Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

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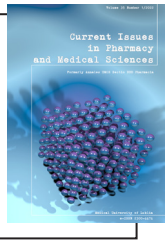

Pre-clinical evidence-based insights into the therapeutic potential of *Murraya koenigii* (curry patta) with a focus on its future application as an anti-inflammatory drug

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ARTICLE INFO

Received 2023-06-07
Accepted xx 202x

Keywords:
Murraya koenigii,
anti-inflammatory activity,
therapeutic potential,
pre-clinical evidence.

ABSTRACT

In recent years, there has been unprecedented growth in the use of plant-based herbal therapeutics for the management of various disease conditions. *Murraya koenigii* has a long history of use in India as a food enhancer and for its numerous therapeutic benefits. Various parts of the plant, including leaves, stems, and bark, are traditionally used to treat disorders such as dysentery, renal pain, gastrointestinal disturbances, and morning sickness. Leaf extracts of *M. koenigii* have been reported to possess cooling, anthelmintic, analgesic, antibacterial, anti-inflammatory, and antipruritic properties. In addition, the leaves are used in the management of leukoderma and as blood-purifying agents. Toasted leaves infused in water are traditionally used as a household remedy to control vomiting, while crushed leaves are applied topically to treat skin eruptions and soothe burns. The present review aims to provide an updated overview of the therapeutic potential of *M. koenigii*, with a particular emphasis on pre-clinical evidence supporting its anti-inflammatory activity.

INTRODUCTION

The use of medicinal plants for the treatment of various diseases has gained considerable attention in recent years. Phytoactive constituents derived from medicinal plants possess a wide range of important pharmacological activities, including antimicrobial, immunomodulatory, anti-inflammatory, and anticancer effects [1]. *Murraya koenigii* (family: Rutaceae) is a common plant used in Indian households and is widely recognized as curry patta. The plant has been reported to possess numerous medicinal benefits [1,2]. It is commonly found in many Asian countries, including India, Myanmar, Indonesia, Sri Lanka, Hainan, Bhutan, Odisha, Vietnam, Laos, and Pakistan. In India, it is predominantly found in the Western Ghats, Assam, West Bengal, and Sikkim [3].

Fresh leaves are commonly used in cooking, while powdered leaves and essential oils are also utilized for flavoring soups, curries, meat, and fish preparations [4]. The leaves are traditionally used to reduce body heat and to treat piles. Essential oils extracted from the leaves are used in the manufacture of soaps and cosmetic products. Boiled curry leaves mixed with coconut oil are traditionally applied to promote hair growth. Phytocomponents of the plant have been used as blood purifiers, febrifuges, and as anti-inflammatory, wound-healing, and antiemetic agents [5]. Leaves of *M. koenigii* have also demonstrated beneficial effects in patients with diabetes mellitus, and leaf paste is applied topically in cases of insect bites [6].

Antimicrobial activities of *M. koenigii* extracts against several disease-causing pathogens have been reported. In one study, hexane, chloroform, and methanol extracts of the plant were tested against *Bacillus subtilis*, *Escherichia coli*, and *Salmonella typhi*, as well as fungal strains such as *Aspergillus niger*, *Candida albicans*, and *Trichophyton rubrum*. The tested extracts exhibited significant antimicrobial activity against all evaluated pathogens [7]. Ethanolic leaf extracts have also shown antipyretic activity, and another report demonstrated a significant reduction in blood glucose and cholesterol levels in experimental mice [8].

Pre-clinical studies indicate that *M. koenigii* leaf extracts possess notable anti-inflammatory properties. These extracts have been shown to inhibit the production of inflammatory mediators, including cytokines and prostaglandins, which play a crucial role in inflammatory responses [9].

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As oxidative stress is closely associated with inflammation, several studies suggest that *M. koenigii* extracts exhibit antioxidant properties that may contribute to their anti-inflammatory effects [10].

Mahanimbine, a carbazole alkaloid and a key phytoactive constituent derived from the leaves, has demonstrated antihyperglycemic and hypolipidemic activities. Koenoline, another important bioactive compound present in the root bark of *M. koenigii*, has shown anticancer activity. Carbazole alkaloids isolated from the stem of the plant have exhibited significant inhibitory effects on the growth of the human leukemia cell line HL-60 [11]. Additionally, leaves of *M. koenigii* have been reported to possess radioprotective activity and may be useful as antioxidants in skincare formulations [12].

