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Classic psychedelics and alcohol use disorders: A systematic review of human and animal studies

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Abstract

Classic psychedelics refer to substances such as lysergic acid diethylamide (LSD), psilocybin, ayahuasca, and mescaline, which induce altered states of consciousness by acting mainly on 5-HT_{2A} receptors. Recently, the interest of psychedelics as pharmacological treatment for psychiatric disorders has increased significantly, including their use on problematic use of alcohol. This systematic review is aimed to analyse the last two decades of studies examining the relationship between classic psychedelics and alcohol consumption. We searched PubMed and PsycInfo for human and preclinical studies published between January 2000 to December 2021. The search identified 639 publications. After selection, 27 studies were included. Human studies ($n = 20$) generally show promising data and seem to indicate that classic psychedelics could help reduce alcohol consumption. Nevertheless, some of these studies present methodological concerns such as low number of participants, lack of control group or difficulty in determining the effect of classic psychedelics in isolation. On the other hand, preclinical studies ($n = 7$) investigating the effect of these compounds on voluntary alcohol consumption are scarce and show some conflicting data. Among these compounds, psilocybin seems to show the most consistent data indicating that this compound could be a potential candidate to treat alcohol use disorders. In the absence of understanding the biological and/or psychological mechanisms, more studies including methodological quality parameters are needed to finally determine the effects of classic psychedelics on alcohol consumption.

KEYWORDS
alcohol, ayahuasca, classic psychedelics, LSD, mescaline, psilocybin

1 | INTRODUCTION

Alcohol consumption is a major clinical, social, and economic problem. In fact, during 2016, 2.3 billion people were current drinkers and the harmful use of this substance resulted in 3 million deaths (5.3% of all deaths) worldwide and 132.6 million disability-adjusted life years (DALYs)—that is, 5.1% of all DALYs in that year.[1] Despite these data, there are only four pharmacological treatments approved in Europe for alcohol use disorders (AUD): Disulfiram, acamprosate, naltrexone, and nalmefene. Also, their success for reducing heavy alcohol

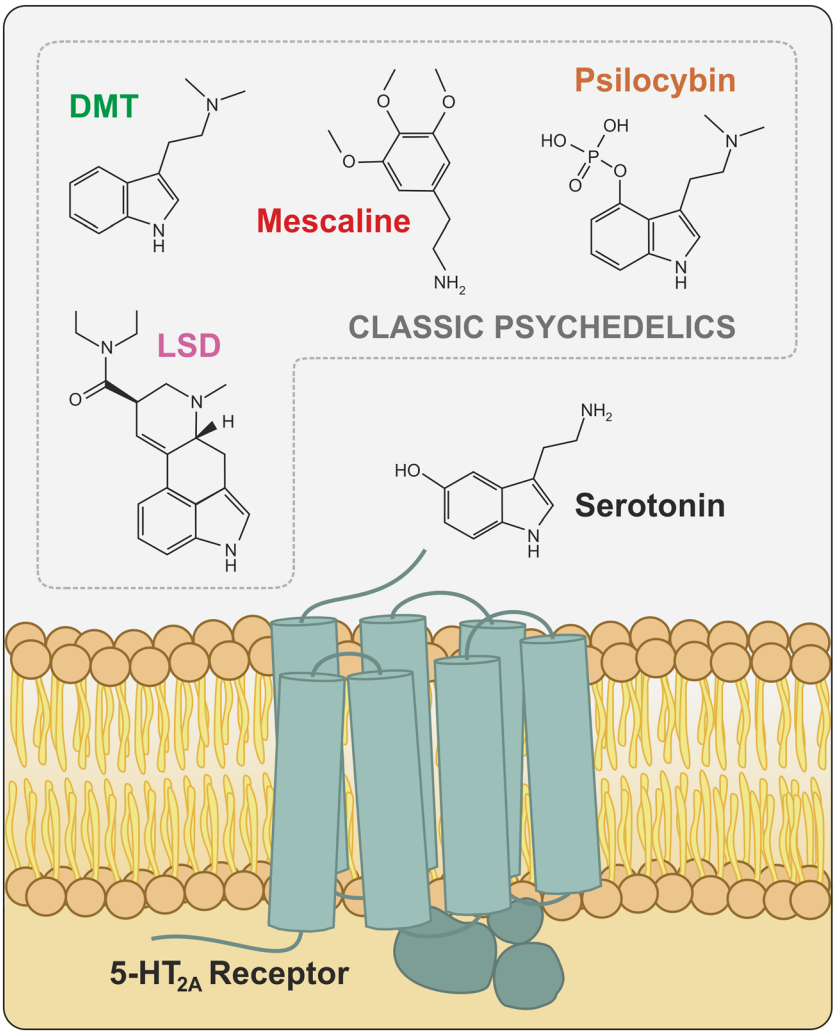

FIGURE 1 Classic psychedelics and 5-HT2A receptor. 5-HT2A receptor and chemical structures of classic psychedelics and serotonin. Although classic psychedelics also bind other serotonin receptors (such as 5-HT1A and 5-HT2C), 5-HT2A is the main site of action responsible for the behavioural effects of psychedelics. The 5-HT2A receptor is a G-protein-coupled receptor (GPCR) that contributes to multiple complex processes in the neocortex by way of multiple cellular mechanisms. Psychedelics can induce long-term neuronal changes, affect gene expression and increase neuronal plasticity through the agonism of the 5-HT2A receptor. Such alterations in synaptic plasticity may well explain some of the observed long-term substantive behavioural and cognitive changes following psychedelic administration. Interestingly, an emerging body of evidence implicates the 5-HT2A receptor as a novel target for pharmacologic intervention for the treatment of substance use disorder (SUD), AUD, and for smoking cessation.

