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Review Article

Health Benefits of Mango (*Mangifera Indica* L) and Mangiferin

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Abstract

Mango (*Mangifera Indica* Linn.) fruit is very popular around the world, which provides a soothing sweet aroma and delicious taste, while mango leaves are becoming increasingly popular for its battery of therapeutic benefits including the treatment of diabetes, blood pressure, restlessness, respiratory problems, gall bladder and kidney stones, dysentery, ear aches, diverse inflammatory responses, wound-healing, heat stroke, cardiovascular problems, diverse gastrointestinal health, regularity and digestion. Mango fruits, pulp and leaves are integral parts of Asian culinary purpose. Especially, raw mangoes are used in salads and pickles, while ripe mangoes are consumed as fruits, milkshakes and desserts. Literature reveals that mango fruits, fruit pulp and leaf have been used for multiple health problems and ailments especially for digestive and gastrointestinal health in Ayurvedic medicines for thousands of years. Chemical investigations have demonstrated that mango and mango leaves contain structurally diverse polyphenolic antioxidants and micronutrients including mangiferin, beta-carotene, lutein, zeaxanthin, riboflavin, thiamine, niacin, anthocyanins and anthocyanidins, flavonoids, alkaloids and minerals. This review provides an overview and highlights on mangiferin and mango leaf extract on multiple health benefits in human health and disease prevention.

Keywords: *Mangifera Indica* Linn: fruit and leaves, mangiferin, antioxidant; anti-inflammatory, anti-diabetic; gastro-intestinal and gut health, regularity

Introduction

Literature reveals that mango [*Mangifera Indica* Linn (family Anacardiaceae)], a popular tropical fruit, originated from the Indian sub-continent and then started becoming popular around the World. Around fifth and fourth centuries BC, cultivation of mango started in Southeast Asia, and then in East and West Africa around 10th century AD, and finally in Brazil, Mexico, Spain, Canary Islands and Portugal,West Indies and Caribbean Islands [1-7]. Today, India, China, Thailand and Mexico are the largest producers and exporters of mango [1,3].

Mango trees, flowers, fruits, seeds, leaves and bark have been reported to exhibit diverse medicinal properties and health benefits. Scientific literature demonstrates that different parts of mango tree and its integral constituents exhibit a number of health benefits including the reduction of chronic inflammatory conditions, anti-viral and anti-bacterial effects, immunomodulatory, anti-spasmodic, gastrointestinal well-being as well as metabolically-mediated chronic diseases [3-5].

Chemical Constituents

Mango contains 15% carbohydrates, 1.6% dietary fiber, 0.38% fat and 0.82% protein [5,8]. HPLC equipped with diode array and mass spectrometric detection, HPLC/atmospheric pressure chemical ionization mass spectrometry (HPLC/APcI-MS), atmospheric pressure chemical

ionization-time-of-flight mass spectrometry [LC-(APcI (+))-MS] and HPTLC techniques have been extensively used for the detection of these structurally diverse constituents [9-11].

Mango fruit, seed, leaves, bark and roots have diverse phytochemical constituents including polyphenolic antioxidants including flavonoids, triterpenoids, micronutrients [5,8], as follows: Flavor of mango fruits contain volatile organic molecules including terpenes, furanones, lactones and esters. Mango leaves contains multiple minerals, vitamins including calcium, magnesium, potassium, sodium, zinc, cadmium, copper and phosphorous, vitamins C, B1, B2 and B4, polyphenolic xanthonoids, mangiferin, selected anthocyanidins including delphinidin, peonidin and cyanidin, leucoanthocyanins, catechin and gallic tannins [5,8]. Mango leaf oil contains sesquiterpenes, mangiferin, δ-3-carene, α-gurjunene, β-selinene and β-caryophyllene. Mango leaf has been demonstrated to contain mangiferin, selected anthocyanidins including delphinidin, peonidin and cyanidin, leucoanthocyanins, catechin and gallic tannins. Mango leaves and flowers also contain essential oils [5,8]. The flower also contains a series of gallic acid derivatives, while the roots contain chromone derivatives. Mango fruit pulp contains vitamins A, C, β-carotene, xanthophylls and cis-9 and cis-15-octadecadienoic. Phenolic antioxidants including protocatechuic acid, catechin, gama-aminobutyric acid (GABA), kinic acid, shikimic acid, as well as tetracyclic triterpenoids, Indicoside A and B, manghopanal, mangoleanone, friedelin, cycloartan-3β-30-diol and derivatives, mangsterol, manglupenone, mangocoumarin, mangiferolic acid derivatives, carbohydrates and polyols were isolated from mango stem bark [5,8].

