SAGE Open Medicine
1: 2050312113508389

DOI: 10.1177/2050312113508389
smo.sagepub.com

Ayahuasca and cancer treatment

Eduardo E Schenberg[1,2]

Abstract

Objectives: Comprehensively review the evidence regarding the use of ayahuasca, an Amerindian medicine traditionally used to treat many different illnesses and diseases, to treat some types of cancer.

Methods: An in-depth review of the literature was conducted using PubMed, books, institutional magazines, conferences and online texts in nonprofessional sources regarding the biomedical knowledge about ayahuasca in general with a specific focus in its possible relations to the treatment of cancer.

Results: At least nine case reports regarding the use of ayahuasca in the treatment of prostate, brain, ovarian, uterine, stomach, breast, and colon cancers were found. Several of these were considered improvements, one case was considered worse, and one case was rated as difficult to evaluate. A theoretical model is presented which explains these effects at the cellular, molecular, and psychosocial levels. Particular attention is given to ayahuasca's pharmacological effects through the activity of *N,N*-dimethyltryptamine at intracellular sigma-1 receptors. The effects of other components of ayahuasca, such as harmine, tetrahydroharmine, and harmaline, are also considered.

Conclusion: The proposed model, based on the molecular and cellular biology of ayahuasca's known active components and the available clinical reports, suggests that these accounts may have consistent biological underpinnings. Further study of ayahuasca's possible antitumor effects is important because cancer patients continue to seek out this traditional medicine. Consequently, based on the social and anthropological observations of the use of this brew, suggestions are provided for further research into the safety and efficacy of ayahuasca as a possible medicinal aid in the treatment of cancer.

Keywords

Ayahuasca, *N,N*-dimethyltryptamine, harmine, cancer, sigma-1 receptor

Introduction

Used for centuries in the Amazon basin by healers and shamans for many different purposes, including the healing and curing of illnesses,[1] ayahuasca is a plant decoction that may be useful in the treatment of some types of cancer. The decoction is most commonly made of two plants in two possible combinations: *Banisteriopsis caapi* with *Psychotria viridis* or *B. caapi* with *Diplopterys cabrerana*.[2] Each of the plants is known by different vernacular names, with the most common shown in Table 1. Photographs of the plants are shown in Figure 1.

There are at least nine reports of cancer patients who consumed ayahuasca during their treatment.[3–10] Four were reported in a peer-reviewed article,[3] one in an institutional magazine,[4,5] one in Internet sources,[6,7] two in a scientific conference[8] (later mentioned in a peer-reviewed article[9]), and one in a book.[10] The origins of these cancers were the prostate, colon, ovaries, breast, uterus, stomach, and brain.[3–10] Three of these cases showed improvements, as measured by the prostate-specific antigen (PSA) or the carcinoembryonic antigen (CEA) level.[4,5,8,9] According to some of these reports, the patients survived longer than initially predicted by their doctors and felt well and healthy. Therefore, it is important to look at these cases in greater detail and investigate the pharmacological and psychological effects of ayahuasca to better understand its potential in the treatment of cancer and to evaluate possible risks of this practice.

Case descriptions

Oral reports of ayahuasca helping people with cancer are common among communities using ayahuasca, but unfortunately, written reports with details and clinical data are scarce. A thorough review of the literature, including peer-reviewed scientific journals indexed at PubMed, as well as lectures and books on the

[1]Departamento de Psiquiatria, Universidade Federal de São Paulo, São Paulo, Brazil
[2]Instituto Plantando Consciencia, São Paulo, Brazil

Corresponding author:
Eduardo E Schenberg, Rua Iraci 340, Jardim Paulistano, CEP 01457-000 São Paulo, SP, Brazil.
Email: eduardoschenberg@gmail.com

Table 1. Common names for the two most frequent forms of ayahuasca concoction, and the source plants in each, with their scientific and vernacular names, as well as main active principles.[2]

Concoction common name	Plants most commonly used	Known active principles
Ayahuasca	*B. caapi* (ayahuasca, caapi, mariri, jagube) + *P. viridis* (chacruna, chacrona, rainha)	Tetrahydroharmine, harmine, and harmaline + *N,N*-dimethyltryptamine (DMT)
Yagé or Yajé[a]	*B. caapi* (ayahuasca, caapi, mariri, jagube) + *D. cabrerana* (chagropanga, chiripanga)	Tetrahydroharmine, harmine, and harmaline + *N,N*-dimethyltryptamine (DMT)

[a]Please note that the Quechua term *Ayahuasca* (*aya* = spirit, ancestor; and *waska* = vine) is largely employed, sometimes referring to *B. caapi* alone, sometimes referring to all forms of the preparation, including some that use only *B. caapi*.

