

Review on ethnobotany, phytochemistry and bioactivity of the Tropical medicinal plant species *Harungana madagascariensis* Lam. ex Poiret. (*Hypericaceae*)



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ABSTRACT

Aims: To provide knowledge on phytochemistry and bioactivity of *H. madagascariensis* Lam. ex Poiret.

Study Design: Multidisciplinary advanced bibliographic surveys, utilization of ChemBioDraw software package and dissemination of the resulted knowledge.

Place and Duration of Study: Faculty of Science, Pedagogical National University, Faculty of Science, University of Kinshasa and Department of Environmental Science, University of Gbadolite, the Democratic Republic of the Congo, between October 2018 and decembre 2019.

Methodology: A literature search was conducted to obtain information about the phytochemistry and pharmacognosy of *H. madagascariensis* from various electronic databases (PubMed, PubMed Central, Science Direct and Google scholar). The scientific name of this plant species was used as a keyword for the search, along with the terms phytochemistry and pharmacognosy. The chemical structures of the *H. madagascariensis* naturally occurring compounds were drawn using ChemBioDraw Ultra 15.0 software package.

Results: *Harungana madagascariensis* Lam. ex Poiret. is a species of shrubs belonging to the family of *Hypericaceae* and is native to Madagascar and grows in the forests of tropical Africa, which is used in several traditional medicines to cure various diseases. The plant is reported to possess antibacterial, antifungal, antidiabetic, anti-inflammatory, hepatoprotective activity and vasodilatory effects. A wide range of chemical compounds including four prenylated anthranols, harunganols C–F, along with kenganthranol A, harunganin, and ferruginin A [were identified from the leaves and two anthronoids named harunmadagascarin A and B, along with the harungin anthrone, harunganol B, methyl 3-formyl-2,4-dihydroxy-6-methyl benzoate, friedelin, lupeol and betulinic acid were identified from the stem bark of *H. madagascariensis*.

Conclusion: This review can therefore help to inform future scientific research for the development of new drugs of relevance for improving human health and well-being. In particular, drug candidates for the treatment of diseases due to oxidative stress such as sickle cell disease.

Keywords: Medicinal plant species, Traditional Medecine, *Harungana madagascariensis*, tropical diseases, Sickle cell anemia

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INTRODUCTION

Background

According to the World Health Organization (WHO), 80% of the population living in developing countries relies on traditional medicine for their primary health care needs.¹

In Democratic Republic of the Congo (DRC), medicinal plants represent the key product for both urban and rural populations for their health care needs because the costs of conventional drugs are often unaffordable. These medicinal plants have found to have therapeutic value for fighting against major health problems.⁶⁻⁹ The present review aims to give updated information on the phytochemistry

and pharmacognosy of this useful medicinal plant species.

Botany and distribution

H. madagascariensis Lam. ex Poir belong to the family '*Hypericaceae*', earlier known as '*Guttiferae*'. It is a tropical much-branched shrub to small tree growing up to 12 m tall, commonly known as 'Dragon's blood tree'. It is native to Madagascar, Mauritius and tropical Africa growing on margins of wet forests. *H. madagascariensis* possess bright orange bark exudates and distinctive broad egg-shaped opposite leaves which are 10-20cm long and 6-10cm wide. Its fragrant flowers are very small whitish with black glands; its orange-brown fleshy

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fruits are also small about 2-3mm and contain 2-4 seeds (Figure 1). The wood is orange-red to yellow, and is particularly attractive.¹⁻⁴ *H. madagascariensis* occurs at medium to low altitudes in evergreen forest, at forest margins and along river and stream banks. It is a common and widely distributed tree from the Sudan to South Africa, often a pioneer when a forest has been cleared. *H. madagascariensis* possess many adaptive features such as forming dense thickets from root suckers for exclusion of all other species around. The plant invades cyclone-damaged and gaps in rainforest. It can re-grow after disturbance and is capable of withstand poor drainage on alluvium. The plant is a vigorous colonizer, hence named 'Harungana madagascariensis' also referred to as pest plant [2, 3, 4, 5a, b].

