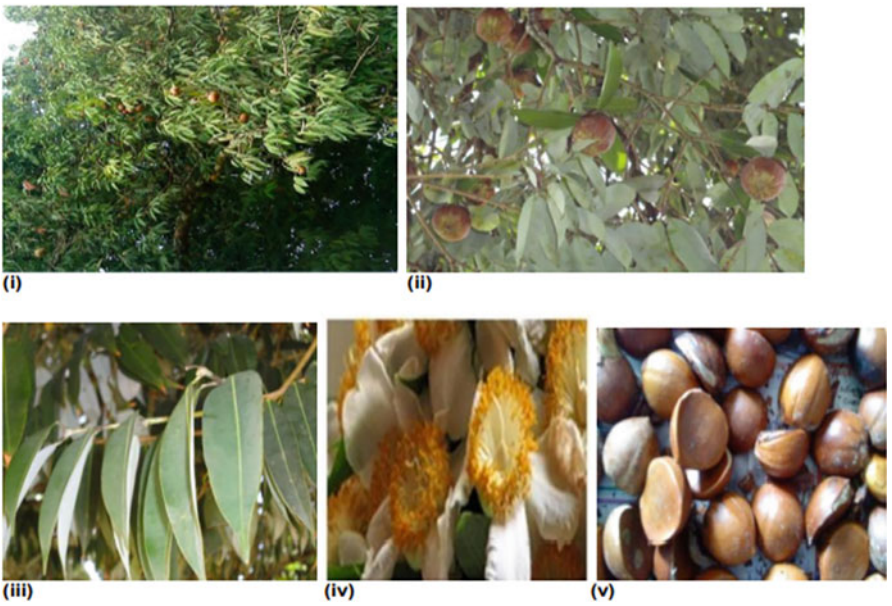
Chapter 6
Mesua ferrea L.: Ethnobotany, Phytochemistry and Pharmacology

Mushfa Khatoon and Amita Dubey



Mesua ferrea L. image is adapted from Chahar et al. (2012) – (i) Tree, (ii) Fruit, (iii) Leaves, (iv) Flower and (v) Seeds

Abstract The plant kingdom has plenty of plants with herbal activities. Amongst them *Mesua ferrea*, also known as "Nagakesar", is a species with several medicinal properties. *M. ferrea* is a rare plant species, typically found in the tropical region.

M. Khatoon · A. Dubey (✉)
Plant Molecular Biology Laboratory, Department of Biosciences, Integral University, Lucknow, Uttar Pradesh, India
e-mail: amita@iul.ac.in

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Possesses various medicinal properties such as anti-inflammatory, anti-arthritic, analgesic, anti-diabetic, anti-cancer, cardioprotective etc. Due to its pharmacological potential, *Mesua ferrea* is traditionally used by tribal people. This chapter summarizes knowledge about its traditional use, phytoconstituents and pharmacological properties.

Keywords *Mesua ferrea* · Pharmacology · Anticancer activity · Anti-inflammatory activity · Traditional uses · Medicinal plant

6.1 Introduction

Mesua ferrea Linn, also popularly called "Nagakesara" in hindi, is from the Calophyllaceae family. The English name for *Mesua* is "Ceylon iron wood" (Sharma et al. 2017). Although *Mesua* is a large genus with approximately 48 species, only *M. ferrea* has been studied by most of the researchers (Chahar et al. 2012). It is a medium to large sized evergreen tree with a small short trunk. *Mesua* trees are ornamental in nature and are produced for their very attractive flowers. The leaves and flowers of the plant possess high medicinal properties and act as an anti-venom agent for fatal snake bites (Kritikar and Basu 1956). The oil extracted from seeds of *Mesua* is used for curing itches. The most important medicinal use of *Mesua* flowers is in treating the burning of feet, as well as in curing bleeding piles by applying a paste of its flowers mixed with sugar and butter (Sharma et al. 2017). The plant is also usually utilized for its antimicrobial, antiprotozoal and antibacterial properties (Mazumder et al. 2003; Verotta et al. 2004).