Figure 1. (a) *B. caapi* growing in front of a tree, (b) *B. caapi* flowers, (c) *P. viridis* shrub, (d) *P. viridis* leaves with fruits, (e) preparation of ayahuasca brew at a community in Alter do Chão, Pará, Brazil, in February 2010, (f) detail of *B. caapi* leaves, and (g) detail of *P. viridis* leaves.

topic of ayahuasca resulted in nine published reports of cancer patients who consumed ayahuasca as part of their treatment.

The first and best published report is the detailed case of Donald Topping,[4,5] a former professor at the University of Hawaii and the president of the Drug Policy Forum of Hawaii. Topping was diagnosed with colon cancer around 1988 at the age of 58 and was given a grim outlook for survival. When given a recommendation for immediate surgery, he requested a natural healing approach. A 4-month trial of a natural healing approach was performed. This regimen included "various

substances, vegetarian diet, visualization, exercise and rest,"[4] which resulted in an unexpected negative biopsy, followed by a positive biopsy 2 weeks later, which was performed given the doctor's surprise with the first result. Topping then had the surgery and was determined to be cured 5 years later. However, in September 1996, new examinations revealed cancer of the liver. In this case, the chances of survival were rated 20%–25% by one surgeon and 15% by another, which included the risks of the surgery. Additionally, after the surgery, he would require a year of intensive chemotherapy. Topping had half of his liver removed but refused to start chemotherapy, claiming that the drugs used during and after the surgery were excessive for him. He tried ayahuasca instead of the traditional chemotherapy. He then participated in two sessions of ayahuasca at a Santo Daime church in Hawaii and two shamanic healing sessions in Peru. After these sessions, he returned to an oncologist to discover that his CEA count was unexpectedly below normal. One year after the original report, he published in a new article that the metastatic cancer was still in full remission and responded to some of the many questions raised by his first report.[5] He died in August 2003 at the age of 73.[11]

A second report, from medical anthropologist Aprile Blake, was published online a decade after Topping's pioneering report; unfortunately, no data from clinical examinations were available in the report.[6] After many ayahuasca sessions with Shipibo healers in Peru, Blake claimed to have been cured of a "brain tumor, caused by a chronic degenerative condition, called 'acromegaly' which had dogged me for 20 years"[6] at the age of 37. A detailed account of the striking physical and subjective psychological effects of this treatment was given. Afterward, at the 2011 Ecology, Consciousness and Cosmos meeting at the October Gallery in London,[7] Blake described the inability to cope with the biomedical treatment currently proposed for acromegaly, which consists mainly of irradiating the brain tumor, because the pituitary gland would be damaged and the gland's hormones would be replaced with pharmaceuticals. Fond of holistic and alternative medicine, Blake tried alternative paths that included traditional Chinese medicine, guidance from a Brazilian medium (João de Deus—John of God), and several ayahuasca ceremonies. Blake tried ayahuasca for the first time in Brazil at the age of 34, followed by more sessions in Europe. In October 2008, when her condition was determined to be terminal because the tumor was dangerously close to the optic nerves and the brain stem, which would eventually cause blindness or death, Blake decided to embrace ayahuasca healing in South America (personal communication). She started her search in Ecuador, but the treatment was to be achieved mainly in Peru with Shipibo healers.[6] Although the currently recommended biomedical treatment was not used, Blake is feeling much healthier than before her Shipibo experience. Blake declares that she learned a great deal about herself from the ayahuasca sessions, about her condition, how to cope with stress, and what foods and environments are beneficial or harmful to improving her health. However, afterward, Blake underwent a complete medical examination, which did not reveal a significant improvement in her condition (personal communication). At the Ecology, Consciousness and Cosmos meeting, another patient with acromegaly reported positive experiences with ayahuasca before it was outlawed in Britain,[7] but no additional data about this case were found.

In 2010, four additional cases of ayahuasca use in cancer treatment were reported by Robert Forte.[8,9] The first two cases, which were only anecdotal, were of melanoma and breast cancer. Inspired by these ayahuasca healing stories, Forte accompanied two patients on their travels and to the sessions and clinical examinations. One patient was a 66-year-old psychiatrist with prostate cancer who underwent surgery many years before trying ayahuasca. The surgery brought the PSA level to 0, but it began to rise again 10 years later. The second patient was a 50-year-old schoolteacher with advanced ovarian cancer with metastasis. Both patients had clinical examinations before and after drinking the Amazonian brew for healing purposes with Maestro Juan Flores, an Ashaninka curandero in Peru, who also uses other medicinal plants. The clinical examinations revealed significant improvements in PSA for the first patient and a CEA-125 drop from 4000 to 600 for the second patient.[8] Robert Forte intends to continue bringing interested patients to ayahuasca healers and documenting their stories, which can be a valuable resource for years to come.

