REVIEW

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Mesua ferrea L.: Unlocking the Therapeutic Potential of a Traditional Medicinal Tree: An Integrative Review of Phytochemistry, Pharmacology, Safety, and Future Perspectives

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ABSTRACT

Mesua ferrea L. (Calophyllaceae), known popularly as Ceylon ironwood or Nagakesara, is an evergreen medicinal tree commonly used in Ayurveda, Siddha, Unani and folk medicine systems of south and Southeast Asia. The plant has been traditionally used as an effective treatment against fever, dysentery, diarrhea, respiratory illnesses, bleeding disorders, skin problems, injuries, and inflammation using various plant parts such as flowers, stamens, bark, leaves, seeds, and seed oil. This review article highlights an exhaustive overview of the ethnomedicinal significance, phytochemical constitution, pharmacological activities, safety evaluation, and future perspective of *M. ferrea.* Extensive phytochemical screenings have reported the presence of multiple bioactive compounds like xanthones, coumarins, flavonoids, phenolic compounds, terpenoids, and essential oils, which collectively make this plant useful for various therapeutic purposes. The plant has also shown significant antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, anticancer, analgesic and wound healing activities experimentally which provide scientific support to many of the therapeutic uses of the plant. Although encouraging results are obtained so far, the majority of evidence are based on in vitro and preclinical studies and lack adequate clinical trials and phytopharmaceutical formulations. Additionally, comprehensive toxicological and pharmacokinetic studies are required to confirm the safety and efficacy of the plant in the longer term. Future research work must focus on phytochemical standardization, identification of molecular mechanism, preparation of pharmaceutical formulations, conservation approaches, and well-designed clinical trials. Taken together, available evidence makes *M. ferrea* an important medicinal plant with considerable potential in the development of phytopharmaceutical drugs and therapeutic agents.

KEYWORDS

Mesua ferrea, Ethnomedicine, Phytochemistry, Pharmacological activities, Phytopharmaceuticals

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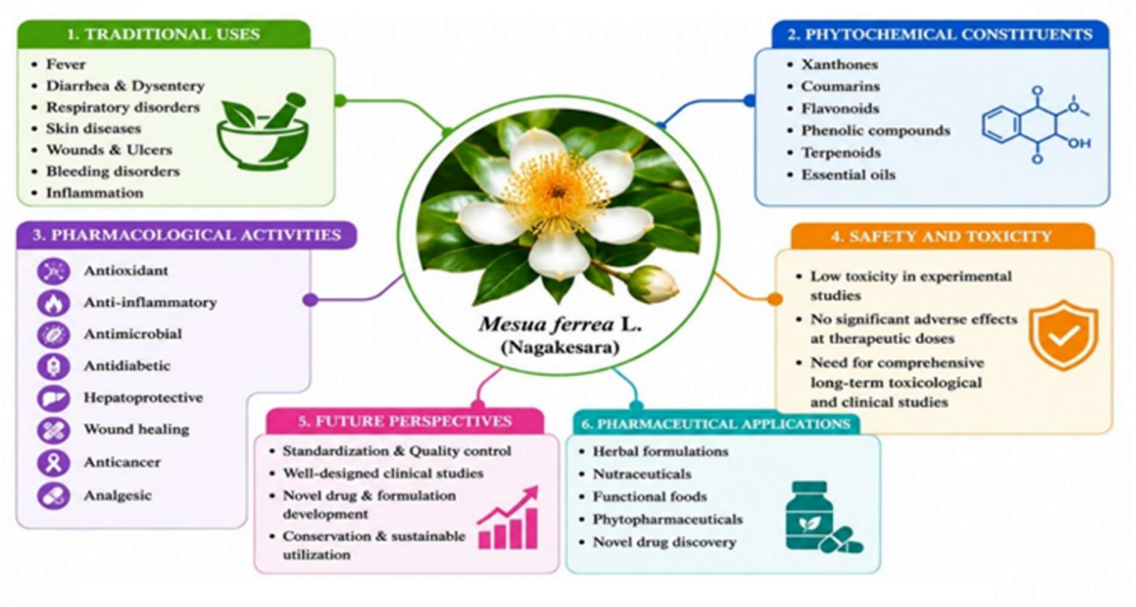
Graphical Abstract



1. INTRODUCTION

Medicinal plants have played an important role as natural sources of therapeutic drugs in past years and even currently play a significant role in the health care system of the whole world. According to the World Health Organization, about 80% of the global population utilizes traditional medicines prepared from medicinal herbs as primary health care providers, especially in the developing countries where medicinal herbs are easily available and acceptable culturally [1]. The wide range of plant secondary metabolites including alkaloids, flavonoids, terpenoids, coumarins, xanthones, tannins, phenols, etc., has largely contributed to the discovery and development of many important drugs. Modern medicines such as paclitaxel, artemisinin, morphine, vincristine, and digoxin have been prepared either directly or indirectly from medicinal herbs as their valuable source of structurally varied bioactive chemicals [2,3]. The increasing incidence of chronic diseases, antimicrobial resistance, metabolic diseases, and cancer has attracted scientific research interest in medicinal plants as new sources of novel safe and effective therapeutic drugs. With advances in areas like phytochemistry, pharmacognosy, molecular pharmacology, and analytical techniques, a number of phytoconstituents having different biological properties have been identified and characterized by which traditional medicinal uses have been scientifically validated. As a result, nowadays medicinal plants are being studied not only for their pharmacological effects but also for various other potential applications [3,4].

Out of the numerous medicinal trees that have received considerable scientific attention for their wide ethnomedicinal applications and phytochemical richness, *Mesua ferrea* L. (commonly known as Ceylon ironwood or Nagakesara) stands out. The plant belongs to the family *Calophyllaceae* (earlier placed in the family *Clusiaceae*) and occurs widely in India, Sri Lanka, Nepal, Myanmar, Thailand, Malaysia, and other parts of Southeast Asia. It is an evergreen tree known for its dense hardwood, white fragrant flowers, and medicinal importance. Different parts of the plant, including flowers, stamens, leaves, bark, roots, fruits, and seeds, have been used traditionally in the system of medicine like Ayurveda, Siddha and other folk medicines in the treatment of inflammation, dysentery, fever, cough, asthma, dermatitis, wound, rheumatism, bleeding piles, gastrointestinal ailments and different types of infectious diseases [5,6]. The phytochemical studies revealed that *M. ferrea* is a rich source of biologically active secondary metabolites such as xanthones, coumarins, flavonoids, triterpenoids, phenolic acids, essential oils and sterols. Several isolated compounds from the plant have shown remarkable biological activities like antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, anticancer, immunomodulatory,

wound healing and neuropharmacological properties. However, most of the studies have been done on the in vitro or preclinical basis and there are very limited numbers of toxicological studies, pharmacokinetic studies, standardization of extracts and clinical studies carried out with *M. ferrea* [5–8]. Earlier some reviews have highlighted some aspects of pharmacological and ethnomedicinal importance of *M. ferrea*. But in view of the rapid expansion of literature related to *M. ferrea*, it becomes necessary to give an updated overview on different aspects of *M. ferrea*. This review article aims at providing an integrated and critical discussion about botany, pharmacognosy, phytochemistry and pharmacological activities of *M. ferrea*, emphasizing the research gaps and suggesting further areas of study.

2. BOTANICAL PROFILE

Mesua ferrea L. is a well-known evergreen species of tropical Asia characterized by unique botanical features, ecological importance, and versatile applications in medicine. It can be easily recognized by its densely pyramidal crown, glossy leaves of dark green color with silvery underside, large and fragrant white flowers with numerous stamens of golden-yellow color, and extremely hard timber. Besides being useful in medical practice, *Mesua ferrea* serves as an ornamental plant, source of excellent quality timber, and is an integral component of tropical evergreen forests. In order to ensure the authenticity, quality and standardization of medicinal crude herbs, their botanical identification is a key element. As a result, in the case of the species under consideration, it is necessary to emphasize the importance of a detailed knowledge about taxonomy, morphology, geographic distribution, ecology and botanical features of the studied species for pharmacognosy and phytochemistry studies.

