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Ethnopharmacology of *Psychotria*: Potential Use of *P. malayana* Jack Leaves as Antidiabetic Agent

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Abstract

This review provides a comprehensive exploration of the *Psychotria* species, a genus of plants known for their medicinal properties and traditional uses. The focus is on the species' ethnomedicinal applications, their potential as an antidiabetic agent, the pharmacologically active antidiabetic compounds possessed, and their toxicological profiles. The escalating global prevalence of diabetes underscores the need for alternative therapeutic agents. The *Psychotria* species, with their antidiabetic properties, present a promising area of research. The traditional medicinal uses of the *Psychotria* species across various cultures are examined, providing valuable insights for the development of novel treatments. This review delves into the mechanisms through which these species exert their antidiabetic effects especially *Psychotria malayana*. The review discusses the pharmacologically active compounds unique to these species, which are of considerable interest for drug development in diabetes treatment. A summary of these studies and their implications is presented. Finally, the review addresses the toxicological studies on the *Psychotria* species, assessing their safety as therapeutic agents.

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Introduction

The species of *Psychotria*, belonging to the *Rubiaceae* family, encompasses over 2000 species. These species are typically found in the understory of forests, preferring areas with limited sunlight and moist soil. *Psychotria* is mostly distributed in subtropical and tropical regions and comprises a variety of forms, including shrubs, herbs, and treelets (Moraes *et al*., 2011b). The species belonging to the subfamily *Rubioideae* and the tribe *Psychotriae*, has been documented as the largest species observed in three distinct tropical regions: Neotropical, Africa, Asia, and Oceania as shown in Fig. 1. (Bremer, 2009; Hamilton, 1989).

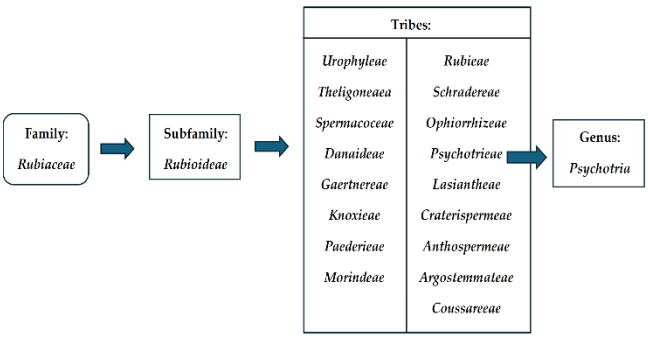

Fig. 1: Subfamily, tribes, and species/genus of *Psychotria* in the *Rubiaceae* family (Bremer, 2009)

The *Rubiaceae* family is characterized by some anatomical features, including hypostomatic leaves, paracytic stomata, dorsiventral mesophyll, and collateral bundles (Britannica, 2020). Furthermore, an additional characteristic commonly observed in the *Rubiaceae* family is the presence of domatia, which are primarily found along the secondary veins on the lower surface of the leaf and occasionally exist along the tertiary veins of the leaf blade. The diagnostic criteria for *Psychotria* include the identification of alkaloids and styloid crystals inside the mesophyll (Moraes *et al*., 2011a; Robbrecht, 1988). The taxonomic complexity of defining the delimited morphology of this species persists despite the absence of sufficient morphological data to accurately characterize its stated features (Nepokroeff *et al*., 1999).

Ethnomedicinal Uses of Psychotria

The *Psychotria* species has been extensively used as medicinal plants by our predecessors across diverse cultures worldwide (Table A2) in supplementary data. For example, the communities residing in the Uttara Kanada district of India have been used the root of *P. dalzellii* to address scorpion bites. This was achieved by grinding the root with lime juice and administering it as both a topical and oral medication (Bhat *et al*., 2012). Similarly, the infusion of the root of *P. flavida* has been employed for the treatment of snakebites (Bhat *et al*., 2012; Kshirsagar & Singh, 2001). The Kani tribes residing in Agasthiayamalai, located in South India, have traditionally incorporated the consumption of leaves and tender fruits from the *P. ophioxyloides*, along with milk, as a remedy for stomach discomfort (Britto & Mahesh, 2007). In the Chittagong Hill Tract region of Bangladesh, individuals have traditionally used the root of *P. adenophylla* for the treatment of mouth sores and rheumatism. Interestingly, the same therapeutic applications of the specific plant parts are also observed among the population of Assam in the Eastern Himalaya (Biswas *et al*., 2010; Choudhury *et al*., 2012). Furthermore, the inhabitants of Assam have traditionally employed the root of *P. denticulata* for the purpose of alleviating toothache, while the leaves of *P. montana* have been employed to mitigate discomfort and colitis (Choudhury *et al*., 2012).

In eastern Nicaragua, the indigenous population known as Rama traditionally employed many *Psychotria* species, including *P. elata* and *P. ipecacuanha*, for the treatment of diarrhea. Additionally, *P. poeppigiana* was used specifically for the management of amoebic dysentery (Coe, 2008). Furthermore, *P. ipecacuanha* has been used by indigenous populations in South America for the treatment of diarrhea and dysentery (Fisher, 1973). This plant also exhibits similar medicinal applications among the inhabitants of Costa Rica and Nicaragua (Fisher, 1973; Ocampo & Balick, 2009). In addition, it is worth noting that this plant, which possesses rhizomes and roots, is used in the form of syrup and powder as stimulants and diaphoretics, respectively (Ocampo & Balick, 2009).

