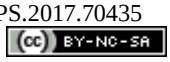
Journal of Applied Pharmaceutical Science Vol. 7 (04), pp. 242-251, April, 2017
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2017.70435
ISSN 2231-3354 

Ethnobotanical and Phytopharmacological attributes of *Mesua ferrea*: A mini review

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ARTICLE INFO

Article history:
Received on: 23/07/2016
Accepted on: 18/12/2016
Available online: 30/04/2017

Keywords:
Mesua ferrea, guttiferae, anticancer, antioxidant, anti-inflammatory, standardised extract.

ABSTRACT

Members of guttiferae family are widely distributed in the tropical areas of the world, especially Asian countries and are traditionally used by the local people for the treatment of various ailments ranging from headache to cancer. *Mesua ferrea* L. is an important member of this family, which has been shown to possess multifactorial pharmacological activities. This review highlights the traditional uses, phytochemical profiling and proven pharmacological attributes of different parts of *M. ferrea*. Almost every part of the plant is reported to have beneficial medicinal properties that can help to fight against different aliments. However, further studies are still required to explore the molecular targets responsible for the observed pharmacological activities and to test the efficacy of isolated compounds or standardized extracts in properly designed experiments. In addition, long term toxicity studies are also required to establish the safety profile of isolated compounds/standardised extracts before the commencement of clinical trials.

INTRODUCTION

The guttiferae family is a rich source of secondary metabolites and is blessed with a variety of medicinal properties. It is comprised of 47 genera with more than 100 species. The well-known genera of this family are *Cratoxylum*, *Hypericum*, *Garcinia*, *Mesua*, and *Vismia* and are widely distributed in the tropical Asia, Africa, Brazil, New Caledonia and Polynesia (Gontijo *et al*., 2012; Piccinelli *et al*., 2005).

Traditionally various species of *Mesua* are used by the inhabitants of Asian countries for the treatment of a variety of ailments including asthma, cough, dyspepsia, fever, itchiness, nausea and renal diseases. Several pharmacological attributes of *Mesua* species such as antioxidant, antimicrobial, antiviral, antitumor and immunomodulatory have already been proved (Teh *et al*., 2012; Asif *et al* 2016).

In the recent years, plenty of research has been conducted to explore the phytochemical composition and pharmacological activities of crude extracts and isolated compounds obtained from different parts of *Mesua ferrea*, therefore, this review article was designed to highlight the recent advancement in the areas of phytochemical characterization and pharmacological profiling of this medicinally important tree.

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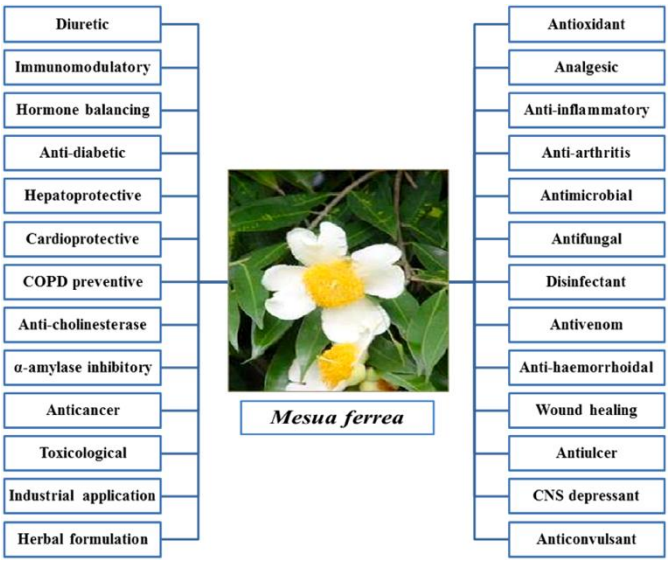

Fig. 1: Brief overview of *Mesua ferra*.

MATERIAL AND METHODS

The information on *Mesua ferrea* was collected from the literature available in the books on medicinal plants and the scientific databases like PubMed, Google Scholar, Springer, and ScienceDirect. Different combination of keywords i.e., "*Mesua*", "*Mesua ferrea*", "Pharmacological", "Anticancer", "Antioxidant', "Review", Phytopharmacological" and "Phytochemistry" were applied to retrieve information available on the topic. The references of selected articles were also screened manually for additional studies. We also searched key journals which included BMC Complementary and Alternative Medicine, Fitoterapia, Journal of Ethnopharmacology, International Journal of Immunopharmacology, Phytomedicine, Phytochemistry, Phytotherapy Research and Tetrahedron to find some relevant information about the topic.

PLANT DESCRIPTION

Mesua ferrea is an evergreen medium to large-sized ornamental tree that is distributed in most of Asian countries including Burma, Cambodia, Indochina region, Malaysia, Myanmar, Nepal (southern), Philippines, Sri Lanka, Sumatra and Thailand. Young leaves are reddish yellow in colour while mature leaves are blue grey to dark green in appearance and are approximately 7-15 cm long. Flowers are large in size, have four white petals containing numerous yellow coloured stamens in the centre and are fragrant. Fruits are often beaked, lightly woody in appearance containing 1-4 seeds. Bark is reddish brown in colour. Flower, fruit, seeds and leaves of this plant are edible. Flowers are eaten in Thailand by the local people for the cure of a variety of disorders. Ripe fruits have chestnut like taste when eaten. Seeds are edible when cooked but have an unpleasant taste. The leaves are edible in raw form and have a sour astringent taste (Lim, 2012).

Botanical names: *Mesua ferrea* L., *Calophyllum nagassarium* Burm. f., *Mesua nagassarium* (Burm. f.) Kosterm.

