




## INVITED REVIEW

# Ayahuasca: A review of historical, pharmacological, and therapeutic aspects

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## Abstract

Ayahuasca is a psychedelic plant brew originating from the Amazon rainforest. It is formed from two basic components, the *Banisteriopsis caapi* vine and a plant containing the potent psychedelic dimethyltryptamine (DMT), usually *Psychotria viridis*. Here we review the history of ayahuasca and describe recent work on its pharmacology, phenomenological responses, and clinical applications. There has been a significant increase in interest in ayahuasca since the turn of the millennium. Anecdotal evidence varies significantly, ranging from evangelical accounts to horror stories involving physical and psychological harm. The effects of the brew on personality and mental health outcomes are discussed in this review. Furthermore, phenomenological analyses of the ayahuasca experience are explored. Ayahuasca is a promising psychedelic agent that warrants greater empirical attention regarding its basic neurochemical mechanisms of action and potential therapeutic application.

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ayahuasca, ceremony, DMT, harmala alkaloids, psychedelic

**BACKGROUND****Historical overview of ayahuasca**

Ayahuasca, originating from the Amazon rainforest, is an entheogenic psychedelic plant brew used in spiritual and religious contexts.<sup>1</sup> The Quechua terms “aya” and “waska” translate to “spirit” or “soul” and “vine” or “rope,” respectively, giving rise to names like the vine of the soul or dead for the brew.<sup>2</sup> The key ingredients of an ayahuasca brew are *Banisteriopsis caapi*, a vine also referred to as ayahuasca independently, and a plant containing *N,N*-dimethyltryptamine (DMT), typically *Psychotria viridis*, also called chacruna.<sup>3</sup> Many preparations with various admixtures are commonly called ayahuasca, even though they may lack key components required for the technical definition, such as using *Peganum harmala* instead of *B. caapi* as a source of harmala alkaloids.\*

Ayahuasca's documented history in the Amazon dates back about 150 years to spruce,<sup>4</sup> although its exact origins are debated.<sup>5</sup> Some scholars propose that indigenous groups in the Amazon have used ayahuasca for millennia.<sup>6,7</sup> Archaeological evidence includes small ceramic vessels associated with ayahuasca rituals dating back to around 2400 BC Naranjo<sup>8</sup> and shamanic snuffs containing bufotenine, DMT, and harmine dating back 1000 years in present-day Bolivia.<sup>5</sup>

Scholars hold differing views on the historical origins of ayahuasca. Some propose that modern ceremonial practices emerged around 300 years ago in a Spanish missionary context, spread through economic activities related to rubber camps.<sup>9,10</sup> This perspective finds support in the common terminology, musical structure, and ritualistic use of tobacco smoke in ayahuasca ceremonies, which show similarities with Catholic practices during that time. However, it is possible that certain ritual elements predate this era.<sup>9,10</sup>

In the 1930s, ayahuasca was introduced to urban areas of Brazil within religious contexts, and by the 1980s, its outreach extended to international cities.<sup>11,12</sup> Syncretic churches such as Santo Daime, Barquinha, and União do Vegetal have incorporated ayahuasca into their traditions.<sup>12</sup> Today, ayahuasca's popularity is increasing among Westerners who seek physical and emotional healing, personal growth, insight, and spiritual experiences, often travelling to South America.<sup>13</sup>

**Traditional use**

Before gaining popularity in the West, ayahuasca was used in combination with other plants for medicinal purposes.<sup>6,14</sup> It is regarded as a plant teacher with healing properties by various

Indigenous groups, such as the Shipibo, employed by shamans for diagnosis and healing.<sup>15,16</sup> The term “shaman” loosely describes individuals who work with spirits, using ritualistic trance states for healing and divination.<sup>17</sup> Ayahuasca practitioners are known by various names, such as taita, vegetalista, ayahuasquero, maestro, onaya, and curandero.<sup>18</sup>

In certain tribes, only the shaman consumed ayahuasca to diagnose diseases and determine appropriate treatments.<sup>14</sup> Ayahuasca's visionary state enhanced the shaman's abilities. Ayahuasca was also used in social contexts, such as in conflicts between shamans using dark magic.<sup>14</sup> Curanderos, native healers, combined ayahuasca with other plants in ritualistic botanical practices to serve, heal, and protect their communities.<sup>19</sup>

**Recent developments**

Use of ayahuasca is spreading rapidly in Western culture. Ayahuasca is thought to have first come to mainstream attention in the global north when William Burroughs published *The Yage Letters*,<sup>20</sup> describing his experiences with ayahuasca. Since then, ayahuasca has been referenced in the news, appeared in documentaries, films, and reality television shows, and been referenced in travel guides, where individuals can rate their ayahuasca retreat experiences.<sup>21</sup>

With the dramatic increase in popularity, various academics, shamans, and self-proclaimed experts have distributed information regarding ayahuasca.<sup>1</sup> A multidisciplinary space has emerged, populated by artists, such as Alex Grey,<sup>22</sup> and inspired musicians, such as Sting and Paul Simon, and has given a voice to indigenous leaders, neuroscientists, psychiatrists, and anthropologists at conferences.<sup>23</sup>

Despite the complexities associated with the investigation of a subject open to multiple disciplines, to minimize harm in this age of misinformation<sup>24</sup> accurate information is required whilst allowing for increased scope in methodologies utilized.

**Pharmacology****Pharmacological overview of ayahuasca**

The psychoactive effects of ayahuasca are primarily attributed to DMT,<sup>25</sup> which shares molecular similarities with other psychedelic tryptamines, including psilocybin, and neurotransmitters such as serotonin and melatonin.<sup>26</sup> DMT is naturally occurring in humans, as well as in various plant and animal species.<sup>27</sup> The oral activity of DMT is facilitated by monoamine oxidase inhibitors (MAOIs) present in the *B. caapi* vine,<sup>28</sup> preventing its breakdown in the body and allowing it to enter the bloodstream and interact with brain receptors.<sup>29</sup> Dysfunction within the serotonergic system has been implicated in psychiatric disorders, including depression,<sup>30-32</sup> and the involvement

\*It remains unclear however how specific this effect is to psychedelic compounds.

of the serotonin (5-hydroxytryptamine) 5-HT<sub>2A</sub> signaling has been proposed.<sup>33</sup> Ayahuasca's psychoactive effects are thought to be mediated primarily by 5-HT<sub>2A</sub> receptor activation,<sup>34,35</sup> although DMT also binds to other serotonin receptors, including 5-HT<sub>2C</sub> and 5-HT<sub>1A</sub>.<sup>36</sup> Notably, harmine and harmaline, present in the *B. caapi* vine, also interact with similar receptors.<sup>37</sup>

### The harmala alkaloids

Numerous studies have focused on DMT and other serotonin agonists.<sup>38-46</sup> However, anthropological and qualitative articles emphasize the significance of *B. caapi*. Traditional ayahuasca typically consists of the *B. caapi* vine combined with a DMT-containing plant like *P. viridis*, where the vine remains a consistent component.<sup>25</sup> In the Peruvian Amazon, ayahuasca is often used to refer to the vine alone.

