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A Review of the Phytochemistry and Pharmacology of the Medicinal Plant: *Khaya Senegalensis* (Desr.) A. Juss

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ABSTRACT

Khaya senegalensis is a well known medicinal plant, widely distributed in Savannah regions and commonly called African mahogany or dry zone mahogany. The plant is known for various medicinal properties in traditional medicinal system and is used to attenuate a variety of diseases. K. senegalensis is reported to contain a variety of bioactive compounds in its different organs including alkaloids, terpenoids, steroids, and phenols. Extensive studies on K. senegalensis revealed its antimicrobial activity, cytotoxicity activity, hepatoprotective activity, antioxidant activity and wound healing activity among several other pharmacological activities. This literature review, based on the multiple researches on K. senegalensis integrated information concerning the phytochemistry and pharmacological activities of the plant which will promote better understanding of the medicinal values, useful to researchers for further study.

Keywords:Khaya senegalensis, medicinal plant, phytochemistry, Pharmacology

1. INTRODUCTION

Medicinal plant represent plant which, in one or more of its organs, contains substances useful for therapeutic purposes or which are candidates for development of useful drugs. Medicinal plants and their products are used extensively since time immemorial for the treatment and prevention of various diseases [1] and the practice continues to show a dominant role in healthcare systems, mainly true for developing countries where traditional medicine has a continuous history of long use. Currently, over 80% of the earth's population depends on plant-derived medicine to meet primary healthcare needs because it has no side effects and most of the therapy involves use of plant extracts and their active components [2]. Notably, as a great source for drug synthesis, more than 50% new therapeutic drugs have been developed and approved for marketing from different plant species as they are relatively safe and economical compared to the synthetic medicines [3]. In view of the fact that several plants are increasingly been monitored by researchers all over the world with the goal of discovering new drug products that have high therapeutic efficacy and low toxicity profile, a comprehensive and updated insight on the therapeutic value of medicinal plants is significant.

For many of the medicinal plants, their traditional uses have been validated through phytochemical and pharmacological studies, accumulating a large body of evidences that highlight the cosmic therapeutic potentials of the medicinal plants used in different traditional systems of medicine. However, there is paucity of a comprehensive documentation regarding the phytochemistry and pharmacological profile of the medicinal plant; Khaya senegalensis. This current study therefore provides an updated insight of Khaya senegalensis which is extensively used in folk therapeutics.

Khaya senegalensis (Desr.) A. Juss. (Meliaceae) is a tall, sturdy, medium to large sized evergreen African tree (that grows up to 30m high and 1-3m in diameter) with shiny foliage, exfoliating barks and young branches, widely distributed in Savannah regions and commonly called African mahogany or dry zone mahogany [4]. Locally, it is called Ono (Igbo), Madaci (Hausa), Chiha (Tiv), Dalehi-kahi (Fulani), Oganwon (Yoruba) [5]. Diverse claims of effectiveness and widespread utilization of this plant in traditional medicine has been reported by various cultures throughout the tropical Africa, including but not limited to Nigeria, Benin, Ghana, Central African Republic, Mali, Togo, Senegal, and Cameroun. Reported medicinal uses include in the folk treatment of diarrhoea, dysentery, wound infections, diabetes, hypertension, jaundice and malarial, dermatitis, scorpion bites, mental illness, leprosy, fever, infertility, headache, syphilis, gum infections, hookworm, allergies, laxative and aphrodisiac [6] [7] [8]. The medicinal value of this plant relies on its chemical composition that produces definite physiological effect on the living system.

