A review of antidiabetic potential of Mangifera indica leaf extract

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A review of antidiabetic potential of *Mangifera indica* leaf extract

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Abstract

*Mangifera indica* Linn. (Anacardiaceae) is commonly called mango or ‘Mamuang’ in Thai. In ethnomedical systems, *M. indica* leaves have been used for the treatment of fever, diarrhea, fainting, abnormality of lymph node and diabetes. Phytochemical screening of *M. indica* leaves showed the presence of flavonoids, tannins, alkaloids, terpenoids, anthraquinones, saponins, cardiac glycosides and steroids. Mangiferin has been regarded as its major compound. Several biological properties of *M. indica* leaves such as anti-inflammatory, antioxidant, hypoglycemic
and hypolipidemic activities were reported. This article is focus on the traditional usage
accompanied with pharmacological activities involving diabetes treatment such as
antioxidant and antidiabetic activity of *M. indica* leaves. This information would be
useful for phytopharmaceutical product development as an adjuvant therapy to diabetes
treatment.

**Keywords:** antidiabetic, antioxidant, *Mangifera indica*, mangiferin, mango

### 1. Introduction

Diabetes is one of the biggest health emergencies of the 21st century. Of the 56.4
million deaths worldwide in 2015, diabetes killed 1.6 million people, up from less than
1 million in 2000 (World Health Organization [WHO], 2017). The worldwide
prevalence of diabetes has continued to increase dramatically. In 2015, 415 million
people or 8.8% of adults are estimated by International Diabetes Federation (IDF) to
have diabetes. By 2040, this number is expected to reach almost 642 million (10.4%)
unless an effective prevention is approachable. Type 2 diabetes is the most common
type and occupied up to 91% of diagnosed adults with diabetes (International Diabetes
Federation [IDF], 2015). In most countries, type 2 diabetes has increased gradually
alongside rapid lifestyle and social changes including aging populations, increasing
urbanization, reduced physical activity, changing food intake pattern by increasing
sugar consumption and low fruit and vegetable intake (WHO, 2002). This disease has a
significant impact on the health, quality of life, life expectancy of patients as well as on
the health care system. Because of increasing use of health services, loss of productivity
and the long term support is needed to overcome diabetes related complications, such as
kidney failure, blindness or cardiac problems. Many countries spent between 5% and 20% of their total health expenditure on diabetes (IDF, 2015).

Different classes of antidiabetic drugs act on lowering blood glucose value through different mode of actions, for example, increased insulin secretion (sulfonylureas and meglitinides), decreased insulin resistance (biguanides and thiazolidinediones), increased prandial insulin secretion (DPP-4 inhibitors), reduced carbohydrate absorption (α-glucosidase inhibitors) and inhibiting glucose reabsorption in the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels (SGLT2 inhibitors) (Chao & Henry, 2010). Even though almost of antihyperglycemic agents available nowadays are effective, they associated with many potential undesirable effects including hypoglycemic episodes, gastrointestinal disturbances, skin reactions, lactic acidosis, fluid retention and weight gain (Krentz & Bailey, 2005). Furthermore, inhibition of intracellular free radical formation would provide a therapeutic strategy to prevent oxidative stress and the related diabetic vascular complications. Therefore, it is preferable to explore the phytochemical substances which could be used as a potential adjuvant therapy in type 2 diabetic patients. This article aims to evaluate the antioxidant and antidiabetic activity of *M. indica* leaves.

2. Botanical data

*Mangifera indica* Linn. (Anacardiaceae), an evergreen perennial woody plant, is commonly known as mango or ‘Mamuang’ in Thai. It is originated in tropical Asia mainly in India and Myanmar (Bally, 2006). Nowadays, mango is cultivated throughout the tropical and subtropical regions around the world. There are several cultivars
globally. In Southeast Asian region (Philippines, Malaysia, Indonesia, Singapore and Thailand), over 500 cultivars have been identified. In Thailand, *M. indica* is cultivated as an economically important fruit. The famous and ubiquitous *M. indica* cultivars in Thailand including Nam Dok Mai, Kiew Savoey, Okrong, Chok Anan, Fah Lan, Gaew, etc.