Certain species of *Psychotria*, such as *P. nudiflora* and *P. nilgiriensis*, have been identified as having similar therapeutic properties for the treatment of rheumatism, as traditionally given by the Kanikkar tribes residing in the Agasthiarmalai region of India. In order to alleviate rheumatism, individuals ingested either the leaves and flowers of *P. nudiflora* or the tender fruits of *P. nilgiriensis* along with honey. Another method involved creating a paste using the leaves and flowers of *P. nudiflora* or the tender fruits of *P. nilgiriensis*, which was also consumed with honey (Rani *et al*., 2011; Sutha *et al*.,

2010; Devadoss *et al*., 2013; Iniyavan *et al*., 2012).

P. viridis, a member of the *Psychotria* species, has been historically employed in the preparation of ayahuasca, a psychoactive beverage originating from the Amazon rainforest. This plant species is recognised for its hallucinogenic property and its significance in religious rituals (Choffnes, 2017; Gambelunghe *et al*., 2008; Schultes & Hofmann, 1980). The beverage has been made through the process of extracting the substance of *P. viridis* leaves and incorporating them into the beverage (Gambelunghe *et al*., 2008).

The inhabitants of Andaman and Nicobar Islands, India, use *P. montana* as a remedy for constipation and *P. sarmentosa* for the treatment of itching and soreness. Similarly, herbalists from Rivercess County, Liberia, employ the leaves of *P. peduncularis* to alleviate stomach soreness (Kamble *et al*., 2008; Lebbie *et al*., 2017). Certain species of *Psychotria* have been used by the Temiar people in Lojing Highland, Kelantan, Malaysia as well as in Madagascar, for the synthesis of an oral antipyretic (fever-reducing) through decoction. These species include *P. malayana*, *P. obtusifalia*, and *P. bulata* (Rao *et al*., 2016; Rasoanaivo *et al*., 1992).

Furthermore, the *Psychotria* species has been historically recognized for its potential in treating injuries and promoting wound healing since ancient times. As an illustration, the Valaya tribes employ the paste derived from *P. octosulcata* leaves for the purpose of treating muscular fractures, while *P. henryiis* finds application in traditional Chinese medicine to stimulate the spleen and alleviate pain (Rajendran *et al*., 2002; Liu *et al*., 2013). *P. colorata* was reportedly used by Amazonian caboclos as a means of alleviating pain. Similarly, tribes residing in southern India employed a dried powder derived from the root of *P. flavida*, which was combined with coconut oil to treat wounds (Elisabetsky *et al*., 1995).

Psychotria as Antidiabetic Agent

Traditional remedies have been extensively used for several centuries and continue to hold significant relevance in the realm of healthcare, particularly in the regions of Asia and Africa (Lezotre, 2014). As per the findings of Pan *et al*. (2014), the World Health Organization reports that a significant proportion, over 75%, of the global population relies on plants as a primary means of obtaining therapeutic substances to fulfil their fundamental healthcare requirements. The use of the *Psychotria* genera in traditional medicinal practices is employed for the alleviation of symptoms and the treatment of specific ailments. To date, researchers from various regions have conducted studies on roughly 41 species of *Psychotria*, resulting in the successful isolation of over 160 phytochemicals (Yang *et al*., 2016). The chemical constituents encompass phenols, alkaloids, terpenoids, steroids, and phenolic compounds that demonstrate antibacterial, antiparasitic, and antiviral properties. Certain components of the *Psychotria* species, namely leaves, rhizomes, and roots, have been employed in traditional medicine for the purpose of alleviating symptoms associated with cough, bronchitis, and ulcers (Calixto *et al*., 2016). The utilization of this plant for the management of stomach pain, gastrointestinal issues, and female reproductive system infections has been reported among populations in Brazil, India, and Indonesia (Benchoula *et al*., 2019). Several studies have demonstrated the potential therapeutic benefits of this plant in the treatment of diabetes mellitus, as it displays antidiabetic properties. Additional investigation is warranted to enhance comprehension of the underlying bioactivity. The objective of this overview is to collate a comprehensive inventory of the phytochemical constituents present in the *Psychotria* species, specifically focusing on those with demonstrated antidiabetic activities.

Recent studies have provided evidence suggesting that different species of *Psychotria* possess characteristics that may be effective in managing diabetes. The antidiabetic effect of these plants can be attributed to the presence of numerous important compounds. Recent studies have generated considerable interest in the possible therapeutic applications of *Psychotria* and its phytochemical constituents for diabetes mellitus (DM), due to their notable antidiabetic properties. This review offers a complete examination of the *Psychotria* species, spanning multiple species and their corresponding phytochemicals that have exhibited antidiabetic activities. A thorough search was carried out across four web-based databases, leading to the discovery of a total of fifteen papers related to different species of *Psychotria*. Based on the data provided in Table A1 (Supplementary data), it can be observed that a cumulative number of 13 unique species of *Psychotria* have been effectively gathered through several research endeavors. The species included in this list are *P. malayana*, *P. leiocarpa*, *P. dalzellii*, *P. viridiflora*, *P.*

calocarpa, *P. carthagenensis*, *P. capillacea*, *P. camptopus*, *P. deflexa*, *P. ipecacuanha*, *P. microphylla*, *P. nilgiriensis*, and *P. insularum*. The phytochemical compounds that demonstrate antidiabetic properties exhibit variability across different species, while there are specific molecules that are commonly found among them.

