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Phytochemistry and pharmacological review of *Mitragyna inermis* (Willd.) Kuntze (Rubiaceae)

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Abstract
As part of the development of traditional medicine rich in Africa and particularly in Bénin, several studies have been conducted for years to evaluate the ethnopharmacological properties of medicinal plants. It is in this context that *Mitragyna inermis* is known for many of these properties mentioned in the traditional pharmacopoeia and whose biological analyses have confirmed some of them. The purpose of this work is to summarise previous work; biological as chemical on this plant. The extracts showed that it has antibacterial, antiviral, antiparasitic properties. The isolated compounds are certainly responsible for these known biological activities. The synergistic action of the compounds present in the extracts can justify also its use in the treatment of several pathologies. Finally, this review of literature carried out on this plant, is a contribution to the synthesis of the previous works carried out in order to deepen its valuation.

Keywords: Phytochemistry, pharmacological, *Mitragyna inermis*, kuntze

Introduction
Studied by different methods, medicinal plants are still the first reservoir of bioactive molecules, sources of new drugs. Thus, recipes and secrets of traditional medicine were bequeathed from generation to generation [1] before the appearance of synthetic drugs which ended up showing several limits of their uses. Among these limitations, we can list: the absence of sanitary or rudimentary infrastructure, the high cost of pharmaceutical products, the low income of rural populations, the defective and counterfeit and / or the misuse of these medicines [2]. Today, medicinal plants constitute a heritage for the majority of poor communities in developing countries, and these depend on them for their primary health care [3]. The World Health Organization [4] estimates that more than 80% of the African population still rely on traditional medicines for their medical safety. Bénin is not spared mainly by the importance of these medicinal and aromatic plants which are used for therapeutic purposes and which have the advantage of being often available and accessible to the population [5].
This study focuses on *Mitragyna inermis*, plant of Beninese flora chosen for its anthelmintic properties but which has been the subject of several previous studies whose synthesis was carried out.

The species *Mitragyna inermis* [6]
synonyms
Mitragyna africana (Willd.) Korth
Mitragyna stipulosa (DC.) O. Ktze
Nauclea africana Willd.
Uncaria inermis Willd.

Classification
Kingdom: Plantae
Class: Equisetopsida
Subclass: Magnoliidae
Super-order: Asteranae
Order: Gentianales
Family: Rubiaceae
Genre: Mitragyna
Species: inermis

Geographical distribution

M. inermis is found in swampy areas in the tropics and subtropics. It is common to the loamy or clayey soils of the valleys from the Senegal River to the maritime Casamance [7]. It is met in several African countries including Senegal, Cameroon, Central African Republic, Chad, DR Congo and Sudan. In Bénin, the plant is distributed almost everywhere [8].

Botanical description [9]

Mitragyna inermis is a specie that grows in the alluvial plains of the Sudano-Sahelian zone of intertropical Africa. It is a shrub 5 to 10 m tall with elliptical leaves up to 7 cm long and 4 cm wide. Its rib is lateral from 6 to 7 pairs. It has a terminal globular inflorescence. The flowers are white and fragrant. It has a spherical fructification, dark brown then composed of many small capsules opening into two valves. Finally, its seeds are small and numerous.