2.1 Taxonomy

Mesua ferrea L., popularly known as Ceylon ironwood or Nagakesara, is an evergreen tropical tree belonging to the *Calophyllaceae* family, formerly classified under *Clusiaceae* (Guttiferae). The species is widespread throughout South and Southeast Asia and is considered one of the most important medicinal plants and timber sources in the Mesua genus. Among various Mesua species, *M. ferrea* has garnered the highest scientific interest for its traditional uses in medicine, high chemical diversity, and extensive experimental evidence of biological effects. Following the APG IV classification, the species belongs to the Malpighiales order and therefore demonstrates a close evolutionary relationship with other pharmacologically valuable genera in *Calophyllaceae* [9,10].

Initially described by Carl Linnaeus in Species Plantarum, the species has since undergone several revisions based on new findings in comparative morphology, anatomy, and phylogenetics. Modern phylogenetic research conducted using chloroplast and nuclear DNA markers has confirmed the transfer of Mesua from *Clusiaceae* to *Calophyllaceae*, a revision that is currently supported by most of the botanical database, such as Plants of the World Online (POWO)[9–11]. Although the recent classification was made, *Mesua ferrea* L. is still considered the proper binomial name in taxonomic, pharmacognostic, and pharmacological literature.

2.2 Synonyms and Vernacular Names

There are several botanical synonyms associated with the species *Mesua ferrea* which have emerged through historical changes in taxonomy. While these names exist in older floras and pharmacognostical literature, *Mesua ferrea* L. is currently considered the scientific name. Because of the wide geographical occurrence and traditional use in medicine, the plant has many common names as well. The Sanskrit and Hindi name for this plant in India is Nagakesera. The Bengali name is Nageshwar, the Tamil name is Nagapoo, the Telugu name is Nagakesaramu, the Malayalam name is Nagapushpa, while the Marathi name is Nagkesar. It is also known internationally as Ceylon Ironwood, Indian Rose Chestnut and Cobra Saffron due to its very hard wood and aromatic flowers (Table 1) [10–12].

2.3 Botanical Description

Habit

Mesua ferrea is a tall, slow-growing, evergreen tree that normally attains a height of 20-30 m, and the height may even exceed 40 m in some mature trees in ideal environmental conditions. The species has a straight, cylindrical bole and dense, pyramidal to conical crown making it aesthetically beautiful for ornamental purposes. It is one of the hardest timber-yielding trees because of its very hard and durable

hardwood. The plant has a long life span and it takes decades to reach maturity [11,13].

Bark

The bark is smooth on younger trees but becomes rough, cracked and peeling off with increasing age. The bark is externally greyish-brown to reddish-brown in color and pale brown inside with slightly bitter taste. It is rich in secondary metabolites, hence the reason why traditionally, it was used in the treatment of inflammatory diseases, fever, dyspepsia, bronchitis, and skin diseases [10,13].

Leaves

Leaves are simple, opposite, entire, leathery, lanceolate to elliptic lanceolate and approximately 7-15 cm in length. Younger leaves are attractive pink to copper red colored, but turn glossy dark green after maturation. The lower side of the leaves is glaucous to silvery white and the upper one smooth and lustrous. Secondary veins running close together toward the leaf margin are distinctive features for identification and pharmacognostic evaluation [11,14].

Flowers

Inflorescence in *M. ferrea* is one of the most characteristic traits of the plant. Flowers are large in size, solitary or paired, bisexual, fragrant, white, measuring 5-8 cm in diameter. Each flower is made up of four thick white petals surrounded by many golden-yellow colored stamens that form an important medicinally active ingredient used in preparing Ayurvedic medicines. Flowering mainly takes place in dry season with individual flowers lasting only for one day before aging [12,15].

Fruits

The fruit is an ovoid to globose capsule having a distinct pointed apex. It becomes woody and dehiscent at maturity, containing one to four seeds inside its hard pericarp. Fruiting starts slowly after flowering, maturing after several months. While being less used than flowers and seeds, fruits still have some medicinal importance in certain traditional medicine practices [10,15].

Seeds

The seeds are large in size, brown in color and smooth, containing fixed oil known as nahor oil. The seeds consist of a high content of phenylcoumarins, xanthones, triterpenoids and fatty acids that give them antimicrobial, anti-inflammatory, antioxidant and wound healing properties. Seed oil has traditionally been applied for treating various skin diseases, rheumatism, wounds, dandruff and inflammation [13,16].

2.4 Distribution and Ecology

Distribution

This tree is endemic to tropical countries of South and Southeast Asia. The geographic distribution of *M. ferrea* is rather extensive. The natural range encompasses India, Sri Lanka, Nepal, Bhutan, Bangladesh, Myanmar, Thailand, Malaysia, and adjacent territories. In India, *M. ferrea* usually grows in Eastern Himalayas, Assam, West Bengal, Western Ghats, Andaman and Nicobar Islands and other areas covered by humid evergreen forests. This tree is extensively cultivated as an ornamental and medicinal tree owing to its appealing foliage, aromatic blossoms and valuable timber [9,14].

Habitat

M. ferrea is known to flourish in tropical evergreen and semi-evergreen forests with high annual precipitation. Fertile, deep, well-drained loamy soils rich in organic matter are preferred, and optimal growth is attained in warm and humid climate conditions. Although young seedlings demonstrate rather good tolerance to shade conditions, mature trees develop much better in full sunlight. The plants occur mostly at altitudes ranging between sea level and 1,500 meters [11,17].

Characteristic of Slow Growth Habit

Biologically distinctive feature of *M. ferrea* is the slow growth habit. Gradual establishment of the seedlings and several years of juvenility prior to considerable vegetation development are typical features of the species. This growth pattern is caused by intensive development of extremely hard hardwood, long period of juvenility and high investment into secondary xylem growth. Thus, timber cultivation requires rather long rotations, and the process of regeneration is also rather slow. However, this tree demonstrates longevity and excellent durability, which make it valuable both for conservation and wood production [16,18].

Flowering and Fruiting

Flowering happens between March and June, depending on geographical location and weather conditions. The heavily fragrant white inflorescences bloom massively in the dry season and attract many insects, including bees. Fruiting begins shortly after pollination, while the ripe fruits

appear mostly in the wet season. Germination is hypogeal and usually succeeds in nursery conditions; however, the seeds are recalcitrant, and their viability significantly decreases within two to three months after ripening, which requires planting immediately [15,18].

2.5 Ecological and Conservation Significance

In addition to the medicinal use, *Mesua ferrea* also has some ecological value, as it contributes to the stability of tropical evergreen forests. The fragrant flowers are an important source of nectar and pollen for bees and other insect pollinators and support the functioning of the ecosystem and natural reproduction. Moreover, *Mesua ferrea* produces very dense hardwood, which acts as a long-term carbon sink and can be useful for mitigating climate changes. However, increasing habitat fragmentation, excessive collection of medicinal plant parts, and poor natural reproduction of *Mesua ferrea* make the wild populations endangered in some areas. Therefore, sustainable cultivation, habitat protection, ex situ germplasm storage, and scientific harvesting methods are needed to preserve this valuable medicinal tree [15–18].

Table 1. Taxonomic classification and vernacular names of *Mesua ferrea* L.