The identification and evaluation of antidiabetic activities were conducted on the plants listed in Tables A1. Six out of the fifteen studies included in the analysis provide a comprehensive description of the mechanism of action for the antidiabetic effect. These processes were recognized as alpha-glucosidase and alpha-amylase inhibitions. Enzymes like alpha-glucosidase and alpha-amylase play a crucial role in the process of carbohydrate hydrolysis, which subsequently results in elevated levels of glucose after a meal. According to Poovitha and Parani (2016), research has demonstrated that the suppression of these two enzymes is an effective approach in the management of postprandial hyperglycaemia and the mitigation of the risk of diabetes. The predominant mode of action for the *Psychotria* species in the reduction of blood glucose levels, as suggested by most studies, is the inhibition of alpha-glucosidase. The process of absorption in the small intestine was hindered due to the occurrence of competitive inhibition of the alpha-glucosidase enzymes. Isomaltase, sucrase, glucoamylase, and maltase are enzymatic catalysts that are essential for the hydrolysis of complex non-absorbable carbohydrates, facilitating their transformation into readily absorbable simple carbs (Tannous *et al*., 2023). As a result, the inhibition of alpha-glucosidase activities will hinder the absorption of carbohydrates, hence limiting the postprandial rise in blood glucose levels (Bhatnagar & Mishra, 2022). Previous research conducted by Abhishek *et al*. (2019) and Chen *et al*. (2021) has revealed that *P. dalzellii* and *P. viridiflora* have the capacity to block alpha-amylase, hence potentially aiding in the modulation of blood glucose levels. The compounds inhibit the activity of alpha-amylase enzymes, which play a crucial role in the initial stage of starch hydrolysis, namely the conversion of starch into maltose. Following this, maltose undergoes additional enzymatic hydrolysis by alpha-glucosidase, resulting in the conversion of maltose into glucose. Therefore, the crucial role of inhibiting alpha-amylase activity to slow down the process of starch hydrolysis is evident in its ability to mitigate the increase in glucose levels that occurs during postprandial hyperglycaemia (Dandekar *et al*., 2021).

Based on the reported findings, it is reasonable to consider *Psychotria* as a potentially efficacious therapeutic approach for the development of a novel antidiabetic medicine soon, characterized by a diminished occurrence of undesirable effects. However, it is crucial to recognize and address the several limitations present. This review study examines the underlying mechanisms that contribute to the antidiabetic characteristics displayed by various species of *Psychotria*. Nevertheless, a considerable proportion of the research (9 out of 15) has not been subjected to a thorough examination of the fundamental mechanisms that contribute to their antidiabetic properties. Additional research is necessary to clarify the complex characteristics of phytochemical compounds and their fundamental mechanisms of action to acquire a more complete comprehension of their potential medicinal properties. Moreover, it has been noted that there exist certain knowledge gaps regarding the contradictory data on phytochemical compounds present in *Psychotria*, which have been recognized for their antidiabetic activities. This suggests that additional research is necessary to provide evidence for the presence of phytochemical constituents in *Psychotria*. In summary, there exists a scarcity of research on *in vivo* evaluations of medicinal plants, despite the abundance of *in vitro* studies focusing on the antidiabetic attributes of these plan.

Phytochemistry of Psychotria

In recent times, there has been a significant surge in interest in the domain of natural products. There is a need for more research on *Psychotria* species due to their significant presence of natural ingredients, including alkaloids (the primary type of compound), flavonoids, coumarins, and terpenoids.All of these compounds were responsible towards antidiabetic activity possessed by *Psychotria.*

Alkaloids

Numerous classes of alkaloids derived from *Psychotria* species have been documented in the scientific literature, with a limited number currently undergoing further investigation. However only one alkaloids (5′-hydroxymethyl-1′-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl)-heptan-1′-one) was reported by Nipun et al. (2020b) corresponding towards antidiabetic activity which presented in a tabulated table (Table A3) in

supplementary data.,

Flavonoids

Flavonoids exhibit distribution patterns among various species within the *Psychotria* species. The flavonoids obtained from several species of *Psychotria* have been compiled and presented in a tabular format (Table A4) in supplementary data. All flavonoids present in *Psychotria* species are classified into few types including flavonoid glycoside (, luteolin-7-O-rutinoside)and flavonol (isorhamnetin, , quercetin). All these flavonoids demonstrate antidiabetic activities.

Terpenoids

This literature presents a comprehensive compilation of terpenoids that have been derived from several species of *Psychotria*. The terpenoids that were discovered and documentedwere assembled and presented in Table A5 (Supplementary data). All terpenoids (β-sitosterol, stigmasterol, ursolic acid) present in *Psychotria* species are classified under triterpenoids group.

Coumarins

Coumarin possesses a structural arrangement with a 2H-chromen-2-one (also referred to as 1,2-benzopyrone or 2H-1-benzopyran-2-one) oxa-heterocycle. This compound has garnered significant attention in scientific research due to its prevalence in numerous biologically active substances (Stefanachi *et al*., 2018). The coumarin discovered and documentedwere presented in Table A6 (Supplementary data). All coumarins present in *Psychotria* species are classified into few types including simple coumarins (1,2-benzopyrones, scopoletin), and angular furanocoumarin (umbelliferone).

Toxicology of Psychotria

The lack of comprehensive data on plant toxicity has limitations on the feasibility of prolonged utilization in the context of chronic illnesses. Therefore, the primary objective of this review was to examine the toxicity studies conducted on several species of *Psychotria*.

