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

Pattarin Patarakijavanich¹, Vilasinee Hirunpanich Sato², Sumet Kongkiatpaiboon³, and Savita Chewchinda¹∗

¹Department of Food Chemistry, Faculty of Pharmacy, Mahidol University, Ratchathewi, Bangkok, 10400 Thailand

²Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Ratchathewi, Bangkok, 10400 Thailand

³Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Ratchathewi, Bangkok, 10400 Thailand

Received: 25 January 2018; Revised: 29 April 2018; Accepted: 10 May 2018

**Abstract**

*Mangifera indica* Linn. (Anacardiaceae) is commonly called mango or ‘Mamuang’ in Thai. In ethnomedical systems, *M. indica* leaves are 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
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 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 (Baily, 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 Savoe, 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 fibris. 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.

(Masud Parvez, 2016)

Kingdom: Plantae
Subkingdom: Tracheobionta

Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: 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 (diabetes, 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 (Edirweera, Tennekoon, & Samarakoon, 2017; Singh, Sharma, 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 stomatchopathy. 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, C10H8O4, a glucosylxanthone (1, 3, 6, 7-tetrahydroxyxanthone-C2-β-D-glucoside) is a prominent polyphenolic constituent mostly found in *M. indica*. Mangi-
Mangiferin 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), and 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, Kitirattrakam, 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-Poppo, Simionatto, & Caeaswkl, 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, catechin, quercetin derivatives, and phenolic acids were also found in mango leaves (Barreto et al., 2008; Mohan, Viswanatha, Savinay, Rajendra, & Halemuni, 2013). Seven volatile acids were identified in leaves that included benzoic acid, pyrogallol, p-hydroxybenzoic acid, vanillic acid, syringic acid, ferulic acid, ethyl gallate, and gallic acid (Elzaawely & Tawata, 2010). The 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 leaf extracts were reported for their various in vitro and in vivo biological activities, for example analgesic (Garrido-Suarez, Garrido, García & Delgado-Hernandez, 2014; Garrido-Suarez et al., 2014; Tarkang et al., 2015), antipycytic (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, 2010; Leeprechanon & Juti, 2010), hypoglycemic (Ediriweera & Manjunatha, 2010; Dineshkumar et al., 2010), and hypolipidemic properties (Dineshkumar et al., 2010; Muruganandan et al., 2005). This review will focus...
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, Swatstang & 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 gallocatechin gallates 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 (Jyotshla, 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, & Halemni, 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. Inhibition of this 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 are no reported human studies of *M. indica* leaf extract.

#### 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 oligosaccharides into monosaccharides, thus delaying intestinal

