

Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com



E-ISSN: 2278-4136 P-ISSN: 2349-8234

https://www.phytojournal.com JPP 2024; 13(1): 412-416 Received: 19-11-2023 Accepted: 28-01-2024

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A concise review on pharmacological applications of potent Unani drug: Mesua ferrea L. (Nagkesar)

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DOI: https://doi.org/10.22271/phyto.2024.v13.i1e.14860

Abstract

Unani is a traditional system of medicine developed during the medieval period, which employs natural drugs composed of herbal, animal and mineral origin for curing human health. Fundamentally, it is based on the humoral theory postulated by Hippocrates, according to him the state of body health and disease are regulated by qualitative and quantitative equilibrium of four humours including blood, phlegm, yellow bile and black bile. *Mesua ferrea* L. belonging to *Calophyllaceae* family and is considered the genuine "Nagkeshara' as vernacular name. *Mesua ferrea* L. is commonly known as Nagkesar and Ceylon ironwood in English and Cobra's Saffron. The phytochemical screening confirms the presence of phenyl coumarins, xanthones, triterpenoids and fats as well as flavonoids as main bioactive constituents. It is possessed anti-oxidant activity, anti-inflammatory activity, analgesics activity, anti-venom activity, antispasmodic activity, hepatoprotective activity, antimicrobial activity, anthelmintic, expectorant and anti-allergic. Traditionally this plant is widely used for curing many ailments in India. This review highlights the general description, phytochemical studies, pharmacological activity as well as traditional uses of *Mesua ferrea* in current scenario.

Keywords: Mesua ferrea, Nagkesar, Flavanoids, flower, Unani system

Introduction

Unani System of Medicine dealing with traditional system of medicine and it has own theory of health and diseases. It is based on the drugs originated from plants, animals and minerals. It has been documented that about 200 drugs of animal origin are described in Unani System of Medicine (USM) which are claimed to be beneficial for the treatment of various ailments [1]. According to Health Organization, most populations still rely on traditional medicines for their psychological and physical health requirements [2]. Herbal medicine represents one of the most important fields of traditional medicine all over the world. As per the given reports of WHO, 80% of the world's population depends upon the traditional medicine for their primary health [3]

The widespread use of herbal remedies and healthcare preparations as those described in ancient texts and obtained from commonly used traditional herbs and medicinal plants has been traced to the occurrence of natural products with medicinal properties ^[4]. *Mesua ferrea* commonly known as Nagkesar, belonging to the *Calophyllaceae* family, is a perennial tree indigenously grown in Bangladesh, India, Southern Nepal, Sri Lanka, Myanmar, Thailand, etc. It is locally familiar as Nageswar in Bangladesh and Nagakesara in India and Nepal ^[5].

Botanical description: *Mesua ferrea* Linn. is an evergreen medium to large-sized ornamental plant and up to 13 mm in height, often buttressed at the base with the trunk up to 90 cm in diameter. The leaves of plant are about 3 to 5 inches long, simple, narrow, ovate and egg-shaped. Leaves are dark green with a whitish underside; the newly growing leaves are red then slowly turn into yellow. The flowers of the plant are about 4 to 7.5 cm in diameter with four white petals and a center of numerous yellow stamens. Fruits are oblong in shape they are about 2.5 to 5.0 cm long with persistent calyx. Seeds are dark brown in color and cotyledon is fleshy and oily. The flower, fruit, seeds and leaves of this plant are edible ^[5-8].

Habitat: Eastern Himalayas, Assam, West Bengal, Western Ghats, Travancore, and Andaman.

Parts used (Hisas-e-mustamalah): Flower (stamen), Seed, Fruits, Leaves, Root Oil, Bark, Bud [9].

Table 1: Vernacular names of *Mesua ferrea*

Sanskrit	Kesara, Nagapuspa, Naga, Hema, Gajakesara
Hindi	Negkesara, Pila Nagesara
English	Cobras Saffron
Assam	Naboor, Nahor
Farsi	Naremushk
Thailand	Bunnak, Bhra ba kaw
Phillippine	Kaliuas
Malaysia	Penaga
Italian	Croco di cobra
Arabic	Narae-kaisar
Russia	Mezua Zheleznaia
Chinese	Tie li mu
Bengali	Nsgesvara, Nagesar
Bihar	Nagkeshur
Gujarati	Nagchampa, Nagkesara, Sachunagkeshara, Pilunagkesar, Tamranagkesar
Marathi	Nagkesara
Telugu	Nagachampakamu, Kesaramu
Tamil	Nangu, Naugaliral, Nagachampakam
Kannad	Nagakesari, Nagsampige
Orissa:	Nageswar
Punjabi	Negeswar
Urdu	Narmushk, Nagkesar
Malyalam	Nangaa, Nauga, Peri, Nagppu, Nagappovu, Veluthapala ^[6, 7]

