

(REVIEW ARTICLE)



Phytochemistry, pharmacology and botanical aspects of *Murraya Koenigii* in the search for molecules with bioactive potential - A review

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GSC Advanced Research and Reviews, 2021, 06(03), 143–155

Publication history: Received on 13 February 2021; revised on 14 March 2021; accepted on 16 March

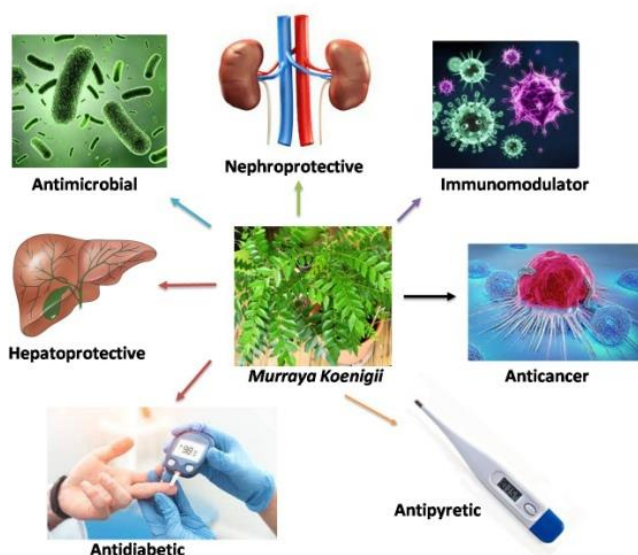
2021 Article DOI: <https://doi.org/10.30574/gscarr.2021.6.3.0055>

Abstract

The magical plant of Indian spice, *Murraya koenigii* (curry leaf) family Rutaceae grows throughout the Indian subcontinent. It is used in the treatment or prevention of many diseases including kidney stone, dysentery disorders, renal pain, stomach upsets & morning sickness. It is one of the main components of formulation in the traditional ayurvedic system of medicine since many centuries. A scrutiny of literature reveals some notable pharmacological activities of plant. These include pharmacological activities such as antioxidant, antidiabetic, antitumor and neuroprotective. The leaves, roots and barks of this plant are rich in source of carbazole alkaloids. The carbazole alkaloids includes koenigin, bicyclomahanim-bicine, cyclomahanimbin, murrayastine, coumarine, koenidine has medicinal activities.

Keywords: *Murrayakoenigii*; Taxonomical classification; Phytoconstituents; Traditional uses; Pharmacological activities

Graphical abstract



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1. Introduction

From the ancient time, plants have a long record of natural remedy in traditional system of medicine. At present there are huge numbers of people in developing countries depend on medicinal plants for healthcare, skin care, economic benefits, and cultural development [1]. Ethno-botanical information on medicinal plants and their usage by indigenous cultures is useful in the conservation of traditional cultures, biodiversity, to promote health care and drug development. India is one of the best initiator in the discovery of herbal medicine and used for the treatment of various disease. Now a day, WHO focusing attention towards the developing countries to encourage them to use herbal medicine, which they have been traditionally, used for centuries [2-13].

Murraya koenigii (L) Spreng belonging to family Rutaceae and it is usually known as *M. koenigii* in English and also known as karipatta or kadipatta in Nepali as well as in Hindi [14]. The leaves of this plant has been used widely in Indian culinary which responsible for its aromatic characteristic is *P. gurjunene*, *P. caryophyllene*, *P. elemene* and *O. phellandrene*. Traditionally, it is used as anti-diarrheal, blood purifier, hair tonic, antinociceptive, antidysentric, anti-amnesic, antifungal, memory enhancer, anti-anemic, anti-emetic and anti-periodic [16]. Similarly, it is also used to cure kidney pain, vomiting, itching, dysentery, blood disorder, diabetes mellitus, leucoderma, hypercholesterolemia lightening [17-18].