*M. indica* or mango tree is a fast-growing and long-lived orchard. It is very vigorous with a large canopy and an almost circular projection. The leaves are perennial, simple alternate and yellow green to purple in color when young that changes to leathery, glossy and deep green in color when mature. The inflorescence occurs in panicles consisting of about 3000 whitish-red or yellowish–green flowers. In tropical regions, the trees can reach up to 30–40 meters in height, while in subtropical areas the growth rate is consistently reduced. The mango fruit has hundreds of varieties, each having its own characteristic taste, shape and size. Each fruit is 5–15 cm long and 4–10 cm in diameter. Usually its weight ranges from 150 grams to around 750 grams (Farina, Corona, Mineo, D’Asaro, & Barone, 2013). The outer peel (exocarp) is smooth and is green in unripe mango, but it turns golden yellow, crimson red, yellow or orange-red in ripe fruits, depending upon the cultivar type. The endocarp is a large ovoid-oblong core that contains a single seed. The pulp (mesocarp) is orange-yellow in color, well-endowed with numerous soft fibrils. Its flavor is pleasant and rich, and its taste is sweet with mild tartness. Mango is consumed fresh or is processed for chutney, pickles, curries, dried products, puree, nectar and canned or frozen slices that are popular worldwide.

Taxonomy of *M. indica* is as following (Masud Parvez, 2016):

Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Sapindales
Family: Anacardiaceae
Genus: Mangifera
Species: *M. indica*

3. Traditional used

*M. indica* is commonly used in traditional medicine for many remedies for over 4000 years (Jiangsu, 1977). According to Ayurvedic medicine, various parts of mango tree possessed several medicinal properties. The root, bark, leaves, flowers, unripe and ripe fruit are acrid, cooling and astringent to the bowels. Different parts of *M. indica* have been used traditionally for treatment of various ailments including gastrointestinal problems (dysentery, piles, stomach upset, biliousness, constipation), respiratory ailments (bronchitis, asthma, hiccup, throat problems), genitourinary problems (urinary discharges, leucorrhoea, vaginal problems) and ophthalmic complaints. It is also used as aphrodisiac, tonic, appetizer, laxative, diuretic, stomachic and for tanning purposes in various parts of the world (Ediriweera, Tennekoon, & Samarakoon, 2017; Singh, Sharma, Kumar, Kumar, & Sinha, 2009). The traditional used of different parts of *M. indica* are summarized in Table 1.
The young leaves, located at the first 5-7 leaves from the branch end and characterized by the softness with yellow green to purple in color, usually found during March to May. Leaves of mango are deemed as worthless and often neglected, although young leaves of mango can be boiled to make them edible (Lim, 2012). In Ayurvedic medicinal system, diabetes has been treated with a drink made from the infusion of fresh mango leaves (Bally, 2006). Leaves are used as astringent, refrigerant, styptic, vulnerary and for the treatment of constipation. They are also useful in conditions of cough, asthma, hiccup, burning sensation, hemorrhages, hemorrhoids, wounds, abscesses, ulcers, diarrhea, dysentery, liver disorders, tooth decay, pharyngopathy, scorpion sting and stomachopathy. The ash of burnt leaves are useful in burns and scalds. The fumes from burning leaves is inhaled for relief of hiccup and throat diseases (Masud Parvez, 2016). Fresh leaves are masticated to tone up the gums (Majumdar & Sharma, 1985) and used as an antitussive in certain Chinese regions such as Guangxi province (Jiangsu, 1977). The leaf tea is used for fever, diarrhea and insomnia (Wong, 1976).

4. Chemical constituents

There are many studies of phytochemical constituents of *M. indica* in several varieties around the world. Phytochemical screening of *M. indica* showed the presence of highly effective bioactive compounds including flavonoids, tannins, alkaloids, terpenoids, anthraquinones, saponins, cardiac glycosides and steroids (Majumder & Paridhavi, 2016; Aiyelaagbe & Osamudiamen, 2009).

