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REVIEW

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Exploring the phytochemistry and pharmacology of *Mangifera indica* L. (Mango) leaves: A review

Humna Mehmood[a*], Jawaria Mehmood[b], Noor Zulfiqar[a]

[a] *University of Agriculture Faisalabad, Department of Chemistry, Faisalabad, Pakistan*
[b] *University of Agriculture, Fisheries and Wildlife, Department of Zoology, Faisalabad, Pakistan*

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ABSTRACT

Mangifera indica L. (Mango), a member of the Anacardiaceae family, is native to the tropical and subtropical regions of the world. Leaves of *M. indica* exhibit pharmacological potential as a panacea. The current study aimed to systematically review the phytochemistry and biological effects of *M. indica* leaves (MILs). Google Scholar, PubMed, Scopus, and Web of Science were used to review the relevant literature. MILs are reported to possess remarkable medicinal properties owing to a plethora of phytochemicals, namely, minerals, vitamins, flavonoids, phenolic acids, terpenes, benzophenones, tannins, saponins, and alkaloids. MILs have been investigated for numerous therapeutic effects, including anticancer, anti-diabetic, antioxidant, antiviral, antibacterial, antifungal, antidiarrheal, antiulcer, gastrointestinal, anti-obesity, cardio-protection, hypotensive, analgesic, and hepato-protection. In this review, phytochemistry, pharmacology as well as toxicology of MILs have been critically discussed. Considering their phytochemical profile and pharmacological benefits, MILs can be used for the development of valuable pharmaceutical products. However, more comprehensive clinical trials are needed to be conducted for further evaluation of its effectiveness.

1. Introduction

One of the basic goals of Millennium Development Goals (MDGs) is the search to fight diseases such as acquired immune deficiency syndrome (AIDS), cancer, and cardiovascular disorders. Plants have always been highly beneficial to mankind for treating implacable diseases from time immemorial. Medicinal herbs are enriched in secondary metabolites, with better safety profile and least or no side effects, which make them an outstanding source of drugs and therapeutics. Therefore, an interest is developing in the application of herbal extracts as therapeutic agents (Mishra et al., 2022; Naik et al., 2020).

Mangifera indica L. is a member of the Anacardiaceae family. It is commonly cultivated in the tropical or subtropical regions of the world. It is considered an important plant in South and Southeast Asia. Pakistan, India, Bangladesh, Thailand, China, Indonesia, Nigeria, Philippines, Mexico, and Nigeria are considered among its main producer countries. *M. indica* also known as the 'king of fruit', is an evergreen tree that has numerous biological properties besides its very popular fruit (Kumar et al., 2021; Parvez, 2016).

Leaves of *M. indica* show remarkable medicinal, biological, and metabolic characteristics. Generally, *M. indica* leaves (MILs) are treated as a waste mainly produced by the pruning of *M.*

Reviewed by:
Great Iruoghene Edo: Delta State University of Science and Technology, Ozoro, Nigeria
Chang Liu: Naval Medical University, 325 Guohe Road, Shanghai, China

* Corresponding author(s):
E-mail address:
humnamehmood19@gmail.com (H. Mehmood)
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indica, but in reality, these are highly important comprising a huge variety of phytoactive substances including phenolic, crude protein, essential oils, dietary fiber, vitamins, and minerals. MILs contain minerals including calcium (Ca), iron (Fe), sodium (Na), potassium (K), phosphorus (P), zinc (Zn), nitrogen (N), magnesium (Mg), manganese (Mn), boron (B), sulfur (S), copper (Cu) and cadmium (Cd), and vitamins including A, B, E, and C. MILs have been extensively studied due to their biological potential owing to a lot of bioactive compounds, namely mangiferin, flavonoids, benzophenones, terpenes, phenolics, alkaloids, saponins, tannins and many other medicinal compounds. The MILs show various pharmacological activities such as antimicrobial, antidiarrheal, antioxidant, anti-diabetic, anticancer, antiobesity, gastrointestinal, cardio-protection, and hepato-protection **(Figure 1)** (Kumar et al., 2021; Pan et al., 2018).

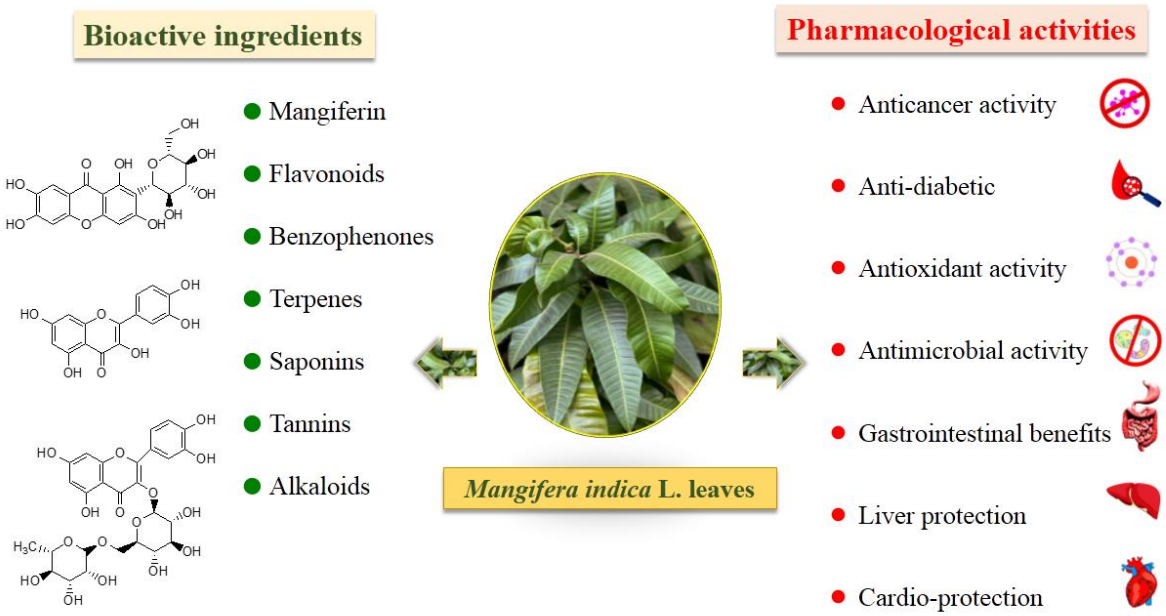

Figure 1. Phytochemistry and pharmacology of *M. indica* leaves

This review aims to discuss traditional uses, phytochemical profile as well as pharmacology of leaves of *M. indica*. Furthermore, the toxicology of MILs is briefly presented.

