthermore, social connections are an essential aspect of positive psychology. For instance, the PERMA model by Seligman (2011) which is a widely applied theory in positive psychology for well-being includes relationships as an essential aspect of well-being. They positively contribute to a sense of belonging and meaning in life (Stavrova & Luhmann, 2016).

Jungaberle et al. (2018) reviewed the correlation of concepts in psychedelic research with the positive psychological framework. They found psychedelics to have beneficial effects on mindfulness-related capabilities, changes in life-values, cognitive flexibility, and prosocial behaviours. Moreover, it is claimed that psychedelic-assisted psychotherapy and positive psychology share some common goals and processes (Eygoren, 2022). Both approaches emphasize the promotion of well-being and positive mental states. Furthermore, they recognize the potential for personal growth and emphasize the importance of integrating insights and experiences gained during therapy or personal exploration into one's daily life (Eygoren, 2022).

Moreover, several papers argue that psychedelics, as well as third-wave behaviour therapies, emphasize the cultivation of mindfulness and self-awareness (Gandy, 2019; Walsh & Thiessen, 2018). They encourage individuals to become more attuned to their thoughts, emotions, and experiences, promoting a deeper understanding of oneself and one's behaviour patterns. Both approaches recognize the significance of a strong therapeutic relationship and supportive environment (Gandy, 2019; Walsh & Thiessen, 2018). While psilocybin-assisted psychotherapy utilizes the specific mechanism of psilocybin to facilitate therapeutic breakthroughs, positive psychology focuses on enhancing positive emotions, character strengths, and meaningful engagement in life. While they are distinct in their approaches, they share common goals of promoting well-being, personal growth, and positive



transformation (Walsh & Thiessen, 2018). Although the link between positive psychological approaches and psychedelic interventions seems to be promising, current research remains quite explorative. Due to that the current review aims to identify potential similarities in psilocybin-assisted psychotherapy and third-wave behaviour therapies.

### **Research Question**

Still, no systematic literature review on the underlying psychological mechanisms of psilocybin was conducted. Therefore, this mixed methods systematic literature review seeks to give an overview of the current state of research regarding the psychological mechanisms of psilocybin's mode of effect on mental illnesses. The effect of psilocybin has been mostly investigated on depression, anxiety, and substance use disorder in the last few years (Hodge et al., 2023). Although its effects on other mental illnesses such as obsessive-compulsive disorder or posttraumatic stress disorder are being researched, the evidence of effectiveness is still limited (Daniel & Haberman, 2017). Due to that, the present review solely focuses on depression, anxiety, and substance use disorder. Based on the objectives following research question is formulated:

*“Which psychological mechanisms underly the effect of psilocybin in the treatment of patients experiencing depression, anxiety, or substance use disorder?”*

### **Methods**

Due to the novelty of the field of psychedelic research and the complexity of conducting RCTs, the number of studies is relatively limited. Therefore, not only single-blind and double-blind placebo-controlled randomized trials were included, but also open-label trials, cross-sectional studies and pilot studies which include patients experiencing mental health conditions. Since existing studies use various research methods, it was chosen to perform a mixed methods systematic literature review. A mixed methods systematic literature review is a research approach that utilizes both qualitative and quantitative research methods to synthesize and evaluate the existing literature on a research question (Pearson et al., 2015). This approach involves a systematic search and selection process, where both qualitative and quantitative studies are identified and appraised using established criteria. The data from the studies are then integrated and analysed, to provide a comprehensive understanding of the topic. The review findings are presented in a structured and transparent manner (Pearson et al., 2015).

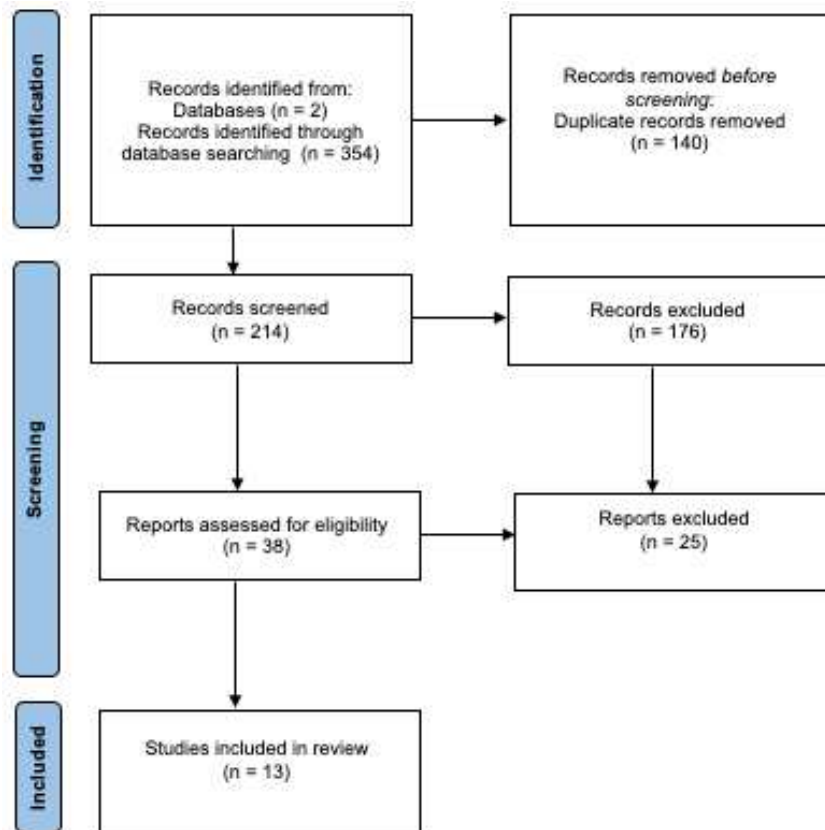
## Searching Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) are used as guiding principles for the search and selection process (Page et al., 2021). A systematic literature search was performed using the databases Scopus and PubMed in February 2023. The search string required to include the substance psilocybin and the construct of mechanisms. To increase the scope of studies investigating possible mechanisms, the term mediators was added to the search, since many existing studies focus on the mediating roles of variables. Mediation is a statistical representation of a mechanism. Mediators are defined as variables that account for critical statistical relations between an intervention and its outcome (Kazdin, 2007). Constructs can only be defined as mediators if they have been statistically tested by performing a mediation analysis (VanderWeele, 2009). Mediators imply a mechanism but do not have to necessarily be one; contrary, mechanisms always involve mediation (VanderWeele, 2009). Furthermore, depression, anxiety, and substance use disorder were included in the search string. The final search string used was: “(psilocybin AND (mechanism\* OR mediat\*) AND (depression OR anxiety OR substance-use-disorder)“.

A total of 354 hits were initially attained, 189 articles resulted in the database Scopus and 165 in PubMed. After the duplicates were removed 214 records remained. The title, abstracts, and keywords of these records have been screened and 38 reports were assessed for eligibility. Finally, 13 articles matching the inclusion criteria have been included in the mixed methods systematic literature review (*Figure 1*).

