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Review Article

A review of the 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 review focuses 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 were estimated by International Diabetes Federation (IDF) to have diabetes. By 2040, this number is expected to reach almost 642 million (10.4%) unless effective prevention is available. Type 2 diabetes is the most common type and occurs up to 91% of diagnosed adults with diabetes (International Diabetic 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 patterns by increasing sugar consumption, and low fruit and vegetable intake (WHO, 2002). This disease has a significant impact on the health, quality of life, and life expectancy of patients as well as on the health care system. Because of increasing use of health services, loss of productivity and long term support is needed to overcome diabetes related complications, such as kidney failure, blindness, and cardiac problems. Many countries spent between 5% and 20% of their total health expenditures on diabetes (IDF, 2015).

Different classes of antidiabetic drugs act on lowering the level of blood glucose through different mode of

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actions, for example increased insulin secretion (sulfonylureas and meglitinides), decreased insulin resistance (biguanides and thiazolidenediones), 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 most of the antihyperglycemic agents available nowadays are effective, they are associated with many potential undesirable effects that include 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 phytochemical substances which could be used as potential adjuvant therapies in type 2 diabetic patients. This review aimed 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 originated in tropical Asia mainly in India and Myanmar (Bally, 2006). Nowadays, mango is cultivated throughout the tropical and subtropical regions around the world. Globally, there are several cultivars. In the Southeast Asian region, that includes the 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 include Nam Dok Mai, Kiew Savoey, Okrong, Chok Anan, Fah Lan, and Gaew.

M. indica or mango tree is fast-growing and long-lived. 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. Inflorescence occurs in panicles consisting of about 3000 whitish-red or yellowish–green flowers. In tropical regions, the trees can reach 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 and 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.

The taxonomy of *M. indica* is as follows (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 Uses

M. indica has been commonly used in traditional medicine for many remedies for over 4000 years (Jiangsu, 1977). According to Ayurvedic medicine, various parts of the mango tree can possess 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 an 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 uses 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, are usually found during March to May. The 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 the Ayurvedic medicinal system, diabetes has been treated with a drink made from the infusion of fresh mango leaves (Bally, 2006). Leaves are used as an 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 string, and stomachopathy. The ashes of the burnt leaves are useful in burns and scalds. The fumes from burning leaves are inhaled for relief of hiccup and throat diseases (Masud Parvez, 2016). Fresh leaves are masticated to tone up the gums (Majumdar & Sharma, 1985) and they are used as an antitussive in certain Chinese regions such as Guangxi Province (Jiangsu, 1977). A tea from the leaves is used for fever, diarrhea, and insomnia (Wong, 1976).

4. Chemical Constituents

Many studies on the phytochemical constituents of *M. indica* have been conducted 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 (Aiyelaagbe & Osamudiamen, 2009; Majumder & Paridhavi, 2016).

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*. Mangi-

Table 1. Traditional use, chemical constituents, and some reported biological activities of different parts of *M. indica*.

Parts of *M. indica*	Traditional use	Chemical constituents in parts of *M. indica*	Some reported biological activities of *M. indica*	Reference
Bark	Diabetes, gastric disorders, asthma, mouth sores, leucorrhea, bleeding hemorrhoids, lung hemorrhage, nerve disorders, syphyllis, cough, and jaundice	Mangiferin, isomangiferin, protocatechuic acid, catechin, gallic acid, linalool,quercetin	Antioxidant activity Antidiabetic activity Anti-inflammatory activity Analgesic effect Antibacterial activity	Barreto *et al.* (2008) Masud Parvez (2016) Ediriweera *et al.* (2017)
Leaves	Diabetes, diarrhea, 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 Antidiabetic activity Anti-inflammatory activity Analgesic effect Hypolipidemic effect	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 Antidiabetic activity Anti-inflammatory activity Immunomodulatory effect	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 Anti-inflammatory activity Analgesic effect	Masud Parvez (2016) Ediriweera *et al.* (2017)
Fruit peel	Menorrhea, vaginal problems	Mangiferin, penta-o-galloyl-glucoside, methyl gallate, quercetin	Antioxidant activity Antidiabetic activity Cytotoxic effect Antibacterial activity	Barreto *et al.* (2008) Masud Parvez (2016) Ediriweera *et al.* (2017)