2. Methodology

The study was conducted by searching electronic databases including Google Scholar, Scopus, PubMed, and Web of Science for studies focused on the phytochemistry and pharmacological activities of MILs. All the articles published between 1990 and 2023 were examined.

3. Taxonomic classification

Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Sapindales
Family: Anacardiaceae
Genus: Mangifera
Species: *Mangifera indica* L. (Yadav et al., 2018)

4. Botanical description

The leaves are lanceolate-elliptical, linear-oblong, spirally arranged on offshoots, located at both ends and release an aromatic odor on crushing. Leaf blades are mostly about 25 cm long and 8 cm wide, occasionally much larger. Leaves are reddish and thinly flaccid when first formed. The upper surface of leaves is dark green and shiny while the lower surface is glabrous light green (Parvez, 2016; Shah et al., 2010).

5. Traditional uses

In traditional medicine, dried leaves of *M. indica* were considered useful in the treatment of respiratory infections and diabetes (Zhang et al., 2019). *M. indica* was enlisted in TRAMIL (Program of Applied Research to Popular Medicine in the Caribbean) as an active agent in treating fever, ulcers, gastritis, and diarrhea (Robineau & Saejarto, 1996). MILs have also been listed in the Dictionary of Chinese Medicine for diabetes resistance and decrement of respiratory ailments (Shi et al., 2020). MILs are the main ingredients in some of the traditional Chinese medicine formulations such as Mango anticough tablets, and Yinhua mango granule (Xu et al., 2018). Moreover, aqueous extract of MILs has been utilized as traditional tea in certain Chinese districts, namely, Guangxi province (Zhang et al., 2013). In tropical Africa, *M. indica* is used medicinally as an astringent for toothache, skin diseases, internal hemorrhage, catarrh, and bronchitis. MILs tea are used for fever and diarrhea. The MILs are used as anti-diabetic agents in the folk medicine of Nigeria (Aderibigbe et al., 1999). The ash of burnt leaves is used to cure burns and scalds. The smoke produced from burning leaves is inhaled for relief of throat sickness (Parvez, 2016).

6. Phytochemistry of *M. indica* leaves

MILs exhibit huge medical value owing to their high concentration of bioactive chemical ingredients (Wu et al., 2020). Minerals, namely, K (589 mg), P (480 mg), Fe (343 mg), Mg (98 mg), Ca (368 mg), Na (28 mg), Zn (14 mg), Mn (3 mg), and N (2 mg) are found per 100 g dry weight in MILs (Ali et al., 2020). Various studies indicated presence of Fe (0.0062–0.034%), P (0.007–0.48%), N (0.003–2.6%), Mg (0.009–1.58%), Zn (0.0024–0.014%), Ca (0.003–4.41%), B (0.0016–0.0042%), S (0.37–0.88), copper (0.0021–0.0029%), Na (0.003–0.23%), cadmium (0.015%), and Mn (0.0028–0.003%) in total content of MILs extract (Kumar et al., 2021). Vitamin A (22.60 mg/100 g), B1 (0.04–0.48 mg/100 g), B2 (0.06–0.21 mg/100 g), B3 (0.38–2.20 mg/100 g), and C (13.20–53 mg/100 g) were also discovered (Okwu & Ezenagu, 2008; Princwill-Ogbonna et al., 2019; Rymbai et al., 2013).

The qualitative phytochemical study of MILs extract showed numerous medicinally significant secondary metabolites including flavonoids, tannins, saponins, and alkaloids **(Table 1)** (Ali et al., 2020). Chemical analysis of crude, ethyl acetate, and methanolic extracts of MILs utilizing ultrahigh pressure liquid chromatography identified various useful bioactive compounds which include nine flavanols, four xanthones, seven terpenoids, ten benzophenones, four derivatives of gallotannins, eleven phenols (Jhaumeer Laulloo et al., 2018). Another phytochemical study resulted in the identification and isolation of seventeen flavonoids and five benzophenones (Pan et al., 2018). In the leaves of the West African species of *M. indica*, quercitin (both free and glycosides), four anthocyanidins (3-monosides of paeonidin, delphinidin, and cyanidin), mangiferin, leucoanthocyanins, gallic and catechic tannins and kaempferol were reported (Okwu & Ezenagu, 2008).