## Inclusion criteria

First of all, merely papers published in peer-reviewed journals were included. Furthermore, the selected qualitative and quantitative studies needed to explore the effects of psilocybin on individuals who were experiencing at least one of the specified mental health conditions. Moreover, the role of psychological mechanisms or mediators was required to be addressed in the studies' outcomes. Since, research on psychological mechanisms is still in its initial stage, not only studies that statistically tested for these constructs were included but also studies that provided indications for potential mediators or mechanisms by interviews or questionnaires. Contrary to conventional systematic literature reviews also open-label trials, cross-sectional studies, and pilot studies were included due to the already mentioned novelty and emerging status of the research field.

**Figure 1***PRISMA Flow Chart*

### Study Quality

The quality of the studies was assessed using the risk of bias assessment tool for RCTs by the Cochrane Collaboration (Higgins et al., 2019). It has to be stressed that not all of the included studies are RCTs. Therefore, the quality assessment tool is not adequately suitable for the present mixed methods literature review. Still, it provides an important indication about the quality of the studies that will be investigated and the reliability of the conclusion that can be drawn from this review. To evaluate the studies' quality following classifications were evaluated: Random sequence generation (1), allocation concealment (2), blinding of participants and personnel (2), blinding of outcome assessment (4), incomplete outcome data (5), selective reporting (6) and other forms of bias (7) (Higgins et al., 2019). For every study, each classification was evaluated by assigning the level of risk of bias. It was scored low if no risk of bias could be identified, high if the criteria for a classification were not met, and unclear was assigned if insufficient information about its quality was available.

## Results

### Study Characteristics

In total, 13 studies have been included in the mixed methods systematic literature review. In *Table 1* the study characteristics and main results regarding mechanisms and mediators of the eight quantitative studies are provided, and *Table 2* provides an overview of the five qualitative studies. Only three of the included studies were RCTs using a placebo or control group in their trial (Barba et al., 2022; Griffiths et al., 2016; Ross et al., 2016). Furthermore, two open-label longitudinal single-group studies, three internet-based cross-sectional studies, and five qualitative interview studies were reviewed. Three of the included studies are follow-up studies of previous RCTs that have been included in this mixed methods systematic literature review as well (Belser et al., 2017; Noorani et al., 2018, Swift et al., 2017). This is important to stress since some participants are part of two different studies. The sample sizes of the included studies ranged from ten to 985 participants. However, the mean sample size of the RCTs, open-label longitudinal single-group studies, and qualitative studies was  $N = 23$ , while the internet-based cross-sectional studies had an average of  $N = 502$  participants. All included studies tested the participants' symptoms of at least one of the included mental disorders (depression, anxiety, or substance-use disorder). Furthermore, all studies also included secondary outcomes. These included acute outcomes such as mystical experiences or non-acute outcomes such as prosocial behaviour.

Moreover, it is essential to stress, that the three cross-sectional online studies did not solely investigate the substance psilocybin but also other classical psychedelics (Davis et al., 2020; Fauvel et al., 2021; Johnson et al., 2017). The patients were requested to indicate the particular psychedelic substances they had ingested and the frequency at which they consumed them. In these cases, psilocybin was ingested by self-administration. Since in the three studies, a moderate to high percentage of the participants consumed psilocybin and the effects among classical psychedelics are comparable, they still were included in the review (Aleksandrova & Phillips, 2021). Moreover, some studies also studied situational or external factors that influenced the psychedelic experience and might have influenced the treatment's success. For instance, Noorani et al. (2018) reported that the affective quality of the first psilocybin session, the rapport with the study team, and the environment influenced the participants' experiences significantly. The external influences in psilocybin-assisted therapy play an important role in the treatment of patients, however, focusing on external or potential moderating factors would go beyond the scope of this review.

Regarding the procedure of the studies, the psilocybin sessions occurred individually

with therapeutic and medical support in six studies. In these cases, the psilocybin sessions were part of a complex intervention with psychotherapy and integration sessions. The three follow-up studies used already existing data in which psilocybin was consumed in a therapeutic and controlled setting. However, four online surveys did not provide detailed information on the dosage and circumstances in which the substances were ingested, since the participants self-administered the consumption of psilocybin. All interventions, besides the four online studies, investigated the effects of two or more psilocybin experiences. Additionally, all studies that investigated the effects of psilocybin, reported significant effects on the participants' mental condition.

Looking at the measurements and outcomes of the included studies, all of the included studies assessed mystical or spiritual experiences through the Mystical Experience Questionnaire (MEQ;  $N=5$ ), the mystical scale ( $N=2$ ), the Ego-Dissolution Inventory (EDI;  $N=1$ ), the Oceanic Boundlessness (OBN;  $N=1$ ), or qualitative interviews ( $N=5$ ). Seven studies reported on complex and strong emotions, both difficult and pleasant emotions. They were measured through qualitative studies ( $N=4$ ) and by various scales from questionnaires that were not specifically mentioned in the studies ( $N=3$ ). Six studies assessed the psychological insights or changes in values of the participants using the Psychological Insight Scale (PIS;  $N=1$ ), Psychological Insight Questionnaire (PIQ;  $N=2$ ), or qualitative interviews ( $N=2$ ). Four studies measured the impact of psilocybin on social relationships and prosocial behaviour, by conducting the Persisting Effects Questionnaire (PEQ;  $N=1$ ), observer ratings ( $N=1$ ), the Quality of Life scale Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-SWB;  $N=1$ ) and qualitative interviews ( $N=2$ ). Furthermore, two studies reported increased self-efficacy or motivation due to the psychedelic experience. This was measured by a qualitative interview and an unnamed questionnaire regarding mechanisms by Johnson et al. (2017). Two studies evaluated the psychological flexibility of the participants, one using the Acceptance and Action Questionnaire II (AAQII) and the other one a qualitative interview. Additionally, two studies measured the participants' thought ruminations by using the Ruminative Response Scale (RRS;  $N=2$ ). Related to thought rumination, one study used the White Bear Suppression Inventory (WBSI) to measure thought suppression and another study measured self-compassion through the Self-Compassion Scale (SCS). Besides that, other secondary outcomes, such as forgiveness, optimism, or death anxiety were reported in some studies. However, they did not provide an indication to be underlying mechanisms and therefore are not further discussed in this review.

**Table 1***Study Characteristics and Outcomes of Quantitative Studies*

<b>Reference</b>	<b>Study Design</b>	<b>Study Objectives and Sample Size (N)</b>	<b>Mental Condition</b>	<b>Dosage</b>	<b>Procedure and Measurement</b>	<b>Statistical Indication for Potential Mechanism/Mediators of Psilocybin</b>
Barba et al., 2022	Randomized, double-blind, controlled trial	Effectiveness of psilocybin compared with escitalopram (SSRI) N = 59	Depression	Twice 25mg of psilocybin and daily capsules of placebo derivative OR Twice 1mg of psilocybin and daily capsules of 10mg of escitalopram	Measured 1 week before and 6 weeks after start of the treatment: RRS, WBSI, PIS-6 (only after 6 weeks)  Measured after first and second psilocybin experience (Week 2 and week 4): CEQ, EBI, EDI	<ul style="list-style-type: none"> <li>• Rumination</li> <li>• Thought suppression</li> <li>• Ego dissolution</li> <li>• Psychological insight</li> </ul>
Davis et al., 2020	Internet-based cross-sectional survey study	Role of psychological flexibility in relationship between psychedelic experience and changes in depression and anxiety N=985	Depression and anxiety	Self-administrated and therefore variable 38% of the participants used psilocybin	One time measurement: MEQ, PIQ, AAQII	<ul style="list-style-type: none"> <li>• Psychological flexibility</li> <li>• Mystical experiences</li> <li>• Psychological insight</li> </ul>

