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Anti-cancer, antimicrobial, and antioxidative potentials of *Mesua ferrea* L. and its phytochemical constituents: a review

Adiana Mohamed Adib*, Nurhanan Murni Yunos, Chee Beng Jin

Natural Products Division, Forest Research Institute Malaysia, 52109 Kepong, Selangor, Malaysia

*For correspondence: adiana@frim.gov.my

Abstract: *Mesua ferrea* (Guttiferae) is known for its valuable wood. It has been used as one of the many ingredients in ancient Ayurveda. The plant grows well in Cambodia, India, Malaysia, Myanmar, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam. Different plant parts were reportedly used as a traditional medicine to treat various ailments including cough, asthma, scabies, dermatopathy, leprosy, dysentery, and hemorrhoids. These traditional usages suggest the presence of active phytochemical ingredients, which may have the potential to be developed into advanced nutraceutical or future pharmaceutical products. This review aims to gather invaluable scientific evidence or references and to relate them with the phytochemicals responsible for the various therapeutic potentials of the plant parts.

Keywords: *Mesua ferrea*, phytochemistry, therapeutic, anti-cancer, antimicrobial, antioxidative

INTRODUCTION

Indigenous herbal medicines have been popular since time immemorial and recently have also commanded major attention worldwide due to their potential nutraceutical values. *Mesua ferrea* is one of the most popular tropical herbal plants, indigenous to Asian countries like India, Sri Lanka, Andaman Islands, Myanmar, Indo-China, Thailand, Peninsular Malaysia, and Singapore. *M. ferrea* is commonly found in evergreen lowland forest and on ridges with shallow soils from sea-level up to an altitude of 500 m. Other vernacular names for *M. ferrea* are Ceylon ironwood, Indian rose chestnut in English. While in other countries as penaga, penaga lilin or lenggapus in Malaysia; nagasari or nagasari gede in Indonesia; ngaw, gangaw in Myanmar; bunnak or saaraphi-doi in Thailand and ka thang or may lek in Laos (Chotchoungchatchai et al., 2012). In India, it is known by various local dialects such as kengobang, micharne, nagakedar, nagachampa, and peri (Husain et al., 1992). In Nepal, it is called champeya, nagesori and narisal (Chua et al., 1995; Quattrocchi, 2012).

M. ferrea is a medium-sized evergreen monopodial tree up to 30 m tall with bole measurement up to 70 cm in diameter (Figure 1). It is an extremely slow-growing tree with

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young attractive brilliant red leaves (Figure 2). As it matures, the leaves turn fresh pale green and gradually become leathery, dark green on the above but waxy white on the underside (Figure 3). It produces attractive fragrant flowers with four spreading white petals with a mass of yellow stamens at the center (Figure 4a). Normally the flower will start to bloom early in the morning and closing up at sundown, lasting only for a single day (Figure 4b). The fruits are ovoid, conical, dark brown with compressed seeds (Corner, 1988; Chin, 2000; Ng, 2010; Gardner, 2011).