Mangiferin

The natural C-glucoside xanthone, mangiferin, chemically known as 2-C-β-D-glucotyranosyl-1,3,6,7-tetrahydroxyxanthen-9-one CAS 4773-96-0 (Formula C19H18O11; Molecular Weight: 422.35; melting point 271°C] (figure1). As indicated earlier, mangiferin is abundant in the mango leaves, fruits, stem bark, heartwoods and roots [2-4]. Mangiferin, a light yellow color crystalline powder, is slightly soluble in ethanol, sparingly soluble in methanol and water and practically insoluble in diethyl ether, acetone, and n-hexane [12]. Mangiferin is a novel antioxidant and exhibit pro-hypoglycemic activity by modulating glucose metabolism, ameliorating insulin resistance, lowering cholesterol synthesis, and inhibiting the expression of the TNFα and inducible nitric oxide synthase [2-5,13].

The acute oral toxicity of mango leaf extract was found to be greater than 5,000 mg/kg body weight p.o. Both gross anatomy check and macroscopic evaluation were conducted and no signs of gross toxicity were observed till 14 days of treatment. Another study demonstrated no signs of gross or organ toxicity up to 18.4 gms mango leaf extract/kg bodyweight p.o. In another independent sub-chronic, repeated dose sub-chronic toxicity study using either 0, 100-, 300- or 900 mg mango leaf extract/kg body weight p.o. doses over a period of 90-consecutive days using exhibited no signs of toxic manifestations were observed, except a lower K+ level was detected in female rats in the high dose group [14-16]. In an independent investigation, Prado et al. demonstrated that acute and subchronic toxicities of mangiferin (p.o.) are low [16]. A detailed anti-mutagenic investigation was conducted by Gold-Smith et al. [17], which affirms the non-mutagenic potential of magniferin.

Antioxidant Benefits

Structurally mangiferin has four hydroxyl groups and exhibits potent free radicals and antioxidant activities by scavenging noxious free radicals [18-22]. Saha et al. [23] postulated that the C-glucosyl linkage and hydroxyl groups in mangiferin contribute significantly to its free radical-scavenging activity. Antioxidant potential of mangiferin is remarkably enhanced in the pro-inflammatory and inflammatory conditions, including infection and diabetic states [18-20]. DPPH assay also demonstrated that mangiferin has potent antioxidant activity and it is comparable to rutin [19]. Hydrogen peroxide-induced lipid peroxidation in human peripheral blood lymphocytes was dramatically reduced in a dose-dependent manner. It is a potent iron chelator and protects against noxious hydroxyl radicals and UV radiation [19,20]. Pardo-Andreu et al. demonstrated that mangiferin counterbalances the iron-induced oxygen free radical formation, Fe2+ accumulation and iron-induced toxicity [24]. Fe2+ Citrate-induced lipid peroxidation in rat liver mitochondria was protected by the iron complexing ability of mangiferin [21,24].

In an independent investigation, the protective ability of mangiferin was assessed against H_2O_2–induced oxidative injury and apoptosis in osteoblast-like cultured MC3T3-E1 cells. Mangiferin protected these cultured cells against oxidative injury through modulation of ERK5/Nrf2 signaling. Thus, it may be serving as a potential therapy in osteoporosis [25].

In vivo hepatoprotective ability of mangiferin against carbon tetrachloride-induced hepatic injury was demonstrated by Pokorski et al. [11,12]. Arsenic-induced oxidative stress in the hepatic tissues and liver dysfunction was also dramatically protected by mangiferin in another independent study [26].

Anti-inflammatory Benefits

The anti-inflammatory potential of magniferin has been demonstrated in both hepatoprotection [27] and cardio-

protection [28,29] models. Lipopolysaccharide (LPS) and D-galactosamine-induced acute liver injury and inflammation was significantly protected by mangiferin [30]. Hepatic lipid peroxidation and oxidative stress were significantly reduced as well as the levels of serum ALT, AST, IL-1β, TNF-α, MCP-1, and RANTES (regulated on activation, normal T cell expressed and secreted) were dramatically reduced [30]. Mangiferin up-regulated the expression of Nrf2 and HO-1 in a dose-dependent manner. Mangiferin also inhibited LPS and D-galactosamine-induced hepatic NLRP3, ASC, caspase-1, IL-1β and TNF-α expression. Overall, the researchers concluded that mangiferin protected against hepatic injury and inflammation by activating the Nrf2 pathway and regulating NLRP3 inflammasome activation [30]. Mangiferin demonstrated the protective abilities of mangiferin against DOX-induced cardiac inflammation, cardiotoxicity and apoptosis in rats via down-regulation of proapoptotic and proinflammatory gene expressions, upregulation of SERCA2a gene expression, and normalization of cytosolic calcium level [28]. An ethanol extract of *Mangifera Indica* L. leaf enriched in mangiferin demonstrated the antioxidant, anti-inflammatory and cardioprotective efficacy [31].