Despite these findings, a comprehensive review compiling the therapeutic benefits of *M. koenigii*, particularly its anti-inflammatory potential, remains limited. Therefore, the present review aims to provide an updated and detailed overview of its anti-inflammatory properties, which may support further research in formulation development and pre-clinical studies [13].

1. Important phyto constituents of *Murraya koenigii*

Important phytoconstituents present in the leaves of *Murraya koenigii* include alkaloids, coumarin glycosides, carotene, vitamin C, riboflavin, niacin, and oxalic acid [14]. Leaf essential oils contain compounds such as caryophyllene, diphellandrene, D-sabinene, D-pinene, and D-terpinol. The roots of the plant contain bioactive constituents including rayagetin, rayanol, and marmesin-1″-O-rutinoside. Benzene extracts of the roots have been reported to contain mukoline and mukolidine.

The fruits contain important phytoconstituents such as mahanimbine and koenimbine, which are extracted using petroleum ether [15]. Essential oils obtained from the leaves are rich in monoterpenoids and their derivatives. Among the major phytoactive components identified by gas chromatography–mass spectrometry of steam distillates are β-caryophyllene (35.8%), β-phellandrene (2.57%), α-pinene (0.26%), β-elemene (0.18%), and β-thujene (4.12%) [16]. Other reported constituents include α-caryophyllene (9.17%), cadinene (8.43%), selinene (8.88%), linalool (0.27%), trans-ocimene (3.12%), and gurjunene (approximately 1.46%) [17].

2. Therapeutic activities of *Murraya koenigii* in a nutshell

Murraya koenigii exhibits a wide range of therapeutic activities, which are summarized in Figure 1.

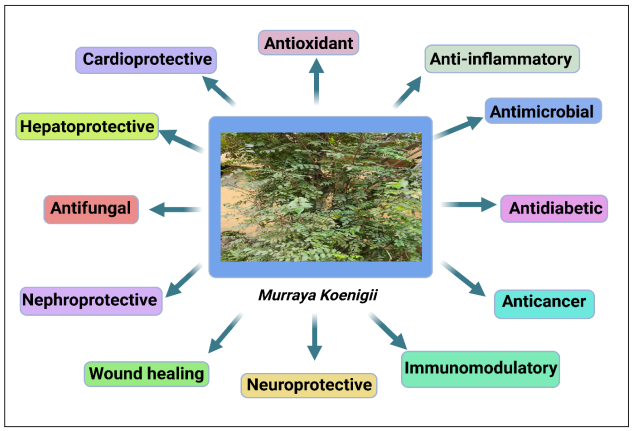

Figure 1. Important therapeutic benefits of *Murraya koenigii*

INFLAMMATION: BASIC MECHANISMS

Inflammation is a pathological process that can occur in any part of the body [18]. It may be defined as a protective response involved in tissue repair following injury and is characterized by a series of cellular and microvascular reactions that facilitate the elimination of damaged tissue and the initiation of tissue regeneration [19]. Inflammation comprises a sequence of events, beginning with the initiation of the inflammatory response, followed by the appearance of cardinal signs, progression toward healing, and ultimately the restoration of tissue and organ function [20].

The inflammatory process involves various cell types, including mast cells, basophils, neutrophils, B cells, and T cells. These cells are selectively recruited to the site of inflammation through tightly regulated mechanisms. The process is mediated by cytokines, growth factors, peptides, and eicosanoids, which coordinate the inflammatory response. Inflammation may present as either an acute or a chronic condition [21].

The inflammatory response can be divided into four major stages:

1. Alterations in local blood flow to the affected area, leading to changes in smooth muscle cell function and subsequent vasodilation [22].
2. Cytoskeletal contraction resulting in increased vascular permeability [23].
3. Migration of phagocytic leukocytes from capillary vessels into the surrounding interstitial spaces and toward the site of inflammation [24].
4. Phagocytosis, representing the final stage of the inflammatory process [25].

The cardinal signs of inflammation include pain, swelling, redness, and loss of function (Figure 2). Inflammatory mediators are released either as newly synthesized proteins or from preformed stores within cells such as mast cells, neutrophils, platelets, and monocytes. These mediators play a crucial role in determining the intensity and duration of the inflammatory response by binding to specific target receptors and increasing vascular permeability. Common chemical mediators involved in inflammation include nitric oxide, leukotrienes, and cytokines [21].