Mesua ferrea has been an important component in Ayurvedic medicines such as Naga-keshara yaga and Nagakeshara-adi-churna for treating piles and bacillary dysentery, respectively. It is also used as an essential ingredient in Unani drugs, Jawarish Shehryaran (a liver tonic) and an appetizer, Hab Pachuluna (Sharma et al. 2017). It also cures seizures and acts as an anti-convulsant agent (Smith and Bleck 1991). *M. ferrea* flowers usually possess germacrene-D, as well as α-copaene. Some of its important biologically active components include flavanoids, glycosides, xanthones, resins and triglycerides. *Mesua ferrea* also contains some steroids, essential oils, fatty acids, proteins, tannins and saponins, as well (Choudhury et al. 1998).

6.2 Taxonomic Characteristics

Mesua ferrea commonly known as "Nagkesar" is a plant of Calophyllaceae family. Its English name is "Ceylon wood" (Sharma et al. 2017). The wood of *Mesua ferrea* is very hard. It is also known as ironwood that is another morphologically different species in the same genus. *Mesua ferrea* and the closely related genus *Kayea* make

up the taxa that form the currently proposed genus *Mesua*. According to the number of seeds present in the fruit, combined *Kayea* under genus *Mesua*. Hence, the taxa which were prior known as *Kayea* were renamed as *Mesua*. Several scholars strongly supported this taxonomic classification of *Kayea/Mesua* (Zakaria et al. 2007).

6.3 Crude Drug Used

Crude drug used: Bark, root, flowers, leaves, fruits, stamens and seeds. Its flowers and leaves are used as anti-venom for scorpion sting and bite of snake. The essential oil is utilized for treating sores, skin infection, wounds, rheumatism and scabies and flowers of this plant are also used as an astringent, stomachic and expectorant. The decoction of roots and bark are used to treat snake bites (Santamaría 1978) and acts as a bitter tonic; used in treating bronchitis and gastritis (Sahni 1998; Husain et al. 1992; Joy et al. 1998; Nadkarni 1976).

On the basis of literature, the major traditional uses of different organs of *Mesua ferrea* have been compiled in Table 6.1.

6.4 Major Chemical Constituents and Bioactive Compounds

Phytochemical studies have found *Mesua ferrea* to contain secondary metabolites of various classes including xanthones, phenyl coumarins and triterpenoides (Chow and Quon 1968; Bandaranayake et al. 1975; Raju et al. 1976). Dichloromethane stem extract consists of Friedelin (composed of α- amyrin and β-amyrin), β-sitosterol and lupeol (Keawsa-ard et al. 2015). The heartwood of *Mesua ferrea* contains

Table 6.1 Traditional uses of *Mesua ferrea*

S. no.	Plant part	Traditional uses	References
1.	Leaves	Cure cold, joint pain and burning sensation in feet and hands	Sharkar et al. (2013)
2.	Kernal	Skin outbreak condition	Sharma et al. (2017)
3.	Root	Used in treating bronchitis and gastritis	Sahni (1998)
4	Flower	Anti-venom for scorpion stings and bite of snake	Santamaría (1978)
5.	Essential oil	Skin infection, wounds, scabies and rheumatism	Sahni (1998)
6.	Whole plant	Used as an antipyretic, cardiotonic and carminative agent, also curing cold, fever and asthma	Sharma et al. (2017)
7.	Bark	Cure dysentery, sore throat, cough and vomiting	Keawsa-ard and Kongtaweelert (2012)

