Banisteriopsis Species: A Source of Bioactive of Potential Medical Application

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Abstract: In recent years, interest in further development of herbal or botanical drug products derived from traditional preparations has been increasing steadily. Plants have been used for thousands of years to treat health disorders and to prevent diseases including epidemics. Several research works have been developed to search for new natural products to be used in pharmaceutical products. Active compounds produced during secondary metabolism are responsible for the biological properties of the plant species and may be used to most diverse purposes, including treatment of several diseases. *Banisteriopsis* species has been described showing interesting activities by its use in popular medicine. The mainly use was described to production of the Ayahuasca, an Amazonian psychotropic plant tea obtained from *Banisteriopsis* caapi, which contains β-carboline alkaloids, mainly harmine, harmaline and tetrahydroharmine. Other species of *Banisteriopsis* genus have been described with biological metabolites as antimicrobial, anticholinesterase, antianxiety and others. These biological activities were described chiefly by the presence of alkaloids, flavonoids, tannins. Thus, to stimulate the study into the *Banisteriopsis* genus, the purpose of the present review is to gather information on the use of the extracts and metabolites of *Banisteriopsis* species (Malpighiaceae) as a resource to diseases treatment or to pharmaceutical purposes.

Keywords: *Banisteriopsis,* alkaloids, harmine, harmaline, flavonoids, quercetin, tannins, terpenoids, *Ayahuasca*, bioactivities.

INTRODUCTION

Banisteriopsis is one of the largest and most widespread genera of the Malpighiaceae family, this neotropical genus is represented by ca 92 species and distributed mainly in Brazil, Bolivia, Colombia, Ecuador, and Peru [1, 2].

The isolated use of plants of the genus *Banisteriopsis*, or its association with *Psychotria viridis* or *Diplopterys cabrerana* give rise to *Ayahuasca* tea [3, 4], term which literally translates as "vine of the soul". The hallucinogenic tea, also known as "Santo Daime's" tea, “hoasca”, “Daime”, “yajé” or “Natema”, is traditionally used in religions celebrations by indigenous peoples of the Amazonian and Andean forests [5-8].

This tea is prepared by aboriginal and indigenous Mestizo populations of Amazon rainforest and Andes using two different plants: the stems from *Banisteriopsis caapi* and the leaves from *Psycotria viridis* [4, 9].

These effects can be primarily associated to harmine (**1**), harmaline (**2**) and tetrahydroharmine (**3**) found in *B. caapi* that act reversibly inhibiting monoamine oxidase A (MAO-A). Their combination with the indole alkaloid N,N-Dimethyltryptamine (DMT) (**4**) found in leaves of *P. viridies*, which is structurally similar to the monoamine neurotransmitter serotonin (**5**) acts on receptors 5-$HT_{2A/2C}$ like a potent psychedelic agent giving to the user the hallucinogenous sensation [3]. Recently also been shown that harmine binds to imidazoline receptors and dopamine transporters [10].

Usually, DMT is a potent and short acting psychedelic agent, but it is rapid oxidation by MAO-A. In the *Ayahuasca*, MAO-A foudeis inhibited by the harmine, thus the DMT causes an agonistic effect on serotonergic receptors [9]. In Brazil, there are other species that also contains this tryptamine in their leaves, such as *Psychotria cartagenensis* and *Diplopterys cabrerana* syn. *Banisteriopsis rusbyana* [11].

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Numerous bioactive metabolites have been found in *Banisteriopsis* species. Among biological properties described for the studied species are: antinociceptive and analgesic effects [12, 13], anticancer properties [14-16], antiproliferative [17], vasorelaxant [18-20] and hypothermic properties [21, 22], antimicrobial activity [23, 24], strong reversible inhibition of monoamine oxidase [25, 26] and inhibitory activity against acetylcholinesterase [27].