The β-carbolines, derived from alkaloids, have been a subject of interest in psychedelic research for their potential psychotropic properties.<sup>47</sup> Recent attention has shifted toward exploring the role of β-carbolines in mental health treatment.<sup>48</sup> They exhibit various biological actions, such as anxiolytic, anticonvulsant, and sedative effects, mainly through interactions with serotonin and benzodiazepine receptors.<sup>49</sup>

### The properties of the harmala alkaloids

Each of the harmala alkaloids has been associated with different effects, psychologically, pharmacologically, and pharmacokinetically. Table 1 summarizes the therapeutic and psychoactive effects of each of the harmala alkaloids and Table 2 provides an overview of their pharmacokinetic profile.

Hallucinations, vomiting, confusion, and ataxia are thought to be due to central nervous system stimulation by MAOIs.<sup>64</sup> In a study by Glennon et al.,<sup>37</sup> the harmala alkaloids were found to bind to 5-HT<sub>2</sub> receptors with a similar affinity to DMT. The psychedelic properties of both harmaline and harmine are thought to arise from their binding at the 5-HT receptors.<sup>65</sup>

### Harmine

Harmine, the most abundant β-carboline alkaloid in ayahuasca, has been linked to various therapeutic effects, including restoration of astrocytic function, anti-inflammatory effects, and human neural progenitor cell proliferation.<sup>56,62,66</sup> Studies have suggested its potential in addiction treatment, reducing relapse rates from methamphetamine, cocaine, and alcohol.<sup>21,54</sup> Harmine's affinity at dual-specificity tyrosine phosphorylation-regulated kinase 1A and imidazole 2 (I2) binding sites may contribute to its pharmacological management of drug dependence.<sup>21</sup>

Studies have shown that harmine can affect brain tissue in relation to depression by altering glutamine synthetase and glial-specific excitatory amino-acid transporter expression (glutamate transporter-1 [GLT-1], glutamate/aspartate transporter [GLAST]).<sup>67,68</sup> Harmine increases GLT-1 protein and gene expression, and enhances glutamate uptake in animal models.<sup>69-71</sup> Its antidepressant action may be attributed to renewing astrocytic function, which protects against chronic unpredictable stress and enhances outcomes in depression-related tests.<sup>70</sup>

Harmine's antidepressant effects are hypothesized to be mediated through brain-derived neurotrophic factor (BDNF) signal restoration. Fortunato et al. demonstrated improvements in the open field and forced swimming tests in rats administered with harmine, with increased hippocampal BDNF levels compared with imipramine

**TABLE 1** The therapeutic and psychoactive effects of the harmala alkaloids.

Therapeutic and psychoactive effects	Reference	Harmine	Harmaline	Tetrahydroharmine
Antidepressant properties	[25]	X	X	X
Anxiolytic properties	[50, 51]	Not assessed	X	Not assessed
Increases serotonin and norepinephrine	[25]	X	X	X
Raises dopamine levels in CNS	[52]	X	X	Not assessed
Anti-addictive properties	[21, 53, 54]	X	Not assessed	Not assessed
Diabetes management, mitogenic for human beta cells (likely target DYRK1A)	[55]	X	Not assessed	Not assessed
Induce brain plasticity and neurogenesis	[56]	(Harmine metabolite harmol)	X	X
Upregulates 5-HT receptor density	[57, 58]	Not assessed but unlikely <sup>59</sup>	Not assessed but unlikely <sup>59</sup>	X
Hallucinogenic properties (at high doses)	[3, 47, p. 293, <sup>60</sup> ]	Gunn and Marshall <sup>61</sup> suggest it is at 2 mg/kg iv or 8 mg/kg po	1 mg/kg iv or 4 mg./kg po <sup>47</sup>	300 mg but unclear <sup>61</sup>
Increases the number of nerve progenitor cells (may be important in treatment of damage by drug use)	[62]	X	Not assessed	Not assessed

Abbreviation: iv, intravenous; po, oral administration; X, present.

**TABLE 2** Overview of the pharmacokinetic profile of the harmala alkaloids with dimethyltryptamine (DMT) for comparison.

Overview of pharmacokinetics	DMT	Harmine	Harmaline	Tetrahydroharmine
Pharmacokinetics profile <sup>63</sup>	-	Pharmacokinetic profile correlates with that of DMT	-	Pharmacokinetic profile independent of harmine
$C_{max}$ (ng/mL)	15.8 ± 4.4	114.8 ± 61.7	6.3 ± 3.1	91.0 ± 22.0
$T_{max}$ (min)	107.5 ± 32.5	102.0 ± 58.3	145.0 ± 66.9	174.0 ± 39.6
AUC (mg min/mL)	5.60 ± 4.53	22.88 ± 11.69	-	47.78 ± 25.88
$T_{1/2}$ (min)	259.4 ± 207.2	115.5 ± 60.1	-	531.9 ± 290.8
IC50 (μM)	-	MAO IC50 = 0.013	MAO IC50 = 0.016	MAO IC50 = 1.77
	-	MAO-A IC50 = 0.002	MAO-A IC50 = 0.003	MAO-A IC50 = 0.074
	-	MAO-B IC50 = 20	MAO-B IC50 = 25	MAO-B IC50 = 100
5HT2A binding capacity (Ki) <sup>37</sup>	-	397	5010	>10,000

Abbreviations: 5HT2A, serotonin 2A receptor; AUC, area under the curve;  $C_{max}$  Maximum serum concentration; IC50, half maximal inhibitory concentration; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B;  $T_{1/2}$ , half life,  $T_{max}$  time to peak drug concentration.

treatment.<sup>72,73</sup> Liu et al. found that harmine administration resulted in increased BDNF levels and hippocampal neurogenesis in mice exposed to chronic unpredictable stress, suggesting similarity to traditional antidepressant drugs.<sup>70</sup>

Morales-García et al.<sup>56</sup> found that harmaline, harmine's metabolite, along with tetrahydroharmine and harmol, induced neurogenesis in adults in vitro, suggesting potential in treating neurological and psychiatric conditions. In a subsequent study, Morales-García et al.<sup>74</sup> demonstrated that DMT promoted the generation of new hippocampal neurons in mice, enhancing memory and spatial learning tasks. The activation of SIGMAR-1 appeared to underlie DMT's neurogenic effects. The authors highlight DMT's more potent neurogenic profile compared with the  $\beta$ -carbolines and its potential as an antidepressant.<sup>56,74</sup>