Table 2: Taxonomical classification of Mesua ferrea

Kingdom	Plantae
Division	Tracheophyta
Class	Mangoliopsida
Order	Malpighiales
Genus	Mesua L.
Family	Guttiferae/Calophyllaceae
Species	Mesua ferrea

Chemical constituents

There are numerous chemical compounds such as glutathayon, lacithine, galic acid and glucoside are widely reported in this medicinal plant. The seeds of this plant contain saturated fatty acid like stearic and palmitic acid [10]. The plant contains glycosides, coumarins, flavanoids, xanthones, triglycerides and resins. Fatty acids, steroids, reducing sugar, tannin, saponin, proteins [2], flavanoids as main constituents responsible for its biological activity in nature (Manoj, 2013). The principal constituents of *M. ferrea* includes mesuaferrone-A and B, mesuaferrol, mesuanic acid, alpha and beta amyrin and beta-sitosterol present in the stamen of flower, while it is reported that seeds contain essential oils such as xanthones and coumarins [4].

Table 3: Phytochemicals activities of different parts of Mesua ferrea

S. No.	Chemical classification	Phytochemical identified	Biological activities	References
1.	Coumarins	Ferruol A	Trunk bark	[12]
2.	Xanthones	1,5-Dihydroxyxanthone (II), euxanthone 7-methyl ether (IV) and β -sitosterol	Heartwood	[13]
3.	Xanthones	Mesuaxanthone A and mesuaxanthone B	Heartwood	[14]
4.	Coumarins	Mesuol, Mammeisin	Seeds	[15]
5.	Terpenes Steroids	Friedelin Stigmasterol	Stembark	[16]
6.	Phenolic acid	Gallic acid	Stamen	[17]
7.		Trans-Caryophyllene, α-Humulene, γ-		
	Terpenes	Muurolol, β-caryophyllene oxide δ-	Flowers	[18]
	respenes	cadinene, γ-Cadinene, β-selinene,	Tiowers	
		germacrene D, β-bisabolene		
	Terpenes	Trans-caryophyllene		
8.	Phenols	Gallic acid, coumaric acid, ellagic acid,	Stems	[19]
	Flavonoids	vanillic acid rutin, quercetin, kaempferol		

Pharmacological action (Afzal)

Mufarreh (Exhilarant), Mugawwi-e-Me'da (Stomachic), Mufattah-e-Sudud Mohallil-e-Riva (Carminative), (Deobstruent)). Mudir (Diuretic), Mudirr-e-Haiz (Emenagogue), Waj-ul-Mufasil (Arthralgai), Mohallil-e-Waram (Anti-Inflammatory), Musakkin-e-Alam (Analgesic), Dafa-e-Tashannuj (Anti-Spasmodic), Tahaffuz-e-Jigar Tahaffuz Qalb (Cardioprotective) (Hepato-protective), Musaffi-e-Khoon (Blood purifier), Qatil-e-Deedan-e-Am'a (Anthelmintic), Muqawwi-e-qalb (Cardic-tonic), Daf-ehumma (Antipyretic), Mushil (Purgative), Daf-e-Dama (Antiasthmatic), Muqawwi-e-aama (Intestinal Tonic), Muharriq-e-Waah (Sexual Stimulant), Kaasir-e-Riyah (Carminative), Qabz (Constipation), Munaffis-e-Balgham (Expectorant), Habis-ud-Dam (Haemostatic), Mujaffif (Desiccant), Mali khuliya (Melancholia), Waswas (Obsession), Habis-e-Is'hal (Anti-Diarrhoeal) [5, 7, 8, 20, 21, 22].

Therapeutic uses (Mehle istemalat)

They were used as traditional remedies for *Su'al* (Cough), *Zeeq-un-Nafas* (Bronchial Asthma), *Jarab* (Scabies), *Amraz-e-Jild* (Dermatopathy), *Juzam* (Leprosy), *Zaheer* (Dysentery), *Bawaseer* (Hemorrhoids), *Qurooh* (Ulcers), *Ananat* (Impotency), *Sailan-e-Rahem* (Leucorrhoea), *Humma* (fever)

and Zo'f-e-Qalb (Cardiac Asthenia) (Adiana, 2019), Su'-e-Hazm (Dyspepsia), Daf-e-Zehar (Antidotes) [5, 23].

The power of stamen of nagkesar is used in Bawaseer Damiya (Bleeding piles) (Jadhav, 2015; Sumitra, 2013). It is a substitute for petroleum gasoline. It is also used in cosmetics, as fire wood and the polymer obtained from seed oil is used in the preparation of resins (Manoj, 2013). The seeds oil known as Kesar oil is used to treat wounds, rheumatism, sores, and scabies and also to relieve itch and as an embrocation for rheumatism [24].

