The Psychotria Link

Phytochemical studies of *Psychotria* and *Calycodendron*

The isolation of *Psychotria*-based alkaloids was an important finding that opened new doors to the chemical understanding of this genus. For instance, investigations of a shrub from Vanuatu, *Psychotria forsteriana*, discovered alkaloids with potent anticancer potential (Roth et al. 1986; Adjibade et al. 1989). Later, analgesic alkaloids with opioid-like properties were found in an Amazonian herb, *Psychotria colorata,* which was traditionally used to ease abdominal distress or earache (Amador et al. 1996; Verotta et al. 1998 and 2002). This inspired a more comprehensive review of the genus, with various Central and South American *Psychotria* species demonstrating analgesic properties.

Investigations were extended to include *Psychotria* species across the world, some of which exhibited good antimicrobial activity e.g. *Psychotria gardneri* and *P. stenophylla* (Sri Lanka); *P. beccarioides* and *P. microlabastra* (New Guinea) (Jayasinghe et al. 2002; Khan et al. 2001). Many were also evaluated for their cytotoxic and anticancer potential e.g. *Psychotria forsteriana, P. klugii, P. serpens, P. spectabilis, P. camponutans, P. leptothrysa* var *longicarpa, P. rubra* and *P. ophioxyloides.* Overall merely 41 species (from around 2000) have been chemically evaluated, resulting in the isolation of 159 compounds (Yang et al. 2016) - among these are at least 70 different indole alkaloids, which confirms the exceptional bioactivity of these plants (Carvalho Junior et al. 2017). Despite this, we know very little about the medicinal and chemical values of genus as a whole.

The search expanded to related Rubiaceae species in the Pacific ie. *Psychotria oleoides* (New Caledonia) and a unique Vanuatu endemic *Calycodendron milnei.* The evaluation of a rare shrub from northern Australia, *Hodgkinsonia frutescens* discovered interesting bioactive alkaloids, notably hodgkinsine, with quadrigemines as minor components (Parry and Smith 1978; Anet et al. 1961). Subsequent investigations revealed potent antibacterial, antifungal and anti-candida activity that, in some instances, were comparable to conventional antibiotics (Saad et al. 1995; Adjibade et al. 1990).

Given the potent activity of these compounds, it is unsurprising to find that many traditional uses of the *Psychotria* genus involve antimicrobial, wound healing and analgesic effects:

- The leaves of a Papua New Guinean *Psychotria* were chewed with Betel nut (*Areca catechu*) for toothache, as well as being applied locally to heal bites from pigs (Weiner 1985).
- In Chinese medicine the leaves of Wild Coffee (*Psychotria rubra*) were applied to traumatic injuries, fractures, snakebite, bleeding wounds, skin infections (pyoderma) and leg ulceration. The decoction (root or fresh young leaves) has been taken for respiratory tract infections (diphtheria, tonsillitis, pharyngitis), dysentery, rheumatic bone pain and lumbago (Cheung 1983).
- The Creeping Psychotria (*Psychotria serpens*) has been utilised as an antirheumatic, muscle relaxant and analgesic. In Chinese traditions a remedy (taken orally) for multiple abscesses decocted the fresh herb with *Polygonum perfoliatum* in water and wine (Cheung 1983). Extracts show antileukaemic activity, with the isolation of ursolic acid as an active component (Yang et al. 2016)
- In the Philippines *Psychotria luconiensis* (syn *P. luzoniensis*) was taken for dysentery, while *Psychotria mindorensis* (leaf infusion) was employed for eye troubles, cleansing ulcers and wounds, as well as being applied topically for headaches (Quisumbing 1951).
- *Psychotria hawaiiensis* is a Hawaiian treatment for wounds and injuries. Extracts have selective antiviral (anti-HIV) and antimicrobial activity, including good antifungal properties against skin fungi (Locher et al. 1995 and 1996).

Evaluations of *Psychotria* continue to explore the analgesic and neuroprotective properties of these herbs for the treatment of disorders such as Alzheimer's disease, Parkinson's and multiple sclerosis. Species that act via MAO inhibition, which affect mood and mental function, have a high priority e.g. *Psychotria myriantha, P. suterella, P. laciniata, P. umbellata* and *P. viridis*. Indole and β-carboline alkaloids have attracted a lot of interest (Klein et al. 2014; Passos et. al. 2013). The evaluation of the anti-Alzheimer's potential of folicanthine (a calycanthaceous alkaloid) could well attract further interest (Yang et al. 2016; Wiart 2012).

In addition, research has revealed the presence of cyclotides in various *Psychotria* species (*P. brachiata, P. capitata, P. deflexa, P. poeppigiana, P. solitudinum, P. suerensis*) and closely related Rubiaceae species such as the well-known Ipecac (*Carapichea ipecacuanha*) – as well as *Chassalia curviflora, Notopleura capacifolia* and *Palicourea tetragona*. Cyclotides with protease-inhibition activity against POP (human prolyl oligopeptidase) have been suggested to have neuroprotective, anti-amnesic and cognition-enhancing properties (Helliger et al. 2015).

It is, however, worth noting that the toxin monofluroacetate has been found in the genus *Palicourea* and *Psychotria* (Cook et al. 2014) and, although there does not appear to be any record of its presence in Australian *Psychotria*, it is found in *Acacia georginae* and the native species of *Gastrolobium* and *Oxylobium* (see McKenzie 2012; Williams 2012). The cardiac toxin pavettamine has also been found in the Rubiaceae family including *Psychotria kirkii* (tropical Africa) and *P. viridiflora* (Malaysia) (Van Elst et al. 2013).