2. PHYTOCHEMISTRY

Khaya senegalensis reportedly contains different classes of important phytocompounds. Studies on different parts of the plant revealed the presence of tannins, steroids, phytates, oxalates, flavonoids, saponins, alkaloids, glycosides, hydroalcoholic, anthocyanins, anthraquinones, terpenoids, phlabatannins and phenols [9] [10] [11]. GC-MS analysis of K. senegalensis stem bark extract revealed presence of mostly acidic chemical compounds including: 9,12-octadecadienoic acid, nHexadecanoic acid, Oleic acid, myristic acid, 2,6-Pyridinedicarboxylic acid, pentadecanoic acid, nhexadecanoic acid, hexadecanoic acid, 9-hexadecenoic acid, stearic acid, ricinoleic acid, 13-decosenoic acid, and 11-octadecenoic acid. The alcoholic organic chemical compounds isolated included Z-3, 13-Octadecadienol, (Z) 6, (Z) 9-Pentadecadeien-1-ol, 2-methyl-Z, and 1, 2, 3-Benzenetriol. Other classes of chemical compounds were Cyclododecyne, 9-Octadecanal, 3-O-methyl-d-glucose, I, E-11, Z-13-Octadecatriene, 9-Hexadecenal, E-9-Tetradecanal, 1 E-11, Z-13- Octadecatriene, 1-Flourodecane and 4-Hepten-3-one [12]. The roots are reported to contain chromones: p-anilinophenol hydrochloride, 7, 8-dihydroxy-2, 3-dihydrochromone, 3-ethyl-5-(3-ethyl-(3H)-benzothiazol-2-ylidene)-2- (p-tolylvinylamino)-4-thiazolidinone, and 5, 7-dihydroxychromone [13]. Eight new limonoids, khayseneganins A-H (1-8), and 31 known limonoids were isolated from the leaves and twigs of the plant and the structures elucidated by 2DNMR spectroscopy and mass spectrometry [14]. Fatty acid composition of Khaya senegalensis include; capric acid, undecylic acid, myristic acid, stearic acid, palmitic acid, oleic acid, arachidic acid, myristoleic acid, isooleic acid, vaccenic acid, petrolinic acid, elaidic acid, and erucic acid [15][16][17]. None of the fatty acids has more than one double bond and all unsaturated fatty acids are monounsaturated with mono-double bond which makes it good feedstock for biodiesel production. Minerals (micro-nutrient) such as sodium, potassium, calcium, magnesium, iron, zinc and manganese are found in the plant [18]. Using NMR, three new triterpenoids of the mexicanolide type including 2-hydroxymexicanolide, 6-deoxydestigloylswietenine and 2, 6-dihydroxy-3-mexicanolide was isolated and it is recommended, the juicy form of the plant bark could be given to patients with skin diseases, diarrhoea, possibly catarrh, epilepsy, rheumatic pains, hemorrhoids, painful menstruation, insanity, hysteria, and ulcers [19]. Using sub-critical fluid extraction (SFE) technique, several sesquiterpenoids including; cycloisolongifol-5-ol, italicene ether, α -dehydro-ar-himachalene, longifolenaldehyde, globulol, spathulenol, ledol, γ -eudesmol, guai-1(10)-en-11-ol, isocalamenediol, cyperenone, phthalic acid, diisobutyl ester and dibutyl phthalate were also found in Khaya senegalensis bark extract [10]. Other chemical groups in Khaya senegalensis include; carotenoids, coumarins, emodols, compound reducers, anthracenosides and carbohydrates [20].

3. PHARMACOLOGY

Pharmacological studies have confirmed that *Khaya senegalensis* exhibit a broad range of biological activities including antidiabetic, antimicrobial, antifungal, antianemic, cytotoxicity, anti-inflammatory, antinociceptive, antioxidant, hepatoprotective, antiulcer, anthelmintic, antitrypanosomal, neuropharmacological, immunomodulatory, antimalarial etc.

Antidiabetic activity

Different organs of *Khaya senegalensis* are reported to exhibit anti-diabetic activities. The ethanol stem-bark extract of the plant demonstrated antihyperglycaemic effect in alloxan induced diabetic rats revealed by significant decrease (p<0.05) in the blood glucose concentration in the extract treated group when compared to the diabetic control group and this effect was attributed to the various biologically active metabolites detected during phytochemical screening [21]. Orally administered buthanol fraction of ethanol root extract in rats at 300mg/kg BW revealed remarkable anti-type 2 diabetic activities and could ameliorate some diabetes-associated complications and hence can be considered as a source of potential anti-type 2 diabetic medicines [22].