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Fauvel et al., 2021	Retrospective cross-sectional anonymous online survey	Mediating role of self-rumination and self-compassion in psychedelic experiences <i>N</i> =164	Depression, anxiety and stress	Self-administered and therefore variable 38% of the participants used psilocybin	One time measurement: MEQ, PIQ, SCF-SF, RRS	<ul style="list-style-type: none"> <li>• Mystical experiences</li> <li>• Psychological insight</li> <li>• Self-rumination</li> <li>• Self-compassion</li> </ul>
Garcia-Romeu et al., 2014	Open-label longitudinal single-group pilot study	Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction <i>N</i> =15	Tobacco addiction	5 <sup>th</sup> week: Moderate dose (20mg/70kg) 7 <sup>th</sup> week: high dose (30mg/70kg) 13 <sup>th</sup> week: optional 3 <sup>rd</sup> high dose	Measurements taken at several times of the intervention and at 6-months follow-up, SASE, HRS, Mysticism Scale, SOCQ	<ul style="list-style-type: none"> <li>• Mystical experiences</li> </ul>
Griffiths et al., 2016	Randomized, double-blind, cross-over trial	Efficacy of psilocybin for treatment of depression and anxiety in psychologically distressed cancer patients	Depression and anxiety in cancer patients	Two sessions:  Placebo like dosage (1 or 3 mg/70kg)  VS	Measurements were taken before start of the intervention during and immediately after each session 5 weeks and 6 months after sessions:  HRS, ASC, Mysticism Scale, SOCQ, MQOL, LAP-R, LOT-R, PEQ,	<ul style="list-style-type: none"> <li>• Mystical experiences</li> <li>• Social relationships</li> </ul>

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		N=51		high dose (22 or 30mg/70kg)	Ratings of community observers	
Johnson et al., 2017	Retrospective cross-sectional anonymous online survey	Identifying conditions for association of psychedelic use with persisting tobacco smoking cessation N=358	Tobacco addiction	Self-administrated and therefore variable:  95% of the participants have used psilocybin in their life	One time measurement: MEQ, Personal meaning of psychedelic experience Spiritual significance of psychedelic experience	<ul style="list-style-type: none"> <li>• Changing life priorities and values</li> <li>• Self-efficacy</li> <li>• Spiritual and meaningful experience</li> <li>• Motivation</li> </ul>
Roseman et al., 2018	Open-label longitudinal single-group trial	Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression N=20	Treatment resistant depression	Two separate sessions (10 and 25mg)	After 5 weeks: OBN, DED, ASC	<ul style="list-style-type: none"> <li>• Mystical experiences</li> </ul>
Ross et al., 2016	Randomized double-blind, placebo-controlled, crossover trial	Symptom reduction following psilocybin treatment for anxiety and depression in	Depression and anxiety associated with a cancer diagnosis	Participants received either psilocybin (0.3mg/kg) the first or the second	Data assessments occurred at various points of intervention:  MEQ, HAI, DTS, FACIT-SWB	<ul style="list-style-type: none"> <li>• Mystical experiences</li> </ul>



patients with  
cancer

$N=29$

session and at  
the other  
session 250g  
niacin

*Note.* RRS: Ruminative Response Scale. WBSI: White Bear Suppression Inventory. PIS-6: Psychological Insight Scale. CEQ: Challenging Experience questionnaire. EBI: Emotional Breakthrough Inventory. EDI: Ego-Dissolution Inventory. MEQ: Mystical Experience Questionnaire. PIQ: Psychological Insight Questionnaire. AAQII: Acceptance and Action Questionnaire II. SCF-SF: Self-Compassion Scale. SASE: Smoking Abstinence Self-Efficacy Scale. HRS: Hallucinogen Rating Scale. SOCQ: States of Consciousness Questionnaire. ASC: Altered States of Consciousness. MQOL: McGill Quality of Life Questionnaire. LAP-R: Life Attitude Profile-Revised (measuring death acceptance). LOT-R: Life Orientation Test-Revised (measuring optimism). PEQ: Persisting Effects Questionnaire. OBN: Oceanic Boundlessness. DED: Dread of Ego Dissolution. HAI: Hopelessness Assessment and Illness scale. DTS: Death Transcendence Scale. FACIT-SWB: Quality of Life scale Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being.

**Table 2***Study Characteristics and Outcomes of Qualitative Studies*

<b>Reference</b>	<b>Study Design</b>	<b>Study Objectives and Sample Size (N)</b>	<b>Mental Condition</b>	<b>Dosage</b>	<b>Procedure, Outcome measures, Measurement timing</b>	<b>Mechanisms and Mediators of psilocybin indicated through interviews</b>
Al-Naggar et al., 2021	Qualitative interview study	Explore experiences and effects of psilocybin on patients with depression and anxiety N=10	Depression and/or anxiety	Self-administered and therefore variable	Single interview	<ul style="list-style-type: none"> <li>• Mystical experiences</li> <li>• New thinking patterns</li> </ul>
Belser et al., 2017  (Follow-up study of Ross et al., 2016)	Qualitative study with Semi-structured interviews	Patient experiences of psilocybin-assisted psychotherapy N=13	Anxiety associated with a cancer diagnosis	Participants received either psilocybin (0.3mg/kg) the first or the second session and at the other session 250g niacin	Semi-structured interview	<ul style="list-style-type: none"> <li>• Social relationships</li> <li>• Emotional range</li> <li>• Interconnectedness</li> <li>• Lasting change of sense of identity and life priorities</li> </ul>
Nielson et al., 2018	Open-label pilot study	Psychedelic Debriefing in Alcohol Dependence	Alcohol dependence	First psilocybin session: 0.3 mg/kg and	17 interview transcripts of previous study Measured at the end of each psilocybin session:	<ul style="list-style-type: none"> <li>• Mystical experiences</li> <li>• Motivation for Change</li> <li>• Dysphoric Experiences</li> </ul>

	(Qualitative content analysis)	Treatment: Illustrating Key Change Phenomena <i>N</i> =10		second session: 0.4 mg/kg	MEQ, HRS, ASC	
Noorani et al., 2018  (Follow-up study of Garcia-Romeu et al., 2014)	Retrospective qualitative interview study	Identifying perceived mechanisms of psilocybin leading to smoking cessation <i>N</i> =12	Tobacco addiction	5 <sup>th</sup> week: Moderate dose (20mg/70kg) 7 <sup>th</sup> week: high dose (30mg/70kg) 13 <sup>th</sup> week: optional 3 <sup>rd</sup> high dose	30 months after initial psilocybin intervention by Garcia-Romeu et al., 2014	<ul style="list-style-type: none"> <li>• Insights into self-identity</li> <li>• Interconnectedness</li> <li>• Altruism and pro-social effects</li> <li>• Feelings of awe/curiosity</li> </ul>
Swift et al., 2017  (Follow-up study of Ross et al., 2016)	Qualitative Semi-structured interviews	Cancer patients' narrative of psilocybin therapy  <i>N</i> =13	Anxiety associated with a cancer diagnosis	Participants received either psilocybin (0.3mg/kg) the first or the second session and at the other session 250g niacin	Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders at different moments after the participants psilocybin session	<ul style="list-style-type: none"> <li>• Spiritual Interpretations</li> </ul>

## **Risk of Bias Assessment**

Since solely three double-blind RCTs and two open-label longitudinal single-group studies were included in the review, the results of the risk of bias assessment showed generally to be of low quality. The first four categories, namely ‘Random Sequence Generation’, ‘Allocation Concealment’, ‘Blinding of Personnel and Participants’, and ‘Blinding of Outcome Assessment’ showed a high risk of bias in all studies except for the RCTs by Barba et al. (2022), Ross et al. (2016) and Griffiths et al. (2016). Moreover, five of the studies were qualitative, and therefore ‘Incomplete Outcome Data’ was difficult to assess and was categorised as ‘low’. Since the qualitative studies did publish solely parts of the participants’ interviews the risk of ‘Selective Reporting’ was evaluated as ‘unclear’.