Parameter	Description	Reference
Kingdom	Plantae	[9]
Division	Magnoliophyta (Angiosperms)	[9]
Class	Magnoliopsida (Eudicots)	[9]
Order	Malpighiales	[9]
Family	*Calophyllaceae* (formerly *Clusiaceae*)	[9,10]
Genus	*Mesua*	[9]
Species	*Mesua ferrea* L.	[9]
Accepted scientific name	*Mesua ferrea* L.	[9]
English	Ceylon ironwood, Indian rose chestnut	[10,11]
Sanskrit	Nāgakeśara (Nagakesara)	[11,12]
Hindi	Nagkesar	[11]
Bengali	Nageswar (Nagkeshar)	[11,12]
Assamese	Nahor	[13]
Tamil	Nagappu (Nagapoo)	[11]
Telugu	Nagakesaramu	[11]
Malayalam	Nagappoovu (Nagapushpa)	[11]
Marathi	Nagkesar	[11]

3. TRADITIONAL AND ETHNOMEDICINAL USES

The *Mesua ferrea* L. species has had wide application in traditional medicine in South and Southeast Asia over the past several centuries owing to its varied medicinal properties. Parts of the plant such as flowers, stamens, bark, leaves, seeds, fruits, roots, and seed oil have found extensive usage in Ayurveda, Siddha, Unani and other folk medicine practices for treating fever, dysentery, diarrhea, blood conditions, respiratory conditions, skin problems, injuries and inflammation. Among these, the dried stamens, often known as Nagakesara, are considered to be the most medicinally significant and serve as an essential component of many classical Ayurvedic medicines. This long history of the use of *M. ferrea* in traditional medicine has attracted considerable scientific attention, thus resulting in thorough pharmacological and phytochemical studies, which have validated many ethnomedicinal uses of this species. The subsequent paragraphs present information on its historical importance and traditional medicinal uses in different systems of medicine (Table 2) [19–22].

3.1 Historical Background

The *Mesua ferrea* has been one of the highly valued plants of traditional medicine in South and Southeast Asia for several centuries already. According to early Ayurvedic literature, Nagakesara was a medicinal plant with hemostatic, digestive, anti-inflammatory and rejuvenating properties. It is known from historical sources that the various parts of the plant have been used for the treatment of disorders of the digestive system, fever, respiratory problems, skin conditions, injuries and excessive bleeding. The dried stamens were especially appreciated owing to their astringent and cooling properties and were widely used in polyherbal preparations to restore physiological balance and

improve general health [20–23]. The sweet-smelling white flowers of the tree are often used in Hindu religious rituals and considered as an auspicious symbol. In Buddhism, this species represents peace, longevity, and spirituality, which led to its cultivation near temples, monasteries, and other religious sites. Such cultural beliefs have been influential in conservation of this species and the utilization of *M. ferrea* in traditional medicine [21,24]. Different plant parts are used for preparation of therapeutic concoctions in the form of decoction, powder, infusion, medicated oil, paste, and poultice. These preparations are still used for treatment of inflammatory conditions, digestive disorders, respiratory disease, skin conditions, rheumatism, and wound healing. Current phytochemical and pharmacological studies revealed that many of these traditional uses are supported by presence of active phytochemicals such as xanthones, coumarins, flavonoids, phenols, and triterpenoids in the plant. However, further clinical studies and herbal formulation are required for proving the safety and efficacy of these preparations [19,22-25].

3.2 Ayurveda

Mesua ferrea (Nagakesara) is an important medicinal plant used in Ayurveda. Ayurvedic classics mention that Nagakesara is Kashaya (astringent), Tikta (bitter), and Madhura (sweet) ras; Laghu (light) and Ruksha (dry) guna; Sheeta virya (cool potency); and Katu vipaka (pungent post-digestive effect). The pharmacological properties of this plant allow it to pacify Pitta and Kapha doshas and improve digestion, reduce inflammation, control bleeding, and improve tissue regeneration [20,21,26].

For many years now, this herb has been considered effective in managing fever especially those associated with inflammation and digestive system problems. The coolness and anti-inflammatory nature of Nagakesara is said to help in reducing fever as well as restoring physiological equilibrium. The flowers and stamens have also been extensively used in the treatment of dysentery and diarrhea whereby its astringent properties cause a reduction in intestinal secretions, improve consistency of stools, as well as reduce abdominal pain [20,26]. The herb is known for its haemostatic property and has generally been used to manage blood disorders such as nose bleeds, vomiting of blood, hemorrhoids, heavy periods and other instances where there is blood loss. Its ability to cause vasoconstriction and contraction of tissues has enabled it to be used in traditional medicine aimed at controlling blood loss. Likewise, Nagakesara has generally been used to manage bleeding piles whereby it helps in reducing inflammation, pain, and rectal bleeding [21,27]. *M. ferrea* has also been used in Ayurveda in the management of respiratory disorders like cough, bronchitis and bronchial asthma. The stamens powder is usually given together with honey or added to herbal remedies to reduce irritation in the throat and facilitate mucous drainage as well as improve respiratory functions. Furthermore, pastes made from barks, leaves and seed oil have always been recommended for treating skin disorders, chronic ulcers, eczema, and other inflammatory skin disorders [22,25].

Aside from being an individual herbal medicine, Nagakesara is a vital component in many Ayurvedic traditional formulations used for the treatment of different diseases such as Chyawanprash, Dasamoolarishta, Ashokarishta, Pushyanuga Churna, Lodhrasava, and many others that are used for the treatment of various gynecological diseases, gastrointestinal diseases, hemorrhage, and general weakness. Long-term usage of these formulations in the treatment of patients in the Ayurvedic system of medicine has proven the therapeutic importance of Mesua ferrea. Pharmacological studies have shown antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, and wound healing effects; however, well-designed clinical trials will be needed for the establishment of standard doses [21,23,25-28].

3.3 Siddha and Unani Medicine

Mesua ferrea L. is considered to be one of the most important medicinal plants in Siddha and Unani medicines because of their therapeutic potential and traditional uses. In Siddha medicine, the medicinal plant is considered to possess the property of cooling, astringent, anti-inflammatory and rejuvenating, while in Unani medicine it is known for its tonic, haemostatic, digestive and anti-infectious properties. Various parts of the plant like flower, stamen, bark, seeds, and seed oil are included in the herbal formulations in isolation or along with other herbs for the treatment of acute as well as chronic diseases [21,22,29].

In Siddha medicine, flowers and stamens are often used as a powder to treat inflammatory conditions,

hyperthermia, fever, and bleeding disorders. The bark decoction is traditionally used to relieve gastrointestinal problems, dysentery, diarrhea, and intestine inflammation. The seed oil is often used as a topical application to treat joint pain, rheumatism, chronic ulcers, and various skin infections because of its anti-inflammatory and antimicrobial activity. Fresh leaf paste is often used as a topical preparation to treat wounds, boils, eczema, and insect bites [22,29,30].

According to the basic principles of Unani medicine, *M. ferrea* is considered an effective treatment for diseases of the digestive system as well as respiratory tract. The flower heads and stamens are used as stomachic, carminative, and haemostatic agents for the treatment of diarrhea, dysentery, hemorrhoids, and internal bleeding. Herbal preparations, which include Nagakesara, are used for the treatment of chronic cough, bronchitis, asthma, and other respiratory diseases due to their expectorant and anti-inflammatory actions. Furthermore, the plant is thought to have a positive effect on the health of the cardiovascular system, digestive function, and overall vital activity [20,29,31].

Also, in traditional medicine, *M. ferrea* is used to treat diseases of gynecological origin. The powder of the stamens is used independently or as part of complex herbal preparations for the treatment of menorrhagia, leucorrhoea, excessive postpartum bleeding, and uterine weakness. The presence of haemostatic and uterine tonic actions of the pla nt explains its popularity in the composition of many traditional medicines used by women. Furthermore, *M. ferrea* is believed to act as a general tonic, which stimulates appetite, improves digestion, promotes tissue regeneration, and aids recovery after long-term diseases [22,30,31]. Even though these traditional uses have been practiced for centuries, modern pharmacological studies show that many of these healing effects are likely due to the biologically active compounds contained in the plant such as xanthones, coumarins, flavonoids, triterpenoids, and phenolic substances. These compounds demonstrate antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory effects. However, systematic clinical researches are needed to confirm traditional claims.

3.4 Folk and Tribal Medicine

The wide geographic spread of *Mesua ferrea* is associated with the fact that this species has long been widely used by many indigenous and tribal peoples of India, Sri Lanka, Nepal, Bangladesh, Myanmar and other South-East Asian countries. Since time immemorial traditional medicine practitioners used locally found parts of plants for treatment of common health disorders. The experience thus gained was passed down orally from generation to generation. Ethnomedicinal practices constitute an important part of the local primary healthcare, especially in remote rural communities where modern medical infrastructure is lacking [19,22,32].