ferin is widely distributed in a variety of plants especially in the families of Anacardiaceae and Gentianaceae. The source of mangiferin was reported mainly in mango leaves, barks, and fruit peels. The amount of mangiferin 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 extracts of mango leaves was quantified to be 3.9-4.6% and 7.8% respectively by high-performance liquid chromatography (Gururaja *et al.*, 2017; Zhang *et al.*, 2013). From studies of mangiferin content in mature leaves of 50 *M. indica* cultivars using enzyme linked immunosorbent 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 were specific to each cultivar may also affect the content of mangiferin (Yusakul, Kitirattrakarn, Tanwanichkul, Tanaka, & Putalun, 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 leaf extracts derived from hydrodistillation and solid phase microextraction (Gebara, de Oliveira, Ré-Poppi, Simionatto, & Caeaswk, 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; Pan, Yi, Wang, Chen, & He, 2016; Severi *et al.*, 2009; Tanaka, Seuyasu, Nanaka, & Nishioka, 1984; Zhang *et al.*, 2011). Gallotannins, cathechin, 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 that included benzoic acid, pyrogallol, *p*-hydroxy-benzoic acid, vanillic acid, syringic acid, ferulic acid, ethyl gallate, and gallic acid (Elzaawely & Tawata, 2010). The chemical structure of some phytochemical compounds present in *M. indica* leaves are shown in Figure 1.

5. Biological Activity

Mangiferin isolated from *M. indica* as well as *M. indica* leaf extracts were 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 (Kant *et al.*, 2011; Tarkang *et al.*, 2015), anti-inflammatory (Carvalho *et al.*, 2009; Garrido *et al.*, 2004; Rivera *et al.*, 2011), antioxidant (Kawpoomhae, Sukma, Ngawhirunpat, Opanasopit, & Sripattanaporn, 2010; Leeprechanon & Juti viboonsuk, 2015; Ling *et al.*, 2009; Pal, Sinha, & Sil, 2013; Rajendran, Ekambaram, & Sakthisekaran, 2008;), hypoglycemic (Aderibigbe, Emudianughe, & Lawal, 2001; Andrew, Yusuf, Jangabe, Lawal, & Adamu, 2013; Dineshkumar, Mitra, & Manjunatha, 2010; Ganogpichayagrai, Palanuvej, & Ruangrungsi, 2017; Kumar, Krishnakumar, Jaganathan, & Mandal, 2013; Muruganandan, Srinivasan, Gupta, Gupta, & Lal, 2005), and hypolipidemic properties (Dineshkumar *et al.*, 2010; Muruganandan *et al.*, 2005). This review will focus

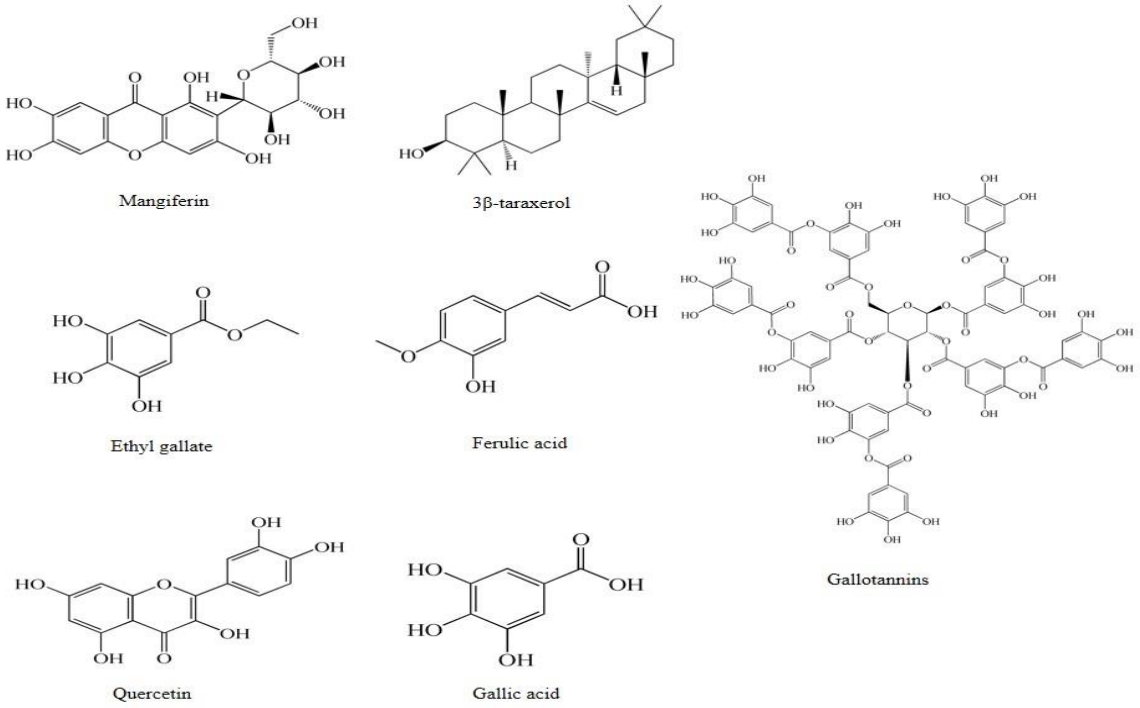

Figure 1. Chemical structure of some phytochemical compounds present in *M. indica* leaves.

primarily on the antioxidant and antidiabetic properties of mangiferin and *M. indica* leaf extract.