Bussmann *et al.* (2010) showed that ethanolic and aqueous extracts of *Banisteriopsis caapi* have interesting activity on *Escherichia coli* demonstrating to be interesting candidates for future research [28]. In the popular medicine, *Banisteriopsis* species have been used to treatment of topic fugal disease. Freitas (2010) proved the utilization of leaves aqueous extract of *B. anisandra* against *Candida albicans, C. krusei*, *C. parapsilosis* and *C. tropicalis* inhibited these yeasts in the same way than fluconazole, a triazole antifungal drug [29]. Hexane, ethyl acetate and methanol extract did not show inhibitory activity against *C. albicans* [30].

ALKALOIDS

Some species of *Banisteropsis*, as *B. caapi,* can be highlighted by its high level of pharmacologically active alkaloids produced, mainly of β-carboline (β-CA) as harmine (HMR), harmaline (HML), tetrahydroharmine (THH) [9]. Other β-CA's also found are harmalinic acid (**6**), harmic amide, harmine-N-oxide (**7**), harmic acid methylester (**8**), norharmine (**9**), ketotetrahydronorharmine (**10**) [31,32] and the alkaloids pyrrolidine bases shihunine (**11**) and S-(+) dihydroshihunine (**12**) [33]. In aqueous extracts, Samoylenko *et al.* (2010) reported the isolation of two alkaloidal glycosides, named banistenoside A (**13**) and banistenoside B (**14**), structure based from the azepino[1,2-a]tetrahydro-β-carboline and the know β-CA harmol (**15**) [34]. From leaves of *B. argetea* it was found the presence of the alkaloids (+)-N-methyl-tetrahydroharmine (**16**), 5-methoxy-tetrahydroharmine (5-MeO-THH) (**17**), N,N-dimethyltryptamine-N-oxide (**18**), N,N-dimethyltryptamine, TTH, harmaline, betaine (**19**) and coline (**20**) [35].

