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REVIEW ARTICLE

The pharmacological interaction of compounds in ayahuasca: a systematic review

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Ayahuasca is a South American psychoactive plant brew used as traditional medicine in spiritual and in cultural rituals. This is a review of the current understanding about the pharmacological mechanisms that may be interacting in ayahuasca. Searches were performed using PubMed, PsycINFO, and Web of Science databases and 16 papers were selected. As hypothesized, the primary narrative in existing research revolved around prevention of deamination of N,N-dimethyltryptamine (N,N-DMT, also referred to as DMT) by monoamine oxidase inhibitors (MAOIs) in ayahuasca. Two of the constituents, DMT and harmine, have been studied more than the secondary harmala alkaloids. At present, it is unclear whether the pharmacological interactions in ayahuasca act synergistically or additively to produce psychoactive drug effects. The included studies suggest that our current understanding of the preparation's synergistic mechanisms is limited and that more complex processes may be involved; there is not yet enough data to determine any potential synergistic interaction between the known compounds in ayahuasca. Our pharmacological understanding of its compounds must be increased to avoid the potential risks of ayahuasca use.

Keywords: Dimethyltryptamine; B-carboline; ayahuasca; tetrahydroharmine; monoamine oxidase inhibitor

Introduction

Ayahuasca is a South American psychoactive plant brew used as traditional medicine in spiritual and in cultural rituals. Within indigenous communities in Brazil, Peru, and Colombia, ayahuasca is believed to have healing properties that are employed to treat spiritual, physical, and psychological ailments. The brew is use often related to mystical experiences and spiritual encounters.[1] The name ayahuasca loosely translates to "vine of the soul" or "vine of the dead."[2] Traditional practices usually involve a shaman, or curandero, who facilitates the experience for individuals in their respective communities.[1] Since the 20th century, the globalization of ayahuasca has spread beyond native indigenous groups and has been incorporated in syncretistic churches, indigenous-like, and non-indigenous ("neo-shamanic") practices.[1]

An ayahuasca brew usually consists of two plant constituents: *Psychotria viridis*, commonly known as "chacruna," and *Banisteriopsis caapi*, also independently referred to as the "ayahuasca vine" or simply "ayahuasca." *Psychotria viridis* contains the psychoactive compound N,N-dimethyltryptamine (N,N-DMT, also referred to as DMT), and *Banisteriopsis caapi* contains β-carbolines, mainly harmine, harmaline, and tetrahydroharmine (THH) ("harmala alkaloids"). Although DMT is psychoactive when smoked or infused intravenously, when ingested orally it is broken down by the stomach enzyme monoamine oxidase, rendering its psychoactive properties void. β-carbolines are reversible inhibitors of monoamine oxidase-A (MAO-A) and act to prevent the deamination of DMT when present in the ayahuasca brew.[3,4] Thus, the psychotropic effects of the brew are a result of combining the compounds in the two plant species. A range of other ingredients is often used in ayahuasca preparations, yet it is understood that the basic mechanism of action is psychoactivity resulting from the increased bioavailability of DMT when ingested with monoamine oxidase inhibitors (MAOIs). Mechanistic data on the psychopharmacological interactions in ayahuasca have been relatively under-researched, focusing on the interaction between DMT and MAOIs. Not much more is known about these pharmacological interactions and how they specifically contribute to the effects or side effects experienced by users.

Strassman et al.[5] administered intravenous DMT (negating the need for a MAOI) to 60 volunteers, finding that DMT's psychoactive effects are much shorter than when ingested in ayahuasca, usually lasting between 10 and 30 minutes, similar to smoked DMT.[5] DMT is a structural analogue of serotonin and melatonin and a functional

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analogue of other tryptamines, such as 4-AcO-DMT, 5-MeO-DMT, 5-HO-DMT, psilocybin (4-PO-DMT), and psilocin (4-HO-DMT).[6] When orally ingested and combined with MAOI alkaloids, the psychotropic effects last longer, between 4 and 6 hours.[7] Riba et al.[8] obtained 24-hour urine samples from six participants who had consumed 25 mg of DMT, assessing the concentration of compounds present before and after either smoking or oral ingestion of DMT. Those who smoked DMT were found to experience the full psychoactive effects of the drug, with metabolized DMT and DMT-NO comprising 10 and 28% of the metabolites found in urine, respectively. When taken orally, 97% of the compounds recovered were MAO-dependent indole-3-acetic acid, with 3% DMT-NO. An inverse correlation was apparent between the indole-3-acetic acid/DMT-NO ratio and the participants' intensity rating. The authors suggested this is indicative of a change in metabolism from MAO to CYP-dependent.[8] This correlates with the psychoactive effects experienced in the above study, as well as those from the combination of DMT and MAOIs found in ayahuasca. MAOIs have also been found to increase levels of other tryptamines, such as 5-MeO-DMT. Halberstadt[9] found that MAOIs directly affect the pharmacodynamics of 5-MeO-DMT, leading to higher levels in the nervous system.