The biochemical parameters affected by diabetes, such as serum glucose, urea, uric acid, SGOT, total cholesterol, alkaline phosphatase, creatinine, and others, show that the methanol extract of *P. dalzelli* (MEPD) controls diabetes as well as glibenclamide. Biochemical parameters increased by ~3–10 folds, and protein levels were normalised by standard antidiabetic drugs, and MEPD, though less effective than glibenclamide, showed marked improvement in parameters, suggesting potential antidiabetic properties. MEPD reduced blood glucose levels at 200 mg/kg b.w. compared to DM control, showing anti-hyperglycaemic action. The changes in these biochemical markers suggest the toxic effect of these on diabetic animals' organs, including kidney and liver toxicity (Pecoits-Filho et al., 2016). Thus, MEPD are safer than synthetic medications and can prevent such problems, making them suitable for long-term usage as diabetes treatments (Abhishek et al., 2019).

The researchers performed the fish embryo acute toxicity (FET) test in accordance with the rules set by the Organization for Economic Cooperation and Development (OECD) on *Psychotria* species. The LC_{50} values of the methanol and water extracts of *P. malayana* leaf extract were exceeded their therapeutic concentrations, specifically 37.50 and 252.45 μg/mL, respectively. The results indicated that both the water and methanol extracts exhibited potential antidiabetic effects and are considered safe for use. Nevertheless, the water extract exhibits a higher degree of favourability owing to its significantly larger therapeutic index (LC_{50}/therapeutic concentration) in comparison to the methanol extract (Nipun *et al*., 2021a).

Besides that, further investigation of FET test was done on optimized extract of *P. malayana*. The optimised extract (OE) exhibited an LC_{50} value of 224.29 μg/mL, exceeding its therapeutic index of 111.03. Additionally, it displayed the most potent alpha-glucosidase inhibitory activity, with an IC_{50} value of 2.02 μg/mL (Syed Mohamad et al., 2023). According to this finding, the therapeutic index of OE was higher than that of the methanol extract (13.84) in previous art. These findings indicate that OE has a reduced level of toxicity, giving it a safer option for use, and is expected to be highly effective in its ability to treat diabetes.

Furthermore, Benchoula et al., (2019) were observed that the *P. malayana* extract did not induce any alterations in the hepatic morphology of the zebrafish specimens that were in a healthy state.

P. malayana Jack Leaves as Antidiabetic Agent

Psychotria malayana Jack (as shown in Fig. 2) is a member of the *Rubiaceae* family, which is recognised as the largest family within the *Plantae* kingdom. It exhibits a significant level of species richness, with around 1600 distinct species. In Malaysia, *P.*

malayana is referred to as "salung" and among the Lombok people, it is known as "lolon jarum." The botanical specimen in question exhibits vertical growth, reaching a range of 1 to 4 metres in height. *P. malayana* is naturally found in Andaman Island, Borneo, Jawa, Lesser Sunda Island, Malaysia, Sulawesi, Sumatera, and Thailand. However, its distribution is primarily concentrated within the western region of the Indonesian archipelago. It is a woody plant that often thrives in the moist tropical ecosystem. *P. malayana* was taxonomically classified within the kingdom *Plantae*, phylum *Streptophyta*, class *Equisetopsida*, subclass *Magnoliidae*, order *Gentianales*, family *Rubiaceae*, and *Psychotria* species. *P. malayana* has synonyms categorized as homotypic and heterotypic synonyms. The homotypic synonyms for this species include *Grumilea aurantiaca* Miq., *P. aurantiaca* Wall., and *Uragoga malayana* (Jack) Kuntze. While the heterotypic synonyms are *P. aurantiaca* var. lanceolata Miq., *P. odorata* Blume ex Miq., *P. stipulacea* Wall., *P. stipulacea* var. grandifolia Craib, and *Uragoga stipulacea* (Wall.) Kuntze (Plant of The World Online, 2024).

Fig. 2: *P. malayana* Jack leaves photographed at Cermin Nan Gedang, Sarolangun, Jambi, Indonesia

Psychotria species plants have been utilised in traditional medicinal practices to address many medical conditions, including diabetes (Situmorang *et al*., 2015), pain management (Anvar & Haneef, 2015), fever, and splenomegaly (Koch *et al*., 2015). Traditionally, *P. malayana* has been employed in the region of Sumatra (specifically Jambi) for the treatment of diabetes.

According to our research findings (Table 1), *P. malayana* has recently become the subject of a study looking into its potential therapeutic effects especially in the management of DM. A lot of research has been done on the antidiabetic effects of *P. malayana* leaf extract by Benchoula *et al.* (2019), Nipun *et al*. (2020a, 2020b, 2021a, 2021b), Fairuz *et al*. (2020) and Syed Mohamad et al., (2023). The results of this study indicated that the extract has potential as a therapeutic intervention for diabetes mellitus (DM). The bioactive compounds exhibiting antidiabetic activity in this study exhibit dissimilarities from those elucidated in other investigations, with several compounds being reported for the first time. An exemplification of compounds such as 4-hydroxyphenylpyruvic acid, glutamine, and 5′-hydroxymethyl-1'-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl) can be furnished.

According to the initial research results (Benchoula *et al*., 2019), it was observed that the administration of water extract derived from *P. malayana* leaves at doses of 1, 2, and 3 g/kg resulted in a significant decrease in blood glucose levels in a zebrafish model with diabetes.