English name: Ceylon Ironwood, Cobra's Saffron, Indian Rose Chestnut, Mesua.

Local name: Penaga Lilin, Penage Putih, Tapis (Malaysian), Tagayasan (Japanese), Croco Di Cobra (Italian), Nagasari Gede, Nagasari (Indonesian), Nagakesar (Indian), Nagasbaum (German), Arbe De Fer (Franch), Ijzerhout (Dutch), Tie Li Mu (Chinese), Nageshwar (Bangladeshi), Narae-Kaisar (Arabic).

Taxonomical order: Kingdom - Plantae; Phylum - Tracheophyta; Class - Magnoliopsida; Order - Malpighiales; Family - Calophyllaceae / Guttiferae; Genus – *Mesua*; Species – *Mesua ferrea* L.

Parts used: Bark, flowers, fruits, leaves, root, stamens and seeds.

TRADITIONAL USES

Various parts of *M. ferrea* are used either alone or in combination with other medicinal herbs by the inhabitants of India, Pakistan, Indochina, Malaysia and Thailand for the treatment of various disorders (Ratnamhin *et al*., 2011). Traditionally, *M. ferrea* is used as an antipyretic, antimicrobial, anticancer, carminative, cardiotonic, diuretic, and expectorant (Chahar *et al*., 2012; Rahman *et al*. 2008). In Malaysia, poultice of seed oils or crushed kernels are used for wound healing while the flowers and root decoction is used by women after child birth (Lim, 2012). In Thailand, seeds are used as aroma, cardiotonic, expectorant and wound healer (Wetwitayaklung *et al*., 2008). In India, it is used in a variety of Ayurvedic formulations (Brahma Ramayana and Chyawanprash) as an immunity booster agent. It is also used as a herbal supplement for the treatment of a variety of diseases including bleeding piles, cough, cardiovascular disorders, dysentery, excessive thirst, headache, hiccup, itching, sweating, scabies, skin problems, small tumors and vomiting respectively (Joseph *et al*., 2010; Lim, 2012). Dried flowers have anti-inflammatory and stomachic properties (Lim, 2012). Bark is traditionally used for the treatment of cough, dysentery, sore throat and vomiting (Keawsa-ard and Kongtaweelert, 2012). Powder of dried fruits and leaves mixed with ghee is used by the local communities of Bangladesh to get relief from burning sensation in hands and feet, joint pain and cold (Sharkar *et al*., 2013). *M. ferrea* is an important ingredient of the Indian Siddha medicine (*Yelaathi Churanam*) which is used internally to treat chancres, leprosy and ulcers. It is prescribed in combination with butter and sugar in Indian system of herbal medicine for the treatment of bleeding piles. Another herbal formulation (*Jawarish-e-Naaremushk*) is prescribed in hepatic and intestinal problems (Khare, 2004). An Ayurvedic formulation *(Maharisi amrit kalash-4*) containing *M. ferrea* is traditionally used to treat cancer in India and neighbouring countries (Saxena *et al*., 2008; Asif *et al*., 2016).

Similarly, *M. ferrea* is also used for the treatment of inflammation and other cancer associated disorders (Rai *et al*., 2000). Another polyhebral formulation named *Kanakasava* containing *M. ferrea* is traditionally used as an anti-asthmatic agent in India (Arora and Ansari, 2014).

PHYTOCHEMICAL STUDIES

A substantial amount of efforts has been invested to identify and isolate different types of phytoconstituents from various parts of *M. ferrea.* In general, it is reported to contain coumarins, xanthones, terpenoids and sterol type of phytochemicals (Keawsa-ard *et al*., 2015). An extensive research is undergoing on the stem, heartwood, roots, stem bark and oleo-gum resin of *M. ferrea* and till date a large number of phytochemicals have been isolated and identified. From heartwood mesuaxanthone-A, mesuaxanthone-B, 1,5-dihydroxyxanthone (II), euxanthone 7-methyl ether (IV) and β-sitosterol were isolated by various research groups (Chow and Quon, 1968; Govindachari *et al*., 1967a). Ferrol-A, an alkylcoumarin, was later isolated by Govindachari *et al*. from the trunk bark of *M. ferrea* (Govindachari *et al*., 1967b). Eight different types of xanthones i.e., 2-Hydroxy-, 2-methoxy-, 4-hydroxy-, 1,5-dihydroxy-, 1,7-dihydroxy-, 1-hydroxy-5-methoxy-, 1-hydroxy-7-methoxy-, 3-hydroxy-4-methoxy- and 1,5,6-trihydroxyxanthone were isolated by Gunasekera and colleagues from the timber (Gunasekera *et al*., 1975). Ferrxanthone, which was chemically characterized as 1,3-dimethoxy-5,6-dihydroxyxanthone was isolated from the heartwood (Walia and Mukerjee, 1984). Choudhury and colleagues analysed the essential oils contents of the bark, leaves, buds, and flowers (full bloom) of *M. ferrea* using high resolution GC and HRGC/MS techniques. The bark oil was found to be mainly composed of (E)-α-bisabolene (31.3%) and α-selinene (12.2%), while the major oils contents of tender and mature leaves were found to be α-copaene (19.3% and 9.9%) and β-caryophyllene (18.8% and 26.0%) respectively. α-copaene (28.7% and 20.2%) and germacrene D (19.0% and 16.1%) were found to be the major oil components of the bud and flowers (Choudhury *et al*., 1998).