Mangiferin, C$_{19}$H$_{18}$O$_{11}$, a glucosylxanthone (1, 3, 6, 7-tetrahydroxyxanthone-C2-β-D-glucoside) is a prominent polyphenolic constituent mostly found in *M. indica*. 
Mangiferin is widely distributed in a variety of plants especially Anacardiaceae and Gentianaceae family. **The main source of mangiferin has been reported mainly in mango leaves, barks and fruit peels.** The amount of mangiferin was varied in the peels (4.94-15.23 g/kg dry matter), kernels (6.40-8.98 g/kg dry matter), bark (4.77-107.18 g/kg dry matter), young leaves (11.11-171.67 g/kg dry matter) and mature leaves (3.71-93.62 g/kg dry matter) in different Brazilian mango varieties (Barreto et al., 2008).

Mangiferin in the methanolic and ethanolic extract of mango leaves was quantified to be 3.9-4.6% and 7.8% respectively by HPLC method (Gururaja et al., 2017; Zhang et al., 2013). From the study of mangiferin content in the mature leaves of fifty *M. indica* cultivars using enzyme linked immunosorbet assay, the mangiferin contents ranged from 1.94±0.13% to 13.79±0.84% dry weight. Various factors such as location, fertilizer, age, and environment that specific to each cultivar may also affect the content of mangiferin (Yusakul, Kitirattrakarn, Tanwanichkul, Tanaka, & Putilun, 2012).

Quantification of phytochemical compositions revealed higher contents of most bioactive compounds especially polyphenolic compounds and flavonoids in young leaves than in mature leaves (Bhuvaneshwari, Khanam, & Devi, 2014; Barreto et al., 2008). Sixty-six terpenoids were found in young leaves extracts derived from hydrodistillation and solid phase microextraction (Gebara, de Oliveira, Ré-Poppi, Simionatto, & Caesw, 2011).

3β-taraxerol, a triterpenoid, was isolated from ethyl acetate and methanolic extract of mango leaves (Sangeetha et al., 2010; Gururaja et al., 2017). Mangiferin and isomangiferin were characterized along with several xanthone-C-glucosides and benzophenone derivatives (Bhusari et al., 2012; Tanaka, Seuyasu, Nanaka, & Nishioka, 1984; Severi et al., 2009; Zhang et al., 2011; Pan, Yi, Wang, Chen, & He, 2016).
Gallotannins, catechin, quercetin derivatives and phenolic acids were also found in mango leaves (Barreto et al., 2008; Mohan, Viswanatha, Savinay, Rajendra, & Halemani, 2013). Seven volatile acids were identified in leaves including benzoic acid, pyrogallol, p-hydroxybenzoic acid, vanillic acid, syringic acid, ferulic acid, ethyl gallate and gallic acid (Elzaawely & Tawata, 2010). Chemical structure of some common compounds present in *M. indica* leaves are shown in Figure 1.

5. Biological activity

Mangiferin isolated from *M. indica* as well as *M. indica* leaves extract have been reported for their various *in vitro* and *in vivo* biological activities, for example, analgesic (Garrido-Suarez, Garrido, Garcia & Delgado-Hernandez, 2014; Garrido-Suarez et al., 2014; Tarkang et al., 2015), antipyretic (Tarkang et al., 2015; Kant et al., 2011), anti-inflammatory (Carvalho et al., 2009; Rivera et al., 2011; Garrido et al., 2004), antioxidant (Rajendran, Ekambaram, & Sakthiasekaran, 2008; Pal, Sinha, & Sil, 2013; Leeprechanon & Jutiviboonsuk, 2015; Kawpoomhae, Sukma, Ngawhirunpat, Opanasopit, & Sripattanaporn, 2010; Ling et al., 2009) hypoglycemic (Ganogpichayagrai, Palanuvej, & Ruangrungsi, 2017; Kumar, Krishnakumar, Jaganathan, & Mandal, 2013; Muruganandan, Srinivasan, Gupta, Gupta, & Lal, 2005; Dineshkumar, Mitra, & Manjunatha, 2010; Aderibigbe, Emudianughe, & Lawal, 2001; Andrew, Yusuf, Jangabe, Lawal, & Adamu, 2013) and hypolipidemic properties (Muruganandan et al., 2005; Dineshkumar et al., 2010). This article will primarily focus on the antioxidant and antidiabetic properties of mangiferin and *M. indica* leaves extract.