## Harmaline

Harmaline exhibits a range of pharmacological functions, including hypothermic and vasorelaxant activity, and antitumoral, antimicrobial, antiplatelet, antileishmanial, and antiplasmodial effects.<sup>51</sup> It has been effective against various microbes<sup>75</sup> and showed cytotoxic effects on promyelocytic cell lines at higher doses of 15–30  $\mu$ g/mL.<sup>76</sup> At 4 mg/kg, when taken orally, harmaline was found to be hallucinogenic,<sup>47</sup> with about half the dose required for psychedelic effects compared with harmine. Despite its lower concentration among harmala alkaloids, harmaline exerts various pharmacological effects, including anxiolytic and antidepressant properties.<sup>50,51</sup>

## Tetrahydroharmine

Platelet serotonin uptake sites increase in ayahuasca users and are associated with positive mental health effects, although the

interpretation of this as indicative of neuronal activity is debated.<sup>57</sup> Callaway hypothesized that tetrahydroharmine upregulates 5-HT uptake sites and conducted a self-experiment with daily tetrahydroharmine dosing over 6 weeks, revealing increased 5-HT receptor density in his prefrontal cortex, which gradually returned to pre-dosing levels after cessation.<sup>58</sup>

Tetrahydroharmine is the only component in ayahuasca known to function weakly as a selective serotonin reuptake inhibitor.<sup>63</sup> Its psychoactive effects are less prominent than those of harmine, with harmaline being the most potent of the harmala alkaloids.<sup>47</sup> Gunn and Marshall<sup>61</sup> administered 300 mg of tetrahydroharmine orally to a volunteer, who reported hallucinogenic effects similar to 100 mg of harmaline, suggesting tetrahydroharmine's effects are roughly one-third those of harmaline.

Callaway et al.<sup>63</sup> observed that in the União do Vegetal (UDV) church, teas with higher levels of tetrahydroharmine relative to harmine and harmaline were preferred by both church elders and the congregation. Similar findings were confirmed in the Santo Daime church.<sup>77</sup> Callaway suggested that the variation in tetrahydroharmine levels in ayahuasca brews could be attributed to the variability in *B. caapi*. Additionally, Kaasik et al.<sup>77</sup> demonstrated that the preparation method of the brew also influences tetrahydroharmine levels.

## Harmala alkaloids in pharmahuasca

Pharmahuasca, an accessible ayahuasca substitute using DMT and harmala alkaloid-containing plants such as *P. harmala* (Syrian Rue) and *B. caapi*, lacks rigorous comparison to ayahuasca's effects. Informal analyses suggest differences in subjective experiences due to varying alkaloid ratios.<sup>78</sup> More research is needed in this area.

## NEUROPHYSIOLOGICAL OVERVIEW

Dos Santos et al.<sup>79</sup> conducted a systematic review of 28 articles on ayahuasca and found it to be well tolerated,<sup>80</sup> increase introspection and positive mood,<sup>81</sup> alter visual perception,<sup>82</sup> activate front and paralimbic regions,<sup>83</sup> and decrease default mode network (DMN) activity.<sup>81</sup> It also showed improvements in inhibitory control and planning,<sup>84</sup> impairments in working memory,<sup>85</sup> and potential anti-addictive<sup>86</sup> and antidepressant effects.<sup>87</sup> However, the review is limited by small sample sizes and a lack of control group data.<sup>79</sup>

### Magnetic resonance imaging

DMT, along with other classic psychedelics like psilocybin, lysergic acid diethylamide (LSD), and mescaline, acts as a partial agonist at the 5-HT<sub>2A</sub> receptor.<sup>88</sup> Neuroimaging studies on serotonergic psychedelics have consistently shown that these substances reduce activation in the DMN and alter connectivity between DMN regions, while increasing connectivity to other subcortical brain regions.<sup>35,89-92</sup> For example, a functional magnetic resonance imaging (fMRI) study by Carhart-Harris et al.<sup>89</sup> demonstrated increased overall brain connectivity and decreased DMN integrity with LSD compared with a placebo group. Similar findings have been observed with psilocybin<sup>93</sup> and ayahuasca.<sup>81,92</sup>

Palhano-Fontes et al.<sup>81</sup> used fMRI to demonstrate that ayahuasca reduced activity in the DMN, specifically the posterior cingulate cortex (PCC)/precuneus and medial prefrontal cortex (mPFC). PCC/precuneus functional connectivity decreased, similar to psilocybin.<sup>93</sup> Ayahuasca did not reduce coupling between the PCC and mPFC significantly.<sup>81</sup> Pasquini et al.<sup>94</sup> found increased functional connectivity between the salience network and the DMN and anterior cingulate cortex (ACC) after ayahuasca administration. Structural differences in the ACC and PCC shown by Bouso et al.<sup>95</sup> may explain the preservation of neuropsychological function.

### Magnetoencephalography and electroencephalography

After ayahuasca, LSD, and psilocybin use, resting state magnetoencephalography (MEG) reveals reduced oscillatory power<sup>89,96,97</sup> and reliable alpha power suppression,<sup>45,98,99</sup> along with increased brain activity entropy.<sup>100</sup> Electroencephalography (EEG) studies also show decreased power in delta and theta bands, and increased gamma power in specific regions.<sup>97,101</sup> Riba et al.<sup>91</sup> confirmed ayahuasca-induced reductions in delta, theta, and alpha power using MEG. Stuckey et al.<sup>102</sup> observed increased gamma-band coherence globally, and Dos Santos et al.<sup>103</sup> found increased beta power across the brain following ayahuasca administration. Alonso et al.<sup>104</sup> reported reduced impact of frontal regions on occipital, parietal, and central sites, along with increased influence of posterior brain regions on anterior signals, indicating transient disruption of neural

hierarchies and enhanced bottom-up control after ayahuasca ingestion.

Schenberg et al.<sup>99</sup> reported reduced alpha power at the left parieto-occipital cortex 50 min after ayahuasca consumption, followed by increased fast oscillatory activity in slow-gamma and fast-gamma bands in various cortical regions 75–125 min after ingestion. These changes were associated with  $\beta$ -carboline and DMT concentrations in the blood, with peak harmine levels at 50 min and peak DMT levels at 75 min, suggesting their involvement in the observed neurophysiological effects. This emphasizes the synergic effect of the ayahuasca compounds, as beta-carbolines also contribute to the brain effects revealed by EEG.