Another research group isolated betulinic acid, (-) epicatechin, 1,6-dihydroxyxanthone, pyranojacareubin along with two novel compounds i.e., mesuabixanthone-A and mesuabixanthone-B from the stem bark of *M. ferrea* (Singh *et al*., 1993). Later, mesuferrol-A and -B, (-) epicatechin, 1,7-dihydroxy- and 5-hydroxy-1-methoxyxanthone were isolated from the stem bark by Iinuma and colleagues (Iinuma *et al*., 2004). Mesuaferrin-A and -B, caloxanthone C, 1,8-dihydro-3-methoxy-6-methylanthraquinone, β-sitosterol, friedelin and betulinic acid have been recently isolated from the root bark by one research group (Teh *et al*., 2011). Similarly, from the stems and stem bark mixture of amyrins (α and β), β-sitosterol, calophyllin-B, dehydrocycloguanandin, euxanthone, euxanthone 7-methyl ether (IV), ferruol A, ferrxanthone, friedelin, lupeol, mesuaxanthone-A and mesuaxanthone-B, 1,5-dihydroxyxanthone (II), stigmasterol, jacareubin and 6-desoxy jacareubin have been isolated by different research groups (Gunasekera *et al*., 1975, Keawsa-ard *et al*., 2015; Lim, 2012). A new xanthone, mesuaferrin C, along with macluraxanthone, caloxanthone C, β-sitosterol, friedelin and betulinic acid was isolated from the root bark by another research group (Ee *et al*., 2012). Likewise, Teh and colleagues isolated seven xanthones namely, caloxanthone C, mesuaferrin-A, -B and -C, macluraxanthone, 1,5-dihydroxyxanthone and tovopyrifolin C from the root bark of *M. ferrea* (Teh *et al*., 2013). HPLC analysis of methanol and chloroform extracts of *M. ferrea* reveals the presence of a variety of natural antioxidants namely coumaric acid, ellagic acid, gallic acid, kaempferol, myricetin, rutin, quercetin,

Table 1: Highlights of phytochemical composition of selected parts of *M. ferrea*.

Plant part	Compounds	References
Heartwood	Mesuaxanthone-A, mesuaxanthone-B	(Govindachari *et al*. 1967)
	1,5-dihydroxyxanthone (II), euxanthone 7-methyl ether (IV), β-sitosterol	(Chow and Quon 1968)
	Ferrxanthone (1,3-dimethoxy-5,6-dihydroxyxanthone)	(Walia and Mukerjee 1984)
Trunk bark	Ferrol-A	(Govindachari *et al*. 1967)
Timber	2-Hydroxy-, 2-methoxy-, 4-hydroxy-, 1,5-dihydroxy-, 1,7-dihydroxy-, 1-hydroxy-5-methoxy-, 1-hydroxy-7-methoxy-, 3-hydroxy-4-methoxy- and 1,5,6-trihydroxyxanthone	(Gunasekera *et al*. 1975)
Bark	(E)-α-bisabolene and α-selinene	(Choudhury *et al*. 1998)
Stem bark	Mesuferrol-A and -B, (-) epicatechin, 1,7-dihydroxy- and 5-hydroxy-1-methoxyxanthone	(Iinuma *et al*. 2004)
	Friedelin, 3β friedelanol, lupeol, 3-oxo-betulin and spinasterol	(Islam *et al*. 2014)
----	Calophyllin-B, dehydrocycloguanandin, euxanthone, mesuaxanthone-A, mesuaxanthone-B, jacareubin, 6-desoxy jacareubin	(Gunasekera *et al*. 1975)
Stems	Amyrin (α and β), β-sitosterol, friedelin, lupeol,	(Keawsa-ard *et al*. 2015)
Root bark	Mesuaferrin-A and -B, caloxanthone C, 1,8-dihydro-3-methoxy-6- methylanthraquinone, β-sitosterol, friedelin and betulinic acid	(Teh *et al*. 2011)
	Mesuaferrin C, macluraxanthone, caloxanthone C, β-sitosterol, friedelin and betulinic	(Ee *et al*. 2012)
	Caloxanthone C, mesuaferrin-A, -B and -C, macluraxanthone, 1,5-dihydroxyxanthone and tovopyrifolin C	(Teh *et al*. 2013)
----	Coumaric acid, ellagic acid, gallic acid, kaempferol, myricetin, rutin, quercetin, and vanillic acid	(Rajesh *et al*. 2013).

---- shows parts of plant used for isolation not mentioned in the study.

and vanillic acid (Rajesh *et al*., 2013). Preliminary phytochemical screening of ethanol extract of *M. ferrea* leaves showed that it contains 14.72 mg/g of dry weight extract of total phenolic contents, 11.25 mg/g of dry weight extract of total tannin contents, 30 mg/g of dry weight extract of total flavonoid contents (rutin equivalent) and 3.60 mg/g of dry weight extract of total flavonol contents (rutin equivalent) respectively (Sahu Alakh *et al*., 2013b). Similarly, another recent study reports the presence of friedelin, 3β friedelanol, lupeol, 3-oxo-betulin and spinasterol in the stem bark of *M. nagassarium* (Islam *et al*., 2014). Two essential oils, namely (E)-α-bisabolene and α-selinene were also identified in the bark oil of *M. ferrea* (Alakh *et al*., 2014). Table 1 highlights the phytochemical composition of some selected parts of *M. ferrea.* From oleo-gum resin, isoledene, a sesquiterpene, has been identified by Asif and colleagues in their recent study (Asif *et al*., 2016).

PHARMACOLOGICAL STUDIES

Recent scientific studies have highlighted the medicinal importance of different parts of *M. ferrea* against a variety of human ailments.