Traditional uses

Aqueous decoction of roots and leaves is used orally in anorexia and constipation and as a steam bath in the treatment of leprosy [10]. In Mali, leaf decoction is used for its febrifuge and stimulating properties in infectious diseases, it is used against jaundice, syphilis, arthritis. It is also reported that in Côte d'ivoire, *M. inermis* is a specie much used by healers, but variously depending on geocultural access. The barks of this plant are often prescribed for the gravid-puerperal states, stomach pains, dysentery, schistosomiasis. In external use, the bark of trunk or stem, freed by scratching of the epidermis, would, after drying and grinding in to powder, a healing of large wounds and an excellent vulnerability. The decoction of the leaves or bark of the stems is used as antidiabetic, antipyretic and then in the treatment of hypertension, dysentery, schistosomiasis, syphilis, jaundice, jaundice, mental illness, contagious diseases , intercosal pain, epilepsy, wounds and arthritis. Different leaf preparations are also used in baths and beverages in cachectic affections, arthritis, myalgia, intercostal pain and enteralgia [11]. In Guinea, the aqueous decoction of trunk bark is used as a diuretic and febrifuge. In Senegal, bark is used against stomach upset, dysentery, schistosomiasis. Bark powder is used to heal large wounds. The very bitter roots are used in decoction against malaria [12]. The bark of *M. inermis* (Willd.) is one of the natural substances recommended for the immunological and nutritional recovery of HIV patients (PvVIH) [13]. In addition, the aqueous decoction of the stem bark is used in the treatment of constipation. In Bénin, the aqueous decoction of the leaves of the plant is used for the treatment of diarrhea, ectoparasitosis, fever, helminthiasis and tuberculosis [14]. For Assogba, [15] an aqueous decoction of the bark of *M. inermis* stem with shea butter is given as a drink to the animal suffering from helminthiasis. The animal, in its turn, rejects helminth eggs in the feces. In Côte d'ivoire, the plant is used in animals, particularly ruminants, to treat diarrhea and eliminate intestinal worms [16]. Finally, sheep and goats look for leaves and young twigs, while cattle do not appreciate very much foliage [17]. Peuls also recommend decoction of bark for diarrhea and maceration of fruit and seeds (with Tapinanthus bangwensis) for infertility of cows [11].

In short, *Mitragyna inermis* is an important drug considered febrifuge by Wolof and Fulani, as a stimulant by the Casamance and Serer, as a specific drug of the gravid-puerperal states by Fulani Toucouleur, Wolof, Serer and as psychosomatic by the Peul-Toulcouleur and the Bainuk [11]. The decoction and the triturate of the same plant are used in Burkina Faso for the treatment of neuropsychiatric pathologies [18].

Toxicological study

Several studies have been carried out on the toxicity of *M. inermis* extracts. Thus, to evaluate the toxicity and genotoxicity of antimalarials, it has been observed that an alkaloid-rich extract derived from *M. inermis* induces a strong inhibition of protein synthesis in mammalian cells, but shows no mutagenic activity or genotoxicity [19]. The acute general toxicity assessed by Ouedraogo in Burkina Faso, classified the *M. inermis* extracts in the category of weakly toxic substances with an LD50 = 810.7468 mg / kg [20]. Monjanel-Mouterde [21] conducted the same study in France of the acute oral toxicity and chronic toxicity of the hydroethanolic extract (60/40) of *M. inermis* leaves. These results indicated that the toxicity of this extract would be greater than 3000mg / kg of body weight [22]. Ivory Coast, the acute oral toxicity of the decoction leaf extract in Swiss strain mice at 4465 mg / kg revealed that the plant is not toxic. In Nigeria, on Swiss strain rats with aqueous extracts and the ethanol extracts [23]. He found a lethal dose greater than 2000 mg / kg and 1587.5 mg / kg body weight respectively. In Bénin, toxicity is assessed *in vivo* for 7 days on male and female Wistar strain albino rats. The result have shown that crude aqueous extract of *M. inermis* stem back is less toxic up to 2500 mg/kg of body weight [24].

Pharmacological studies

Several studies were performed on various organs of *M. inermis* and revealed that this plant has antimicrobial, antioxidant, neuroprotective and antiamnesic, myorelaxant and antispasmodic properties, anti-bacterial and antiviral, antiamnesic.

***In vitro* anthelminthic activity**: Methanol-water extract and acetone-water extract of *M. inermis* leaf inhibit at different concentration the eggs, the larval and adult worms of *Haemonchus contortus*. The IC 50 was 59.14 µg/ml for egg hatching; 96.62 µg/ml for larval migration inhibition assay and 131.34 µg/ml for adult worm motility inhibition assay [25].

***In vivo* anthelminthic activity**: The study of in vivo anthelminthic activity on *H. controtus* of *M. inermis* leaves on three different breeds of sheep showed at the dose of 3.2 g/kg, that the plant could be applied for the control of gastrointestinal nematodes in small ruminants [26].