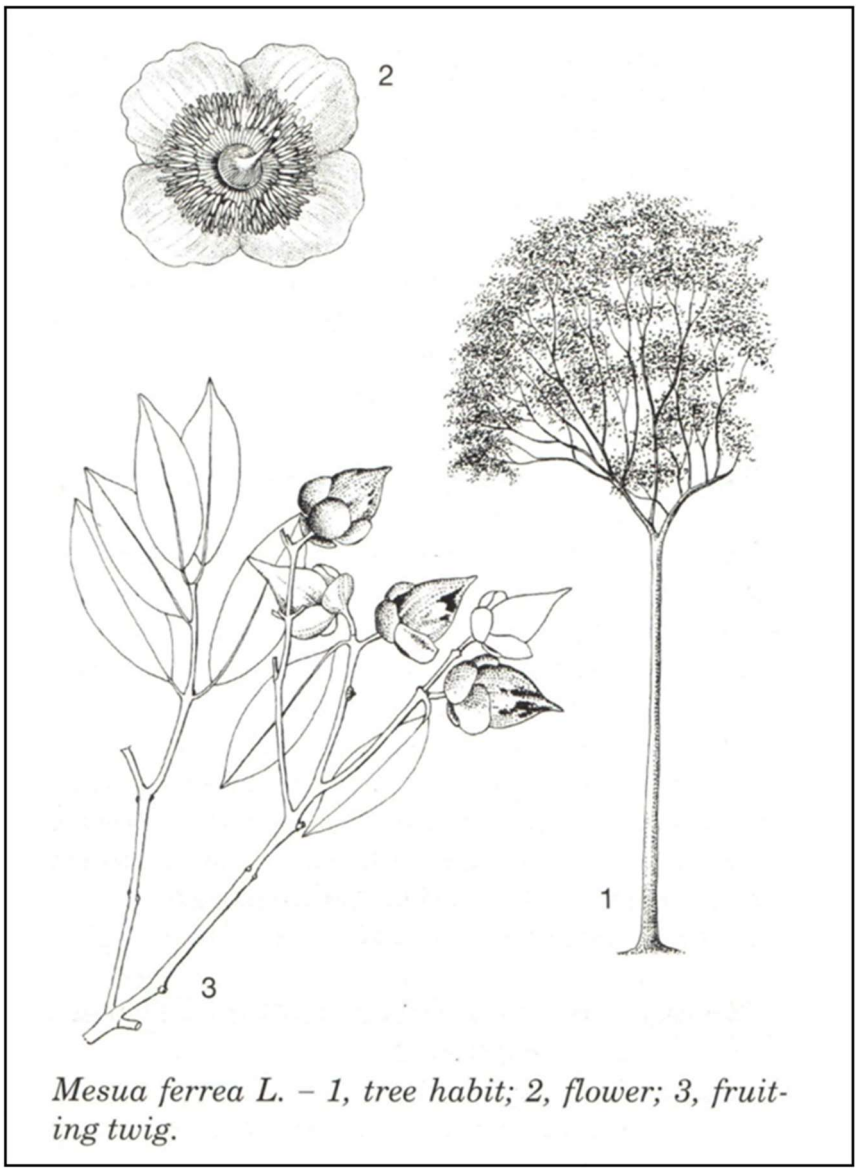

Figure 1. Botanical drawing of the plant 3 (Chua et al., 1995)

M. ferrea has many uses in various cultures throughout the world, especially in the traditional treatments. In India, *M. ferrea* was used in the past generations and was regarded as one of the many useful medicinal plants. The flowers were reported to have

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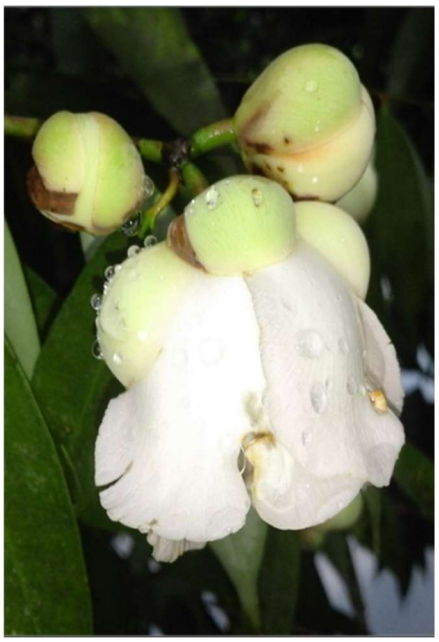
Figure 3: Waxy white layer on the underside of matured leaves

(a)



(b)

Figure 4: (a) Attractive fragrant flowers and (b); Flower closing up at sundown (Chin, 2000)

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several significant properties and uses such as bitter, acrid, mild heat generating, astringent, carminative, constipating, anthelmintic, diuretic, expectorant, stomachic, hemostatic, aphrodisiac, febrifuge, and cardiotonic. They were used as traditional remedies for cough, asthma, scabies, dermatopathy, leprosy, dysentery, hemorrhoids, ulcers, impotency, leucorrhoea, fever, and cardiac weakness (Varier, 1995). Besides, the stamens of *M. ferrea* L. constitute the genuine 'Nagkeshara' of Ayurveda which is an ingredient of ayurvedic formulations considered to be astringent, stomachic, and expectorant (Shome et al., 1982; Rajopadhye and Upadhye, 2012). The plant is also traditionally used to treat various ailments including pain, inflammation, rheumatic conditions, improve immunity, and used as antiseptic, antiasthmatic, and antiallergic remedy (Jalalpure et al., 2011; Chahar et al., 2012). The oil from the seed was used for skin diseases (Varier, 1995).

In Sri Lanka, the bark of this tree is considered as mild astringent. A combination of the bark and ginger is used to induce sweating. The flowers are used to treat cough, piles, and uterine bleeding, acute bronchitis, and pneumonia while the flower buds are used for dysentery (Jayaweera, 1981). In Malaysia, the fruits are crushed and applied to cuts, bruises and to treat skin diseases, while decoction from the flowers was reported to be used in post-natal treatment health tonic. Furthermore, the floral buds and flower parts were known to be used as skincare ingredients. The leaves are crushed and used to treat snakebites. The decoction of the root was also reported to be used after childbirth (Burkill, 1966; Kamarudin, 2002; Ong, 2006). The oil from the seed is suitable for soap making after a tedious refinement process to remove its reddish or dark brown color. The extracted oil from the seeds is used for lighting and in perfumes. The kernel meal as the residue is rich in nitrogen and phosphorus and suitable as fertilizers (Chua et al., 1995; Sastri, 1962).

The fragrance is strongest in the stamen of the flowers and is reported to be used in incense or face powder. Some are used for scenting clothes and stuffing cushions and bridal pillows on bridal beds (Gardner, 2011). The wood of *M. ferrea* is valuable. It is classified as heavy hardwood in Malaysia. The heartwood is dark reddish-brown. Physically it is very hard, very dense and heavy, durable and extremely strong. It has a density of 945-1185 kg/m3 and is slightly difficult to saw and crosscut. It is used for railway sleepers, in heavy construction, in boat-building industry and used to manufacture fine products like quality golf club heads and walking sticks, musical instruments, parquet floorings and heavy-duty furniture (Sastri, 1962; Whitmore, 1973; Wong, 1973).

M. ferrea is also a common ornamental tree. Its uniform and regular conical, bushy crown with big fragrant flowers and vibrant green leaves make it a beautiful shade tree to be planted along roadsides and recreational parks (Chua et al., 1995).