The reduction in alpha-band power at the left parieto-occipital region corresponds to an increased blood oxygenation level-dependent (BOLD) signal in the visual cortex during visionary experiences with ayahuasca.<sup>82</sup> Gamma power increases, as demonstrated by Schenberg et al., have also been found in lucid dreaming<sup>105</sup> and meditation.<sup>106</sup> Gamma frequencies are involved in visual integration,<sup>107</sup> synchronizing frontal and parietal cortices for subjective experiences,<sup>108</sup> and memory/attention.<sup>109</sup> Increased gamma power during ayahuasca may relate to internal awareness of intentions and memories through visual imagery.<sup>82,99</sup> The rise in frontal gamma power with decreased occipito-parietal alpha power aligns with emotional regulation during cognitive appraisal<sup>110</sup> and problem solving,<sup>111</sup> resembling increased emotional awareness reported after ayahuasca consumption.<sup>99</sup>

The validity of gamma-band findings using scalp EEG has been contested due to potential contamination from musculoskeletal activity overlapping with gamma oscillations.<sup>96</sup> Therefore, caution should be exercised in interpreting the results presented by Schenberg et al.<sup>99</sup> and Stuckey et al.<sup>102</sup> until confirmed by advanced signal separation and processing techniques. Future studies could utilize spatial filtering techniques or independent component analysis to reduce EMG artefact contamination.<sup>96</sup>

## SHORT-TERM EFFECTS

### Phenomenology

Riba et al.<sup>112</sup> administered orally lyophilized ayahuasca, finding the experience lasted 4–6 h. Users reported euphoria, a sense of transcending space and time, and oneness.<sup>112</sup> Strassman's study<sup>113</sup> involved intravenous dosing of volunteers with DMT.<sup>114</sup> Participants reported interactions with nonhuman beings like spirits, angels, and aliens.<sup>44</sup> DMT experiences share similarities with near-death experiences (NDEs) and folkloric, shamanic, and alien abduction experiences.<sup>46,115</sup> NDEs often involve reviewing past life events, travelling through a tunnel toward a light, and out-of-body experiences.<sup>116</sup>

### Physical effects

Ayahuasca exhibits uniqueness in various aspects compared with other psychedelics. Notably, it has a prominent somatic component,

with somatic symptoms comprising 12.43% of qualitative reports in one study.<sup>117</sup> Enhancements in kinaesthetic and somatic awareness during the ayahuasca experience are well-documented.<sup>118-120</sup> Shanon<sup>121</sup> emphasized the somatic aspect as the primary psychotherapeutic modality.

Following ayahuasca ingestion, people often experience purgative effects due to the disturbance to stomach enzymes caused by the MAOI alkaloids and the serotonergic effect of DMT on 5-HT receptors in the gut.<sup>122</sup> Nausea and vomiting are the most common purgative effects, reported by 62% of respondents in one survey.<sup>123</sup> Traditionally, vomiting is seen as an expelling of physical toxins and psychological traumas.<sup>124</sup> Some practitioners even refer to the beverage as “la purga” (Spanish: the purge),<sup>125</sup> with others referring to the purge as “getting well”.<sup>120,121,126-128</sup> Bouso et al.<sup>123</sup> reported that 17.8% of participants experienced headache, followed by abdominal pain (12.8%), aching muscles (7.5%), breathing difficulties (7.3%), chest pains (4.7%), and fainting (4.1%). In addition, 1.3% of participating individuals had fits or seizures, but 30.1% did not report any side effects.

Riba et al.<sup>65</sup> found that high dosages of freeze-dried ayahuasca (0.85 mg of DMT/kg) led to acute physiological effects, including a diastolic blood pressure increase (9 mm Hg after 75 min). Moderate rises in systolic blood pressure and heart rate were observed but were not statistically significant. Other studies reported effects like elevated body temperature, exhaustion, and heaviness.<sup>117</sup>

Ayahuasca users often report a sensation of something foreign entering their body at the beginning of ceremonies, connecting physical effects with psychological insights and spiritual experiences.<sup>120</sup> This intimate awareness of the body and heightened proprioception is associated with self-healing,<sup>120,121</sup> involving a spectrum of sensations, from pain and emotional release to an ecstatic sense of love and awe.<sup>120</sup>

Van der Kolk<sup>129</sup> highlighted the importance of connecting deep psychological states to identify emotions linked to bodily sensations, aiding emotion recognition and control. Ayahuasca consumption activates brain regions like the anterior insula and paralimbic areas, involved in emotional processing, interoception, and somatic awareness.<sup>83,130</sup> Disruptions in these areas are associated with depression, addiction, childhood trauma, and post traumatic stress disorder (PTSD).<sup>131-133</sup> This theory underpins somatic-oriented psychotherapies gaining interest.<sup>134</sup> Interestingly, ayahuasca drinkers may experience reduced bodily dissociation over time.<sup>119</sup>

## Changes in perception

Ayahuasca drinkers frequently experience complex thought processes, visual imagery, and heightened awareness during peak DMT levels.<sup>112,117,135,136</sup> They may have synaesthesia-like experiences,<sup>137</sup> but less commonly than with other classic psychedelics.<sup>138</sup> Psychedelic users, including ayahuasca users, often report deep introspection and self-awareness during sessions. Participants have ranked events induced by classical psychedelics as being as significant as life

events like falling in love, having a first child, or getting married.<sup>44,139,140</sup>

Phenomenological analyses suggest that LSD, DMT, ayahuasca and psilocybin can elicit alterations in perception, whether visual, auditory, or tactile.<sup>115,117,141,142</sup> In addition, these compounds have been reported to induce feelings of happiness,<sup>141,142</sup> help process difficult memories,<sup>117,143,144</sup> alter the capacity for memory recollection,<sup>117,142</sup> and change time perception.<sup>117</sup>

Various classical psychedelics tend to produce similar subjective experiences.<sup>145</sup> Strassman et al.<sup>146</sup> developed the Hallucinogen Rating Scale to assess the effects of hallucinogens in six domains: volition, somaesthesia, perception, affect, intensity, and cognition. A similar measure, the Mystical Experience Questionnaire, categorizes the potential subjective effects of psychedelics differently, with four subscales pertaining to difficulties putting the experience into words, alterations to the sense of both time and space, positively valenced feelings such as love or peace, and an authoritative sense of unity or connectedness accompanied by feelings of reverence.<sup>147</sup>

Ayahuasca often leads to emotional release and corrective experiences.<sup>117</sup> Unpleasant states are often followed by resolution and pleasant emotions.<sup>117</sup> This aligns with psychodynamic psychotherapy processes that challenge defence mechanisms for positive outcomes.<sup>148-150</sup> Ayahuasca may disable defence mechanisms, allowing direct confrontation of intense emotions.<sup>151,152</sup>

The quality of the acute psychedelic experience predicts therapeutic efficacy, as shown with psilocybin.<sup>153</sup> Low dread of ego dissolution and high oceanic boundlessness were associated with positive depression outcomes.<sup>153</sup> Challenging psychedelic experiences may not adversely affect therapeutic outcomes if resolved through emotional breakthrough.<sup>154</sup> Therapists emphasise the significance of working through such emotional states,<sup>155-158</sup> and resolving these experiences can predict long-term well-being.<sup>154</sup>

Ayahuasca is linked to increased self-love and empathy.<sup>159</sup> Participants report heightened self-awareness and presence during ceremonies,<sup>160</sup> which enhance psychological well-being.<sup>161</sup> These positive emotional states align with compassion-focused therapy in cognitive behaviour therapy.<sup>162</sup>

Ayahuasca has been shown to enhance the ability to observe thoughts and emotions with detachment, a process known as “decentering.”<sup>163</sup> Decentering is important in mindfulness-based cognitive therapy and is an index of psychopathology.<sup>160</sup> Self-correction is associated with response to addiction treatment and therapeutic outcomes related to self-acceptance and self-love.<sup>164-166</sup>

Supportive entities have been reported anecdotally in psilocybin and LSD sessions, but are more commonly associated with ayahuasca and DMT.<sup>115,136,167,168</sup> This phenomenon is a distinctive aspect of traditional ayahuasca use and sets it apart from Western psychedelic-assisted therapy.<sup>136,169</sup> However, it is worth mentioning that such occurrences are rarely described in Western psilocybin-assisted psychotherapy sessions and nondrug-assisted psychotherapy.<sup>155</sup> In internal family systems therapy, supportive entities are often perceived as guiding spirits from family members.<sup>170</sup> Exploring the impact, nature, and role of subjective perceptions and expectations in

these experiences and outcomes presents an intriguing avenue for future research.