consumption, craving symptoms, or abstinence rates is modest.[2] That has led to the exploration of new compounds to treat AUD, among them, serotonergic hallucinogens.[3]

Serotonergic hallucinogens, also known as psychedelics, are a class of compounds that exert profound effects on the brain via serotonin receptors.[4] Classic psychedelics refer to substances such as lysergic acid diethylamide (LSD), psilocybin, ayahuasca (DMT) and mescaline, which induce altered states of consciousness by acting mainly on 5-HT_{2A} receptors[5] (Figure 1). Classic psychedelics were widely used by clinicians and researchers in the 1950–1970s to treat several psychiatric pathologies as schizophrenia, anxiety, mood disorders, or addiction. For AUD, the most used was LSD throughout these two decades.[3] Several studies reported that classic psychedelics led to reductions in craving and alcohol consumption through an improvement in self-acceptance and interpersonal relationships. Furthermore, the studies indicated that these compounds showed a low risk of compulsive use and low levels of physiologic toxicity.[6] However, these studies presented methodological problems such as absence of control groups, treatment groups inconsistently defined, or absence of blinding procedures, among others.[7,8] In 1965, LSD was listed as prohibited substances in the United States and were removed from legal circulation and other psychedelics followed later. The same happened in the United Kingdom and Europe, leading to the cessation of psychedelic-assisted interventions.[9]

However, after decades of suspension, the interest was renewed in the 1990s, carrying out studies designed with a slightly more

careful experimental methodology. Currently, some of the pathologies studied are major depression, anxiety, or substance use disorders.[10] The objective of this systematic review is to provide an overview of the last two decades of human and preclinical studies on the therapeutic effects of classic psychedelics in treatment of AUD.

2 | MATERIAL AND METHODS

2.1 | Search strategy

Literature search was conducted on Pubmed and PsycInfo databases for studies published since 01/01/2000. Since the purpose was to assess recent evidence regarding the topic, this particular period was chosen. The search was restricted by English and Spanish language and conducted with the following search string "(classic psychedelics OR lysergic acid diethylamide OR psilocybin OR ayahuasca OR mescaline) AND alcohol." Only journal articles were selected for screening. All the searches were conducted during November and December of 2021. The Systematic Reviews and Meta-Analysis guidelines (PRISMA) served as guiding principles for the data collection for this review.[11]

2.2 | Inclusion and exclusion criteria

We included research papers, experimental and observational data, showing the relationship/association between classic psychedelics use and alcohol consumption, conducted in both human and animal models and published from 2000. We excluded review, commentary, conference and interview papers, qualitative data studies, and no full-text available articles. Likewise, studies focus on other psychedelic substances, such as MDMA or ketamine, were not included. In human studies, both the data of AUD participants and people without diagnosis were analysed. We did not limit studies to type or purpose of classic psychedelic use (i.e., recreational or therapeutic) or apply any age, ethnicity, or geographic setting limitations. In animal studies, there were no restrictions based on outcome measurement, such as direct alcohol intake or other phenomena associated with alcohol consumption in preclinical models.

2.3 | Data screening and extraction

We screened all citations and abstracts retrieved from the search strategy and identified articles for full-text extraction. Two authors (JCC and JAMG) performed the literature search and screening independently. Any unresolved disagreements were directed to an independent author (JALM) for a final decision and resolution. All the authors agreed on the included articles. The reported findings from each study were extracted by JCC and checked by JAMG. Two authors (JCC and VEA) assessed the included studies using the National Institutes of Health quality assessment tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) to identify potential biases in the studies related to the research question (criteria used to quality assessment are listed in the Supporting Information). Discrepancies on the quality assessment were resolved through discussions with a third author (JALM). For human studies, collected data included in Table 1 were as follows: Substance, sample size, study characteristics, main results, and quality assessment. For preclinical studies (Table 2), the following data were collected: Species, substance and doses used, model, and main results. Studies were grouped by psychedelic substance for the synthesis.

3 | RESULTS

3.1 | Search results

Figure 2 shows a flowchart of the selection process. Twenty-seven articles were included in this review. Mendeley Reference Manager software was used to identify duplicate articles in the cited databases. Among the 585 nonduplicate articles initially included, 155 manuscripts (26.5%) did not meet the article type criteria (reviews, interviews, etc.) and were rejected. The remaining 430 articles were subjected to title and abstract review and 93.9% of them ($n = 404$) were discarded because they did not refer to classic psychedelics ($n = 151$), did not show data related to alcohol consumption ($n = 216$), or did not analyse quantitative data ($n = 37$). When there was disagreement or ambiguity about inclusion during the title and abstract screening, the full reference was obtained to allow further scrutiny of the study eligibility. In the next step, two articles (7.7%) were excluded due to not having full text available. Finally, 24 articles were selected from this search. After carefully reading these studies, we found that they referenced three additional manuscripts that were not included in the initial search, reaching the 27 definitive articles included. Studies carried out in humans present two main types of experimental designs: Observational studies ($n = 17$) and psychedelic-assisted interventions ($n = 3$). Among preclinical studies ($n = 7$), 57% evaluated the effect of classic psychedelics on alcohol consumption and the rest of studies, other phenomena associated with alcohol consumption in animal models (e.g., alcohol-induced conditioned place preference). Tables 1 and 2 show the main characteristics of the studies carried out in humans and animals, respectively.