The various multiple biological properties of *M. koenigii* such as its anti-oxidant, anti-bacterial, anti-diabetic, anti-protazoal, anti-mutagenic, hepatoprotective, anti-tumor, anti-viral, anti-leukemial, anti-inflammatory activities [19-25]. The soap and cosmetic aromatherapy industry utilizes the essential oil of *M. koenigii* as an important ingredient in soap, bath oils, massage oils, perfume oils, lotions, diffusers, facial steams, potpourri, towel scenting, air fresheners, incense, body fragrance, scent, aromatherapy products [26-27]. *M. koenigii*, boiled with coconut oil are condensed to blanked residues that are then used as a dominant hair tonic for retaining and maintaining natural hair tone, hair growth stimulation and prevention of premature growing of hair [28].

The World Health Organization (WHO) projected that 80% of the population depends on traditional medicine, which is clearly elucidate by the 19.4 billion USD global revenue for herbal remedies in 2010 [29]. The demand for traditional medicinal plants is increasing nowadays. The market for medicinal plants is expanding at an annual rate of 20% in all over India and similarly in China 30% to 50% of the total medicinal consumption [30]. Almost, 76.7% of the citizens of Thailand have reported mainly using traditional herbal medicine for their primary healthcare [31-32]. Therefore, the medicinal plants used in traditional medical treatments are significant in both developing and industrialized countries.

2. Taxonomical classification

Detail taxonomical classification of plant is given bellow [33-35].

Kingdom: Plantae	Subclass: Rosidae
Subkingdom: Tracheobionta	Order: Spindales
Super division: Spermatophyta	Family: Rutaceae
Division: Magnoliophyta	Genus: <i>Murraya</i> J. Koenig ex L.

3. Synonyms or vernacular names

The plant is known by various local names as given bellow [35].

Language	Vernacular name	Language	Vernacular name
English:	<i>Murrayakoenigii</i>	Malayalam:	<i>Kariveppilei, Kareapela</i>
Hindi:	<i>Curry patta, MeethaNeem, Kathnim</i>	Sanskrit:	<i>Girinimba, Suravi</i>
Marathi:	<i>Karipat, Karhipatta, Karhinimb</i>	Telugu:	<i>Karepaku, Karuvepaku</i>
Kannada:	<i>Karibevu</i>	Gujrati:	<i>MithoLimdo</i>
Tamil:	<i>Karivempu, Karuveppilei, Karivepila</i>	Bengali:	<i>Barsunga</i>

4. Plant description and habitat

Murrayakoenigii has little tapering out spreading shrub which is about 2.5 meters in height and the color of the stem is dark green to brownish (Fig. 1). Upon peeling of the bark longitudinally the beneath white wood is visible and the main stem diameter is about 16cm. The flower is white funnel-shaped, having a sweet aromatic characteristic and the average diameter of fully opened flower would be 1.12cm and it is bisexual and the leaves are about 30 cm long with each bearing 24 leaflets and it have a reticulate venation. The fruits are round to oblong in shape with 1.4cm to 1.6cm in length and 1cm to 1.2cm in the diameter. The fully riped fruit will be black in color with a shining surface and the pulp will be in wisteria blue and the seed will be spinach green with 11mm long and weigh about 445mg [36-37].



Figure 1 Leaves of *M. koenigii*

5. Phytoconstituents

Medicinal properties of the plants are attributed to active phytoconstituents present in the plant. These compounds may be volatile or non-volatile [42-55]. There are various analytical techniques by which active chemical compounds are determined. These methods can also be used for analysis of phytoconstituents in pharmaceutical formulations including ayurvedic products [56-61].

The *M. koenigii* have a diverse chemical composition. Solvents like ethyl acetate, ethanol, petroleum ether, water and chloroform have been used by researchers to prepare the plant extracts, and chemical compounds such as alkaloids, flavonoids and sterols. They are also rich in diverse sources such as proteins, fibers, carbohydrates, minerals, nicotinic acid, vitamin C and carotene and have a huge content of oxalic acid, crystalline glycosides, carbazole, alkaloids, resin and koenigin [62]. Leaves also contain triterpenoid alkaloids for example cyclomahanimbine and tetrahydromahanimbine.