Wolff et al.<sup>117</sup> reported that seven of the nine participants in their study gained insightful and personal meaning during ayahuasca ceremonies. Five subcategories emerged: interpersonal psychological insights, relational issues, motives and issues of others, social wisdom, and mystical experiences. Relationship issues were commonly mentioned by participants. Ayahuasca-therapy, like other psychedelic-assisted therapies, offers new perspectives on interpersonal issues.<sup>155,157</sup> Ayahuasca enables a state in which participants can reevaluate and gain new perspectives on intrapersonal conflicts, past experiences, relational conflicts, and social representations, suggesting potential psychotherapeutic benefits.<sup>171</sup>

Most individuals seek psychedelic therapy with the expectation of emotional healing and self-understanding.<sup>172</sup> Psychedelics have been found to induce insightful psychodynamic, cathartic, and interpersonal experiences.<sup>157</sup> Psychotherapy often aims for new self-narration, involving the reevaluation of identity and life narrative.<sup>173</sup> Connection to nature and the universe is commonly experienced in psychedelic use and is associated with spiritual values.<sup>158,173</sup> These mystical and spiritual insights have therapeutic benefits, including the treatment of mental illnesses and gaining new perspectives on life.<sup>165,174-177</sup> Ayahuasca consumption can also lead to perceived near-death experiences, which have been linked to improvements in psychological well-being and health-related behaviors, and diminished death anxiety.<sup>46,143,178</sup>

Incorporating spiritual and religious counselling alongside ayahuasca consumption has shown benefits for integration, mental well-being, and personal insights.<sup>161</sup> It is also well established in psychedelic research that the strength of participants' perceived mystical experiences predicts therapeutic outcomes.<sup>161,179,180</sup> Furthermore, these mystical experience have been associated with greater feelings of connection with plant intelligence, the natural world and the interconnected reality between all things.<sup>120,161,181-183</sup>

Participating in ayahuasca ceremonies often leads to therapeutic insights and perspectives.<sup>175,184</sup> These experiences are associated with the re-evaluation of past events and have been linked to improvements in depression, anxiety, and well-being, and reduced substance use.<sup>161,182,183</sup> They also impact physical health, creativity, life purpose, and interpersonal dynamics.<sup>120,175,185</sup> Meaningful life changes have been observed in these areas following ayahuasca experiences.<sup>143,178,186,187</sup>

Visual phenomena are a common experience in ayahuasca ceremonies,<sup>117,120</sup> occasionally resulting in the reprocessing of autobiographical memory, including traumatic experiences.<sup>120,188,189</sup> Despite being in an altered state of consciousness, participants' mental clarity is often described as being enhanced, allowing for an accelerated psychotherapeutic process with intense self-evaluation. The identification of dysfunctional coping strategies, as well as maladaptive emotional and behavioral patterns, are often identified and addressed.<sup>164,165,184,187</sup>

Ayahuasca use often enhances thought processes, increasing understanding for most participants<sup>117,190</sup> and leading to critical self-

analysis of interpersonal relationships, self-care, and causes of psychological distress.<sup>143,177,187</sup> However, it can bring distress as individuals confront unpleasant issues.<sup>143,177,187</sup> Nonetheless, these experiences are generally seen as therapeutic, similar to conventional psychotherapies.<sup>120,143,175,190</sup>

Ayahuasca can facilitate deep cognitive processes by accessing emotions typically inaccessible and activating higher cortical areas.<sup>151</sup> It promotes various therapeutic factors, including transpersonal experiences, corrective experiences, problem actualization, and rescripting of past behaviours,<sup>191</sup> enabling the reprocessing, reframing, and reintegration of significant events and emotions.<sup>151</sup> The relaxed beliefs under pSychedelics model by Carhart-Harris and Friston<sup>192</sup> supports this theory by highlighting the relaxation of existing beliefs and resulting emotional and psychological insights. Integration after these experiences is emphasized to ensure positive change and prevent harm.<sup>189</sup>

## Mystical experiences

Allman et al.<sup>193</sup> define mystical experience as characterized by feelings of harmony and unity with "the divine" and all existence. Evidence suggests that psychoactive substances like ayahuasca occasion such states.<sup>40,194,195</sup> Compared with psilocybin and LSD, ayahuasca appears to elicit certain features of the mystical experience more prominently. Griffiths et al.<sup>168</sup> found ayahuasca consumption was linked to encounters with nonhuman entities and telepathic communication. However, no significant difference in the frequency of mystical experiences was observed when comparing LSD, psilocybin, and ayahuasca.<sup>168</sup> Additionally, the extent of the mystical experience has been associated with therapeutic outcomes, including depression and anxiety reduction, in both psilocybin and ayahuasca users.<sup>40,153,161,194,195</sup>

## Acute neurological effects

Ayahuasca users engaging in a closed-eye imagery task demonstrated increased activity in neural regions associated with memory and imagination.<sup>82</sup> The extensive activation of vision, memory, and intention-related areas may contribute to the inner experience's vividness.<sup>82</sup> Ayahuasca use was also linked to enhanced divergent thinking and reduced convergent thinking during acute effects.<sup>196</sup> Additionally, improvements in convergent thinking were sustained for 4 weeks post ayahuasca consumption,<sup>197</sup> and participants in ritual ayahuasca sessions showed increased originality in a creative thinking test, with results sustained at two week follow-up.<sup>198</sup>

## LONG-TERM EFFECTS

### Brain imaging

The long-term neurophysiological effects of ayahuasca use have been investigated.<sup>95</sup> Comparing ayahuasca users and controls,

cortical thinning in the posterior cingulate cortex (PCC) and increased cortical thickness in the anterior cingulate cortex (ACC) were found in long-term ayahuasca consumers.<sup>95</sup> The degree of PCC thinning was inversely correlated with age at initial ayahuasca use, frequency of consumption, and self-transcendence and spiritual ratings.<sup>95</sup> The cross-sectional methodology used prevents establishing direct causation, and caution should be exercised due to the small sample size and specific ayahuasca church affiliation of the participants (Santo Daime, Spain).<sup>95</sup>