In recent investigations conducted by Nipun *et al*. (2020b, 2021b), unique phytochemical substances, including heptan-1'-one, α-terpinyl-β-glucoside, and machaeridiol-A, were identified in this plant. However, it has been discovered that 4-hydroxyphenylpyruvic acid, a phenolic molecule, lacks antidiabetic effects. Nevertheless, it exhibits considerable promise for numerous additional biological activities, namely in terms of its antibacterial and antioxidant properties. The antidiabetic properties of the following three bioactive compounds (5′-hydroxymethyl-1'-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl), α-terpinyl-β-glucoside, machaeridiol-A) were confirmed through molecular analyses conducted *in silico* by Nipun *et al*. (2020b). The present experiments employed computational methodologies to predict the interaction, binding, and mechanism of action of these drugs, together with their precise binding sites on the enzyme.

Fairuz *et al*. (2020) examined blood glucose and pancreatic cells in induced type 1 diabetic rats. This study used alloxan to induce six rat cohorts. All treatment groups showed a considerable drop in blood glucose levels, with the highest reduction at 1000 mg/kg BW (49.76%).

Additional study has been conducted to optimise the extraction of *P. malayana* leaf extract in order to increase its inhibitory effect against α-glucosidase linked to diabetes. The optimised extract (OE) had a notable inhibitory effect on alpha-glucosidase, with an IC_{50} value of 2.02 μg/mL, as reported by Syed Mohamad et al. (2023). In comparison, the methanol extract, as stated by

Table 1: Literature Review Matrix of *P. malayana* Jack as Antidiabetic Agent

References	Part	Medicinal Value / Activity	Profiled Metabolites / Active Compounds
(Benchoula *et al*, 2019)	Leaves	Antidiabetic activity (Type 1 diabetes) * using diabetes zebrafish model	Phytosterols, Sugar alcohols, Sugar acid, Free fatty acids, Cyclitols, Phenolics, Alkaloid
(Fairuz *et al*., 2020)	Leaves	Antidiabetic activity (Type 1 diabetes) * using diabetes rat model	Chimonanthus, (+) Chimonanthus, Meso-Chimonanthus, Calychanthine, Hodgkinsine, 2-ethyl-6-methylpyrazine, 3-methyl-1,2,3,4-tetrahydro-gamma- carboline
(Nipun *et al*., 2020b; Nipun *et al*., 2021b)	Leaves	Antidiabetic activity (alpha-glucosidase inhibition)	5′-hydroxymethyl-1'-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl), α-terpinyl-β-glucoside, Machaeridiol-A, 1,3,5-benzenetriol, Palmitic acid, Cholesta-7,9(11)-diene-3-ol, 1-monopalmitin, β-tocopherol, α-tocopherol, 24-epicampesterol, stigmast-5-ene, 4-hydroxyphenylpyruvic acid, Glutamine
Syed Mohamad et al., 2023	Leaves	Antidiabetic activity (alpha-glucosidase inhibition)	Propanoic acid, Succinic acid, D-tagatose, Myo-inositol, Isorhamnetin, Moracin M-3′-O-β-D-glucopyranoside, Procyanidin B3, and Leucopelargonidin

Nipun et al. (2021a), had an IC_{50} value of 2.71 µg/mL. Various substances, including propanoic acid, succinic acid, D-tagatose, myo-inositol, isorhamnetin, moracin M-3′-O-β-D-glucopyranoside, procyanidin B3, and leucopelargonidin, have been identified as possessing antidiabetic properties (Syed Mohamad et al., 2023). This discovery has significant possibilities for future investigations in the field of diabetes therapy.

Conclusion

Our studies have shown that there has been a growing interest in the *Psycothria* genus in recent years, as seen by a rising number of publications. This interest is primarily driven by the genus' traditional applications and pharmacological properties. This review provides an overview of the primary conventional applications, as well as the pharmacological characteristics, phytochemistry, and chemotaxonomy, associated with the subject. The genus *Psychotria* has an intricate taxonomy, and its phytochemical analysis has proven to be a valuable tool for comprehending and establishing chemotaxonomy. This genus is known to contain several types of natural products such as alkaloids, flavonoids, and terpenoids.

Authors contributions

Conceptualization, S.N.A.S.M. and A.K.; methodology, S.N.A.S.M. and A.K.; software, S.N.A.S.M.; validation, S.N.A.S.M. and A.K.; formal analysis, S.N.A.S.M. and A.K.; investigation, S.N.A.S.M. and A.K.; resources, S.N.A.S.M., and A.K.; data curation, S.N.A.S.M. and A.K.; writing—original draft preparation, S.N.A.S.M.; writing—review and editing, S.N.A.S.M., A.K., S.Z.M.S., Q.U.A., Z.I., and T.S.N.; visualization, S.N.A.S.M. and A.K.; supervision, A.K.; project administration, S.N.A.S.M. and A.K.; funding acquisition, S.N.A.S.M. and A.K. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used AI-assisted technologies to enhance readability and clarity. The author reviewed, edited, and verified the content to maintain accuracy and integrity, with full responsibility for the final publication.