The bark also contain carbazole alkaloids (Fig. 2). The fruit pulp of *M. koenigii* contains non-reducing and reducing sugars along with some amounts of tannins and acids. The trace amounts of phosphorous, potassium, calcium, magnesium and iron are present along with vitamin C [63]. Seeds contain xanthotoxin, isobyakangelicol and other minor Furocoumarines have also been isolated. The volatile oil present in fresh leaves is a rich source of vitamin A and calcium. The essential oil composition showed the presence of D-sabinene, D- α -terpinol, di- α -phellandrene, D- α -pinene, caryophyllene and dipentene. Roots (Fig. 3) contain girinimbine, koenoline [64].

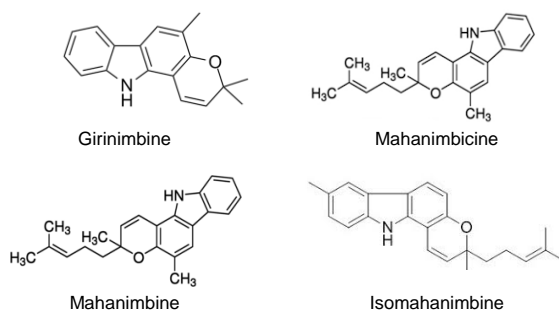


Figure 2 Phytoconstituents of *M. koenigii*



Figure 3 Roots (A) and roots powder (B) of *M. koenigii*

6. Traditional uses of plant

The leaves are aromatic and have a characteristic taste. Ayurvedic system of medicine uses powdered dry curry leaf mixed with honey and betel nut juice as an anti-periodic. The leaves of this plant are used externally for application onto bruises, burns, eruption, and treatment of bites of poisonous animals. Internally, they are used to cure dysentery and also for the treatment of diabetes mellitus. It is also being used as a stimulant and they have also been helpful in leucoderma and influenza and rheumatism can also be treated with these leaves [65-66].

The leaves and roots, owing to their bitter and acrid properties, show cooling, anti-helminthic, analgesic actions and also used for curing piles, allaying body heat, thirst, itching and inflammation. The juices of the roots have hepatoprotective actions and are verified to be good for kidney related pains and the fruits are highly nutritious with several medicinal properties. [67-68]. An infusion of the roasted leaves is used as an antiemetic. The steam distillates of the leaves are used as stomachic, carminative, purgative, febrifuge and anti-anemic [69]. It is also been used as blood purifier, tonic and cure for stomachache and used as flavoring agents in curries and chutney [70-71].

For the treatment of morning sickness; fresh juice of leaves together with lime juice and sugar is given and it is also applicable for vomiting due to indigestion and can also prevent the progression of cataract. In the case of stomach upsets, the leaves of the plant is grounded to a fine paste and mixed with buttermilk and consumed orally. A paste of leaves is applied on the boils for swift relief, in addition that, renal pain can be cured by consuming the root as a juice.

M. koenigii will retain the black color of the hair or in other words, it will prevent the premature greying of the hair and are boiled with a coconut oil mixture until they are reduced to a black residue to produce an excellent hair tonic for retaining a normal hair tone and improving hair growth. *M. koenigii* were also used as calcium source to those having calcium deficiency besides that it also consist Vitamin A, Vitamin B and B2, Vitamin C and iron [72]. *M. koenigii* have a traditional use, either whole or in parts, as antidiarrheal, antifungal, blood purifying, anti-inflammatory, and anti-depressant agents [73-78].

7. Pharmacological activities

The pharmacological activities of *M. koenigii* are discussed in detail.