Among different parts of *Mesua ferrea* dried flowers and stamens are the most often used ones. They are usually ground to powder and given with honey, milk, hot water for the treatment of diarrhea, dysentery, fever, cough, bleeding, weakness. Because of their powerful astringent effect the flowers are also used to stop internal bleeding and improve gastrointestinal tract functions. In some tribes of north-eastern India the powdered stamens are taken as a restorative drink after long periods of sickness and childbirth [20,29,33].

Bark is widely used in the form of decoctions or infusions to treat fever, stomach disorders, dyspepsia, intestinal infections, inflammatory processes. In some localities bark decoction is used as a gargle for sore throat and mouth ulcers because of antimicrobial and anti-inflammatory effect. The paste made from leaves is traditionally applied topically to cuts, wounds, boils, eczema and other skin conditions [22,30,32].

Seeds and seed oil have been traditionally known to have a remarkable importance in the practice of traditional medicine. Seed oil, which is called the Nahor oil, is traditionally applied to the body to treat rheumatism, arthritis, sprain, chronic ulcers, burns, dandruff, scabies, eczema, and different kinds of fungal skin infections. It is common among traditional bone setters and village healers to massage with warmed seed oil the joints of patients suffering from joint problems, thus reducing pain and improving mobility. In some cases, seed oil is used as a hair tonic to make hair stronger and healthy [21,30,33].

Although fruits and roots are rarely used in comparison to other parts of the plant, they were found in ethnobotanical surveys as well. In some cases, root decoctions were taken to treat digestive problems and inflammation; fruits were used to treat intestinal problems and fever in some geographical regions. Depending on the disease and culture, traditional formulations are prepared in form of decoction, powder, infusion, medicated oil, topical paste, poultice, and herbal combination. Different kinds of traditional formulations reveal the medicinal flexibility of the species and highlight its relevance to indigenous medical systems [22,31–33]. Thus, ethnobotanical studies revealed the fact that virtually all parts of *M. ferrea* are traditionally used medicinally. Such regularity in application of different parts of the species in many geographical regions has promoted numerous phytochemical and pharmacological studies, most of which prove the antimicrobial, antioxidant, anti-inflammatory, wound-healing, hepatoprotective, and antidiabetic properties of the species. Still, standardized dosing, quality control, and clinical validation should be considered important issues in this case [19,21,25].

3.5 Ethnomedicinal Uses of Different Plant Parts

Almost all the plant parts have been used in treating a variety of diseases from ancient times to date. Therapeutic use has mainly been attributed to its flowers, stamens, bark, leaves, seeds, fruits, roots, and seed oil with different ethnopharmacological applications. However, the selection of the plant parts along with different preparations depends on various factors like the disease condition, availability, and cultural practices. Different dosage forms used include powder, decoction, infusion, medicated oil, topical paste, poultice, and raw extract taken orally or externally [19,21,22]. Among all the plant parts, dried stamens (Nagakesara) are the most important ones that find their extensive usage in Ayurveda, Siddha, Unani, and traditional folk medicine. These stamens are usually taken in the form of powder and as a part of polyherbal formulation in the management of diarrhea, dysentery, fever, piles, bleeding disorders, excessive vaginal discharge, chronic cough, bronchial asthma, and digestive disorders. Because of their astringent, hemostatic, anti-inflammatory, and digestive effects, Nagakesara are regarded as an important herbal drug in the Ayurvedic tradition [20,23,29]. Flowers of the plant are known to possess cooling, aromatic, and antioxidant actions. They are mostly prescribed for fever, polydipsia, inflammatory conditions, and digestive disorders. In some indigenous communities, powdered flowers are taken as a tonic to boost digestion, to overcome fatigue, and increase overall health. Because of their nice smell, these flowers are also used in religious ceremonies [21,24,30]. The bark has been widely used in traditional medicine and prepared in the form of decoction or infusion to be taken internally in case of dysentery, diarrhea, fever, gastritis, bronchitis, rheumatism, and inflammation. Due to the high content of tannins and astringency, the bark is used as a mouthwash for oral ulcers and sore throat; the topical use helps to cure skin infections and wound healing [22,25,31]. Fresh leaves are used topically. The paste from crushed leaves is applied on wounds, cuts, burns, boils, eczema and other skin conditions to reduce inflammation, prevent bacterial infection and accelerate tissue growth. In some tribes, leaf extract is consumed orally to treat fever and gastrointestinal problems; however, this practice is rare [21,30,32]. Seeds of *M. ferrea* have significant content of fixed oil, known as Nahor oil, which has significant importance in traditional medicine. Seed oil is widely used externally in treatment of rheumatism, arthritis, muscle pains, sprain, chronic ulcers, burns, dandruff, scabies, eczema, fungal infections and other diseases of skin. Besides, traditionally, this oil serves as hair tonic to improve scalp health and stimulate hair follicles' growth. In some places, seeds are used as antimicrobial and anti-inflammatory agent [22,29,33]. Despite the limited information about fruits and roots, ethnobotanical data shows that they are used in treatment of gastrointestinal disorders, intestinal infections, fever, inflammation, and weakness. Sometimes, root decoction is prescribed as a tonic, while fruits are used to treat mild gastroenteric problems and fever [20,22,31].

Table 2. Ethnomedicinal Uses of Different Plant Parts of *Mesua ferrea* L.

Plant part	Traditional preparation	Ethnomedicinal uses	Traditional system	References
Flowers	Powder, infusion, decoction	Fever, dyspepsia, inflammation, digestive tonic, excessive thirst	Ayurveda, Siddha, Folk	[20,21,30]
Stamens (Nagakesara)	Powder, churna, decoction, polyherbal formulations	Diarrhea, dysentery, bleeding disorders, haemorrhoids, asthma, cough, menorrhagia	Ayurveda, Siddha, Unani	[20,23,29]
Bark	Decoction, infusion, paste	Fever, dysentery, diarrhea, bronchitis, rheumatism, oral ulcers, skin diseases	Ayurveda, Folk	[22,25,31]
Leaves	Fresh paste, decoction	Wounds, boils, eczema, burns, skin infections, inflammation	Folk, Siddha	[21,30,32]
Seeds	Powder, paste	Anti-inflammatory, antimicrobial, digestive disorders	Folk medicine	[22,29,33]
Seed oil (Nahor oil)	External application, medicated oil	Rheumatism, arthritis, sprains, chronic ulcers, burns, dandruff, eczema, scabies	Ayurveda, Folk, Siddha	[22,29,33]
Fruits	Decoction, powder	Fever, intestinal disorders, digestive complaints	Folk medicine	[20,31]
Roots	Decoction	Inflammation, fever, digestive disorders, general weakness	Folk medicine	[22,31,32]

4. PHYTOCHEMISTRY

Mesua ferrea L. has been considered an excellent source of structurally diverse secondary metabolites that play an important role in providing biological activity of wide variety. Phytochemical studies conducted on different plant parts such as flowers, stamens, leaves, bark, fruits, seeds, and seed oil have resulted in the discovery of a large number of phytochemicals belonging to different chemical groups, including xanthones, coumarins, flavonoids, phenolic compounds, terpenoids, steroids, fatty acids, and essential oils [34–36]. However, the content and variability of the phytochemicals are influenced by plant part used for extraction, geographical location, environmental factors, solvent used for extraction, and developmental stage of the plant. Among the listed phytochemicals, xanthones and coumarins are considered the major chemotaxonomic markers for *M. ferrea* and the major factors responsible for various biological activities, including antioxidative, antimicrobial, anti-inflammatory, hepatoprotective, antidiabetic, and anticancer activities [35–37]. Modern methods of chromatographic and spectroscopic analysis, such as HPLC, LC–MS, GC–MS, NMR spectroscopy, have greatly helped in the identification of major and minor phytoconstituents, which has greatly expanded the information about chemical composition of the plant (Table 3) [36–38].