Acute users of DMT-containing ayahuasca have reported feelings of transcending time and space, euphoria, meaningful encounters with seemingly sentient entities, and a sense of oneness.[7] Narrative accounts of the DMT experience present considerable overlap with phenomena associated with a near-death experience, including out-of-body experience, the presence of an irreversible threshold, travelling towards light via a tunnel or a void, and life review.[10] DMT has been colloquially called "the spirit molecule."[4] DMT is a serotonergic psychedelic drug, a class including psilocybin and lysergic acid diethylamide. Evidence from animal and human studies demonstrates that the psychedelic effects of these substances, including distorted sensation and perception, are mediated by binding action at the 5-HT2A receptor.[11,12] These drugs also bind to a number of 5-HT receptor subtypes, as well as other monoamine receptors.[12] DMT, specifically, binds to 5-HT1A, 5-HT1B, 5HT-1D, 5HT2A, 5-HT2B, 5-HT2c, 5-HT5A, 5-HT6, and 5-HT7A.[11] It has been found that lesser-known tryptamines, such as 5-MeO-DMT, also have an affinity for 5HT receptors. Halberstadt[9] used rat models to show that 5-MeO-DMT can disrupt pre-pulse inhibition by activating 5-HT2A receptors and can act on 5-HT1A.

After a research hiatus following the UK's Misuse of Drugs Act 1971, psychedelic drugs are again being investigated. New techniques, such as positron emission topography and functional magnetic resonance imaging are studying the neurobiological activity of these compounds. The DMT-containing brew is more complicated than many of its psychedelic counterparts since it contains multiple psychoactive compounds. This makes it difficult to produce standardized, medical grade ayahuasca for clinical research. This is further exacerbated by variation in the DMT/MAOI proportions used in ayahuasca preparations (and often, the addition of other plant compounds) across studies.[13-15] To achieve dose uniformity, encapsulated lyophilized (freeze-dried) ayahuasca has been used in a number of studies[8,13] involving oral administration of ayahuasca. The DMT and alkaloid concentrations in ayahuasca preparations have been quantified via various methodologies.[14,15]

This review aims to investigate the current literature on the pharmacological interaction of compounds present in ayahuasca. Although it is generally accepted that interaction between DMT and MAOIs makes the DMT bioavailable, it is unclear how DMT and MAOIs interact pharmacologically in ayahuasca, whether synergistically or additively, to produce the substance's unique psychoactive, psychedelic, and adverse effects.

Methods

The PubMed, PsycINFO, and Web of Science databases were searched through September 2019 for the following terms: (ayahuasca OR DMT OR dimethyltryptamine) AND (B-carboline OR constituents OR chemistry OR harmine OR harmaline OR harmala alkaloids OR tetrahydroharmine OR harmalol OR MAOI OR monoamine oxidase inhibitor OR pharmacology OR pharmacokinetics OR pharmacodynamics OR psychopharmacology OR synergy).

The reference lists of relevant studies were checked for additional papers, and secondary searches were performed using related keywords. This database was also manually searched to find abstracts or titles including the aforementioned search terms. A total of 2,141 papers were identified, of which 1,957 were extracted, following the removal of duplicates. A review of the titles and abstracts eliminated all but 202 papers, which were screened in greater detail for eligibility. The abstracts, methods, and findings of these papers were assessed, reducing the number to 57 for full text analysis. A total of 16 studies examined the pharmacology of ayahuasca as a brew or its known active compounds, either isolated or synergistically, and were included in the review. Only papers that had undergone full peer review and were published in English were included. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16]

Data from the included studies were identified and collected in a standardized form by two researchers. The data collected included the authors, date, study design, sample characteristics (sample size, age, sex), measures, and key findings – including established pharmacological mechanisms of action and limitations. The review employed a two-phase content synthesis: the literature was first analyzed according to study design, and findings across studies were then included to provide a depiction of the pharmacological action of the compounds present in ayahuasca. Risk of bias was assessed, including randomization, handling of missing data, and selective reporting. When discrepancies in article inclusion arose, consensus was reached via discussion.

A summary of the findings is shown in Table 1.