The last category, ‘other bias’, was rated to be high risk for all 13 studies, since in psychedelic research several risks of bias exist. Firstly, achieving and maintaining successful blinding of psychedelics is challenging in RCTs. Previous research suggests that treatment effects in existing psychedelic clinical trials are overestimated due to participants becoming aware of whether they received the psychedelic or the placebo (Aday et al., 2022). When participants correctly believe they received the treatment, their treatment response may be influenced by expectancy effects, potentially leading to a greater response. On the other hand, disappointment among those who know they received a placebo may decrease the placebo response (Aday et al., 2022). Furthermore, with increasing media coverage on the positive therapeutic effects of psychedelics, it is reasonable to assume that expectancy effects may be growing (Muthukumaraswamy et al., 2022).

Secondly, it is important to recognize that psilocybin interventions are often combined with psychotherapy, adding complexity to controlling treatment variables. The therapeutic alliance between the patient and practitioner plays a significant role in treatment outcomes (Muthukumaraswamy et al., 2022). Increasing interaction in clinical studies can enhance the placebo response by exposing participants to non-specific treatment effects, such as emotional and cognitive care provided by the research team. Moreover, therapists may become aware of a patient's treatment allocation based on their immediate reaction to the administered drug, leading to potential differential therapy across the groups (Muthukumaraswamy et al., 2022). To the previously mentioned issues, self-selection bias poses a barrier to achieving representative ethnic and demographic sampling in mental health studies. (Muthukumaraswamy et al., 2021).

Another factor contributing to demographic participant bias is the underrepresentation of minorities among psychedelic researchers, similar to other areas of medical research. The lack of minority representation in sample populations limits the generalizability of results and may exacerbate existing healthcare inequities. Additionally, it is important to consider other biases related to the experimenters themselves. The field of psychedelic science often blurs the lines between investigators and advocacy, raising concerns about the objectivity of data reported from psychedelic studies for future healthcare consumers (Muthukumaraswamy et al., 2021). Overall, merely the studies by Barba et al. (2022), Ross et al. (2016) and Griffiths et al. (2016) showed a low risk of bias. The remaining ten studies have shown to have a high risk of bias (Appendix).

## **Mechanisms and Mediators**

### ***Mystical experiences***

The most frequently identified potential mechanism or mediator in the treatment of psilocybin is mystical experiences. All 13 studies identified mystical experience or some aspects of it to play an important role in the treatment. Looking at the longitudinal studies, the study by Griffiths et al. (2016) found that the high-dose psilocybin experience led to significant reductions in depressed mood and anxiety. The patients scores on the mysticism scale were found to be significantly correlated with long-lasting changes observed in therapeutic outcome measures such as mood, behaviour, attitudes, and spirituality after five weeks. Furthermore, after controlling for the overall intensity of the psilocybin effect, most of the measures continued to show a significant correlation with the scores obtained immediately after the first session. This suggests that mystical-type experiences play a significant role in therapeutic outcomes, independent of the overall intensity of the drug effect. Furthermore, a mediation analysis was conducted which revealed that mystical-type experiences mediated the positive therapeutic response.

The study's results by Ross et al. (2016) showed similar results. The participants receiving psilocybin compared to the placebo-control (niacin) group scored significantly higher on the mystical experiences score. Ross et al. (2016) found that psilocybin-produced mystical-type experiences correlated with positive changes in primary outcome measures such as anxiety and depression. Additionally, they performed a mediation analysis that showed that mystical experiences mediated the effect of psilocybin on anxiety and depression.

Furthermore, the study by Garcia-Romeu et al. (2014) specifically investigated the role of mystical experiences in treating tobacco addiction with psilocybin-assisted

psychotherapy. The results showed that 60% of the participants had a "complete" mystical experience during one or more of their psilocybin sessions. Significant correlations were displayed between mystical experiences and the participants' cravings to smoke at a 6-month follow-up. Additionally, the study found that participants who experienced stronger mystical experiences during the psilocybin sessions were more likely to quit smoking successfully. Although no mediation analysis was conducted in the study by Garcia-Romeu et al. (2014), the significant correlation between smoking cessation outcomes and "complete" mystical experience might indicate that mystical experience is a mediator.

Eight other studies identified that participants frequently experienced strong mystical or spiritual experiences during psilocybin use (Al-Naggar et al., 2021; Barba et al., 2022; Davis et al., 2020; Fauvel et al., 2021; Johnson et al., 2017; Nielson et al., 2018; Roseman et al., 2018; Swift et al., 2017). However, in these cases, no mediation or correlation analysis between mystical experiences and a decrease in symptoms was performed.

### ***Complex Emotional Experiences***

Various studies reported complex emotional experiences of the participants during the psilocybin session. No statistical evidence supports it to be an underlying mechanism. However, patients recurrently reporting on the intensity and complexity of emotions in qualitative studies give reason to consider complex emotional experiences as a potential mechanism. According to Belser et al. (2017), all 13 participants describe strong emotional states which they have not experienced in this intensity before. Some of these emotions were extremely positive, such as feelings of joy, love, or bliss. However, many participants reported emotionally difficult experiences as well. Furthermore, five individuals described experiencing emotions they had repressed before, such as traumatic pain or grief. For example, one participant mentioned: *"I feel like what happened was that in a very short period of intense time I dealt with some really powerful things and put it behind me."* This shows that the participant experienced very difficult emotions, however, she was able to deal with them and afterwards it was relieving for her to let these emotions go. Similar findings were made by Nielson et al. (2018). In their study, many participants reported dark and difficult emotional states during their psilocybin session. Nevertheless, most of them were able to deal with the painful experience and learned something from it about themselves or experienced a feeling of relief.

Additionally, Al-Naggar et al. (2021), Griffiths et al. (2016), Noorani et al. (2018), Roseman et al. (2018) and Ross et al. (2016) identified that the participants experienced strong positive emotions and optimism in their psilocybin experience. However, it has to be

considered that these were also overlap with other factors, as for example, mystical experiences entail strong positive emotions such as bliss or awe.

***Psychological Insights: Self-identity, Values and Life Priorities***

Further reoccurring and potential mechanisms of the treatment with psilocybin were the participants' insights into their identity, values, and life priorities. Although for this framework no direct causal evidence was reported by means of mediation analyses in any of the studies, there is supportive evidence from one RCT, three cross-sectional, and two qualitative studies. The RCT by Barba et al. (2022) found that the psychological insight of the participants after the psilocybin session was positively correlated with a decrease in rumination and thought suppression. Since decreased rumination and thought suppression have been shown to positively affect decreased symptoms of depression, psychological insight might indirectly influence or mediate symptoms of depression. However, Barba et al. (2022) provided no results on the direct relationship between psychological insight and depressive symptoms. Furthermore, no mediation analysis was conducted.