Antioxidant activity

70% ethanol extract of *M. ferrea* leaves have been shown to have better antioxidant activity in DPPH, superoxide and hydroxyl radical scavenging assays as compared with other solvent extracts i.e., hexane, ethyl acetate and methanol. However, the antioxidant activity of 70% ethanol extract was found to be lower when compared with standard antioxidant agent (ascorbic acid) (Prasad *et al*., 2012). Another study conducted by Sahu Alakh and colleagues showed modest antioxidant activity of methanol extract of flowers in DPPH free radical (IC_{50} = 300 µg/mL), superoxide (IC_{50} = 273.56 µg/mL), and hydrogen peroxide (IC_{50} = 21.70 µg/mL) scavenging assays (Sahu Alakh *et al*., 2013a). Similarly, in another study polar extract (methanol) of *M. ferrea* roots was found to be more active as compared with less polar and non-polar extracts (Teh *et al*., 2013). Essential oils obtained from the leaves showed moderate antioxidant activity in the DPPH assay with an IC_{50} value of 31.67 mg/mL (Keawsa-ard and Kongtaweelert, 2012). Another study reported the promising antioxidant activities of water and hot water extracts of *M. ferrea* flowers in the DPPH scavenging assay and effects were shown to be even stronger than standard agent i.e., butylated hydroxytoulene (BHT) with an EC_{50} values of 7.49 and 6.95 µg/mL respectively (Makchuchit *et al*., 2010). Chloroform and methanol extracts of *M. ferrea* stem bark have been shown to have good antioxidant activity in the *in vitro* antioxidant models. Both extracts protected erythrocytes, haemoglobin and DNA against oxidative stress-induced damage. The methanol extract showed strong activity (> 90%) as compared with chloroform extract (> 70% < 90%). This was suggested to be due to higher total phenolic and flavonoid contents of methanol extract (Rajesh *et al*., 2013). In another recent study, n-hexane extract of *M. ferrea* stamens has been reported to possess good free radical scavenging activity with an IC_{50} value of 66.3 µg/mL. However, one major drawback of this study was that no standard drug was used to compare the efficacy of active stamen extract (Barbade and Datar, 2015).

Analgesic activity

In an acetic acid-induced visceral pain mouse model, non-polar (n-hexane) fraction of *M. ferrea* leaf extract showed better antinociceptive activity in terms of percent reduction in writhing response as compared with polar fractions (methanol and ethyl acetate) (Hassan *et al*., 2006; Lim, 2012).

Anti-inflammatory and anti-arthritis activities

Anti-arthritis activities of *M. ferrea* seed extracts were evaluated in two different *in vivo* models i.e., Formaldehyde-induced and Complete Freund's Adjuvant (CFA) -induced arthritis in rats. In formaldehyde-induced model, significant reduction in the swelling of formaldehyde injected paw was observed in the seed extract treated rats compared to the control animals. Similarly, in CFA model, reduction in the arthritis lesions as noted by swelling volume in CFA injected paw was observed in *M. ferrea* seed extracts treated animals. An increase in body weight of *M. ferrea* seed extract treated rats was also observed, while in control CFA injected rats a decrease in body weight was observed at the end of treatment (Jalalpure *et al*., 2011).

In vivo anti-inflammatory activities of xanthones i.e., mesuaxanthone-A, mesuaxanthone-B, calophyllin-B, dehydrocycloguanandin, euxanthone, jacareubin and 6-desoxy jacareubin isolated from *M. ferrea* were studied using three different rat inflammation models. All the xanthones were revealed to have promising anti-inflammatory activities in carrageenan-induced paw oedema, cotton pellet granuloma and granuloma pouch inflammatory models (Gopalakrishnan *et al*. 1980). In addition, an ayurvedic formulation (*Shirishavaleha*) containing *M. ferrea* in combination with other herbs has been shown to inhibit oedema development in carrageenan-induced paw oedema model (Yadav *et al*., 2010). Similarly, another recent study, reports the promising anti-inflammatory activity of 80% ethanol extract of stem bark in a variety of *in vitro* bioassays. The finding of the study revealed that 80% ethanol extract at the concentration of 100, 200 and 500 µg/mL has stronger anti-inflammatory activity in all the *in vitro* bioassays as compared with standard drug i.e., Indomethacin (100 µg/mL) (Ranganathaiah *et al*., 2016).

Antimicrobial and antifungal activities

Antimicrobial activities of different parts of *M. ferrea* have been highlighted by various scientific studies. Coumarins (4-alkyl and 4-phenyl 5,7-dihydroxycoumarins) isolated from the blossoms showed selective antibacterial activities towards resistant strains of gram positive bacteria (Verotta *et al*., 2004). Methanol extract of the leaves has been shown to possess broad spectrum antibacterial activities against *Bacillus species, Escherichia coli,*

Staphylococcus aureus, *Shigella*, *Salmonella* and *Lactobacillus arabinosus* bacterial strains respectively (Mazumder *et al*., 2003). In addition to *in vitro* antibacterial activity, methanol extract of leaves has shown profound protective effects in the mice against *Salmonella typhimurium* infection (Mazumder *et al*., 2004). Narender Prasad and colleagues also reported that methanol extract of *M. ferrea* leaves at the concentration of 1200 µg/mL has reasonable antibacterial activity (Narender Prasad *et al*., 2011).