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Table A1. Data from published research papers on *Psychotria* species related to their antidiabetic property

References	Plant - parts & extraction method	Antidiabetic mechanism of action	Bioactive compounds	Identification method
(Nipun et al., 2020b)	○ *P. malayana* ○ Leaves ○ Sonication technique by using methanol at different ratio (0%, 25%, 50%, 75% & 100%)	Alpha-Glucosidase Inhibition	○ 5′-Hydroxymethyl-1' -(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl) -heptan-1' -one ○ *α*-Terpinyl-β-glucoside ○ Machaeridiol-A	○ LC-MS analysis ○ *In Silico* Molecular Docking
(Nipun et al., 2021b)	○ *P. malayana* ○ Leaves ○ Sonication technique by using methanol at different ratio (0%, 25%, 50%, 75% & 100%)	Alpha-Glucosidase Inhibition	○ 1,3,5-Benzenetriol ○ Palmitic acid ○ Cholesta-7,9(11)-diene-3-ol ○ 1-Monopalmitin ○ β-Tocopherol ○ *α*-Tocopherol ○ 24-Epicampesterol ○ Stigmast-5-ene ○ 4-Hydroxyphenylpyruvic acid ○ Glutamine	○ GC-MS analysis ○ H-NMR analysis
(Abhishek et al., 2019)	○ *P. dalzellii* ○ Leaves ○ Soxhlet extraction (1:3 W/ V) using methanol for 10 hours	○ Alpha-Glucosidase Inhibition ○ Alpha-Amylase Inhibition	NA	NA

References	Plant - parts & extraction method	Antidiabetic mechanism of action	Bioactive compounds	Identification method
(Benchoula et al., 2019)	○ *P. malayana* ○ Leaves ○ A mixture of 3 g of leaf powder and 30 mL of distilled water was boiled for 15 minutes until reduced to 20 mL. The extract was filtered, and the supernatant was stored at -80˚C prior to force-feeding into the zebrafish	Alpha-Glucosidase Inhibition	○ Stearic acid ○ Palmitic acid ○ Myo-inositol ○ Erythritol ○ Beta-sitosterol ○ Quinic acid ○ Shikimic acid ○ 1-Monopalmitin ○ Glycerol monostearate ○ α-Tocopherol	○ LC-MS analysis fingerprinting ○ GC-MS analysis
(Chen et al., 2021)	○ *P. viridiflora* ○ Stem ○ A total of 6.2 kg of powder was extracted with hexane, dichloromethane, ethyl acetate, methanol, and water.	○ Alpha-Glucosidase Inhibition ○ Alpha-Amylase Inhibition	○ Fortunellin ○ Proanthocyanidins	○ LC-MS analysis ○ HPLC-MS analysis
(Bristy et al., 2020)	○ *P. calocarpa* ○ Leaves ○ 500 g of powder was soaked in 2 L of methanol for 15 days with occasional shaking and stirring at 27 ± 2 ˚C, followed by filtration	NA	○ Alkaloid ○ Flavonoid	○ *In silico* molecular docking

References	Plant - parts & extraction method	Antidiabetic mechanism of action	Bioactive compounds	Identification method
(Formagio et al., 2014)	○ *P.carthagen-ensis, P. deflexa, P. leiocarpa,* and *P. capillacea* ○ Leaves ○ Maceration with methanol at room temperature	NA	○ *p*-Coumaric acid	○ High-Performance Liquid Chromatography (HPLC/PAD)
(Nipun et al., 2020a)	○ *P. malayana* ○ Leaves ○ Sonication technique by using methanol at different ratio (0%, 25%, 50%, 75% & 100%)	Alpha-Glucosidase Inhibition	○ Alkane ○ Alkene ○ Aldehyde ○ Aromatic	○ Fourier-Transform Infrared Spectroscopy (FTIR)
(Fokoua et al., 2021)	○ *P. camptopus* ○ Stem bark ○ Maceration in water and methanol	NA	○ Rutin ○ Butin ○ Psycotrianoside B ○ Bauerenone ○ 10-Hydroxy-antirhine ○ 10-Hydroxy-iso-deppeaninol ○ Emetine ○ Hodkinsine	○ Liquid Chromatography-Mass Spectroscopy (LC-MS)
(Rosales-López et al., 2020)	○ *P. ipecacuanha* ○ Leaves, Stems & Roots ○ Vortex agitation, maceration with agitation, maceration without agitation, and ultrasonic bath using 70 % ethanol, methanol, acetone, ethyl acetate, and hexane	NA	○ Emetine ○ Cephaeline	○ High-Performance Liquid Chromatography (HPLC)

References	Plant - parts & extraction method	Antidiabetic mechanism of action	Bioactive compounds	Identification method
(Orji et al., 2020)	○ *P. microphylla* ○ Leaves ○ Maceration in ethanol with intermittent shaking using water bath shaker	NA	○ Quercetin	○ High-Performance Liquid Chromatography (HPLC)
(Iniyavan et al., 2012)	○ *P. nilgiriensis* ○ Fruit, stem, and leaves ○ Soxhlet extraction using petroleum ether, chloroform, acetone, and methanol.	NA	○ Nakijiquinone B ○ 2-Hydroxy-2, N-dimethyloctanoic acid amide octanamide, 2-hydroxy-N,2-dimethyl ○ (Z)-2-Methylhex-4-en-3-yl Nphenylcarbamate ○ 9-Octadecenoic acid (Z) ○ 3,4-Epoxy-7-octen-2-one	○ Gas Chromatography-Mass Spectroscopy (GC-MS)
(Frankova et al., 2021)	○ *P. insularum* ○ Leaves ○ Maceration with 80% ethanol in an orbital shaker for 24 hr at room temperature	NA	NA	○ High-Performance Liquid Chromatography (HPLC)