7.1. Antioxidant Activity

The aqueous extracts of *M. koenigii* leaf give significant protection to rat cardiac tissue against cadmium-induced oxidative stress probably due to its antioxidant activity either environmentally or occupationally. The results of the oxidative stress have been seen the alterations in the levels of lipid peroxidation, reduced glutathione, protein carbonyl content, changes in the activities of cardiac antioxidant and pro-oxidant enzymes and indicate that the cadmium-induces tissue [79].

7.2. Anti-inflammatory activity

The leaves of *M. koenigii* was subjected to drawing out with three various solvents such as petroleum ether, chloroform and ethanol. A dose of 250mg/kg was selected via oral route for administration which is a 1/10th of 2500mg/kg which was considered as LD50. Compared to the three solvents, it was found that ethanolic extract shows significant reduction

in carrageenan induced paw edema in the Albino rats of the wistar strain [80]. Moreover, it was found that the methanol and aqueous the extract of leaves is effective against carrageenan- induced edema in male albino rats as compared to petroleum ether and hexane extracts which results in no decrease in the inflammation.

The methanol extract was found to have an utmost anti-inflammatory activity compared to aqueous extract [81]. Reported that the crude roots extract of *M. koenigii* shows anti-inflammatory activities. The ethanolic extract of *M. koenigii* (EEMK) is the mainly cell stabilization, anti-histaminic effects were recommended to suitable mechanisms for its anti-inflammatory action.

The ethanolic extract shows significant anti-inflammatory effects as compared with petroleum ether and chloroform extracts. Wound healing is a complex, multifactor process involving several biochemical and cellular processes which helps in the restoration of functional and anatomical continuity. *M. koenigii* leaves extend wound healing in male albino rats through significantly increased wound contraction and reduces epithelialization [82-84].

7.3. Hepatoprotective Activity

The liver is the site of drug metabolism and the detoxification site of toxic products, and so it is the organ most exposed to xenobiotics. The methanolic extract of *M. koenigii* leaves at the doses of 200mg/kg, 300mg/kg, 500mg/kg has shown decrease in the elevation on hepatic marker enzymes such as aspartate transaminase, alanine transaminase, serum bilirubin and alkaline phosphate as a result of administration of carbon tetrachloride on adult spraguedawley rats and the maximal dose of 500mg/kg was comparable to the standard drug, silymarin.

Silymarin has been used clinically for the treatment of the liver disease [85]. Since ancient times, herbs have been used when treating various disease conditions; plant extracts and natural compounds have significant applications as hepatoprotective agents [86]. In experimental animals, *M. koenigii* extended hepatoprotective activity when crude aqueous extracts were investigate aligned with ethanol induced hepatotoxicity. It was also reported that the protective effect in liver impairments in chronic alcoholism was proved to be effective in maintaining the enzymatic oxidant status [87-88].

7.4. Nephroprotective activity

Oral administration of aqueous extract of leaves in a daily manner for 30 days in streptozotocin induced diabetic in male rats were found more significant reduction in serum urea and creatinine levels. It also promotes tissue regeneration in kidney. *M. koenigii* protective activity has been shown to provoke significant dose dependent decreases in serum urea and creatinine levels, as well as marked increases in the levels of plasma antioxidant capacity, in diabetic rats, compared to controls. The histological integrity of kidneys which showed comparable tissue regeneration induced by the aqueous extract [89-90].

7.5. Neuroprotective activity

Ethanolic extracts of leaves results in increase in grab strength of streptozotocin induced diabetic rats that developed neuropathy. Prior to that the treatment with *M. koenigii* extracts increased the withdrawal time and licking latency in hot plate and tail flick tests. This indicates that the chronic treatment with *M. koenigii* decreased by glycemic levels and offered neuroprotective benefits [91].

M. koenigii promotes neuroprotective potential against orofacial dyskinesia induced by reserpine. In addition, it stabilizes the levels of protective antioxidant enzymes like SOD, catalase (CAT), and GSH, and inhibits LPO in the forebrain regions of reserpine treated animals. Haloperidol with *M. koenigii* significantly restored the levels of protective antioxidant enzymes and inhibited LPO in the forebrain region when compared with reserpine, and inhibits catalepsy [92-93]. Preclinical studies have reported that *M. koenigii* leaves could enhance memory in rats [94-95]. The various activities of *M. koenigii* against neurotoxicity are shown in Fig. 4.