In 2010, a peer-reviewed study was published investigating people who tried ayahuasca as a treatment for different illnesses, including cancer.[3] Four cancer patients were identified: a 59-year-old man with prostate cancer, a 40-year-old woman with uterine cancer, a 36-year-old woman with benign uterine myoma, and a 43-year-old woman with stomach cancer. The study does not include many details about each patient, but the inclusion criteria "included a professionally diagnosed disorder by a medical expert."[3] The prostate cancer case was rated as "no effect," the uterine cancer case was labeled a "complete recovery," the uterine myoma case was determined to be "worse," and the stomach cancer case was "unratable" because the patient reported feeling the remission of her cancer but refused to undergo medical examinations. The uterine myoma was accompanied by borreliosis, and the authors determined that this "could also be considered a normal course for her illness."[3] Importantly, independent of any medical examinations or conclusions of being cured or not, all of the patients declared that ayahuasca had a positive impact and none criticized the rituals as negative or worthless. The effects of ayahuasca were frequently described as profound, life-changing and contributing to an individual's general well-being.

The final case reported here is from a musician, Margareth De Wys,[10] who described her journey to heal from breast cancer with a Shuar healer from the upper Amazon in a book. Although she went to the Amazon with a diagnosis with breast cancer, she did not tell anyone there about her disease. However, the Shuar healer was able to "see through" her body and diagnosed the cancer as a "Black Smoke" in her breast.

This resulted in 11 healing trips to South America, mostly in Ecuador, between 2000 and 2003.[10] The healing was centered on the spiritual and healing powers of this Shuar master, ayahuasca, other plants, and diet, which involved avoiding salt and oil and consuming only foods boiled in water. After the trips to heal with the Shuar, De Wys underwent medical examination and no trace of the cancer was found.

Main effects of active principles regarding cancer

The ayahuasca brew is one of the most sophisticated ethnomedicines known, and more than 20 plants have been identified as part of the preparation.[1] However, it is usually made from only two plants, *B. caapi* and *P. viridis* (or *D. cabrerana*, mainly in preparations from Colombia, as shown in Table 1). *P. viridis* and *D. cabrerana* contain *N,N*-dimethyltryptamine (DMT) in the leaves, and *B. caapi* contains β-carbolines such as harmine, harmaline, and tetrahydroharmine in the stem.[1] These harmala alkaloids receive their name from the *Peganum harmala* plant (Syrian Rue), where they were first identified, which is used to treat cancer since ancient times.[12]

Given the increasing number of people drinking ayahuasca in the last decade, especially in urban environments, biomedical studies were conducted in humans, repeatedly demonstrating the safety of consuming this brew in a variety of settings.[13–19]

DMT is a simple molecule found throughout the plant and animal kingdoms. It is found in human blood and cerebrospinal fluid, and its formation has been proposed to occur in adrenal and lung, where high levels of the enzyme responsible for its synthesis—indole-*N*-methyltransferase (INMT)—have been reported.[20] DMT is the only mammalian *N,N*-dimethylated trace amine known[20–25] and the physiological functions of endogenous DMT remain unclear. However, it is well established that DMT has agonist properties at 5-hydroxytryptamine (5-HT) receptors, mainly 5-HT_{2A} and 5-HT_{2C}.[26] Furthermore, it was recently revealed that DMT binds to the sigma-1 receptor,[27] which provides new opportunities for understanding how ayahuasca may produce its marked effects on the body and mind and what might be the role of endogenous DMT and how ayahuasca may have effects on cancer.

The human sigma-1 receptor has been cloned and shows no homology with other mammalian proteins.[28] Single-photon emission tomography (SPET) analysis in humans revealed that these receptors are present in organs such as the lung and liver and most concentrated in the brain.[29] Sigma-1 receptor activity has been implicated in a variety of diseases, including cancer, depression, and anxiety.[30] Sigma-1 receptors are found in high densities in many human cancer cell lines, including lung, prostate, colon, ovaries, breast, and brain; thus, sigma ligands are regarded as potential novel antineoplastic tools.[31] Remarkably, there is much overlap between the tissues identified with high sigma-1 receptor densities and the case reports presented here.