Table 3.0 Phytochemical studies *Psychotria* and *Calycodendron* (Rubiaceae) focusing on medicinal potential and alkaloid components

Species (geographic source)	**Component or extract/plant part: activity**	**References**: *Psychotria* chemical reviews see Yang (2016) and Calixto (2016)
Psychotria **(Rubiaceae)**		
Psychotria acuminata (Central/South America)	Indole alkaloids (vallesiachotamines): nervous system activity (MAO and ChE inhibition)	Calixto et al. (2016); Yang et al. (2016)
	Alkaloid: stictosidinic acid (MAO inhibition) with antidepressant potential	Perviz et al. (2016)
Psychotria ankasensis (Ghana, Africa)	Extract: antidepressant, anti-anxiety supporting traditional use for nervous disorders	Armah et al. (2021)
Psychotria apoda (Central/South America)	Extract (and indole alkaloids): antiplasmodial (antimalarial) potential; high level of parasite growth inhibition	Gontijo et al.(2021)
Psychotria brachyceras (Central/South America)	Extract: analgesic	Gregianini et al. (2003); do Nascimento et al. (2007); Calixto et al. (2016)
	Brachycerines: anti-inflammatory, antioxidant, radioprotective and antimutagenic properties	
	tryptamine-iridoid alkaloids	Berger et al. (2015)
Psychotria brachypoda (Central/South America)	Alkaloids: analgesic, opioid-like activity; sedation and significant reduction of body temperature	Leal & Elisabetsky (1996a)
	tryptamine-iridoid alkaloids	Berger et al. (2015)
	Extract: anticancer potential (antiproliferative); chemoprotective (active against glyphosate toxicity)	Frescura et al. (2013)
Psychotria buchtienii (Andes, South America)	Extract: antiparasitic, anti-leishmania activity	Cardona-G et al. (2020)
Psychotria calocarpa (Bangladesh)	Extracts: neuropharmacological (anti-anxiety, antidepressant), analgesic, antidiarrhoeal and antioxidant activity	Bristy et al(2020)
Psychotria camptopus (Cameroon, Africa)	Extracts (flavonoids, alkaloids including hodgkinsine, emetine): substantial antioxidant neuroprotective, anticonvulsant activity; used in traditional medicine for treatment of epilepsy	Fokoua et. al. (2021a & 2021b)

Psychotria capensis (South Africa)	Extract: anti-mycobacterial (anti-tuberculosis potential) and anti-inflammatory	Aro et al. (2019)
	Extract: cosmetic potential, moderate skin ageing signs (anti-elastase, anti-hyaluronidase activities); used in traditional medicine for treating gastric disorders	Ndlovu et al. (2013)
Psychotria capillacea (Brazil, South America)	Extracts (and phenolic components, p-coumaric acid): antioxidant	Formagio et al. (2014)
Psychotria capitata (Brazil, South America)	Extract: insecticidal against Maize weevil	Tavares et.al.(2013)
	Extract: potent cytotoxic activity (anti-tumour potential)	Da Silva et al. (2016)
Psychotria carthagenensis (Central/South America)	Extract: sedation and significant reduction of body temperature	Leal & Elisabetsky (1996b)
	Herbal mixture: Ayahuasca component, contains DMT	McKenna et al. (1984); Formagio et al. (2014)
	Extracts (and phenolic components, p-coumaric acid): antioxidant	Formagio et al. (2014)
Psychotria colorata (Central/South America)	Alkaloids: analgesic activity; opioid-like chimonanthines i.e. chimonanthine, hodgkinsine, calycosidine and psychotridine are present; also calycanthine and quadrigemines	Amador et al. (1996 & 2000); Verotta et al. (1998 & 2002); Calixto et al. (2016)
	Alkaloid: hodgkinsine shows antiviral, antibacterial, antifungal, analgesic and spasmolytic activity	
	Extract (and indole alkaloids): antiplasmodial (antimalarial) potential; high level of parasite growth inhibition	Gontijo et al.(2021)
Psychotria deflexa (now *Palicourea deflexa*) (Brazil, South America)	Extracts: β-carboline alkaloids (AChE inhibition); also bioactive cyclotides are present that have potential neuroactive properties	Hellinger et al. (2015); Bertelli et al.(2017)
Psychotria forsteriana (Vanuatu)	Alkaloids: quadrigemines A and B, psychotridine and isopsychotridine show cytotoxic activity; psychotrimine and psychopentamine also present	Roth et al. (1986); Adjibade et al. (1989); Calixto et al. (2016)
	Alkaloids: hodgkinsonine, calycanthine, iso-calycanthine, meso-chimonanthine, vatine, vatamine and vatamidine	
Psychotria goyazensis (Brazil, South America)	Extract: insecticidal against Fall armyworm moth	Tavares et.al.(2013)
Psychotria graeffei (Samoa)	Extract: antibacterial activity with wound healing potential	Frankova et al. (2021)
Psychotria hawaiiensis (Hawaii)	Extract: antifungal activity, active against skin fungi i.e. *Microsporum, Trichophyton* and *Epidermophyton*; also selective anti-viral activity	Locher et al. (1995 & 1996)
Psychotria hoffmannseggiana (Brazil, South America)	Extract: insecticidal against Maize weevil	Tavares et.al.(2013)