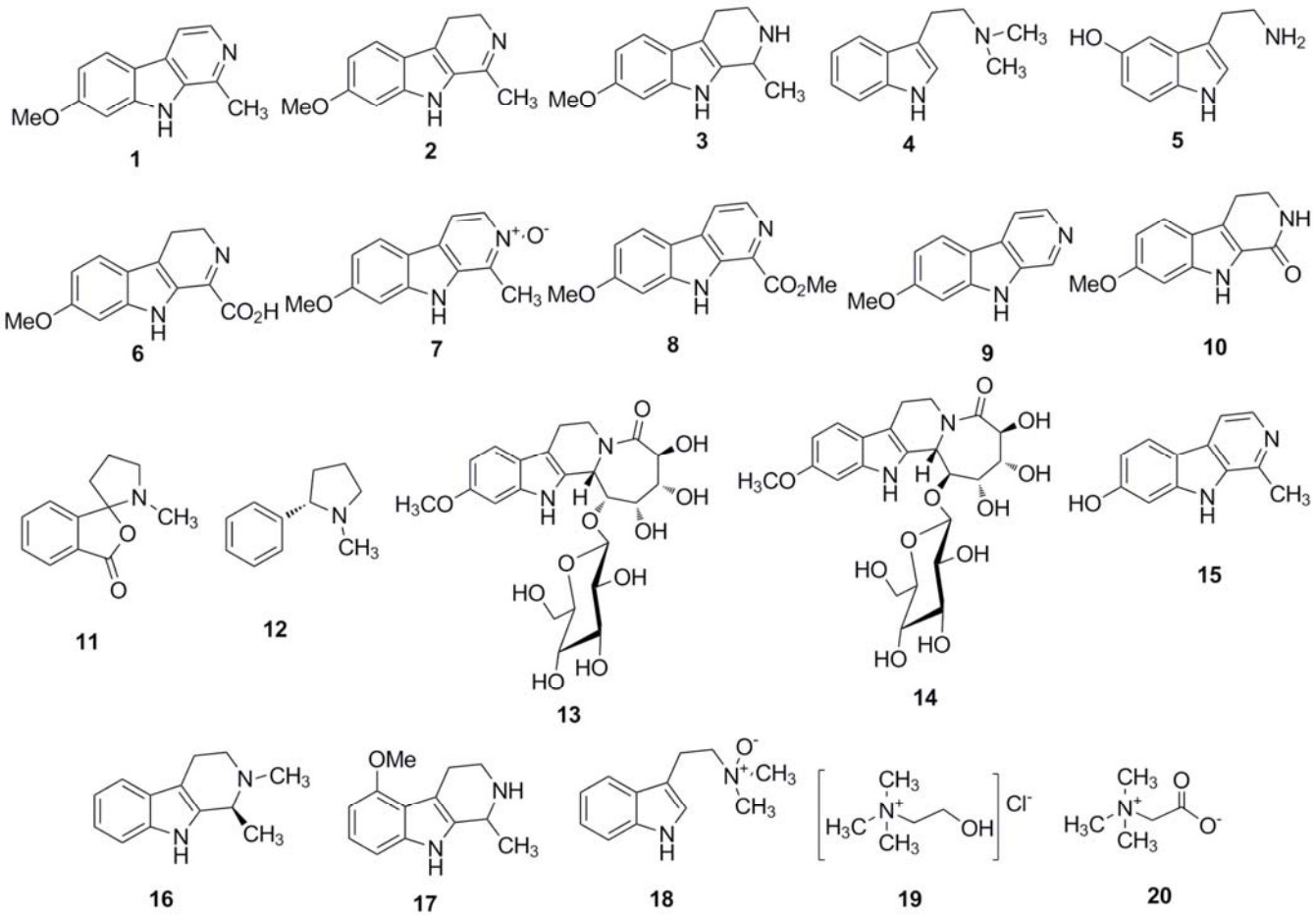

Figure 1: Example of nitrogenous compounds found in *Banisteriopsis* species and similar substances.

The β-CA's present a wide spectrum of therapeutic activities such as: antianxiety, mood control, panic-like, hopelessness and antidepressant effects. The exogenous administration of β-CA's have demonstrated a reduction in the behaviors associated with depression and anxiety in rats [8]. These effects appear to be linked with the increase of extra cellular dopamine and serotonin caused by the inhibition of MAO-A and by the increase of their respective metabolites, homovanillic acid, and 5-hydroxyindole acetic acid levels. The β-CA's are a potent endogenous ligand of the benzodiazepine receptor, causing the stimulation of this receptor in an inverse way [8, 36].

Individually, the β-CA's found in *Banisteriopsis* species showed antimicrobial effects against many species of microorganisms. In *B. caapi* extract, harmine showed effects against *Proteus vulgaris, Bacillus subtilis* and *Candida albicans*, while harmaline was effective against *P. vulgaris* and *C. albicans* [37].

Im *et al*. (2009) evaluated the effect of β-CA's on collagen-induced PLCγ2 activation in washed rabbit platelets in which harmine and harmane displayed a complete suppression on collagen-induced PLCγ2 phosphorylation demonstrating that β-carboline alkaloids have structural antiplatelet activity [38]. It is was reported the potential to reduce systemic arterial blood pressure by the administration of harmine and the vasorelaxant activity of harmane with a hypotensive effect. Thus the beneficial property of harmane and harmine on cardiovascular system may be relevant in the inhibition of thrombus formation by an anti-aggregation platelet activity [39].

Ayahuasca was reported like a prophylactic agent against malaria and other parasites [40]. Hopp *et al.* (1976) observed that harmine exhibited significant anti-trypanosomal activity against *Trypanosoma lewisii* [41]. Harmine and harmaline have been also reported like an inhibitory activity against *Plasmodium* species (Malaria disease) [42, 43]. Astulla *et al.* (2008) evaluated the inhibitory effects and showed a moderate *in vitro* antiplasmodial activity against *P. falciparum* (harmine: IC_{50} 8.0 µg/ml; harmaline $IC_{50:}$ 25.1 µg/ml) [20].