Antibacterial activity: The antimicrobial activity of the sequential *n*-hexane, acetone and 50% aqueous methanol extracts of leaves, stem bark and roots of *M. inermis* were tested against *Bacillus subtilis*, *Pseudomonas syringae* and *Cladosporium herbarum*. Acetone leaf extract and acetone root extract showed a strong inhibition on *Bacillus subtilis* and *Cladosporium herbarum* respectively. While 50% aqueous methanol extract of leaf showed moderate inhibition on *Pseudomonas syringae* [27].

Antimalarial activity: In a previous study, the alkaloids contained in chloroform ((IC_{50} = 4.36–4.82 µg/ml) extracts and ursolic acid (IC_{50} = 15–18 µg/ml), purified from the hydromethanol extract of *M. inermis* induced a significant decrease of *P. falciparum* proliferation. However, aqueous extracts ((IC_{50} > 500 µg/ml), traditionally used for medication did not show high antimalarial activity [28].

Neuroprotective and Antiamnesique activity: These results suggest that *M. inermis* leaf extract possess potential antiamnesic effects. The activity levels of superoxide dismutase and catalase were significantly increased, whereas the thiobarbituric acid reactive substance was significantly decreased after 8 consecutive days of treatment with *M. inermis* at the dose of 393 mg/kg [29].

Muscle relaxant and antispasmodic activity: The aqueous extract of bark of *M. inermis* concentration 0.5 mg/ml, 0.75 mg/ml, and 1 mg/ml induces a significant decrease of the ileal basal tone, respectively 37.1%; 51.1% and 75.2%. This same exract inhibited submaximal contractions induced by 0.01 mg/ml of acetylcholine with IC_{50} value of approximately 0.75 mg/ml [30].

Cardiovascular activity: The aqueous extract of *Mitragyna inermis* produced *ex-vivo* an increase in cardiac contractile response and coronary flow, and then induced relaxation in the coronary arteries without altered heart rate in rats thus confirming the traditional use of this plant as antihypertensive [31].

Stimulant effect: Extracts of *M. inermis* breeds on the system rabbits immune system, an important stimulation of the production of white blood cells, lymphocytes, platelets, total proteins and different classes of globulins and then a noticeable decrease in red blood cells, as well as albumin [32].

Anticonvulsant property: Both aqueous and ethanolic extracts of *Mitragyna inermis* was a statistical significant difference between the effect of the extracts (at 250 and 500mg/kg) and the negative control ($p < 0.05$). Extracts differents doses dependently increased the onset of clonic convulsion induced by pentylenetetrazol and strychnine. Note that the ethanol extract has better protection compared to aqueous extraction [23].

Anticonvulsant activity: The chloroformic extract of the leaves of *M. inermis* did not show protection against maximal electro shock convulsion but demonstrated shortened recovery period which was not statistically significant with the negative control [33].

Antitifodic activity: The combined of *Monetes kerstingii* flower, *Mitragyna inermis root* and *Boswellia dalzielii* bark is used to prepare ethanol and aqueous extracts. *S.* Typhi and *S.* Paratyphi had MICs of 12.5 mg/ml for ethanolic extract. While for the aqueous extract, both organisms had MICs of 12.5 mg/ml and 25 mg/ml respectively. The MBC of ethanolic extract for both organisms was found to be 100 mg/ml and 200 mg/ml respectively. Similarly the aqueous extract we have 200 mg/ml and 400 mg/ml respectively [34].

Antitifodic activity: With the mixture of both plants (*Mitragyna inermis* and *Monotes kerstingii)*, two extracts are prepared. The combined ethanol and aqueous plant extracts shows activity against *S. Typhi* with diameter of zones of inhibition ranging from 14.00 mm and 15 - 24 mm respectively. The combined extracts were also active against *S. Paratyphi* A with diameter of zones of inhibition ranging from 10 - 24 mm and 11 - 26 mm for ethanol and aqueous extracts respectively [35].

Antibacterial activity: The methanolic extract of the leaves of *M. inermis* showed antibacterial activity on *Staphlococcus aureus*, *Escherichia coli* and *Klebsiella pnuemoniae* with MIC of 50 mg/ml, 50 mg/ml, and 25 mg/ml respectively [36].

Antitripanoside activity: At 100 mg/ml, the aqueous extracts of *M. inermis* leaves had a significantly high effect ($P < 0.05$) on *Trypanosoma brucei brucei* of ruminants than the control PBS [37].