Psychotria insularum (Samoa)	Extract: antibacterial activity with wound healing potential	Frankova et al. (2021)
Psychotria ipecacuanha (now *Carapichea ipecacuanha*) (Central/South America)	Alkaloids: two main pharmacologically active components emetine and cephaeline (at least 90% of the alkaloids present); psychotrine also present	Chaves Valadao et al. (2015)
	Cephaeline: cytotoxic (significant activity) and antiparasitic with potent activity against *Leishmania* parasites and antimalarial anti-plasmodial activity	Yang et al. (2016)
	Emetine: anticancer (induce apoptosis), anti-leukaemic; anti-amoebic and anti-leishmania activity (toxic potential is higher than that of cephaeline)	Moller et al. (2007); Moller & Wink (2007); Yang et al. (2016)
	Emetine (and derivatives): used clinically as an emetic, expectorant, anti-amoebic (for dysentery and human fascioliasis); also shows spermicide (emergency contraceptive) potential; recent studies indicate anticancer (leukaemia, neuroendocrine tumours) and antiviral (HIV-1inhibition) activity	Chaves Valadao et al. (2015)
Psychotria klugii (Central/South America)	Alkaloids: klugine, emetine, cephaeline, isocephaeline etc.	Calixto et al. (2016)
	Klugine: potent antimalarial activity	Muhammad et al. (2003)
Psychotria lanciniata (Central/South America)	Alkaloids: vallesiachotamines and angustine with nervous system activity (MAO and cholinesterase inhibition)	Dos Santos Passos et al. (2013); Yang et al. (2016)
Psychotria leiocarpa (Brazil, South America)	Extract (indole alkaloids, vincosamide): anticholinesterase activity and anti-inflammatory	Formagio et al. (2019)
	Vincosamide: antioxidant stress protection against wounds, UV exposure, and other environmental stresses	McKenna et al. (1984); Matsuura & Fett-Neto et al. (2013); Formagio et al. (2014)
	Alkaloids: anti-tumour activity; acetylcholinesterase (AChE) inhibition	Volobuff (2019)
Psychotria luzoniensis (Philippines)	Glycosides: cytotoxic activity	Ramil et al. (2020)
Psychotria lyciiflora (New Caledonia)	Alkaloids: hodgkinsine and chimonanthines with substantial antiviral and analgesic properties	Jannic et al. (1999); Amador et al. (2000); Yang et al. (2016)
Psychotria malayana (Indo-Chinese region, Malaysia, Indonesia)	Alkaloids: chimonanthines, calycanthine and hodgkinsine	Calixto et al. (2016)
	Extract: antidiabetic (anti-hyperglycaemic, blood sugar regulation)	Benchoula et al. (2019); Nipun et al. (2020a & 2020b)
Psychotria microphylla (Africa)	Extract: flavonoid-rich (quercetin) shows antioxidant, chemoprotective (against heavy metal toxins) and hepatoprotective properties	Orji et al. (2020)
Psychotria myriantha (Central/South America)	Extract: analgesic, antipyretic and anti-inflammatory	Farias et al. (2010 & 2012)
	Alkaloid: strictosidinic acid influences neurological function (MAO inhibition), also analgesic and antipyretic	Calixto et al. (2016)
Psychotria nemorosa (Central/South America)	Indole alkaloids: affect neurological function: (MAO and cholinesterase inhibition)	Klein-Junior et al. (2016 & 2020)
Psychotria nilgiriensis (India)	Extracts (fruit and root): antioxidant and have a wide spectrum of antibacterial activity with the fruit showing best activity against *Klebsiella pneumoniae*	Devadoss et al. (2013)
Psychotria nuda (South America: Brazil)	Extract (alkaloids): antimycobacterial (anti-tuberculosis potential) and anti-inflammatory	De Carvalho Junior et al. (2019)
Psychotria oleoides (New Caledonia)	Alkaloids: hodgkinsine with analgesic properties	Jannic et al. (1999); Amador et al. (2000); Yang et al. (2016)

	Alkaloids: quadrigemines show antimicrobial activity	
	Alkaloids: psycholeine and psychotridine possess analgesic, antiplatelet aggregation and cytotoxic properties; isopsychotridine also present	
Psychotria pilifera (China)	Strychnine alkaloids: antimicrobial with potent activity against *E. coli*	Liu et al. (2016)
Psychotria prainii (Vietnam)	Extract: significant anti-inflammatory activity	Tran et al. (2019)
Psychotria prunifolia (Central/South America)	Prunifoleines: affect nervous system (MAO and ChE inhibition)	Yang et al. (2016)
	Alkaloids: antiprotozoal, showing activity against *Leishmania*	Kato et al. (2012 & 2018)
Psychotria reevesii (Southeast Asia, China)	Extract: antibacterial with activity against *S. aureus*, *Shigella* species, *Ps. aeruginosa*, but not active against *Candida* or *E. coli*	Giang et al. (2007)
Psychotria rostrata (Malaysia)	Alkaloids: quadrigemine, psychotrimine and psychopentamine; quadrigemine B was bactericidal against *E. coli* and *S. aureus*	Mahmud et al. (1993); Calixto et al. (2016)
Psychotria sarmentosa (Sri Lanka)	Extract: traditionally used for treating trauma and injury; potent analgesic activity	Ratnasooriya & Dharmasiri (1999)
Psychotria serpens (China)	Extract: antiviral and cytotoxic	Yang et al. (2016)
	Extract: anticancer potential	Wang et al. (2019); Wang et al. (2020)
	Ursolic acid (triterpenoid): anticancer potential with activity against lung carcinoma cells and antileukaemic properties	
	Additional components (flavonoids): rutin, quercetin, kaempferol, taxifolin, chrysin etc.	Calixto et al. (2016); Zhou et al. (2018)
	Psychotramide glycosylsphingolipids	Wang et al. (2020)
Psychotria solitudinum (Costa Rica, Central America)	Cyclotides: protease inhibition (POP: human prolyl oligopeptidase) suggestive of neuroprotective and memory supportive potential	Hellinger et al. (2015)
Psychotria sp. (China)	Triterpene saponin: anticancer potential of psychotrianoside C (antiproliferative, induce apoptosis)	Zhang et al. (2013)
Psychotria sp. (Amazon, South America)	Extract: strong activity against *Streptococcus mutans*	Silva et al. (2014)
Psychotria spectabilis (Central/South America)	Extract: antifungal against *Cladosporium*	Benevides et al. (2005)
	Soliadagenone and psoralene: cytotoxic activity	
	Additional components: coumarin, umbelliferone (7-hydroxycoumarin) and flavonoids (quercetin, quercetrin)	Calixto et al. (2016)
Psychotria stachyoides (Brazil, South America)	Extract: anti-mycobacterial studies identified promising anti-tuberculosis potential	Moraes et al. (2011)
Psychotria suterella (Central/South America)	Extract: nervous system activity (MAO inhibition)	Dos Santos Passos et al. (2013)
	Extract (alkaloids): antiplasmodial activity (antimalarial potential)	Gontijo et al. (2019)
Psychotria umbellata (Central/South America)	Extract: analgesic, antioxidant and antimutagenic	Fragoso et al. (2008)
	Alkaloids: psychollatine, umbellatine; umbellatine shows analgesic activity	Both et al. (2005); Paranhos et al. (2005); Calixto et al. (2016)
	Psychollatine: antioxidant, antimutagenic, analgesic and nervous system activity (MAO inhibition and cholinesterase inhibition) with anxiolytic, antipsychotic and antidepressant effects	Both et al. (2005 & 2006); Fragoso et al. (2008), Porto et al. (2009)
Psychotria viridiflora	Antidiabetic (clinical use): blood sugar regulation,	Chen et al. (2021)