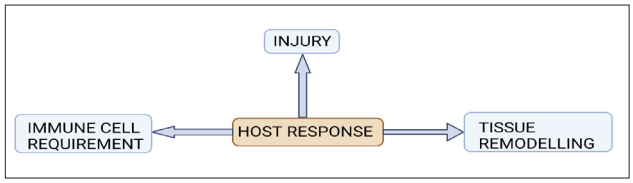

Figure 2. Basic mechanisms involved in inflammation

RECENTLY REPORTED STUDIES ON THE THERAPEUTIC POTENTIAL OF *MURRAYA KOENIGII*

Numerous studies have documented the anti-inflammatory potential of *Murraya koenigii*. In one study, leaf extracts demonstrated significant anti-inflammatory activity using the tail-flick and Eddy's hot plate methods in albino rats [26]. Carrageenan-induced paw edema was evaluated at specific time intervals to assess chemically induced pain and inflammation. A significant increase in average response time was observed at a dose of 600 mg/kg compared to the control group, indicating pronounced anti-inflammatory activity of the aqueous leaf extract [26,27].

Another study investigated the anti-inflammatory activity of methanolic extracts of *M. koenigii* using both in vivo and *in vitro* models. In acute inflammation models, the extract exhibited dose-dependent inhibition, while in chronic inflammation studies, it significantly reduced cotton pellet-induced granuloma formation in rats. Male Wistar rats were used to evaluate the anti-inflammatory effects of *M. koenigii* Spreng [28,29]. Similar findings suggested that the bitter leaves of the plant reduce inflammation and itching and are useful in blood-related disorders such as leukoderma [30].

Kumaresan *et al*. demonstrated anti-inflammatory activity of curry leaves in dairy cows suffering from endometritis. Endometritis was identified by cervicovaginal discharge and the presence of pus flakes in uterine lavage. Animals were divided into control and treatment groups, with the treated group receiving 200 g of leaf powder orally for nine days. The extract significantly reduced bacterial load and uterine inflammation [31].

In vitro anti-inflammatory activity of *M. koenigii* was evaluated using arachidonate 5-lipoxygenase and xanthine oxidase inhibition assays [32]. Another in vivo study demonstrated dose-dependent reduction in carrageenan-induced paw edema in albino rats weighing 175–200 g. Thirty rats were divided into five groups, including control (gum acacia), standard (aspirin), and test groups receiving methanolic leaf extracts. The extract significantly reduced paw edema, with efficacy comparable to aspirin [33].

Ethanolic leaf extracts were also evaluated for anti-inflammatory activity using protein denaturation assays. A significant reduction in inflammation-related protein denaturation was observed, likely due to the presence of polyphenolic compounds such as tannins, phenols, flavonoids, and steroids [34].

In another study, eighteen carbazole alkaloids isolated from leaf and stem extracts were characterized using HR-ESI-MS-NMR techniques. Both *in vitro* and in vivo anti-inflammatory activities were evaluated. Compounds such as murrayanine, O-methylmurrayamine, and mukolidine exhibited significant activity by inhibiting histamine- and 5-hydroxytryptamine-induced edema during the early phase and kinin-mediated vascular permeability in later phases [35].

Singh *et al*. studied the anti-inflammatory activity of methanolic extracts of dried *M. koenigii* leaves administered orally at doses of 100, 200, and 400 mg/kg in albino rats. Carrageenan-induced paw edema was assessed using a plethysmograph, with diclofenac sodium as the standard drug. The extract significantly reduced paw edema in a dose-dependent manner, particularly at 400 mg/kg, possibly by suppressing inflammatory mediators [29].

Zhang *et al*. analyzed the methanolic leaf extract using GC–MS and PerkinElmer GC Clarus 500 systems [38]. Compounds were further separated using a Shimadzu LC-2010 HPLC system. Among the identified phytoconstituents, 9,12-octadecadienoic acid exhibited potent anti-inflammatory activity, reducing paw edema by 85% at a concentration of 150 µg/mL, compared to 68.62% reduction by aspirin. The compounds showed no cellular toxicity [36]. Hydroalcoholic extracts also reduced pancreatic inflammation, while leaf paste application reduced inflammation by up to 73% compared to indomethacin.

Yadav *et al*. investigated the hemostatic potential of *M. koenigii* leaves in Wistar rats. Treatment groups receiving leaf extract at concentrations of 25%, 50%, 75%, and 100% showed significant reducions in bleeding time compared to the control group, as assessed using the Duke method. ANOVA analysis confirmed statistically significant differences among groups [37].