5.1 Antioxidant activity
Recent evidence suggests that oxidative stress may contribute to the pathogenesis of type 2 diabetes by increasing insulin resistance or impairing insulin secretion (Montonen, Knekt, Jarvinen, & Reunanen, 2004). Hyperglycemia is associated with the promotion of auto-oxidation of glucose to form free radicals beyond the scavenging abilities of endogenous antioxidant defenses, thus resulted in macro and microvascular dysfunction (Bajaj & Khan, 2012).

Several parts (bark, leaves and fruit) of *M. indica* are reported to contain polyphenols, phenolic acids, and flavonoids. Structurally, phenolic groups serve as a source of readily available hydrogen atoms that the radicals produced can be delocalized over the phenolic structure. They have been demonstrated to have preventive and therapeutic effects in many diseases (Robards, Prenzler, Tucker, Swatsitang & Glover, 1999). The antioxidant property of *M. indica* extract could be attributed to mangiferin, the major active compound. Moreover, common compounds found in various parts of *M. indica* such as gallic acid, catechin, quercetin, and gallotannins have been reported to have antioxidant activities in several *in vitro* and *in vivo* studies. Carotenoids, tocopherols and ascorbic acid which mostly found in fruit peel and flesh of *M. indica* have also been reported (Ediriweera et al., 2017).

The chemical structure of mangiferin comprises of two aromatic rings, nonaromatic secondary hydroxyl groups, one lactonic carbonyl group, and one primary glycosidic hydroxyl group. The scavenging ability of the mangiferin is mainly due to the presence of hydroxyl groups in its chemical structure. Mangiferin is also an efficient iron chelator. Catechol moiety of mangiferin forms a stable complex with iron and preventing the generation of hydroxyl radical in Fenton-type reactions (Jyotshna, Khare & Shanker, 2016). Hyperglycemia generates reactive oxygen species, which can cause
lipid peroxidation and membrane damage (Hunt, Dean & Wolff, 1988). Being a potent radical scavenger, it inhibits the free radical-mediated formation of advanced glycation end products (AGEs) and thus is beneficial for counteracting the complications associated with diabetes (Wolff, Jiang & Hunt, 1991).

**In vitro studies**

The potential free radical scavenger of mangiferin have been proposed in many studies. The antioxidant activity of leaves, fruit peels, bark and kernel of 2 mango varieties which are popularly consumed in Pakistan was investigated. For the DPPH radical scavenging activities, the fruit peels extract significantly displayed the higher antioxidant potential (p<0.05). Similarly, the fruit peels extract contained the significantly higher amounts of total phenolic and flavonoid compounds (p<0.05). The amount of total phenolic, total flavonoid contents of different parts of mango were in the following order: fruit peels > leaves > bark > kernel (Sultana, Hussain, Asif, & Munir, 2012).

Mangiferin isolated from leaves of *M. indica* var. Namdokmai in 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay showed the potent antioxidant activity of with an IC$_{50}$ value of 6.38 µg/mL whereas ascorbic acid and trolox produced IC$_{50}$ values of 5.24 and 7.89 µg/mL, respectively (Leeprechanon & Jutiviboonsuk, 2015).

*In vitro* antioxidant assay using DPPH, ABTS and other methods showed the potent free radical scavenging activities of *M. indica* leaves as shown in Table 2. Furthermore, the biological radicals such as hydrogen peroxide, superoxide and hydroxyl radicals were scavenged and ferrous ions were also chelated by these extracts (Barreto et al., 2008; Pan et al., 2016; Kawpoomhae et al., 2010; Badmus et al., 2011; Fidrianny, Rahmiyani, & Wirasutisna, 2013; Mohan, Viswanatha, Savinay, Rajendra, &
Halemani, 2013; Ling et al., 2009). Several studies determined total phenolic/flavonoid content which revealed considerable amounts of those compounds (Barreto et al., 2008; Pan et al., 2016; Kawpoomhae et al., 2010; Badmus et al., 2011; Tarkang et al., 2015; Fidrianny et al., 2013; Ling, Radhakrishnan, Subramaniam, Cheng, & Palanisamy, 2010).