CHEMICAL CONSTITUENTS

Several preliminary studies had been conducted to identify the phytochemicals from *M. ferrea* (Govindachari et al., 1967 (a); Govindachari et al., 1967 (b); Chow and Quon, 1968; Chakraborty et al., 1969; Bala et al., 1971; Walia et al., 1984; Dennis et al., 1998; Dennis et al., 1988). A wide range of chemical compounds had been isolated and characterized from *M. ferrea.* Some of them include coumarins, triterpenoids, xanthones, alkaloids, steroids, and terpenes. In 1967, Govindachari et al. (1967a) isolated a new 4-alkylcoumarin from the trunk bark of Mesua ferrea L. Later, a biflavanone named M. ferrone-b was isolated from the stamens of *M. ferrea* (Raju at al., 1976). The heartwood of *M. ferrea* L. was found to contain mesuaxanthone A, mesuaxanthone B, 1,5-dihydroxyxanthone (II), euxanthone 7-methyl ether (IV) and β-sitosterol (Govindachari et al. (1967a); Chow and Quon, 1968). De A (1991) reported the crystal structure

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and conformational aspects of an optically inactive bitter antibiotic compound named mesuol from *M. ferrea*. Verotta and co-workers (2004) identified compounds namely, isomammeisin, mesuagin ,and assamene from the seeds *of M. ferrea* as well as 4-alkyl- and 4-phenyl coumarins from the blossoms. Friedelin and stigmasterol were later purified from the stembark (Mong, 2005). The stamen part of the flower contained gallic acid (Bagul et al., 2006). This was followed by the identification of 12, 13-furano-8-hydroxynapthyl-6-0-β-2′,3′,4′,6′-tetrahydroxy-5′5′dimethyl cyclohexyl ether by Rahman et al. (2008) from the leaves of *M. ferrea.* Mesuanic acid, α- and β-smyrin, β-sitosterol, 1, 5-dihydroxyxanthone and euxanthone-7-methyl ether were isolated from the stamens of the plant (Chahar et al., 2013). Ee and co-workers (2012) identified a new furanoxanthone, mesuaferrin A, and macluraxanthone from the root bark of *M. ferrea*, which was later reported to possess strong anti-cancer activities *in vitro* (Teh et al. 2013a). Another group discovered the presence of mesuaferrin B, caloxanthone C1, 8-dihydro-3-methoxy-6-methylantraquinone, and β-sitosterol from the root bark of *M. ferrea* (Teh et al. 2011).

Fig. 5 depicts the structure of some of the coumarins isolated from the *n*-hexane extract of *M. ferrea'*s flower buds namely, 5,7-dihydroxy-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-4-phenyl-2H-chromen-2-one (**1**), 5,7-dihydroxy-4-(1-hydroxypropyl)-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-2H chromen-2-one (**2**), 5-hydroxy-8,8-dimethyl-6-(2-methylbutanoyl)-4-phenyl-2Hpyrano[2,3-h]chromen-2-one (**3**), 5,7-dihydroxy-6-(2-methylbutanoyl)- 8-(3-methylbut-2-enyl)-4-phenyl-2H-chromen-2-one (**4**), 5,7-dihydroxy-8-(2-methylbutanoyl)-6-(3-methylbut-2-enyl)-4-phenyl-2H-chromen-2-one (**5**), 5,7-dihydroxy-6-(2-methylbutanoyl)-4-phenyl-2H-chromen -2-one (**6**) and 8,9-Dihydro-5-hydroxy-8-(2-hydroxypropan-2-yl)-6-(2-methylbutanoyl)-4-phenylfuro[2,3-h] chromen -2-one (**7**) (Roy et al., 2013). Keawsa-Ard and Kongtaweelert (2012) isolated terpenes from the flowers namely, trans-caryophyllene, α-humulene, γ-muurolol, β-caryophyllene oxide δ-cadinene, γ-cadinene, β-selinene, germacrene D and β-bisabolene. Flavonoids such as rutin, quercetin, kaempferol were isolated from the stems of the plant (Rajesh et al., 2013)

The seeds contain a substantial amount of chemical compounds like mesuol and mammeisin also demonstrated noticeable bacteriostatic activity (Subramanyam and Subba, 1974). Even though various types of chemical compounds have been isolated and characterized from *M. ferrea*, research reports on the bioactivity and the mechanism of action of the isolated compounds under *in vivo* conditions are limited. Additionally, the effects of these compounds on other ailments like cancer, blood pressure, cardiovascular disease, and others need to be investigated in detail. **Table 1** shows the isolated chemical compounds and the biological activities of different parts of *M.ferrea* plant.

VOLATILE OILS

The volatiles (aroma compounds) of each plant species possess their characteristic smell, which might be useful from differentiating the plant from other closely related subspecies. An earlier work by Choudhury *et al.* (Choudhury et al., 1998) revealed that the bark oil was rich in (E)-α-bisabolene (31.3%) and α-selinene (12.2%). Later, Jadhav *et al.* (Jadhav et al., 2016) had analyzed the essential oils in *M. ferrea* by GC/MS and headspace analysis. The GC/MS analysis of essential oils from whole flowers of *M. ferrea* showed the presence of the following components

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Table 1: Phytochemicals and biological activities of different parts of *M. ferrera*