Table 1. An overview of reported phytochemicals in leaves of *M. indica*

Type of extract	Chemical analysis	Phytochemicals	Reference
70% ethanol-water (3 × 50 l) extract	Positive-ion HR-ESI-TOF-MS	**Polyphenols:** Iriflophene, quercetin-3-*O*-β-D-xylopyranoside, quercetin-3-*O*-β-D-glucoside, quercetin-3-*O*-α-L-rhamnoside, quercetin-3-*O*-β-D-arabinoside, quercetine-3-*O*-β-D-galactoside, isovitexin, isoswertisin, vitexin, quercetin-4′-*O*-β-D-glucoside, luteolin-7-*O*-β-D-glucoside, quercetin, 3′,5′-dimethoxy-4′,5,7-trihydroxyflavone, mangiferin, 4′-*O*-*p*-hydroxybenzoyl mangiferin, amentoflavone, hypericin, and taxifolin	(Pan et al., 2018)
Ethanolic and methanolic extract	UPLC-MS/MS (positive mode)	**Xanthones:** Mangiferin, mangiferin-6′-*O*-gallate, mangiferin 3-methyl ether **Polyphenolic compounds:** Protocatechuic acid, gallic acid, derivative of gallic acid, methyl gallate, 2,5-di-tert-butyl phenol, tetrahydroxy sodium benzoate, ellagic acid, theogallin, derivative of theogallin with one OH missing **Flavonols:** Quercetin, rhamnetin, quercetin carboxylic acid, quercetin pentoside, quercetin 3-*O*-rhamnoside, epicatechin gallate hexamalonate, rhamnetin hexoside **Benzophenones:** Maclurin, iriflophenone glucoside derivative, iriflophenone 3-C-*β*-D-glucopyranoside, maclurin 3-C-(6′′-*O*-*p*-hydroxybenzoyl)*β*-D-glucoside, iriflophenone-di-*O*-galloyl-glucoside, iriflophenone tri-*O*-galloyl-glucoside **Terpenoids:** Lupeol, mangiferonic acid, manglanostenoic acid, cycloart-25-ene-3,24,27-triol, cycloartane-3,24,25-triol	(Jhaumeer Laulloo et al., 2018)
Ethanolic and methanolic extract	UPLC-MS/MS (negative mode)	**Phenolic compounds**: Sodium gallate **Xanthones:** Mangiferin, isomangiferin, mangiferin 3-methyl ether, mangiferin-6′-*O*-gallate **Flavanols:** Kaemferol, quercetin 3-*O*-glucoside **Benzophenones**: Maclurin 3-C-β-D-glucoside; 3-glucosyl-2,3',4,4',6-pentahydroxybenzophenone, maclurin 3-C-(6′-*O*-*p*-hydroxybenzoyl)*β*-D-glucoside, maclurin mono-*O*-galloyl-glucoside, maclurin di-*O*-galloyl-glucoside **Terpenoids:** Cycloartane-3,29-diol, 3*β*-form, 3,27-dihydroxycycloart-24-en-26-oic acid **Gallotannins:** Digalloyl glucoside, tri-*O*-galloyl glucoside, tetra-*O*-galloyl glucoside, penta-*O*-gallose-glucose **Other compounds:** Ferulic acid hexoside	(Jhaumeer Laulloo et al., 2018)
Essential oil obtained by hydro-distillation	GC–MS analysis	**Terpenes:** (-)-α-pinene, 1-terpineol, 3-methyl-camphenilol, α-humulene, α-elemene, 4-terpineol, camphor, α-gurjunene, α-guaiene, α-selinene, γ-selinene, (-)-α-panasinsen, palustrol, globulol, viridiflorol, α-eudesmol, octadecane, α-copaene, *cis*-guriune, α-cadinene, isocaryophyllen, elemol, guaiol, δ-cadinol, phytol isomer, α-terpinolene, *p*-cymene-8-ol, γ-cadinene, germacrene D, eremophilene	(Ouf et al., 2021)
Aqueous extract	High-resolution electrospray ionization mass spectrometry (HRESIMS) (positive mode)	**Benzophenone:** Acarbose, manindicin A, manindicins B, mangiferin, norathyriol	(Gu et al., 2019)
Aqueous extract	GC–MS analysis	Furfural, 2-furanometanol, *o*-catechol, hydroquinone, pyrogallol, oleic acid	(Martínez-Bernett et al., 2016)

MILs extract have flavonoids (1.054 ± 0.001 mg/g), tannins (0.977 ± 0.001 mg/g), alkaloids (0.300 ± 0.141 mg/g), and saponins (0.244 ± 0.001 mg/g) (Ali et al., 2020). Mangiferin has been reported as a major constituent (7.43%) (Pan et al., 2018). Flavonols including quercetin, quercetin 3-*O*-glucoside, quercetin carboxylic acid, quercetin pentoside, rhamnetin, quercetin 3-*O*-rhamnoside, epicatechin gallate hexamalonate, rhamnetin hexoside, and kaemferol were indicated in ultra performance liquid chromatography-MS/MS (UPLC-MS/MS) analysis (Jhaumeer Laulloo et al., 2018). Another spectrometry investigation indicated neomangiferin, kaempferol-3-*O*-rutinoside, and iso-quercitrin (Wu et al., 2020). Quercetin concentration of MILs was reported to range from 0.76-1.16 mg/g (Fitmawati et al., 2020).

Gallotannins such as digalloyl glucoside, tri-*O*-galloyl glucoside, tetra-*O*-galloyl glucoside, and penta-*O*-gallose-glucose were discovered in UPLC-MS/MS (negative mode) analysis of ethanolic and methanolic extract of MILs (Jhaumeer Laulloo et al., 2018). 4-Hydroxybenzoic, gallic, protocatechuic, coumaric, caffeic, and vanillic acids were found in MILs using mass spectrometry as the allelopathic bioactive compounds (Akhtar & Arshad, 2013). The gallic acid content ranged from 5.23 to 35.48 mg/g dry weight (Fitmawati et al., 2020). Additionally, cinnamic, and ferulic acids were also found (Kato-Noguchi & Kurniadie, 2020).

Benzophenones such as maclurin, iriflophenone 3-C-β-D-glucopyranoside, iriflophenone tri-*O*-galloyl-glucoside, maclurin 3-C-(6''-*O*-*p*-hydroxybenzoyl)β-D-glucoside, and iriflophenone-di-*O*-galloyl-glucoside were found in ethanolic and methanolic extract through UPLC-MS/MS (positive mode) analysis. Maclurin 3-C-β-D-glucoside, 3-Glucosyl-2,3',4,4',6-pentahydroxybenzophenone, maclurin 3-C-(6'-*O*-*p*-hydroxybenzoyl)β-D-glucoside, maclurin mono-*O*-galloyl-glucoside, and maclurin di-*O*-galloyl-glucoside were discovered in MeOH and EtOH extract though UPLC-MS/MS (negative mode) analysis (Jhaumeer Laulloo et al., 2018). Four derivatives of benzophenones such as acarbose, manindicins A and B, norathyriol, and mangiferin were discovered in an aqueous extract of MILs using high-resolution electrospray ionization mass spectrometry (HRESIMS) (Gu et al., 2019).