Moreover, Belser et al. (2017) reported that the participants experienced lasting impacts regarding their life priorities and sense of identity after the psilocybin treatment. They rediscovered forgotten aspects of themselves and felt reborn, more confident, connected, and alive. The experience empowered them and resulted in healthier behaviours. One participant stated: *"I feel more in touch with who I really am...my real self, myself that's connected to everyone and everything."*

According to Davis et al. (2020) participants who scored high on the Psychological Insight Questionnaire experienced decreases in depression and anxiety after receiving psilocybin and were more likely to change their maladaptive behaviour. Furthermore, Noorani et al. (2018) found that out of the 12 participants, seven reported gaining valuable insights about themselves during their psilocybin experiences that were relevant to their efforts to quit smoking. Participants described experiencing a deeper, better, or more essential sense of self that led to a decreased desire to smoke. One participant reported "Coming to a profound realization during her second psilocybin session that smoking did not have to define who she was". Moreover, Johnson et al. (2017) identified changes in life priorities or values as the most significant psychological factor associated with quitting or reducing smoking. The study's findings suggested that psychedelics could be a promising treatment for tobacco addiction, possibly by mediating changes in priorities or values. Moreover, Fauvel et al. (2021) conducted a regression analysis that demonstrated that psychological insight into identity, values, and life priorities is associated with decreased anxiety and depression. This

supports the assumption of psychological insight being an underlying mechanism of psilocybin-accompanied treatment.

### ***Interconnectedness and Prosocial Behaviour***

A reoccurring topic that has been identified in two RCTs, as well as two qualitative studies, was the impact of psilocybin on social relationships. However, no mediation or correlation analyses have been conducted in any of these studies. Griffiths et al. (2016) identified significantly increased altruistic and prosocial behaviour after the psilocybin sessions using the PEQ. This was also confirmed by observer ratings of the participants' family members and friends. Accordingly, the RCT by Ross et al. (2016) found increased altruistic behaviour in the participants measured with the FACIT-SWB.

In the follow-up interview study by Belser et al. (2017) each of the 13 participants experienced an outstanding insight about an important personal relationship. The participants universally described deeply meaningful attachments to important family members and significant others. Relationships were woven throughout participant narratives, including themes of forgiveness, loved ones as spirit guides, the importance of narrating one's experience with loved ones, and improved relationships posttreatment. For instance, one participant said: *“I felt like I let go of a lot of anger and resentment towards my parents. I mean, I thought I had already done that, but I really hadn't, and I kind of saw them more as, like, these flawed human beings who did the best they could.”* which shows his forgiveness towards his parents during the psilocybin session. Nearly all participants reported having an experience of love and joy, which arose primarily through a specific human relationship with another person.

Additionally, Noorani et al. (2018) identified increased altruism and prosocial behaviour in the participants due to the intake of psilocybin. One participant mentioned: *“I've been involved with the local literacy council all the time now ... And then the other thing is I've become very involved with this environmental group as well ... instead of sitting around and just watching television and smoking and doing nothing, I'm putting all this extra time I have to good use.”* (Noorani et al., 2018). This citation displays the long-lasting effect of increased prosocial behaviour and connectedness due to psilocybin.

### ***Psychological Flexibility***

Four studies looked at psychological flexibility as a possible important aspect in psilocybin-assisted psychotherapy. In the study by Davis et al. (2020), the role of psychological flexibility triggered by psychedelics was particularly investigated. It was found that increased psychological flexibility mediated the relationship between acute psychedelic



effects and decreases in depression and anxiety symptoms. However, as this study is cross-sectional its outcomes should be interpreted carefully.

Additionally, a participant in the study by Al-Naggar et al. (2021) stated: "*I feel like it has changed my thinking and processing information better (...).*" Another Participant mentioned: "*It works by making new connections in the brain that creates new perspectives.*". Moreover, Barba et al. (2022) and Fauvel et al. (2021) hypothesised that increased psychological flexibility might be correlated with a decrease in experiential avoidance and rumination. However, no statistical evidence supporting this assumption was displayed in either one of the studies.

### ***Rumination, Self-compassion, and Thought Suppression***

A decrease in rumination and thought suppression as a non-acute outcome was reported in the RCT by Barba et al. (2022), as well as in the cross-sectional online study by Fauvel et al. (2021). Barba et al. (2022) found a decrease in rumination in participants who received psilocybin-assisted treatment. Additionally, they identified a reduction in thought suppression in the psilocybin group. They showed that the treatment with psilocybin had been linked to an enhanced ability to accept negative memories, emotions, and thoughts in people with depression. However, they did not conduct a mediation analysis, and therefore decreased thought suppression and rumination cannot be identified as mediators. Additionally, it is important to mention that the control group that received the SSRI escitalopram experienced a decrease in rumination as well. Therefore, the reduction of rumination lead to a decrease in depressive symptoms in both groups. Barba et al. (2022) hypothesised that the reduction in rumination after psilocybin treatment could be related to cognitive openness and flexibility, while the decrease in rumination in escitalopram responders might be related to dampening emotional responsivity. Nevertheless, they do not provide statistical evidence for that assumption.

In the study by Fauvel et al. (2021), it was found that there is a connection between psychedelic experiences and changes in self-rumination and self-compassion. Fauvel et al. (2021) identified a decrease and self-rumination and an increase in self-compassion as mediators of the effect of psychological insight on the decrease in depression and anxiety, by conducting a mediation analysis. The results showed that they partially mediated this relationship. The study also suggests that therapies that focus on self-compassion, such as compassion-focused therapy and mindful self-compassion, could be combined with psychedelic therapy to improve outcomes further. Nevertheless, these results should be evaluated cautiously as they are retrieved from a cross-sectional online survey. Additionally,

the mediation analysis was conducted on the effects of psychological insight and not on the direct effect of psilocybin intake on decreasing anxiety and depression.

### ***Self-efficacy and Motivation***

The cross-sectional online study by Johnson et al. (2017) and the qualitative interview study by Nielson et al. (2018) identified increased self-efficacy and motivation as important aspects that influenced the participants' treatment success positively. Although no direct causal evidence was reported by means of mediation analyses in any of the studies, and both studies scored low in the quality assessment, its influences might still be important to consider. Johnson et al. (2017) reported that 79% of the participants who consumed psychedelics in order to quit smoking mentioned a stronger belief in their own ability to quit. Moreover, a participant in the study of Nielson et al. (2018) mentioned: *"I feel more positive about being able not to drink. I know there will be those times there's a craving and it's there and the opportunity to do it but then maybe having a chance to tell myself. . . bring out the tools from the session that I felt and see if they work, try to use those."* Further one individual expressed his motivation and said: *"I can change this. Right now. Today, in the moment, right then and there."* Nevertheless, there is no statistical evidence proving them to be underlying mechanisms of psilocybin-assisted interventions.