4.1 Xanthones

Xanthones form one of the largest and most important groups of secondary metabolites isolated from *M. ferrea*. Structurally, xanthones are considered oxygen-containing heterocyclic compounds having dibenzo-γ-pyrone skeleton, which allows obtaining a great variety of hydroxylated, methoxylated, prenylated, and glycosylated xanthones. Their biological activity is determined mainly by these structural features [35,37]. As a result of the phytochemical studies of Mesua ferrea, many derivatives of xanthones were found out, being mostly abundant in the flowers, stamens, bark, and seeds of the plant. Such compounds as mesuaxanthone A, mesuaxanthone B, mesuaxanthone C, mesuaxanthone D, jacareubin, caloxanthone C, caloxanthone E, 1,5-dihydroxyxanthone, and some prenylated xanthones were identified [35,36,39]. They gained much pharmacological attention owing to their strong antioxidant, antimicrobial, anti-inflammatory, hepatoprotective, and cytotoxic effects. A number of studies showed that xanthones possess their antioxidant properties through their ROS-scavenging abilities, inhibition of lipid peroxidation, and enhancement of the body's antioxidant defense system. Moreover, prenylated xanthones extracted from *M. ferrea* proved their antibacterial effect on both Gram-positive and Gram-negative bacteria, which indicates their ability to be used as natural

antibiotics. Some xanthone derivatives were proven to possess cytotoxic effects on various human cancer cells because of their ability to induce apoptosis and block the cell cycle, as well as their effect on mitochondrial signaling pathways [36,38,39]. In addition to their medicinal importance, xanthones can be used as chemotaxonomic markers for the family *Calophyllaceae*. Moreover, they have been widely used in phytochemical fingerprinting and quality control of herbal medicines. The great structural diversity of xanthones in *M. ferrea* promotes their further study and search for novel leads for developing drugs [35,37].

4.2 Coumarins

Coumarins are another important group of phytochemicals found in *M. ferrea*. Benzopyrones, which are produced through the phenylpropanoid pathway, are known for their antioxidant, antimicrobial, anti-inflammatory, anticoagulant, and anticancer properties. Moreover, the genus Mesua is characterized by the presence of many prenylated and phenyl-substituted coumarins with significant biological effects [34,36]. The most studied among those coumarins that are found in *M. ferrea* are mesuol, mesuagin, mammeisin, mammea-type coumarins, mesuaferrin A, mesuaferrin B, mesuaferrin C, and mesuaferrone [35,39,40]. These compounds are mainly found in the seeds, flowers, and stamens; however, their appreciable amounts were found in the bark and leaves as well. Pharmacological studies show that coumarins significantly contribute to the wide range of medicinal properties of *M. ferrea*. According to researchers, mesuol has significant antioxidant and anti-inflammatory properties due to the reduction of oxidative stress and inhibition of pro-inflammatory mediators. Many phenylcoumarins have strong antibacterial properties against clinical isolates such as S. aureus and B. subtilis. In addition, some coumarin derivatives have antiviral, antifungal, immunomodulatory, and antiproliferative effects [38–40]. Moreover, structural variations of coumarins in *M. ferrea* also attracted significant attention of medicinal chemists since structural modification of natural coumarins resulted in obtaining a number of semi-synthetic derivatives with improved pharmacological effects, which can be considered as prospective templates for new drugs [36,39].

4.3 Flavonoids

Flavonoids belong to the polyphenolic compounds that are widespread in the leaves, flowers, bark, and seeds of *M. ferrea*. Secondary metabolites play an important role in physiology of plants due to protection against ultraviolet radiation, oxidative stress, pathogenic microorganisms and environmental factors. In addition, flavonoids provide medicinal properties of *M. ferrea* due to their powerful antioxidant and anti-inflammatory properties [34,37]. Some of the phytochemical studies have discovered several flavonoids, including quercetin, kaempferol, rutin, catechin, epicatechin, myricetin and their respective glycosides. Even though flavonoids are present in relatively small amounts compared to xanthones and coumarins, they significantly contribute to the pharmacological profile of the plant because of their wide range of biological activities [35,36]. Antioxidant property of flavonoids is attributed mainly to their ability to donate hydrogen atoms or electrons and hence neutralize free radicals, preventing oxidative damage to lipids, proteins, and nucleic acids. Many flavonoids also inhibit pro-inflammatory enzymes like cyclooxygenase (COX) and lipoxygenase (LOX) along with inhibiting the formation of inflammatory cytokines including TNF-α, IL-1β, and IL-6. Thus, these substances are responsible for anti-inflammatory, hepatoprotective, cardioprotective and antidiabetic activities described for *Mesua ferrea* [37-40]. Moreover, recent studies have revealed that flavonoids extracted from *Mesua ferrea* can be used in cancer treatment owing to their activity on many signaling pathways associated with apoptosis, angiogenesis, oxidative stress, and cell cycle regulation. It is thought that the interactions between flavonoids, xanthones, coumarins, and phenolic compounds increase the activity of crude plant extracts, which emphasizes the importance of preservation of natural complexity of phytochemical composition of herbs, as compared with individual chemicals [35,38,40].

4.4 Phenolic Compounds

Phenolic compounds are another type of secondary metabolites present in *Mesua ferrea* and significantly responsible for its antioxidant and therapeutic activities. They are characterized by one or more hydroxyl groups in an aromatic ring and are

widespread in the flowers, leaves, bark and seeds. Phenolic compounds are vital for the defense of plants against oxidative stress, microbial infections, UV radiation, and other stresses in environment. The presence of high amounts of phenols in *Mesua ferrea* is connected with many of pharmacological activities of crude extracts, especially their antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, and antimicrobial activities [34-36]. Phenolic acids and their derivatives found in *Mesua ferrea* include gallic acid, ellagic acid, ferulic acid, caffeic acid, p-coumaric acid, syringic acid, vanillic acid, and protocatechuic acid. Tannins and other polyphenols are important for the strong astringency of this plant, which has long been used in the treatment of diarrhea, dysentery, bleeding conditions, and wounds [35,37,41]. Phenolic antioxidants act through their ability to donate hydrogen atoms or electrons in order to eliminate ROS. Phenols chelate transition metals that can take part in radical formation and control intracellular levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Besides, phenols interfere with inflammatory mediators by suppressing nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines [36,38,41]. The current studies proved that phenolic components possess an antimicrobial effect toward several pathogens and protect hepatocytes and other cell types from oxidation injuries. The synergic effect of phenolics together with xanthones, coumarins, and flavonoids increases the general pharmacological effects of *M. ferrea*, and therefore it is necessary to conserve the whole composition of phytoconstituents rather than to use isolated compounds in herbal preparations [35,40,41].

4.5 Terpenoids

Terpenoids are complex molecules synthesized by the plants through the mevalonate and methylerythritol phosphate pathways. Terpenoids are mostly distributed in the leaves, bark, flowers, fruits, and seeds of Mesua ferrea, and they play roles in plant defense, growth regulation, and other ecological processes. Phytochemical analysis of this plant revealed a variety of monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids with strong pharmacological activities [35,36]. Among the main terpenoids isolated from *M. ferrea* include β-amyrin, α-amyrin, lupeol, betulinic acid, ursolic acid, oleanolic acid, and friedelin in addition to phytosterols like β-sitosterol, stigmasterol, and campesterol [36,39,42]. These chemicals display various bioactivities ranging from anti-inflammatory, analgesic, antioxidant, hepatoprotective, antidiabetic, antimicrobial, and anticancer. Triterpenoids act as anti-inflammatory agents through inhibition of phospholipase A_2, cyclooxygenase, lipoxygenase, and inflammatory pathways mediated by NF-κB. Many of the terpenoids have been found capable of inducing apoptosis of cancer cells through activation of caspase-dependent pathway and alterations in expression of Bcl-2 family proteins and alteration in mitochondrial membrane potential. Besides, pentacyclic triterpenoids like ursolic acid and betulinic acid have shown hepatoprotective and antidiabetic properties through regulation of oxidative stress and glucose metabolism [38,39,42]. Therefore, the presence of these terpenoids in *M. ferrea* forms a scientific explanation for the use of the plant in the management of inflammatory disorders, rheumatism, liver conditions, and metabolic disturbances. The various medicinal properties of the chemicals form the basis for development of phytopharmaceuticals and functional nutraceuticals [35,41,42].