3.2 | General findings

3.2.1 | LSD

LSD is a semisynthetic natural product derived in nature from the rye fungus, *Claviceps purpurea*, first synthesized in 1938 by Albert Hofmann. The study of LSD as a candidate substance for the treatment of drug abuse began in the 1950s and continued until the 1970s. During

TABLE 1 Summary of studies exploring the relationship between classic psychedelics and alcohol use in humans

Reference number	Substance	Sample size	Study characteristics	Main results	Quality assessment
14	LSD Psilocybin	22	Retrospective Interviews about Previous LSD/Psilocybin Use	LSD blocked the subjective effects of alcohol in 86.7% of the participants. Psilocybin did not block these effects	Good
15	LSD Psilocybin Ayahuasca Mescaline	343	Retrospective survey about the effect of classic psychedelic use on alcohol consumption.	After the psychedelic experience, 83% no longer met Alcohol Use Disorders criteria.	Poor
16	LSD Psilocybin Others	1102	Online survey exploring people's experiences of using psychedelics at microdoses	58% of participants reduced or stopped their alcohol since commencing microdosing.	Good
17	LSD Psilocybin	278	Retrospective survey analysing subjective microdosing benefits.	42.3% of participants indicated decreased their alcohol consumption	Fair
22	Psilocybin	10	Evaluation of a Psilocybin-assisted therapy for alcoholism.	Per cent drinking days decreased during weeks 5–12 relative to baseline (Mean Difference = 27.2%) and relative to weeks 1–4 (MD = 21.9%)	Good
25	Psilocybin	409	Observational assessment of psilocybin use and its association with the consumption of other drugs	No difference was observed between users and nonusers of psilocybin.	Poor
36	Ayahuasca	84	Analysis of alcohol consumption in a sample of adolescent ayahuasca users.	Ayahuasca adolescents used less alcohol (46.3%) than the control group (74.4%).	Good
37	Ayahuasca	242	Assessment of the severity of alcohol addiction in ayahuasca users.	Ayahuasca users showed significantly lower scores than controls on the Addiction Severity Index Alcohol Use.	Good
38	Ayahuasca	57	Assessment of social and psychological variables in ayahuasca users.	Ayahuasca users showed less recent use of alcohol than controls.	Good
39	Ayahuasca	96.901	Online survey exploring problematic drinking among ayahuasca users, other classic psychedelics users and controls	The Ayahuasca User group (9.41) had a lower total AUDIT score than the Classic Psychedelic User group (10.33) but higher score than Controls (8.45).	Good
40	Ayahuasca	7.939	Evaluation of alcohol and tobacco consumption in ayahuasca users.	Alcohol use disorders were significantly lower in ayahuasca users than in controls in all age ranges (18–24 years: 4.9 vs. 19.2%; 25–34: 2.3 vs. 14.7%; ≥35: 1.0 vs. 10.4%).	Good
41	Ayahuasca	8.629	Online cross-sectional study of people who have consumed ayahuasca.	A positive association was observed between the number of ayahuasca uses and the likelihood of lower alcohol use.	Fair
42	Ayahuasca	121	Descriptive analysis of DMT use patterns in a sample of consumers.	Among the DMT users, 89.3% indicated having consumed alcohol in the previous 30 days and 31.4% of the sample reported binge drinking during that period.	Fair
43	Ayahuasca	10	Evaluation of an Ayahuasca-assisted intervention for problematic substance use.	After the intervention, a decrease in alcohol consumers was observed (from 5 to 2).	Good
44	Ayahuasca	36	Evaluation of an Ayahuasca-assisted intervention for problematic substance use.	The intervention led to a significant reduction in severity of alcohol use (measured by Addiction Severity Index composite scores) from 0.38 to 0.06.	Good
55	Mescaline	452	Online questionnaire evaluating psychiatric disorders in mescaline users.	Of those respondents reporting a prior alcohol misuse or AUD, 76% reported improvements in these conditions following mescaline use.	Poor

TABLE 1 (Continued)

Reference number	Substance	Sample size	Study characteristics	Main results	Quality assessment
56	Mescaline	3.861	Epidemiologic investigation of substance use among American Indian youth.	Thirty-day alcohol use was related to both spiritual and recreational peyote use	Fair
57	LSD Psilocybin Mescaline	149	Interviews evaluating the patterns of simultaneous polysubstance use in university students.	46.6% of the university students indicated a simultaneous consumption of alcohol and mescaline, 41.2% psilocybin and alcohol and 25% LSD and alcohol.	Good
59	LSD Psilocybin Others	98	Survey analysing simultaneous polysubstance use in young adults who reported use of MDMA or hallucinogens	Alcohol was typically consumed before, during and after LSD (67% of the participants) and psilocybin (54%) use.	Fair
60	LSD	13.840	Survey analysing psychosocial factors related to LSD use in adults	Participants who reported using alcohol before the age of 21 years were 23.5 times more likely to report lifetime LSD use.	Fair

TABLE 2 Summary of studies exploring the effects of classic psychedelics on alcohol consumption and phenomena associated in animal models