## **Discussion**

The present mixed methods systematic literature review investigated the current literature on psychological mechanisms and mediators of psilocybin use in treating depression, anxiety, and substance use disorders. The purpose was to identify potential mechanisms of successful treatment with psilocybin and give future direction on important factors to be considered in psilocybin-assisted psychotherapy. Out of 214 hits during the search process, 13 studies were included in the mixed methods systematic literature review. The included studies comprise three RCTs, two open-label longitudinal single-group studies, three cross-sectional studies, and five qualitative interview studies.

In general, the present review found nine potential (groups of) mediators or mechanisms underlying the treatment with psilocybin, including mystical experiences, complex emotional experiences, interconnectedness and prosocial behaviour, psychological insight, psychological flexibility, rumination, thought suppression and self-compassion, and lastly self-efficacy and motivation to change. However, only for mystical experiences, mediation analyses from two longitudinal studies were conducted, and its mediating effect was confirmed (Griffiths et al., 2016; Ross et al., 2016). Furthermore, psychological flexibility and self-compassion (Davis et al., 2020), as well as rumination and thought

suppression (Fauvel et al., 2021; Barba et al., 2022), qualify as potential mechanisms, considering the initial, although limited, indications of it playing a mediating role. Additionally, the results of the included quantitative and qualitative studies give indications for further potential psychological mechanisms of psilocybin intake that might impact the successful treatment of the patients. However, no further mediation analyses have been reported.

Mystical experiences stood out as a potential mechanism. Two RCTs confirmed the mediating effect of mystical experiences through a mediation analysis (Griffiths et al., 2016; Ross et al., 2016). Additionally, every included study reported on the occurrence of mystical or spiritual experiences during the psilocybin intake. This is in accordance with the paper by van Elk and Yaden (2022), as well as an earlier review that found that mystical experiences are an important factor in the success of psychedelic-assisted therapy (Johnson et al., 2019). Based on these findings, it can be assumed that mystical experience at least partially mediates the effect of psilocybin-assisted therapy on mental health. This is an important finding for the development of psychotherapeutic treatments using psilocybin. For instance, it could be beneficial to integrate enhancing factors for the occurrence of mystical experiences and support the recovery of the patients. External factors that might reinforce mystical experiences could be the integration of meditation, music, nature-based settings, or spiritual practices (Gandy, 2022). Furthermore, it would be essential to implement the processing of mystical experiences into post-integration sessions, as they might be overwhelming and challenging (Hearn, 2021). The therapist could support the patient in developing insight into the experience and making meaning out of it (Hearn, 2021).

Van Elk and Yaden (2022) already defined cognitive and psychological flexibility as a possible mechanism. Indeed, psychological flexibility qualifies as a potential mechanism, given the preliminary but weak evidence of a mediating role (Davis et al., 2020), which supports further testing in high-quality studies. This aligns with evidence from other studies regarding the effect of psychedelic experience on psychological flexibility (Watts & Luoma, 2020; Wolff et al. 2022). Still, the present review did not identify evidence for cognitive flexibility to be a psychological mechanism.

Potential mechanisms that have not been discussed in the paper by van Elk and Yaden (2022) are rumination, thought suppression and self-compassion. The present review identified their potential mediating role based on weak statistical evidence (Barba et al., 2022; Fauvel et al., 2021). Rumination describes a pattern of thinking where an individual repetitively and obsessively focuses on negative thoughts, feelings, or experiences from the

past, without making any progress towards resolving them (Watkins & Moulds, 2009). This can lead to feelings of anxiety, depression, and stress (Watkins & Moulds, 2009). Looking at additional existing research, the role of rumination in psilocybin-assisted psychotherapy is essential to consider. For instance, Mertens et al. (2020) identified a decrease in rumination at one week and at three months after the psilocybin experience. This decrease in rumination was correlated with a reduced ventromedial prefrontal cortex-right amygdala functional connectivity, which is hypothesized to be responsible for disturbed emotional processing in depression (Mertens et al., 2020). As rumination is an example of inflexibility and rigidity that often is a factor in depression, the concept of rumination overlaps with psychological flexibility (Kashdan & Rottenberg, 2010). This overlap of concepts indirectly supports the hypotheses that rumination, as well as psychological flexibility, are essential aspects in psilocybin-assisted psychotherapy. It is therefore highly recommended to further statistically test if rumination is an underlying mechanism of psilocybin.

The study by Barba et al. (2022) is the first one to investigate the effect of thought suppression in psilocybin treatments. Thought suppression is the deliberate attempt to suppress or push away unwanted thoughts, memories, or emotions from one's consciousness (Watkins & Moulds, 2009). Research has shown that attempting to suppress unwanted thoughts can lead to an increase in the frequency and intensity of the unwanted thoughts (Watkins & Moulds, 2009). Assuming psilocybin decreases thought suppression, the patient could be able to develop alternative strategies to deal with negative thoughts. Implementing techniques such as mindfulness or cognitive restructuring can be more helpful in managing unwanted thoughts and would contribute to a decrease in emotional distress (Watkins & Moulds, 2009). Although limited evidence on thought suppression being a mechanism is available, the present review identifies the possibility and stresses the need to study its role in the future.

Moreover, research showed that self-compassion is linked to various positive outcomes, such as increased well-being, reduced symptoms of anxiety and depression, and greater resilience (Neff, 2011). Self-compassion is a multidimensional construct involving a kind, non-judgmental, and understanding attitude towards oneself, particularly during emotional distress or failure (Neff, 2011). Similar to the findings of the present review, Agin-Liebes et al. (2023) found that psilocybin enhances self-compassion and potentially reduces the long-lasting effects of self-critical thought patterns. They suggest to further investigate its role in the psychological change process (Agin-Liebes et al., 2023). Taking into account that psilocybin increases self-compassion and self-compassion positively affects mental health it

qualifies as a psychological mechanism. Still, research from high-quality RCTs is required to statistically prove this assumption.

A possible mechanism that was not particularly elaborated in the paper by van Elk and Yaden (2022) is the complex emotional experiences of the participants during the psilocybin interventions. However, no statistical evidence was reported that supports the assumption of its functioning as a potential mechanism. Considering existing literature, Mertens et al. (2020) argued that conventional antidepressants suppress the emotional responsiveness of a patient, while psychedelics enable the user to completely engage with the emotions and give them the opportunity to deal with their feelings. Assuming, the hypothesis by Mertens et al. (2020) is correct, complex emotional experiences partially cause a change in the patients and might be considered a potential mechanism. However, there is no statistical evidence confirming this assumption. Moreover, Roseman et al. (2019) developed the Emotional Breakthrough Inventory which intends to measure complex emotional experiences during a psychedelic experience. Roseman et al. (2019) suggest emotional breakthroughs to be a key mediator for positive changes in the patients' mental health. This would support the assumption that complex emotional experiences are a possible mechanism of psilocybin. The present review reveals the urge to further research on the role of complex emotional experiences in psilocybin-assisted psychotherapy.

Psychological insight into self-identity values and life priorities is assumed to be a potential underlying mechanism by the present review. This aspect was not yet discussed in the paper by van Elk and Yaden (2022), however, it shows similarities to their hypothesis that changes in beliefs and worldviews are a psychological mechanism. Self-identity refers to individuals' sense of who they are and how they perceive themselves (Drummond, 2021). It incorporates their beliefs, values, personality traits, experiences, and social relationships. Developing psychological insight is a crucial aspect of many psychotherapies and promotes self-awareness and self-growth (Peill et al., 2022). The psychodynamic theory suggests that greater self-understanding leads to more adaptive responses to stress and negative experiences, improving well-being and life satisfaction. Cognitive-behavioural therapy emphasises developing insight into negative thought patterns to reduce symptoms by understanding difficulties and reducing negative beliefs (Peill et al., 2022). Although the present review suggests that psychological insight potentially acts as a mechanism in psilocybin treatment, statistical evidence is still scarce. Consequently, it is suggested to be investigated in future RCTs.