Antiplasmodial Activity: Extracts have been tested *in vitro* against Chloroquine resistant strain (K1) and chloroquine-sensitive strain (3D7) of Plasmodium falciparum. Aqueous extracts exhibited the best results against K1 with the 50% inhibitory concentration (IC_{50}) values of 0.54±0.18, 1.72±0.99, 1.54±0.04 µg/mL for *M. inermis* leaves. Hydroethanolic extract from the leaves of *M. inermis* gave also IC_{50} value of 0.87 ± 0.10 g/mL with 3D7. As for the hydroacetone extract of the roots, the IC_{50} values recorded with *P. falciparum* K1 are 1.82 ± 1.50 µg/mL [38].

Anti-diabetic Effect: 350 mg/kg is the dose that showed good activity with ethanol extract of *M. inermis* after the result of the evaluation of hypoglycemic effects [39].

Anti-Plasmodial activity: Uncarine D is a compound isolated from leaves of *M. inermis*. Test on strains of plasmodium falciparum, the results showed that pure uncarine D was less active in the chlorhydrate form (IC50 > 20 µg/mL) than in the basic form (IC50 = 17.03 µg/mL), as was observed for total alkaloids. Clearly, uncarine D is not the most active compound in the total alkaloids. The improved activity of the total alkaloids in the leaves of *M. inermis* was probably due to synergistic action between alkaloids [40].

Antiplasmodial activity: The IC50 were 2.61 µg/ml for *M. inermis* leaves and 2.35 µg/ml for *M. inermis* roots for the alkaloid extracts. Tannins extracted from leaves and roots of *M. inermis* did not show antiplasmodial activity (IC50 > 100 µg/ml) [41].

Anti-Plasmodial activity: Antiplasmodial activity of aqueous crude vegetal extracts of *M. inermis* on various *P. falciparum* strains FcM29-Cameroon, FcB1-Colombia and Nigerian gave respectively as IC_{50} after 72h of experience 40.71 µg/ml; 44.86 µg/ml; 45.49 µg/ml [42].

Antioxidant activity: The acetone, methanol and water extracts of *M. inermis* roots have showed strong radical scavenging activity against DPPH for all the three extracts [43].

Biopesticide effects: The application of the total aqueous extract of *Mitragyna inermis*, with concentrations of 0,208 kg/L and 0,104 kg/L, has reduced significantly, to J49, the peak of proliferation of Lepidopterous caterpillars infesting plants of Cotton, observed on the treated objects compared to the control's plant, with respectively the percentages of 72% and 64% of reduction [44].

Chemical composition of the plant *M. inermis*

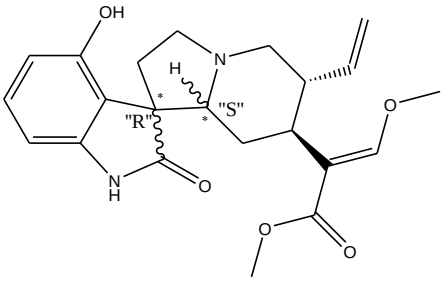
The phytochemical screening carried out on the powder of the leaves or on various extracts of *M. inermis* shows that the chemical composition of the leaves or extracts of leaves of this plant very often indicates the presence of certain chemical groups such as tannins, alkaloids, sugars reducing agents, flavonoids, carbohydrates and cardiac glycosides [36];

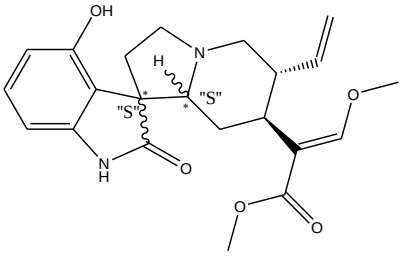
anthraquinones, reducing compounds, triterpenes [23]; steroids, carotenoids and xanthophylls, coumarins, leucoanthocyanins, anthocyanins and saponosides [20] and quinone compounds [22].