Reference	Species	Substance	Dose	Model	Main results
18	Mice	LSD	25 and 50 μg/kg	Voluntary alcohol consumption (2-bottle choice drinking paradigm)	50 μg/kg LSD reduced alcohol consumption (17.9%) over an interval of 46 days following LSD administration.
19	Rats	LSD Psilocybin	0.08 and 0.32 mg/kg 0.1, 1, 2.5, and 10 mg/kg	Alcohol Deprivation Effect (2-bottle choice drinking paradigm)	Only a sub-chronic treatment with psilocybin produced a 20% reduction in alcohol consumption during the first day of relapse. No effects of LSD observed
26	Rats	Psilocybin	1 and 2.5 mg/kg	Relapse-like behaviour (Operant Self-Administration)	Psilocybin led to a reduction (40–50%) in relapse for alcohol. Also, psilocybin was capable of restoring mGluR2 expression levels, altered by alcohol consumption.
45	Mice	Ayahuasca	30, 100, 200, 300, or 500 mg/kg	Alcohol-induced behavioural sensitization	Ayahuasca showed high sensitivity in preventing the development of alcohol-induced behavioural sensitization, without affecting the locomotor activity of the animals.
46	Mice	Ayahuasca	30, 100, and 300 mg/kg	Alcohol-induced Conditioned Place Preference	Ayahuasca blocked the development of Alcohol-induced Conditioned Place Preference.
47	Mice	Ayahuasca	1.76 mg/kg	Alcohol-induced behavioural sensitization	Ayahuasca attenuated the expression of ethanol-induced behavioural sensitization, caused an anxiolytic effect during ethanol withdrawal and modulated several neuroplastic changes induced by ethanol
52	Rats	Ayahuasca	0.13, 0.26, and 0.52 mg/kg	Voluntary alcohol consumption (Intermittent access to 2-bottle choice)	Ayahuasca treatment for 5 days had no effect on voluntary alcohol consumption, but reversed the effect of alcohol consumption on cFos.

this period, studies indicated the beneficial potential of this molecule in AUD.[12] A meta-analysis of six randomized controlled trials (1966–1970) administering a single dose of LSD for treatment of AUD found that participants receiving LSD showed greater odds of improvement in alcohol consumption (OR = 1.96, $p = 0.0003$) than control participants.[13]

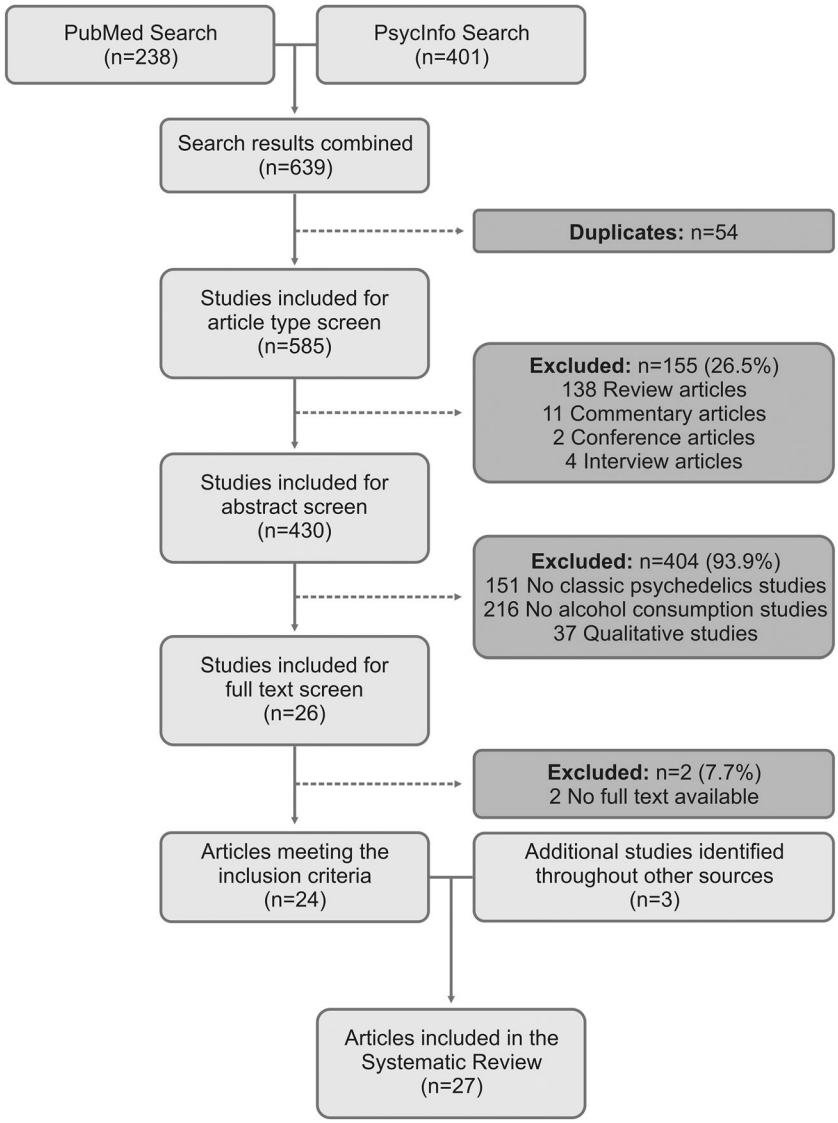

FIGURE 2 Flow diagram of records identified, screened, and included

Contrary to what happened during the past century, in recent years few studies have studied the effect of LSD on AUD. In addition, those carried out in humans are observational and sometimes the results refer to subjective variables of the participants. Thereby, in 2000, Barrett et al. conducted a study in which they analysed the participant's previous experiences with alcohol and LSD/psilocybin when used alone or in combination. The main result showed that 86.7% of the participants who performed a concurrent use of alcohol and LSD reported a complete blockade of alcohol's subjective effects, while the remainder reported a diminished effect. Compared with psilocybin, LSD showed greater effects reducing the alcohol-induced subjective effects.[14] Another observational study analysed the effect of classic psychedelic use on alcohol consumption. Among the sample of participants, 38% reported having used LSD. The most relevant result of the study indicates that, after the psychedelic experience, 83% no longer met AUD criteria. Interestingly, 28% stated that classic psychedelics caused a change in life priorities and values that led to a reduction in alcohol consumption. When interpreting the results of this study, it is important to note that one of the inclusion criteria was "Had used a classic psychedelic outside of a university or medical setting, followed by reduction or cessation of subsequent alcohol use." In other words, one of the requirements to participate in this study was to have reduced alcohol consumption after having used a classic psychedelic. This type of recruitment may compromise the full conclusions of the study. In addition, the results refer to the entire sample of participants, in which there are subjects who consumed LSD, psilocybin, or ayahuasca. Therefore, the individual effect of each psychedelic is unknown.[15] The same occurs in a study published by Lea et al. in 2020.[16] These researchers conducted an international online survey that aimed to examine people's experiences using psychedelics at microdoses (very low doses of psychedelic drugs on a routine schedule without the intention of experiencing effects typically experienced at higher psychedelic doses) as self-managed therapies to improve mental health or reduce alcohol consumption. Among