(Malaysia)	potential in treat post-meal increases in blood sugar	
Psychotria viridis (South America)	Harmine alkaloids: harmine, harmaline, tetrahydroharmine etc.; also DMT (N,N-dimethyltryptamine) with psychoactive neurological effects	Riba et al. (2012); Calixto et al. (2016)
	Extract (leaf): cytotoxic anticancer activity against certain cell lines	Soares et al. (2017)
	Extract: leaf extracts plus active components (cycloartenol, DMT, and a mixture of β-sitosterol and stigmasterol) showed significant acetylcholinesterase (AChE) inhibition properties	Soares et al. (2017)
	Medicinal applications: review of the psychoactive DMT and harmala alkaloids harmine, harmaline and tetrahydroharmine; their potential therapeutic value in mental and psychiatric disorders, and forensic aspects of DMT and ayahuasca evaluated	Simao et al. (2019 & 2020); Brito-da-Costa et al.(2020)
	Ayahuasca: potential use for treating mental distress (anti-anxiety, anti-depressant etc.); eating disorders and reduce alcohol dependence	Cata-Preta et.al. (2018); see also Hamill et al. (2019); Renelli et al. (2020)
	Extract and alkaloids (notably DMT): virucidal activity against Zika virus	Moraes et al. (2021)
	Ayahuasca matrix plants, harmine and DMT: neuroprotective (synergistic components) with potential for Parkinson's disease	Katchborian-Neto et al. (2020)
Psychotria zombamontana (South Africa)	Extract: antioxidant and anti-inflammatory; synergistic antimycobacterial effect with rifampicin	Aro et al. (2016)
	Extract: significant antimycobacterial (anti-tuberculosis) potential	Aro et al. (2019)
	Extract: anti-inflammatory	Aro et al. (2019)
Calycodendron (Rubiaceae)		
Calycodendron milnei (Vanuatu)	Alkaloids: chimonanthines, plus unique alkaloids i.e. vatine, vatine A, vatamine and vatamidine	Adjibade et al. (1990); Saad et al. (1995)
	Alkaloids: quadrigemine, psychotridine, isopsychotridine, vatine and vatamine demonstrate significant cytotoxic activity	
	Alkaloids: hodgkinsine and quadrigemine C demonstrate potent antibacterial, antifungal and anti-candida activity. Some studies demonstrated activity comparable to conventional antibiotics	
	Alkaloid: isopsychotridine present with antiplatelet aggregation activity (antithrombotic potential)	

Resources:

Adjibade Y, Kuballa B, Cabalion P, Jung ML, Beck JP, Anton R. (1989). Cytotoxicity on human leukemic and rat hepatoma cell lines of alkaloid extracts of *Psychotria forsteriana*. Planta Medica. 55/6:567-68

Adjibade Y, Saad H, Sévenet T, Kuballa B, Quirion JC, Anton R. (1990). New polyindolenine alkaloids from *Calycodendron milnei*. Planta Medica. 56/2:212-15

Amador TA, Elisabetsky E, Souza DO. (1996). Effects of *Psychotria colorata* alkaloids in brain opioid system. Neurochemical Research 21(1):97-102.

Amador TA, Verotta L, Nunes DS, Elisabetsky E. (2000). Antinociceptive profile of hodgkinsine. Planta Medica. 66(8):770-2.

Amador TA, Verotta L, Nunes DS, Elisabetsky E. (2001). Involvement of NMDA receptors in the analgesic properties of psychotridine. Phytomedicine 8(3):202-06

Anet FAL, Hughes GK, Ritchie E. (1961). Hodgkinsine, the alkaloid of *Hodgkinsonia frutescens* F.Muell. Australian Journal of Chemistry. 14:173-74

Armah FA, Henneh IT, Amponsah IK, Biney RP, Malcolm F, Alake J, Ahlidja W, Ahmed MA, Adokoh CK, Adukpo GE, Acheampong DO, Gathumbi PK. (2021) Antidepressant and Anxiolytic Effects and Subacute Toxicity of

the Aerial Parts of *Psychotria ankasensis* J.B.Hall (Rubiaceae) in Murine Models. Evidence Based Complementary & Alternative Medicine. 2021:5543320.

Aro AO, Dzoyem JP, Eloff JN, McGaw LJ. (2016). Extracts of six Rubiaceae species combined with rifampicin have good in vitro synergistic antimycobacterial activity and good anti-inflammatory and antioxidant activities. BMC Complementary and Alternative Medicine. 16(1):385.

Aro AO, Dzoyem JP, Goddard A, Fonteh P, Kayoka-Kabongo PN, McGaw LJ. (2019) In vitro Antimycobacterial, Apoptosis-Inducing Potential, and Immunomodulatory Activity of Some Rubiaceae Species. Frontiers in Pharmacology. 10:185.

Benchoula K, Khatib A, Quzwain FMC, Che Mohamad CA, Wan Sulaiman WMA, Abdul Wahab R, Ahmed QU, Abdul Ghaffar M, Saiman MZ, Alajmi MF, El-Seedi H. (2019). Optimization of Hyperglycemic Induction in Zebrafish and Evaluation of Its Blood Glucose Level and Metabolite Fingerprint Treated with Psychotria malayana Jack Leaf Extract. Molecules. 2019 Apr 17;24(8). pii: E1506.

Benevides PJC, Young MCM, da Silva Bolzani V. (2005). Biological Activities of Constituents from *Psychotria spectabilis*. Pharmaceutical Biology. 42(8):565-569

Berger A, Kostyan MK, Klose SI, Gastegger M, Lorbeer E, Brecker L, Schinnerl J. (2015) Loganin and secologanin derived tryptamine-iridoid alkaloids from *Palicourea crocea* and *Palicourea padifolia* (Rubiaceae). Phytochemistry. 116:162-169.

Bertelli PR, Biegelmeyer R, Rico EP, Klein-Junior LC, Toson NSB, Minetto L, Bordignon SAL, Gasper AL, Moura S, de Oliveira DL, Henriques AT. (2017) Toxicological profile and acetylcholinesterase inhibitory potential of *Palicourea deflexa*, a source of β-carboline alkaloids. Comparative Biochemistry & Physiology C. Toxicology & Pharmacology. 201:44-50.

Both FL, Meneghini L, Kerber VA, Henriques AT, Elisabetsky E. (2006). Role of glutamate and dopamine receptors in the psychopharmacological profile of the indole alkaloid psychollatine. Journal of Natural Products. 69(3):342-5.

Both FL, Meneghini L, Kerber VA, Henriques AT, Elisabetsky E. (2005). Psychopharmacological profile of the alkaloid psychollatine as a 5HT2A/C serotonin modulator. Journal of Natural Products. 68(3):374-80.