Moreover, social connectedness and prosocial behaviour have been shown to play a relevant role in the treatment's success. This is in line with the findings by van Elk and Yaden (2022). Furthermore, that psychedelic use enhances the feeling of social connectedness and consequently also prosocial behaviour is supported by other studies as well (Agin-Liebes et al., 2021; Forstmann et al., 2020). Furthermore, psilocybin-assisted group therapy has shown promising effects on patients experiencing a mental disorder (Agin-Liebes et al., 2021). According to Agin-Liebes et al. (2021), group therapy in combination with psilocybin may benefit trauma processing by reinforcing social unity, safety, trust, and belonging. Integrating psilocybin into a group setting might be an interesting aspect of future research in developing psilocybin-assisted psychotherapy techniques. Nevertheless, no mediation analysis or statistical tests controlling for potential mechanisms were conducted. Due to that, the findings indirectly support the importance of investigating if they act as mechanisms of psilocybin-assisted psychotherapy.

The current review identifies self-efficacy and motivation to be potential mechanisms, although no statistical evidence was reported in the included studies (Johnson et al., 2017; Nielson et al., 2018). Their possible importance in the psychological change process was not addressed by van Elk and Yaden (2022). Individuals with high self-efficacy and motivation are more likely to believe that they have the ability to overcome their addiction and are more willing to put in the effort and time required for treatment (Bozdağ & Çuhadar, 2022). This can lead to greater engagement in treatment and a higher likelihood of success. On the other hand, individuals with low self-efficacy and motivation may struggle to believe in their ability to overcome their addiction or may lack the drive to make the necessary changes in their lives (Bozdağ & Çuhadar, 2022). The two studies provided evidence that increased self-efficacy and motivation are important outcomes of psilocybin intake especially in the treatment of substance abuse disorders. A past study by Bogenschütz et al. (2018) already suggested investigating the potential mediating effect of self-efficacy and motivation in psilocybin-assisted psychotherapy for alcohol use disorder. However, in existing studies that investigated the mediation effect of self-efficacy and motivation in substance disorder that did not include any intake of psychedelics, no significant mediation effect was identified (Carpenter et al., 2002; Kadden et al., 2011). This could be understood as an argument against self-efficacy and motivation being mediators of psilocybin-assisted therapy. Although no direct statistical evidence was reported the present review acknowledges them as possible mechanisms that should be investigated in the future.

Coming back to the research question: “*Which psychological mechanisms underly the effect of psilocybin in the treatment of patients experiencing depression, anxiety, or substance use disorder?*” the findings of this mixed methods systematic literature review provide a current view on the evidence. Nine potential (groups of) mechanisms underlying the treatment with psilocybin were identified. However, still, statistical evidence on psychological mechanisms is scarce. In order to collect statistical evidence of mechanisms, usually mediational analyses are conducted. However, a mediational test is a simplified model, that depends on one or more assumptions. Due to that, potential alternative variables that may also influence the process of change might be ignored. This makes it complicated to determine mechanisms and requires research targeted at specific psychological mechanisms. As statistical evidence is not sufficient to determine psychological mechanisms at the moment, the present review provides an overview of mediators of psilocybin that potentially act as mechanisms. To answer the research question the present review categorised the potential mechanisms into three groups. These are mediators with strong statistical evidence, mediators with weak statistical evidence, and mediators with no direct statistical evidence. Mystical experience is the only mediator that was proven by strong statistical evidence from RCTs of high quality. Secondly, rumination, psychological flexibility, thought suppression, and self-compassion are categorised as mediators with weak statistical evidence. Mediation analyses showed significant results for these constructs. However, no RCTs tested their mediating effect and therefore the statistical evidence is weak. Consequently, the present review considers them as probable mediators however, mediation analyses in future RCTs are highly recommended. Lastly, social connectedness and prosocial behaviour, self-efficacy and motivation, psychological insight, and complex emotional experiences have been shown to positively affect the therapeutical outcome of psilocybin-assisted psychotherapy. However, no statistical evidence tested and proved their mediating effect. Still, the present review found that all of these factors provide explanations of how improvement in mental health occurs when using psilocybin. Consequently, the present review identifies them as potential mediators with no direct statistical evidence. It is recommended for the future to conduct mediation analyses to determine if these suggestions can be proven statistically.

Although this review could identify potential mediators of psilocybin-assisted psychotherapy there is still too little evidence to determine certainly which variables act as mediators and which do not. Beyond that, it was not possible to determine the psychological mechanisms of psilocybin interventions. According to VanderWeele (2009) mechanisms need to indicate a mediation; however, it is not the same the other way around. A mediator

provides an implication for a mechanism, but it does not need to be the case. Even with strong statistical evidence from a mediational analysis, a true mechanism cannot be proven. Due to that performing experimental studies in the future in order to determine the causal mechanisms of psilocybin-assisted psychotherapy is suggested. For that, it is suggested to conduct RCTs in which potential mechanisms are targeted and manipulated. For instance, the sample could be divided into two groups in which in one group the set and setting are designed in a way that enhances the occurrence of mystical experiences. One option to achieve that would be to provide the treatment environment with spiritual pictures and candles or to play spiritual music. In the second group, the participants would be situated in a more neutral and unbiased setting. These kinds of studies would provide insight into the causal mechanisms of psilocybin-assisted psychotherapy.

In line with earlier literature, the results of the present review show that various identified mediators are related to concepts of third-wave behavioural therapies (Jungaberle et al., 2018). This provides considerable input for developing psilocybin-assisted psychotherapy approaches that implement positive psychological interventions. For instance, psychological flexibility was determined as a mediator with weak statistical evidence. This is also an important aspect of ACT. Davis et al. (2020) suggested that psychedelic-assisted psychotherapy could be integrated with therapies designed to target psychological flexibility, such as ACT. The study also suggested that psychedelics can occasion mindfulness or acceptance processes and commitment and behaviour change processes. Accordingly, Luoma et al. (2019) and Yaden et al. (2022) argue that ACT could be a suitable therapeutic approach to enlarge and deepen the effects of psilocybin-assisted therapy.

Furthermore, self-compassion, is an essential construct in many positive psychological frameworks (Neff et al., 2007). Pots and Chakhssi (2022) suggested combining psilocybin-assisted psychotherapy with compassion-focused therapy (CFT). CFT helps individuals challenge self-critical thoughts and beliefs, reduce self-judgment, and cultivate self-acceptance. It also encourages the cultivation of compassion towards others, fostering empathy, understanding, and supportive relationships. Pots and Chakhssi (2022) hypothesised that CFT would enhance the therapeutical effects on the patients.

Moreover, positive psychological therapy forms commonly target the enhancement of positive emotions. This is based on the broaden and build theory, which assumes that when individuals experience positive emotions, it expands their immediate range of thoughts and actions (Frederickson, 2001). This contributes to the development of long-term personal resources, including physical, intellectual, social, and psychological factors (Frederickson,



2001). However, no research on the broaden and build theory in psychedelic therapy has been conducted yet.