**In vivo studies**

In vivo studies demonstrated that mangiferin restored the levels of catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione s-transferase and reduced glutathione while diminishing lipid peroxidation and protein carbonylation in animal models (Rajendran et al., 2008; Pal et al., 2013). Mangiferin also showed significant protective activity in Human Umbilical Vein Endothelial Cells (HUVEC) under H$_2$O$_2$-induced stress, indicating the potential benefits in the prevention of oxidative stress-associated diseases (Luo et al., 2012). Moreover, *in vivo* antioxidant activity of *M. indica* leaves extracts were evaluated on various biochemical parameters such as catalase, superoxide dismutase, reduced glutathione level and lipid peroxidation.

*M. indica* leaves extracts enhanced catalase and superoxide dismutase enzyme activities and also prevented the reduced glutathione levels depletion and lipid peroxidation in a dose-dependent manner (Viswanatha, Shylaja, & Mohan, 2013).

**Human studies**

At present, there is no literature report of *M. indica* leaf extract on human studies.

5.2 Antidiabetic activity

In vitro studies

α-glucosidase and α-amylase inhibitory activities
One of the targeting enzymes in diabetic treatment is α-glucosidase, which is present in the brush border of enterocytes lining in the intestinal villi. Inhibition of this enzyme prevents the cleavage of disaccharides and oligosaccharides into monosaccharides, thus delaying intestinal glucose absorption. Generally, α-glucosidase inhibitors minimize the rise in postprandial blood glucose levels and thereby reduce postprandial insulin concentrations (Lebovitz, 1998). Mangiferin showed α-glucosidase and pancreatic α-amylase inhibitory activities with the IC\textsubscript{50} of 0.58 and 1.05 mg/mL, respectively (Ganogpichayagr'ai et al., 2017). Another study observed that mangiferin exhibited appreciable α-glucosidase and α-amylase inhibitory effects with the IC\textsubscript{50} value of 41.88±3.9 µg/mL and 74.35±1.9 µg/mL (Dineshkumar et al., 2010). In the 3T3-L1 cells study, mangiferin at the concentration of 1 mM isolated from \textit{M. indica} stem bark increased the glucose utilization in a dose-dependent manner up to 2-fold compared to the untreated control (Kumar et al., 2013).

Several studies have been performed to evaluate the α-glucosidase and α-amylase inhibitory activity of \textit{M. indica} leaf extracts. Some benzophenones and triterpenoids in ethanolic leaf extract exhibited pronounced α-glucosidase inhibitory effect (Pan et al., 2016). An aqueous extract and ethanolic extract of leaves inhibited yeast α-glucosidase enzyme with the IC\textsubscript{50} value of 59.0±0.17 and 50 µg/mL, respectively (Ganogpichayagr'ai et al., 2017; Andrew et al., 2013). Ethanolic leaf extract also showed pancreatic α-amylase inhibitory activity with the IC\textsubscript{50} value of 2.28 mg/mL (Andrew et al., 2013). Methanolic extract of young leaves exhibited the stronger pancreatic α-amylase inhibitory activity when compared with extract of mature leaves with the IC\textsubscript{50} value of 22.01 and 35.73 µg/mL, respectively (Bhuvaneshwari et al., 2014).
**Enhancing glucose uptake and glycogen synthesis**

3β-taraxerol, isolated from ethyl acetate extract of leaves, exerted antidiabetic potential by enhancing glucose uptake and glycogen synthesis in 3T3-L1 adipocytes in a dose-dependent manner (Sangeetha et al., 2010).

**Dipeptidyl peptidase-4 inhibitory activity**

Glucagon-like peptide 1 (GLP-1) is an incretin released from L cells in the intestine after meal intake. Due to the ability of GLP-1 to enhance insulin secretion in a glucose-dependent manner, it has been proposed as a new treatment for type 2 diabetes. However, the therapeutic potential of GLP-1 is limited by its rapid degradation and inactivation *in vivo* by dipeptidyl peptidase-4 (DPP-4). The inhibitory effect of DPP-4 enhances the level of GLP-1, which would consequently improve glucose tolerance and increased insulin secretion. The methanolic extract of *M. indica* leaves were tested *in vitro* for dipeptidyl peptidase-4 (DPP-4) inhibitory activity and showed a potent activity with an IC$_{50}$ value of 182.7 µg/mL (Yogisha & Raveesha, 2010).