The sigma-1 receptor is a molecular chaperone situated at the mitochondria-associated endoplasmic reticulum (ER) membrane (MAM).[30] The spatial and temporal interaction between the ER and mitochondria is crucial for controlling the fate of the cell through the regulation of calcium dynamics, the control of mitochondrial membrane permeabilization, and the initiation and/or propagation of apoptosis by the activation of the Bcl-2 protein family[32] or by caspase-independent factors, such as apoptosis-inducing factors and endonuclease G.[33] After activation, sigma-1 receptors at the MAM disassociate from the binding immunoglobulin protein (BiP), allowing it to act as a molecular chaperone to inositol 1,4,5-trisphosphate (IP3) receptors, stabilizing them and protecting from degradation by proteasomes.[34] This effect enhances calcium flow from the ER to the mitochondria, activating the tricarboxylic acid (TCA) cycle and increasing the production of adenosine triphosphate (ATP).[34] Importantly, sigma-1 receptors mediate calcium influx to the mitochondria specifically from the ER through 1,4,5-triphosphate receptor type III (IP3R3) but not from the cytosol, which is mediated by 1,4,5-triphosphate receptor type I (IP3R1),[35] indicating a specific mechanism of action for calcium dynamics. When stimulated by higher concentrations of its ligands, sigma-1 receptors may translocate from the MAM to the plasma membrane region. After translocation, it can exert inhibitory effects on many ion channels, including *N*-methyl-D-aspartate (NMDA) receptor modulation through small conductance K^+ (SK) channels,[36] the $K_v1.4$ channel,[37] the $Na_V1.5$ channel,[26] the voltage-gated N-, L-, and P/Q-type Ca^{2+} channels,[38] the acid-sensing ion channel,[39] and the volume-regulated Cl^- channel.[40] The interaction between the sigma-1 receptor and the volume-regulated Cl^- channel may have important implications for cancer because these Cl^- channels modulate the cell cycle and influence cell volume regulation.[40] Also important for cancer treatment may be the $Na_V1.5$ channel, which is expressed in many cancers, including breast and prostate, and is also associated with metastatic processes.[41,42] It is important to note that many of these effects were studied in different cells and tissues; therefore, the sigma-1 receptor roles are most likely tissue dependent. Consequently, cell- and tissue-specific effects are important factors that must be considered in oncology studies related to sigma-1 receptors.

DMT binds sigma-1 receptors with moderate affinity (K_D = 14.75 μM, approximately half the affinity for 5-HT_{1A} and 5-HT_{2A} receptors) and, at high concentrations, is also capable of inhibiting voltage-gated sodium channels.[27] Thus, DMT may exert two types of effects through sigma-1 receptors: at low concentrations, it regulates calcium flow from the ER to the mitochondria, whereas at higher concentrations, it exerts diverse effects at the plasma membrane region.[30] The effect on calcium influx into the mitochondria may be extremely important for cancer treatment given that an energetic imbalance between excessive cytosolic aerobic glycolysis and reduced mitochondrial oxidative phosphorylation (the Warburg effect)

was recently suggested as the seventh hallmark of cancer.[43] This metabolic profile of cancer cells is accompanied by a hyperpolarization of the mitochondrial membrane potential[44] that may be reduced by the calcium influx triggered by DMT binding to the sigma-1 receptor at the MAM. This effect may facilitate the electrochemical processes at the electron transport chain inside the mitochondria, thus increasing the production of reactive oxygen species (ROS) and leading these cells to apoptotic pathways.[43] When high DMT concentrations induce sigma-1 receptor translocation to the plasma membrane, many cellular effects would occur due to the receptor's interaction with different ion channels. At high concentrations of DMT, a calcium influx and mitochondrial membrane depolarization might be enough to also activate the permeability transition pore (PTP), inducing mitochondria swelling, rupture, and apoptosis.[45]

For all these effects to help explain the available case reports of ayahuasca on cancer treatment, DMT's physiological degradation by enteric monoamine oxidase (primarily MAO-A) after oral consumption should be inhibited, thus allowing the DMT to pass into circulation. The pharmacological activity of β-carbolines (primarily harmine) in ayahuasca inhibits MAO, with a high affinity for MAO-A.[46] Therefore, the specific effects of ayahuasca on the different types of cancer could also vary depending on the predominant MAO subtype, given that the ratio of MAO-A to MAO-B varies, for example, from 1:3 in the brain to 4:1 in the intestine,[47] and the placenta has only MAO-A and blood platelets have only MAO-B.[48] Another consequence of inhibiting MAO in different tissues is interference with apoptotic pathways,[48] thus strengthening the synergistic action of β-carbolines and DMT.

In addition to allowing DMT to exert its effects on cancer tissues and cells, β-carbolines may have other important roles. It was recently demonstrated that harmine activates pathways of apoptosis in B16F-10 melanoma cells;[49] it inhibits tumor-specific neo-vessel formation, both in vitro and in vivo in mice, through a series of mechanisms involving decreased serum levels of pro-angiogenic factors and an increase in antitumor factors[50] and displays an inhibitory effect on cell proliferation against human carcinoma cells.[51] Harmine and harmaline were also shown to reduce cell proliferation in the human leukemia cell line HL60.[52] Harmine was also shown to induce apoptosis in the human hepatocellular carcinoma cell line HepG2.[53] Harmine may also be beneficial in cancer treatment due to its inhibitory effect on the DYRK1A kinase.[54] This kinase is implicated in the resistance of many cancerous tissues to pro-apoptotic stimuli and the enhancement of proliferation, migration, and reduced cell death.[55] Another pharmacological effect of harmine that may be important in brain cancer is its role on the EAAT2 glial glutamate reuptake transporter.[56] Harmine was identified as one the most efficient molecules to upregulate this transporter in glial cells among a library of 1040 Food and Drug Administration (FDA)-approved substances.[56] This fact may be of importance because most brain tumors are of glial origin and involve excessive glutamate release, causing neurotoxicity.[57] Also important for gliomas may be the binding of harmine to imidazoline I2 receptors.[58] These receptors are highly expressed in gliomas,[59] and their density increases with malignancy in human cells.[60] However, their physiological role in these tissues remains unclear.