7.6. Immunomodulatory activity

The leaf extracts do not only have antidiabetic property but it also acquire assured effects to control immunology related to oxidative stress metabolism. This immunomodulatory and anti-inflammatory activity was marked by interleukin (IL)-2, 4, 10 and tumor necrosis factor alpha (TNF-alpha) expression [97].

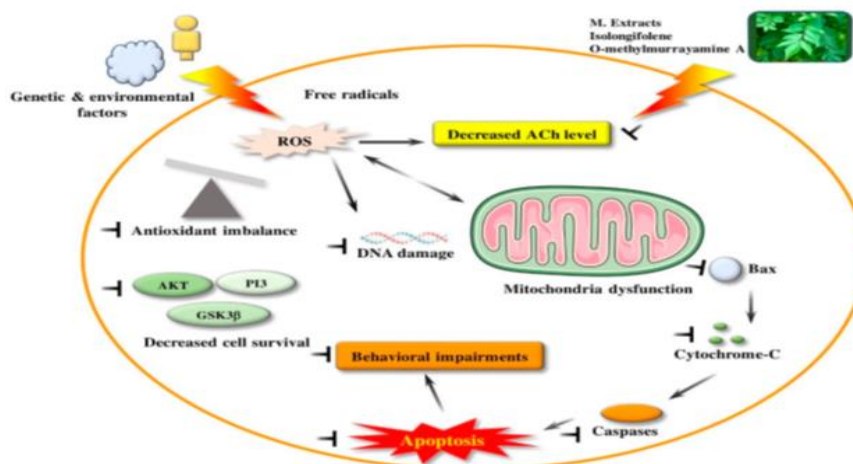


Figure 4 *In-vitro* and *in-vivoneuroprotective* effects of bioactive compounds [95]

7.7. Anticancer activity

Girinimbine, acarbazole isolated from the bark of *M. koenigii* significantly induced programmed cell death in Hep-G2 cells suggesting the necessity for further evaluations in preclinical human hepatocellular carcinoma models [98] (Fig. 5). The results from the study conducted by Bhattacharya et al. 2010 provides evidence for the involvement of death receptor mediated extrinsic pathway of apoptosis in mahanine-induced anticancer activity [99-102].

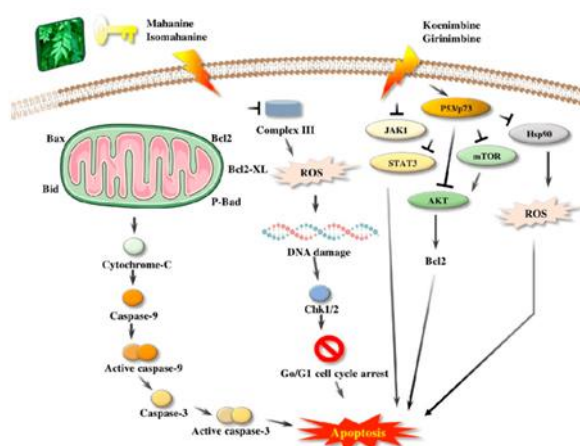


Figure 5 Apoptosis induced by *M. koenigii* bioactive compounds in cancer [107]

The methanolic extract leaves demonstrated a significant increase in the phagocytic index by the rapid deletion of carbon particles from blood stream. It also verified an increase in the antibody titer against ovalbumin and protection against cyclophosphamide-induced myelosuppression. *M. koenigii* holds promise as an immunomodulatory agent acting by stimulating humoral immunity and phagocytic function and these extracts were unable to stimulate cellular immunity [103].