Moreover β-CA's showed the inhibitor potential of multiple cytochrome P450 enzymes, could be influence the hepatic activities. Harmine and harmol inhibited the activity of CYP3A4 mediated by testosterone 6β hydroxylation suggested by the authors as the result of a noncompetitive inhibition. However harmaline, harmine and harmol exhibited a moderate inhibition on CYP2D6 suggesting a competitive inhibition [44].

El Gendy (2012) observed that harmine and its metabolite, harmol, are new inhibitors of dioxin-mediated effects. Harmine and harmol significantly inhibited the dioxin-mediated induction of CYP1A1 at mRNA, protein, and activity levels in a concentration-dependent manner in human and murine hepatoma cells. At post-translational level, harmine and harmol decreased the protein stability of CYP1A1, suggesting that posttranslational mechanism is involved [45, 46].

Mono amino oxidase inhibitors MAOI´s are used for the treatment of depressive disorders, anxiety disorders, Parkinson's disease, and Alzheimer's disease. This BCA´s may attenuate the dopamine- and 6-hydroxydopamine (6-OHDA)-induced anterad brain mitochondrial and sinaptosomal functions and viability loss in PC12 cells. The study demonstrated the property to decrease alterations of the Ca^{2+}, and succinate-induced swelling and membrane potential formation in mitochondria caused by preincubation of catecholamines. BCA´s showed protective effects on dopamine-induced mitochondrial damage provided a defense against 6-hydroxydopamine (6-OHDA). This property can help in the treatment of the Parkinson´s disease (PD) because dopamine is preferentially deaminated by MAO-B in the human brain, MAO-B inhibitors should increase the basal central dopamine levels in patients with PD, one time the BCA´s in elevated concentrations may exert a protective effect on oxidative neuronal damage attenuating of mitochondrial and synaptosomal dysfunction [47].

MAO-B inhibition also has neuroprotective effects. Remarkably, MAO-B activity increases in aging and is particularly high around senile plaques in patients with Alzheimer's disease. By inhibiting MAO-B, the neurodegenerative processes that occur in the Alzheimer's disease brain would be suppressed [48] or by the inhibition of the acetylcholinesterase [30].

Miralles (2005) determinated the affinity and biding profile of harmine and harmaline for imidazoline I_2 receptors and catalytic sites of monoamine oxidase (MAO)-A/B in rat brain and liver and showed that BCA´s bind with high affinity to imidazoline I_{2B} receptors, and similarly to I_2 ligands (LSL 60101) can block the behavioral and biochemical effects of opiate withdrawal. These results suggest that some BCA´s and selective imidazoline I_2 drugs can be useful agents