Chemical classification	**Phytochemical identified**	**Plant part**	**Biological activities**	**References**
Coumarins	Ferruol A	Trunk bark	NR	Govindachari *et al.* (1967a)
Xanthones	1,5-Dihydroxyxanthone (II), euxanthone 7-methyl ether (IV) and β-sitosterol,	Heartwood	NR	Chow *et al.* (1968)
Xanthones	Mesuaxanthone A and mesuaxanthone B,	Heartwood	NR	Govindachari *et al.* (1967b)
Coumarins	Mesuol, Mammeisin	Seeds	Antibiotic	Verotta *et al.*(2004)
Terpenes Steroids	Friedelin Stigmasterol	Stembark	Anti-oxidant	Mong (2005)
Phenolic acid	Gallic acid	Stamen	Antioxidant	Bagul *et al.* (2006)
Furano-napthyl-hydroxy cyclohexyl	12,13-Furano-8-hydroxynapthyl-6-0-b-2′,3′,4′,6′-tetrahydroxy-5′5′dimethyl cyclohexyl ether	Leaves	NR	Rahman *et al.* (2008)
Terpenes Steroids Cyclohexadione Xanthones	α- and β-Amyrin β-Sitosterol Mesuanic acid 1, 5-Dihydroxyxanthone, euxanthone-7-methyl ether	Stamens	Antioxidant	Chahar *et al.* (2013)
Xanthones	Mesuaferrin A	Root bark	Anti-cancer	Ee *et al.* (2012)
Xanthones Anthraquinones Terpenes	Mesuaferrin A, mesuaferrin B caloxanthone C 1, 8-Dihydro- 3-methoxy-6-methylantraquinone β –Sitosterol, friedelin, betulinic acid	Root bark	Anti-cancer	Teh *et al.* (2011)
Coumarins	5,7-Dihydroxy-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-4-phenyl-2H-chromen-2-one , 5,7-dihydroxy-4-(1-hydroxypropyl)-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-2H chromen-2-one, 5-hydroxy-8,8-dimethyl-6-(2-methylbutanoyl)-4-phenyl-2Hpyrano[2,3-h]chromen-2-one, 5,7-dihydroxy-6-(2-methylbutanoyl)- 8-(3-methylbut-2-enyl)-4-phenyl-2H-chromen-2-one (4), 5,7-dihydroxy-8-(2-methylbutanoyl)-6-(3-methylbut-2-enyl)-4-phenyl-2H-chromen-2-one, 5,7-dihydroxy-6-(2-methylbutanoyl)-4-phenyl-2H-chromen -2-one, 8,9-Dihydro-5-hydroxy-8-(2-hydroxypropan-2-yl)-6-(2-methylbutanoyl)-4-phenylfuro[2,3-h]chromen-2-one	Flowers	Antibacterial	Roy *et al.* (2013)
Terpenes	Trans-Caryophyllene, α-Humulene, γ-Muurolol, β-caryophyllene oxide δ-cadinene, γ-Cadinene, β-selinene, germacrene D, β-bisabolene	Flowers	Anti-oxidant Antibacterial	Keawsa-Ard and Kongtaweelert (2012)
Coumarins	4-Alkyl- and 4-phenyl coumarins	Blossoms	Antiprotozoal agents and antibacterial activity	Verotta *at al.* (2004)
Terpenes Phenols Flavonoids	Trans-caryophyllene Gallic acid, coumaric acid, ellagic acid, vanillic acid rutin, quercetin, kaempferol	Stems	Anti-oxidant	Rajesh *et al.* (2013)

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alpha-copaene, trans-alpha-bergamotene, benzoate geranyle-1 and dioctyl Phtalate, whereas essential oil extracted from the petals of *M. ferrea* contained alpha-copaene, trans-alpha-bergamotene and dicotyl terephthalate. Further, the major components identified in stamens of the flowers by headspace technology were alpha copaene, beta caryophyllene, trans-beta-farnesene, trans-alpha-bargamotene, and alpha bisabolene whereas in petal of the flowers were α-copaene, β-selinene, trans-alpha-bargamotene and alpha bisabolene. Recently, Asif and co-workers reported that there are at least 22 compounds detected by GC-MS to be present in the stem bark hexane extract and among them include α-amyrin (10.62%) was identified as one of the major compounds followed by globulol (7.02%), phthalic acid mono-2-ethylhexyl ester (3.88%), n-hexadecanoic acid (3.76%), (-)-aromadendrene (3.56%), (+)-aromadendrene (3.53%), (-)-aristolone (2.06%) and 2,4-di-tert-butylphenol (Asif et al., 2016b).

EVIDENCE-BASED PHARMACOLOGY

Anti-cancer: Preliminary *in vitro* colorimetric or fluorescence assays on plant extracts treated in various cancer cell lines were employed by many laboratories around the world to provide a proof-of-concept on whether the plant tested can be further explored for drug discovery and development as an anti-cancer agent. Boik and Newman (2008) had outlined a few criteria if a compound can be pursued into pre-clinical studies, in which the compound shall be able to inhibit multiple cancer cell lines *in vitro* at modest to low concentrations (IC_{50} of 50 mM and below), has low systemic toxicity (rat LD_{50} < 1920/ mg/ kg/ day) and exhibited from low to modest oral clearance (<83L/hr in human). Before identifying the active compound, a series of plant extracts will be prepared and screened using available bioassays. Adopting from Wall et al. (1987) screening assessments, a plant extract that gives an IC_{50} of 20 mg/mL is considered to be active and worth for further detailed studies including compound isolation and characterization studies. One of the earliest *in vitro* anti-cancer studies employing MTT assay was performed on the ethanolic extract of the flowers of *M. ferrea*. The extract was tested in cholangiocarcinoma cell line (CL-6), human laryngeal carcinoma cell line (Hep-2) and human hepatocarcinoma cell line (HepG2) that gave the IC_{50} values of 48.23 ± 5.84 mg/mL, 19.22 ± 5.31 mg/mL and 86.47 ± 4.38 mg/mL, respectively (Mahavorasirikul et al. 2010). The hexane and dichloromethane extracts of *M. ferrea*'s flowers treated at 10 mg/mL in a leukaemia cell line (CCRF-CEM) had shown strong growth inhibition (> 80%) when assessed using XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium- 5-carboxanilide) assay (Noysang et al. 2014). Asif and co-workers had also included the *in vitro* anticancer study of methanolic extract of *M. ferrea*' s flowers against human colon cancer cell line (HCT 116) that gave IC_{50} value of 21.21 ± 1.58 mg/mL (Asif et al (2016a).