ferrxanthone, which can be chemically characterized as 1, 3- dimethoxy-5,6-dihydroxyxanthone (Walia and Mukerjee 1984). 1,5-dihydroxyxanthone (II), β-sitosterol, mesuaxanthone-A, euxanthone 7-methyl ether (IV) and mesuaxanthone-B were isolated from heartwood by several researchers (Govindchari et al. 1967; Chow and Quon 1968). Govindachari et al. later isolated an alkylcoumarin, Ferrol-A from the *M. ferrea* trunk bark (Govindchari et al. 1967). Gunasekera and his colleagues isolated several different types of xanthones such as 4-hydroxy-, 1- hydroxy-5-methoxy-, 3-hydroxy-4- methoxy, 1-hydroxy-7-methoxy-, 2-Hydroxy-, 2-methoxy-, 1,5-dihydroxy-, and 1,5,6-trihydroxyxanthone (Gunasekera et al. 1975). The main oil extracted from mature and young leaves consists of β caryophyllene (26.0% and 18.8%) and α-copaene (9.9% and 19.3%) respectively, while the oil extracted from bark consists of α-selinene (12.2%) and (E)-α-bisabolene (31.3%). The oil extracted from the flowers and bud of the plant mainly contains germacrene D (16.1% and 19.0%) and α-copaene (20.2% and 28.7%) (Choudhury et al. 1998). A study revealed that the root bark of *Mesua* consists of macluraxanthone, β-sitosterol, betulinic acid, caloxanthone C and friedelin, a new xanthone was isolated from root bark, mesuaferrin C (Ee et al. 2012). Another group studied root bark and isolated Mesuaferrin-A and -B, 1,8-dihydro-3-methoxy-6- methyl anthraquinone, caloxanthone C, friedelin, betulinic acid and β-sitosterol (Teh et al. 2012). A combination of amyrins were isolated from stem and stem bark of *Mesua* along with calophyllin-B, euxanthone, ferruol A, friedelin, mesuaxanthone-A, β-sitosterol, dehydrocycloguanandin, euxanthone 7-methyl ether (IV), ferrxanthone, lupeol, mesuaxanthone-B, stigmasterol, 6-desoxy jacareubin, 1,5-dihydroxyxanthone (II) and jacareubin (Gunasekera et al. 1975; Keawsa-ard et al. 2015; Lim 2012). Rajesh et al. extracted *M. ferrea* in chloroform and methanol and its HPLC analysis revealed that it contains several types of antioxidants such as ellagic acid, kaempferol, rutin, vanillic acid, coumaric acid, gallic acid, myricetin and quercetin (Rajesh et al. 2013). Alakh et al. isolated two essential oil components from the bark oil i. e. α-selinene and (E)-α-bisabolene (Alakh et al. 2014). The primary phytochemical studies of leaves extract of *M. ferrea* revealed that it consists of total tannin of about 11.25 mg/g of dry weight extract, total flavonoid content of about 30 mg/g of dry weight extract, total phenolic content of about 14.72 mg/g of dry weight extract and total flavanol content of about 3.60 mg/g of dry weight extract respectively (Sahu Alakh et al. 2013). In the stem bark of *M. nagassarium*, the presence of 3β friedelanol, 3-oxo-betulin, spinasterol, friedelin and lupeol was reported (Islam et al. 2014).

6.5 Morphological Description

Mesua ferrea is an evergreen tree with a height ranging between 20 and 30 m usually pinkish or creamy white in colour. Its base is grooved having very hard, bitter, dark red coloured heart wood. The bark surface of the plant is smooth (Orwa et al. 2009). *Mesua sp.* possesses entire and simple and oppositely located leaves. The flowers are

dioecious- polygamous, attractive, red, white or yellow in colour. *M. ferrea* flowers consist decussated or imbricated two to six sepals. It also consist two to six imbricated petals with several stamens which have golden colour. Because of the presence of various secondary veins reaching to the margin of the leaves, they appear to be glossy. The fruit of the plant is conically pointed consist of globose to ovoid shape. They are striate having one to four seeds and one to ten locules (Sharma et al. 2017). In dry season, *Mesua* flowers and produces leaves after it, in the monsoon. The flowering time of bisexual flowers is between 3 a.m. and 4 a.m. with closure around the sunset (Orwa et al. 2009). The mature leaves are blue grey to dark green in colour, whereas the young leaves appear reddish yellow in colour with a length of 7–15 cm. The length of the fruit is about 2.5–5 cm (Dassanayake 1980).

6.6 Geographic Distribution

The distribution of *M. ferrea* is vast; it expands to the southern part of Konkon, eastern Himalaya's dense mountains, vast forests of Western Ghats to Travancore via southern Kanara, Andamans, Tenasserim Burma, Bengal and Assam (Kritikar and Basu 1981). *M. ferrea* is most profusely found in the Himalayas to an altitude of about 1500 m, in North India, from eastward Nepal, the Andaman Island and Deccan peninsula (Sharma et al. 2017).

6.7 Ecological Requirements

Mesua ferrea tolerates shade, thrives in dense or moist fertile soils, and has important mycorrhizal relationships for nitrogen fixation (Mitra et al. 2021). It grows on fertile loamy soil as well as well drained soils. The usual pH values for the cultivation of *Mesua sp.* range between 5 and 5.5, it has been reported to tolerate pH-values between 4.3 and 6.9 (Fern 2022).