Antimicrobial and antifungal activity

Studies on seed oil isolated from *Khaya senegalensis* showed that, the oil possessed some activity against *Staphylococcus aureus* (Gram-positive) and *Pseudomonas aeruginosa* (Gram-negative) bacteria. The oil was found to have higher activity against *S. aureus* at low concentration of 5% than at 20%, whereas as the concentration increased, the sensitivity increased for *P. aeruginosa* [23]. The bark extracts of the plant displayed strong inhibitory activity against *P. mirabilis, K. pneumonia, G. duodenalis A. baylyi* and was moderate inhibitors of *P. aeruginosa* and *S.pyogenes* growth [10]. Three limonoid compounds seneganolide A, 2-acetoxyseneganolide A and methyl 6- hydroxyangolensate isolated from the plant's fruits showed antifungal activities on the fungus *B. cinerea.* 2-acetoxyseneganolide A at concentrations of 1000 and 1500ppm showed and inhibition of mycelia growth of 61.50% and 68.33%, respectively, without significant differences from seneganolide A and methyl 6- hydroxyangolensate [24]. Defatted acetone extract of the plant flowers was also found to be effective against tested microorganism revealing potent growth inhibitory effect on *S. typhimurium* ATCC 25566, *E. coli* NRRN 3008, *P. aeruginosa* ATCC 10145 and fungus *Candida albicans* EMCC105, with MIC \leq 25µg/µl while MIC \leq 50µg/µl for *B. cereus* and *S. aureus* ATCC 6538 [25]. Leaf aqueous extracts of *K. senegalensis* at different concentrations of 100, 200, 300, 400, and 500mg/ml inhibited mycelia growth of Rhizopus spp and Mucor spp. The results revealed that antifungal activities of the extract were concentration dependent [26].

Antianemic activity

Aqueous extracts of the stem bark and leaves of *Khaya senegalensis* were found to exhibit strong anti-anemic activity and further in *vitro* bioassay guided fractionation led to isolation of rearranged limonoid $1\alpha, 2\beta, 3\alpha, 6, 8\alpha, 14\beta$ -hexahydroxy4, 2, 1, 1-tricyclomeliac-7-oate, whose activity was found to much higher at any concentrations and incubation conditions compared to pentoxifylline used at standard [27].

Anticancer activity

Khaya senegalensis fresh flower oils extracted by hydro-distillation method displayed potent and moderate cytotoxic activity against liver (HepG-2), breast (MCF-7), and colon (HCT-116) human cancer cell lines with IC50 61.1, 79.7, and 61µg/mL respectively compared to Doxorubicin. Sesquiterpene content of the Khaya oils which included caryophyllene oxide (14.85%), β-caryophyllene (43.59%), and α-humulene (15.72%) were suggested to have contributed to its cytotoxic activity [28]. Hydroethanol stem bark extract of the plant was also found to initiate cytotoxicity against HepG-2 cell lines upon treatment and a gradual increase in the number of compromised cells was demonstrated which indicates that the extract possessed a sustained acute toxicity on the cancer cells. It also suggested that the plant extract activity was both necroic and apoptotic [29]. *K. senegalensis* bark extract (KSBE) also displayed antiproliferative and pro-apoptotic effects on colon cancer cells (HT-29 IC50=1.00µg/µl, HCT-15 IC50=0.30µg/µl, and HCA-7 IC50=0.22µg/µl,) after 24h of treatment. Expression of cyclooxygenase-2 (COX-2) gene showed that for all the three cell lines, COX-dependent and COX-independent pathways were activated by the plant extract which suggest its usefulness in prevention and treatment of colorectal cancer [30]. Two limonoids, 3α , 7α -dideacetylkhivorin (1) and 1-*O*-acetylkhayanolide B (2) isolated from the methanol extract of *K. senegalensis* were assayed and compound 1 showed significant growth inhibitory activities against MCF-7, SiHa and Caco-2 cells with IC₅₀ values in the range of 0.07-0.14µM (35-69ppm) while compound 2 did not [31].