5.1 Antioxidant activity

Recent evidence has suggested 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 which results in macro and microvascular dysfunction (Bajaj & Khan, 2012).

Several parts (bark, leaves, and fruit) of *M. indica* were reported to contain polyphenols, phenolic acids, and flavonoids. Structurally, phenolic groups serve as a source of readily available hydrogen atoms that scavenge free radicals that are produced and delocalized them over the phenolic structure. They were demonstrated to have preventive and therapeutic effects in many diseases (Robards, Prenzler, Tucker, Swatsitang & Glover, 1999). The antioxidant properties of *M. indica* extract may 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 were reported to have antioxidant activities in several *in vitro* and *in vivo* studies. Carotenoids, tocopherols, and ascorbic acid, which are found mostly in the fruit peel and flesh of *M. indica*, were also reported (Ediriweera *et al.*, 2017).

The chemical structure of mangiferin is comprised 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 the hydroxyl groups in its chemical structure. Mangiferin is also an efficient iron chelator. Catechol moiety of mangiferin forms a stable complex with iron and prevents the generation of hydroxyl radicals 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 and thus is beneficial for counteracting the complications associated with diabetes (Wolff, Jiang & Hunt, 1991).

5.1.1 *In vitro* studies

The potential free radical scavenging by mangiferin has been proposed in many studies. The antioxidant activity of the leaves, fruit peels, bark, and kernel of two mango varieties that are popularly consumed in Pakistan was investigated. For the DPPH radical scavenging activities, the fruit peel extract significantly displayed higher antioxidant potential (p<0.05). Similarly, the fruit peel extract contained 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 the leaves of *M. indica* var. Namdokmai in a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay showed the potent antioxidant activity with a 50% inhibitory concentration (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 (Table 2). Furthermore, biological radicals such as hydrogen peroxide, superoxide, and hydroxyl radicals were scavenged and ferrous ions were also chelated by these extracts (Badmus *et al.,* 2011; Barreto *et al.,* 2008; Fidrianny, Rahmiyani, & Wirasutisna, 2013; Kawpoomhae *et al.,* 2010; Ling *et al.,* 2009; Mohan, Viswanatha, Savinay, Rajendra, & Halemani, 2013; Pan *et al.,* 2016). Several studies that determined the total phenolic/flavonoid content revealed considerable amounts of those compounds (Badmus *et al.,* 2011; Barreto *et al.,* 2008; Fidrianny *et al.,* 2013; Kawpoomhae *et al.,* 2010; Ling, Radhakrishnan, Subramaniam, Cheng, & Palanisamy, 2010; Pan *et al.,* 2016; Tarkang *et al.,* 2015;).

5.1.2 *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 (Pal *et al.,* 2013; Rajendran *et al.,* 2008). Mangiferin also showed significant protective activity in human umbilical vein endothelial cells under H_2O_2-induced stress, which indicated the potential benefits in the prevention of oxidative stress-associated diseases (Luo *et al.,* 2012). Moreover, *in vivo* antioxidant activities of *M. indica* leaf extracts were evaluated on various biochemical parameters such as catalase, superoxide dismutase, reduced glutathione level, and lipid peroxidation. *M. indica* leaf extracts enhanced catalase and superoxide dismutase enzyme activities and also prevented glutathione depletion and lipid peroxidation in a dose-dependent manner (Viswanatha, Shylaja, & Mohan, 2013).

5.1.3 Human studies

At present, there have been no reports of human studies using *M. indica* leaf extract.

5.2 Antidiabetic activity

5.2.1 *In vitro* studies

1) 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 oligo-saccharides into monosaccharides, thus delaying intestinal

Table 2. *In vitro* antioxidant activities and total phenolic contents of *M. indica* leaf extracts.