Bristy TA, Barua N, Montakim Tareq A, Sakib SA, Etu ST, Chowdhury KH, Jyoti MA, Aziz MA, Reza ASMA, Caiazzo E, Romano B, Tareq SM, Emran TB, Capasso R. (2020) Deciphering the Pharmacological Properties of Methanol Extract of *Psychotria calocarpa* Leaves by In Vivo, In Vitro and In Silico Approaches. Pharmaceuticals (Basel). 13(8):183.

Brito-da-Costa AM, Dias-da-Silva D, Gomes NGM, Dinis-Oliveira RJ, Madureira-Carvalho Á. (2020) Toxicokinetics and Toxicodynamics of Ayahuasca Alkaloids N,N-Dimethyltryptamine (DMT), Harmine, Harmaline and Tetrahydroharmine: Clinical and Forensic Impact. Pharmaceuticals (Basel). 13(11):334.

Calixto NO, Pinto MEF, Ramalho SD, Burger MCM, Bobey AF, Young MCM, Bolzam VS, Pinto AC (2016). The Genus *Psychotri*a: Phytochemistry, Chemotaxonomy, Ethnopharmacology and Biological Properties. Journal of the Brazilian Chemical Society 27(8): 1355-78

Cardona-G W, Robledo S, Alzate F, Yepes AF, Hernandez C, Velez ID, Calderon JC, Tabares IV. (2020) Antileishmanial and cytotoxic activities of four Andean plant extracts from Colombia. Vet World. Oct;13(10):2178-2182.

Carvalho Junior AR, Vieira IJ, Carvalho MG, Braz-Filho R, S Lima MA, Ferreira RO, José Maria E, Oliveira DB. (2017). 13C-NMR Spectral Data of Alkaloids Isolated from *Psychotria* Species (Rubiaceae). Molecules. 22(1). pii: E103.

Cata-Preta EG, Serra YA, Moreira-Junior EDC, Reis HS, Kisaki ND, Libarino-Santos M, Silva RRR, Barros-Santos T, Santos LC, Barbosa PCR, Costa JL, Oliveira-Lima AJ, Berro LF, Marinho EAV. (2018) Ayahuasca and Its DMT- and β-carbolines - Containing Ingredients Block the Expression of Ethanol-Induced Conditioned Place Preference in Mice: Role of the Treatment Environment. Frontiers in Pharmacology. 9:561.

Chaves Valadão AL, Abreu CM, Dias JZ, Arantes P, Verli H, Tanuri A, de Aguiar RS. (2015) Natural Plant Alkaloid (Emetine) Inhibits HIV-1 Replication by Interfering with Reverse Transcriptase Activity. Molecules. 20(6):11474-89.

Chen Q, Toy JYH, Seta C, Yeo TC, Huang D. (2021) Inhibition Effect of Extract of *Psychotria viridiflora* Stem on α-Amylase and α-Glucosidase and Its Application in Lowering the Digestibility of Noodles. Front Nutrition 8:701114.

Cheung SC: 1983 Chinese Medicinal Herbs of Hong Kong 2. Hong Kong Chinese Medical Research Institute (CMRI), Commercial Press, Hong Kong.

Cook D, Lee ST, Taylor CM, Bassüner B, Riet-Correa F, Pfister JA, Gardner DR. (2014) Detection of toxic monofluoroacetate in *Palicourea* species. Toxicon. 80:9-16.

da Silva TB, Costa CO, Galvão AF, Bomfim LM, Rodrigues AC, Mota MC, Dantas AA, Dos Santos TR, Soares MB, Bezerra DP. (2016) Cytotoxic potential of selected medicinal plants in northeast Brazil. BMC Complementary & Alternative Medicine. 16:199.

de Carvalho Junior AR, Oliveira Ferreira R, de Souza Passos M, da Silva Boeno SI, Glória das Virgens LL, Ventura TLB, Calixto SD, Lassounskaia E, de Carvalho MG, Braz-Filho R, Curcino Vieira IJ. (2019). Antimycobacterial and Nitric Oxide Production Inhibitory Activities of Triterpenes and Alkaloids from *Psychotria nuda* (Cham. & Schltdl.) Wawra. Molecules. 24(6). pii: E1026.

Devadoss S, Murugaiyan I, Murugan R, Thangaraj P. (2013). Evaluation of Phytochemical, Antioxidant and antimicrobial properties of Ethnomedicinal plant *Psychotria nilgiriensis* Deb. & Gang. International Journal of Pharmacy and Pharmaceutical Sciences. 5(3):417-422

do Nascimento NC, Fragoso V, Moura DJ, e Silva AC, Fett-Neto AG, Saffi J. (2007). Antioxidant and antimutagenic effects of the crude foliar extract and the alkaloid brachycerine of *Psychotria brachyceras*. Environmental and Molecular Mutagenesis. 48(9):728-34.

Dos Santos Passos, Soldi TC, Torres Abib R, Anders Apel M, Simões-Pires C, Marcourt L, Gottfried C, Henriques AT. (2013). Monoamine oxidase inhibition by monoterpene indole alkaloids and fractions obtained from *Psychotria suterella* and *Psychotria laciniata*. Journal of Enzyme Inhibition and Medicinal Chemistry. 28(3):611-8.

Farias FM, Passos CS, Arbo MD, Barros DM, Gottfried C, Steffen VM, Henriques AT. (2012). Strictosidinic acid, isolated from *Psychotria myriantha* Mull. Arg. (Rubiaceae), decreases serotonin levels in rat hippocampus. Fitoterapia. 83(6):1138-43.

Farias FM, Passos CS, Arbo MD, Zuanazzi JA, Steffen VM, Henriques AT. (2010). Monoamine levels in rat striatum after acute intraperitoneal injection of strictosidinic acid isolated from *Psychotria myriantha* Mull. Arg. (Rubiaceae). Phytomedicine. 17(3-4):289-91.

Fokoua AR, Ajayi AM, Ben-Azu B, Chouna R, Folarin O, Olopade J, Nkeng-Efouet PA, Aderibigbe AO, Umukoro S, Nguelefack TB. (2021b) The antioxidant and neuroprotective effects of the *Psychotria camptopus* Verd. Hook. (Rubiaceae) stem bark methanol extract contributes to its antiepileptogenic activity against pentylenetetrazol kindling in male Wistar rats. Metabolic Brain Disease. 36(7):2015-2027.