Table 1 List of research studies included in the systematic review

Authors	Year	Title	Findings	Further comments
Mckenna[4]	1984	Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and ß-carboline constituents of ayahuasca	Showed MAOI effect in vitro. Proposes that inhibition experiments using mixtures of ß-carbolines indicate that their effects in combination are additive, rather than synergistic or antagonistic.	Original proposal regarding DMT deamination prevention via MAOI in harmala alkaloids from *P. viridis.*
Callaway[17]	1994	Platelet serotonin uptake sites increased in drinkers of ayahuasca	Increased number of serotonin mRNA transporter sites in regular ayahuasca drinkers against control group.	-Shows an increased number of binding sites in platelets. -No evidence of this for DMT alone, which is suggestive of a synergistic effect.
Strassman[5]	1994	Dose-response study of N, N-dimethyltryptamine in humans	-Peak DMT blood levels and subjective effects were seen within 2 minutes after drug administration and were negligible at 30 minutes. -DMT dose-dependently elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to elevating blood concentrations of ß-endorphin, corticotropin, cortisol, and prolactin. Growth hormone blood levels rose equally in response to all doses of DMT, and melatonin levels were unaffected. -Threshold doses for significant effects relative to placebo were also hallucinogenic ($>$ 0.2 mg/kg) -Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine had less robust pupil diameter effects than those exposed two times of less. -Evidence that DMT is unique in the inability to develop tolerance to its psychological effects.	Dose-response data for IV DMT fumarate, neuroendocrine, cardiovascular, autonomic, and subjective effects in a group of experienced hallucinogen users.
Smith[18]	1998	Agonist properties of N, N-dimethyltryptamine at serotonin 5-HT2A and 5-HT2C receptors	-DMT fully substituted for DOI. Intact choroid plexus was used to evaluate the agonist properties at endogenous 5-HT2C receptors. -DMT was a partial agonist at 5-HT2C receptors in this native preparation. -DMT behaves as an agonist at both 5-HT2A and 5-HT2C receptors. -One difference was evident in that the 5-HT2C, but not the 5-HT2A, receptor showed a profound desensitization to DMT over time (suggestive of limited application for repeat prescription).	Evidence of DMT 5HT2a(c) agonism.
Callaway[19]	1999	Pharmacokinetics of Hoasca alkaloids in healthy humans	-THH shows PK profile independent to harmine. -Affinities and other PK values provided.	-Evidence that THH alone may be a weak SSRI. -Implies further synergistic effects on the serotonin system.
Ott[20]	1999	Pharmahuasca: human pharmacology of oral DMT plus harmine	-MAO inhibition from simultaneous ingestion of ß-carbolines confirmed by eight self-experimenters. -Results of a total of some 70 bioassays are summarized and the literature on this subject is reviewed.	-Evidence that DMT and harmine in tablet form create similar effects to ayahuasca, further reinforcing the DMT MAOI interaction. -When orally ingested, DMT without harmine is non-active.

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Table 1 (*continued*)

Authors	Year	Title	Findings	Further comments
Glennon[21]	2000	Binding of ß-carbolines and related agents at serotonin (5-HT2 and 5-HT1A), dopamine (D2) and benzodiazepine receptors	Affinity scores at 5-HT2 for harmine/harmaline.	Shows that other harmala alkaloids also bind to the 5HT2 receptors, further suggesting synergistic potential in the serotonergic system.
Riba[22]	2003	Human pharmacology of ayahuasca	-Diastolic blood pressure significant increase. -Heart rate moderate increase. -Increased urinary normetanephrine excretion. -Deaminated monoamine metabolite levels did-not decrease (contrary to typical MOAI effect profile). -The negligible harmine plasma levels found suggest a predominantly peripheral (gastrointestinal and liver) site of action for harmine.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -PK angle. -Small sample size (n=18).
Riba[23]	2006	Increased frontal and paralimbic activation following ayahuasca	-Significant activation of frontal and paralimbic brain regions. -Increased blood perfusion observed bilaterally in anterior insula, gather intensity in right hemisphere, and anterior cingulate/frontal medial cortex of right hemisphere. -Increases observed in left amygdala/parahippocampal gyrus. -Concludes that ayahuasca interacts with neural systems that are central to interoception and emotional processing.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -Neuroimaging angle. -Used SPECT.
Fortunato[24]	2010	Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus	-Increased BDNF protein levels in rat hippocampus. -Concludes that findings within support the hypothesis that harmine could bring about behavioral and molecular effects.	Further evidence that the synergistic mechanisms of DMT + harmine are more than just effects of MAOIs.
dos Santos[25]	2011	Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with D-amphetamine	-Significant increases in prolactin. -Percentage of CD3/4 were decreased, natural killer cells increased. -Maximum changes occurred around 2 hours, returned to baseline after 24 hours. -Ayahuasca displayed moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.	Focuses on the synergistic effects of ayahuasca rather than individual action of compounds. Immunological, rather than neuropsychological, perspective.
McIlhenny[26]	2011	Methodology for determining the major constituents and metabolites of the Amazonian botanical medicine ayahuasca in human urine	-Showed that the major metabolite of a DMT is the corresponding DMT-NO, the first time this metabolite has been described in *in vivo* studies in humans. -Very little DMT detected in urine, despite the MAOI. -Major alkaloid excreted was THH. -List of other products and metabolites quantified.	-Provides methodology for identifying and quantifying constituents of ayahuasca in human urine. -PK data of tested samples provided.Excretion and metabolism of THH should be further investigated.

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Table 1 (*continued*)