References	Plant - parts & extraction method	Antidiabetic mechanism of action	Bioactive compounds	Identification method
(Situmorang et al., 2015)	○ *Psychotria* sp. ○ Leaves ○ A handful of dried leaves is combined with 2 liters of water, then heated until the water has been reduced to around one-third of its original volume. The rest of the liquid/water is taken twice a day.	NA	○ Alkaloid ○ Steroid ○ Flavonoid	○ Phytochemical screening
(Formagio et al., 2019)	○ *P. leiocarpa* ○ Leaves ○ Maceration with methanol	NA	○ Vincosamide	○ Isolation ○ LC-DAD

NA: Not available

Table A2. Conventional and contemporary applications of the *Psychotria* species

***Psychotria* species**	**Plant part used**	**Indications**	**Herbal preparation**	**Method of administration**	**References**
P. dalzellii	Root	Scorpion bite	Ground with lime juice to make a paste	Topical and oral	(Kshirsagar & Singh, 2001)
P. ophioxyloides	Leaves and tender fruits	Stomach indigestion	Consumed with milk	NAD	(Britto & Mahesh, 2007)
P. adenophylla	Root	Mouth sore, rheumatism	Powder	NAD	(Biswas et al., 2010)
P. adenophylla	Root	Mouth sore, rheumatoid, lung ailments	NAD	NAD	(Choudhury et al., 2012)
P. denticulata	Root	Toothache	NAD	NAD	
P. montana	Leaves	Pain, colitis	NAD	NAD	
P. poeppigiana	Leaves, root, and wood	Amebic dysentery	Decoctions	NAD	(Coe et al., 2008)
P. elata	Roots, leaves, and flowers	Ear infections, Diarrhea, Emetic (induce vomiting for poisoning), Fever, Respiratory & Pulmonary Disorders (cold, coughs, etc.)	Decoctions and/or poultices	NAD	
P. ipecacuanha	NAD	Diarrhea	NAD	NAD	
P. ipecacuanha	NAD	Diarrhea and dysentery	NAD	NAD	(Fisher, 1973
	Root	Amoebicide, emetic, expectorant	NAD	NAD	(Ocampo & Balick, 2009)
	Rhizomes and roots	Expectorant	Syrup form	NAD	

	Rhizomes and roots	Diaphoretic	Powdered form	NAD	
	Rhizomes and roots	Emetic	Syrup form	NAD	
P. nudiflora	Leaves and flowers	Rheumatism	Consumed along with honey	NAD	(Rani et al., 2011)
P. nudiflora	Leaves and flowers	Rheumatism	Paste	NAD	(Tabart et al., 2009)
P. nilgiriensis	Tender fruit	Rheumatism	Paste	NAD	
P. nilgiriensis	Tender fruits	Rheumatism	Consumed along with honey	NAD	(Rani et al., 2011)
P. nilgiriensis	Tender fruit	Rheumatism	Consumed with honey	NAD	(Devadoss et al., 2013)
P. nilgiriensis	Tender fruit	Rheumatism	Consumed along with honey	NAD	(Iniyavan et al., 2012)
P. viridis	NAD	Perception	NAD	Oral (beverages)	(Choffnes, 2017)
P. viridis	Leaves	Hallucinogen	Concoction	Oral	(Gambelunghe et al., 2008)
P. viridis	NAD	Hallucinations	NAD	NAD	(Schultes & Hofmann, 1980)
P. andamanica	Leaves	General health complaints	NAD	NAD	(Kamble et al., 2008)
P. platyneura	Leaves	General health complaints	NAD	NAD	
P. montana	Leaves	Constipation	NAD	NAD	
P. sarmentosa	Leaves	Itches and sores	NAD	NAD	
P. flavida	Root	Snakebite	Infusion	Oral	(Kshirsagar & Singh, 2001)
P. peduncularis	Leaf	Sore in stomach	NAD	NAD	(Lebbie et al., 2017)

Psychotria sp.	Bark	Hernia	NAD	NAD	
P. malayana	Whole plants	Fever	Decoction	Oral	(Rao et al., 2016)
P. obtusifalia	Aerial part	Febrifuge	Decoction	Oral	(Rasoanaivo et al., 1992)
P. bulata	Aerial part	Febrifuge	Decoction	Oral	
P. ipercacuanha	NAD	*Entameoba hystolitica* infection	NAD	NAD	(Selvaraj & Jeyasankar, 2018)
P. camptopus	Bark	Paralysis and activate nerves	Concoction	Orally and part used as an anal wash	(Focho et al., 2009)
P. henryiis	NAD	Revitalizing spleen and to reduce pain	NAD	NAD	(Liu et al., 2013)
P. octosulcata	Leaf	Muscle fracture	Paste	NAD	(Rajendran et al., 2002)
P. colorata	NAD	Pain killer	NAD	NAD	(Elisabetsky et al., 1995)
P. flavida	Root	Wound	Dried powdered and mixed with coconut oil	Topical	(Ayyanar & Ignacimuthu, 2009)

NAD: Not appropriately described

Table A3. Alkaloids of *Psychotria* species[a]