Similarly, polar extract (chloroform) of stem bark has been reported to exert strong antibacterial activity against gram positive *Streptococcus aureus* as well as gram negative *Escherichia coli* bacterial strains (Ali *et al*., 2004; Lim, 2012). Likewise, another research group tested the antibacterial efficacy of flower extract against five different strains of *Salmonella* spp and was found to be active towards all the strains at the concentration of 50 µg. In addition, flower extract also showed promising *in vivo* antibacterial activity in *S. Typhimurium* NCTC 74 challenged mice and caused a statistically significant reduction in viable count of bacterial strain in liver, spleen and heart blood at the dose of 2-4 mg/mouse (Mazumder *et al*., 2005). Methanol extract of *M. ferrea* seeds also showed fungicidal activities against different strains of fungus, including C*andida albicans*, *Trichosporon beigelii*, *Mucor hiemalis* and different species of *Aspergillus* (Lim, 2012). Likewise, a recent study reports the antibacterial activity of *M. ferrea* seed oil epoxy resin against *Klebsiella pneumoniae* (gram negative) and Staphylococcus aureus (gram positive) strains of bacteria (Das *et al*., 2014). A gel formulation containing six different herbs, including *M. ferrea* was screened for its potential to prevent skin infections associated with the resistant strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Corynebacterium* spp. Within 2 hours of contact, 100% bactericidal efficacy was observed in herbal gel treated animal group while complete eradication of infection with no rough or dry skin remnants was observed after 20 days of treatment. Moreover, herbal gel formulation showed no toxicity in skin toxicity tests (Deshmukh *et al*., 2009).

M. ferrea bio-oils extracted from deoiled cakes through the process of pyrolysis has been reported to have broad range of antimicrobial activities against a variety of bacterial and fungal strains, which gives a hint about possible pharmaceutical application of bio-oils (Phukan *et al*., 2013).

Water disinfectant properties

M. ferrea seed kernel oil (NSKO) has been reported to have water disinfectant properties and can be used as natural disinfectant alternative to chlorine. The study showed that kernel oil has remarkable disinfection potential and the kinetic studies suggested that NSKO fitted first-order model with a k value of -0.040 (Adewale *et al*., 2011).

Antivenom activity

Water extract prepared from the leaves of *M. ferrea* has been shown to have considerable (40%) anti-venom activity against *Heterometrus laoticus* (scorpion) venom in the *in vitro* chick embryo fibroblast cell lysis model (Uawonggul *et al*., 2006).

Diuretic properties

Polyherbal combination (*Draksharishta-T and –M*) and its marketed formulation comprising of stamens of *M. ferrea* has been shown to induce significant diuretic, kaliuretic and natriuretic effects in the albino rats at the dose of 2.0 mL/Kg over a period of 5 hours compared to the control group (Tiwari and Patel, 2011).

Anti-hemorrhoid activities

A polyhedral formulation containing *M. ferrea* was evaluated for its efficacy to treat bleeding piles in a preliminary clinical study using 22 subjects. Finding of the study revealed that out of 22 subjects, 16 patients had improvement in terms of reduced bleeding with no noticeable adverse effects (Paranjpe *et al*., 2000). Another recent study also highlights the efficacy of standardized herbal preparations (Daflon® and Roidosanal®) containing *M. ferrea* in terms of improvement of ano-rectal conditions in Grade I and II patients. Both preparations reduced the bleeding and pain in the hemorrhoid patients (Aggrawal *et al*., 2014).

Wound healing activity

Tannins isolated from the ethanol extract of aerial parts of *M. ferrea* have been shown to have promising wound healing activity in excision and incision wound healing rat models when applied in the form of an ointment. Increased epithelialization and wound contraction were proposed to be the possible mechanisms responsible for the wound healing activity of aerial parts (Choudhary, 2012).

Antiulcer activity

Xanthones i.e., jacareubin and 6-desoxy jacareubin obtained from *M. ferrea* prevented ulceration in the rats as compared with control groups where extensive ulceration, perforations and haemorrhagic spots were observed. On the other hand, in xanthones treated rats only hyperaemia and occasional haemorrhage spots were noticed (Gopalakrishnan *et al*., 1980; Lim, 2012).

Central nervous system (CNS) depressant and anticonvulsant activities

CNS depressant effects of xanthones (mesuaxanthone-A, mesuaxanthone-B, calophyllin-B, dehydrocycloguanandin, euxanthone, jacareubin and 6-desoxy jacareubin) obtained from *M. ferrea* were evaluated in both mouse and rat models. Typical CNS depressant effects, i.e., ptosis, sedation, loss of muscle tone and reduced spontaneous motor activity were observed in the xanthones treated animals respectively. Similarly, potentiation of anaesthetic effects of ether and phenobarbitone-induced sleeping time was also observed in the xanthone treated animals (Gopalakrishnan *et al*., 1980; Lim, 2012). Likewise, another research group showed that *M. ferrea* flower extract caused a

significant increase in the pentobarbital-induced sleeping time in mouse model (Chakma *et al*., 2006). Ethanol extract of *M. ferrea* also exhibited anticonvulsant effects in the mice when tested in maximum electroshock seizures (MES) assay. The extract was revealed to reduce the duration of hind limb tonic extensions in a concentration-dependent manner (Lim, 2012).

Immunomodulatory and hormone balancing activities

Effect of mesuol isolated from the seed oil of *M. ferrea* on the immune system was studied using both humoral and cellular immune models. In humoral immune response assay, mesuol resulted in a significant increase in the antibody titer values in the rats, which were previously antibody challenged and immunized by the introduction of sheep red blood cells (SRBCs) followed by immunosuppression by cyclophosphamide. Similarly, mesuol also elicited cellular immune responses in cyclophosphamide-induced immunosuppressant rats due to the stimulation of T-cells. An increase in the thickness of foot pad was observed in mesuol treated rats when exposed to SRBCs (used as an irritant) (Chahar *et al*., 2012). In addition, flower extract of *M. ferrea* has also been shown to possess estrogen and progesterone-like effects which were proposed to be helpful in the correction of hormonal imbalance during menstrual disorders (Lim, 2012).