Anti-inflammatory and anti-nociceptive activity

Stem bark methanol extract of *Khaya senegalensis* at 250-500 µg/mL significantly demonstrated anti-inflammatory effect by inhibiting heat induced albumin denaturation, with inhibition rate of 76.01 \pm 0.31, 78.02 \pm 0.23 respectively in comparison with standard drug with an inhibition action of 84.21 \pm 0.32, 88.10 \pm 0.11 respectively. At similar concentrations, the plant also inhibited significantly the hypotonicity induced haemolysis activity with inhibition rate of, 91.02 \pm 0.31, 93.10 \pm 0.21 in comparison with standard drug with an inhibition rate of, 94.20 \pm 0.35, 97.01 \pm 0.32. The result obtained indicated that the extract of *Khayasenegalensis* can be a potential source of anti-inflammatory agent [32]. Kolawole *et al.*, also reported that, aqueous stem bark of extract *Khaya senegalensis* produced significant dose-dependent inhibition of carrageenan-induced ear edema in mice (acute inflammation), a significant reduction in granuloma formation and paw edema in rats (chronic inflammation). At concentration range of 125-500 µg/ml, the plant extract protected the erythrocyte membrane against lysis induced by heat and hypotonic medium and also reduced significantly, the licking/biting time of the formalin-injected rat paw in the early (19-51% reduction) and late (13-57% reduction) phases. The extract demonstrated significant antinociceptive activity in the hot-plate and writhing tests which indicated, *Khaya senegalensis* stem bark aqueous extract possesses anti-inflammatory activity and antinociceptive effect mediated via central and peripheral mechanisms [33]. Furthermore, a new andirobin-type limonoid with modified furan ring, isolated from *K. senegalensis* stem back exhibited anti-inflammatory activity, which was attributed to inhibition of the release of lipopolysaccharide (LPS)-stimulated inflammatory mediators via suppressing the activation of NF-_kB, AP-1, and upregulating the induction of $_{P}38$ MAPK/Nrf2-mediated heme oxygenase-1 [34].

Anti-oxidant activity

Aqueous extracts of different parts of *Khaya senegalensis* reportedly showed a reduction in DPPH with IC_{50s} of 27.89±0.07µg/ml, 44.88±0.43µg/ml, 54.62±0.87µg/ml and 55.56±0.23µg/ml for bark, leaves, hulls and seeds, respectively. This revealed that the different parts are gifted with antioxidant activity and the barks are more powerful than the others. However, hydroalcoholic extracts of the different organs of the plant showed activities with IC_{50s} of 47.14±1.22µg/ml, 34.52±0.64µg/ml, 15.61±0.24µg/ml, and 11.54±0.93µg/ml for bark, leaves, hulls and seeds, respectively. These results show that for hydroalcoholic extracts, the seeds and hulls could be used as a replacement for the bark of trunk, but factors such as the periodicity of fruiting, the difficulty of harvesting and high cost of producing these extracts, would limit their use [35]. Opawale and Adaramola-Ajibola [36] also reported a significantly high free radical scavenging activity from oils isolated from leaf and stem of *K. senegalensis*. Antioxidant activity from the study revealed that at 100µg/cm³ extract concentrations, water, ethanol, ethyl acetate and petroleum ether stem bark extract gave percentage inhibition of 68.17%, 66.47%, 67.23% and 58.38% respectively as compared to standard (ascorbic acid), 82.64% inhibition [37].

Hepatoprotective activity

Studies showed that, aqueous extract of *K. senegalensis* stem back orally administered to rats at 250 and 500mg/kg body weight for five days significantly alleviated CCl4 (3ml/kg) induced liver damage comparable to the standard drug Silymarin. The hepatoprotective activity of the extract was demonstrated via significant decrease in levels of liver biomarkers (AST, ALT, ALP, bilirubin, total protein and albumin) in groups treated compared to CCl4 group which may be due to the high content of polyphenols and antioxidant activities [38].

Anti-ulcer activity

Anti-ulcer potential of *Khaya senegalensis* has been demonstrated by its significant dose dependent effect on ethanol-induced gastric ulcer. Fractions (aqueous methanol, hexane and ethyl acetate) of the plant's crude methanol extract were found to significantly lower gastric ulcer indices at 400 and 800mg/kg when compared with ethanol treated group. The findings strongly suggested *Khaya senegalensis* has anti-ulcerative properties, which could be due to its anti-secretory and antioxidative activities reported in the study [39]. Investigation of the effect of piroxicam co-administration with ethanol stem-bark extract of *Khaya senegalensis* on gastrotoxicity in rats also showed that, the interaction of plant extract with piroxicam resulted in the gastroprotective beneficial effects [40].