Essential oil of MILs contains monoterpenes (46.98 %), some trace amount of their analogs (10.67 %), sesquiterpenes (38.17 %), minor quantities of oxygenated hydrocarbons (4.19 %) and non-terpenoid hydrocarbons such as β-elemene, α-pinene, α-humulene, α-gurjunene, β-caryophyllene, β-selinene, and 3-carene (Džamic et al., 2010). 1-Terpineol, 3-methyl-camphenilol, α-elemene, 4-terpineol, camphor, α-guaiene, α-selinene, γ-selinene, viridiflorol, α-panasinsen, α-eudesmol, octadecane, α-copaene, *cis*-guriune, α-cadinene, palustrol, isocaryophyllen, elemol, guaiol, δ-cadinol, phytol, eremophilene, α-terpinolene, *p*-cymen-8-ol, γ-cadinene, and globulol were found in gas chromatography-mass spectrometry (GC-MS) analysis of MILs essential oil obtained by hydro-distillation (Ouf et al., 2021). Terpenoids such lupeol, mangiferonic acid, manglanostenoic acid, cycloartane-3, 24, 25-triol, and cycloart-25-ene-3, 24, 27-triol were found in UPLC-MS/MS (positive mode), and cycloartane-3, 29-diol and 3, 27-dihydroxycycloart-24-en-26-oic acid were observed in UPLC-MS/MS (negative mode) analysis of ethanolic and methanolic extract of MILs (Jhaumeer Laulloo et al., 2018).

Iriflophene, quercetin-3-*O*-β-D-xylopyranoside, quercetin-3-*O*-β-D-glucoside, quercetin-3-*O*-α-L-rhamnoside, quercetin-3-*O*-β-D-arabinoside, quercetine-3-*O*-β-D-galactoside, isovitexin, isoswertisin, vitexin, quercetin-4'-*O*-β-D-glucoside, luteolin-7-*O*-β-D-glucoside, quercetin, 3',5'-dimethoxy-4',5,7-trihydroxyflavone, mangiferin, 4'-*O*-*p*-hydroxybenzoylmangiferin, amentoflavone, hypericin, and taxifolin were found in 70% ethanol-water (3 × 50 l) using positive-ion HR-ESI-TOF-MS analysis (Pan et al., 2018). In a GC-MS analysis of aqueous extract, furfural, 2-furanometanol, *o*-catechol, hydroquinone, pyrogallol, and oleic acid were found (Martínez-Bernett et al., 2016). Chemical structures of some biologically active compounds present in MILs are depicted in Figure 2.

7. Pharmacological activities of *M. indica* leaves

Leaves of *M. indica* are considered a useful source of nutritive ingredients and cost-effective food supplements for the improvement of health as well as the treatment of mild and severe ailments. These show excellent medicinal, biological, and metabolic characteristics. The MILs extracts have been investigated because of their various medical effects including antioxidant, anticancer, antimicrobial, anti-diabetic, gastrointestinal, antidiarrheal, lipid-lowering, cardioprotective, and hepatoprotective effects.

7.1. Anticancer activity

Cancer is considered a highly dominant global disease after cardiovascular disorders. Therefore, it is necessary to propose a novel approach to control this worldwide problem. Polyphenols found in MILs, such as phenolic acids, gallotannins, mangiferin, and quercetin show chemo-preventive properties against several types of cancer owing to their potent antioxidant and anti-inflammatory effects (Jung et al., 2012). Mangiferin was found to diminish various tumors by hindering them from migration, invasion, and proliferation (Klein-Júnior et al., 2020).

An investigation was conducted to analyze the anti-tumoral activities of MILs extracts on MCF-10 and MCF-7 non-carcinogenic cells minimally and highly invading breast cancer cells. Leaves' extract exhibited protective activities against oxidation as well as cytotoxic actions on breast cancer and minimum harm to normal cells (Fernández-Ponce et al., 2017). The cytotoxic effect of different *M. indica* leaf extracts was assessed on lung cancer (A549) cells. The ethyl acetate extract exhibited the highest cytotoxicity against A549, followed by methanolic extract (Quizon et al., 2022). *M. indica* leaves extract was employed to prepare silver nano-rods. These nano-rods showed potential in vitro anticancer and antioxidant potential against cell lines of breast cancer and colorectal carcinoma (Anoop et al., 2018).

Ethanolic extract of *M. indica* leaves, at a concentration of 200 µg/ml, exhibited cytotoxicity against human cancer cell lines such as liver hepatoblastoma, bronchogenic carcinoma, ductal carcinoma, colon adenocarcinoma, and gastric carcinoma. The extract increased the percentage survival of normal cell lines, skin fibroblasts. At high doses, mangiferin increased the percentage of survival of lung and skin fibroblasts (Ganogpichayagrai et al., 2017). The bioactive components of *M. indica* leaves, extracted using methanol, showed high cytotoxicity on adenocarcinoma cell lines (Joona et al., 2013). The hexane-ethyl acetate extract of *M. indica* leaves showed cytotoxic activity on the L929 cell lines (Helen et al., 2013).

7.2. Anti-diabetic effect

Diabetes is known as a fetal disease that strongly disturbs human life. It is considered a danger for people regardless of their location geographically. It is defined by above-normal or high glucose level and it is partially because of damage due to the oxidation of β-cells of the pancreas, resulting in a cease in insulin secretion (Singab et al., 2014). An effective approach to treat diabetes mellitus (DM) is the inhibition of α-glucosidase and α-amylase enzymes, which results in the regulation of postprandial glucose absorption (Nair et al., 2013).