Antidiabetic activity

Methanol extract of *M. ferrea* leaves has been shown to have promising antidiabetic activity in streptozotocin-induced diabetic rats. Extract was suggested to increase the secretion of insulin from pancreatic β-cells. In addition to the insulin secretory effect, the leaf extract also reduced the blood glucose levels and normalized the body weight in the diabetic rats compared to the untreated rats. *In vitro* studies using mouse insulinoma pancreatic β-cell line (MIN6 β-cells) showed a dose-dependent increase in the levels of insulin as a result of methanol extract treatment and the effects were more prominent in the hyperglycemic conditions compared to normal cell culture conditions (Balekari and Veeresham, 2015).

Hepatoprotective activities

In vivo hepatoprotective effects of methanol extract of *M. ferrea* flowers were evaluated in *Staphylococcus aureus* inoculated male Wistar rats. One week treatment with 50, 100 and 200 mg/Kg of methanol extract showed significant improvement in the levels of liver enzymes, namely CAT, SOD, GPx, and GR with concomitant decrease in the levels of AAT and AST enzymes. Profound effects were observed at the dose of 100 mg/Kg of methanol extract (Garg *et al*., 2009). In another study, hepatoprotective effects of different extracts of stamens were evaluated using *in vitro* carbon tetrachloride-induced oxidative stress liver slice culture model. Among different extracts, n-hexane and ethanol extracts of stamens protected cultured liver slice cells against carbon tetrachloride-induced oxidative stress.

The active extracts also showed promising antioxidant activities in different *in vitro* free radical scavenging models i.e., DPPH, $ABTS^{+}$, SOD and NO respectively (Rajopadhye and Upadhye, 2012).

Cardioprotective activities

A polyherbal formulation (*Ashwagandharishta*) and its marketed preparation containing stamens of *M. ferrea* have been shown to protect against isoproterenol-induced myocardial infarction in the albino rat model. Treatment with herbal formulation also significantly prevented the isoproterenol-induced adverse changes in the levels of serum marker enzymes such as alanine aminotransferase, aspartate aminotransferase, creatine kinase and lactate dehydrogenase with concomitant improvement in the serum lipid profile. In addition, herbal formulation pre-treated animals also showed significant increase in glutathione (GSH) and reduction in malondialdehyde (MDA) contents. It was proposed that the cardioprotective activity of herbal formulation may be due to increase in *in vivo* antioxidants levels such as GSH and inhibition of lipid peroxidation of cardiac membranes in the treated rats (Tiwari and Patel, 2012).

Protection against experimentally-induced Chronic Obstructive Pulmonary Disease (COPD)

A study conducted in the rats showed that herbal formulation (Bresol®) comprising of *M. ferrea* flowers has protective effects against cigarette smoke-induced COPD in rats. The rats treated with 250 and 500 mg/Kg for five weeks showed improvement in terms of reduction in tracheal inflammation, decrease in TNF-α and total protein levels in the bronchoalveolar lavage fluid and maintained the normal cellular architecture of the trachea and lungs (Rafiq *et al*., 2013).

Anticholinesterase and α-amylase inhibitory activities

Teh and colleagues in their recent study highlighted that the secondary metabolites isolated from different species of *Mesua* including *M. ferrea* have acetylcholinesterase inhibitory activities and have potential to be used in Alzheimer's disease (Teh *et al*., 2016). *In vitro* α-amylase inhibitory assay conducted by Chakrabarti and team revealed that *M. ferrea* extract has moderate α-amylase inhibitory activity with an IC_{50} value of 146.8 µg/mL while standard drug, acarbose, showed strong α-amylase inhibitory activity with an IC_{50} value of 14.24 µg/mL (Chakrabarti *et al*., 2014).

Anticancer activities

Considerable amount of work has been done to explore the anticancer potential of different parts of *M. ferrea*. Variety of crude extracts and pure compounds have shown promising anticancer activities in the preliminary *in vitro* anticancer screening assays. Volatile oils rich methanol extract of *M. ferrea* flowers showed strong cytotoxic activities against T-lymphocyte leukaemia cells with an IC_{50} value of 12.5 µg/mL (Nordin *et al*., 2004). Ethanol extract of *M. ferrea* flower was tested against three human cancer cell lines viz., CL-6 (cholangiocarcinoma), Hep-2 (human laryngeal cancer) and Hep G2 (human hepatocarcinoma) cell lines. The finding of the study showed that ethanol extract was