Reference	*M. indica* extract	Antioxidant activity			
		Total phenolic content	DPPH (IC_{50})	ABTS (IC_{50})	Others
Ling *et al.* (2009)	Aqueous extract	189±109 mg GAE/g	0.49±0.4 mg/mL	0.13±0.03 mg/mL	Galvinoxyl : IC50 = 0.22 ± 0.006 mg/mL
	Ethanol extract	590±48 mg GAE/g	0.17±0.02 mg/mL	0.02±0.003 mg/mL	Galvinoxyl : IC50 = 0.049 ± 0.003 mg/mL
Kawpoomhae *et al.* (2010)	Methanol extract	420±4.30 mg GAE/g	6.18±0.15 µg/mL	1.33±0.13µg/mL	Superoxide scavenging : IC_{50} = 0.07 ± 0.01 µg/mL
	Aqueous extract	187±3.20 mg GAE/g	5.57±0.18 µg/mL	2.96±0.05 µg/mL	Superoxide scavenging : IC_{50} = 0.06 ± 0.01 µg/mL
	Chloroform extract	96±2.52 mg GAE/g	72.4±3.24 µg/mL	6.56±0.49 µg/mL	
Badmus *et al.* (2011)	Ethyl acetate extract	0.127 µg /mg GAE	1.5 µg/mL		Hydroxyl radical scavenging : IC_{50} = 5 µg/mL
	Aqueous extract	0.111 µg /mg GAE	6.0 µg/mL		Hydroxyl radical scavenging : IC_{50} = 26 µg/mL
	Methanol extract	0.106 µg /mg GAE	6.5 µg/mL		Hydroxyl radical scavenging : IC_{50} = 5 µg/mL
	Chloroform extract	0.089 µg /mg GAE	22.5 µg/mL		Hydroxyl radical scavenging : IC_{50} = 66 µg/mL
Mohan *et al.* (2013)	Aqueous fraction		31.42 µg/mL		
	Ethyl acetate fraction		3.55 µg/mL		
	Water soluble fraction		96.26 µg/mL		
	n-butanol fraction		14.19 µg/mL		
Leeprechanon & Jutiviboonsuk (2015)	Methanol extract		6.38 µg/mL		Trolox : IC_{50} = 7.89 µg/mL; Ascorbic acid : IC_{50} = 5.24 µg/mL

GAE = gallic acid equivalent, IC_{50} = 50% 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

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 IC_{50} values of 0.58 and 1.05 mg/mL, respectively (Ganogpichayagrai *et al.,* 2017). Another study observed that mangiferin exhibited appreciable α-glucosidase and α-amylase inhibitory effects with IC_{50} values of 41.88±3.9 µg/mL and 74.35±1.9 µg/mL, respectively (Dineshkumar *et al.,* 2010). In a study of 3T3-L1 cells, mangiferin at the concentration of 1 mM isolated from *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 were performed to evaluate the α-glucosidase and α-amylase inhibitory activities of *M. indica* leaf extracts. Some benzophenones and triterpenoids in ethanolic leaf extract exhibited pronounced an α-glucosidase inhibitory effect (Pan *et al.,* 2016). An aqueous extract and ethanolic extract of leaves inhibited yeast α-glucosidase enzyme with IC_{50} values of 59.0±0.17 and 50 µg/mL, respectively (Ganogpichayagrai *et al.,* 2017; Andrew *et al.,* 2013). Ethanolic leaf extract also showed pancreatic α-amylase inhibitory activity with an IC_{50} value of 2.28 mg/mL (Andrew *et al.,* 2013). Methanolic extract of young leaves exhibited the stronger pancreatic α-amylase inhibitory activity compared with the extract of mature leaves with IC_{50} values of 22.01 and 35.73 µg/mL, respectively (Bhuvaneshwari *et al.,* 2014).

2) 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).

3) 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 increase insulin secretion. Methanolic extracts of *M. indica* leaves were tested *in vitro* for dipeptidyl peptidase-4 (DPP-4) inhibitory activity. They showed potent activity with an IC_{50} value of 182.7 µg/mL (Yogisha & Raveesha, 2010).

5.2.2. *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 an improvement in the lipid profile in STZ-induced diabetic rats. Moreover, it also showed improvement in oral glucose tolerance in normoglycemic rats (Murugannan dan *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 a 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-A^y mice (Zhang *et al.,* 2013).

In another study, the ethanolic extract of young leaves significantly normalized the blood glucose level more rapidly 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* leaf extracts are shown in Table 3.

5.2.3 Human studies

At present, there have been no reports of human studies using *M. indica* leaf extract.

6. Toxicity

Toxicological studies of several solvent extracts of *M. indica* leaves have been investigated. Both single oral administration of aqueous decoction extract in 20 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. No signs or symptoms of toxicity were observed. There were no significant changes in water or food consumption. No mortality or abnormal changes were found in any organs after 14 days of administration (Gururaja *et al.,* 2017; Severi *et al.,* 2009).

7. Conclusions

Current pharmacological modalities for diabetes are expensive and not ideal because of their side effects and reduced 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 safety profiles, *M. indica* is a strong candidate for further development as a dietary supplement or as adjuvant treatment for diabetes.

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

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

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

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