The plant is utilized for septic and inflammatory disorders. Other therapeutic application including abortifacient, diuretic, and antispasmodic, snake bite, asthma, dyspepsia, renal diseases, fever, and cosmetics were also reported. The bark and root decoction are beneficial for bronchitis and gastroenteritis. The Assamese tribal people use this plant for antibacterial, purgative, blood purifier, worm control and tonic effects [24].

Dose (*Miqdaar*): 1gm; 2 gm; 3-5 gm, 4.5 gm ^[7,23]. **Temperament** (*Mizaj*): Hot (1) and Dry (2); Hot (2) and Dry (2) ^[7,22,23].

Side Effect (*Muzir*): For Liver and Bladder and also for person of hot temperament [7, 23].

Corrective (*Musleh*): Tukhme Kasni, Tabasheer; Honey [Nabi, 2007; Kabeer, YNM].

Substitute (*Badal*): Sumbul-ut-Teeb (*Nardostachys jatamansi*), Naryal (*Cocos nucifera*) [23].

Important Formulation: *Mufarreh Yaqooti* [7].

Pharmacological activities

Anticancer activity: Crude ethanolic extract of Nagkesar flower tested against human cancer cell i.e., human laryngeal cancer (Hep-2), cholangiocarcinoma, human hepatocarcinoma cell lines in the *in vitro* studies, but it found selectively against Hep-2 cell lines. The crude extract of this medicinal plant possesses potent cytotoxic activity against Hep-2 and human hepatocarcinoma [25]. An Essential oil obtained from Nagkesar leaves shows activity against cancer cell lines i.e., oral carcinoma, breast adenocarcinoma (Michigan cancer foundation-7) and (metastatic lung carcinoma) neuronal ceroid lipofuscinoses [26].

Antidiabetic activity

Balekari *et al.*, reported that the methanolic extract of *Mesua ferrea* leaves have promising antidiabetic activity in streptozotocin-induced diabetic rats. It was found that the extract reduced the blood glucose levels and normalized the body weight in diabetic rats ^[27].

Anti-oxidant activity

Nagkesar leaves shows significant antioxidant activity, which shows activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical scavenging. The ethanolic extracts shows 70% of antioxidant activity [28]. Another study of antioxidants by using methanolic extract of Nagkesar flower possesses activity against DPPH free-radical, super-oxide and hydrogen-peroxide in scavenging-assays [26]. A study on Nagkesar root methanol polar extract discovered that it was more active than less polar or non-polar extract [27].

Anti-arthritis activity

Jalalpure *et al.*, investigated that the seed extract of *Mesua ferrea* possesses potent anti-arthritis activity in two different *in vivo* models i.e., Formaldehyde-induced and Complete Freunds's Adjuvant (CFA) induced arthritis in rats. The result showed a reduction in the arthritis lesion by swelling volume in CFA injected paw in rat models ^[29].

Antispasmodic activity

An *in vitro* study was conducted by Prashad *et al.*, for the evaluation of the antispasmodic activity of petroleum extract of *Mesua ferrea* in the rat ileum. The contraction of the rat ileum was measured on a kymograph. The normal contraction of acetylcholine was reduced up to 70 and 86% whereas the normal response of acetylcholine in presence of atropine was reduced to 55% [30].

An extract of nagkesar seed oil based on petroleum has been proven to have antispasmodic effects in the rat ileum in *in vitro* studies. Acetylcholine and carbachol cause contraction up to 2.61 cm and 3.2 cm, respectively. According to the crude oil content, which can range between 1:5 and 1:10, the contraction of acetylcholine is often reduced by up to 70% and 86%, respectively. Atropine typically reduces the cholinergic response by up to 55%. The rat ileum's activity was measured using a kymograph [31].

Analgesic activity

The non-polar (n-hexane) fraction of *M. ferrea* leaf extract shown better antinociceptive efficacy in terms of percent reduction in writhing response as compared with polar fractions (methanol and ethyl acetate) in a mouse model of visceral pain caused by acetic acid [32].

In acetic acid-induced visceral pain mouse model, non-polar (n-hexane) fraction of M. ferrea leaf extract showed better antinociceptive activity in terms of percent reduction in writhing response as compared with polar fractions (methanol and ethyl acetate) $[^{33}]$.

Anti-venom activity

Uawonggul *et al.*, investigated that the aqueous extract of *Mesua ferrea* leaves possesses anti-venom activity against fibroblast cell lysis after *Heterometrus laoticus* scorpion bite. The extract was evaluated against the viability of fibroblast cells after 30 min treatment with mock control or with 0.706 mg/ml plant extracts pre-incubated with *H. laoticus* venom. Viability of fibroblast cells after 30 min treatment with mock control or with 0.706 and 0.406 mg/ml showed efficiency in protecting against venom-induced lysis [34].