4.6 Essential Oils

Mesua ferrea has fragrant essential oils found in the flowers, leaves, and seeds. The volatile oils form some of the medicinal components of the plant through exhibiting antimicrobial, antioxidant, insecticidal, and anti-inflammatory actions. They are mainly composed of monoterpenes, sesquiterpenes, and oxygenated aromatic compounds [34,36]. Various volatile components of the plant identified using gas chromatography-mass spectrometry include α-pinene, β-pinene, limonene, linalool, α-terpineol, β-caryophyllene, caryophyllene oxide, germacrene D, α-humulene, and spathulenol among others [39,41,43]. Inhibitory activity of essential oils derived from *M. ferrea* on different clinical pathogens such as Staphylococcus aureus, Escherichia coli, Bacillus subtilis, and Candida albicans shows its possible use as natural antibacterial compounds. Moreover, the volatile compounds show antioxidant activity by scavenging the reactive oxygen species and lowering the amount of lipid peroxidation. Fractions rich in terpenoids were also shown to possess insecticidal and larvicidal activity [36,40,43]. Taking into account the nice smell and biological activity of *M. ferrea*

essential oils, their application in pharmaceuticals, cosmetics, perfumes, and food industries is getting more attention. Nevertheless, further research regarding characterization of the volatile compounds, developing the quality control system, determining the toxicity, and standardization should be carried out.

Table 3. Major Phytoconstituents of *Mesua ferrea* L.

Phytochemicals	Compounds	Plant part	Biological activities	References
Xanthones	Mesuaxanthone A–D, Jacareubin, Caloxanthone C, Caloxanthone E	Flowers, stamens, bark, seeds	Antioxidant, antimicrobial, anti-inflammatory, anticancer	[35–39]
Coumarins	Mesuol, Mesuagin, Mesuaferrins, Mammeisin, Mammea-type coumarins	Seeds, flowers, stamens	Antimicrobial, antioxidant, anti-inflammatory, cytotoxic	[36,39,40]
Flavonoids	Quercetin, Kaempferol, Rutin, Catechin, Epicatechin, Myricetin	Leaves, flowers, bark	Antioxidant, hepatoprotective, cardioprotective, antidiabetic	[35,37,40]
Phenolic compounds	Gallic acid, Ellagic acid, Ferulic acid, Caffeic acid, Syringic acid	Leaves, bark, flowers	Antioxidant, anti-inflammatory, antimicrobial	[36,41]
Terpenoids	Lupeol, α-Amyrin, β-Amyrin, Betulinic acid, Ursolic acid, Oleanolic acid, Friedelin	Leaves, bark, seeds	Anti-inflammatory, analgesic, anticancer, hepatoprotective	[39,42]
Phytosterols	β-Sitosterol, Stigmasterol, Campesterol	Seeds, bark	Anti-inflammatory, hypolipidemic	[35,42]
Essential oils	α-Pinene, β-Pinene, Limonene, Linalool, β-Caryophyllene, Germacrene D	Flowers, leaves, seeds	Antimicrobial, antioxidant, insecticidal	[36,41,43]
Fixed oils	Linoleic acid, Oleic acid, Palmitic acid, Stearic acid	Seeds	Nutritional, emollient, wound healing	[35,42]

5. PHARMACOLOGICAL ACTIVITIES

Consequent to the wide-ranging traditional applications of *Mesua ferrea* L., there have been many pharmacological studies that have uncovered many biologic activities due to its diverse phytochemical components, including xanthones, coumarins, flavonoids, phenolic compounds, and terpenoids. Several experimental studies revealed potent antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, anticancer, analgesic, and wound-healing activities of extracts and isolated components obtained from different plant parts. The pharmacologic actions of *Mesua ferrea* L. are mainly achieved through free-radical scavenging, modulation of inflammatory pathway, suppression of microbial growth, regulation of glucose metabolism, protection from oxidative tissue damage, and induction of cancer cell apoptosis. Even though most of the evidence comes from in vitro and animal experiments, the scientific data sufficiently supports many traditional medical applications of *M. ferrea*. However, more systematic clinical studies, standardized formulations of plant extracts, and safety evaluations are required in order to confirm the effectiveness and to enable the development of phytopharmaceutical drugs based on *Mesua ferrea* L. (Figure 1, Table 4) [35–43].

5.1 Antioxidant Activity

Oxidative stress, characterized by an imbalance between increased production of reactive oxygen species (ROS) and decreased efficiency of antioxidants, is a common factor involved in the development of many chronic diseases such as cancer, diabetes, cardiovascular disease, neurodegenerative disease, and liver injury. Taking into account the wide range of its phytochemicals, especially xanthones, coumarins, flavonoids, and phenolic compounds, *Mesua ferrea* L. possesses potent antioxidant properties in several in vitro and in vivo studies. The extracts obtained from flowers,

stamens, leaves, bark, and seeds of this plant are effective free-radical scavengers that inhibit lipid peroxidation and increase the expression of endogenous antioxidants, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [35–39]. Methanolic and ethanolic extracts of *Mesua ferrea* showed strong radical scavenging ability in 2,2-Diphenyl-1-picrylhydrazyl (DPPH), 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), Ferric Reducing Antioxidant Power (FRAP), and nitric oxide scavenging tests; the higher antioxidant potential of these extracts was strongly related to their total phenolic and flavonoids content. Many isolated xanthones and coumarins, including mesuol and jacareubin, have been found to possess strong antioxidant activity due to their ability to scavenge reactive oxygen species and regulate signaling pathways that are involved in oxidative stress. The mentioned above provides a sound scientific rationale for the traditional usage of *M. ferrea* in treating inflammatory and oxidative-stress-related diseases [36–40].

5.2 Anti-inflammatory Activity

Inflammation is considered one of the complex biological processes that play an important role in the pathogenesis of many acute and chronic diseases. *Mesua ferrea* was used in ancient traditional medicine to treat inflammatory diseases, and its current pharmacological studies have confirmed its applicability. Flower, bark, leaf, and seed extracts of *M. ferrea* have shown good anti-inflammatory activity in experimental models, as they reduce edema formation, inhibit inflammatory cells migration, and lower the production of pro-inflammatory mediators [35,36,40]. The anti-inflammatory activity of *Mesua ferrea* is mainly provided by the action of its xanthones, coumarins, flavonoids, and triterpenoids. They are able to inhibit NF-κB, COX-2, LOX, iNOS pathways, as well as the synthesis of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6). In addition, the antioxidant activity of *M. ferrea* phytochemicals promotes inflammation control by reducing oxidative stress. Therefore, the antioxidant and anti-inflammatory activities provide a scientific rationale for the application of *M. ferrea* in the treatment of inflammatory diseases, including rheumatism, arthritis, skin diseases, and wound healing. Nonetheless, most of the data is based on preclinical research [37–43].

5.3 Antimicrobial Activity

Antimicrobial resistance has led to the need for searching novel antimicrobial compounds among the natural products. *Mesua ferrea* has been studied extensively due to the presence of various natural bioactive molecules that exhibit antimicrobial properties against a wide range of pathogenic bacteria and fungi. Extracts as well as the isolated phytochemicals extracted using methanol, ethanol, and aqueous solvents from the flowers, bark, leaves, and seeds have shown inhibitory action against Gram-positive and Gram-negative bacteria such as Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa as well as fungi such as Candida albicans and Aspergillus niger [35–40]. The bioactivity of *M. ferrea* is mostly linked to xanthones, coumarins, flavonoids, phenols, and essential oils that target the disruption of microbe cell membranes, inhibition of DNA/RNA/protein synthesis, blocking of necessary metabolic reactions, and generation of oxidative stress in the microbes. The bioactivity of mesuol, mesuaferrins, and some prenylated xanthones has been found to be particularly effective against bacteria. This finding confirms the traditional uses of *M. ferrea* in the treatment of skin infections, wounds, gastrointestinal infections, and respiratory diseases. However, more research is needed to establish the pharmacokinetics, safety, and efficacy of these natural molecules [37–43].