selectively toxic towards Hep-2 cell line with an IC_{50} value of 19.22 µg/mL (Mahavorasirikul *et al*., 2010). Essential oils isolated from *M. ferrea* leaves have also been shown to possess cytotoxic activities against three cancer cell lines viz., KB (oral carcinoma), MCF-7 (breast adenocarcinoma) and NCI-H187 (metastatic lung carcinoma) and the order of cytotoxicity was revealed to be MCF-7 > NCI-H187 > KB respectively. While no toxic effects were observed against African green monkey normal kidney cells (Vero) (Keawsa-ard and Kongtaweelert, 2012). n-hexane and dichloromethane extracts of *M. ferrea* roots have been reported to possess broad spectrum cytotoxic activities against a panel of human cancer cell lines. The order of sensitivity of cancer cells towards n-hexane extract was Hep G2 (human hepatocellular liver carcinoma) > HeLa (human cervical cells) > NCI-H23 (human lung adenocarcinoma) > SNU-1 (human gastric carcinoma) > IMR-32 (human neuroblastoma) > LS-174T (human colorectal adenocarcinoma) > K-562 (human erythroleukemia cells) > SK-MEL-28 (human malignant melanoma cells) > Raji (human B lymphocyte). On the other hand, order of sensitivity of cancer cells towards the dichloromethane extract was Hep G2 (human hepatocellular liver carcinoma) > K-562 (human erythroleukemia cells) > NCI-H23 (human lung adenocarcinoma) > IMR-32 (human neuroblastoma) > SNU-1 (human gastric carcinoma) > LS-174T (human colorectal adenocarcinoma) > SK-MEL-28 (human malignant melanoma cells) > Raji (human B lymphocyte) respectively (Teh *et al*., 2013). In another study, n-hexane and dichloromethane extract of *M. ferrea* flowers has also been reported to have cytotoxic effects against CCRF-CEM (human lymphoblast leukaemia cell line). In addition both extracts were also shown to reduce resistance against doxorubicin in resistant CEM/ADR5000 cells by modulating P-glycoprotein function (Noysang *et al*., 2014). Another recent study also reports the anticancer activities of *M. ferrea* stem extracts and isolated compounds against three cancer cell lines i.e., KB (oral carcinoma), MCF-7 (breast adenocarcinoma) and NCI-H187 (metastatic lung carcinoma). Among different extracts, n-hexane was found to be inactive in terms of induction of cytotoxicity against all the three cancer cell lines, while dichloromethane and methanol extract was found to be more active against KB than rest of two cell lines. Interestingly, isolated compounds, i.e., β-sitosterol, friedelin and mixture of α- and β-amyrin were either found to be less active or even inactive in terms of cytotoxic effects as compared with active crude extracts. It was proposed in the study that multi-components are responsible for the anticancer properties of *M. ferrea* stamen extracts (Keawsa-ard *et al*., 2015). Another recent study conducted by Asif *et al* shows that oleo-gum resin extract has broad spectrum anticancer activities towards human colon carcinoma cell lines.

Table 2: Highlights of anticancer activities of *M. ferrea*.

Part used	Model/Cell line	Extract/ Compound	Findings	References
Flowers	T-lymphocyte leukaemia cells	Methanol	Inhibited the growth of leukaemia cells with an IC50 value of 12.5 µg/mL.	(Nordin *et al.* 2004)
Flowers	CL-6, HepG2, Hep-2	Ethanol	Ethanol extract showed selective cytotoxicity towards Hep-2 cells with an IC_{50} value of 19.22 µg/mL compared with other two cell lines where IC_{50} was found to be above 40 µg/mL	(Mahavorasirikul *et al*. 2010)
Leaves	KB, MCF-7, NCI-H187, Vero	Essential oils	Essential oils exerted strong cytotoxic effects towards all the cancer cell line. Strongest cytotoxic effects were observed in MCF-7 with an IC_{50} value of 16.19 µg/mL. No cytotoxic effects were observed in normal Vero cells.	(Keawsaard and Kongtaweelert 2012)
Roots	HeLa, Hep G2, IMR-32, K562, LS-174T, NCI-H23, SNU-1, SK-MEL-28, Raji	n-hexane	The order of cytotoxic susceptibility of cell lines was Hep-G2(11.45) > Hela (13.75) > NCI-H23 (16.67) > SNU-1 (17.50) > IMR-32 (20.30) > LS-174T (21.88) > K562 (21.88) > SK-MEL-28 (43.75) > Raji (inactive)	(Teh *et al*. 2013)
		Dichloromethane	The order of cytotoxic susceptibility of cell lines was Hep-G2(8.85) > K562 (11.45) > NCI-H23 (13.75) > IMR-32 (15.64) > SNU-1 (22.91) > LS-174T (41.67) > SK-MEL-28 (43.75) > Raji (inactive) > HeLa (inactive)	
Flowers	CCRF-CEM, CEM/ADR5000, PBCECs	n-hexane	n-hexane extract exhibited 85% growth inhibitory effects against CCRF-CEM (leukemic cells) at the concentration of 10 µg/mL, while dichloromethane extract inhibited 98% growth of CCRF-CEM cells at the concentration of 10 µg/mL. Both extracts also showed activity against doxorubicin resistant CEM/ADR5000 cells and effects were found to be due to modulation of p-glycoprotein function.	(Noysang *et al*. 2014)
		Dichloromethane		
Stems	KB, MCF-7, NCI-H187, Vero	n-hexane	n-hexane showed no cytotoxic effects against any of the cell lines tested	(Keawsa-ard, Liawruangrath and Kongtaweelert 2015)
		Dichloromethane	The order of cytotoxic susceptibility of cell lines was KB (18.01) > NCI-H187 (18.42) > MCF-7 (28.83) > Vero (nontoxic)	
		Friedelin	Inactive against all the cell lines tested	
		Amyrin (α and β)	Amyrins mixture was only active against MCF-7 with an IC_{50} value of 28.45 µg/mL	
		Lupeol	The order of cytotoxic susceptibility of cell lines was NCI-H187 (21.56) > KB (30.12) > MCF-7 (34.25) > Vero (nontoxic)	
		β-sitosterol	Inactive against all the cell lines tested	
Flowers	Ehrlich ascites carcinoma mice model	Chloroform	Chloroform extract significantly (** $p < 0.001$) reduced the tumor cells (54.8% tumor growth inhibition) in treated mice	(Rana *et al*. 2004)
		Ethyl acetate	Percent inhibition of tumor growth in treated rats was 41.7%	
Oleo-gum resin	HCT 116, HT29, LIM1215	n-hexnae	Isoledene rich sub-fraction induced apoptosis in HCT 116 cells by modulating the activity of multiple proteins	(Asif *et al*., 2016)