Fokoua AR, Ndjenda MK 2nd, Kaptué Wuyt A, Tatsinkou Bomba FD, Dongmo AK, Chouna R, Nkeng-Efouet PA, Nguelefack TB. (2021a) Anticonvulsant effects of the aqueous and methanol extracts from the stem bark of *Psychotria camptopus* Verdc. (Rubiacaea) in rats. Journal of Ethnopharmacology. 272:113955.

Formagio AS, Volobuff CR, Santiago M, Cardoso CA, Vieira Mdo C, Valdevina Pereira Z. (2014) Evaluation of Antioxidant Activity, Total Flavonoids, Tannins and Phenolic Compounds in Psychotria Leaf Extracts. Antioxidants (Basel). 3(4):745-57.

Formagio ASN, Volobuff CRF, Kassuya CAL, Cardoso CAL, do Carmo Vieira M, Pereira ZV, Bagatin MC, de Freitas Gauze G. (2019). *Psychotria leiocarpa* Extract and Vincosamide Reduce Chemically-Induced Inflammation in Mice and Inhibit the Acetylcholinesterase Activity. Inflammation. 42(5):1561-1574.

Fragoso V, do Nascimento NC, Moura DJ, e Silva AC, Richter MF, Saffi J, Fett-Neto AG. (2008). Antioxidant and antimutagenic properties of the monoterpene indole alkaloid psychollatine and the crude foliar extract of *Psychotria umbellata* Vell. Toxicology In Vitro. 22(3):559-66.

Frankova A, Vistejnova L, Merinas-Amo T, Leheckova Z, Doskocil I, Wong Soon J, Kudera T, Laupua F, Alonso-Moraga A, Kokoska L. (2021) In vitro antibacterial activity of extracts from Samoan medicinal plants and their effect on proliferation and migration of human fibroblasts. Journal of Ethnopharmacology. 264:113220.

Frescura VD, Kuhn AW, Laughinghouse HD 4th, Paranhos JT, Tedesco SB. (2013) Post-treatment with plant extracts used in Brazilian folk medicine caused a partial reversal of the antiproliferative effect of glyphosate in the *Allium cepa* test. Biocell. 37(2):23-8.

Giang PM, Son HV, Son PT. (2007). Study on the chemistry and antibacterial activity of *Psychotria reevesii* Wall. (Rubiaceae). Journal of Chemistry. 45(5):628–633

Gontijo DC, do Nascimento MFA, Rody HVS, Magalhães RA, Margalho LF, Brandão GC, de Oliveira AB. (2021) In vitro antiplasmodial activity, targeted LC-MS metabolite profiling, and identification of major natural products in the bioactive extracts of *Palicourea* and *Psychotria* species from the Amazonia and Atlantic Forest biomes, Brazil. Metabolomics. 17(9):81.

Gontijo DC, Leite JPV, Nascimento MFAD, Brandão GC, Oliveira AB. (2019). Bioprospection for antiplasmodial activity, and identification of bioactive metabolites of native plants species from the Mata Atlântica biome, Brazil. Natural Product Research. Jun 24:1-6

Gregianini TS, da Silveira VC, Porto DD, Kerber VA, Henriques AT, Fett-Neto AG. (2003). The alkaloid brachycerine is induced by ultraviolet radiation and is a singlet oxygen quencher. Photochemistry and Photobiology. 78(5):470-4.

Hamill J, Hallak J, Dursun SM, Baker G. (2019) Ayahuasca: Psychological and Physiologic Effects, Pharmacology and Potential Uses in Addiction and Mental Illness. Current Neuropharmacology. 17(2):108-128.

Hellinger R, Koehbach J, Puigpinós A, Clark RJ, Tarragó T, Giralt E, Gruber CW. (2015) Inhibition of Human Prolyl Oligopeptidase Activity by the Cyclotide Psysol 2 Isolated from *Psychotria solitudinum*. Journal of Natural Products. 78(5):1073-82.

Jannic V, Guéritte F, Laprévote O, Serani L, Martin MT, Sévenet T, Potier P. (1999). Pyrrolidinoindoline alkaloids from *Psychotria oleoides* and *Psychotria lyciiflora*. Journal of Natural Products. 62(6):838-43.

Jayasinghe UL, Jayasooriya CP, Bandara BM, Ekanayake SP, Merlini L, Assante G. (2002). Antimicrobial activity of some Sri Lankan Rubiaceae and Meliaceae. Fitoterapia 73(5):424-27

Katchborian-Neto A, Santos WT, Nicácio KJ, Corrêa JOA, Murgu M, Martins TMM, Gomes DA, Goes AM, Soares MG, Dias DF, Chagas-Paula DA, Paula ACC. (2020) Neuroprotective potential of Ayahuasca and untargeted metabolomics analyses: applicability to Parkinson's disease. Journal of Ethnopharmacology. 255:112743.

Kato L, de Oliveira CMA, Faria EO, Ribeiro L|C, Carvalho BG, da Silva CC, Santin SMO, Schuque ITA, Nakamura CV, Britta EA, Miranda N, Iglesias AHH, Delprete PG. (2012). Antiprotozoal alkaloids from *Psychotria prunifolia* (Kunth) Steyerm. Journal of the Brazilian Chemical Society. 23:2

Kato L, Moraes AP, de Oliveira CMA, Vaz BG, de Almeida Gonçalves L, E Silva EC, Janfelt C. (2018) The Spatial Distribution of Alkaloids in *Psychotria prunifolia* (Kunth) Steyerm and *Palicourea coriacea* (Cham.) K. Schum Leaves Analysed by Desorption Electrospray Ionisation Mass Spectrometry Imaging. Phytochemical Analysis.29(1):69-76.

Khan MR, Kihara M, Omoloso AD. (2001). Antimicrobial activity of *Psychotria microlabastra*. Fitoterapia. 72(7):818-21

Klein LC Jr., Passos CS, Moraes AP, Wakui VG, Konrath EL, Nurisso A, Carrupt PA, de Oliveira CM, Kato L, Henriques AT. (2014). Indole alkaloids and semisynthetic indole derivatives as multifunctional scaffolds aiming the inhibition of enzymes related to neurodegenerative diseases--a focus on *Psychotria* L. Genus. Current Topics in Medicinal Chemistry. 14(8):1056-75.