Authors	Year	Title	Findings	Further comments
McIlhenny[27]	2012	Methodology for determining major constituents ofayahuasca and its metabolites in blood	-DMT concentrations lower than DMT-NO at all time points. -Plasma DMT-NO concentrations three to four times higher than DMT. -DMT-NO forms rapidly after drug administration. -THH levels peaked at around 4.5 hours. -Harmine and harmaline present in most samples.	-Single methodology combining HPLC and gas chromatography to identify ayahuasca constituents in blood following oral consumption. -First report of presence of DMT-NO in human blood following ayahuasca/DMT administration. -Method for the most complete profile of DMT, harmala alkaloids, and metabolite concentrations.
Riba[13]	2012	Metabolism and disposition of N, N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca	-Less than 1% of DMT excreted unchanged. -Fifty per cent was recovered as indole-3-acetic acid or DMT-NO. -Ten per cent was other MAO-independent compounds. -Recovery of DMT plus metabolites reached 68%. -Harmol, harmalol, and THH conjugates were abundant in urine. -The recovery of each harmala alkaloid plus its 0-demethylated metabolite varied greatly (between 9 and 65%).	-PK study with implications regarding alternative metabolic routes for DMT other than biotransformation by MAO. -Freeze-dried ayahuasca. -Urine samples obtained. -Small sample (n=10).
Morales-Garcia[28]	2017	The alkaloids of *Banisteriopsis caapi*, the plant source of the Amazonian hallucinogen ayahuasca, stimulate adult neurogenesis *in vitro*	Significant neurogenesis in adult hippocampal cells *in vitro* with harmine.	Suggests that ayahuasca brew may have more complex synergistic properties than we currently understand. Shows that harmine alone could be partially responsible for the neurological changes seen in ayahuasca users.
Sampedro[29]	2017	Assessing the psychedelic ‘‘after-glow’’ in ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities	-Magnetic resonance spectroscopy showed post-acute reductions in glutamate + glutamine, creatine, and N-acetylaspartate+N- acetylaspartylglutamate in the posterior cingulate cortex. -Connectivity was increased between the posterior cingulate cortex and the anterior cingulate cortex, and between the anterior cingulate cortex and limbic structures in the right medial temporal lobe. -Glutamate + glutamine reductions correlated with increases in the ‘‘nonjudging’’ subscale of the Five Facets Mindfulness Questionnaire-Increased anterior cingulate cortex-medial temporal lobe connectivity correlated with increased scores on the self-compassion questionnaire. -Post-acute neural changes predicted sustained elevations in nonjudging 2 months later.	-DMN activity decrease and increased neural connectivity to other areas of the brain. -Supported by other studies on 5HT2a agonists. -Long-term neurological differences found after ayahuasca administration.

BDNF = brain-derived neurotropic factor; DMN = default mode network; DMT = N,N-dimethyltryptamine; DMT-NO = DMT-N-oxide; DOI = 2,5-dimethoxy-4-iodoamphetamine; HPLC = high-performance liquid chromatography; IV = intravenously; MAO = monoamine oxidase; MAOI = MAO inhibitor; PK = pharmacokinetic; SPECT = single photon emission tomography; SSRI = serotonin reuptake inhibitor; THH = tetrahydroharmine.

Description of studies

Mechanistic data of DMT as an isolated compound

Strassman et al.[5] provided dose-response data regarding the neuroendocrine, cardiovascular, autonomic, and subjective effects of intravenously administered dimethyltryptamine fumarate in a group of experienced hallucinogen users. Peak DMT blood levels and subjective effects were seen within 2 minutes of drug administration and were negligible at 30 minutes. Intravenous DMT elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to dose-dependent elevation of blood concentrations of β-endorphin, corticotropin, cortisol, and prolactin. Blood levels of growth hormone rose equally in response to all doses of DMT, although melatonin levels were unaffected. Threshold doses for significant effects relative to placebo were also psychedelic (0.2 mg/kg and higher). Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine demonstrated less robust pupil diameter effects than those exposed two times or less.

Smith et al.[18] produced supporting data using intact choroid plexuses, evaluating agonist properties at endogenous 5-HT2A/C receptors. These receptors are highly expressed on layer V pyramidal neurons in the cortex and are also found in the hippocampus, striatum, and amygdala.[30] It was concluded that although DMT behaves as an agonist at both 5-HT2A and 5-HT2C receptors, it was only a partial agonist at 5-HT2C receptors. In addition, the 5-HT2C, but not the 5-HT2A, receptor showed a profound desensitization to DMT over time. Finally, this study showed that DMT's 5HT affinity was equal to that of 2,5-dimethoxy-4-iodoamphetamine. DMT has an affinity with numerous other serotonergic receptors, including 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2B, 5-HT5A, 5-HT6, and 5-HT7.[11]

It has been suggested that DMT may be an endogenous ligand of the sigma-1 receptor, which implies that it could play a role in neuromodulation of 5-HT, as well as being a 5-HT agonist.[12] This hypothesis has not yet received any support, since it has not been validated with scientific methods.[31] It should also be noted that DMT's affinity for sigma-1 is 100 times lower than its affinity for 5-HT2A. Furthermore, since there is a relatively low level of endogenous DMT circulating in the body, it appears unlikely that sigma-1 plays a major role in relation to endogenous DMT.[32]

The pharmacological interaction between DMT and MAOs

McKenna et al.[4] demonstrated that the β-carbolines in ayahuasca have an inhibitory effect on MAO *in vitro*. Ott,[20] achieved the same effect *in vivo* using tablet-form DMT combined with the β-carboline alkaloid harmine, providing evidence that without MAOIs, DMT would be non-psychoactive when orally ingested. McKenna[4] reported that inhibition experiments using mixtures of β-carbolines and DMT indicated that their combined effects are additive, rather than synergistic or antagonistic.