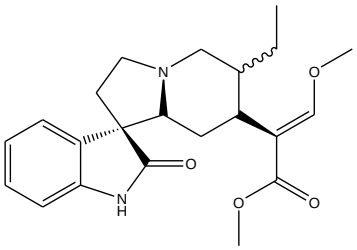
Some isolated compounds of the plant *M. inermis*

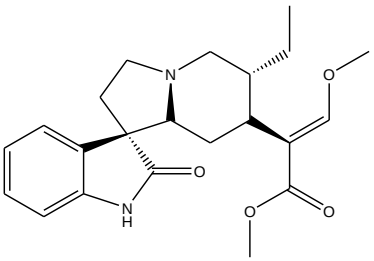
Several natural compounds have been isolated in various organs of *M. inermis*. The alkaloid compound are rotundifoleine, isorotundifoleine, rhynchophylline, isorhynchophylline, ciliaphylline, rhynchociline, speciophylline, mitraciliatine, uncarine F, uncarine D, Pteropodine ou uncarine C, isomitraphylline, mitraphylline, 9-methoxy-3-*epi*-α-yohimbine, naucléctone D, nauclefiline, naucleficine, nauclefidine, angustoline, angustine, pentacyclic indole, tetracyclic indole, pentacyclic oxindole, tetracyclic oxindole, isorhynchophilline, strictosamide [45-50]. The triterpenoid and triterpenoid saponins compounds are ursolic acid, oleanolic acid, betulinic acid, barbinervic acid, quinovic acid 3-*O*-α-L-rhamnopyranoside, quinovic acid 3β-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-28-*O*-β-D-glucopyranoside, 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl]quinovic acid, 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl]quinovic acid, quinovic acid 3-O-β-D-quinovopyranoside, quinovic acid 3β-*O*-β-D-glucopyranoside, Quinovic acid 3-*O*-β-D glucopyranosyl-28-*O*-β-D-glucopyranoside, quinovic acid, 3-oxoquinovic acid, inermiside I, inermiside II, β-D-glucopyranosyl-[3-O-(β-D-glucopyranosyl)]quinoviate, 3-O-(b-d-6-deoxy-glucopyranosyl)-quinovic acid, 3-O-[b-d-glucopyranosyl-(1—>4)-a-l-rhamnopyranosyl]quinovoic acid [47, 48, 51-53]. Phenolic compounds like Quercetin, dihydrodehydrodiconiferyl alcohol, Isolariciresinol, isolariciresinol-3α-O-β-D-glucopyranoside [27, 47]. Glycosides sécoiridoïdes compounds as dihydroépinauclédal, sweroside and other compounds as 1-(2,3,4 trimethyl phenyl) ethanone, Phenol 2,5 – dimethyl acetate, 3- acetate pentane-2,4-dione, 4H-pyran 4-one- 3-acetyl-2,6-dimethyl, 5-cholesten-3-phenyl-22, 24-β-diketone [43, 39].

Chemical structures of compounds


Rotundifoleine


Isorotundifoleine


rhynchophylline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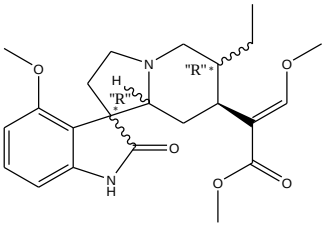
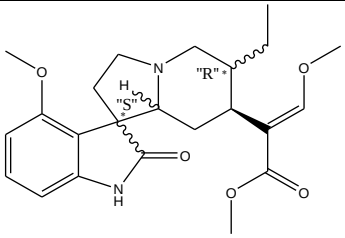