the 1102 participants, 45% used LSD (average consumption = 11 μg). The results indicate that 58% of the participants reduced or stopped their alcohol consumption since commencing microdosing. Although this is a promising result, the individual effect of LSD is unknown, since the sample consisted of participants who used LSD, psilocybin or other substances. This reduction is similar to that shown in the manuscript published by Anderson et al. in 2019 concerning microdoses.[17]

The first study to analyse the effects of LSD on animal models of alcohol intake was carried out in 2018 in mice.[18] Alcohol consumption was assessed using a two-bottle choice drinking paradigm and two doses of LSD (25 and 50 μg/kg) were tested. The results showed that mice treated with 50 μg/kg LSD reduced their alcohol consumption compared to the control group, as was alcohol preference. The reduction in consumption was sustained over an interval of 46 days following LSD administration. No significant effects were observed in mice treated with 25 μg/kg LSD. Given these results, the authors argued that the effect reported in previous clinical studies may be not fully explained by psychological factors and involves a biologically mediated effect. Another recent study carried out in Wistar rats did not produce such promising data. The objective of this research was to analyse the effect of three different treatment schedules with psilocybin/LSD on the alcohol deprivation effect, a model used to study alcohol relapse in animal models. As in the previous study, alcohol consumption was assessed using a two-bottle choice drinking paradigm. However, in this study neither of the two doses of LSD used (0.08 and 0.32 mg/kg) had an effect on alcohol deprivation effect.[19]

3.2.2 | Psilocybin

Psilocybin is the main psychedelic ingredient of mushrooms of the genus *Psilocybe*,[20] first isolated in 1958 by Albert Hofmann. Although some research was carried out in the context of psycholysis, clinical research on psilocybin during the past century was not as significant as in the case of LSD. However, recent interest in treatment with classic psychedelics has led to the development of several clinical trials whose objective is to study the effect of psilocybin on alcohol consumption (ClinicalTrials.gov Identifiers: NCT04718792, NCT04141501, NCT04620759, NCT04410913, NCT01534494, NCT02061293).

Bogenschutz et al. have made important contributions to the study of psilocybin as a treatment for AUD. These researchers have designed an experimental psilocybin-assisted therapy for alcoholism[21] whose results have been published in several papers. This therapy consists in a psychosocial intervention involving 12 sessions. Four sessions before the first psilocybin session, four sessions between the first and second psilocybin sessions, and four sessions after the second psilocybin session. For the first psilocybin session, participants received a dose of 0.3 mg/kg. For the second session, the dose was increased to 0.4 mg/kg. The dose range was chosen according to published psilocybin research with healthy volunteers and doses of LSD used historically in the treatment of alcoholism. The first study based on this therapy was carried out in 10 subjects who presented an active alcohol dependence. The results showed that following the first psilocybin session, per cent heavy drinking days and per cent drinking days were significantly lower than baseline at all follow-up points. For example, per cent drinking days decreases 27.2% during weeks 5–12, compared to baseline. Importantly, the improvement was not statistically significant during the first 4 weeks of participation, when participants received weekly therapy but had not yet received psilocybin.[22,23] Later studies of Bogenschutz et al. aimed at investigating several potential mediators of treatment effect, including motivation, self-efficacy, craving, depression, anxiety, and spiritual dimensions of the experience.[24] Although this article is based on three descriptive case studies, some of the conclusions were that the participants experienced an increased control over choices, as well as acute and lasting alterations in their perception of self and their relationship with alcohol.

In 2013, Hallock et al. carried out an observational study in 409 undergraduate participants aimed to analyse the perception towards the consumption of psilocybin and its association with the consumption of other drugs[25]; 29.5% of the sample reported psilocybin use. Results showed that psilocybin users were significantly more likely to use other drugs such as cocaine, ecstasy, opiates, nonprescribed prescription drugs, and LSD than nonusers of psilocybin. Regarding alcohol consumption, no difference was observed between users and nonusers of psilocybin (97% and 96%, respectively). These data suggest that the regular use of alcohol for the most part of the population makes it difficult to find an association between psilocybin and alcohol consumption. Barrett et al. investigated the interaction of LSD and psilocybin on the subjective effects of alcohol. No participants reported that the administration of psilocybin completely blocked the subjective effects of alcohol, although 60% of the psilocybin users reported a diminished response to alcohol. And as stated previously, psilocybin antagonism of the alcohol effect was significantly lower than LSD.[14] Regarding animal models, psilocybin has shown interesting data in the studies published by Meinhardt et al.[19,26] The study carried out by these authors in 2020 analysed the effect of three different treatment schedules on a relapse-like drinking model in rats. In the first study, a subchronic moderate treatment of 1 mg/kg psilocybin was used; the second one explored the effect of medium to high doses of LSD and psilocybin and the third experiment analysed the effect of chronic intermittent microdosing of psilocybin during abstinence on subsequent relapse-like drinking behaviour. The results obtained showed that only a subchronic treatment with psilocybin (1 mg/kg), produced a 20% reduction in alcohol consumption during the first day of relapse.[19] These data are supported by the article published in 2021 in which these authors showed that psilocybin (1 and 2.5 mg/kg) led to a reduction (40–50%) in relapse for alcohol compared to the vehicle.[26] It is important to note that these authors go further and propose a biochemical pathway for the observed effect. Psychedelic drugs have been reported to act via a complex interplay between $5HT_{2A}$, metabotropic glutamate receptors 2 (mGluR2), and NMDA receptors to mediate