H. madagascariensis have many social applications: Its light wood is utilized in construction of hut, store-houses, thwarts and seats in canoes, yam-sticks and hockey-sticks; The wood is utilized as fuel in local metallurgy; Its gummy delicate dye is useful for dying velvet, it is also a good stain for wood and sealing-wax on newly fired pots. The species is widespread in tropical Africa, and is found in clearings in forest regions and fringing forest in savanna regions [2, 3, 5a, b].

METHODOLOGY

A deep literature search was carried out in order to obtain information about the phytochemistry and bioactivities of *H. madagascariensis* from various electronic databases namely PubMed, PubMed Central, Science Direct and Google scholar. The scientific name of this plant species was used as the keyword for the search, along with the terms phytochemistry, pharmacology and pharmacognosy. Different chemical structures of *H. madagascariensis* naturally occurring compounds were drawn using ChemBio Draw Ultra 15.0 software package.⁷

RESULTATS AND DISCUSSION

Ethnobotany

Ethnobotanical information from the south eastern part of Nigeria has shown that *H. madagascariensis* (Lam. ex. poir) (family Hypericaceae) is an edible medicinal plant.¹⁰ In traditional African medicine, different parts of this plant are highly valued for the treatment of various human diseases including leprosy, jaundice, ulcers, asthma and the prevention of poultry diseases. Its gum is styptic and haemostatic, blocking blood circulation and is applied to cut and wound dressings.

Proximate analysis of *H. madagascariensis*

Bassey *et al.* (2015)⁴² carried out the proximate analysis of the stem bark of *H. madagascariensis* by determining the proximate, mineral, vitamin, antinutrient composition (table 1). Their study revealed that the stem bark of *H. madagascariensis* which is consumed contain all necessary macromolecules, vitamins, minerals and antinutrient.

Mineral elements

The elemental analysis of *H. madagascariensis* stem bark sample revealed the presence of 15 elements and heavy metals, Ca, K, Mn, Sr, Cl, Br, Cr, Cd, Cu, Fe, Ni, Pb, Zn, Mo and Hg in three categories of various concentrations. For example, Cd, Ni, Mo, Cr and Br were in the range of 0.02–0.9 mg/g, while Pb, Zn, Fe, Cu and Hg were in the range of 1.5–7.2 mg/g. The elements with very high concentration were Ca, K, Sr, Mn and Cl and were in the range of 10.5–774.3 mg/g.

Antinutrient composition

Levels of hydrogen cyanide, oxalate, phytic acid, and tannins in the dichloromethane and methanol extracts of *H. madagascariensis* stem bark are given in Table 3. The content of hydrogen cyanide (0.75 mg/100 g) in the methanol extract was far below the lethal dose of 35mg/ 100g.³⁴ Also, the quantity of soluble oxalates in the methanol extract (3.03±0.02 mg/100 g DW) was below the toxic level of 2–5 mg/100 g.³⁵ Oxalates are known to bind to calcium to form calcium oxalate crystals, which are deposited as urinary calcium (stones) that are associated with blockage of renal tubules.³⁶ Based these values, it could be speculated that the danger of toxicity arising from hydrogen cyanide or oxalate in *H. madagascariensis*. Contents of phytic acid and tannins were found to be low in both extracts.

Vitamin composition

The vitamin content of *H. madagascariensis* stem bark was higher in the methanol extract than the dichloromethane extract. Vitamins decreased in the following order: B1> B2>A>C. A trace amount of vitamin C was recorded (0.26±0.01 mg/100 g DW) in the methanol extract. Lee *et al.*⁴⁰ have reported that edible plants possess chemopreventive and chemoprotective activities and these activities have been attributed to dietary constituents such as vitamin E, vitamin C, and more recently, polyphenols.⁴¹

H. madagascariensis stem bark is an interesting source of minerals (magnesium, manganese, potassium, phosphate, and iron) (Table 2).³³ However, potassium is lower than potassium content in green vegetables (132 mg/ 100 g).³⁷ Minerals have been reported to play significant roles in many