Harmala alkaloids have been shown to primarily inhibit MAO-A, rather than MAO-B. The effective concentrations necessary to inhibit MAO-A have been reported as 8×10^{8} M for harmine, 6×10^{-8} M for harmaline, and 1.4×10^{-5} M for THH. At higher concentrations, both harmine and harmaline begin to inhibit MAO-B.[33] In addition, a case study of β-carboline alkaloid intoxication following ingestion of *Peganum harmala* seed extract also found that they had affinity for 5-HT receptors independently of DMT.[34] Ataxia, hallucinations, vomiting, and confusion have been attributed to CNS stimulation by MAOIs, as has the ability of THH to inhibit the reuptake of serotonin in the presynaptic membrane.[35]

Glennon et al.[21] investigated the affinity values of β-carbolines and related agents at 5-HT2 and 5-HT1A, as well as at dopamine and benzodiazepine receptor sites, concluding that harmala alkaloids also bind to 5-HT2 receptors with a potency comparable to that of DMT. Callaway et al.[17] found that regular ayahuasca drinkers had more 5-HT mRNA transporter sites in platelets than non-ayahuasca drinking controls. This finding suggests that, when prepared as a brew, ayahuasca causes an upregulation of 5-HT receptors. It appears that this is not the case with DMT as an isolated compound or with chronic administration of β-carbolines alone. Taken together, this suggests that the complexity of ayahuasca's synergistic mechanisms may be greater than is currently understood.[36]

Isolated harmine had an antidepressant effect in a rat model after chronic administration in hippocampal tissue, leading to increased brain-derived neurotrophic factor protein levels.[24] Nevertheless, as with all animal studies, caution is necessary when applying the results to humans.

Another study by Callaway et al.[37] showed that the pharmacokinetic profile of THH is independent of any of the other β-carbolines present in *B. caapi*, particularly in contrast to harmine. This study established that THH acts as a weak serotonin reuptake inhibitor (SSRI), providing evidence that it is the only harmala alkaloid that causes neurochemical shifts in presynaptic tissue. This again implies that synergistic mechanisms are at play when ayahuasca is consumed as a brew, since it increases the amount of 5-HT in synaptic clefts and has a direct serotonin agonist effect on postsynaptic receptors. Morales-García et al.[28] studied the impact of harmala alkaloids (vs. a saline control sample) on murine hippocampal tissue *in vitro*, finding that harmine triggers neurogenesis in stem cells.

The neurobiological effects of ayahuasca

Using single-photon emission computed tomography (SPECT), Riba et al.[23] carried out a double-blind placebo-controlled clinical trial using freeze-dried ayahuasca. Significant activation of the frontal and paralimbic brain regions was observed. Increased blood perfusion was observed bilaterally in the anterior insula, with greater intensity in the right hemisphere. This was also the case in the anterior cingulate and frontal medial cortex of the right hemisphere. Increased activation of the left amygdala and

parahippocampal gyrus were also recorded. The authors concluded that ayahuasca interacts with neural systems that are central to introspection and emotional processing, increasing serotonergic neurotransmission in these processes. The study had a small sample (n=15) consisting only of men of a limited age range (28-48).[23]

Using magnetic resonance spectroscopy technology, Sampedro et al.[29] found post-acute reductions in glutamate and glutamine, creatine, and N-acetylaspartate + N-acetylaspartylglutamate in the posterior cingulate cortex. Increased activity was observed between the posterior cingulate cortex and the anterior cingulate cortex, as well as between the anterior cingulate cortex and limbic structures in the right medial temporal lobe. Glutamate and glutamine reductions correlated with increases in "non-judging" subscale scores in the Five Facets Mindfulness Questionnaire. Additionally, increased anterior cingulate cortex-medial temporal lobe connectivity correlated with increased scores in the Self-Compassion Questionnaire. Post-acute neural changes predicted sustained elevation in non-judging after two months, which was deemed a long-term result. This study could provide a mechanistic explanation for the often described experiential effect of post-ayahuasca "after-glow."[29]

McIlhenny et al.[26] provided methodological guidelines for identifying the constituents of ayahuasca samples, using sample dilution and high-performance liquid chromatography in human urine. They also provided pharmacokinetic profiles of the constituent compounds of ayahuasca. They found that that the major metabolite of N, N-DMT is the corresponding N-oxide. This was the first time that this metabolite has been described in human *in vivo* studies. Minute amounts of DMT were detected in urine samples from three individuals, despite the fact that MAOIs were present in the administered ayahuasca. The major alkaloid excreted was THH. The presence of other β-carbolines was deemed to be below significant thresholds. The authors conducted a follow-up study to determine the metabolites of ayahuasca constituents in blood following oral consumption of the brew, using a combination method of high-performance liquid chromatography and gas chromatography.[27] The plasma concentration of DMT-N-oxide (DMT-NO) was three to four times that of DMT. This is the first study to find DMT-NO in human blood following ayahuasca/DMT consumption. DMT-NO levels peaked 1.5 hour after ayahuasca administration ($\sim$ 45 μg/mL). THH was observed to peak at around 4.5 hours ($\sim$ 55 μg/mL), being the major harmala excretion product in human urine.[26] Harmaline, harmine, harmalol, harmol, 7-hydroxy-THH (THHOH), and 2-methyl-1,2,3, 4-tetrahydro-P-carboline (2-MTHBC) were found in most samples. Significant increases of plasma levels of indoleacetic acid were observed.[27]

Riba et al.[13] added greater scope to the above findings. Using pharmacokinetic assessment of urine, they found that less than 1% of the excreted DMT remained unchanged. A total of 50% was recovered as indole-3-acetic acid and DMT-NO, with 10% other MAO-independent compounds. However, 68% of DMT plus metabolites was recovered, and harmol, harmalol, and tetrahydroharmine conjugates were abundant. The recovery of each harmala alkaloid plus its O-demethylated metabolite varied between 9 and 65%. These results imply that there may be another metabolic route for DMT besides biotransformation by MAO. It should be noted that the sample was small (n=10) and consisted solely of men, limiting generalization of the results.