neurobehavioural and pharmacological actions. In that sense, psilocybin would reduce relapse for alcohol through the interaction between 5-HT_{2A} and mGluR2, which can assemble into a functional complex and modulate each other's function.[27,28] Interestingly, mGluR2 are particularly abundant in the neural circuits connecting the medial prefrontal cortex (mPFC) with the nucleus accumbens (NAc), which regulate drug craving and relapse[29–31] and cognitive flexibility.[32] Also, it has been reported that long-term exposure to drugs of abuse can lead to diminished function and down-regulation of mGluR2.[33,34] These authors describe that alcohol dependence in humans and rodents is associated with a long-term reduction of mGluR2 expression, specifically in the infralimbic subregion of mPFC. The results obtained by them suggest that psychedelic treatment may be able to restore deficits in several behavioural domains caused by mGluR2 dysfunction in the mPFC.

3.2.3 | Ayahuasca

Ayahuasca is a botanical drink prepared by the decoction of *Banisteriopsis caapi* (rich in β-carbolines such as harmine, harmaline, and tetrahydroharmine) and *Psychotria viridis*, which contains N,N-dimethyltryptamine (DMT, a tryptamine hallucinogen with a chemical structure similar to serotonin).[35] In recent years, a growing number of scientific publications indicate that ayahuasca could have beneficial effects in the treatment of substance use disorders. Specifically, several studies indicate that ritual and recreational ayahuasca users have lower alcohol consumption and fewer alcohol-related problems than control groups.[36–41] An exception to these interesting findings would be the one carried out by Cakic et al. in 2010 in which they analysed alcohol use patterns in a sample of 121 consumers who had used DMT at least once in their lifetime.[42] Among the participants, 89.3% indicated having consumed alcohol in the previous 30 days and almost one third of the sample reported binge drinking during that period. Additionally, 27.2% of DMT smokers reported commonly smoking DMT with alcohol.

Unlike these observational studies, Thomas et al. proposed and tested in 2013 an ayahuasca-assisted intervention for problematic substance in 10 participants.[43] This was titled "Working with Addiction and Stress" and consisted of four consecutive days and three nights incorporating two ayahuasca ceremonies, one on the second and another one on the third evening. At various intervals during the 4 days, therapy sessions were held to elicit personal reflection and insights about traumatic life experiences and consequent emotional and psychological responses. Before starting the intervention, five participants reported problematic alcohol use. The main results of the study showed that alcohol, tobacco, and cocaine were used by fewer participants in the 4 weeks preceding the final follow up (seventh week) than in the baseline. Regarding alcohol, the participants who reported having a problematic consumption decreased from five to two. Additionally, the study showed improvements in several cognitive and behavioural states (enhanced mindfulness, personal empowerment, hopefulness and changes in quality of life meaning) that could be determining the recovery from problematic substance use. There is another study published by Berlowitz et al. in 2019 that shows the effect of the combination of Amazonian medicine, which includes preparations based on the ayahuasca plant, and conventional therapeutic methods (e.g., relapse prevention, psychodrama, and biomedical health checks).[44] This study was carried out in 36 dependence-diagnosed participants (63.9% of them presenting AUD) for a period of 3 and 12 months. The main result of the study indicated that the intervention led to a significant reduction in severity of alcohol use from 0.38 to 0.06 according to the Addiction Severity Index composite scores.

The conclusions of these studies would indicate that ayahuasca could help reduce alcohol consumption through the modification of some cognitive and behavioural states that might be restricted to humans. To challenge this idea, recent experimental studies have been carried out in animal models, which are exempt from these human factors. In 2015, a study published by Oliveira-Lima et al. indicated that five different doses of lyophilized ayahuasca (30, 100, 200, 300, or 500 mg/kg) showed high efficacy in preventing the development of alcohol-induced behavioural sensitization in mice, without affecting the locomotor activity of the animals.[45] Behavioural sensitization is a phenomenon that is thought to be an underlying adaptation responsible for addiction to drugs of abuse and to share neuronal mechanisms with craving. In a later study it was shown that pretreatment with ayahuasca (30, 100, and 300 mg/kg) blocked the development of alcohol-induced conditioned place preference.[46] This paradigm informs us about the rewarding intrinsic properties of any substance. In addition, it was studied whether the components of ayahuasca separately, *B. caapi* and *P. viridis*, could have a similar effect. But these components did not produce such an effect. Another recent study carried out by Almeida et al. found that oral administration of ayahuasca (1.76 mg/kg DMT) during eight consecutive days attenuated the expression of alcohol-induced behavioural sensitization in mice. In addition, ayahuasca caused an anxiolytic effect during ethanol withdrawal and modulated several neuroplastic changes induced by ethanol. Specifically, ayahuasca prevented the ethanol-induced changes on 5-HT_{1A} receptor and prodynorphin levels in the hippocampus and reduced ethanol effects in the dynorphin/prodynorphin ratio levels in the striatum.[47] This effect on dynorphin could help explain the therapeutic potential of these substances on alcohol consumption. On the one hand, the striatum has an essential role in cognitive and limbic functions,[48] whereas hippocampus is related to memory, motivation, and reward.[49] On the other hand, it has been shown that the system formed by the dynorphin and kappa opioid receptors modulates alcohol consumption in animal models, being able to mediate the ability of stress to increase drinking.[50,51]

We have only found one study investigating the effect of ayahuasca on voluntary alcohol consumption in animal models, specifically in Wistar rats. In this study, ayahuasca treatment for 5 days at doses around the ritual dose (0.5×, 1×, and 2×) had no effect on voluntary alcohol consumption using the intermittent access to 2-bottle choice protocol.[52] The authors indicate that the ritual dose corresponds to 150 ml of ayahuasca taken by a 70-kg person, and to 0.26 mg/kg bw

DMT, 2.58 mg/kg bw harmine, 0.171 mg/kg bw harmaline, and 0.33 mg/kg bw tetrahydroharmine.