Table 1 Ethnomedicinal importance of *H. madagascariensis*

Plant part used	Ethnomedicinal use	References
Leaves	Boiled decoction of plant leaves is used to treat malaria It is a remedy against coughing with bloody sputum and dysentery. It also stops bleeding, diarrhea, gonorrhoea, sore throat and fever. The leaf and roots of <i>H. madagascariensis</i> are considered to be feverish and antimalarial. In the southeastern part of Nigeria, cold and hot infusions of <i>H. madagascariensis</i> in water are commonly administered for the treatment of gastrointestinal disorders such as diarrhea, dysentery, typhoid fever and as a laxative and abortion.	12, 13, 17, 20, 23-25, 32
Fruit	In Sierra Leone, the red juice is employed to arrest postpartum bleeding while in Liberia, puerperal infection is treated by eating the unopened bud sheaths beaten up with palm oil. Ointment made from the fruit of <i>H. madagascariensis</i> in animal fat is used on inflamed lymph nodes. <i>H. madagascariensis</i> fruit has been shown to have hypoglycemic effects, lowering blood sugar levels in diabetes mellitus, and others such as anti-inflammation, antioxidants, antihepatotoxicity and antimicrobial activities.	16, 21, 23, 26-27, 28-31
Stem bark	Bark crushed with <i>Pentaclethra macrophylla</i> is used in the treatment of leprosy while washed red sap from the bark of the stem is drunk as a remedy against tapeworm infection, for crawling or as a wound dressing in Ghanaians. Recently, antifungal and antibacterial activities of different extracts from the bark of the plant stem have been reported.	11-14
Root	Bark and root decoctions are remedies for dysentery and heaps and also acts as a placental embolism and emmenagogue. It relieves stomach aches, painful menstrual periods and menstrual problems, dysmenorrhoea, menstrual irregularities, miscarriages, sterility and hematuria. Decoction of the bark of the root and stem of the plant is used as a remedy against dysentery, bleeding, trypanosomiasis, fever, colds and cough. ¹⁵ Plant exudate is used by the Ondo people (Southwest Nigeria) to cure acute enteritis, scabies and jaundice. Among Yoruba herbalists (southwest Nigeria), aqueous decoction of the plant's roots is used in the treatment of suspected liver or kidney disease.	10, 15, 17-21

Table 2 Levels of Minerals, Vitamins, and Antinutrients content and LD50 of *H. madagascariensis* Extracts

	Dichloromethane extract (mg/100gDW)	Methanol extract (mg/100gDW)
Fe	2.03–0.01	2.50–0.02
Mg	13.52–0.04	25.99–0.04
Mn	20.33–0.03	29.44–0.03
Phosphorus	0.56–0.0	0.11–0.01
K	45.31–0.07	31.22–0.05
Vitamin B ₂	10.14–0.03	18.22–0.03
Vitamin B ₁	28.31–0.04	23.14–0.03
Vitamin C	0.16–0.01	0.26–0.01
Vitamin A	2.60–0.02	4.18–0.02
Tannin	0.51–0.01	0.97–0.02
Phytic acid	0.03–0.01	0.01–0.01
Total oxalate	3.64–0.02	4.63–0.04
Soluble oxalate	2.05–0.01	3.03–0.02
Hydrocyanate	0.54–0.01	0.75–0.02
LD ₅₀	1000–8.0mg/kg	1414–8.2mg/kg

Source : Bassey et al. (2015)⁴²

health-promoting systems within the body,³⁸⁻³⁹ and thus, consumption of *H. madagascariensis* might play useful roles in optimizing their availability and utilization in human body.