In a previous double-blind placebo-controlled trial with freeze-dried ayahuasca, Riba et al.[22] found significantly increased diastolic blood pressure, moderate increases in heart rate, as well as increased urinary excretion of normetanephrine. However, deaminated monoamine metabolite levels did not decrease, unlike a typical MOAI effect profile. Furthermore, negligible harmine plasma levels were found, suggestive of predominantly peripheral (gastrointestinal and liver) sites of action.

Dos Santos et al.[25] investigated the autonomic, neuroendocrine, and immunological effects of short term ayahuasca use, principally from a synergistic perspective. Focusing on immunological implications of the brew, neuropsychological outcomes were of secondary importance. They observed significant increases in prolactin, along with a decrease in the percentage of CD3/4 T cell co-receptors. Significant increases in natural killer cells were also recorded. Such changes peaked around 2 hours and returned to baseline after 24 hours. The sample was of limited size and all male. They concluded that ayahuasca had moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.

Discussion

This review clearly demonstrates that the published research is insufficient to determine potential synergistic interactions between the known compounds of ayahuasca. Although it has been previously suggested that the mechanisms may be additive, rather than synergistic or antagonistic,[4] the data presented here suggest that such conclusions cannot be drawn from our current understanding.

The majority of studies that have reached conclusions have focused on DMT and harmine, both as isolated compounds or in combination with each other, finding that DMT deamination in the gut is prevented when the compounds are combined.[4,20] The exception to this is Riba et al.,[38] who suggest that there may be more complex metabolic routes for DMT. It is evident at this stage that even the most basic principles of interaction are not thoroughly understood. In addition to this, much of the data may not be directly applicable *in vivo* to humans, with the majority of findings being from either animal or *in vitro* studies. Human samples are limited by small size and/or gender and age range issues.

Cortical oscillatory activity is a key part of brain function due to its connection in input selection, temporal activity management, and synaptic plasticity. Changes in oscillatory activity have been related to schizophrenia, and the study of brain oscillations between frequencies has been considered a useful instrument in schizophrenia research. Variations in cortical oscillatory activity also occur in other models of psychosis.[39] The neurobiological basis of

hallucinogenic action suggests that changes in primary sensory areas (V1) and the prefrontal association cortex are associated.[23] Schenberg et al.[40] used electroencephalogram recordings to demonstrate that ayahuasca has a biphasic effect on the brain. Fifty minutes after ayahuasca was ingested, power was reduced in the alpha band, largely apparent in the left parieto-occipital cortex. After 75-125 minutes, both fast and slow wave gamma power increased. The increase in fast wave gamma power was located in the right frontal, left frontal temporal, right parietal-occipital, and left central-parietal-occipital cortices, whereas the slow wave increase occurred in the left frontal temporal, left central-parietal-occipital, and right frontal cortices. Circulating levels of DMT, β-carbolines, and some of their metabolites, were found to correlate with these changes.[40] Similarly, through electroencephalogram monitoring, Valle et al.[41] found decreases in alpha, theta, and delta bands in people who had consumed ayahuasca. The intensity of visual imagery was inversely correlated with the density of alpha oscillations found in the occipital and parietal cortex.

Heise & Brooks[42] reviewed a total of 538 ayahuasca exposure reports made to the American Association of Poison Control Centers' National Poison Data System. The most frequent clinical manifestations reported were hallucinations (35%), tachycardia (34%), agitation (34%), hypertension (16%), mydriasis (13%), and vomiting (6%). Endotracheal intubation was required in 28 cases, cardiac arrest was reported in four cases, respiratory arrest in seven, seizure in 12, and death in three. Further research that includes broad drug testing will be needed to better identify the risks and effects of ayahuasca.

It has been determined that DMT binds to multiple 5-HT receptors,[18] which is also the case for β-carbolines harmine and harmaline.[21] Thus, all of these compounds have a direct agonist effect on serotonin pathways by affecting postsynaptic tissue. Valle et al.[41] administered the 5-HT2A antagonist ketanserin alongside ayahuasca in a double-blind placebo control experiment. Ketanserin inhibited the subjective and neurophysiological effects of ayahuasca, illustrating the role of 5-HT2A receptors in the ayahuasca experience. Callaway et al.[19] found that THH is a weak SSRI, making it the only known β-carboline that affects presynaptic membranes. With all of these compounds present in a typical ayahuasca preparation, it is reasonable to assume that this is a display of synergistic pharmacology in humans, and could account for some of the effects. Callaway et al.[19] also found that regular ayahuasca users had more serotonin mRNA transporter sites, which implies that synergistic mechanisms are at work. Kummrow et al.[43] tested ayahuasca samples and concluded that they are mutagenic, which partially explained one of the β-carbolines present in the beverage. Other mutagenic compounds seem to be present and should be further investigated. This is further supported by the fact no such effects have been observed to result from DMT alone or any isolated β-carbolines. This suggests that further research is needed regarding mutagenic compounds in ayahuasca samples.