3.2.4 | Mescaline

Mescaline is a naturally occurring phenethylamine that can be prepared synthetically or extracted from the peyote or San Pedro cactus. It is a compound often used by Native Americans as a religious sacrament, which has also long been used in the treatment of chronic alcoholism among this group, in which alcohol consumption represents a serious problem.[53–55] Recent research on the effect of mescaline on alcohol consumption is very scarce and provides conflicting results. Thereby, Prince et al. published an epidemiological paper[56] in 2019 exploring the relationship between 30-day alcohol consumption and peyote use by young American Indians ($n = 3.861$). Contrary to what historical reports suggest, the results showed that alcohol consumption was positively associated with peyote use. Specifically, 30-day alcohol use was related to both spiritual and recreational peyote use. Odds ratios were larger for recreational peyote use as compared with spiritual use, suggesting a greater likelihood of recreational peyote use for current alcohol users. Whether these substances were used concurrently is not known. On the other hand, an article published in 2006 shows that 46.6% of the university students who consume mescaline reported simultaneous consumption with alcohol.[57] In another study, Agin-Liebes et al. examined whether mescaline use was associated with improvements in self-reported depression, anxiety, posttraumatic stress disorder, and alcohol/drug use disorders. The study was carried out in a sample of adult participants ($n = 452$) who reported use of mescaline in naturalistic settings. Of those respondents reporting a prior alcohol misuse or AUD, 76% reported improvements in these conditions following mescaline use.[55]

4 | DISCUSSION

This systematic review provides an overview of the last two decades of research of classic psychedelics and alcohol consumption. Since the beginning of this century, a large number of reviews have been published about the therapeutic potential of these compounds. However, these reviews often refer to classical studies, that is, 1950–1970s period. Contrary to old reports, which were limited to some case reports, the recent research presents mainly three types of studies: (1) Observational studies consisting of interviews or cross-sectional surveys, (2) psychedelic-assisted interventions, and (3) studies carried out in animal models.

In general, observational studies show positive results and place these compounds as candidates for treating AUDs. However, these studies present some methodological concerns that make it difficult to draw definitive conclusions. One of these concerns presented by observational studies is that there is not always control over the administered dose. This compromises the association between doses and therapeutic effects. Another methodological concern is that the effects examined after psychedelic use depends on the subjectivity of the participant and seems to be determined by the specific characteristics of psychedelic experiences.[58] Also, the inclusion of participants in these studies may not have the control shown by other experimental designs and the inclusion criteria of some studies may make it difficult to generalize the results obtained. It is important to note that some of the observational studies reviewed do not aim to analyse the effect of these compounds on alcohol consumption but rather show descriptive data on the consumption of different psychoactive substances. Therefore, we cannot infer any causality. Also, it is difficult to conclude a specific effect of these compounds on alcohol consumption in such studies, since alcohol is a frequently consumed substance and is often part of recreational activities. For example, a study carried out in participants who reported the use of MDMA or hallucinogens in the past 12 months, showed that more than half of LSD or psilocybin users often used concurrently with alcohol.[59] In relation with this, this review refers to the effect of classic psychedelics on alcohol consumption, but there are also observational studies that explore the opposite direction, that is, the effect of alcohol consumption on psychedelic use. For example, a study published in 2019 by Yockey et al. showed that participants who reported alcohol use before the age of 21 years were 23.5 times more likely to report lifetime LSD use.[60] This suggest that early alcohol consumption could be a risk factor for LSD use.

Unlike some of the observational studies, psychedelic-assisted interventions can be designed from the beginning and therefore overcome some of the problems presented by observational studies. This type of studies shows promising data, in which classic psychedelics can be understood as therapy enhancers, facilitating psychic/psychological responding, thus deepen psychotherapy. Because of that, it is not easy to isolate the pharmacological effects of these compounds from the results of psychotherapy. Regarding this, according to Romeo et al., several factors could modulate the quality of a psychedelic session, such as the environment in which the session takes place, the expectations of the subject and the intensity of the acute psychedelic experience.[10] It should be noted that these interventions show positive results. However, they have important limitations that include a small sample size and the lack of control or blinding.

Although previous studies seem to indicate that classic psychedelics would help reduce alcohol consumption by promoting several variables as the understanding of potential outcomes of choices and improving decision making, some studies have been carried out in animal models. The studies reviewed in this manuscript have not only evaluated the effect on voluntary consumption, but also on other phenomena associated with alcohol consumption in animal models such as alcohol-induced conditioned place preference or alcohol-induced behavioural sensitization, showing a reduction on the psychophysiological effects of alcohol. Among these studies, the compound showing the strongest data is psilocybin,[19,26] possibly acting on alcohol consumption through the interaction between 5-HT_{2A} and mGluR2 receptors. These data, together with those obtained in humans, place this compound as a potential treatment for AUD and point out the need for studies to evaluate the long-lasting effects of psilocybin on alcohol consumption. Concerning the

rest of substances, among studies that evaluated alcohol consumption directly, only a LSD 50 μg/kg dose had an effect in the study by Alper et al.[18] Results shown in the manuscript of Meinhardt et al. in 2020[19] do not support this data, since in this study two higher doses of the same substance (0.08 and 0.32 mg/kg) had no effect. Obviously, these differences may be due to the species used in the studies (rats vs. mice), the alcohol consumption paradigm or the treatment schedule applied, among others. Therefore, there is a need for replication of results.