Klein-Júnior LC, Cretton S, Vander Heyden Y, Gasper AL, Nejad-Ebrahimi S, Christen P, Henriques AT. (2020) Bioactive Azepine-Indole Alkaloids from *Psychotria nemorosa*. Journal of Natural Products. 83(4):852-863.

Klein-Junior LC, Viaene J, Salton J, Koetz M, Gasper AL, Henriques AT, Vander Heyden Y. (2016). The use of chemometrics to study multifunctional indole alkaloids from *Psychotria nemorosa* (*Palicourea* comb. nov.). Part II: Indication of peaks related to the inhibition of butyrylcholinesterase and monoamine oxidase-A. Journal of Chromatography A. 1463:71-80.

Leal MB, Elisabetsky E. (1996a). Opioid-like activity of *Psychotria brachypoda*. International Journal of Pharmacog.34/4: 267-272

Leal MB, Elisabetsky E. (1996b). Absence of alkaloids in *Psychotria carthagenensis* Jacq. (Rubiaceae). Journal of Ethnopharmacology 54(1):37-40

Liu L, Song CW, Khan A, Li XN, Yang XW, Cheng GG, Liu YP, Luo XD. (2016). A potent antibacterial indole alkaloid from *Psychotria pilifera*. Journal of Asian Natural Product Research 18(8):798-803.

Locher CP, Burch MT, Mower HF, Berestecky J, Davis H, Van Poel B, Lasure A, Vanden Berghe DA, Vlietinck AJ. (1995). Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. Journal of Ethnopharmacology. 49(1):23-32.

Locher CP, Witvrouw M, De Béthune MP, Burch MT, Mower HF, Davis H, Lasure A, Pauwels R, De Clercq E, Vlietinck AJ. (1996). Antiviral activity of Hawaiian medicinal plants against human immunodeficiency Virus Type-1 (HIV-1). Phytomedicine. 2(3):259-64.

Mahmud Z, Nusa M, Ismail N, Lajis NH. (1993). Cytotoxic and bactericidal activities of *Psychotria rostrata*. International Journal of Pharmacognosy. 31/2:142-6.

Matsuura HN, Fett-Neto AG. (2013) The major indole alkaloid N,β-D-glucopyranosyl vincosamide from leaves of Psychotria leiocarpa Cham. & Schltdl. is not an antifeedant but shows broad antioxidant activity. Natural Product Research. 27(4-5):402-11.

McKenna DJ, Towers GH, Abbott F. (1984) Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and beta-carboline constituents of ayahuasca. Journal of Ethnopharmacology. 10(2):195-223.

McKenzie R. (2012). Australia's Poisonous Plants, Fungi and Cyanobacteria. A Guide to Species of Medicinal and Veterinary Importance. pp. 34-36. CSIRO Publishing.

Moller M, Herzer K, Wenger T, Herr I, Wink M. (2007). The alkaloid emetine as a promising agent for the induction and enhancement of drug-induced apoptosis in leukemia cells. Oncology Reports. 18(3):737-44.

Moller M, Wink M. (2007). Characteristics of apoptosis induction by the alkaloid emetine in human tumour cell lines. Planta Medica. 73(13):1389-96.

Moraes TFS, Ferraz AC, da Cruz Nizer WS, Tótola AH, Soares DBS, Duarte LP, Vieira-Filho SA, Magalhães CLB, de Magalhães JC. (2021) A methanol extract and N,N-dimethyltryptamine from *Psychotria viridis* Ruiz & Pav. inhibit Zika virus infection in vitro. Archives of Virology. Sep 18.

Moraes TM, de Araújo MH, Bernardes NR, de Oliveira DB, Lasunskaia EB, Muzitano MF, Da Cunha M. (2011). Antimycobacterial activity and alkaloid prospection of *Psychotria* species (Rubiaceae) from the Brazilian Atlantic Rainforest. Planta Medica. 77(9):964-70.

Muhammad I, Dunbar DC, Khan SI, Tekwani BL, Bedir E, Takamatsu S, Ferreira D, Walker LA. (2003). Antiparasitic alkaloids from *Psychotria klugii*. Journal of Natural Products. 66(7):962-7.

Ndlovu G, Fouche G, Tselanyane M, Cordier W, Steenkamp V. (2013) In vitro determination of the anti-aging potential of four southern African medicinal plants. BMC Complementary & Alternative Medicine. 13:304.

Nipun TS, Khatib A, Ahmed QU, Redzwan IE, Ibrahim Z, Khan AYF, Primaharinastiti R, Khalifa SAM, El-Seedi HR. (2020a) Alpha-Glucosidase Inhibitory Effect of *Psychotria malayana* Jack Leaf: A Rapid Analysis Using Infrared Fingerprinting. Molecules. 25(18):4161.

Nipun TS, Khatib A, Ibrahim Z, Ahmed QU, Redzwan IE, Saiman MZ, Supandi F, Primaharinastiti R, El-Seedi HR. (2020b) Characterization of α-Glucosidase Inhibitors from Psychotria malayana Jack Leaves Extract Using LC-MS-Based Multivariate Data Analysis and In-Silico Molecular Docking. Molecules. 25(24):5885.

Orji OU, Awoke JN, Harbor C, Igwenyi IO, Obasi OD, Ezeani NN, Aloke C. (2020) Ethanol leaf extract of *Psychotria microphylla* rich in quercetin restores heavy metal induced redox imbalance in rats. Heliyon. 6(9):e04999.

Paranhos JT, Fragoso V, Henriques AT, Ferreira AG, Fett-Neto AG. (2005). Regeneration of *Psychotria umbellata* and production of the analgesic indole alkaloid umbellatine. Tree Physiology. 25(2):251-5.

Parry KP, Smith GF. (1978). Quadrigemines-A and-B, two minor alkaloids of *Hodgkinsonia frutescens* F. Muell. Journal of the Chemical Society, Perkin Transactions. 1:1671-1682

Passos CS, Simões-Pires CA, Nurisso A, Soldi TC, Kato L, de Oliveira CM, de Faria EO, Marcourt L, Gottfried C, Carrupt PA, Henriques AT. (2013). Indole alkaloids of *Psychotria* as multifunctional cholinesterases and monoamine oxidases inhibitors. Phytochemistry. 86:8-20.