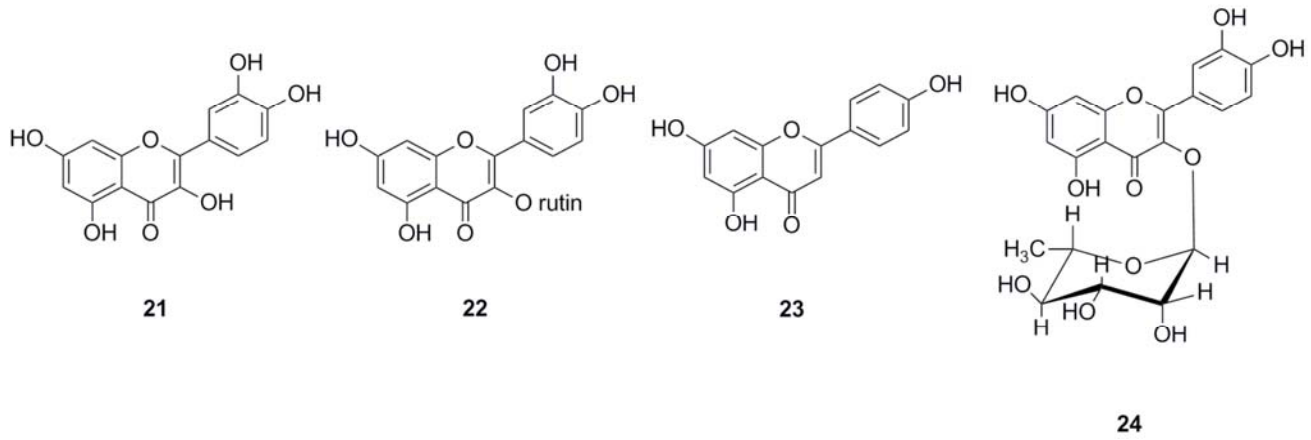

Figure 2: Flavonoids founded in *Banisteriopsis* species.

for the treatment of the opiate abstinence syndrome in humans [49]. The BCA´s also stimulate locus coeruleus neurons in anaesthetized rats, showing this stimulation occurs directly in the LC by a mechanism independent of I_1- and I_2- imidazoline receptors [50].

FLAVONOIDS

Flavonoids are a group of polyphenols widely occurring in plants and foods of plant origin. Inside this pharmacognostic class, many exhibit a multitude of biological activities like anticarcinogenic [51, 52], antioxidative [53], enzyme-modulating activities [54-56] and protective effect on carviovascular disease [57, 58].

In preliminary studies, Frias *et al*. (2011) founded flavonoids associated to the flowers and leaves of the *B. anisandra, B. campestri, B. laevifolia* and *B. malifolia* [59]. *B. variabilis* extract showed activity against bovine herpes viruses type 1 (BoHV-1), and S133 strain withdraw avian reovirus [60]. From metanolic extract of *B. variabilis*, there were isolated the flavonoids quercetin (**21**), rutin (**22**), apigenin (**23**) [61]. From ethanolic extract of *B anisandra*, was found the flavonoid quercetin-3-O-rhamnoside (**24**) [29]. Quercetin is found in a wide variety of plants and studies showed that can reduce infectivity of target cells and replication against a wide variety of respiratory viruses, like HSV-1 and HSV-2, adenovirus (AdV-3, AdV-8 and AdV-11) and coronavirus [62-64], parainfluenza virus type 3, respiratory syncytial virus [65] and rhinovirus [66].

TANNINS

Tannins are defined as water-soluble phenol compounds that are able to bind and precipitate proteins and other macromolecules within aqueous solutions [67]. They are found in all of plants and play important roles of defense against herbivory by generalists [68] and pathogenic microorganisms [69]. They have very high variability in their structures with several hundred unique molecules detected in plants [70]. However, the overall tannin composition of many plant species is yet unknown.

The Malpighiaceae family, as well as the *Banisteriopsi*s species, presented high concentration of condensed tannins [71, 72]. These consist of two or