The essential oil from the leaves of *M. ferrea* was reported to exhibit anti-cancer activities against epidermoid (KB), breast carcinoma (MCF-7) and small cell lung carcinoma (NCI-H187) cell lines with IC_{50} values less than 30 mg/mL and the most active was against MCF-7, but it was non-cytotoxic to Vero cell line (Keawsa-Ard and Kongtaweelert, 2012). Adewale et al. (2012) found that methanolic extract from the leaves of *M. ferrea* was toxic to the brine shrimps with IC_{50} of 500 ppm (µg/mL) suggesting that the extract may contain bioactive compounds. Other studies found that dichloromethane extract from the leaves showed a selective anti-cancer effect *in vitro* in a pancreatic adenocarcinoma cell line (Panc-1) without much toxicity on normal lung fibroblast cell line (WI-38) (Rajendran, 2016)

Recently, Keawsa-Ard et al. (2015) reported that the dichloromethane extract from stem exhibited anticancer activities against oral cancer (KB), breast cancer (MCF-7) and small lung cancer (NCI-H187) cell lines with the IC_{50} values of 18.01, 28.83 and 18.42 µg/mL, respectively. The report also mentioned on further fractionation and isolation steps on the dichloromethane extract in which four compounds had been characterized as friedelin, β-sitosterol, lupeol and a

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mixture of α-amyrin and β-amyrin. Lupeol was reported to give IC_{50} values of 30.12, 30.12 and 21.56 µg/mL, respectively in KB, MCF-7 and NCI-H187 cancer cell lines. Asif et al. (2016b) reported that different extracts (n-hexane, chloroform, ethyl acetate, and methanol) from the stem bark had also being tested in colorectal cancer (HCT 116, ATCC1 CCL-247 and HT-29), breast cancer (MCF-7 and MDAMB-231), pancreatic cancer (PANC-1, MIA PaCa-2 and Capan-1), prostate cancer (PC-3) and gastric cancer (MKN-74) cell lines. Hexane extract and its terpene-rich fraction F3 were found to be the most active especially in HCT 116 cell line with an IC_{50} value of 14 µg/mL in which its mode of action was via down-regulating the expressions of NF-kB and HIF-1a transcription factors (Asif et al., 2016a). In another study, the same group of researchers (Asif et al., 2016b) had investigated the anti-cancer effect of isoledene rich sub-fraction (IR-SF) from oleo-gum resin in a colorectal cancer cell line (HCT116) using MTT assay in which the IC_{50} value evaluated was 16.62 ± 0.38 µg/ mL. This IRSF was found to inhibit the proliferation of HCT116 cell line via apoptosis by increasing the expressions of a few pro-apoptotic proteins (i.e. caspase-3, cytochrome-c) and suppressing the expressions of a few anti-apoptotic proteins (i.e. Bcl-2, Bcl-w).

On the other hand, hexane, dichloromethane, ethyl acetate and methanol extracts of the root bark of *M. ferrea* had shown anti-cancer effects *in vitro* in at least nine different cancer cell lines (Teh et al. 2013a). Hexane, dichloromethane and ethyl acetate extracts were subjected to the separation of pure compounds via column chromatography. From this separation technique, four compounds identified as mesuaferrin A, mesuaferrin C, caloxanthone C and macluraxanthone were yielded from hexane extract, mesuaferrin B was yielded from dichloromethane extract and 1,5-dihydroxyxanthone and tovopyrifolin C were yielded from the ethyl acetate extract. Mesuaferin A and macluraxanthone were found to inhibit the cancer cells proliferation in human B lymphocyte (Raji), human gastric carcinoma (SNU-1), human erythroleukemia cells (K562), human colorectal adenocarcinoma (LS-174T), human cervical cells (HeLa), human malignant melanoma cells (SK-MEL-28), human lung adenocarcinoma (NCI-H23), human neuroblastoma (IMR-32) and human hepatocellular liver carcinoma (Hep G2) with IC_{50} values ranging from 0.36 ± 2.38 to 18.25 ± 1.25 mg/mL. Mesuaferin B and caloxanthone C were also found to inhibit cancer cells proliferation in a few of these cancer cell lines (including K562, HeLa, HepG2, NCI-H23) at IC_{50} values below 20 mg/mL.

In summary, the anticancer effects were preliminarily reported at *in vitro* level on various extracts obtained from the flower, leaves, root bark, stem and essential oil of *M. ferrea*. The information on the anti-cancer activities of the compounds present in the active extracts from all of these plant parts are still lacking. In vivo, mechanistic and toxicity studies on these active extracts and compounds are a potential area to be further studied to validate their efficacy before venturing into drug discovery and development of anticancer agent.