In addition to inhibiting MAOI-A in the gut and liver, reducing the first-pass effect of DMT and increasing its circulation by minimizing deamination, it has been suggested that harmine, harmaline, and THH exert psychoactive effects independently of DMT.[7,44,45] The independent administration of harmine has been found to result in locomotor ataxia, agitation, both visual and auditory hallucinations, nausea, vomiting, and confusion.[34] β-carboline alkaloids have also been found to interact with benzodiazepine receptors, as well as to intercalate into DNA and inhibit both topisomerase and cyclin-dependent kinases.[45] Grella et al.[46] demonstrated that β-carbolines have a non-specific binding profile and can bind to most receptor types, with the exception of a modest affinity for α-adrenergic receptors. Specifically, harmaline displays little/no affinity for serotonergic, dopaminergic, and norepinephrine neurotransmitter transporters and can bind with low affinity at most receptors.[46]

Ayahuasca is becoming increasingly available in Latin America, Central America and, more recently, much of the Western world, often administered by neo/pseudo-shamans with limited experience in its use.[47] The Western media has also reported a large number of anecdotal stories about ayahuasca's healing potential.[48] Globally, ayahuasca use is increasing[49] and it does not appear that it will slow down any time soon. The complexity of a typical preparation containing *B. caapi* and *P. viridis* has been outlined above. There are at least four active compounds present, all at varying levels per brew.[14] It is also well reported that many other admixtures go under the name of ayahuasca.[49] In addition to the globalization of ayahuasca, combinations of synthetic compounds analogous to ayahuasca have become increasingly popular worldwide. The use of MAO-A inhibitors and tryptamines capable of producing psychedelic effects has been referred to as "pharmahuasca."[44,50] The extent of the pharmacological interactions that may be taking place in ayahuasca are unknown. More research is required to identify the potential risks of use.

Research methods that could further our understanding of how ayahuasca works in the body and lead to better standardization of ayahuasca constituents for practical research purposes are outlined below. Clinical testing should aim to isolate each compound and test them individually at set doses, in line with standardized early-phase testing of multi-target combination drugs. Once achieved, the isolated ayahuasca compounds can be tested in combination with each other, adding in secondary constituents in order of their overall prevalence. Such a methodology would provide a better understanding of the interactions with each compound, as well as the safety and efficacy of combining them. The polypharmacology paradigm is a useful framework within which to consider the multitarget actions of ayahuasca components.

Blending MAOIs (e.g., some β-carbolines) with monoaminergic and serotoninergic substances (e.g., SSRIs, tryptophan, or antidepressants) might result in serotonin syndrome. The irreversible, nonselective MAOIs phenelzine and tranylcypromine are associated with serotonin syndrome, and cases have also been described with opiates, analgesics, tricyclic antidepressants, SSRIs, and antimigraine drugs.[51,52]

There are known interactions between irreversible MAOIs and certain drugs and food. The right combination, including tyramine and MAOIs, can potentially lead to hypertensive crisis and other typical adverse effects.[52,53] Studies with healthy volunteers have shown that non-selective irreversible MAOIs interact more with tyramine than selective reversible MAO-A inhibitors. There is less risk of interaction between tyramine and reversible MAO-A inhibitors than between tyramine and irreversible MAOs.[53,54] However, a study with moclobemide, a reversible MAO-A inhibitor, in healthy volunteers indicated that moclobemide levels during long-term drug administration (300 mg daily) were low and, thus, large fluctuations of drug levels occurred between doses. This suggests that larger doses or more frequent smaller doses, or both, may induce adverse events.[54] As previously described, harmala alkaloids primarily inhibit MAO-A, rather than MAO-B. The effective concentrations for inhibiting MAO-A have been reported as 8 $\times$ 108 M for harmine, 6 $\times$ 10-8 M for harmaline, and 1.4 $\times$ 10-5 M for THH. At higher concentrations, both harmine and harmaline also begin to inhibit MAO-B.[29] Therefore, β-carbolines have a higher selectivity for MAO-A than MAO-B, as well as a lower affinity for liver MAO. High concentrations could inhibit both MAO-A and MAO-B.[55]