**In vivo studies**

In animal models, chronic administration of mangiferin isolated from *M. indica* leaves (10 and 20 mg/kg) once daily for 28 days revealed significant reduction in plasma glucose level and improvement of lipid profile in STZ-induced diabetic rats. Moreover, it also showed the improvement in oral glucose tolerance in normoglycemic rats (Murugannandan et al., 2005). In another study, administration of mangiferin exhibited potential antidiabetic and hypolipidemic effects by lowering blood glucose level and improving lipid profiles in STZ-NA-induced type 2 diabetic rats but these effects were not found in STZ-induced type 1 diabetic rat models (Dineshkumar et al., 2010). The combination of DPP-4 inhibitor (sitagliptin 1 mg/kg) and 20 mg/kg of
mangiferin significantly improved glucose tolerance with an increase in plasma insulin level and active GLP-1 levels in streptozotocin-diabetic rats. Islets of Langerhans from combination-treated diabetic rats had markedly increased β-cell/islet area ratio compared to islets from the diabetic rats (Hou et al., 2012). In animal models, administration of aqueous mango leaf extract resulted in a reduction of blood glucose level which was accompanied by an elevation of insulin level in type 2 diabetic mice. Furthermore, administration of aqueous mango leaf extract also improved serum lipid profiles, cardiovascular and endothelial dysfunctions in type 2 diabetic rats (El-Sheikh, 2012). The aqueous extract lowered the blood glucose levels in both normoglycemic and glucose-induced hyperglycemic mice (Aderibigbe et al., 2001). This may be due to stimulation of the pancreatic beta cells to release insulin or the reduction in the intestinal absorption of glucose. Administration of mango leaf ethanolic extract showed the similar tendency in reduction of serum glucose and lipid level in KK-Ay mice (Zhang et al., 2013).

In another study, the ethanolic extract of young leaves significantly normalized the blood glucose level more rapidly when compared with the mature leaves in oral glucose tolerance test in normoglycemic rats (Bhuvaneshwari et al., 2014). The results of in vivo antidiabetic activities of mangiferin and M. indica leaves extracts are shown in Table 3.

**Human studies**

At present, there is no literature report of M. indica leaf extract on human studies.

6. Toxicity
Toxicological studies of several solvent extracts of *M. indica* leaves have been investigated. Both single oral administration of aqueous decoction extract in twenty male Swiss mice and methanol extract in female Albino Wistar rats at a dose of 5 g/kg showed no toxic effects in acute toxicity test in treated animals. Any signs or symptoms of toxicity were not observed. There were no significant alteration in water or food consumption. No mortality or abnormality changes were found in any organs after 14 days of administration (Gururaja et al., 2017; Severi et al., 2009).

### 7. Conclusion

Current pharmacological modalities for diabetes are expensive and not ideal because of their side effects and reduction of response after prolonged use. The ethnopharmacological use of herbal medicine for the treatment of diabetes mellitus could potentially be developed as an alternative and inexpensive therapy for treating the disease. Due to the abundance of young mango leaves in Thailand, diverse and high level of active compounds and the safety profiles, *M. indica* is a strong candidate for further development for the treatment or dietary supplements as an adjuvant to diabetes.