Nonetheless, care should be taken because there are also some contradictory reports regarding possible genotoxic or mutagenic effects of β-carbolines in different experiments with cell cultures. Although some of these reports focus specifically on harman and horhaman,[61] which are not found in ayahuasca preparations, others included research into harmine and harmaline. For example, it has been reported that harmine and harman are genotoxic in V79 Chinese hamster fibroblasts[62] and may induce DNA lesions in *Saccharomyces cerevisiae* cell lines.[63] On the contrary, it was found that harman and harmine do not induce chromosomal alterations in *Salmonela typhimurium* and *Escherichia coli* cell lines[64] and that harmine and harmaline may even have antimutagenic and antigenotoxic activities related to their antioxidant properties.[65] It was also shown that harmine may inhibit tumors as assessed by Lewis Lung Cancer and S180 cell lines, although with some toxic effects.[66]

Physiological effects of human consumption of ayahuasca

To explain ayahuasca's effects on cancer, plant constituent concentrations, concentrations in different ayahuasca preparations, plasma levels and issues of bioavailability, clearance, and volume of distribution must be considered. The present results do not offer enough data to make any definite conclusions, but some important considerations can be made. Variability in the concentration of the major molecules in the brew was reported.[67] The plasma concentrations of harmine were highly variable ranging from approximately 5.0 ng/mL[68] to 114.8 ± 61.7 ng/mL (mean ± standard deviation (SD)),[69] with one study failing to detect harmine in the plasma after consumption of freeze-dried, encapsulated ayahuasca.[70] The doses used in these studies were mainly determined by the DMT content in the original tea, but the available data showed that the harmine content was approximately 1.5 mg/kg. This value is lower than the 10 mg/kg dose used in the studies of harmine on cancer in rodents[50] but caution must be exercised when comparing studies conducted in rodents with humans. Additionally, ayahuasca consumption by humans usually involves more than one dose per session, and in some therapeutic cases, many doses and sessions are conducted over time, with plasma levels potentially reaching much higher values than observed in the laboratory. The plasma concentrations of DMT were measured in a series of published reports. The C_{max} values (mean ± SD) ranged from 15.8 ± 4.4 ng/mL[69] to 17.44 ± 10.49 ng/mL,[68,70] with a peak at 32.57 ± 20.96 ng/mL[17] in the first study using

two repeated doses of ayahuasca in a laboratory environment. This range on the order of nanogram per milliliter seems low compared with the concentrations in the original brew used in these studies: 0.24 mg/mL[69] and 0.53 mg/mL.[17,68,70] In addition, in comparison to a K_i of 14 μM in the in vitro experiment showing DMT's action on sigma-1 receptors,[27] the detected plasma concentrations may be low. To estimate the bioavailability of DMT after ayahuasca consumption, the data from blood collected after ayahuasca ingestion and the data from intravenous DMT were combined and a tentative value of 10%–15% was determined.[71] Furthermore, the important differences between the data from oral ayahuasca consumption and intravenous DMT originated from different experiments with a limited number of subjects; this suggests that only a small amount of DMT in the brew reaches systemic circulation, posing challenges regarding DMT metabolism that remain unresolved. With the inhibition of MAO, DMT can be metabolized to DMT-*N*-oxide both in vitro and in vivo; this metabolite was recently found in urine[72] and blood[73] after freeze-dried ayahuasca administration to human volunteers. The metabolization of DMT to DMT-*N*-oxide still leaves considerable amounts of DMT available in the blood;[73] however, the amount is low compared with the K_i of DMT at sigma-1 receptors and the administered doses of DMT. One possible solution for this dilemma comes from a recent in vitro discovery that DMT exhibits substrate behavior at the serotonin uptake transporter (SERT), with a K_i value of 4.00 ± 0.70 μM (mean ± SD), and also at the vesicle monoamine transporter (VMAT2), with a K_i value of 193 ± 6.8 μM.[74] This mechanism of sequestering DMT to the intracellular space may be responsible for the discrepancy in plasma concentrations between ayahuasca ingestion and in vitro studies. Recently, other authors suggested this same mechanism to explain how DMT concentrations may reach higher values inside the cells than in the blood, through a "three-step mechanism"[75] involving active transport of DMT through the blood–brain barrier, transport across cells membrane via SERT, and finally a sequestration into synaptic vesicles mediated by VMAT2.[75] These same authors also highlight possible antitumor effects of DMT through regulations of the immune system, such as increased numbers of circulating NK-cells and production of interferons and argue that the downregulation of the INMT gene (*Inmt*) in malignant prostate and lung cancers might also point to an important role of DMT, the *Inmt* final product, in suppressing tumors in these tissues.[75] Corroborating these suggestions of positive interactions of DMT with the immune system in cancer, a recent study has shown that DMT inhibits the indoleamine 2,3 dioxygenase enzyme. This enzyme, when upregulated, is associated with malignant cells escaping immune surveillance, and thus DMT may help increase immune functions against malignant cells.[76]