MILs have strong anti-diabetic potential owing to their hypoglycaemic compounds like flavonoids and benzophenones. In an investigation, four bioactive phytochemicals isolated from MILs extract, norathyriol, mangiferin, and manindicins A and B, were found to exhibit high anti-diabetic potential. Norathyriol had potent α-glucosidase inhibition with IC_{50} of 4.22 ± 0.19 µg/ml, which was four times more effective as compared to commercially used acarbose inhibitor (IC_{50}: 16.28 ± 1.22 µg/ml). Mangiferin exhibited lower α-glucosidase inhibition which can be enhanced by replacing the glucose group with hydrogen which may decrease the steric

hindrance during the mangiferin–enzyme interaction (Gu et al., 2019).

A study assessed MILs extract for its anti-diabetic effects using an in vitro model. The extract had pronounced inhibition towards α-amylase up to 51.4% ± 2.7 at 200 µg/ml of concentration. Furthermore, the extract showed a glucose adsorption capacity of 2.7 ± 0.19 mM glucose/g extract. Moreover, the extract significantly increased the uptake of glucose up to 143% ± 9.3 in LO-2 liver cells (Ngo et al., 2019). Anti-diabetic activity of mature as well as tender leaves of *M. indica* var. *totapuri* was conducted. Mature leaves extract (500 mg/kg) showed α-glucosidase inhibition with IC_{50} of 21.03 µg/ml, whereas, extract of tender leaves (500 mg/kg) showed α-amylase inhibition of IC_{50} 22.01 µg/ml (Bhuvaneshwari et al., 2014).

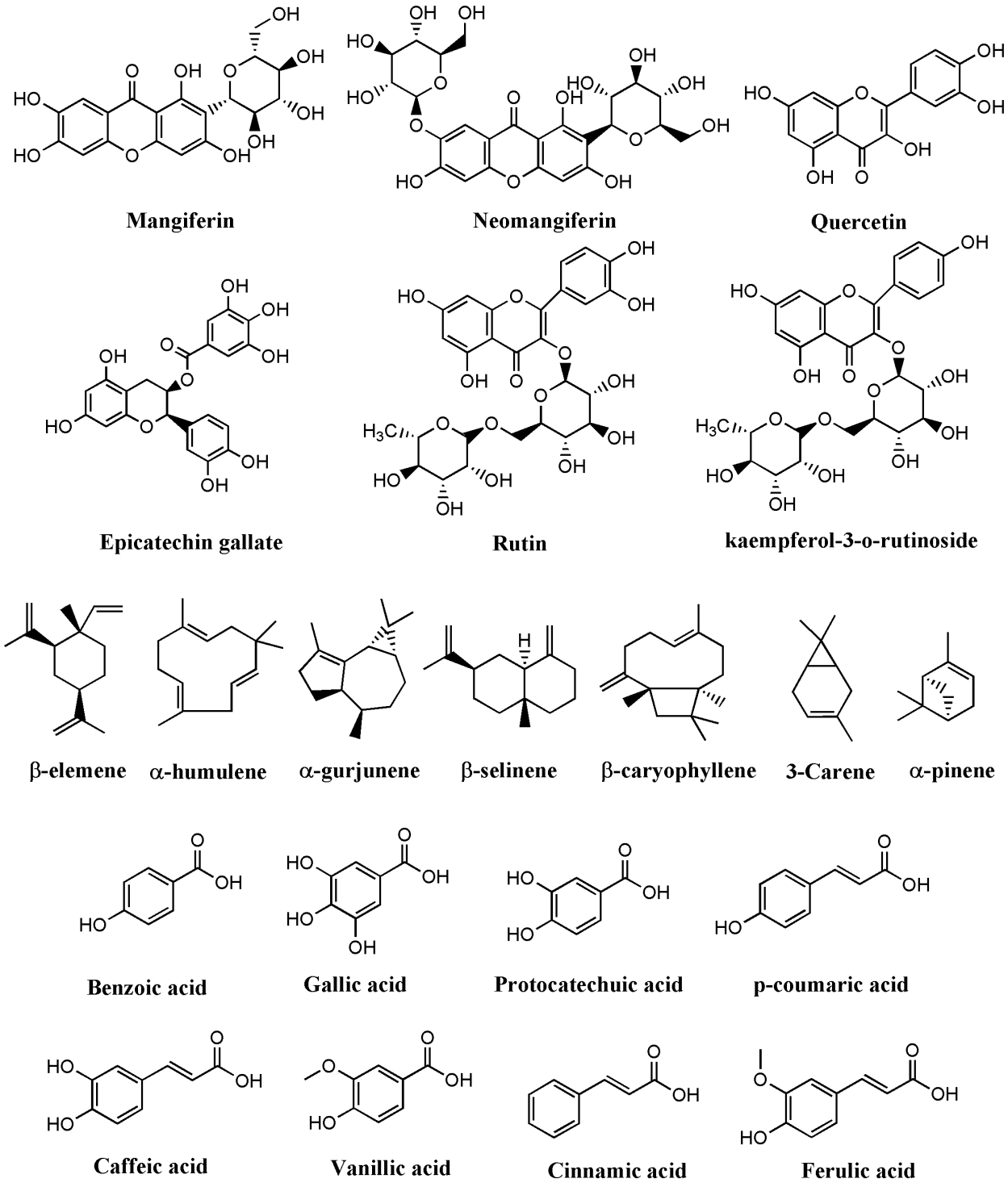

Figure 2. Chemical structures of important bioactive compounds in *M. indica* leaves

The anti-diabetic potential of ethanol extract of leaves of *M. indica* cv. *okrong* and its bioactive substance, mangiferin, was determined against yeast α-glucosidase and rat α-glucosidase employing *p*-nitro phenyl-α-D-glucopyranoside (1 mM) as substrate. Extract and mangiferin showed concentration-dependent inhibitory potential against yeast α-glucosidase with an IC_{50} of 0.0503 mg/ml and 0.5813

mg/ml, respectively, and against rat α-glucosidase with the IC_{50} of 1.4528 and 0.4333 mg/ml, respectively (Ganogpichayagrai et al., 2017). In another study, the antihyperglycaemic potency of *M. indica* leaves was studied in rats. The results indicated that aqueous MILs extract showed no significant impact on the blood glucose level in either STZ-induced hyperglycaemic or normoglycaemic rats. However, a reduction in elevation of blood glucose was observed in glucose-induced hyperglycaemic rats due to the aqueous extract (Aderibigbe et al., 1999).