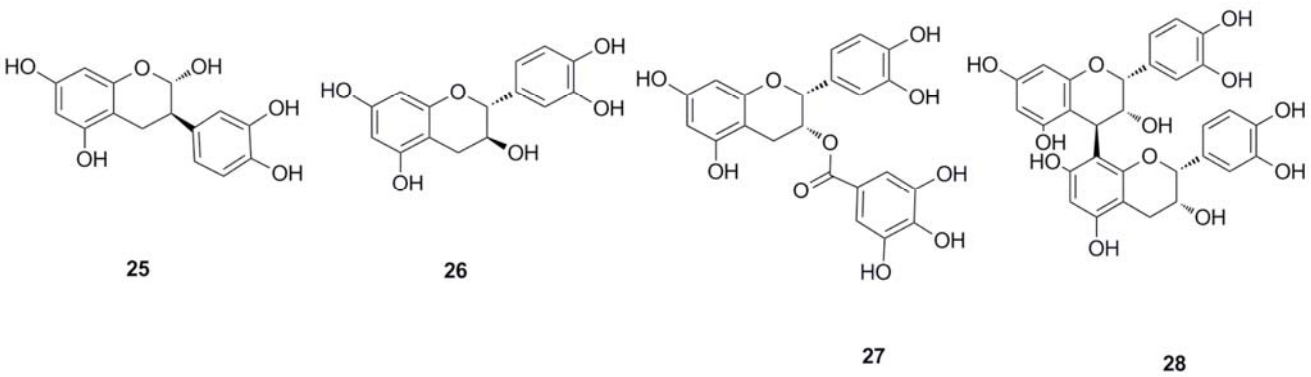

Figure 3: Tannins founded in *Banisteriopsis* species.

more monomeric (+) – catechin (**25**) or (-) – epicatechin (**26**) units [67]. From metanolic extract of *B. variabilis*, were isolated the epicatechin and epicatechin gallate or epigallocatechin (**27**) (Queiroz *et al.* 2011) and procyanidin was found in *B. caapi* extract B2 (**28**) [61].

Oki (2005), studying four species of *Banisteriopsis* (*B. stellaris*, *B. pubipetala*, *B. adenopoda*, *B. argyrophylla)* during two years in Cerrado areas verified that the tannin concentration varied according to species, development phase and seasons of year. Among the species studied, the lowest concentration was found in *B. adenopoda* leaves (5.3% dw) while *B. stellaris* presented the highest concentration (16.9% dw) during dry season. The study also showed that the old leaves had higher tannin concentration than new leaves during dry season. For *Banisteriopsis* species, the exposure time of the leaves and water stress can favor the production of tannin in dry season [71].

On the other hand, during rainy season the old leaves presented lower concentration of tannin than new leaves in almost all species studied. In this rainy period there is a high diversity of herbivores and it is probable that the high content of tannin found in new *Banisteriopsis* species leaves is related to herbivore pressure [71]. New leaves are considered as an ephemeral resource and it is frequent the investment in chemical defense mainly in period of high herbivory pressure.

TERPENOIDS

Aquino *et al*. (1991) reported terpenoids from *B. caapi* [72]. In leaves of *B. anisandra,* there were reported the steroids stigmasterol (**28**), β-sitosterol (**29**), β-sitosterol oleate (**30**), the pentacyclic triterpene ursolic acid (**31**), oleanolic acid (**32**), fridelin (**33**), glochidonol (**34**), lupenone (**35**) and the sesquiterpene