Effect on hematological parameters

Oral administration of aqueous extract of *Khaya senegalensis* stem-bark for 21days at 50, 100, and 200mg/kg concentrations resulted in a significant dose dependent decrease in Red Blood Cells (RBC), Packed Cell Volume (PCV), and Hemoglobin level (Hb). This suggested that prolonged use of aqueous extract of *Khaya senegalensis* stem-bark extract may adversely affect the body [41]. Further studies on the sub-chronic effect of aqueous stem-bark extract of the plant showed that, administration of graded doses of 400, 800, 1200, 1600, and 2000 mg/kg respectively did not affect the hematological indices assayed compared to the control values, however biochemical and histological results obtained from the study indicated the aqueous stem bark extract of *K. senegalensis* may affect the cellular integrity of vital organs [42]. Methanol extract of the plant leaves was also found to cause decreased total erythrocytes (TEC) and packed cell volume (PCV) respectively with increased total leukocytes (TLC) at a median lethal concentration of 199.69mg/L in African catfish (*Clariasgariepinus*) over a period of 96h exposure [43].

Anthelmintic Activity

Direct anthelmintic effects of ethanol and aqueous extracts of *Khaya senegalensis* bark toward different gastrointestinal nematode was investigated in *vitro* and in *vivo*. In *vitro* larval development assay revealed that presence of plant extract in the cultures decreased the viability of larval of strongyles at LC_{50} of 0.69mg/ml and 0.51mg/ml for aqueous and ethanol extracts respectively. Oral administration of the extracts (in vivo) in sheep harboring naturally acquired infection of gastrointestinal nematodes at dose rate of 125, 250, and 500mg/kg revealed a concentration dependent activity. Sheep drenched with 500mg/kg *K. senegalensis* ethanol extract had an 88.82% reduction of mean faecal egg count (FEC) and this suggest the extract could find application in anthelmintic therapy in veterinary practice, thus further research is required to establish the rational use of the extract control strategy as a possible alternative to the use of existing synthetic anthelmintic drugs [44]. In another study, in vitro exposure of eggs, larvae, and adult worms of parasite (*Haemonchuscontortus*) to gradual increasing concentrations (75, 150, 300, 600, 1200, and 2400 µg/ml) of acetone and methanol extracts of *K. senegalensis* resulted to over 75% inhibition of egg-hatching compared to Levamisole treated group (negative control). The lethal effect was dose dependent and at 2400 µg/ml or 1200 µg/ml of acetone or methanol extract exposure, 75% or 100% worms died within 24h respectively, thus *K. senegalensis* extract could be a suitable alternative to chemical drug against Haemonchosis in goats and sheep from endemic areas like Africa [45].

Wound healing activity

In traditional therapeutics, *K. senegalensis* has been used typically to manage wounds. Often determined by wound closure (i.e. rate at which wound decrease with time), *K. senegalensis* stem-bark was used to treat wounded rabbits and the wound healing curve showed that wound closure in the experimental group was more rapid compared to the control group. In post-surgery days 15-21, a great reduction in wound area of experimental group was recorded with wound size of 175mm² compared to 235mm² in the control group. This showed that the stem bark used in the experiment may play a role in wound healing by accelerating wound closure, however further analysis is required before extrapolating the effect of *K. senegalensis* stem bark on human wounds [46].

Anti-trypanosomal Activity

Aqueous root, leaf and stem-bark parts of *Khaya senegalensis* were found to dose-dependently suppress parasite (*Trypanosoma evansi*) establishment and the manifestation of mild clinical diseases, with absolute clearance of the parasite from circulation at post-treatment day 9 for 120mg/ml stem-bark, day 15 for 120mg/ml leaf and root extracts respectively. Treatment with standard drug diminazene aceturate at 3.5mg/kg cleared the parasites from circulation and suppressed the manifestation of clinical signs of the disease within 24h with no relapse. The stem bark extract was found to be most active while the leaf extract showed weak trypanocidal activity. This suggested the traditional use of *K. senegalensis* has a pharmacological basis [47]. Methanol extract of *K. senegalensis* root bark also demonstrated trypanocidal activity against *Trypanosoma evansi* in vitro. Treatment of the Vero cell lines with the methanol extract (at 250μ g/ml) resulted to immobilization, reduction of average trypanosomes counts and complete killing of trypanosomes at 6h of incubation, equivalent to standard drug (diminazene aceturate, 50μ g/ml) at 4h. Both the root bark extract and standard drug were cytotoxic to Vero cells at all concentrations except 3.13-1.56 and 6.25-1.56 μ g/ml respectively [48].