7.3. Antioxidant effect

Free radicals produced during processes of metabolism cause several degenerative disorders including ischaemic disorders, AIDS, neurological disorders, and many others (Schraml & Grillari, 2012). Antioxidant compounds, on the other hand, also provide a strong antioxidant potential to reduce the harmful effects of free radicals. MILs extract showed significant inhibition of 63.3% ± 2.1 and 71.6% ± 4.3 in scavenging of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and 2,2-azinobis-3-ethyl benzothiazoline-6-sulfonic acid (ABTS) radicals, respectively. An inhibition of 66% ± 4.9 was observed in NO production from RAW264.7 cells without any sort of cytotoxicity (Ngo et al., 2019).

In another study, superoxide dismutase and DPPH assays demonstrated that MILs have a moderate antioxidant potential (Itoh et al., 2020). MILs methanolic extract also showed significant radical scavenging potential (Mohan et al., 2013). The antioxidant activity of leaves owing to the flavonoids and phenolics has been revealed in various investigations (Kumar et al., 2020). Flavonoids present in leaves have potential antioxidant features to protect cells from oxidative damage (Ali et al., 2020). Recently, mangiferin has been revealed to show antidepressant activity and regulation of the brain's biogenic amines. It decreases oxidative stress in the neurodegenerative diseases (Dutta et al., 2023). Polyphenols found in MILs such as phenolic acids, gallotannins, mangiferin, and quercetin show chemo-preventive properties against several types of cancer due to their antioxidant activity (Jung et al., 2012). Benzophenones as bioactive phytochemicals showed potential antioxidant and immunosuppressive activities (Gu et al., 2019). Tannins inhibit the formation and removal of reactive oxygen species, resulting in the reduction of scar tissue and improved wound healing (Ali et al., 2020).

The effectiveness of MILs was investigated in chitosan-incorporated films and the antioxidant potential of the MILs-incorporated chitosan films was enhanced in a dose-dependent aspect (Rambabu et al., 2019). The hydro-alcoholic extract of MILs fermented with either effective microorganisms or *Lactobacillus casei* exhibited high antioxidant potential. This examination displayed that fermented extract reduced the lipo-polysaccharide produced reactive oxygen species (Park et al., 2015). An advanced study demonstrated that MILs extract was highly appropriate as an antioxidant for the enhancement of biodiesel storage life (Neuana et al., 2021). In summary, several interesting reports have demonstrated that MILs are effective antioxidants with major applications in food and other industries (Kumar et al., 2021).

7.4. Antimicrobial activity

There is great interest in investigating the role of phytochemicals. Some medicinal plants with anti-microbial properties can destroy the effect of multidrug-resistant microbes, helping to cope with resistance to antimicrobial agents (Dzotam & Kuete, 2017). The major phytochemicals in MILs that are responsible for antimicrobial activity include alkaloids, phenolics, saponins, terpenes, glycosides, and tannins (Kumar et al., 2021). Its polyphenols can cease the growth of microbes (Ediriweera et al., 2017). Mangiferin exhibits various pathophysiological properties (Dutta et al., 2023). The essential oil from *M. indica* leaves also shows bacteriostatic activities as it contains various antimicrobial compounds like camphor (Ouf et al., 2021). Saponins have natural potential for the removal of microbes which enable them to be suitable for the treatment of yeast and fungal infections. These substances act as natural antibiotics which is helpful for the body to fight microbial invasion and infections. Plant-derived alkaloids are useful as fundamental therapeutic agents for their antispasmodic, analgesic, and antibacterial properties and they also protect against chronic diseases (Ali et al., 2020).

The antibacterial activity of MILs extract and its fabricated silver nanoparticles (AgNPs) was evaluated against three bacteria. The extract showed the inhibition of 12.5%, 24.9%, and 32.16%, respectively, and its AgNPs possessed the inhibition of 86.95%, 95.23%, and 99.99% against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, respectively (Hai et al., 2022). Antimicrobial analysis of essential oils of leaves extract of five Egyptian *M. indica* cultivars revealed notable antibacterial potential against *Staphylococcus* species, *E. coli*, *Bacillus subtilis*, *Aspergillus flavus*, and *P. aeruginosa* (Ouf et al., 2021). MILs extracts showed favorable anti-bacterial activities against *Enterobacter aerogenes* and *Mycobacterium tuberculosis* (Bharti, 2013).

The antibacterial potential of MILs extract against bacteria was assessed by using the disc diffusion method and poisoned food approach. Extract of MILs exhibited significant inhibition potential against a variety of gram-positive bacteria, including *B. cereus*, *Streptococcus agalactiae*, *B. subtilis*, *Lactobacillus bulgaricus*, *B. megaterium*, and two gram-negative bacteria including *Shigella sonnei* and *S. flexneri*. But *Proteus* spp. and *Salmonella typhi* showed resistance to the extract. This study showed that the leaf extract had significant antibacterial effects against gram-positive bacterial species and had no or weak potency against gram-negative bacterial species (Islam et al., 2010).

Ethanol, ether, and water extracts of MILs were studied for antibacterial activity utilizing the well diffusion approach. Ethanol extract exhibited inhibition diameters of 22 mm, 15 mm, and 19 mm, ether extract exhibited inhibition diameters of 23 mm, 5 mm, and 6 mm, and water extract possessed inhibition diameters of 7 mm, 5 mm, and 19 mm against *S. aureus*, *E. coli*, and *P. aeruginosa*. The ethanol extract was notably effective with a minimum inhibitory concentration (MIC) of 5481.0-43750.0 $\mu g.ml^{-1}$ (Bbosa et al., 2007a).