6.8 Traditional Use Part(s) Used and Common Knowledge

The edible parts of *Mesua ferrea* are fruits, seeds, leaves and flowers. Local people in India use *M. ferrea* for boosting immunity. In Thailand, people eat flowers which treat numerous diseases. Although seeds are edible after cooking, they do not taste good. When the ripe fruit is eaten, they taste like chestnut. The leaves are eaten raw despite their astringent-sour taste (Lim 2012).

Various species of *Mesua* genus have been traditionally utilized by the people of Asian countries for curing illnesses such as renal disease, cough, fever, nausea, asthma, dyspepsia and itchiness etc. *Mesua* species possesses several

pharmacological properties like antimicrobial, antitumor, immunomodulatory, antioxidant and antiviral, which already have been proved (Teh et al. 2012; Asif et al. 2016). *M. ferrea* is traditionally utilized as an antimicrobial, carminative, diuretic, antipyretic, anticancer, cardiotonic and expectorant (Chahar et al. 2012; Rahman et al. 2008). Traditionally, the barks are used for curing dysentery, sore throat, cough and vomiting (Keawsa-ard and Kongtaweelert 2012). The local communities of Bangladesh use powder of dried leaves and fruits, mixing it with ghee for curing the cold, joint pain and burning sensation in feet and hands (Sharkar et al. 2013). *Mesua ferrea* is used in septic conditions and in cases of inflammation (Rai et al. 2000). The local people from tribals of Assam use Mesua for its purgative, worm-control, antiseptic tonic and blood purifier properties (Parukutty and Chandra 1984). *Mesua ferrea* is used as herbal medicine for treating several ailments such as cough, dysentery, headache, itching, scabies, small tumors, bleeding piles, cardiovascular diseases, dehydration, hiccup, sweating, skin diseases and vomiting (Roshy Joseph et al. 2010; Lim 2012). The ashes of leaves of *Mesua* are used for curing sore eye. The plant is utilized as an antipyretic, cardiotonic and carminative agent, also curing cold, fever and asthma. The skin outbreak condition is cured by *Mesua ferrea* kernels (Sharma et al. 2017). Skin infection, wounds, scabies and rheumatism is treated by using *M. ferrea* oil (Sahni 1998).

6.9 Modern Medicine Based on Its Traditional Medicine Uses

6.9.1 Analgesic Activity

A significant amount of analgesic activity was shown by ethyl acetate, n-hexane and methanol extract of leaves of *M. ferrea* (at 125 and 250 mg/kg) in writhing response induced by acetic acid in mouse. For higher dosage, the writhing response was reduced by 19.63%, 42.21% and 17.06% in ethyl acetate, n- Hexane and methanol extract respectively while in lower dosage it was 16.33%, 36.08% and 10.21% respectively (Hassan et al. 2006).

6.9.2 Anti-inflammatory and Anti-arthritis Activity

The xanthones from *M. ferrea* such as Mesuaxanthone A(MXA) and Mesuaxanthone B (MXB) were tested in albino rats through cotton pellet implantation, carrageenan induced hind paw oedema and granuloma pouch tests. These xanthones were applied at the dosage level of 50 mg/kg in the above methods. By the oral intake of *Mesua* xanthone i. e. MXA and MXB showed 37% and 49% reduction in comparison to control group in carrageenan induced hind paw oedema.

The xanthones, MXA and MXB showed substantial anti-inflammatory activity in normal rats and in adrenalectomized rats also. The reduction in inflammation in comparison to control group in MXA is 38% and MXB is 22%. In cotton pellets granuloma experiment, the reduction of 47% was reported in inflammation. The xanthones MXA and MXB reported 46% and 49% reduction in inflammation respectively in granuloma pouch tests. Thus, significant anti-inflammation potential was reported in xanthones of *Mesua* in this study (Gopalakrishnan et al. 1980). An ayurvedic medicine, Shirishavaleha which consists of *Mesua* along with several other herbs has showed inhibition of oedema development present in carrageenan-induced paw oedema model (Yadav et al. 2010).

Two separate *in vivo* models i.e. CFA (Complete Freund's Adjuvant) and FI (Formaldehyde induced) were examined in rats for the anti-arthritic potential of seed extracts of *Mesua ferrea*. Significant reduction in the arthritic lesions was shown in CFA injected paw by observing the swelling volume by the seed extracts of *Mesua* in treated animals. Similarly, in FI model; the swelling in formaldehyde injected paw was reduced in treated animals in comparison to the control by the *M. ferrea* seed extract.