Importantly, as the in vitro results were obtained from specific cell lineages, differences between various human tissues in DMT kinetics should be expected. A specific mechanism for how DMT enters cells is also important in regard to its possible effects on sigma-1 receptors, given that these are intracellular proteins. Recently, a study of radiolabeled DMT injected intravenously in rabbits revealed that DMT reaches the brain rapidly (10 s) and is also detected primarily in the heart and liver.[77] Although DMT was not detected in the urine after 24 h, it was still present in the brain after 48 h and was found in small amounts (0.1 %) 7 days after the injection; this corroborates the idea that DMT is rapidly absorbed in some tissues and cleared from the blood. The rapid clearance, metabolism, and transport of DMT through the cell membrane makes it difficult to obtain clinical data about DMT in humans; however, it is a reminder of the physiological safety of the use of this naturally occurring substance, whose metabolism is finely regulated in the human body.

In summary, it is hypothesized that the combined actions of β-carbolines and DMT present in ayahuasca may diminish tumor blood supply, activate apoptotic pathways, diminish cell proliferation, and change the energetic metabolic imbalance of cancer cells, which is known as the Warburg effect (Figure 2). Therefore, ayahuasca may act on cancer hallmarks such as angiogenesis, apoptosis, and cell metabolism. This hypothesis gives some scientific credibility to the cases reported and supports the realization of more scientific studies of ayahuasca and cancer. However, to improve the safety and efficacy of those who eventually search the use of ayahuasca for the treatment of cancer, more studies should be performed considering the remarkable psychological effects of the ritual use of ayahuasca and its possible influences on cancer patients.

Psychological effects of the ritual use of ayahuasca

Ayahuasca has very powerful psychological effects, generally described as psychedelic effects. These experiences, in general and with ayahuasca, evoke powerful subjective perceptions and feelings, which are usually termed "hallucinogenic" in the medical and scientific literature but held in high regard by ancient cultures that consider these experiences as sacred. Apart from cultural discrepancies reflected in the meaning and terminology for these experiential states, these experiences include the perception of colored and vivid images with eyes closed, the exacerbation of emotions, feelings of numinousness, peacefulness, insights, or distressing reactions, and the triggering of deep, transformative spiritual experiences.[78] The complete outcome of the experience is highly dependent on the context and meaning attributed to it. These characteristics, known as *set and setting*, are important in understanding the complete healing effects of ayahuasca. The *set* is a complex and dynamic composition of the personal motives, purposes, intentions, and beliefs of the person, as well as the physical characteristic, genetics, and the emotional and cognitive state at the time of the experience. The *setting* includes