The bactericidal effect of MIL extracts against *Clostridium tetani*, which causes many deaths all over the world, was evaluated. Ether and ethanol extracts exhibited anti-bacterial potential with a MIC of 6.25 mg/ml and 12.5 mg/ml, respectively (Bbosa et al., 2007b). Furthermore, a chemical investigation of MILs extract to estimate antimicrobial potential showed the existence of five important flavonoid phytochemicals. These phytochemicals were found to be synthesized immediately after fungal attack and reduced the growth of targeted fungal species such as *Alternaria* and *Aspergillus* from 97% to 56% (Kanwal et al., 2010). Secondary metabolites with antibacterial properties have been found in MILs. Mangiferin, as an antibacterial agent, has shown effectiveness in preventing *S. aureus*, which has a high ability to trigger skin infections (Lubis et al., 2023).

Extract of MILs demonstrated antifungal potential against different species of fungi such as *A. niger* through disc diffusion method (Islam et al., 2010). In an investigation, flavonoids isolated from MILs showed significant antifungal activity against five fungal strains, such as *Penicillium citrii*, *A. alternata*, *A. fumigatus*, *A. niger*, and *Macrophomina phaseolina* (Kanwal et al., 2010). The antifungal assay of MILs extract and its fabricated silver nanoparticles (AgNPs) exhibited inhibitions of 28.55% and 99.99% against *Candida albicans* (Hai et al., 2022).

In vitro, mangiferin and isomangiferin can inhibit the replication of *Herpes simplex* virus type 1 (HSV-1) within cells (Zheng & Lu, 1990). The antiviral activity of mangiferin extracted from MILs was studied in vitro against *H. simplex* virus type 2 (HSV-2). Mangiferin was found to not directly inactivate HSV-2, but to inhibit the late stage of HSV-2 replication (Zhu et al., 1993). In another in vitro investigation, mangiferin was found to antagonize the cytopathic activity of human immunodeficiency virus (HIV) (Guha et al., 1996).

7.5. Gastrointestinal benefits

Diarrhea is known as an infectious disease and its main causes include drinking dirty water, consuming uncooked meat, poor hygiene and sanitation, and food intolerance (Mehesare et al., 2017). The key microorganisms that cause this ailment are various microbial agents such as *Vibrio cholera*, *C. albicans*, *E. coli*, *S. aureus*, and *S. flexneri* (Mokomane et al., 2018). The potential MILs extract was investigated on gram-negative gastrointestinal disorders caused by bacteria and the phytoconstituents of the extract were observed to have an excellent effect as an anti-diarrheal agent. Aqueous MILs extract were investigated against various pathogens such as *S. typhi*, *E. coli*, *S. sonnei*, and *V. cholera* at the dose level of 50, 100, 200, and 300 mg/ml. The antidiarrheal potential is increased by increasing the dose amount. So, the aqueous extract of MILs was confirmed to have the potential to treat diarrhea (De & Pal, 2011).

The antiulcer activity of the ethanol and petroleum ether extracts of MILs was assessed in vivo against aspirin-induced gastric ulcers. The ethanol extract (250 mg/kg) and petroleum ether extract (250 mg/kg) remarkably decreased the ulcer index (Neelima et al., 2012). Mangiferin of MILs can alleviate damaged gastrointestinal motility and reduce intestinal inflammation, consequently facilitating gastrointestinal transit. It also showed the anti-ulcerogenic activity (Severi et al., 2009). In another study, mangiferin was found to significantly suppress inflammatory mediators, cytokines, NO_3^-/NO_2^- levels, myeloperoxidase effect, and adhesion compounds in the ileum portion of the small intestine. Mangiferin may act as an excellent therapeutic agent for the treatment of human inflammatory bowel ailments (Swaroop et al., 2018).

7.6. Hepatoprotective activity

Oxidative stress can cause cell and tissue damage. Liver disorders like cirrhosis, necroinflammatory hepatitis, subclinical icteric hepatitis, and carcinoma have an association with oxidative stress and redox imbalance. Therefore, compounds or herbs with antioxidant potency and lipid peroxidation inhibition can exhibit hepato-protective potential (Pourahmad et al., 2010). MILs tea consists of mangiferin and other biologically active substances. Its hepato-protective effects were studied on rats with high-fat-induced obesity. Tea increased antioxidant potential, antioxidant enzymes, AdipoR2 and PPAR-α mRNA, and protein expressions. It also inhibited the SREBP1c and NF-κB p65 gene expressions in the liver. This tea also caused Cpt1 overexpression. There was a significant reduction in the accumulation of fat droplets and hepatic steatosis was also improved.

Consumption of MILs tea showed a strong hepatoprotective effect by decreasing oxidative stress and steatosis, and regulating lipid metabolism (Ramírez et al., 2018). The hepatoprotective effect of ethanol and methanol extract of MILs was investigated in mercuric chloride-triggered toxicity in Swiss albino mice. Mice treated with extracts showed the recovery of damaged hepatocytes. However, the effect of methanolic extract (50 mg/kg) was better than that of ethanolic extract, which may be due to its strong radical scavenging potential. The results showed that oral intake of MILs extract supplement significantly reduced liver toxicity in mice, probably due to its high antioxidant potential (Karuppanan et al., 2014).

7.7. Anti-obesity and cholesterol-lowering effects

A study evaluated the anti-obesity properties of MILs tea in obese male Wistar rats fed with a high-fat diet. The consumption of tea (24.7 ± 2.1 ml/day) exhibited anti-inflammatory and antioxidant benefits. Tea increased the interleukin-10 serum concentration and total antioxidant capacity, reduced accumulation of abdominal fat, increased lipoprotein lipase and PPAR-γ expression, and decreased FAS expression. Studies suggested that MILs tea had remarkable medicinal effects in the treatment of obesity and other related disorders through the regulation of the expression of transcriptional factors and enzymes associated with adipogenesis (Ramírez et al., 2018).