Phytochemistry

Phytochemical screening of the dichloromethane and methanol stem bark extracts of *H. madagascariensis* revealed the presence of alkaloids, anthraquinones, flavonoids, cardiac glycosides, saponins, tannins, and terpenes. Alkaloids were absent in the dichloromethane extract, while phlobatannin was absent in the stem bark (Table 3). The presence of these phytochemicals in the stem bark of *H. madagascariensis* makes it beneficial to the consumer as these compounds have potent medicinal values, including analgesic, antiparasitic, bactericidal, wound healing, hypoglycemic, anti-inflammatory, and antioxidant properties, among others.⁴³⁻⁴⁵

The MeOH extract of the leaves of *H. madagascariensis* contains four new prenylated anthranols, harunganols C–F (1–4), along with kenganthranol A (5), harunganin (6), and ferruginin A (7).⁴⁸

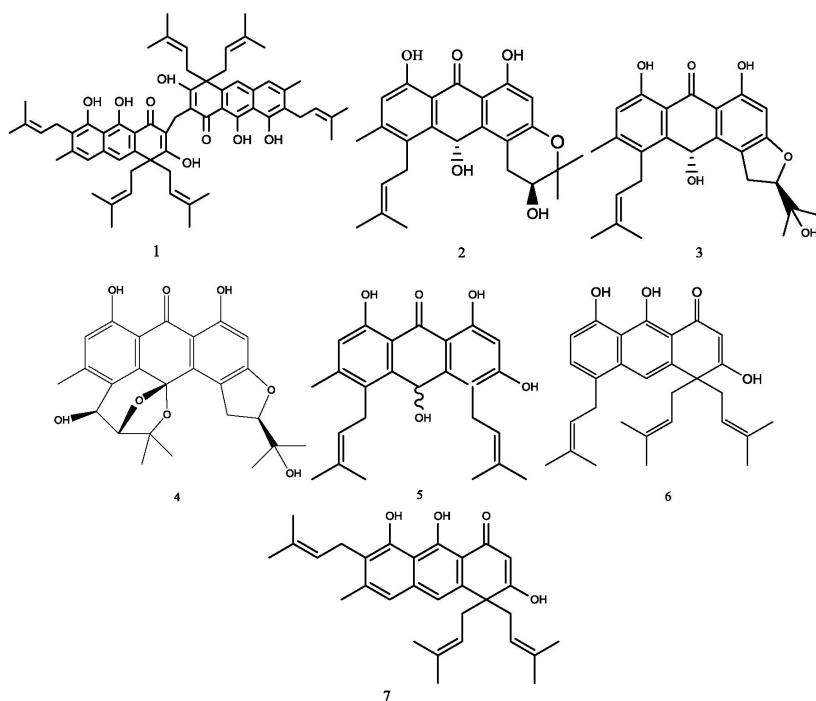
The hexane soluble fraction of the methanolic extract of stem bark of *H. madagascariensis* contains anthronoids named harunmadagascariens A (1) and B (2), along with the known harungin anthrone (3), harunganol B (4), methyl 3-formyl-2,4-dihydroxy-6-methyl benzoate (5), friedelin (6), lupeol (7) and betulinic acid (8) (Figure 2).⁴⁹

The analysis of hydro-distilled essential oils of the leaf, stem bark and fruit of *H. madagascariensis* carried out by gas chromatography-mass spectroscopy (GC-MS) revealed the presence

Table 3 Contents of Phytochemicals in *H. madagascariensis* Extracts

Phytochemical	Test/reagents	DCM extract	MHM extract
Alkaloids	Dragendroff's	-	+
	Mayer's	-	+
Anthraquinones	Benzene/ammonia solution	+	+
Flavonoids	Magnesium metal, HCl acid	+	+
Cardiac glycosides	Liebermann's	+	+
	Keller-Killiani's	+	+
Phlobatannins	HCl acid solution	-	-
Saponins	Frothing	+	+
	Fehling's tests	+	+
Tannins	Ferric chloride solution	+	+
Terpenes	Chloroform, H ₂ SO ₄ acid	+	+

+, present ; -, absent.