### References


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Figure 1 Chemical structure of some common compounds present in *M. indica* leaves.
<table>
<thead>
<tr>
<th>Parts of <em>M. indica</em></th>
<th>Traditional used</th>
<th>Chemical constituents in parts of <em>M. indica</em></th>
<th>Some reported biological activities of <em>M. indica</em></th>
<th>Reference</th>
</tr>
</thead>
</table>
| Bark                 | Diabetes, gastric disorders, asthma, mouth sores, leucorrhea, bleeding hemorrhoids, lung hemorrhage, nerve disorders, syphilis, cough, and jaundice | Mangiferin, isomangiferin, protocatechuic acid, catechin, gallic acid, linalool, quercetin | Antioxidant activity | Barreto et al. (2008)  
Masud Parvez (2016)  
Ediriweera et al. (2017) |
| Leaves               | Diabetes, diarrhoea, hemorrhage, dysentery, cough, gall bladder and kidney diseases, wounds, diseases in throat, hiccups, burns, and scalds | Mangiferin, quercetin catechin, gallic acid, 3β-taraxerol, ethyl gallate, gallotannins, benzophenones | Antioxidant activity | Barreto et al. (2008)  
Dineshkumar et al. (2010)  
Pan et al. (2016)  
Ediriweera et al. (2017) |
| Fruit                | Exhaustion, heat stroke, gastrointestinal disorders, night blindness, urethrorrhoea, vaginopathy, laxative, cardiotonic, haemostatic, aphrodisiac, and tonic | Mangiferin, kaempferol, linalool, quercetin, lupeol, vitamins A and C, β-carotene and xanthophylls | Antioxidant activity | Masud Parvez (2016)  
Ediriweera et al. (2017) |
| Flower               | Ulcers, diarrhea, hemorrhage, anemia, dyspepsia, and dysentery | Gallic acid, ethyl gallate, methyl gallate, n-propyl gallate, n-pentyl gallate, and dihydrogallic acid | Antioxidant activity | Masud Parvez (2016)  
Ediriweera et al. (2017) |
| Fruit peel           | Menorrhea, vaginal problems | Mangiferin, penta-o-galloyl-glucoside, methyl gallate, quercetin | Antioxidant activity | Barreto et al. (2008)  
Masud Parvez (2016)  
Ediriweera et al. (2017) |

Table 1 Traditional used, chemical constituents and some reported biological activities of different parts of *M. indica*
<table>
<thead>
<tr>
<th>Reference</th>
<th>M. indica extract</th>
<th>Total phenolic content</th>
<th>DPPH (IC$_{50}$)</th>
<th>ABTS (IC$_{50}$)</th>
<th>Others</th>
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<tr>
<td>Ling et al. (2009)</td>
<td>Aqueous extract</td>
<td>189 ± 109 mg GAE/g</td>
<td>0.49 ± 0.4 mg/mL</td>
<td>0.13 ± 0.03 mg/mL</td>
<td>Galvinoxyl: IC$_{50}$ = 0.22 ± 0.006 mg/mL</td>
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<td>Ethanol extract</td>
<td>590 ± 48 mg GAE/g</td>
<td>0.17 ± 0.02 mg/mL</td>
<td>0.02 ± 0.003 mg/mL</td>
<td>Galvinoxyl: IC$_{50}$ = 0.049 ± 0.003 mg/mL</td>
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<td>Kawpoomhae et al. (2010)</td>
<td>Methanol extract</td>
<td>420 ± 4.30 mg GAE/g</td>
<td>6.18 ± 0.15 µg/mL</td>
<td>1.33 ± 0.13 µg/mL</td>
<td>Superoxide scavenging: IC$_{50}$ = 0.07 ± 0.01 µg/mL</td>
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<td>Aqueous extract</td>
<td>187 ± 2.20 mg GAE/g</td>
<td>5.57 ± 0.18 µg/mL</td>
<td>2.96 ± 0.05 µg/mL</td>
<td>Superoxide scavenging: IC$_{50}$ = 0.06 ± 0.01 µg/mL</td>
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<td>Chloroform extract</td>
<td>96 ± 2.52 mg GAE/g</td>
<td>72.4 ± 3.24 µg/mL</td>
<td>6.56 ± 0.49 µg/mL</td>
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<td>Badmus et al. (2011)</td>
<td>Ethyl acetate extract</td>
<td>0.127 µg /mg GAE</td>
<td>1.5 µg/mL</td>
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<td>Hydroxyl radical scavenging: IC$_{50}$ = 5 µg/mL</td>
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<td></td>
<td>Aqueous extract</td>
<td>0.111 µg /mg GAE</td>
<td>6.0 µg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC$_{50}$ = 26 µg/mL</td>
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<tr>
<td></td>
<td>Methanol extract</td>
<td>0.106 µg /mg GAE</td>
<td>6.5 µg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC$_{50}$ = 5 µg/mL</td>
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<td>Chloroform extract</td>
<td>0.089 µg /mg GAE</td>
<td>22.5 µg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC$_{50}$ = 66 µg/mL</td>
</tr>
<tr>
<td>Mohan et al. (2013)</td>
<td>Aqueous fraction</td>
<td>31.42 µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethyl acetate fraction</td>
<td>3.55 µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Water soluble fraction</td>
<td>96.26 µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-butanol fraction</td>
<td>14.19 µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leeprechanon &amp; Jutiviboonsuk (2015)</td>
<td>Methanol extract</td>
<td>6.38 µg/mL</td>
<td></td>
<td></td>
<td>Trolox: IC$<em>{50}$ = 7.89 µg/mL; Ascorbic acid: IC$</em>{50}$ = 5.24 µg/mL</td>
</tr>
</tbody>
</table>