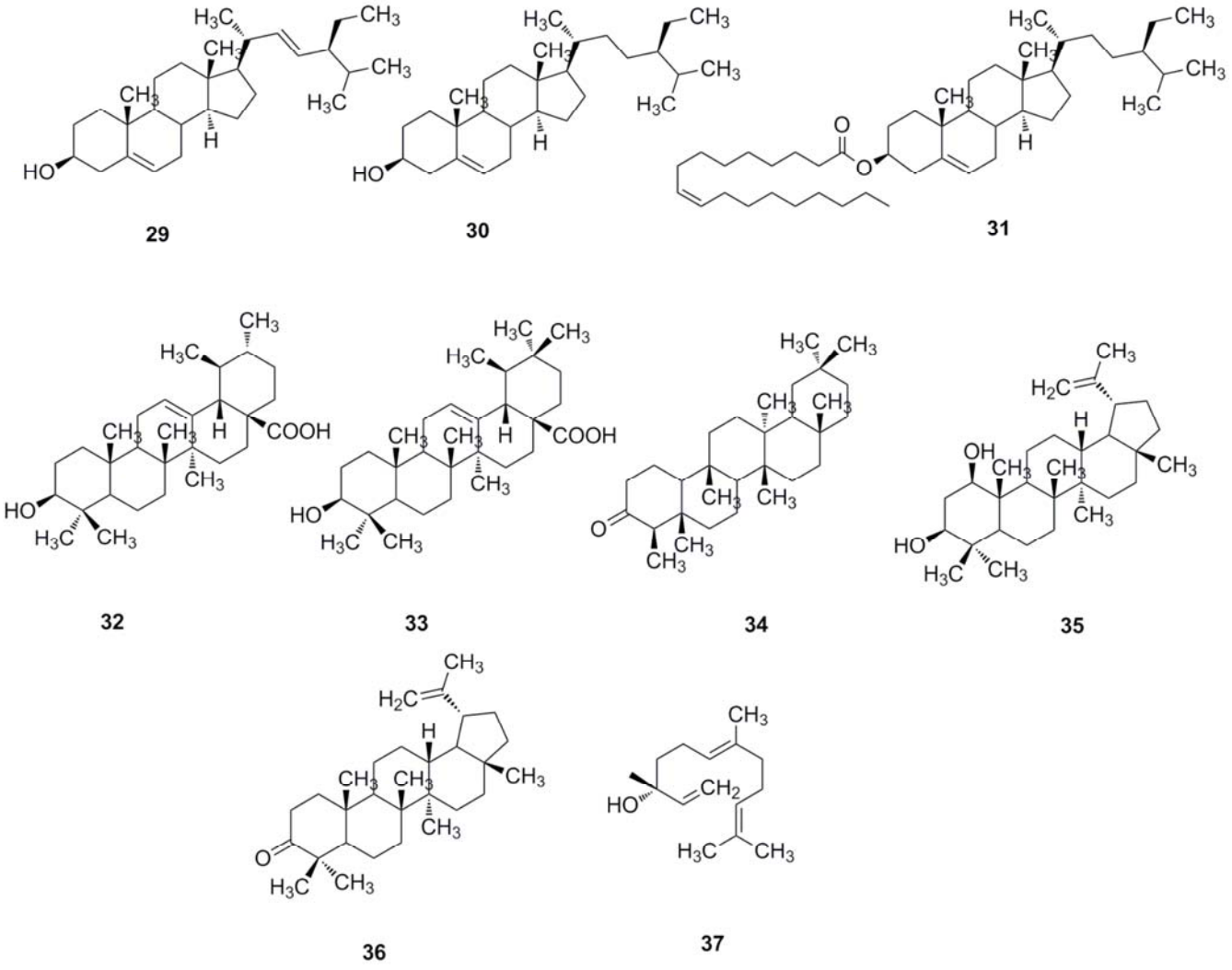

Figure 4: Terpenoids founded in *Banisteriopsis* species.