Values shown in brackets are expressed in µg/mL

The oleo-gum resin extract was shown to induce apoptosis in HCT 116 cells through ROS-mediated apoptotic pathways. Interestingly, oleo-gum resin extract did not induce toxicity in the normal colon cells (CCD-18co) (Asif *et al*., 2016) Similarly, Asif *et al*. in their recent study showed that terpenes rich stem bark extract has broad spectrum anticancer activities. The order of sensitivity (high to low) of cancer cell lines towards F-3 was HCT 116 > MNK–74 > PC–3 > T-47D > MIA PaCa–2 > HT–29 > PANC–1 > MCF–7 > Capan-1 > EA.hy926 > 3T3-L1 > CCD- 18co respectively (Asif *et al*., 2017). In addition to variety of *in vitro* anticancer studies, there is also one study that reports the *in vivo* efficacy of chloroform and ethyl acetate extract of *M. ferrea* flowers against Ehrlich ascites carcinoma in Swiss albino mice. Percent inhibition of carcinoma in chloroform and ethyl acetate treated animals was 54.8 and 41.7% respectively (Rana *et al*., 2004). Table 2 highlights the anticancer activities of *M. ferrea* against different cancer cell lines.

Toxicological studies

Acute toxicity studies on different extracts of *M. ferrea* were conducted using albino mouse and rat models. In rat model, 5g/Kg doses of three different seed extracts i.e., petroleum ether, ethyl acetate and alcoholic did not provoke any signs of toxicity during the first 24 hours and no mortality in any of the test groups was observed (Jalalpure *et al*., 2011). Similarly, acute toxicity studies of methanol extract of *M. ferrea* flowers were performed in Swiss albino mice using three different doses i.e., 50, 500 and 2000 mg/Kg. In all the treated groups, none of the mice showed any visible signs of toxicity with zero mortality rates. Moreover, there was no differences in haematological and biochemical profiles of *M. ferrea* flowers feed and control mice, respectively (Udayabhanu *et al*., 2014). In another recent study, n-hexane extract of *M. ferrea* stamens has been reported to be safe in the acute toxicity mouse model, however, the doses used and safety level was not mentioned in the study (Barbade and Datar, 2015).

INDUSTRIAL APPLICATIONS

Apart from pharmacological attributes, numerous studies have highlighted the industrial applications of *M. ferrea* seed oils as an alternative biofuel in the diesel and compression ignition engines, in paint industry, as a multi-purpose industrial coating preparation and as biomaterials (nanocomposites etc.). Stamens are used as a fragrant stuffing for cushions and pillows. Wood is considered suitable for all types of heavy construction including railway sleepers, transmission posts, heavy-duty furniture, posts and tool handles (Lim, 2012).

PROPOSED PHARMACEUTICAL APPLICATIONS

Based on scientific studies reported above, we hereby propose that *M. ferrea* has potential to be developed as a herbal pharmaceutical product in the form of topical antibacterial gel/cream, as a standardised extract for internal bleeding disorders i.e., ulcers and hemorrhoids and as a chemopreventive and chemotherapeutic agent respectively. However, further studies are still needed in this aspect.

CONCLUSION

Recent scientific studies have highlighted that *M. ferrea* is a rich source of secondary metabolites which are having multiple health promoting benefits including antioxidant, anti-inflammatory, antimicrobial, anticancer and others. Several studies have recurrently highlighted the antioxidant, antimicrobial and anticancer effects of whole extracts, active fractions and pure compounds isolated from different parts of *M. ferrea*. However, there are some problems which need to be addressed, (i) conclusion of majority of studies are based on preliminary *in vitro* screening assays. Still further research is needed to confirm these activities by employing proper experimental tools. (ii) In majority of the studies no standard marketed drug was used as positive control and where positive control is used the efficacy of the active extract/ compound was not compared. The efficacy of active extract/ compound must be compared with standard drug as well. (iii) None of the study has reported the pharmacokinetic profile of active extract and isolated compounds. Further research is needed in this regard to estimate the feasibility of active samples for commercial drug formulation. (iv) Stamens are most commonly used in the polyherbal formulations, however, efficacy of other parts such as seeds, flowers, stems, bark and oleo-gum resin are also needed to be evaluated for the effective pharmaceutical product development. (v) Only few studies have reported the toxicity profile of selected parts, however, further studies are highly recommended in this regards before commencement of clinical studies. (vi) Standardization of active extracts is highly recommended in order to develop product of uniform composition and biological activity. (vii) Majority of studies did not identify molecular targets responsible for the biological activity; further studies to identify the molecular targets responsible for these medicinal properties especially anticancer, can help in the development of cost-effective and natural remedies against this chronic disorder.

ACKNOWLEDGEMENT

Financial support and sponsorship: Authors would like to acknowledge Universiti Sains Malaysia (USM) for supporting this project through USM research grant (304/PFARMASI/650735/K123) and Institute of Postgraduate Studies Fellowship (P-FD0009/12 (R).

Conflict of Interests: There are no conflicts of interest.

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How to cite this article:

Asif M, Jafari SF, Iqbal Z, Revadigar V, Oon CE, Majid ASA, Majid AMSA. Ethnobotanical and Phytopharmacological attributes of *Mesua ferrea*: A mini review. J App Pharm Sci, 2017; 7 (04): 242-251.