5.4 Antidiabetic Activity

Diabetes mellitus can be described as a chronic metabolic disease characterized by hyperglycemia, which results from deficiency of insulin production or insulin resistance or both. Various traditional medicine practices have used *Mesua ferrea* for managing diabetes, and a number of experiments have confirmed the antidiabetic property of this plant. The extracts from flowers, leaves, bark, and seeds of this plant show antihyperglycemic activity and have been found to reduce fasting blood sugar levels, increase glucose tolerance, and improve insulin sensitivity [35,36,41]. The antidiabetic activity of *M. ferrea* is mainly attributed to its flavonoids, xanthones, coumarins, phenolics, and triterpenoids. The action of the aforementioned bioactive compounds includes inhibition of α-amylase and α-glucosidase enzymes in the intestine, increase in the rate of peripheral glucose uptake, enhancement of insulin release, decrease in

oxidative stress levels, and protection of pancreatic β-cells against free radicals. Furthermore, the antioxidant and anti-inflammatory effects of these compounds play an important role in the development of complications related to diabetes such as hepatic, renal, and cardiovascular disorders. However, the lack of clinical research makes further studies necessary [36–43].

5.5 Hepatoprotective Activity

The liver is involved in the regulation of metabolic functions and detoxification and hence is susceptible to injury from xenobiotic exposure, drug usage, ethanol ingestion, and oxidative stress. Several in vivo investigations have indicated the protective effect of *Mesua ferrea* extract against experimentally induced hepatotoxicity. It was found that methanolic and ethanolic extracts from the flowers, leaves, bark, and seeds considerably reduced serum levels of hepatic biomarkers – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin – as well as restored the histoarchitecture of the liver [35,36,41–43]. The main mechanisms of *M. ferrea* hepatoprotection are associated with the antioxidant and anti-inflammatory properties of xanthones, flavonoids, coumarins, and phenols present in the plant and protecting hepatocytes from oxidative stress through the scavenging of reactive oxygen species, inhibition of lipid peroxidation and upregulation of the body's antioxidant systems. In addition, they inhibit the production of proinflammatory cytokines and maintain integrity of cellular membrane, thus preventing the development of hepatotoxicity and supporting the regeneration of damaged tissues. Preclinical data on hepatoprotection show good prospects, but further studies are required to clarify the nature of active substances, their action mechanism, and effectiveness in humans [35–43].

5.6 Anticancer Activity

Despite significant medical advances in cancer treatment and management, this disease still constitutes one of the major health problems and stimulates the search for plant-based anticancer agents. Several xanthones, coumarins, flavonoids, and triterpenoids isolated from *Mesua ferrea* have been shown to possess anticancer activity. Different extracts and their constituent compounds have been found to exhibit anticancer activity against various human cancer cell lines, such as those of breast, liver, colon, lung, and leukemia [37–43]. *Mesua ferrea* exerts its anticancer activity via several molecular mechanisms, namely, apoptosis induction, cell cycle arrest, angiogenesis inhibition, metastasis inhibition, and modulation of oxidative stress. There are many xanthones and prenylated coumarins known to activate caspase-mediated apoptotic pathways, control the balance between Bcl-2 family proteins, depolarize mitochondrial membranes, and block survival signaling pathways, such as NF-κB and PI3K/Akt axis. All these mechanisms lead to the selective antiproliferative effect on cancer cells without damaging normal cells. Though in vitro studies provide positive results regarding *M. ferrea* derivatives as prospective anticancer compounds, thorough in vivo studies, pharmacokinetic assessments, and clinical trials are still needed to validate their therapeutic potential [37–43].

5.7 Analgesic Activity

Traditional medicinal practices include the use of *Mesua ferrea* for the treatment of pain caused by inflammatory conditions, rheumatism, injuries, and diseases of musculoskeletal system. Experimental studies have confirmed the existence of strong analgesic properties of the extracts from the flowers, bark, and seeds of *M. ferrea* in animal models with acetic acid-induced writhing and hot plate tests, indicating both peripheral and central actions and supporting the use of the plant in folk medicine [35,36,40]. Analgesic activity is mainly due to flavonoids, xanthones, coumarins, and triterpenoids, which reduce the synthesis of prostaglandins and other inflammatory mediators by blocking cyclooxygenase (COX) and lipoxygenase (LOX) pathways. In addition, antioxidative and anti-inflammatory activities of the compounds also play a role in the pain relief by decreasing oxidative injury of tissues and inflammation reactions. Though all the data is promising, further pharmacological and clinical researches are necessary to prove the effectiveness in humans [35–40].

5.8 Wound-Healing Activity

It is well known that *Mesua ferrea* possesses potent wound healing properties, as the extracts of leaves, bark, and seeds are traditionally used for the treatment of cuts, burns, ulcers, and infections in traditional medicine. Recent researches suggest that extracts of *M. ferrea* significantly accelerate wound contraction, increase collagen synthesis, promote re-epithelialization, and improve tissue remodeling in

the experimental wound models [35,36,41]. Such wound healing effects are associated with the action of flavonoids, xanthones, coumarins, phenols, and terpenoids, which exhibit antioxidant, antimicrobial, and anti-inflammatory properties. Phytochemicals decrease the risk of microbial infection, inhibit excessive inflammation reactions, stimulate fibroblast proliferation, induce angiogenesis, and enhance the production of extracellular matrix; hence, they contribute to the acceleration of the tissue regeneration process. The traditional application of seed oil and leaf paste in chronic wounds and infections is confirmed by experiments. However, more studies are needed in order to standardize formulations, identify mechanisms of action, and carry out clinical trials [35–43].

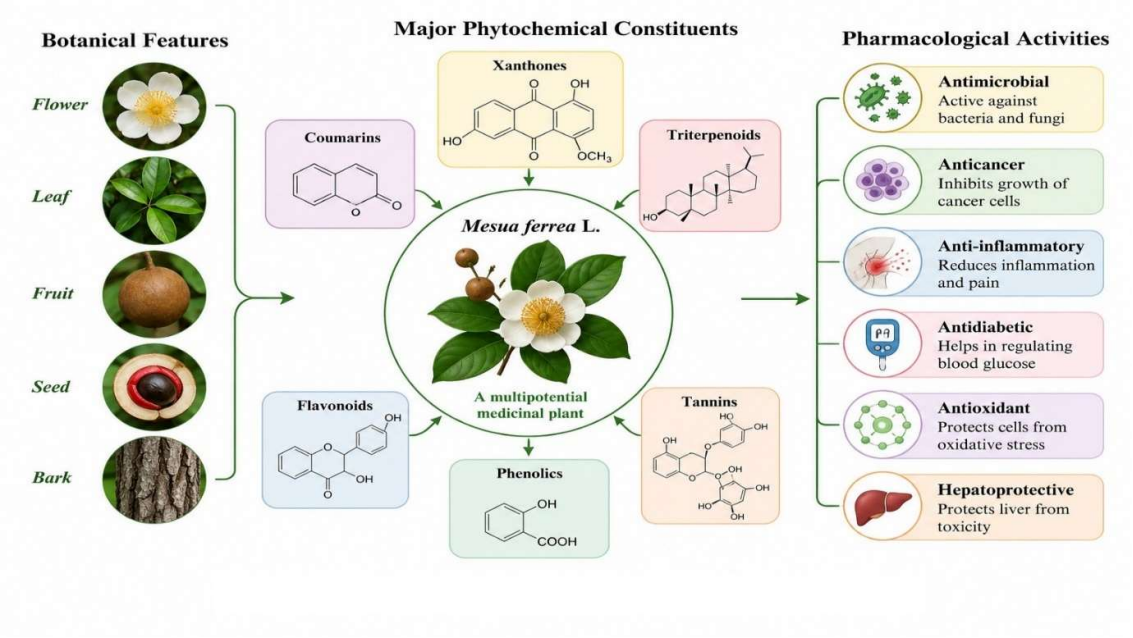


Figure 1. Overview of the ethnopharmacological significance, phytochemical composition, pharmacological activities, and future pharmaceutical prospects of *Mesua ferrea*.