Further studies suggest that *M. koenigii* exhibits both anti-inflammatory and anticancer properties. Girinimbine, a carbazole alkaloid present in the plant, induced apoptosis and reduced viability of human colon cancer cells. It inhibited nitric oxide production in interferon-γ-induced cells and suppressed nuclear factor-kappa B (NF-κB) translocation. In vivo, girinimbine reduced inflammation in carrageenan-induced peritonitis models in mice. These effects are attributed to the plant's high phenolic and flavonoid content [2].

Sandamali *et al*. reported cardioprotective effects of *M. koenigii* leaf extracts against doxorubicin-induced cardiotoxicity in albino rats, with treated groups showing significant protection [38].

Murrayanine, another important bioactive constituent, exhibited carminative, anti-anemic, and stomachic activities. *In vivo* studies demonstrated significant reduction in paw edema following administration of methanolic extracts at doses of 250 and 500 mg/kg, compared with diclofenac sodium as the standard [39].

In vitro evaluation of aqueous extracts demonstrated anti-inflammatory activity through inhibition of lipoxygenase, proteinase activity, and albumin denaturation. Carbazole alkaloids such as mahanine, mahanimbicine, and mahanimbine, along with essential oils, enhanced wound healing activity in rats. Topical application of extracts resulted in faster wound contraction, improved epithelialization, increased collagen deposition, fibroblast formation, and reduced inflammatory cell infiltration [40].

Further in vivo studies using carrageenan-induced paw edema models showed that ethanolic extracts reduced edema by up to 52.7%, petroleum ether extracts by 39%, and chloroform extracts by 36%. Ibuprofen demonstrated significant edema reduction from the third hour onward. Among all extracts tested, the ethanolic extract showed the most pronounced anti-inflammatory activity [41].

Table 1. Therapeutic activities of *Murraya koenigii* reported in pre-clinical studies

Formulation	Activity	Model	Findings	Ref.*
Methanolic leaf extract	Anti-inflammatory	*In vivo*	The methanolic leaf extract produced a statistically significant, dose-dependent reduction in rat paw edema, comparable to the standard drug aspirin	[26]
Methanolic leaf extract	Anti-inflammatory and analgesic	*In vivo*	The extract demonstrated significant anti-inflammatory and analgesic effects in experimental rats compared with the control group and the standard drug diclofenac sodium (10 mg/kg, p.o.)	[33]
Chloroform and methanolic crude extracts	Anti-inflammatory and antimicrobial	*In vitro* and *in vivo*	Active phytoconstituents (compounds 1, 3, and 18) significantly inhibited the release of pro-inflammatory cytokines TNF-α and IL-6 and reduced LPS-induced TNF-α and IL-6 production in human PBMCs. Compounds 12 and 19 exhibited notable antimicrobial activity	[35]
Aqueous leaf extract	Anti-inflammatory and analgesic	*In vivo*	The aqueous extract significantly reduced paw edema volume in laboratory rats in a dose-dependent manner when compared with the standard drug	[29]
Aqueous leaf extract	Hypoglycemic and antihyperglycemic	*In vivo*	In normal rats, glucose reduction was minimal. In mild and moderate diabetic rats, administration of 5%, 10%, and 15% (v/v) extract produced a maximum reduction in blood glucose levels of 13.1%, 16.3%, and 21.4%, respectively	[37]
Aqueous leaf extract	Cardioprotective	*In vivo*	Doxorubicin-treated rats showed extensive myocardial damage, whereas extract-treated groups exhibited preserved myocardial architecture with a reduced degree of damage	[38]
Aqueous leaf extract	Anticancer and anti-inflammatory	*In vivo*	Treatment with an optimized aqueous leaf extract formulation resulted in a significant reduction in tumor cell count and tumor weight in tumor-induced mice	[39]
Ethanolic extract	Anti-inflammatory	*In vitro* and *in vivo*	Wounds treated with mahanimbicine (88.54%) and *M. koenigii* extract (91.78%) showed enhanced collagen deposition, organized collagen bands, fibroblast formation, hair follicle development, and reduced inflammatory cell infiltration	[40]
Ethanolic extract	Analgesic	*In vivo*	The ethanolic leaf extract produced significant, dose-dependent analgesic and CNS-stimulating effects in experimental animal models	[41]
Aqueous extract	Analgesic and anti-inflammatory	*In vivo*	The aqueous leaf extract demonstrated significant analgesic and anti-inflammatory activity in both thermal- and chemically induced pain models	[42]

*Ref. - References

CHALLENGES RELATED TO THE PRACTICAL APPLICATION OF PHYTOMEDICINES

Phytomedicines have been used for centuries for the prevention and treatment of various diseases. Despite their promising therapeutic potential, several challenges limit their practical application and broader acceptance in modern healthcare systems. The key challenges associated with phytomedicines and phytonanomedicines are discussed below.