The *M. Ferrea* treated rats showed significant weight gain when compared to control in the final stage of treatment where as in untreated rats, a loss of weight was detected (Jalalpure et al. 2001). Another group of researchers reported the anti-inflammatory potential in several *in vitro* bioassays of 80% ethanol extract of *Mesua ferrea* stem bark.

When compared to the standard drug available which is Indomethacin in concentration of 100 µg/mL, reported significant anti-inflammatory potential in the 80% ethanol extract at the conc. of 100, 200 and 500 µg/mL (Ranganathaiah et al. 2016).

6.9.3 Diuretic Properties

Kaliuretic, diuretic and natriuretic properties were induced in the albino rats by the application of combination of herbs i. e. Draksharishta-M and -T and its formulation available in the market which consists of *M. ferrea* stamens for a period of 5 h at the dosage of 2.0 ml/Kg in comparison to the control group (Tiwari and Patel 2011).

6.9.4 Anti-hemorrhoidal Activity

In initial clinical research which involved 22 participants, a polyhedral formulation containing *M. ferrea* was investigated for its efficiency in treating bleeding piles. The study reported that 16 patients showed improvement out of 22 patients, with negligible harmful effects with reduction in bleeding (Paranjpe et al. 2000). *M. ferrea* has been reported to be effective in the standard herbal formulations i. e. Roidosanal® and Daflon® by studying the improvement in Grade I and grade II

patients of anorectal conditions. The pain and bleeding were reduced in the hemorrhoid patients by the above medications (Aggrawal et al. 2014).

6.9.5 CNS Depressant and Anticonvulsant Activities

The CNS depressive potential of *M. ferrea* xanthone which are mesuaxanthone-B, dehydrocycloguanandin, jacareubin, mesuaxanthone-A, calophyllin-B, euxanthone and 6-desoxy jacareubin were studied in both rat and mouse models. Usual CNS depressive effects, such as ptosis, muscular tone reduction, drowsiness, and decreased spontaneous muscular movement, were detected in xanthone-treated rats. Furthermore, rats treated with xanthone, the anaesthetic potential of phenobarbitone and ether-induced sleeping time was enhanced (Gopalakrishnan et al. 1980; Lim 2012).

The *M. ferrea* flowers extracted in ethanol was tested for its anticonvulsant property in albino mice using the Maximum electroshock seizure (MES) test at three distinct dosing levels which are 200, 400 and 600 mg/kg. In comparison to the MES model, the extract shortened the duration of hind limb tonic extension (HLTE) in a dose-dependent manner. *M. ferrea* ethanolic extract prevented MES-induced convulsions. The inhibition percentage of the extract at the dosage of 200, 400, and 600 mg/kg were 100% ($p < 0.01$), 60% ($p < 0.01$) and 100% ($p < 0.001$), respectively. According to the findings of this investigation, *M. ferrea* flowers significantly enhanced the start time and decreased the duration of seizures induced by electroconvulsive shock (Tiwari and Patel 2012).

6.9.6 Immunomodulatory and Hormone Balancing Activities

When irradiated animals were compared to drug-treated or normal animals, there was no substantial difference in their haemoglobin content. Also, no significant change was shown by ACII in the ratio of lymphocyte-neutrophil. The cellularity of bone marrow was greatly improved, as were the -esterase positive cells. The mass of the thymus increased in ACII-treated mice in comparison to irradiated animals (Tharakan et al. 2006). Furthermore, the immunomodulatory effect by ACII was reported in animals treated with cyclophosphamide (Tharakan et al. 2003) an in normal animals as well (Tharakan et al. 2004).

The activity of mesuol extracted from *M. ferrea* seed oil on the immune system was investigated utilising both humoral and cellular immunological models. The mesuol in humoral immunological models in rats substantially increased the antibody titer values. These antibodies were already tested and immunized by introducing SRBCs (sheep red blood cells) which is then immunosuppressed by cyclophosphamide. Moreover, mesuol stimulated T-cells and produced cellular immunological reaction in immunosuppressant rats induced by cyclophosphamide.

When rats treated with mesuol, were exposed to SRBCs which is an irritant, the thickness of their foot pads increased (Chahar et al. 2012). The *Mesua* ferrea flower extract were reported to show effects similar to progesterone and oestrogen. It was proposed for helping in the balancing of menstrual diseases (Lim 2012).