Table 4. Summary of Pharmacological Activities of *Mesua ferrea* L.

Pharmacological activity	Plant part	Extract/ Compound	Experimental model	Outcomes	References
Antioxidant	Flowers, leaves, bark, seeds	Methanol, ethanol extracts; xanthones; flavonoids	DPPH, ABTS, FRAP, nitric oxide scavenging assays; animal models	Strong free radical scavenging activity, inhibition of lipid peroxidation, increased antioxidant enzyme activity	[35–40]
Anti-inflammatory	Flowers, bark, leaves	Methanol and ethanol extracts; coumarins; xanthones	Carrageenan-induced paw edema, inflammatory animal models	Reduced edema, inhibition of COX-2, LOX, NF-κB, TNF-α, IL-1β, and IL-6	[35–43]
Antimicrobial	Flowers, bark, leaves, seeds	Methanol, ethanol, aqueous extracts; essential oils	Antibacterial and antifungal assays	Effective against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*	[35,37–43]

Antidiabetic	Flowers, bark, leaves	Crude extracts; flavonoids; phenolics	Streptozotocin- and alloxan-induced diabetic animal models	Lowered blood glucose, improved insulin sensitivity, inhibition of α-glucosidase and α-amylase	[35,36,41–43]
Hepatoprotective	Flowers, leaves, bark	Methanol and ethanol extracts	CCl_4- and paracetamol-induced hepatotoxicity models	Reduced ALT, AST, ALP, bilirubin; improved liver histology	[35,36,41–43]
Anticancer	Flowers, seeds, bark	Xanthones, coumarins, flavonoids	Human cancer cell lines	Induced apoptosis, inhibited cell proliferation and angiogenesis, caused cell-cycle arrest	[37–43]
Analgesic	Flowers, bark	Methanol and ethanol extracts	Acetic acid-induced writhing, hot plate, tail-flick tests	Significant peripheral and central analgesic activity	[35,36,40]
Wound-healing	Leaves, bark, seed oil	Leaf paste, seed oil, ethanol extracts	Excision and incision wound models	Accelerated wound contraction, collagen synthesis, re-epithelialization, antimicrobial effect	[35,36,41–43]

6. TOXICITY AND SAFETY

Despite the long history of *Mesua ferrea* L.'s application in traditional medicine, the scientific information about the toxicity and safety of this natural remedy is rather poor. Currently, it has been demonstrated that the extracts from flowers, leaves, bark, and seeds of *M. ferrea* possess a high safety profile at therapeutic dosages. According to acute and subacute toxicity experiments, *M. ferrea* extracts do not cause any death and significant side effects in terms of body weight, hematological and biochemical blood parameters, and vital organs' tissue structure [44-46]. The safety of *M. ferrea* is primarily due to its complex composition of phytoconstituents, including xanthones, coumarins, flavonoids, phenolic compounds, and terpenoids that exhibit potent antioxidant and cytoprotective activity. However, the changes in phytochemicals' composition caused by the geographical variability, type of plant's parts used, season, and methods of extraction and formulation can affect the efficacy and safety of these phytoconstituents. Besides, their excessive consumption may result in dose-dependent negative effects. Thus, the importance of standardization and proper dosing of *M. ferrea* formulations and phytochemicals should be emphasized [45-48]. Despite promising results obtained in preclinical studies, the safety data are still rather insufficient. There is a lack of information regarding chronic toxicity, reproductive and developmental toxicity, genotoxicity, mutagenic, carcinogenic, and herb-drug interactions. Taking into consideration an increasing popularity of the development of *M. ferrea*-based phytopharmaceuticals and nutraceuticals, thorough safety evaluations are required according to internationally approved regulations, such as those issued by the Organisation for Economic Co-operation and Development (OECD). Taking all the above-discussed aspects into account, it may be stated that *Mesua ferrea* is generally considered to be a safe plant provided that it is used within the frames of traditional therapeutic regimens and proper medical guidance. However, the necessity for conducting comprehensive long-term toxicological studies and randomized clinical trials is evident in order to prove its evidence-based safety profile, determine dosage range and possible drug–herb interactions [47–50].

7. FUTURE PERSPECTIVES

The progress made in terms of identification of phytochemical compounds and pharmacological properties of *Mesua ferrea* L. allows us to state that there are still some obstacles on the way towards successful use of its beneficial properties in an evidence-based manner. The key priorities for future research may include standardization of herbal

extracts, clinical trials, pharmaceutical development and conservation approaches that would ensure safe, effective and sustainable exploitation of this medicinal plant. The first priority that needs to be considered is related to standardization of herbal preparations based on Mesua ferrea. Due to considerable variability that can be observed in terms of geographical origin, climatic conditions, plant parts, harvesting time and extraction technique, a large difference in phytochemical composition and biological activity may be observed. It means that it is important to establish standardized cultivation, extraction, phytochemical fingerprinting and quality control techniques based on such approaches as HPLC, LC–MS and GC–MS [51–55]. Despite the availability of many in vitro and in vivo studies, proving the presence of many biological properties, it is necessary to conduct clinical trials in order to confirm its efficacy, determine dose range, safety profile, pharmacokinetics and herb-drug interactions [56–57]. The rich collection of bioactive substances found in *Mesua ferrea* represents many valuable opportunities for application in the pharmaceutical field. Modern drug delivery systems including nanoparticles, nanogels, liposomes, polymeric micelles, and phytopharmaceuticals are promising tools for improving the solubility, stability, bioavailability, and delivery of the bioactive compounds of the medicinal plant. In addition, the investigation of possible synergistic effects of xanthones, coumarins, flavonoids, and phenolic compounds may allow the creation of new multi-target drugs for treatment of inflammatory diseases, microbe-induced infections, metabolic disorders, and tumors [58–61]. Moreover, conservation and sustainable use of *M. ferrea* should be taken into consideration owing to increasing commercial interest and habitat destruction. The conservation methods should include sustainable harvesting, cultivation, germplasm conservation, tissue culture techniques, and involvement of communities in order to conserve the plant and genetic diversity. Combination of traditional ethnomedicinal knowledge and modern scientific studies will promote the sustainable development of herbal drugs made from *M. ferrea* while ensuring biodiversity conservation and sustainable resource supply [62–63].

8. CONCLUSION

Mesua ferrea L. is a medically important plant with a great significance for traditional medicine, including Ayurvedic, Siddha, Unani, and folk medicine. Different parts of the plant, such as the flowers, stamens, bark, leaves, seeds, and seed oil, have been used to treat gastrointestinal diseases, inflammation, respiratory tract diseases, skin infections, wounds, and hemorrhages. Modern phytochemical studies have revealed a variety of different bioactive substances, including xanthones, coumarins, flavonoids, phenolic substances, terpenoids, and essential oils. Experiments carried out have indicated that *M. ferrea* is associated with antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, anticancer, analgesic, and wound-healing activity among others. These findings have provided scientific backing to various traditional medical uses of the plant. Even though the above findings indicate the high pharmaceutical potential of the plant, a majority of the existing information on it comes from in vitro and pre-clinical experiments. More importantly, the variation in phytochemicals and failure to conduct long-term safety assessment have contributed to the lack of clinically relevant data on *M. ferrea*. Future research needs to focus on comprehensive phytochemical analysis, standardization of herb preparations, mechanism of action, pharmacokinetic, toxicity testing, and clinical trials in order to establish the efficacy and safety of *M. ferrea*–based medicines. In addition, application of advanced drug delivery systems and cultivation strategies, together with conservation measures, can help develop effective phytopharmaceutical products. In conclusion, *Mesua ferrea* provides a good source of therapeutic substances with wide application in contemporary medicine.

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