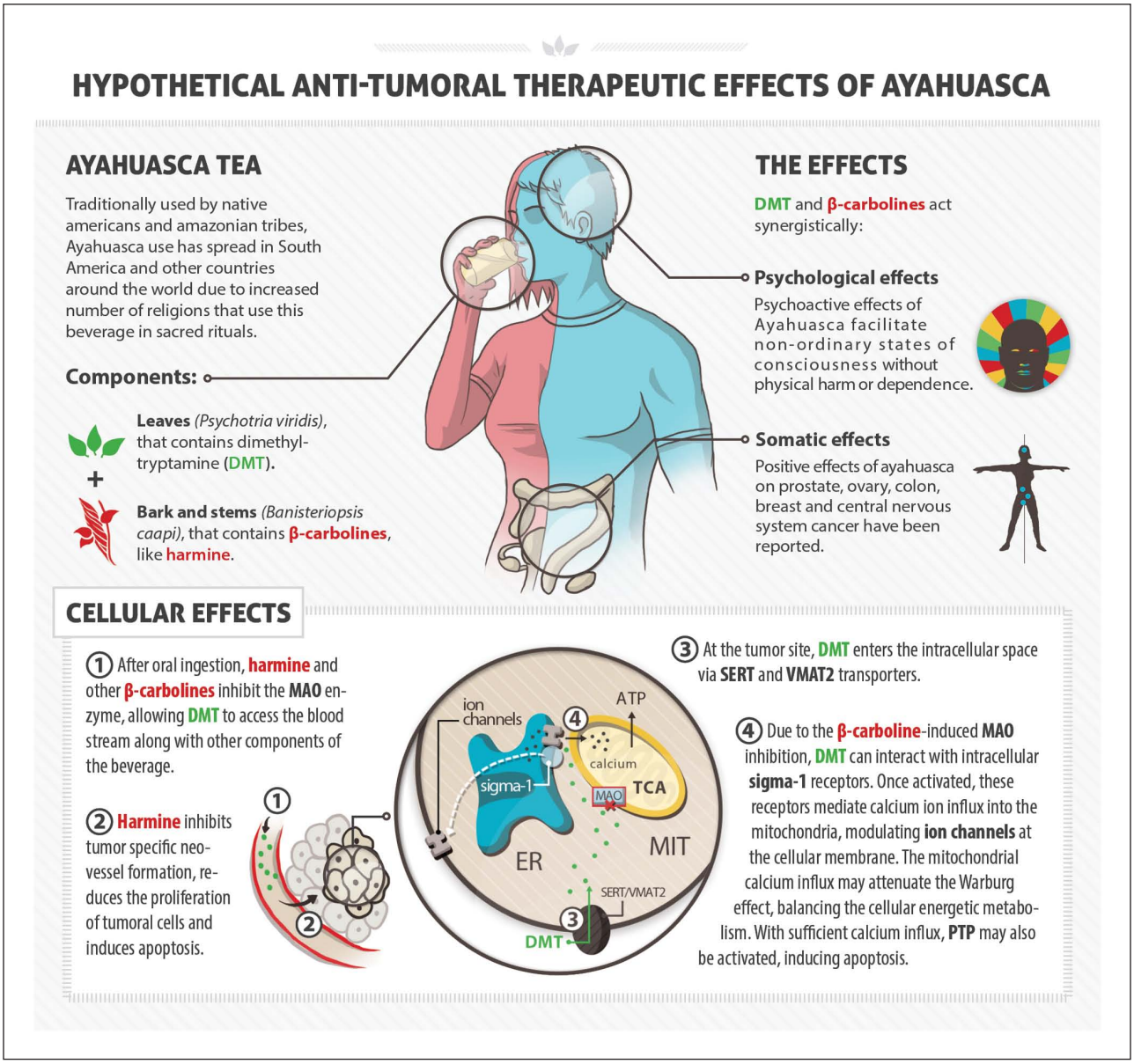

Figure 2. An explanatory model of ayahuasca's effects in cancer treatment.
ATP: adenosine triphosphate; DMT: *N,N*-dimethyltryptamine; ER: endoplasmic reticulum; MAO: monoamine oxidase; MIT: mitochondria; PTP: permeability transition pore; SERT: serotonin uptake transporter; TCA: tricarboxylic acid cycle; VMAT2: vesicle monoamine transporter.

things such as the physical environment where the experience is to occur, the person(s) who will be guiding the experience, and the person(s) who will be accompanying the experience. Both *set and setting* can occur in short and long time frames and include the preparations before and the activities after the experience itself.[79] Thus, *set and setting* may also be described as the who, what, where, when, how, and why of the experience. A careful approach considering these factors is crucial if any psychedelic experience or therapy is to succeed, as clearly demonstrated by the classic experiments using lysergic acid diethylamide (LSD) to treat alcoholism during the 1950s[79] and as highlighted recently.[80]

The idea of considering other variables in cancer treatment, such as *set and setting*, emotions, patient beliefs, cultural values, and spiritual experiences, is not a new and radical suggestion; it is part of some alternative cancer treatment approaches for many years. These include the method pioneered by Simonton et al.,[81] which employs visual imagery, later popularized by other authors,[82] the model known as the Bonny Method of Guided Imagery,[83,84] and also other approaches that employ imagery[85,86] (for a critical review of guided imagery as an adjuvant cancer therapy, see Roffe et al.[87]). These imagery techniques may be especially important regarding ayahuasca in the treatment of cancer,

given that visual imagery is a common phenomenon during ayahuasca sessions, where visualizations are strongly potentiated due to the powerful effects of ayahuasca on visual imagery, with brain activations, as measured by functional magnetic resonance imaging (fMRI), reaching the occipital pole, including primary cortical visual areas.[88] Other alternative cancer treatment techniques employ music therapy,[84,89] and this may be also important to consider, given that music has a central role in ayahuasca ceremonies.[90]

The original model proposed by Simonton et al., as well as some of the others mentioned, focuses on specific psychological interventions to evaluate beliefs and attitudes and minimize distress, emotional pain, depression and anxiety, thus aiming to improve the quality of life.[81] Issues such as hope, purpose, and spiritual beliefs are considered,[81] resembling the *set and setting* approach of responsible and informed psychedelic science and of some carefully performed ayahuasca healing ceremonies. This holistic approach to treat cancer is also in agreement with the proposition that therapeutics with ayahuasca work in three domains: psychological, spiritual, and organic.[91] According to these authors,[91] ayahuasca "is a disinhibitor of energy blockages perceived as thoughts at a mental level, as feelings at an emotional level, and as symptoms at the physical body."[91] Even the spiritual experience, a more controversial topic from a Western scientific point of view, has recently been shown to be regularly, safely, and reproducibly induced by another psychedelic tryptamine, 4-phosphoryloxy-DMT, or psilocybin, which is structurally similar to DMT.[92] In fact, DMT was shown to trigger powerful spiritual experiences when injected in normal volunteers,[93] and psilocybin was recently shown to be effective in treating anxiety in advanced-stage cancer patients.[94] Therefore, a holistic approach to cancer treatment that includes the ritualistic or religious use of ayahuasca may help not only to treat the organic aspects of the cancer but also to treat anxiety, depression, and associated psychological conditions and to improve the patient's quality of life, survival time, and, ultimately, their quality of death and dying.