Antiulcer activity

Xanthones i.e., jacareubin and 6-desoxy jacareubin obtained from *M. ferrea* prevented ulceration in the rats as compared with control groups where extensive ulceration, perforations and haemorrhagic spots were observed. On the other hand, in xanthones treated rats only hyperaemia and occasional haemorrhage spots were noticed [35].

Various crude extracts and pure compounds have shown promising anticancer activities in the preliminary *in vitro* anticancer screening assays. Volatile oils-rich methanol extract of *Mesua ferrea* flowers showed strong cytotoxic activities against T-lymphocyte leukemia cells with IC50 value of $12.5 \,\mu\text{g/ml}$ [36].

Antibacterial and antifungal activity

Antimicrobial activities of different parts of *Mesua ferrea* have been highlighted by various scientific studies. Verotta *et al.*, investigated that the coumarins (4-alkyl and 4-phenyl 5,7-dihydroxycoumarins) isolated from flower of *Mesua ferrea* have antimicrobial activity against the strains of grampositive bacteria [37].

Diuretic activity

Tiwari *et al.*, reported a polyherbal combination (Draksharishta-T and–M) and its marketed formulation comprising of stamens of *Mesua ferrea*. The formulation was found to induce significant diuretic, kaliuretic and natriuretic effects in the albino rats over 5 h compared to the control group [37].

Anti-hemorrhoid activity

Paranjpe *et al.*, evaluated a polyhedral formulation containing *Mesua ferrea* for its efficacy to treat bleeding piles in a preliminary clinical study using 22 human subjects. The finding revealed that out of 22 subjects, 16 patients showed improvement in terms of bleeding with no noticeable adverse effects ^[38]. Another recent study also highlighted the efficacy of standardized herbal preparations (Daflon and Roidosanal) containing *Mesua ferrea* in terms of improvement of anorectal conditions in Grade I and II patients ^[39].

Wound healing activity

Choudhary *et al.*, reported that the tannins isolated from the ethanolic extract of aerial parts of *M. ferrea* have been shown to have promising wound healing activity in excision and incision wound healing rat models when applied in the form of an ointment. Increased epithelialization and wound contraction were proposed to be the possible mechanisms responsible for the wound healing activity of aerial parts [40].

Hepatoprotective activity

Garg *et al.*, evaluated the hepatoprotective effects of methanol extract of *Mesua ferrea* flowers in *Staphylococcus aureus* inoculated male Wistar rats. One weak treatment with 50,100 and 200 mg/kg of methanolic extract showed significant improvement in the levels of liver enzymes like CAT, SOD, GPX and GR with a concomitant decrease in the level of AAT and AST enzymes [41]. In another study, hepatoprotective effects of different extracts of stamens were evaluated using *in vitro* carbon tetrachloride-induced oxidative stress liver slice culture model. The finding revealed n-hexane and ethanolic extracts of stamens protect cultured liver slice cells against carbon tetrachloride-induced oxidative stress [42].

Cardio protective activity

Mesua ferrea stamens have been found to prevent isoproterenol-induced myocardial infarction in the albino rat model. The serum levels of marker enzymes like alanine aminotransferase, aspartate aminotransferase, creatine kinase, and lactate dehydrogenase were significantly reduced during treatment with herbal formulation, and the serum lipid profile also improved. The rise in *in vivo* antioxidant level of GSH and suppression of lipid peroxidation of cardiac membranes in the treated rats were responsible for the herbal formulation's cardio protective action [43].

Anti-histaminic activity

A portion of *Mesua ferrea* seed oil that contains phenol was reported to have potentiated the relaxation of guinea-pig tracheal smooth muscle caused by isoprenaline both *in vitro* and *in vivo*. Additionally, in cases of chopped lung and passive peritoneal anaphylaxis, the phenolic fraction prevented histamine from being released [44].

Anti-convulsant activity

The convulsions generated by an albino mouse's MES (maximum electroshock seizure) were significantly reduced by an ethanolic extract of M. *ferrea* flowers. Electroconvulsive shock convulsions lasted for fewer seconds and began more quickly [45].



Fig 1: Nagkesar

Conclusion

M. ferrea has many uses in various cultures throughout the world, especially in the traditional treatments. In India, M. ferrea was used in the past generations and was regarded as one of the many useful medicinal plants. This plant possesses many bioactive chemical constituents like coumarins, xanthones, pyranoxanthones, flavonoids, terpenoids and steroids which can be easily isolated. The flowers were reported to have carminative, constipating, anthelmintic, diuretic, expectorant, stomachic, hemostatic, aphrodisiac, Febrifuge and cardiotonic. They were used as traditional remedies for cough, asthma, scabies, dermatopathy, leprosy, dysentery, hemorrhoids, ulcers, impotency, leucorrhoea, fever and cardiac weakness.

Conflict of interest: None

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