Antimicrobial: The search for new classes of antimicrobial compounds is crucial since there are still occurrences of resistance to all major classes of antibiotics (Genilloud, 2014). A recent report had mentioned that drug resistance had also occurred in the newer antibiotics in treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections including vancomycin and linezolid (Saager et al. 2008). Plant-based natural products is still a very useful source to discover a new potential antimicrobial agents since it naturally produces secondary metabolites with highly diversified and unique chemical structures that may exert different mechanisms of action or target molecule in killing or controlling the growth of pathogenic bacteria. *In vitro* antimicrobial screening assessment based on the results of MIC (Minimum Inhibitory Concentration) values is one of the popular approaches to identify active extracts from respective plant species for further compound isolation and characterization towards drug discovery and development. Gibbon (2008) had reported based on his review that phytochemicals with MIC values less than 10 µg/mL

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and ideally less than 2 µg/mL are considered as being of interest to the pharma industry, whereas compounds with MIC values greater than 100 µg/mL are poorly active. An earlier review by Gibbon (2004) encompasses the literature from 1995 to 2003 on plant-derived anti-staphylococcal compounds abounds with claims of natural products and extracts displaying antibiotic activity with many papers describing compounds with MIC values over 1000 µg/ml, which from a clinical perspective has little relevance. This review paper will highlight some of the research findings on antimicrobial activities of different plant parts of *M. ferrea*. The antimicrobial activities of the phytochemicals extracted and isolated from flowers, leaves, stems and fruits of *M. ferrea* against Gram-positive and Gram-negative bacteria had been reported by a few researchers.

Mazumder et al. (2004) had reported the antimicrobial activities of the methanolic extract of the whole flower of *M. ferrea* treated at a concentration range between 5 to 400 µg/ml against four Gram-positive bacteria and eight Gram-negative bacteria with a total of 173 strains. The flower extract-treated on two strains from *E. coli* and one strain from *Vibrio cholera* gave MIC values of 10 µg/ml. Of 41 tested strains of *Staphylococcus aureus*, 30 were inhibited by $_{50}$ µg/ml of the extract, 1 and 2 at 100 and 200 µg/ml concentrations respectively, and eight strains were relatively resistant to the extract. The flower extract also has shown significant protection when treated at concentrations of 100 and 200 µg/g of body weight of Swiss strain of albino male mice when challenged with 50 median lethal doses (MLD) of a virulent strain *Salmonella typhimurium* ATCC 6539. The extract at 200 µg/g body weight dosage were reported to significantly reduce the viable count of the strain *S. typhimurium* ATCC 6539 in liver, spleen and heart blood of these tested mice (Mazumder et al., 2004).

Adewale et al. (2012) had reported on the antimicrobial activities of the leaves of *M. ferrea* using disc-diffusion assay and broth dilution method on two Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and two Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*). The inhibition zones for the tested microbes when treated with the ethanolic and methanolic extracts from the leaves were in the range of 16.0 ± 0.5 mm to 18.0 ± 0.5 mm as compared to the inhibition zones when treated with streptomycin were in the range of 20.0 ± 0.5 to 24.0 ± 0.5 mm. The MIC values of the extracts were in the range of 2.5 - 0.625 mg/mL with MBC (Minimum Bactericidal Concentration) value at 5 mg/mL was obtained for the gram-negative bacteria while the MIC values in the range of 1.3- 0.313 mg/mL with MBC value at 2.5 mg/mL was obtained for the gram-positive bacteria). An earlier report by Narender et al. (2011) on the polar and non-polar extracts from the leaves for its antimicrobial effect concluded that the methanol extract showed better activity compared to the other extracts at 1200 µg/mL concentrations against gram-negative bacteria. The antimicrobial activity of the fruit and leaves methanolic extracts of *M. ferrea* on the *S. aureus* had also been reported in which the extracts exerted MIC values of 48 µg/mL for both extracts (Aruldass et al, 2013). In 2012, Keawsa-ard and Kongtaweelert reported that the essential oil of *M. ferrea* leaves exhibited significant antibacterial activity against *E. coli* and *S. aureus* with the MIC values of 2_{50} and 125 mg/mL, respectively.

An antimicrobial study on the stems of *M. ferrea* had been conducted using microtitre broth method and reported in Keawsa-Ard et al (2015) in which the hexane, dichloromethane, and methanol extracts were tested against *E. coli* and *S. aureus*. The methanol and dichloromethane extract tested against *E. coli* gave MIC values of 31.25 and 62.5 µg/mL, respectively. The methanol extract and the dichloromethane extract exhibited the highest activity against *S. aureus* with the MIC values of 31.25 µg/mL. Hexane extracts were the least active when tested against *E. coli* and *S. aureus.* This report also revealed that friedelin, lupeol, and β-sitosterol isolated from dichloromethane extract gave MIC values that ranged from 250 to 1000 µg/mL when tested against these bacteria. Coumarins isolated from the flower buds of *M. ferrea* showed promising modulator and efflux pump inhibitor activities against clinical strains as well as NorA-over

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expressed strain of *Staphylococcus aureus* 1199B (Figure 5) (Roy et al., 2013). Although there are many compounds reported to be present in the different plant parts of *M. ferrea*, information on its antimicrobial effects against pathogenic bacteria is still lacking. Some of these findings on active extracts have the potential to be further explored towards the identifications of potent antimicrobial compounds.