Pardo-Andreu GL et al. demonstrated the anti-inflammatory potential of magniferin in both in vitro and in vivo models. Mangiferin dose-dependently inhibited inflammatory cytokines, TNFα, NO and NF-κβ [19-21,24]. Saha et al. hypothesized that C-glucosyl linkage and hydroxyl groups in mangiferin contribute to its free radical-scavenging activity, and exhibited that mangiferin exerts its anti-inflammatory benefits by modulating various transcription factors including NF-κβ, Nrf2, TNFα and COX-2 [23,26]. Mangiferin also protected against renal ischemia-reperfusion injury by inhibiting inflammation, oxidative stress and inducing adenosine production in a mice model [32]. Mangiferin improved kidney function, increased CD73 expression in kidney's suffering from ischemia-reperfusion injury, adenosine production, as well as inhibited pro-inflammatory responses and tubular apoptosis [32].

Pulmonary inflammation model was investigated by Gong et al. and exhibited that mangiferin can attenuate cecal ligation and puncture-induced mortality and acute lung injury as demonstrated by reduced systemic and pulmonary inflammatory responses [33]. Mangiferin also inhibited sepsis-activated MAPK and NFκβ signaling, demonstrating its inhibition ability against inflammatory mediators in sepsis-induced acute lung injury. Mangiferin was demonstrated to upregulate HO-1 in the pulmonary tissues of septic mice in a dose-dependent manner [33]. The protective ability of magniferin against 2,4,6-trinitrobenzensulfonic acid (TNBS)-induced colitis in rodents was demonstrated by Szandruk et al. Mangiferin dramatically reduced the macro- and microscopic damage, as well as reduced MDA level in the colon [34]. Furthermore, TNF-α and IL-17 levels were reduced, while enhancing the SOD activity in the colon tissues. Thus, mangiferin significantly protected against TNBS-induced inflammation and colitis in rats by potent xiating anti-inflammatory and antioxidant activity [34].

Anti-Diabetic Therapy

Potential anti-diabetic therapy of mangiferin has been demonstrated by several investigators [35]. Mangiferin demonstrated a pro-hypoglycemic role by regulating glucose metabolism and insulin resistance. It also lowers cholesterol synthesis and inhibits the expression of tumor necrosis factor (TNFα) and nitric oxide synthase [35].

Mangiferin treatment over a period of 8 weeks significantly lowered plasma glucose and triglyceride levels in diabetes prone db/db mice [36]. Mangiferin also increased pancreatic beta cell mass and uptake of glucose and insulin uptake with increased phosphorylation of AMP activated protein kinase (AMPK) [36]. Chronic treatment with mangiferin prevented renal fibrosis as well as decreased collagen IV in diabetic rats [37]. Furthermore, mangiferin treatment can reduce IL-1β in the serum and kidneys of diabetic rats. Mangiferin treatment 15, 30 and 60 mg/kg body weight treatment for 9 weeks improved chronic renal problems in diabetic rats and reduced kidney weight, as well as normalized blood urea nitrogen [37]. In another independent study, mangiferin significantly reduced diabetes-induced lipid peroxidation (TBARS) level to a healthy level [38]. In addition, Pokorski et al. also exhibited its potent in vivo hepatoprotective ability [38,39]. In another independent study, mangiferin exerted anti-diabetic efficacy in streptozotocin-induced diabetic rats [40].

As we all realize that diabetes treatment causes both health and economic burden on society, thus, it will be unique if mangiferin can exhibit a novel therapeutic intervention. Plant-based diet has been demonstrated to effectively reduce high blood sugar level and eliminating the regular use of anti-diabetic medication and insulin, which will eliminate the risk of side effects of medicines. A recent clinical investigation by Dr. Roychowdhury exhibited 84% of patients reported controlled blood glucose level and reduced glycemic index by using raw mango fruits and the subjects were strictly on vegetarian diet [41]. These researchers indicated that consumption of hot water extract of mango leaves and mango leaf powder are very beneficial for diabetics.

Obese, diabetic and pre-diabetic subjects were also benefitted by using mango leaf extract. Research demonstrated that other components in mango including quercetin and mangiferin derivatives can trigger the cellular components, which are the target of anti-diabetic drugs [41].