Neuropharmacological activity

Spontaneous recurrent seizures (generalized tonic-clonic seizures) and anxiety-like behaviour in kainite (12mg/kg, i.p.) induced rats was significantly reduced by *Khaya senegalensis* aqueous extract at concentrations of 50, 100, and 200 mg/kg compared to negative control group and the effect were more marked than standard drug sodium valproate (300mg/kg) and phenobarbital (20mg/kg). The extract also increased significantly GABA concentration, attenuated oxidative stress, and mitigated neuronal loss in the dentate gyrus of the hippocampus. These suggest the plant extract possesses antiepileptic and anxiolytic-like effects, accompanied by neuromodulatory and antioxidant activities. Further study to identify the bioactive compounds in the extract and their mechanism of action for possible therapeutic development is recommended [49].

Immunomodulatory activity

Two Proanthocyanidins, catechin- $(4\alpha, 6)$ -catechin and catechin- $(4\alpha, 8)$ -catechin) isolated from bark of *Khaya senegalensis* where found to exhibit immunomodulating activity-mediated antileishmanial effect. Though not active against the tested promastigotes (EC₅₀>25.omg/ml), the bioactive

compounds showed significant effects with EC_{50} s of 3.85 and 3.98mg/mL respectively against intracellular amastigotes with no cytotoxicity, which indicates indirect immunomodulating of macrophage defense mechanisms [50].

Antimalarial activity

Methanol extract of the plant was evaluated for anti-malarial activity (*Plasmodium falciparum*) in vitro at different concentrations (500, 250 and 125µg/mL), using Artemether (51.20nM/L) as reference control. The extract exhibited a concentration dependent activity and within 72h, a variedly high mortality of 81% was recorded at concentration 500μ g/mL; compared to Artemether which gave 85% inhibition at the same time. The results proved that *K. senegalensis* (bark) has potent anti-malarial activities and verifies the use of the plant in traditional medicine among different populations worldwide [51]. Further studies exploring three different parts of the plant (leaves, stem-bark and roots) for their in vitro anti-malarial potency reported IC₅₀ values of >100µg/mL, 5µg/mL and 50µg/mL for the leaf, stem-bark and root extracts respectively. The good therapeutic index of the stem-bark extract shows its high selectivity against malarial (*Plasmodium falciparum*), when tested against the HUH-7 cell line of mammalian macrophages. *K. senegalensis* stem bark proves to be highly potent against malarial and should be explored for possible development of new anti-malarial drug [52].

Antidiarrheal activity

Stem bark aqueous and methanol extracts of *K. senegalensis* was also found to alleviate castor oil induced diarrheal in rats at varying doses of 300, 600, and 1200 mg/kg. The extracts dose dependently reduced the distance travelled by activated charcoal meal in the gastrointestinal motility test. The antidiarrheal activity of the plant extracts may be attributed to the flavonoid and tannin constituents present in the extract and this justifies the plant's use in traditional management of human and animal diarrheal. Further research is required to fractionate and purify the extract, in order to isolate active compounds responsible for the anti-diarrheal activities evaluated [53].

Antifeedant activity

Limonoids isolated from acetone and ether extracts of *K. senegalensis* stem bark have been assayed for their feeding deterrent properties by conventional choice leaf disc method against larvae of *Spodopteralittoralis* (Boisd.). The result showed that some of the limonoids including; methyl angolensate, khayanolide D, khayanolide A, 2-hydroxyseneganolide, 1-O-acetylkhayanolide A and Khayalactol at 1000µg/mL displayed strong antifeedant activity with antifeedant percentages of 55.7, 57.1, 59.5, 60.1, 61.9 and 83.8 respectively. Other limonoids like khayanolide D and2-Hydroxyseneganolide showed higher activity at 200, 300 and 500 µg/mL while 1-O-acetylkhayanolide A was the only limonoid compound with antifeedant activity at a concentration as low as 100µg/mI [54].

4. CONCLUSION

This review article would essentially be useful for researchers as it summaries comprehensively the different studies carried out till date on the plant. Different parts of the plant have been used extensively, validating its important traditional usage globally. The phytochemistry reveals diversity of important bioactive compounds found in the plant which are suggested to be responsible for its therapeutic efficacy. Further research to explore this plant is still required to validate its usage in folk medicine.

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