In this regard, ayahuasca, which translates to "vine of the soul" (see Table 1), may have important effects, given the observed benefits of psychedelic experiences in alleviating fear of death and dying.[95–99] This alleviated fear is important not only to patients but also to families and doctors, given the repressive culture western medicine has developed toward death.[99] This repression becomes a very important aspect of cancer treatment, once that many of these patients will, inevitably, face the final transition, which in the current culture is dealt with very anxious behaviors marked by professionals shying away from dealing with the subject in order to help the patient to accept the inevitable. This anxious situation can be soothed by guided psychedelic experiences[95–99] and probably through well-guided ayahuasca rituals, as reported by some of the cancer patients whose cases were reviewed here.[4–6]

To further test the hypothesis presented here that ayahuasca may have important effects in helping to treat cancer, data should be gathered from many different fields. The systematic collection of more case reports, with detailed clinical data, would help elucidate which types of tumors ayahuasca may provide beneficial effects. Furthermore, it is important to consider when ayahuasca was used in the time course of the disease. Systematically gathering more cases may also uncover negative results that were unreported, due to patients who may have been discouraged to discuss a treatment that did not help them. This factor could also reveal the possible risks of physically ill patients, some having undergone surgery, consuming ayahuasca. It should be noted that apart from the chemical differences between ayahuasca and other psychedelic substances, such as LSD and *N,N*-dipropyltryptamine (DPT), they were used with cancer patients to treat anxiety and depression and were well tolerated. The adverse effects observed in these patients were reported as manageable and similar to the effects observed in physically healthy individuals.[98,99] Experiments with ayahuasca's active principles both individually and in combination with cell and tissue cultures are important. Further studies need to be conducted to confirm which cell lineages and tissues are more susceptible to ayahuasca and to evaluate the possible role of ayahuasca in cancer treatment. These efforts would be important to validate safety and efficacy for patients seeking this alternative treatment.

To advance the ideas put forward in this article, scientists must overcome common misconceptions about shamanism[100] and should engage with healers in a clear dialogue to foster communication and develop common research projects.[101] This approach might help to improve the treatment available for and the quality of life of cancer patients and to avoid the possible underreported dangers of ayahuasca use by cancer patients, such as the dangers of the so-called drug tourism[102] and issues created by outlawing ayahuasca, such as preventing safe contexts for use and fostering the dangerous practices of drug tourism. A holistic framework, such as the one presented here, may indeed spark even more interest in ayahuasca use, especially by cancer patients, and thus, to increase safety and efficacy, a responsible approach is necessary.[103,104] Ayahuasca use for healing purposes is not allowed in most countries. Legislation tends to interfere with *set and setting* issues; in a prohibitionist culture, both *set and setting* are negatively affected because of anxieties, prejudices, and fears related exclusively to the penalties of infringing the law or using an unconventional healing path. If ayahuasca is scientifically proven to have the healing potentials long recorded by anthropologists, explorers, and ethnobotanists,[105] outlawing ayahuasca or its medical use and denying people adequate access to its curative effects could be perceived as an infringement on human rights, a serious issue that demands careful and thorough discussion. In view of the current expansion of ayahuasca use, careful international regulation may also help to reduce the harm and maximize the benefit of ayahuasca use.[103]

In conclusion, the data available so far is not sufficient to claim whether ayahuasca indeed helps in cancer treatment or not. However, there is enough available evidence that ayahuasca's active principles, especially DMT and harmine, have positive effects in some cell cultures used to study cancer, and in biochemical processes important in cancer treatment, both in vitro and in vivo. Therefore, the few available reports of people benefiting from ayahuasca in their cancer treatment experiences should be taken seriously, and the hypothesis presented here, fully testable by rigorous scientific experimentation, helps to understand the available cases and pave the way for new experiments.

Acknowledgements

The author would like to thank Fabrício Pamplona and Sidarta Ribeiro for their valuable comments on earlier versions of the manuscript; Brian Anderson for his help with English language revisions; Denizar Missawa Camurça, Marcelo Simão Mercante, Maria Betânia Barbosa Albuquerque, and Clara Novaes for the photographs included in Figure 1; Dartiu Xavier da Silveira for his help with ayahuasca studies in general and with publishing costs in particular, and Aprile Blake for her generous personal communication and efforts to assist with further investigations.

Declaration of conflicting interests

The author declares that there is no conflict of interest.

Funding

This work was financed by Fundação de Amparo à Pesquisa do Estado de São Paulo—FAPESP.

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