Antioxidative: Plant antioxidants are believed to play a crucial role in protection against several diseases and delaying the aging process. The advantages of antioxidants from plants are probably because of their protective effects against free radicals which are reactive oxygen species (ROS). ROS consists of all highly reactive molecules including superoxide anion, hydrogen peroxide, hydroxyl radical, hypochlorous acid and peroxynitrite. Free radical molecules are molecules that have electric charges due to it has unpaired electrons and tend to affect healthy cells of the body to lose their structure and functions. Antioxidants are believed to have the ability to reduce free radical that can cause cell damage in human bodies. Cell damage caused by free radicals may lead to lipid peroxidation which leads to aging and other degenerative diseases like cancer, cataracts, poor immune system and brain dysfunctionality (Sies et al., 1992)

To date, several studies reported on the anti-oxidant activities of the flowers, leaves, stem bark, root bark and seed oil from *M. ferrea*. Various methods have been used to assess the antioxidative potency of these extracts using various *in vitro* colorimetric assays to assess the capacity of radical scavenging and inhibition of lipid peroxidation or other free radicals (i.e. DPPH (1,2-diphenyl-2-picrylhydrazyl), superoxide anion, nitric oxide to name a few). Yadav and Bhatnagar (2010) had reported that the ethanolic extract from flowers of *M. ferrea* causing inhibition on iron-induced lipid peroxidation (LPO) indicating the presence of antioxidative activity. The LPO was measured as thiobarbituric acid reactive substances (TBARS) by the reaction with malondialdehyde (MDA) equivalents formed from the peroxidation of lipids. The extract also showed strong reducing power and superoxide radical scavenging activity (Sahu et al., 2013).

Sahu et al. (2013) had also investigated the antioxidative effect of the methanol extract from the flowers by assessing the capacity of total anti-oxidant, radical scavenging and inhibition of lipid peroxidation using DPPH free radical scavenging assay, scavenging of superoxide radical by alkaline DMSO method and scavenging of hydrogen peroxide method. The total antioxidant capacity measured was 91.67 ± 2.16% whereas the percentage of inhibitions (IC_{50}) using DPPH free radical scavenging assay, scavenging of superoxide radical by alkaline DMSO method and scavenging of hydrogen peroxide method were 300.01 µg/ml, 273.56 µg/ml and 21.70 µg/ml, respectively. As for comparison, The IC_{50} of rutin from DPPH assay was 54.76 µg/ml and the IC_{50} of ascorbic acid from scavenging of superoxide radical and hydrogen peroxide methods were 34.71 µg/ml and 16.02 µg/ml, respectively.

Earlier, *in vivo* study on the methanolic extract of the flowers had been reported by Garg et al. (2009). In this study, three doses of the extract at 50, 100, and 200 mg/kg of body weight were given to male Wister rats that were initially inoculated with *Staphylococcus aureus* (ATCC 43300) to evaluate possible antioxidant and hepatoprotective effects. Treatment with methanol

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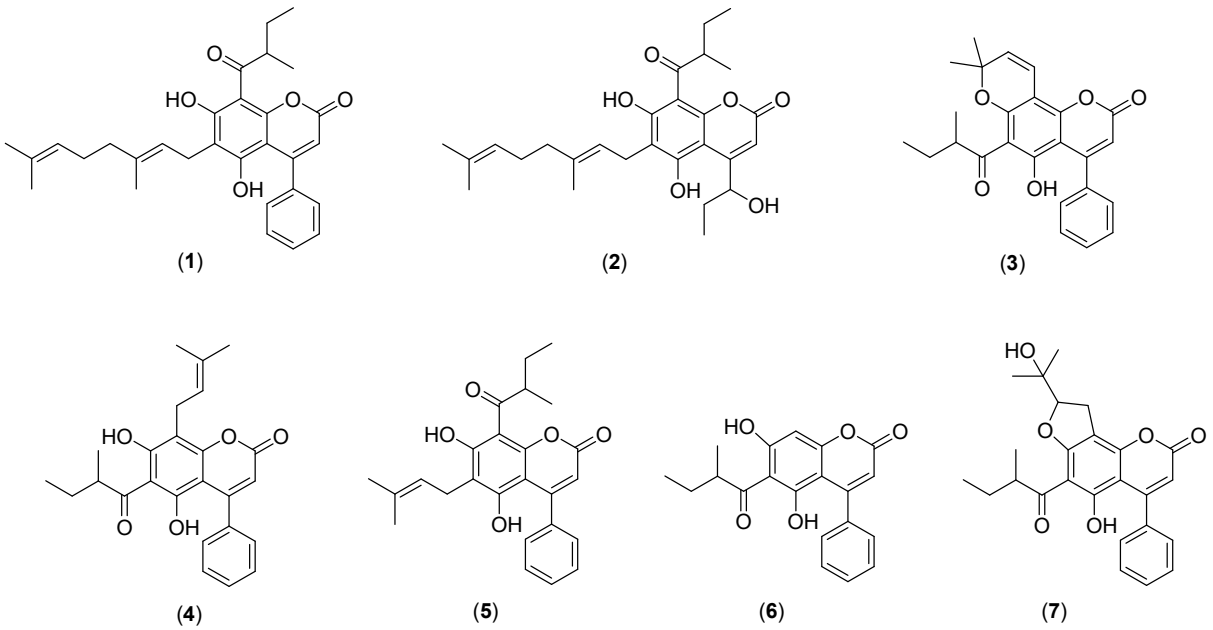