In addition to the interaction between 5-HT_{2A} and mGluR2 receptors suggested by Meinhardt et al., another molecular mechanism underlying the observed effects could be the role of 5-HT_{2A} receptors on the ventral tegmental area (VTA). In the mesocorticolimbic circuit, VTA plays an essential role in reward, motivation, cognition, and aversion. VTA neurons mainly consist of dopaminergic projection neurons under the inhibitory control of GABAergic interneurons. On the one hand, since the VTA receive substantial innervations from the dorsal raphe serotonergic neurons, 5-HT_{2A} receptor is believed to modulate these neurons in the VTA.[61–63] On the other hand, it is known that alcohol effects on VTA are mediated by GABA receptors and that alcohol exposure produces inhibitory neurocircuit plasticity in the VTA (i.e., excitation of GABA neurons) that can promote subsequent alcohol consumption.[64–66] These data are important since this inhibitory plasticity is reversible by 5-$HT2_{2A}$ receptor agonism via functional enhancement of the potassium-chloride cotransporter KCC2.[62] In that sense, a recent study by Kimmey et al.[67] demonstrates that 5-HT_{2A} receptor agonists reduce alcohol consumption in rodents by restoring VTA Cl- homeostasis.

In addition to communication between the VTA and GABAergic neurons, the transition from a nondependent to a drug-dependent motivational state is accompanied by increased levels of brain-derived neurotrophic factor (BDNF) in the VTA.[68,69] As a result, BDNF-mediated adaptions in the reward circuit produce and maintain a state of dependence in response to withdrawal by setting up aversive motivational mechanisms.[70] Since 5-HT_{2A} receptors and GABAergic neurons differentially regulates the expression of BDNF in the brain, it has been suggested that 5-HT_{2A} agonists could reduce the expression of BDNF through GABAergic pathways.[71,72] Vargas-Pérez et al.[73] confirmed this hypothesis in 2017, showing that the administration of a 5-HT_{2A} agonist can prevent and reverse the VTA neural modifications by preventing the up-regulation of BDNF and thus the key neural changes in the VTA. All together, these results suggest potential cellular and synaptic mechanisms by which 5-HT_{2A} activation can treat stress- and alcohol-related disorders.

Although the reviewed articles seem to indicate a great potential of these compounds, few studies have been carried out. Progress in this field has been slowed down due to its bad reputation regarding its side-effects.[74] However, research consistently assesses psychedelics as much less harmful to the user as well as to society compared to alcohol and almost all other controlled substances.[75] In fact, in nonclinical settings there have been rare cases of psychedelics triggering serious mental health effects, such as psychosis.[76] Also, this risk is greatly reduced with psychiatric screening. Thus, individuals with a predisposition towards psychotic illnesses should be excluded from clinical treatment with psychedelics.[77] On the other hand, very few psychedelic users report a loss of control over their use of these compounds and scientific research has often shown that psychedelics do not cause dependence or compulsive use.[78–80] In relation to the possible physiological risks, most researchers now consider classic psychedelics to be nontoxic and physiologically safe (overdose deaths have occurred due to ingestion of very large doses or by mixing psychedelics with other drugs).[75] Finally, another problem with this therapeutic alternative is that these compounds are psychoactive drugs. However, there are precedents of drugs of abuse that have been used in the clinic, as in the case of lisdexamfetamine dimesylate, a pro-drug of d-amphetamine that was first approved by the FDA in 2007 for the treatment of attention-deficit/hyperactivity disorder (ADHD) and Binge-eating disorder.[81,82]

Taken together, the data collected indicate that classic psychedelics are potential candidates for treating excessive alcohol consumption. It is important to note that no study shows an increase in alcohol consumption as a consequence of psychedelic use. This is contrary to the effect shown by other psychoactive substances such as nicotine,[83] cocaine,[84] amphetamine,[85] cannabinoids,[86,87] morphine,[88] or caffeine,[89] which have been shown to increase alcohol consumption. On the other hand, due to psilocybin studies seem to indicate a mediation of cognitive aspects, we could hypothesize that the overall effect observed is produced through a modification of some cognitive and behavioural states leading to a "personal transformation" (i.e., changes in the perception of self and in the life meaning, as well as an increase in self-efficacy and in ability to calmly attend to the present moment, leading to the perception of personal growth). We can hypothesize that these changes act indirectly on alcohol consumption through an increase in motivation or improvements in anxiety and affective states,[44] since a decrease in depressive and anxiety symptoms might help improve AUD, due to the association between cognitive and emotional processes and addictive disorders.[10,20] However, it is necessary to deepen into this association to analyse how this "personal transformation" leads to a reduction in alcohol consumption. In the absence of understanding of the mechanisms underlying the possible effects, more studies including methodological quality parameters are needed to analyse if some of these compounds placed into a highly restrictive category can be effective to treat the problematic use of a substance widely accepted socially, but responsible for 3 million deaths a year.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTION

JCC and JALM were involved in the planning and conceptualization of the study. JCC and JAMG performed the literature search and screening. JCC and VEA performed the quality assessment of the included studies. JALM reviewed the inclusion process of the studies. JCC extracted the data. JCC, KMB, EG, and JALM wrote the first draft of the manuscript. All the authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

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