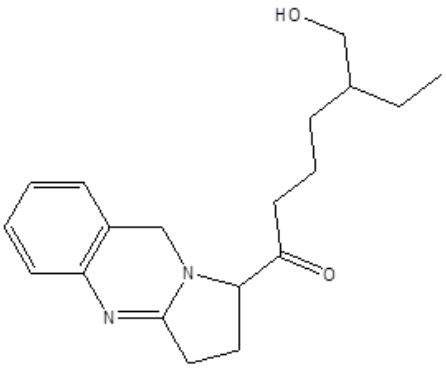
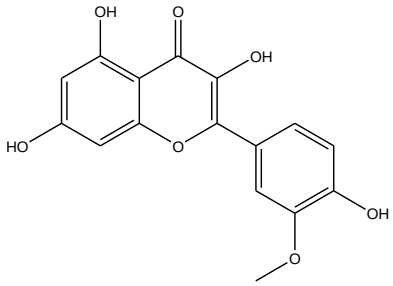
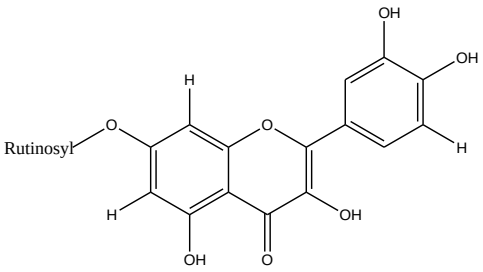
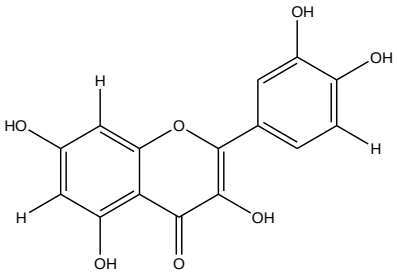
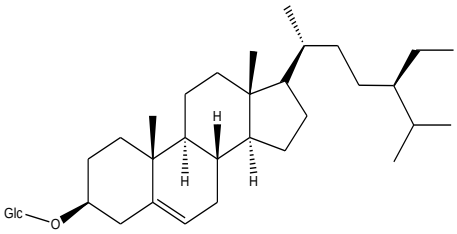
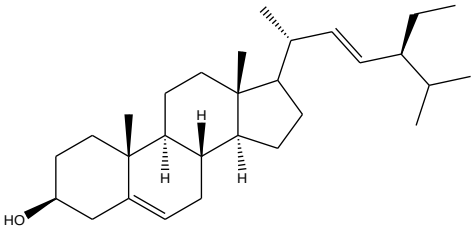
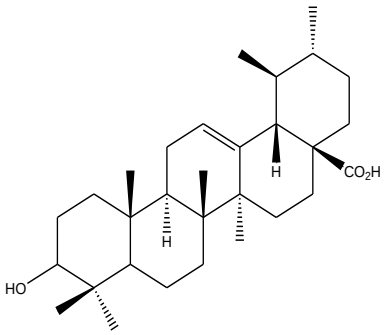
Compounds	Species	Chemical Structure	References
5′-hydroxymethyl-1′-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-b) quinazolin-1-yl)-heptan-1′-one	*P. malayana*		Nipun et al., 2020b

Table A4. Flavonoids of *Psychotria* species[a] related to antidiabetic activity

Compounds	Species	Chemical Structure	References
Isorhamnetin	*P. serpens*		(Zhou et al., 2018; Kalai et al., 2022)
Luteolin-7-O-rutinoside	*P. rubra*		(Subash-Babu et al., 2023)
Quercetin	*P. haianensis* *P. serpens* *P. spectabilis*		(Benevides et al., 2005; Yang et al., 2020)

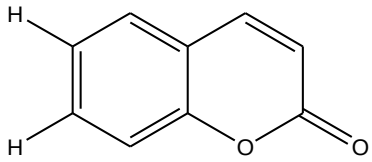
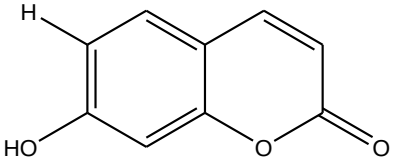
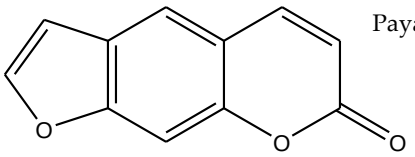
[a]Compounds are arranged according to their alphabetical order

Table A5. Terpenoids of *Psychotria* species[a]

Compounds	Species	Chemical Structure	References
β-sitosterol	*P. adenophylla* *P. haianensis* *P. mariniana*		(Cao et al., 2020; Babu & Jayaraman, 2020)
Stigmasterol	*P. vellosiana*		(Bakrim et al., 2022; Nualkaew et al., 2015)
Ursolic acid	*P. adenophylla* *P. mariniana* *P. serpens*		(Mlala et al., 2019)

[a]Compounds are arranged according to their alphabetical order

Table A6. Coumarins of *Psychotria* species[a]

Compounds	Species	Chemical Structure	References
1,2-benzopyrones	*P. spectabilis*		(Benevides et al., 2005; Xu et al., 2015; Sharifi-Rad et al., 2021; Santos Junior et al., 2023)
Scopoletin	*P. stachyoides* *P. vellosiana*		(Jang et al., 2018)
Umbelliferone	*P. spectabilis*		(Benevides et al., 2005; Mazimba, 2017; Hoult & Payá, 1996; Ramu et al., 2014)

[a]Compounds are arranged according to their alphabetical order