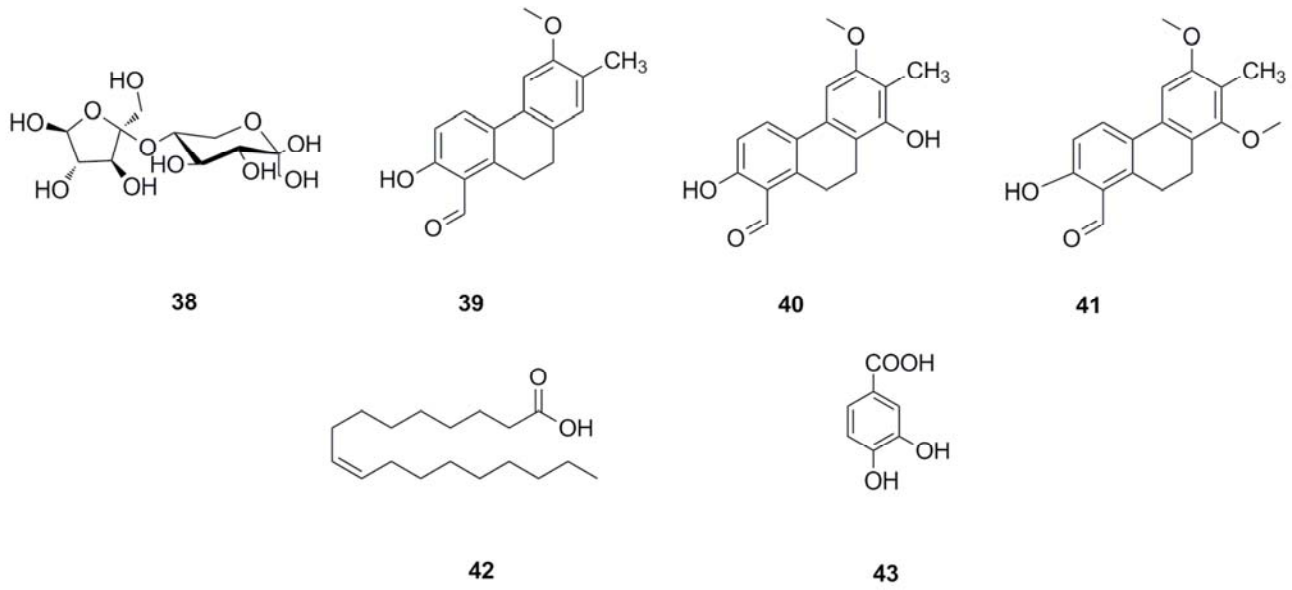

Figure 5: Example of Miscellaneous metabolites founded in *Banisteriopsis* species.

nerolidol (**36**) [29]. Recently, Pinho *et al*. (2009) reported that the seeds of *B. pubipetala* and *B. harleyi* contains high concentrations of oil (43.5% and 46.5% respectively), largely unsaturated, with high content of linoleic acid, high oleic and linolenic fatty acid (*B. pubipetala*) and mono-unsaturated gadoleic acid (*B. harleyi*) [73].

The administration of oleanolic acid demonstrated decrease CCl4 induced liver parenchymal cell necrosis, steatosis, and prevents CCl4 plus alcohol-induced chronic cirrhosis in rats [74, 75]. Oleanolic acid protects against the hepatotoxicity produced also by acetaminophen, cadmium, bromobenzene, phalloidin, thioacetamide, furosemide, colchicine [76]. However ursolic acid also protects against D-galactosamine-induced liver injury in rats, and prevents acetaminophen-induced cholestasis [77]. The anti-inflammatory effect of oleanolic acid was described by Gupta *et al*. (1969). They reported the inhibitory effects of oleanolic acid on carrageenan-induced rat paw edema and formaldehyde-induced arthritis [78]. The mechanisms of anti-inflammatory effects have been attributed to the following aspects: (1) Inhibition of histamine; (2) inhibition of lipoxygenase and cyclooxygenase activity reducing some inflammatory factors produced during arachidonic acid cascade; (3) inhibition of elastase [79].

MISCELLANEOUS METABOLITES

The disaccharide β-D-fructofuranosyl-(2→5)-fructopyranose (**38**) were also isolated by Samoylenko (2010) [34]. The metabolites 2-hydroxy-6-methoxy-7-metil-9,10-dihydrophenanthrene-1-carbaldehyde (**39**), 2,8-hydroxy-6-methoxy-7-methyl-9,10-dihydrophenanthrene-1-carbaldehyde (**40**), 2-hydroxy-6,8-methoxy-7-methyl-9,10-dihydrophenanthrene-1-carbaldehyde (**41**); oleic acid (**42**) and protocatechuic acid (**43**) were reported in extracts of *B. anisandra* [29].

CONCLUSION

Banisteriopsis species are both metabolically and taxonomically diverse and showing enormous metabolic capabilities and production of diverse bioactivity structures. The metabolites found in *Banisteriopsis* can be used to drug prototypes to many pathological or physiological situations.

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