GAE = gallic acid equivalent, IC$_{50}$ = the half maximal inhibitory concentration, DPPH = 2,2-diphenyl-1-picrylhydrazyl, ABTS = 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), Galvinoxyl = 2,6-Di-tert-butyl-α-(3,5-di-tert-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-p-tolyloxy

**Table 2** *In vitro* antioxidant activities and total phenolic contents of *M. indica* leaf extracts
<table>
<thead>
<tr>
<th>Reference</th>
<th>Participant</th>
<th>Hyperglycemic inducer</th>
<th>Duration</th>
<th>Dosage regimen</th>
<th>Experimental evidence for its use for diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aderibigbe et al. (2001)</td>
<td>4 wk old female Balb/c mice</td>
<td>STZ (100mg/kg, i.p.), 50% glucose (1g/kg, p.o.)</td>
<td>8 weeks</td>
<td>1g/kg of aqueous extract of leaves</td>
<td>Decreased blood glucose level in normal and glucose loaded mice</td>
</tr>
<tr>
<td>Muruganandan et al. (2005)</td>
<td>Male Wistar rats (100–125 g)</td>
<td>STZ (55 mg/kg, i.v.)</td>
<td>28 days</td>
<td>Mangiferin (10 and 20 mg/kg, i.p.)</td>
<td>Decreased fasting plasma glucose levels in diabetic rats and improved oral glucose tolerance in normal rats after oral glucose tolerance test</td>
</tr>
<tr>
<td>Dineshkumar et al. (2010)</td>
<td>Male Wistar rats (150-200 g)</td>
<td>STZ (65 mg/kg i.p.) with NA (110 mg/kg, i.p.)</td>
<td>30 days</td>
<td>Mangiferin</td>
<td>Reduced fasting blood sugar level in type-2 diabetic rats</td>
</tr>
<tr>
<td>El-Sheikh. (2012)</td>
<td>Male Wistar albino rats (180-220 g)</td>
<td>STZ (40 mg/kg, s.c.)</td>
<td>42 days</td>
<td>1 mL/ 100 g of leaves water extract</td>
<td>Reduced serum glucose level and elevated insulin level in STZ-induced diabetic rats</td>
</tr>
<tr>
<td>Zhang et al. (2013)</td>
<td>KK-A’ mice and C57BL/6 J (6 weeks old, male and female, 18-22 g)</td>
<td>-</td>
<td>8 weeks</td>
<td>200, 500 mg/kg/day of ethanolic extract of leaves</td>
<td>Reduced serum glucose level in a dose-dependent manner</td>
</tr>
<tr>
<td>Bhuvaneshwari et al. (2014)</td>
<td>Wistar Albino rats (200-250 g)</td>
<td>Glucose (1 g/kg, p.o.)</td>
<td></td>
<td>500 mg/kg of methanolic extract of young and mature leaves</td>
<td>Normalized the blood glucose level in oral glucose tolerance test in normoglycemic rats more rapidly in young leaves extract</td>
</tr>
</tbody>
</table>

STZ = Streptozotocin, NA = nicotinamide, i.p. = intraperitoneal, p.o. = orally, i.v. = intravenous, s.c. = subcutaneous

Table 3 *In vivo* antidiabetic activities of mangiferin and *M. indica* leaf extracts