7.8. Antidiabetic activity

Alkaloids present in the leaves of *M. koenigii* have been explored and reported to have inhibitory effects on the aldose reductase enzyme, glucose utilization, and other enzyme systems for extending anti-diabetic effects. It was also tested for the α -glucosidase inhibitory property and was found to inhibit α glycosidase. Alpha glucosidase inhibitors are widely used in the treatment of patients with type 2 diabetes [104-105].

7.9. Antimicrobial activity

The hexane, methanol and chloroform extract of the *M. koenigii* root were tested against *B. subtilis*, *S. aureus*, *E. coli*, *S. typhi* and fungal strain of *A. niger*, *C. albicans* and *T. rubrum*. The hexane, methanol and chloroform extract of the root

was effective on all the tested strains and methanol extract showed more significant antimicrobial activity. The *S. aureus* were susceptible to the all the three extracts above, additionally the aqueous extract of the root were found to be effective against the tested microorganism [106].

The essential oil from roots showed antibacterial effect against *B. subtilis*, *S. aureus*, *C. pyogenes*, *P. vulgaris* and *P. multocida* and the pure oil was active against the first three organisms even at a dilution of 1:500. The acetone extract of the roots of *M. koenigii* on fractions gives three bioactive carbazole alkaloids such as mahanimbine, murrayanol and mahanine which shows activities in mosquito cidal, anti-microbial and topoisomerase I and II inhibition [107].

7.10. Cytotoxic activity

The alkaloid koenoline isolated from the roots bark is found to demonstrate cytotoxic activity against KB cell culture system. The carbazole alkaloid shows the significant cytotoxicity effect against HL-60 cells Mahanine, Pyrafoline-D, Murrafoline-I and Girinimbine. Carbazole alkaloids isolated from the stem are found to effects the growth of the human leukemia cell line HL-60 and also induced loss of mitochondrial membrane potential [109].

7.11. Anthelmintic activity

The leaves poses as antihelmintic effects, by which the ethanolic and aqueous extract of the leaves shows an anthelmintic effects against *pheretima posthuma* was comparable to the standard drug Piperazine [110]. It is supposed that tannins which are the polyphenolic compound found in *M. koenigii* leaves shows antihelminth effects. The methanolic extract of *M. koenigii* shows anthelmintic effects against the Indian earthworm (*P. posthuma*) in a dose dependent manner and also act by binding of the tannins to the free protein in the git of the host or binding to the glycoprotein on the cuticle of the parasite and causes the lethal effects on it. The methanolic extract causes the paralysis of Indian earth worm at 18 minutes and promotes lethal effect at 45 minutes [111].

7.12. Antipyretic activity

The rats were fevered with the parentral administration of brewer's yeast and were found that the ethanol extract of *M. koenigii* leaves poses an antipyretic activity. It was compared with petroleum ether extract and chloroform extract, with paracetamol dose as a standard drug [112].

7.13. Inotropic activity

Inotropic Activity- The ethanolic extract of the fresh leaves of *M. koenigii* shows a positive inotropic effect on the isolated frog heart in a dose dependent. It was recommended that the positive inotropic activity is achieve by an increase in the ease of use of calcium from the extracellular sites by the *M. koenigii* [113-114].

8. Conclusion

M. koenigii is one of the medically beneficial plant which has been used many century ago by our ancestors. In the current globalization era, it is difficult to find a curry plant in majority of the houses and many diets has been dependent to synthetic agent as taste enhancer against *M. koenigii*. Thus, the importance of these beneficial plant should be emphasized and the bioactive components of plants should be analyzed further and used against the disease that have been developed resistance and synergistic studies should be carried out.

Compliance with ethical standards

Acknowledgments

Authors are thankful to Shri. Yogendraji Gode, President, IBSS's Dr. Rajendra Gode Institute of Pharmacy, Amravati and Dr. Rajendra Gode College of Pharmacy, Amravati for providing necessary facility to undertake this work.

Disclosure of conflict of interest

The author declares no conflict of interest.

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