<table>
<thead>
<tr>
<th>Reference</th>
<th><em>M. indica</em> extract</th>
<th>Antioxidant activity</th>
<th>Total phenolic content</th>
<th>DPPH (IC_{50})</th>
<th>ABTS (IC_{50})</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ling <em>et al.</em> (2009)</td>
<td>Aqueous extract</td>
<td>Ethanol extract</td>
<td>189±109 mg GAE/g</td>
<td>0.49±0.4 mg/mL</td>
<td>0.17±0.02 mg/mL</td>
<td>Galvinoxyl: IC50 = 0.22 ± 0.006 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Aqueous extract</td>
<td>Ethanol extract</td>
<td>590±48 mg GAE/g</td>
<td>0.13±0.03 mg/mL</td>
<td>0.02±0.003 mg/mL</td>
<td>Galvinoxyl: IC50 = 0.049 ± 0.003 mg/mL</td>
</tr>
<tr>
<td>Kawpoomhae <em>et al.</em></td>
<td></td>
<td></td>
<td>420±4.3 mg GAE/g</td>
<td>6.18±0.15 μg/mL</td>
<td>1.33±0.13μg/mL</td>
<td>Galvinoxyl: IC50 = 0.07 ± 0.01 μg/mL</td>
</tr>
<tr>
<td>(2010)</td>
<td>Ethanol extract</td>
<td>Aqueous extract</td>
<td>187±3.2 mg GAE/g</td>
<td>5.57±0.18 μg/mL</td>
<td>2.96±0.05 μg/mL</td>
<td>Galvinoxyl: IC50 = 0.06 ± 0.01 μg/mL</td>
</tr>
<tr>
<td>Badmus <em>et al.</em></td>
<td>Chloroform extract</td>
<td></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>
<td>Hydroxyl radical scavenging: IC50 = 5 μg/mL</td>
</tr>
<tr>
<td>(2011)</td>
<td>Ethyl acetate extract</td>
<td></td>
<td>0.127 μg /mg GAE</td>
<td>1.5 μg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC50 = 5 μg/mL</td>
</tr>
<tr>
<td></td>
<td>Aqueous extract</td>
<td></td>
<td>0.111 μg /mg GAE</td>
<td>6.0 μg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC50 = 26 μg/mL</td>
</tr>
<tr>
<td></td>
<td>Ethanol extract</td>
<td></td>
<td>0.106 μg /mg GAE</td>
<td>6.5 μg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC50 = 5 μg/mL</td>
</tr>
<tr>
<td></td>
<td>Chloroform extract</td>
<td></td>
<td>0.089 μg /mg GAE</td>
<td>22.5 μg/mL</td>
<td></td>
<td>Hydroxyl radical scavenging: IC50 = 66 μg/mL</td>
</tr>
<tr>
<td>Mohan <em>et al.</em></td>
<td>Aqueous fraction</td>
<td></td>
<td></td>
<td>31.42 μg/mL</td>
<td></td>
<td>Trolox: IC50 = 7.89 μg/mL</td>
</tr>
<tr>
<td>(2013)</td>
<td>Ethyl acetate fraction</td>
<td></td>
<td></td>
<td>3.55 μg/mL</td>
<td></td>
<td>Ascorbic acid: IC50 = 5.24 μg/mL</td>
</tr>
<tr>
<td></td>
<td>Water soluble fraction</td>
<td></td>
<td></td>
<td>96.26 μg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-butanol fraction</td>
<td></td>
<td></td>
<td>14.19 μg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leeprechanon &amp; Jutiviboonsak</td>
<td>Methanol extract</td>
<td></td>
<td></td>
<td>6.38 μg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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 IC50 values of 0.58 and 1.05 mg/mL, respectively (Ganoppichayagrai et al., 2017). Another study observed that mangiferin exhibited appreciable α-glucosidase and α-amylase inhibitory effects with IC50 values of 41.88±3.9 μg/mL and 74.35±1.9 μg/mL, respectively (Dinesh kumar 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 IC50 values of 59.0±0.17 and 50 μg/mL, respectively (Ganoppichayagrai et al., 2017; Andrew et al., 2013). Ethanolic leaf extract also showed pancreatic α-amylase inhibitory activity with an IC50 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 IC50 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 IC50 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 (Murugannadan 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 (Dinesh kumar 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’ 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 are no reported human studies of 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.

<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 <em>et al.</em> (2001)</td>
<td>4 wk old female Balb/c mice</td>
<td>STZ (100 mg/kg, i.p.), 50% glucose (1 g/kg, p.o.)</td>
<td>8 weeks</td>
<td>1 g/kg of aqueous extract of leaves</td>
<td>Decreased blood glucose level in normal and glucose loaded mice</td>
</tr>
<tr>
<td>Muruganandan <em>et al.</em> (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 <em>et al.</em> (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 (10 and 20 mg/kg, i.p.)</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 <em>et al.</em> (2013)</td>
<td>KK-A’F mice and C57BL/6 J</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>Bhuvaneshvari <em>et al.</em> (2014)</td>
<td>Wistar Albino rats (200–250 g)</td>
<td>Glucose (1 g/kg, p.o.)</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 leaf extract</td>
<td></td>
</tr>
</tbody>
</table>

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

References


Farina, V., Corona, O., Mineo, V., D’Asaro, A., & Barone, F. (2013). Qualitative characteristics of mango fruits (Mangifera indica L.), which have undergone preservation (Italian). Acta Italus Hortus, 12, 70-73.