1. Standardization and quality control

One of the major challenges in the development of phytomedicines is ensuring consistent quality and standardization. The chemical composition of medicinal plants may vary significantly depending on geographical origin, climatic conditions, soil characteristics, harvesting time, and processing methods. Therefore, the establishment of standardized protocols for cultivation, extraction, formulation, and quality control is essential to ensure product safety, efficacy, and batch-to-batch reproducibility.

2. Lack of regulatory frameworks

In many countries, phytomedicines are not governed by comprehensive and harmonized regulatory guidelines. This lack of specific regulatory frameworks creates challenges related to quality assurance, labeling, safety surveillance, and efficacy evaluation. The absence of strict regulations may result in variability in product quality and safety, making it difficult for healthcare professionals and consumers to make informed decisions regarding their use.

3. Limited scientific evidence

Although traditional knowledge and ethnopharmacological use support the therapeutic benefits of many phytomedicines, robust scientific evidence is often insufficient. Well-designed pre-clinical and clinical studies are required to validate their pharmacological efficacy, safety, and optimal dosage regimens. However, conducting such studies is challenging due to the complex chemical composition of plant extracts, variability in raw materials, and difficulties in standardization, blinding, and placebo-controlled trial design.

4. Drug safety and herb-drug interactions

Phytomedicines contain multiple bioactive constituents that may interact with conventional pharmaceutical drugs, potentially leading to adverse reactions or altered therapeutic outcomes. Data on herb-drug interactions remain limited, and healthcare professionals often lack access to comprehensive databases addressing these interactions. Additionally, adverse effects associated with phytomedicine use may be underreported, complicating accurate safety assessment.

5. Intellectual property and commercialization issues

Many medicinal plants and their associated knowledge originate from indigenous and traditional medical systems. Protecting intellectual property rights and ensuring fair benefit-sharing with local communities present significant challenges. Furthermore, large-scale commercialization of phytomedicines may promote overharvesting, unsustainable agricultural practices, and biodiversity loss if appropriate conservation strategies are not implemented.

Addressing these challenges requires coordinated efforts among researchers, clinicians, regulatory authorities, and traditional medicine practitioners. Strengthening scientific

research, implementing rigorous quality control systems, developing clear regulatory guidelines, and promoting evidence-based use of phytomedicines are essential to fully harness their therapeutic potential while ensuring safety, efficacy, and sustainability.

5. CONCLUSION

The use of phytoconstituents for the management of various disease conditions has gained considerable attention in recent years. Phytopharmaceuticals, owing to their favorable safety profile, cost-effectiveness, biocompatibility, and relatively low toxicity, have emerged as promising alternatives and complements to conventional synthetic drugs. Among these, *M. koenigii* demonstrates substantial therapeutic potential and may serve as a promising candidate for future drug development.

Although different parts of *M. koenigii* possess diverse medicinal properties, its anti-inflammatory activity has been extensively reported in numerous pre-clinical studies. These studies indicate that various extracts and bioactive constituents of the plant effectively modulate inflammatory pathways and mediators, supporting its potential role in the management of inflammatory disorders.

Despite encouraging pre-clinical evidence, several challenges remain before *M. koenigii* – based formulations can be translated into clinical applications. In particular, comprehensive *in vivo* studies, robust *in vitro-in vivo* correlation (IVIVC) data, and well-designed clinical trials are required to establish safety, efficacy, pharmacokinetics, and optimal dosing strategies. Furthermore, successful technology transfer, large-scale industrial production, and regulatory approval of phytobioactive constituents from *M. koenigii* will depend on strong collaborative efforts between academic researchers and pharmaceutical industries.

Overall, addressing these translational challenges may facilitate the development of *M. koenigii* as a scientifically validated, clinically effective, and sustainable anti-inflammatory therapeutic agent in the future.

ACKNOWLEDGMENT

The authors sincerely acknowledge the Dean, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan University, for constant support, guidance, and encouragement throughout the course of this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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