Figure 5: Coumarins isolated from the flower buds of *M. ferrea* with promising modulator and efflux pump inhibitor activities against clinical strains as well as NorA-over expressed strain *of Staphylococcus aureus* 1199B (Roy et al., 2013)

extract at 100 mg/kg body weight, marked a significant increase in biochemical parameters and posed hepatoprotective effect. Values of CAT (liver catalase), SOD, GPx (glutathione peroxidase) and GR (glutathione reductase) were measured for evaluation of antioxidant activity and were found to contain higher activity in the extract fed rats than control. While the AAT (alanine aminotransferase) and AST (aspartate aminotransferase) level showed a significant decrease in extract fed groups of animals, this analysis demonstrated the effective antioxidant activity of the prepared flower extract.

In another experiment, hexane and ethanol extracts were prepared from the stamens of the flowers to investigate the possible liver protective effect against oxidative stress induced by CCl4 in liver slice culture model. Both extracts significantly inhibited DPPH, NO, SOD and ABTS+ (2,2'azinobis (3-ethylbenzothiazoline-6-sulfonate) radical in a dose-dependent manner. The culture system treated with hexane extract, ethanol extract, and ascorbic acid showed a significant reduction in LDH, lipid peroxidation, antioxidative enzymes SOD, CAT and GR readings (Rajopadhye and Upadhye, 2012).

Significant antioxidant activity was detected in the chloroform and ethanol extracts prepared from the stem bark of *M. ferrea*. The ethanol extract showed 90% protection to erythrocytes, Hb and DNA due to the high total phenolics of 1.005 ± 0.005 mgEGAmg-1 and total flavonoids of 514.8 µg/mg. The chloroform extract showed 70% antioxidant protective activity probably due to 0.596 ± 0.002 mg EGA mg-1 total phenolics and 275.9 µg EQ mg-1 total flavonoid content (Rajesh et al. 2013). Some other studies showed that the methanol extract of the root bark of *M. ferrea* has high antioxidant activities when evaluated using DPPH scavenging radical assay and Folin-Ciocalteu method that showed low EC_{50} values of 9.77 g/mL, which is comparable to that of ascorbic acid at EC_{50} of 5.62 g/mL (Teh et al., 2013b).

Keawsa-Ard and Kongtaweelert (2012) reported that the essential oil obtained from the leaves of *M. ferrea* showed antioxidant activity with the IC_{50} of 31.67 mg/mL when tested using

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the DPPH (1,1-diphenyl-2-picrylhydrazyl) radicals scavenging assay. The ethanolic extract from the leaves showed significant IC_{50} of DPPH, superoxide, and hydroxyl free radicals values of 147, 243, 215 µg, respectively. While, the mean IC_{50} value of ascorbic acid was found to be 59.3 µg (Narender et al, 2012).The capacity and efficacy of antioxidants *in vivo* may be assessed by the effect of antioxidant compounds or extracts on the level of oxidation in biological fluids and tissues, such as plasma, erythrocytes, urine, and cerebrospinal fluids, from humans and experimental animals (Niki E, 2010). Chahar et al. (2012) had reported that the chemical compound mesuol, isolated from seed oil of *M. ferrea* showed significant antioxidant and immunomodulatory activity as using *in vivo* humoral immune response model, cellular immune response model, and cyclophosphamide-induced myelosuppression model. In humoral immune response model, mesuol evoked a significant dose-dependent increase in antibody titer values in cyclophosphamide (50 mg/kg, i.p., 9th and 16th day) induced immunosuppression which was sensitized with sheep red blood cells (SRBC) on the 7th and 14th day of the experiment. In cellular immune response model, an increase in paw volume was recorded on the 23rd day in cyclophosphamide-induced immunosuppressed rats treated with SRBC on the 21st day. It may be noted that SRBC acted as antigen for the rat immune system, whereas, cyclophosphamide (a cytotoxic drug) was used to suppress the immune function and generate free radicals in the biological system. It was also found that mesuol restored the hematological profile in the cyclophosphamide-induced myelosuppression model and it had also potentiated the percentage of neutrophil adhesion in the neutrophil adhesion test in rats and phagocytosis in carbon clearance assay.

CONCLUSION

Phytochemical studies have revealed *M. ferrea* to be rich in many classes of secondary metabolites including phenylcoumarins, xanthones, and triterpenoids. It is evident from the available literature that *M. ferrera* possesses an adequate therapeutic potential and could be explored further for commercial purposes, and nevertheless could be designated as a future drug candidate. Nevertheless, all these biological activities have only been studied *in vitro* using cell lines and *in vivo* using laboratory animal. These results require further study to apply to humans. Gaps in conducted studies do exist and these gaps need to be filled to fully exploit the potential of *M. ferrera*. Concrete evidence in the areas of safety, quality and efficacy are still insufficient in many of the literature especially with regards to the advanced usage of *M. ferrea* as a traditional medicine method of treatment or into clinical testing. Continuous research initiatives will further strengthen the effort of upcoming new research into the discovery of potential lead compounds to benefit future drug developments from *M. ferrea*.

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DECLARATION OF CONFLICT OF INTEREST

No conflict of interest to declare.

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