Gastrointestinal Motility and Health

Mangiferin transits through the gastrointestinal tract, metabolized into different phenolic acid derivatives including 3,4-dihydroxybenzoic acid, 3,4-dihydroxy-phenylacetic acid, 2,4,6-trihydroxybenzoic acid, 3,4,5-trihydroxybenzoic acid and the mangiferin aglycone 1,3,6,7-tetrahydroxyxanthen-9-one, also known as norathyriol, by intestinal microflora in the colon and exerts the medicinal benefits [42,43]. Research studies have demonstrated that mangiferin attenuates intestinal inflammation and impaired gastrointestinal motility, and ultimately facilitates gastrointestinal transit and demonstrated anti-ulcerogenic potential [44]. It was emphasized that mangiferin remarkably suppressed myeloperoxidase activity, nitrate/nitrite levels, cytokines, adhesion molecules, and pro-inflammatory mediators in the ileum. Based on these extensive mechanistic investigations, it was emphasized that mangiferin may serve as an ideal therapeutic intervention for human inflammatory bowel disorders [45,46]. Another independent study demonstrated that mangiferin exerted significant gastroprotection in rodents. Mangiferin also exerted antioxidative and gastroprotective activity against ethanol and endomethacin-induced gastric lesion, ulcer score and depletion of gastric mucosal non-protein sulfhydryl content in mice [47].

Kakino et al. exhibited that mangiferin exerted the laxative effect via acetylcholine receptors, which was demonstrated in a mouse model of constipation [48], and enhances gastrointestinal regularity. In a mouse model of colitis and inflammatory bowel disease (IBD), Somani et al exhibited that mangiferin reduced colonic injury by reducing oxidative stress and inflammation by modulating TNF-α and MMP-9, and thus, Somani et al. [49] concluded that mangiferin may have potential to treat IBD.

Sanugul et al. [50] reported that a specific intestinal bacterium is involved in the metabolism of mangiferin, which is mediated through the production of a novel and inducible C-glucosyl-cleaving enzyme. Mahmoud-Awny et al. [51] demonstrated that mangiferin exerted its gastro protective ability in a rat gastric ulcer model partly via inducing the expression of Nrf2, HO-1 and PPAR-γ along with downregulating NF-κβ while anti-inflammatory benefits were demonstrated by reducing serum IL-1β and sE-selectin levels. Mangiferin enhanced the total antioxidant capacity and glutathione level, reduced the malondialdehyde level, and attributed anti-apoptotic benefits by escalating Bcl-2 level and reducing caspase-3 in a dose-dependent manner [51].

Most interestingly mangiferin was demonstrated to effectively eradicate *Helicobacter pylori*, the most noxious bacteria responsible for chronic gastrointestinal inflammation, ulcer and gastric cancer [52,53]. Mangiferin effectively eradicated *H. pylori* and remarkably inhibited inflammatory markers NF-κB subunit p65, IL-1β, IL-8, and TNFα [52,53], downregulated inflammatory enzymes COX-2 and iNOS, as well as deactivated NF-p65 by blocking the inflammatory response. Thus, a mangiferin-enriched dietary supplement will be a good choice to serve as a novel gastroprotective supplement.

Conclusion

Mango leaves, barks, flowers, fruits and pulp are unique resources of mangiferin and structurally diverse antioxidants including vitamins A, B6, E and C, pectin, flavonoids, beta-cryptoxanthin, omega-3 and omega-6 fatty acids, fibers, micronutrients and minerals including copper, which provides a soothing taste and smell and diverse pharmacological and therapeutic benefits. Moreover, mango is enriched in mangiferin, a natural polyphenol of C-glycosylxanthone structural moiety, and its derivatives. Both mango and mango leaf extract can improve insulin production and sensitivity, stabilizing blood sugar level and normalizes glycemic in pre-diabetics and diabetics. The tender leaves of mango tree are enriched in anthocyanidins, which help in treating pre-diabetic subjects, and the dried powdered leaves helps to treat diabetic angiopathy and diabetic retinopathy. Overall, these are safe and novel antioxidant, anti-inflammatory, anti-diabetic, anti-ulcerogenic, nephroprotectant, gastrointestinal health and bowel movement.

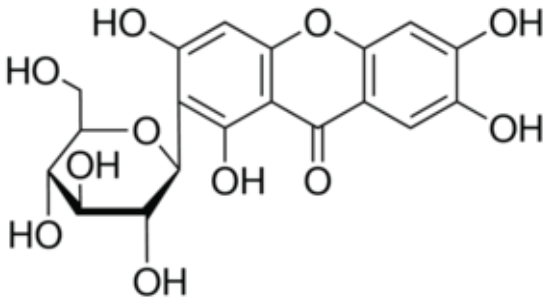

Figure 1. Chemical Stucture of mangiferin.

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