**Figure 1** Chemical structures of some compounds isolated from the leaves of *H. madagascariensis*

of sesquiterpene hydrocarbons (66.8-69.6%). β -caryophyllene (32.4% and 18.4% respectively, for leaf and fruit oils only), α -humulene (10.4%, 9.8% and 7.3% respectively for leaf, stem bark and fruit oils), germacrene D (8.7% for leaf oil only), and α -farnesene (37.4% and 10.4% respectively, for stem bark and fruit oils only).⁵⁶

Bioactivity

Hepatotoxic effect of the aqueous root extract

Recent findings revealed that *H. madagascariensis* aqueous root extract (100-500 mg/Kg) significantly

protect rats against acute and repeated acetaminophen, hepatotoxic effects by decreasing of enzyme markers levels (like ALT, AST, ALP) and fasting blood glucose.

In addition, the extract significantly attenuated reduction in the serum levels of total protein (TP) and albumin (ALB) while inducing non-significant alterations in the serum lipids.²⁹

Acute and sub-acute toxicity of stem bark methanol extract

The LD₅₀ value was greater than 5000 mg/Kg. But in sub-acute treatment, *H. madagascariensis* extract caused a decrease in neutrophils, monocytes, red blood cells and platelets number. Biochemical parameters showed an increase in total cholesterol, LDL, urinary proteins, glucose and creatinin elimination speed while a reduction in triglycerides, HDL, serum glucose, bilirubin and transaminases activity were noted. An increase in liver and heart relative weights was observed. Histopathological analysis revealed urinary tract constriction, liver vascular constriction and heart, lungs, ovaries and testes necrosis.⁵⁰

Anti-diabetic activity aqueous leaf extract

The aqueous leaf extract of *H. madagascariensis* was reported to possess antihyperglycaemic and antihypercholesterolaemic activity, their justifying its folkloric use as a diabetic agent and appears to have the propensity to restore damaged liver cells back to functionality.⁵¹

Anti-viral activity

The inhibitory property of the crude ethanolic extract of *H. madagascariensis* roots on Newcastle disease virus was studied in two weeks old chicks. Results revealed a significant inhibitory effect at the concentration of 100 mg/mL of the extract.⁵²

Antimicrobial activities

The stem bark of *H. madagascariensis* revealed antimicrobial activities against *Microsporium canis* (MIC: 0,04 mg/mL), *Sporotrichum schenckii* (MIC: 0,06 mg/mL), *Staphylococcus aureus* (MIC: 0,34 mg/mL).⁵³

The Aqueous extract of the leaf of *H. madagascariensis* was evaluated for antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and *Pseudomonas aeruginosa*. *B. subtilis*, *E. coli* and *S. typhi*, but not *P. aeruginosa*, showed susceptibility toward tested extracts (MICs of 2.0 and 15.6 mg/mL; and MBCs of 2.0–3.9 mg/mL and 15.6–31.3 mg/mL, respectively, for the cold and hot extracts). *S. aureus* showed susceptibility only to the hot extract.