6.9.7 Antidiabetic Activity

In diabetic mice induced by streptozotocin, the M. ferrea leaves extracted in methanol showed good antidiabetic action. It has been proposed that extract can boost insulin release from pancreatic β -cells. In terms of increasing insulin secretion, the leaf extract lowered blood glucose levels and restored body weight in diabetic rats when compared to untreated animals. In vitro investigations employing a MIN6-β-cells (mouse insulinoma pancreatic β-cell line) revealed an increase in insulin levels depending upon dosage, as a result of treatment by methanol extract, with the effects being more pronounced in hyperglycemic settings in comparisons to normal cell culture settings (Balekari and Veeresham 2015).

6.9.8 Hepatoprotective Activity

In male Wistar rats inoculated with Staphylococcus aureus, the hepatoprotective properties of *M. ferrea* flowers extracted in methanol were tested in vivo. After 1 week of treatment with methanol extract at dosage of 50, 100 and 200 mg/kg demonstrated increment in the liver enzyme levels such SOD, GR, CAT and GPx with decrement in the level of enzymes such as AST and AAT At a dose of 100 mg/kg of methanol extract, significant effects were detected (Garg et al. 2009). In another experiment, the hepatoprotective properties of several stamen extracts were assessed utilising an in vitro carbon tetrachloride-induced oxidative stress liver slice culture model. Among the extracts tested, n-hexane and ethanol extracts of stamens preserved cultured liver slice cells from oxidative stress caused by carbon tetrachloride. The effective extracts also exhibited improved antioxidant properties in various in vitro free radical scavenging models, including DPPH, ABTS+, SOD, and NO (Rajopadhye and Upadhye 2012).

6.9.9 Cardioprotective Activities

In the albino rat model, "Ashwagandharishta" (a polyherbal combination) and its commercial preparation incorporating *M. ferrea* stamens were demonstrated to defend from isoproterenol-induced myocardial infarction. Herbal medicine treatment also substantially reduced changes induced by the isoproterenol in serum

marker enzyme like aspartate aminotransferase, lactate dehydrogenase, alanine aminotransferase and creatine kinase resulting in the serum lipid profile improvement. Furthermore, pre-treatment with a herbal formulation in animals resulted in a decrease in malondialdehyde (MDA) levels and a considerable rise in glutathione (GSH) levels.

Thus, it was postulated that the cardioprotective property of herbal medicine in the treated rats may be attributed to an increment in in vivo antioxidant levels such as GSH and decrement in lipid peroxidation of cardiac membranes (Tiwari and Patel 2012).

6.9.10 Anti-cancer Activities

The extract of oleo-gum resin was demonstrated ROS-mediated apoptotic pathways to trigger apoptosis in HCT 116 cells. Unexpectedly, the extract of oleo-gum resin did not cause toxicity in CCD-18co (normal colon cells) (Asif et al. 2016). Furthermore, Asif et al. found that terpene-rich stem bark extract exhibits broad-spectrum anti-cancerous properties in their previous work. The sensitivity order towards F-3 of cancer cell lines from high to low was HCT 116 > MNK–74 > PC–3 > T-47D > MIA PaCa–2 > HT– 29 > PANC–1 > MCF–7 > Capan-1 > EA. hy926 > 3 T3-L1 > CCD- 18co (Asif et al. 2016). There is one study that indicates the in vivo efficacy of *M. ferrea* flowers extracted in ethyl acetate and chloroform against Ehrlich ascites cancer in Swiss albino mice, in addition to a number of in vitro anticancer investigations. The percentage decrement of cancer in rats treated with ethyl acetate and chloroform was 41.7% and 54.8%, respectively (Rana et al. 2004).

6.10 Conclusions

Mesua ferrea is an important medicinal plant belonging to the family Calophyllaceae. It contains various bioactive compounds that are responsible for its important anti-inflammatory, anti-arthritic, analgesic, anti-diabetic, anti-cancer, cardioprotective. Each plant organ contains several phytoconstituents. Tribal people in India have been using its crude drug, as *Mesua* is known for its numerous medicinal properties. Despite of it being used not only in India but also throughout the world, the validation of its pharmacological properties remains to be made. There is a need for more research to reveal its true medicinal potentials.

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