Perviz S, Khan H, Pervaiz A. (2016). Plant Alkaloids as an Emerging Therapeutic Alternative for the Treatment of Depression. Frontiers in Pharmacology 7:28

Porto DD, Henriques AT, Fett-Neto AG. (2009). Bioactive alkaloids from South American *Psychotria* and related species. The Open Bioactive Compounds Journal 2:29-36

Quisumbing E. (1951). Medicinal Plants of the Philippines. Technical Bulletin No.16, Department of Agriculture and Natural Resources. Manila.

Ramil RJD, Ramil MDI, Konno T, Murata T, Kobayashi K, Buyankhishig B, Agrupis SC, Sasaki K. (2020) A new hexenoic acid glycoside with cytotoxic activity from the leaves of *Psychotria luzoniensis*. Natural Product Research. May 13:1-6.

Ratnasooriya WD, Dharmasiri MG. (1999). A water extract of leaves and stems of *Psychotria sarmentosa* has analgesic and antihyperalgesic activity in rats. Medical Science Research. 27:715

Renelli M, Fletcher J, Tupper KW, Files N, Loizaga-Velder A, Lafrance A. (2020) An exploratory study of experiences with conventional eating disorder treatment and ceremonial ayahuasca for the healing of eating disorders. Eating & Weight Disorders. 25(2):437-444.

Riba J, McIlhenny EH, Valle M, Bouso JC, Barker SA. (2012). Metabolism and disposition of N,N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca. Drug Test Analysis. 4(7-8):610-6.

Roth A, Kuballa B, Bounthanh C, Anton R. (1986). Cytotoxic activity of polyindoline alkaloids from *Psychotria forsteriana* (Rubiaceae) 1. Planta Medica. 52(6):450-53

Saad HE, el-Sharkawy SH, Shier WT. (1995). Biological activities of pyrrolidinoindoline alkaloids from *Calycodendron milnei*. Planta Medica. 61(4):313-6.

Silva JP, Castilho AL, Saraceni CH, Díaz IE, Paciencia ML, Suffredini IB. (2014) Anti-Streptococcal activity of Brazilian Amazon Rain Forest plant extracts presents potential for preventive strategies against dental caries. Journal of Applied Oral Science. 22(2):91-7.

Simão AY, Gonçalves J, Duarte AP, Barroso M, Cristóvão AC, Gallardo E. (2019) Toxicological Aspects and Determination of the Main Components of Ayahuasca: A Critical Review. Medicines (Basel). 6(4):106.

Simão AY, Gonçalves J, Gradillas A, García A, Restolho J, Fernández N, Rodilla JM, Barroso M, Duarte AP, Cristóvão AC, Gallardo E. (2020) Evaluation of the Cytotoxicity of Ayahuasca Beverages. Molecules. 25(23):5594.

Soares DBS, Duarte LP, Cavalcanti AD, Silva FC, Braga AD, Lopes MTP, Takahashi JA, Vieira-Filho SA. (2017). *Psychotria viridis*: Chemical constituents from leaves and biological properties. Anais da Academia Brasileira de Ciências. 89(2):927-938.

Tran PH, Le VD, Do TH, Nguyen TL, Nguyen PT, Nguyen TT, Nguyen TD. (2019). Anti-inflammatory constituents from *Psychotria prainii* H. Lév. Natural Product Research. 33(5):695-700

Van Elst D, Nuyens S, van Wyk B, Verstraete B, Dessein S, Prinsen E. (2013) Distribution of the cardiotoxin pavettamine in the coffee family (Rubiaceae) and its significance for gousiekte, a fatal poisoning of ruminants. Plant Physiology & Biochemistry. 67:15-9.

Verotta L, Orsini F, Sbacchi M, Scheildler MA, Amador TA, Elisabetsky E. (2002). Synthesis and antinociceptive activity of chimonanthines and pyrrolidinoindoline-type alkaloids. Bioorganics and Medicinal Chemistry 10/7:2133-42

Verotta L, Pilati T, Tato M, Elisabetsky E, Amador TA, Nunes DS. (1998). Pyrrolidinoindoline Alkaloids from *Psychotria colorata*. Journal of Natural Products. 61/3:392-96

Volobuff CRF, Junior PCO, Dos Santos SM, Pereira ZV, Ferreira DC, Cardoso CAL, Ruiz ALTG, Foglio MA, de Carvalho JE, Formagio ASN. (2019). Antitumoral and Anticholinesterasic Activities of the Seven Species from Rubiaceae. Current Pharmaceutical Biotechnology. 20(4):302-308

Wang YM, Wu AZ, Zhong Y, Peng GT, Fan Q, Zhu CC, Zhang CX. (2019). New glycosylsphingolipids from *Psychotria serpens* L. Natural Product Research. Feb 19:1-6.

Wang YM, Wu AZ, Zhong Y, Peng GT, Fan Q, Zhu CC, Zhang CX. (2020) New glycosylsphingolipids from *Psychotria serpens* L. Natural Product Research. 34(14):2095-2100.

Weiner MA (1985). Secrets of Fijian Medicine. University of California, Berkeley, CA.

Wiart C. (2012). Medicinal Plants of China, Korea and Japan: Bioresources for Tomorrow's Drugs and Cosmetics. CRC Press, Taylor & Francis Group, Boca Raton.

Williams C. (2012). Medicinal Plants in Australia Vol.3 Plants, Potions and Poisons, pp. 255-56. Rosenberg Publishing, Dural.

Yang HM, Zhang H, Yang C, Chen Y. (2016). Chemical Constituents of Plants from the Genus *Psychotria*. Chemistry and Biodiversity. 13(7):807-20

Zhang CX, Zhang DM, Chen MF, Guan SY, Yao JH, He XX, Lei LF, Zhong Y, Wang ZF, Ye WC. (2013) Antiproliferative triterpenoid saponins from the stem of *Psychotria* sp. Planta Medica. 79(11):978-86.

Zhou BD, Zhang XL, Niu HY, Guan CY, Liu YP, Fu YH. (2018) Chemical constituents from stems and leaves of *Psychotria serpens*. Zhongguo Zhong Yao Za Zhi. 43(24):4878-4883. [Chinese].