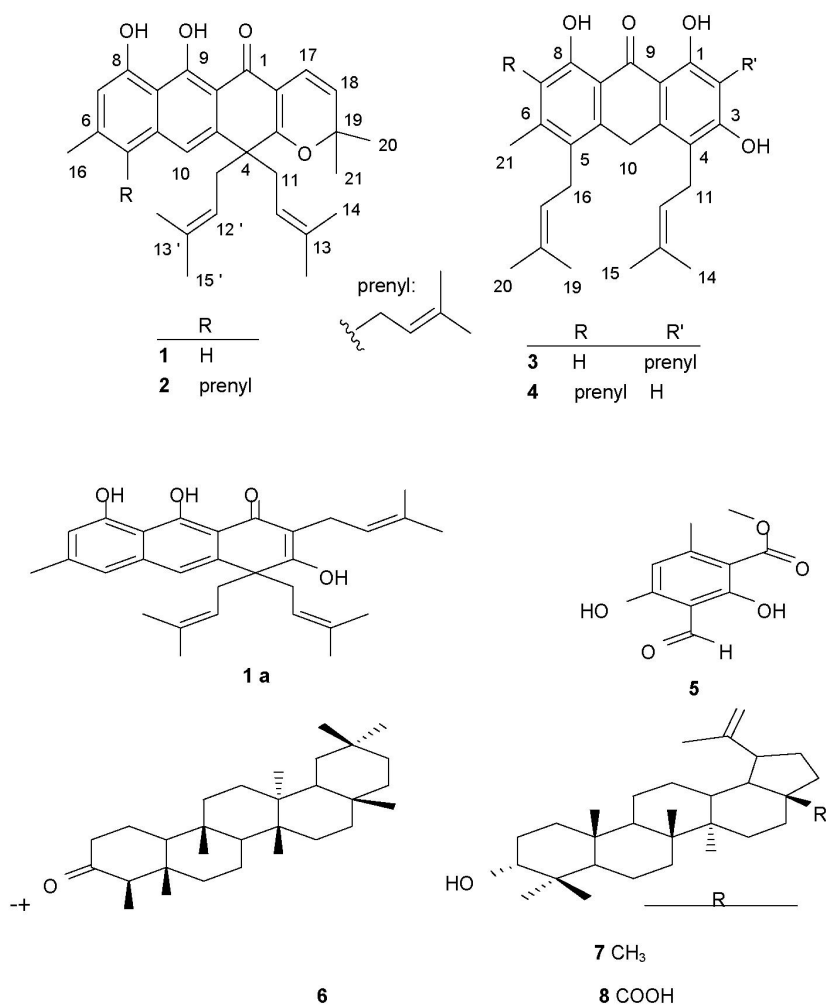


Figure 2 Structures of secondary metabolites isolated from the stem bark of *H. madagascariensis*

The hot extract needed higher concentrations and longer treatment to achieve similar levels of bacterial cell killing.⁵⁴ The aqueous stem bark extract of *H. madagascariensis* had also bactericidal activity on *P. aeruginosa*, *S. aureus*, *E. coli*, *P. mirabilis* and bacteriostatic activity on *S. Typhi*.⁵⁹

Vasodilatory Effects

The stem bark aqueous extract of *H. madagascariensis* was reported to possess vasodilatory properties *ex vivo* suggesting thus *H. madagascariensis* can be used as phytoalternative treatment for hypertension and other cardiovascular diseases.⁵⁵

Anti-inflammatory activity

The leaves extract of *H. madagascariensis* exhibited mild inhibition of acute and chronic edema but has no effect on granuloma formation.⁵⁷

Antioxydant activity

Antioxydant potentials of the stem bark extracts were assessed by the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay, metal chelating activity, and ferric reducing power. The methanolic extract showed a better antioxydant activity ($IC_{50} = 87.66 - 0.97$ mg/mL) in the DPPH system. The metal chelating activity was higher in the methanolic extract (92.4% at 20 mg/mL), but lower than the control ethylenediaminetetraacetic acid (EDTA). The methanolic extract also showed greater ferric reducing power and was richer in phenolics (132.24 – 0.61 mgGAE/g) and flavonoids (259.05 – 2.85 mgQE/g).⁴²

Anti-protozoan activity

The aqueous leaf extract of *H. madagascariensis* had significant anti-typhoid activities with hepatoprotective effects at the therapeutic doses and induced haematopoiesis.⁶¹ The stem bark extract exhibited significant anti-protozoan effects against *Trichomonas* and *Plasmodium* both *in vivo* and *in vitro*.⁶⁰ Bazouanthrone, ferruginin A, harunganols A and B, harunganin, and betulinic acid, isolated from root of *H. madagascariensis* displayed antiplasmodial activity on *Plasmodium falciparum* W2.⁶¹

Anti-sickling activity

The hydro-ethanolic bark extract of *H. madagascariensis* was reported to protect the sickle red blood cell membrane.⁶² Mpiana *et al.*⁶³ reported that this plant species is traditionally used to treat sickle cell disease in the Tsopo province in Democratic Republic of the Congo.

CONCLUSION

It is evident that *Harungana madagascariensis* is potential sources of drugs against various ailments including sickle cell disease. The phytochemical composition of this medicinal plant species is depending on geographical locations and seasons. Cell biology and biochemistry studies on the interaction of the *H. madagascariensis* extracts with red blood cell membrane and hemoglobin S are in progress.

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