Callaway & Grob.[55] reported a case of serotonin syndrome in a patient who used the SSRI fluoxetine in conjunction with ayahuasca. St. John's wort, Ginseng, amphetamine, or the empathogen-entactogen 3,4-methylendioxymethamphetamine ("ecstasy"), dextromethorphan might also have a risky interaction with ayahuasca.[51,52,55-58] Studies have found that harmine is a selective inhibitor of the human cytochrome P450 isozyme 2D6 (CYP2D6), which also metabolizes harmaline.[22,59-61] Adding drugs that inhibit cytochrome isoform CYP2D6 to the therapeutic use of selective SSRIs has been associated with serotonin syndrome.[51,52] Given that drugs such as psilocybin, mescaline and cannabis can also produce significant interactions with ayahuasca,[43,50,52,61] the combined use of DMT-containing ayahuasca and other drugs, such as cannabis and 3,4-methylendioxymethamphetamine, can cause meaningful interactions.[50] Although there is a paucity of literature on the interactions between ayahuasca and cannabis, case reports suggest that possible risks include anxiety and panic reactions, psychotic reactions, and potential cardiac problems.[62] Consumption of either cannabis or ayahuasca alone can, in some cases, produce states of extreme anxiety, panic, or psychosis.[52,63,64] Umut et al.[64] describes a case in which the subject developed psychotic symptoms immediately after consuming a mixture of DMT and cannabis, concluding that DMT worsened the symptoms of previous chronic cannabis use-induced mania. In one reported case, a combination of ayahuasca and cannabis resulted in a psychotic episode[65] in a subject with no history of psychosis. The subject had used cannabis regularly for 6 years prior to the onset of these symptoms. It is possible that the psychoactive properties (e.g., hallucinogenic effects) of both cannabis and ayahuasca are potentiated with combined use. Clinical studies demonstrated a lack of cross tolerance between Δ9-tetrahydrocannabinol (one of the main psychoactive constituents of cannabis) and lysergic acid diethylamide, whose mechanisms of action are similar to and overlap those of DMT.[61,66]

This systematic review has shown that the basic principles of ayahuasca pharmacology have not yet been established. SPECT, positron emission topography, electroencephalogram and functional magnetic resonance imaging could be used where appropriate. Animal studies should aim to use microdialysis following adequate mapping of activation sites. Cerebrospinal analysis could also aid in determining the metabolites of ayahuasca and subsequent changes in neurotransmitter production and neurobiology. At this stage, it is clear that only basic pharmacokinetic and pharmacodynamic principles have been determined. Although absorption, distribution, metabolism and excretion values have been preliminarily outlined by a number of studies listed in this paper, all of these are limited and lack detailed constituent analysis.

Sklerov et al.[67] described the fatal intoxication of a 25-year-old white male following ingestion of 5-MeO-DMT in an ayahuasca preparation. No anatomical cause of death was found at autopsy. Toxicological analysis of heart blood identified N, N-dimethyltryptamine (0.02 mg/L), 5-methoxy-N, N-dimethyltryptamine (1.88 mg/L), THH (0.38 mg/L), harmaline (0.07 mg/L), and harmine (0.17 mg/L). The medical examiner ruled that the cause of death was hallucinogenic amine intoxication and that the manner of death was undetermined. Several cases of intoxication or even death associated with the abuse of 5-MeO-DMT and harmaline have also been reported in humans. In addition, depending on the combined dose, CYP2D6 genotype/phenotype influences harmaline-5-MeO-DMT DDI, despite the fact that the CYP2D6 enzyme inactivates harmaline and activates 5-MeO-DMT.[68] The lack of literature describing the pharmacological and toxicological properties of tryptamine hallucinogens limits assessment of potential harm to public health following 5-MeO-DMT-containing ayahuasca use.

As outlined above, ayahuasca contains at least four primary active compounds, and others may be discovered. Current models simply do not adequately cater for such intricacy. This review shows that two of the constituents, DMT and harmine, have been studied to a greater extent than secondary harmala alkaloids (MAOIs). Based on data from individual constituents, which often show overlapping biochemical pharmacokinetic and pharmacodynamic action, it seems that there are more synergistic mechanisms involved than is currently understood. It is unclear at present whether these actions are of a true synergistic nature.

This systematic review concludes that current pharmacological understanding of the compounds in ayahuasca is limited, and their possible synergistic properties are even less well understood. The results of the included studies suggest that we are not fully aware of the complexity of the processes involved. It is clear that greater effort is required to investigate the pharmacology of the chemical constituents in ayahuasca. Only then can the pharmacokinetic and pharmacodynamic effects of

ayahuasca and its components be better understood and help prevent the potential risks of use.

Disclosure

The authors report no conflicts of interest.

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A citation inaccuracy has been pointed out in the article titled "The pharmacological interaction of compounds in ayahuasca: a systematic review", by Ruffell et al., recently published in the *Brazilian Journal of Psychiatry* (https://doi.org/10.1590/1516-4446-2020-0884) in ahead of print mode. In section "Description of studies," subsection "The pharmacological interaction between DMT and MAOs," fifth paragraph, the authors cite:

"Morales-García et al.[28] studied the impact of harmala alkaloids (vs. a saline control sample) on human hippocampal tissue in vitro, finding that harmine triggers neurogenesis in stem cells."

In fact, the tissues used in the cited study by Morales-García et al. was not obtained from humans, but rather from mice. Therefore, the sentence should read as follows:

"Morales-García et al.[28] studied the impact of harmala alkaloids (vs. a saline control sample) on murine hippocampal tissue in vitro, finding that harmine triggers neurogenesis in stem cells."