The hypocholesterol effect of methanol extract of MILs was studied through pancreatic cholesterol esterase inhibition analysis in vitro. This investigation showed that the methanol extract of MILs had remarkable hypo-cholesterol potential which was attributed to the presence of 3b-taraxerol (IC_{50}: 0.86 µg/ml) in the extract (Gururaja et al., 2015). In another investigation, the cholesterol-lowering potential of MILs extract was evaluated in vivo in female albino Wistar rats. Plasma triglycerides were significantly reduced using an oral dose of the extract (90 mg/kg) during days 21-42; this confirmed the cholesterol-lowering potential of MILs extract. (Gururaja et al., 2017).

7.8. Cardioprotective activity

A study was conducted to evaluate the activity of alcoholic extract of MILs on cardioprotection against doxorubicin (DOX)-induced cardiac stress. The results revealed remarkable protective effects of the alcoholic extract of MILs against oxidative stress. There was an increase in tissue antioxidant levels and a decrease in serum biomarker enzyme levels. Additionally, animals treated with MILs extract showed improvement in histological score, electrocardiographic parameters, lipid profile, and mortality. (Bhatt & Joshi, 2017).

Mangiferin (a bioactive component of MILs) reportedly protects against DOX-induced high mortality rates and electrocardiogram abnormalities. It also reduced biochemical markers of cardiac toxicity. (Arozal et al., 2014). A study reported that mangiferin ameliorates cardiac toxicity, reduces intracellular levels of reactive oxygen species (ROS) and downregulates related signaling cascades in STZ-induced diabetic models. Mangiferin protects cardiac and renal tissues from streptozotocin (STZ)-induced oxidative damage (Muruganandan et al., 2002).

Mangiferin is highly beneficial against isoproterenol-induced myocardial infarction in rats. Mangiferin pretreatment has been

shown to inhibit isoproterenol-induced effects on changes in mitochondrial infrastructure, functions of various enzymes involved in the TCA cycle, lipid peroxidation level, intracellular ATP level, and endogenous antioxidant mechanisms associated with cardiovascular diseases. The anti-inflammatory and antioxidative properties of mangiferin have been found to be the reason behind the protection caused by mangiferin (Prabhu et al., 2006). A study investigated the antihypertensive effect of ethanol extract of MILs using in vitro and in vivo assays. The dichloromethane fraction of the extract demonstrated hypotensive activity via ACE inhibition (99% ± 8), providing benefits in cardiac hypertrophy and baroreflex sensitivity (Ronchi et al., 2015).

7.9. Other health benefits

MILs have potential curative effects in respiratory disorders, especially whooping cough (respiratory tract infection). It is also useful in treating colds, bronchitis and asthma. Therefore, it is considered a powerful agent for respiratory disorders. The therapeutic properties of MILs make them an outstanding herbal mouthwash that acts as a pain reliever for gingivitis and other gum problems. Ashes of burnt leaves provide quick relief when applied to burns (Muralikrishna et al., 2014).

8. Toxicology of *M. indica* leaves

Various studies have reported beneficial activities of *M. indica* leaves extract against various diseases such as diabetes, cancer, neurodegenerative and cardiovascular disorders. These beneficial effects are confirmed by the presence of a wide range of bioactive substances. However, the harmful effects of leaf extract due to allergens have also been reported in a few studies. There are two ways in which *M. indica* allergy can be observed: immediate hypersensitivity reaction, including erythema, anaphylaxis, wheezing, angioedema, dyspnea, and urticaria, or late reaction, including periorbital edema and contact dermatitis. (Sareen & Shah, 2011). Transcriptome analysis of *M. indica* leaves and fruits reported the presence of sixty-six strong allergenic genes, mainly associated with the pollen allergen, NADPH-dependent flavin mononucleotide reductase, and the pathogenesis-related protein Bet v I family. A study reported that human subjects previously exposed to poison ivy/oak allergy had a chance of developing allergic contact dermatitis due to Mangifera indica upon initial exposure (Hershko et al., 2005). However, studies have generally suggested that Mangifera indica has some allergic reactions, but these side reactions are limited to the pollen allergen, latex, or previous exposure to urushiol (Goldstein, 2004). In a study, *M. indica* leaves extract showed toxicity in lung fibroblast (WI-38 VA-13 subline 2RA, ATCC CLS 300421) (Ganogpichayagrai et al., 2017).

9. Conclusions

According to numerous research reviews, M. indica leaves contain potent chemical compounds with distinct pharmacological activities. MILs have remarkable biological, medical and metabolic effects. MILs form bioactive compounds as well as minerals and vitamins. Its phytoactive compounds include flavonoids, benzophenones, terpenes, phenolic compounds, anthocyanidins, xanthones, saponins, tannins, and alkaloids. Reportedly, MILs have anticancer potential against lung cancer, breast cancer cell lines, colorectal carcinoma, adenocarcinoma, liver hepatoblastoma, bronchogenic carcinoma, ductal carcinoma, colon adenocarcinoma, and gastric carcinoma. MILs have strong antibacterial, antifungal, and antiviral properties. Chemical compounds of MILs are effective against HSV-1, HSV-2, and HIV. The leaves are very important as anti-obesity and lipid-lowering agents. MILs have potent hepato-protective, gastro-protective, cardio-protective and antihypertensive effects. They have been found to be very useful in treating numerous ailments such as diarrhoea, ulcers, diabetes and fatty liver disease. Thus, it was concluded that MILs contain potent phytochemical compounds with remarkable therapeutic benefits.

Phytochemical studies have shown that further investigation of *M. indica* leaves is needed to uncover other phytoactive agents and potential therapeutic effects. Clinical studies should also be conducted on MILs to further investigate their effectiveness.

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Conflict of interest

The authors confirm that there are no known conflicts of interest.

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In this study, no method requiring the permission of the “Ethics Committee” was used.

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Jawaria Mehmood: Manuscript editing
Noor Zulfiqar: Manuscript editing

ORCID Numbers of the Authors

H. Mehmood: 0009-0009-9552-6542
J. Mehmood: 0009-0009-2439-233X
N. Zulfiqar:: 0009-0004-4171-682X

Supplementary File

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