## Personality

Cross-sectional and prospective studies have examined personality changes related to ayahuasca use. Church-based settings were primarily studied, with UDV church members showing lower scores in the harm avoidance and novelty-seeking domains compared with controls.<sup>186,199-201</sup>

Bouso et al.<sup>186</sup> conducted an observational study comparing long-standing ayahuasca users ( $\geq 15$  years) from various ayahuasca churches with control subjects engaged in nonayahuasca religious practice. Ayahuasca users scored lower in harm avoidance and reward dependence at baseline and maintained reduced levels of harm avoidance at 1 year follow-up. Additionally, ayahuasca users exhibited higher temperament and character inventory self-transcendence, which is related to openness to new experiences in the five factor model (FFM) of personality traits.<sup>202,203</sup> Self-transcendence has also been linked to nature relatedness and environmental concern.<sup>204</sup>

Bouso et al. found similar results in two studies when comparing long-term ayahuasca users from the Santo Daime church with non-users.<sup>186,295</sup> Long-term ayahuasca users showed lower harm avoidance and higher self-transcendence. Kavenská and Simonová<sup>185</sup> assessed personality in tourists who participated in ayahuasca ceremonies in the Amazon rainforest using the personality styles and disorders inventory. The experimental group displayed higher scores in optimism, intuition, ambition, helpfulness, and charm compared with the general Czech population, suggesting an optimistic, pleasant, trustful, and empathic personality style. However, the lack of baseline data makes it difficult to attribute these differences to ayahuasca use.<sup>185</sup>

Six prospective studies have assessed personality changes following ayahuasca use. The most consistent finding (in five studies) was a long-term reduction in FFM neuroticism or harm avoidance<sup>199,205,206</sup> (c.f. Netzband and colleagues<sup>194,207,208</sup>). This reduction has been corroborated by close significant others/peers of participants<sup>208</sup> and in comparisons with control groups.<sup>194</sup> Barbosa et al.<sup>199</sup> found reductions in reward dependence in Santo Daime and UDV church members 6 months after ayahuasca use, which was positively correlated with ayahuasca frequency. However, the influence of church membership and a supportive community on these changes is challenging to disentangle.<sup>199</sup>

Ayahuasca use has shown adaptive changes in personality traits, including increased FFM openness,<sup>194,208</sup> increased agentic extraversion, and decreased narcissistic antagonism.<sup>209</sup> These changes have been linked to mystical experiences.<sup>194,208</sup>

## General well-being

Long-term ayahuasca use is associated with enhanced cognition, mood, and spirituality.<sup>86,186,210</sup> Users report greater subjective well-being, quality of life, and positive personality changes.<sup>199,211,212</sup> Compared with nondrinkers, drinkers show higher well-being, improved executive functioning, and reduced psychopathology.<sup>186,211</sup> Ayahuasca can reduce grief, improve quality of life, and alleviate feelings of panic and hopelessness.<sup>213-215</sup> Short-term effects include increased mindfulness, improved convergent thinking, and general well-being.<sup>197,216</sup> Ayahuasca showed comparable effects to an 8-week mindfulness course, enhancing mindfulness capacities and emotion regulation.<sup>160</sup>

## AYAHUASCA AND MENTAL HEALTH OUTCOMES

### Depression

Ayahuasca has reduced depression symptoms in clinical studies. Sanches et al.<sup>217</sup> reported significant reductions in depression scores in a sample of 17 participants within hours of ayahuasca administration. The effects persisted throughout the study, with the lowest scores reported on the last assessment 21 days postadministration. A secondary analysis revealed reductions in suicidality, with the greatest effect size observed after 21 days.<sup>218</sup> These studies built on a report by Osório et al.<sup>87</sup> showing reductions in depression in a sample of six following the same study design. However, these studies had small sample sizes, lack of placebo and control groups, and no systematic investigation of side effects. The clinical setting also limits the findings' generalizability to naturalistic settings.

There has been one randomized controlled trial (RCT) comparing a single dose of ayahuasca to a placebo in a population suffering from treatment-resistant depression (TRD). This parallel-arm, double-blind, randomized placebo-controlled trial included 29 participants with a history of TRD.<sup>40</sup> The ayahuasca group experienced significant reductions in depression compared with the placebo group. When assessed a week later, the ayahuasca group displayed further reductions, with a trend toward depression remission.<sup>40</sup>

### Anxiety and panic-like disorders

Studies exploring the impact of ayahuasca on anxiety in different settings show mixed results. In a Santo Daime ritualistic setting, panic-like disorder symptoms decreased, but anxiety remained



unchanged.<sup>2</sup> Open-label studies demonstrated significant improvements, but results from RCTs, case-control, longitudinal, and pre-clinical studies are inconsistent. Some studies found no improvement in anxiety during a public speaking test after ayahuasca administration,<sup>219</sup> while others reported reduced anxiety in ayahuasca church attendees at 1-year follow-up.<sup>186</sup> Additionally, a case-controlled study in adolescent religious ayahuasca users found reduced state anxiety but similar trait anxiety.<sup>220</sup>

Studies exploring the impact of ayahuasca on anxiety in rodents have produced mixed results. Some studies ( $n = 7-18$ ) reported no effect on anxiety levels.<sup>221-223</sup> However, others found that ayahuasca administration reduced anxiety.<sup>224-226</sup> Additionally, investigations in zebrafish revealed anxiogenic behavior following ayahuasca administration.<sup>227,228</sup>

## Substance misuse

Numerous studies have investigated ayahuasca's impact on substance use disorders and related outcomes.<sup>86,166,182,211,221,229</sup> Fábregas et al.<sup>86</sup> found lower drug use subscale scores in jungle-based users at 1-year follow-up, while urban-based users scored worse on the family/social relationships subscale. Thomas et al.<sup>166</sup> reported significant reductions in problematic cocaine habits with ayahuasca and group counselling. Perkins et al.<sup>212</sup> observed reduced alcohol and cannabis use, improved mood, and increased self-efficacy in ayahuasca-naïve drinkers. Berlowitz et al.<sup>229</sup> found reduced drug use and craving in substance use disorder inpatients after ayahuasca-assisted psychotherapy. Online surveys also linked ayahuasca use to reduced substance use and improved mental health.<sup>211,221</sup>

A survey by Daldegan-Bueno et al.<sup>221</sup> found that ayahuasca attendees reported quitting or reducing smoking following consumption, possibly due to mystical experiences.<sup>230</sup> Cohort and cross-sectional studies on ceremonial ayahuasca use also show promise in populations with substance misuse, with reductions in psychiatric issues, cravings, and drug use.<sup>231</sup>

Rodent studies have demonstrated that ayahuasca decreases ethanol-induced C-Fos expression in the medial orbital cortex, and blocks place preference and ethanol-induced sensitization.<sup>232-235</sup> Repeated ayahuasca ingestion reduces amphetamine self-administration and C-Fos expression in drug-seeking brain areas, as well as methylphenidate-induced place preference.<sup>222,236</sup> Preclinical works also suggest therapeutic potential in the use of  $\beta$ -carbolines, especially harmine, in substance misuse disorders.<sup>21,237</sup> However, there is currently no randomized controlled trial investigating ayahuasca and substance misuse.