ciliaphylline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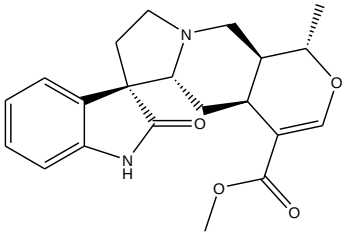
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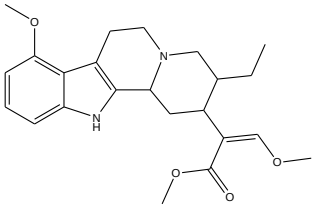
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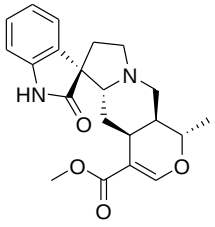
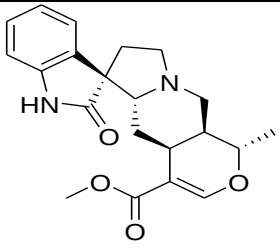
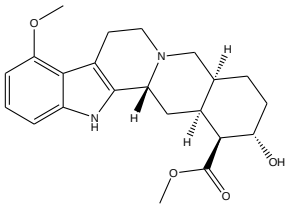
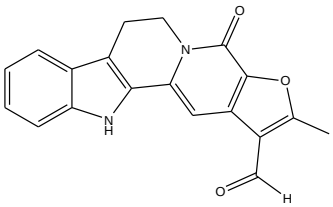