Prosocial behaviour and interconnectedness are important components of positive psychology as well, as it was proven that social relationships contribute to mental health (O'Connell et al., 2016). Due to that, it would be interesting to investigate in the future how positive psychological interventions such as acts of kindness could benefit patients in psilocybin-assisted psychotherapy.

In earlier studies, the connection between mystical experiences and meditation was already investigated. Similar to psychedelic experiences, intensive meditation on its own is associated with mystical experiences (Zanesco et al., 2023). Moreover, a study identified that psychedelics and meditative states overlap in their neurophysiology (Simonsson & Goldberg, 2023). Additionally, a cross-sectional study showed a positive effect of psychedelic use in combination with meditation on mental health (Azmoodeh et al., 2022). Consequently, longitudinal studies to provide standardized measures of the effectiveness of a combined treatment of psychedelics and meditation are highly recommended.

### **Limitations**

This mixed methods systematic literature review has to be considered in light of its limitations. First of all, the use of psychedelics in mental health research is a novel and extraordinary domain. Testing its effects with standardized statistical studies discloses various challenges, such as blinding, use of placebos, or bias (Muthukumaraswamy et al., 2022). The included studies often consisted of very homogenous and small samples, limiting the results' generalizability. Additionally, the studies were possibly influenced by self-selection or expectancy biases and did not have sufficient control groups. Moreover, several cross-sectional studies were included due to a lack of existing longitudinal RCTs. Furthermore, some cross-sectional online studies are based on self-administered and self-reported use of psilocybin, which limits the reliability of the review's findings.

The review only included a limited number of studies. Despite a recent resurgence in interest in studying psychedelics, permission to study psychedelic substances is only granted to a few research facilities and is accompanied by significant administrative and financial challenges (Nutt et al., 2013). Moreover, no inter-rater reliability was tested in the present review. If multiple coders are included in the screening and data extraction, the results are more reliable (Belur et al., 2021). Consequently, the present review is limited due to the potential biases of a single reviewer.

Due to the research field's novelty, the number of not yet considered psychological mechanisms is probably high. This restricts the present review in its ability to identify psychological mechanisms of psilocybin interventions. Missing out on mechanisms prevents the development of effective therapeutic treatment methods in the future. This stresses the urgency to conduct RCTs that investigate how psilocybin works on a psychological level. Furthermore, looking at the existing studies of psilocybin it stands out that many studies are conducted by the same or similar research groups. The different studies often refer back to the same past studies and reviews. Particularly mystical experiences stand out as a frequently discussed and studied aspect of psilocybin. Without doubting the relevance of investigating the functioning and role of mystical experiences, it is crucial to raise the concern that it might be a result of a bias among researchers resulting in testing this phenomenon more often. Additionally, Forstmann and Sagioglou, (2021) addressed that many scientists in psychedelic research seem to be very convinced about the benefits of psychedelic substances, although statistical evidence is limited. Their bias towards psychedelics might influence the quality of the studies, the way of reporting the results, and the expectancies of the patients (Forstmann & Sagioglou, 2021). Taking these limitations into account is crucial when conducting research on psilocybin-assisted therapy. Furthermore, minimising the risks of bias and promoting diversity in research groups is essential for future research.

### **Future Research**

In order to determine the underlying mechanisms and mediators of psilocybin-assisted psychotherapy, it is important for future research to focus on increasing the representativeness and generalizability of results. This can be achieved using larger and more diverse samples, which include individuals with varying socioeconomic status, ethnicity, and attitudes towards psychedelic drugs. To ensure the reliability of results, it is recommended that rigorous longitudinal double-blind, placebo-controlled, crossover experimental designs with standardized dosages are employed, as this will minimize blinding and expectancy effects. Additionally, it is highly recommended to particularly target identified mediators and test if they can be determined as causal mechanisms of psilocybin-assisted psychotherapy as well. For that, the targeted variable needs to be manipulated and compared to a control group.

The present review solely included studies investigating depression, anxiety and substance use disorder. This makes the review less generalisable to all mental disorders. For instance, for the mediator with the strongest statistical evidence, mystical experience, mediation analyses were only conducted for depression and anxiety. This is essential to consider in future research and studies on the whole spectrum of mental disorders are

necessary. Ignoring the individual symptoms and experiences of patients could be very dangerous as psychological mechanisms and mediators are not the same for all mental illnesses. Developing one treatment approach for all mental conditions would neglect the patients' individual needs. Therefore, for future research, it is recommended to expand the investigation of psychological mechanisms of psilocybin to a larger variety of mental disorders.

Moreover, it is recommended to investigate the effects of integrating positive psychological approaches into psilocybin-assisted psychotherapy. For the moment there is no therapeutic protocol that is widely used in current trials. Furthermore, most RCTs do not report on the therapeutical methods used in the psilocybin interventions. The present review provided an overview of potential psychological mechanism underlying psilocybin-assisted therapy. This is the first step in developing and testing standardised therapy protocols by integrating for example mindfulness exercises, compassionate-focused therapy, or ACT into the psychotherapy accompanying the psilocybin treatment.

### **Conclusion**

The present mixed methods systematic literature review provides an overview of existing literature about underlying mechanisms and mediators of the effect of psilocybin on depression, anxiety, and substance use disorder. RCTs providing high-quality statistical evidence in psilocybin research are scarce. Still, mystical experience could be identified as a mediator with strong statistical evidence. Rumination, psychological flexibility, thought suppression, and self-compassion were identified as mediators with weak statistical evidence. Furthermore, social connectedness and prosocial behaviour, self-efficacy and motivation, psychological insight, and complex emotional experiences were determined as mediators with no direct statistical evidence. Nevertheless, longitudinal and high-quality RCTs that test mediators and mechanisms of psilocybin-assisted therapy are recommended for the future. Additionally, the review revealed that frameworks from positive psychology might be beneficial to integrate when developing protocols for conducting psilocybin-assisted psychotherapy.

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## Appendix

**Table**  
*Study-level Cochrane risk of bias ratings*

<b>Study</b>	<b>Random Sequence Generation</b>	<b>Allocation Concealment</b>	<b>Blinding of Personnel &amp; Participants</b>	<b>Blinding of Outcome Assessment</b>	<b>Incomplete Outcome Data</b>	<b>Selective Reporting</b>	<b>Other Bias</b>
Al-Naggar et al., 2021	High	High	High	High	High	Unclear	High
Barba et al., 2022	Low	Low	Low	Low	Low	Low	High
Belser et al., 2017	High	High	High	High	High	Unclear	High
Davis et al., 2020	High	High	High	High	Low	Unclear	High
Fauvel et al., 2021	High	High	High	High	Low	Unclear	High
Garcia-Romeu et al., 2014	High	High	High	High	Low	Unclear	High
Griffiths et al., 2016	Low	Low	Low	Low	Low	Low	High
Johnson et al., 2017	High	High	High	High	Low	Unclear	High
Nielson et al., 2018	High	High	High	High	High	Unclear	High
Noorani et al., 2018	High	High	High	High	High	Unclear	High
Roseman et al., 2018	High	High	High	High	Low	Unclear	High
Ross et al., 2016	Low	Low	Low	Low	Low	Low	High
Swift et al., 2017	High	High	High	High	High	Unclear	High