## Trauma

Many prevalent conditions in Western society, including anxiety, depression, PTSD, and addiction, are suggested to be rooted in

developmental trauma.<sup>238</sup> Ayahuasca, with its broad range of neurobiological effects, may be a transdiagnostic treatment option.<sup>239</sup>

A study by Ackerman et al. found that 40%–60% of adults have experienced trauma and a subset developed PTSD.<sup>240</sup> Trauma exposure increases the risk of conditions such as anxiety and eating disorders, major depression, and addiction.<sup>241-243</sup> Maladaptive coping strategies can contribute to developing PTSD, and reduced mindfulness and cognitive flexibility have also been proposed as contributing factors.<sup>244-247</sup>

Ayahuasca shows promise for trauma-related conditions, with preliminary data indicating positive effects on therapeutic targets.<sup>152,216</sup> It has alleviated symptoms of depression, anxiety, mood disorders, and drug dependence.<sup>40,79,248</sup> Qualitative studies have reported reduced hopelessness, improved quality of life, and addressing underlying trauma in individuals with eating disorders and addiction ( $N = 16$ ,<sup>127</sup>  $N = 11$ ,<sup>164</sup>  $N = 14$ <sup>177</sup>). The need for psychological interventions alongside ayahuasca when addressing trauma has been emphasized.<sup>127</sup> Further empirical research is needed to examine ayahuasca's impact on PTSD and trauma-related symptoms.<sup>11,151,249</sup>

## CONNECTION TO SELF, OTHERS, AND NATURE

Ayahuasca and other psychedelics have been associated with increased connectivity experiences, including blurring boundaries between individuals and others.<sup>138,250,251</sup> Observational studies of Canadian First Nations members and indigenous Canadians found ayahuasca retreats enhanced mindfulness and connections with nature, spirit, self, and others.<sup>164,166</sup> Ayahuasca consumption in nonclinical samples has been linked to enhanced connectedness, mental health, well-being, and addiction recovery.<sup>252,253</sup> Additionally, naïve drinkers have reported reduced bodily dissociation and reduced self-alienation and increased self-efficacy following ayahuasca consumption.<sup>182</sup>

Nature relatedness is a measure of affinity with nature, representing one's prolonged sense of connection with nature,<sup>254,255</sup> and is strongly associated with eudaimonic well-being<sup>256</sup> and personal growth.<sup>257</sup> Ayahuasca experiences often involve significant connection to nature, including experiences of interconnection and nature relatedness.<sup>13,176,205,252,258</sup> Amazonian shamanism emphasizes this connection between nature and humans, and how nature influences ritualistic practices.<sup>259,260</sup>

Psychedelic use aids in resolving feelings of disconnection from nature.<sup>158,261,262</sup> A Brazilian survey found that past and current ayahuasca/DMT usage was positively associated with nature relatedness.<sup>263</sup> However, a study of 53 ayahuasca-naïve participants in the United States reported no significant increase in nature relatedness on the Nature Relatedness Scale, perhaps due to relatively high baseline scores.<sup>212</sup>

## SAFETY CONSIDERATIONS

It is important to outline some of the research suggesting that the risks of ayahuasca use are minimal when used appropriately. Gable<sup>26</sup> estimates that a fatal dosage of DMT would be about 20 times higher than standard ayahuasca practice. A review of animal studies on ayahuasca toxicity supports the safety of ceremonial-level doses, except for alterations in aorta parameters observed in one study.<sup>264</sup> Serotonin syndrome (SS) was only seen at doses significantly higher than those used in ceremonies.<sup>264</sup> Overall, the therapeutic window for ayahuasca appears wide, with no acute or long-term toxicity reported in humans.<sup>265</sup>

Ayahuasca has a low addiction potential<sup>86</sup> and cardiovascular risk.<sup>65</sup> No serious negative consequences have been reported in responsible contexts when consumed by healthy individuals.<sup>265,266</sup> The responsible use of ayahuasca is considered acceptably safe in the short, medium, and long term.<sup>267</sup> However, caution should be exercised as some plant and chemical admixtures used in conjunction with ayahuasca may be dangerous (Kaasik et al., 2020).<sup>268</sup> Deaths associated with ayahuasca ceremonies have generally been attributed to malpractice.<sup>265</sup> Research on physical pain in participants of the UDV found no adverse effects in naive users.<sup>199</sup>

Anecdotal evidence suggests no negative effects of ayahuasca on pregnant women.<sup>12</sup> However, studies on pregnant rats indicate developmental toxicity with high-dose consumption,<sup>269,270</sup> although the relevance to humans remains uncertain.<sup>271</sup> Surprisingly, rat offspring exposed to ayahuasca during perinatal development showed reduced anxiety.<sup>226</sup> Limited data on potential toxic effects in human pregnancy, offspring, and long-term consumption necessitates further research.<sup>265</sup>

MAOIs used with certain substances, such as tyramine-rich foods, cold and flu medications, cocaine, ecstasy 3,4-Methylenedioxymethamphetamine, and specific alcoholic beverages, may pose risks, including hypertensive crisis.<sup>57,272</sup> While there is no direct evidence linking ayahuasca to SS, a case report suggests similarities in symptoms.<sup>135</sup> Reports of deaths related to ayahuasca have received media attention, with SS proposed as a potential cause.<sup>273</sup> However, it is important to note that while media reports have speculated about deaths following ayahuasca use, these claims often lack a clear link to ayahuasca itself.<sup>274</sup> In a recent comprehensive report, it was found that out of 58 deaths associated with ayahuasca, none could be attributed to acute ayahuasca intoxication involving *B. caapi* and *P. viridis*.<sup>275</sup> Deaths related to ayahuasca can frequently be prevented by adhering to appropriate safety standards. Many retreat centers situated in the Amazon rainforest prioritize participant safety by screening individuals for mental and physical conditions. This precautionary measure helps minimize the potential for harm during ayahuasca ceremonies.<sup>265</sup> It is important to note that media reports may not always rely on accurate data and can sometimes propagate false or exaggerated claims.<sup>265</sup> Therefore, a careful and evidence-based examination of such reports is crucial when considering the safety and efficacy of ayahuasca use.