Uncarine F


uncarine D ou speciophylline


9-methoxy-3-*epi*-α-yohimbine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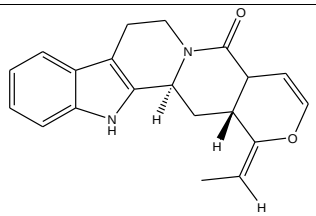
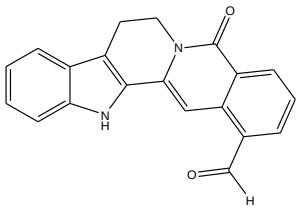
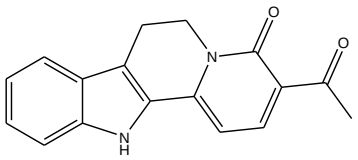
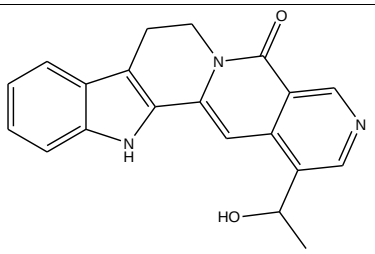
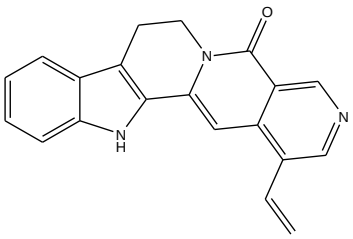
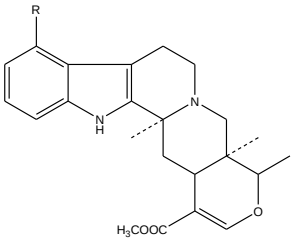
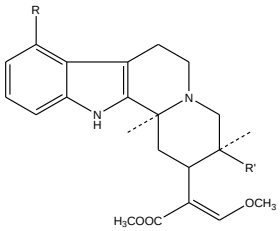
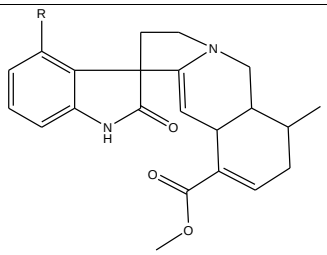
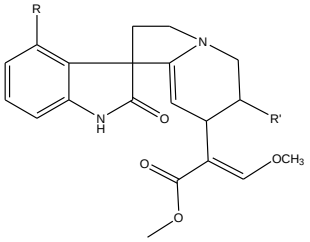
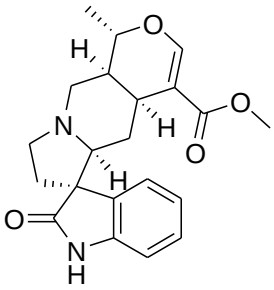
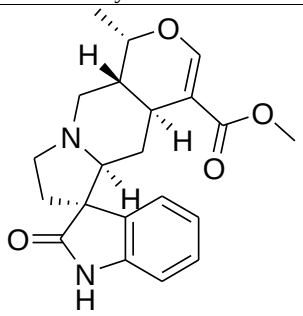
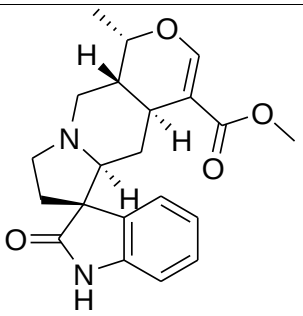
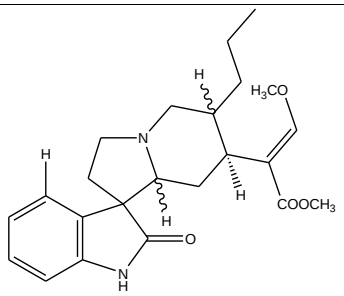
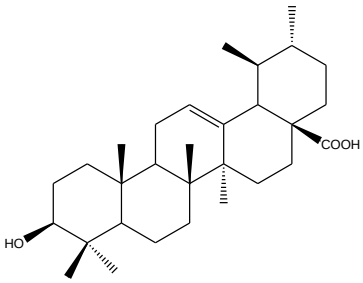
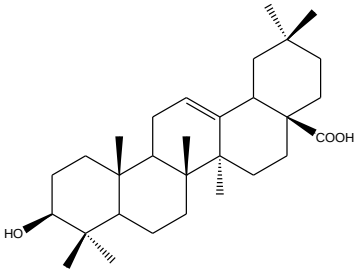
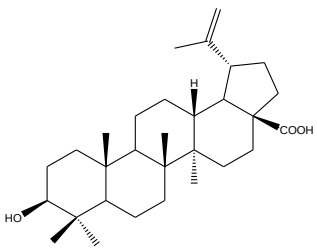
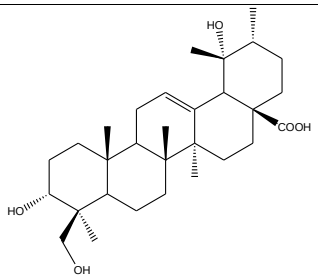
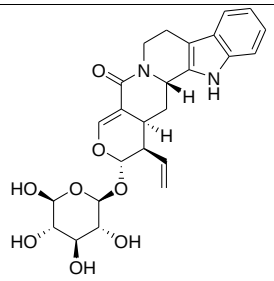
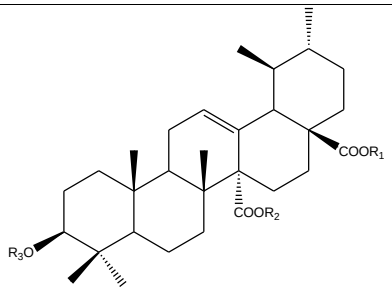
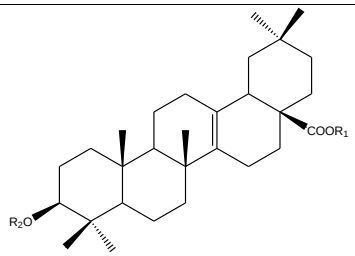
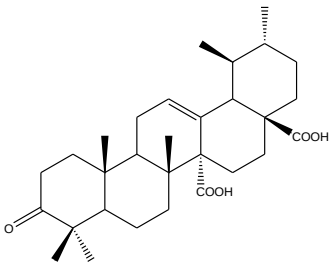
 Nauclefiline	 naucleficine	 nauclefidine
 Angustoline	 Angustine	 Pentacyclic indole
 Tetracyclic indole	 Pentacyclic oxindole	 Tetracyclic oxindole
 Pteropodine ou uncarine C	 mitraphylline	 isomitraphylline
 isorhynchophilline	 ursolic acid	 oleanolic acid
 betulinic acid	 barbinervic acid	 **Strictosamide**