## Adverse mental health outcomes

Unlike psychostimulants and opiates, psychedelics are generally considered psychologically safe.<sup>276-278</sup> Research suggests that long-term ayahuasca use does not negatively impact cognitive ability, lead to addiction, or worsen mental health problems.<sup>86,182,183,186,199,220</sup> Rather, ayahuasca use has been associated with improved cognition, psychopathological measures, and well-being.<sup>186</sup> Ritualistic use of ayahuasca has also been linked to lower rates of alcoholism and addiction.<sup>86,182,221,230</sup>

Inappropriate psychedelic use, including ayahuasca, has been associated with psychological distress and potential harm.<sup>140,186,279</sup> Adverse mental health effects, including increased anxiety and distress, are less common.<sup>212,280</sup> While there are cases linking ayahuasca consumption to psychosis, establishing causality is challenging due to pre-existing conditions and substance use.<sup>48,281</sup> The rate of psychotic episodes among ayahuasca users appears comparable to that in the general population.<sup>26,282</sup> Notably, ayahuasca's risk profile seems relatively safe compared with cannabis, which has been associated with a higher risk of developing psychotic disorders.<sup>283</sup>

## The importance of setting

Debate continues surrounding the importance of ceremony amid the potential medicalization of ayahuasca. Researchers have discussed the role of shamans and icaros in ayahuasca experiences.<sup>117</sup> Palhano-Fontes et al.<sup>40</sup> suggested that participants may be influenced by the placebo effect, while Weiss et al.<sup>208</sup> linked mystical states and prior perceptions of shamanic tradition to positive outcomes. Purging, but not all shamanic features, predicted positive change.<sup>208</sup> Shamanic/spiritual perspectives offer insights into healing and consciousness,<sup>284</sup> influencing beliefs and outcomes within the psychospiritual container.<sup>285,286</sup> Delivering an ayahuasca ceremony requires skill, akin to spiritual surgery.<sup>213</sup>

Recent works by Pontual et al. have further emphasized the importance of the setting in ayahuasca experiences. They developed a psychometric instrument to quantify various elements of the setting, identifying six main factors: leadership, decoration, infrastructure, comfort, instruction, and social dynamics.<sup>287</sup> Moreover, in a subsequent survey-based study, they provided data on the association between setting and the nature of ayahuasca experiences, including challenging and mystical aspects.<sup>288</sup>

Psychedelic-assisted psychotherapy trials reveal the impact of the therapeutic container and therapist artistry on outcomes.<sup>289,290</sup> The quality of the therapeutic relationship influences results, regardless of the modality.<sup>291,292</sup> Positive press on psychedelics may offer hope, initiating the healing process and reinforcing the appeal of practices like ayahuasca that blend science, spirituality, and mysticism (UDV and Santo Daime churches).

Ayahuasca trials in clinical settings have shown positive outcomes for depression.<sup>293</sup> Although these results may seem

counterintuitive given the importance of shamanic elements and spiritual paraphernalia in psychedelic assisted psychotherapy, the demographics of the sample groups, such as low-income status and limited access to medical care, indicate a setting of luxury and care, influencing participants' views on treatment quality.<sup>40</sup> Large-scale multisite comparison studies incorporating biological, neurological, psychometric, and qualitative data are needed to address this knowledge gap.

Music is a significant factor in both ayahuasca practices and PAP, with ongoing research exploring its influence on human consciousness.<sup>294</sup> Sound frequencies and pitch changes are believed to carry archetypal connotations that impact emotional responses in humans, underpinning sound healing practices.<sup>295</sup> Using music or sound, therapists can guide therapeutic experiences and evoke specific emotional processes.<sup>296</sup>

Ayahuasca studies show that with optimized settings, positive outcomes can be achieved for depression, addiction, and PTSD/complex PTSD, akin to psychotherapy. Qualitative data indicate that the framework supports healthy reprocessing of the traumatic episodes underlying these conditions.<sup>297</sup> The psychedelic literature seems to align with psychotherapy research, showing promising complementarity so far.

## Future perspectives

The study of shamanic practices using conventional scientific methods faces limitations due to the variability of individual experiences, making generalization challenging.<sup>298</sup> Bridging science and spirituality involves innovative projects using advanced techniques such as portable neuroimaging and genomics to explore parallels and distinctions between these converging paradigms. Ayahuasca's efficacy in healing-oriented settings is well-documented<sup>299</sup> and resonates with historical use of similar shamanic practices.<sup>300</sup>

The psychedelic movement is expanding, and research on ayahuasca is advancing with innovative methods like virtual reality, neuroimaging, and genomics. The future of ayahuasca may be influenced by governmental regulations and public perceptions, potentially leading to regulated sites in Western nations.<sup>301</sup> As efficacy reaches a plateau, future research may delve into spiritual and philosophical aspects. Ongoing analysis is exploring the potential directions for ayahuasca research.

## CONCLUSION

Ayahuasca is a traditional psychedelic brew with DMT and harmala alkaloids that has been used ceremonially for centuries. Users report profound experiences and improved well-being. Ayahuasca is generally safe, with mild, transient side effects. Long-term use does not seem to negatively affect cognition or mental health, and clinical studies show promising results. Although evidence supports ayahuasca's therapeutic potential, it is unclear to what extent this

efficacy is attributable to the drug's pharmacology alone, as other factors such as (neo-)shamanic or alternative surrounding frameworks may contribute. Research on ayahuasca's effects must consider individualized responses and avoid sensationalism. Rigorous scientific investigation is crucial for therapeutic protocols, risk assessment, and future research. Understanding spiritual elements and indigenous knowledge can enrich the study. Larger trials and longitudinal and multisite studies using advanced technology are necessary to evaluate ayahuasca's potential as a medicine in Western healthcare. This will help to optimize therapeutic experiences based on individual preferences and frameworks.

## AUTHOR CONTRIBUTIONS

Conceptualisation: Simon G. D. Ruffell and Devin B. Terhune. Original manuscript: Simon G. D. Ruffell, Nige Netzband, WaiFung Tsang, Sam Gandy, Daniel Perkins, Tessa Cowley-Court, Andreas Halman, Diana McHerron, Tom Kennedy, Eleanor White, Devin B. Terhune, and Jerome Sarris. Revisions: Max Crosland-Wood, Rob Palmer, Brandon Weiss, and Angelina Jong. Supervision: Daniel Perkins, Devin B. Terhune, and Jerome Sarris.

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## CONFLICTS OF INTEREST STATEMENT

Simon G. D. Ruffell, Nige Netzband, and WaiFung Tsang are directors of a not-for-profit research institute. Jerome Sarris and Daniel Perkins are directors of a not-for-profit medicinal psychedelics research institute. Simon G. D. Ruffell, Tessa Cowley-Court, and Diana McHerron are employed at this not-for-profit medicinal psychedelics research institute. Jerome Sarris is supported by an National Health and Medical Research Council (NHMRC) Clinical (Fellowship APP1125000).

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## ETHICS APPROVAL STATEMENT

NA

## PATIENT CONSENT STATEMENT

NA

## CLINICAL TRIAL REGISTRATION

NA

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