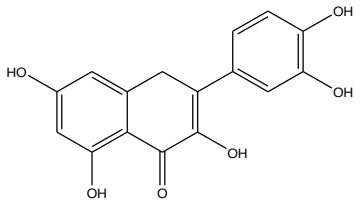
R_1	R_2	R_3	Name of compound
H	H	α-L-rha	Quinovic acid 3-*O*-α-L-rhamnopyranoside
β-D-Glcp	H	β-D-glc−(1 —> 4)-α-L-rha	quinovic acid 3β-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-28-*O*-β-D-glucopyranoside
H	H	β-D-glcp−(1 —> 4)-α-L-rha	3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl]-quinovic acid
H	H	6-deoxy-β-D-glc	quinovic acid 3β-*O*-β-D-quinovopyranoside
H	H	β-D-glc	quinovic acid 3β-*O*-β-D-glucopyranoside
β-D-Glcp	H	6-deoxy-β-D-glc	Quinovic acid 3-*O*-β-D glucopyranosyl-28-*O*-β-D-glucopyranoside
H	H	H	quinovic acid
glc	H	glc	β-D-glucopyranosyl-[3-O-(β-D-glucopyranosyl)]-quinoviate
H	H	6-deoxy-D-glc	cytotoxic 3-O-(b-d-6-deoxy-glucopyranosyl)-quinovic acid
H	H	glc-rha	3-O-[b-d-glucopyranosyl-(1—>4)-a-l-rhamnopyranosyl]-quinovoic acid



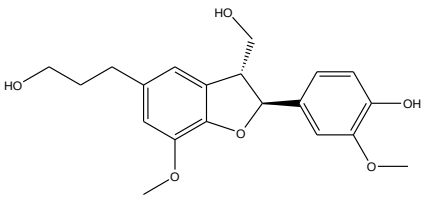
R_1	R_2	
6-deoxy-β-D-glc	β-D-glc−(1—> 6)−β-D-glc	inermiside I
H	6-deoxy-β-D-glc	inermiside II



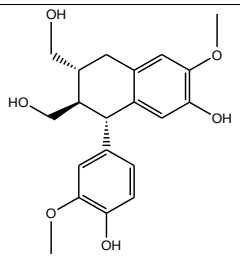
3-oxoquinovic acid



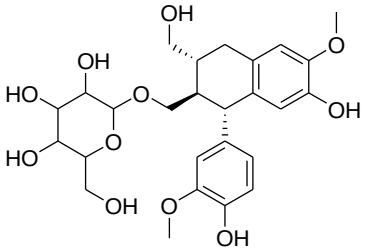
Quercetin



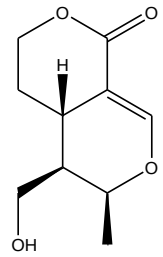
dihydrodehydrodiconiferyl alcohol



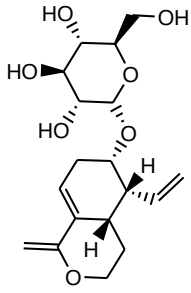
Isolariciresinol



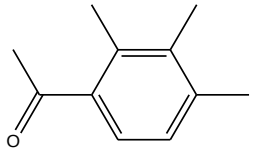
isolariciresinol-3α-O-β-D-glucopyranoside



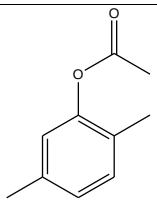
Dihydroépinauclédal



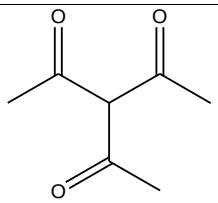
Sweroside



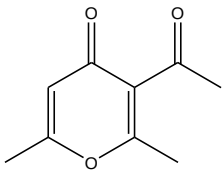
1-(2,3,4 trimethyl phenyl) ethanone



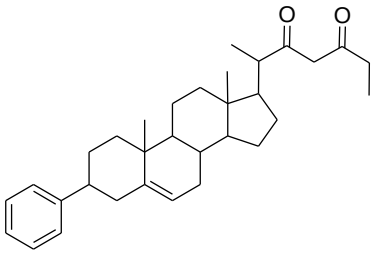
Phenol 2,5 – dimethyl acetate



3- acetate pentane-2,4-dione



4H-pyran 4-one- 3-acetyl-2,6-dimethyl



5-cholesten-3-phenyl-22, 24-β-diketone.

Conclusion

Medicinal plants play a very important role in the health defense of men. This is how *Mitragyna inermis* is also used due to his numerous therapeutic virtues. This plant has been the subject of several biological and chemical studies which made it possible to verify these therapeutic indications. Note that about 12 pathologies are treated with extracts of this plant and about 54 compounds are isolated from the different parts of this plant. Complementary studies are necessary to approve the medical actions of the other mentioned properties of this plant.

Remerciements

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