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Mango (*Mangifera indica* Linn*)* and Anti-Inflammatory Benefits: Versatile Applications in Mitochondrial Bio-Energetics and Exercise Physiology

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ABSTRACT

Background: Mangoes are a popular fruit enjoyed worldwide. The mango is known for its pleasing aroma in addition to its refreshing and soothing taste. Researchers around the globe have demonstrated the diverse beneficial effects of *Mangifera indica* Linn in human health and disease prevention. Additionally, we should acknowledge how Ayurvedic medicine uses different parts of the mango tree. This branch of medicine has used the leaves, twigs, bark, seeds, flowers, raw and ripe fruits of mango to treat diverse degenerative diseases for thousands of years. This study is aimed to investigate diverse health benefits of Mango and mangiferin.

Ethnobotany: The mango (*Mangifera* indica) originally came from India about 4,000 years ago. Since then, the mango has slowly spread across the world. The mango belongs to the family "Anacardiaceae" under the genus "*Mangifera*" and species "*indica*". The mango is also referred to as "Asia's King of Fruits" or a Royal fruit. The color of the mango fruit varies from green, yellowish green, yellow, yellowish red, orange red and red. The smell and taste of the mango fruit varies based on its state of maturity in addition to place of origin and climate. Different parts of a mango tree and mango fruit are rich in vitamins and antioxidants including vitamins B, C, E and beta-carotene, alkaloids, flavonoids, and polyphenolic compounds which include mangiferin,

anthocyanins and anthocyanidins, micronutrients and essential minerals, structurally diverse carbohydrates, dietary fibers, fat, and protein.

Health Benefits: Previous and current research demonstrate that the mango fruit and leaf extract, which is enriched in mangiferin and contains structurally diverse chemical constituents, are beneficial. The mango fruit and leaf extract have been shown to boost vitality, vigor, and endurance, leading to extensive application in exercise physiology. Furthermore, these constitutes ameliorate diverse degenerative disease related to metabolic syndrome, bacterial infections, gastrointestinal, and immunomodulatory disorders.

Conclusions: Mango and mangiferin exhibit diverse health benefits including energy boosting, exercise performance, and human health.

Keywords: Mango (*Mangifera indica)*, mangiferin, vitamins and anthocyanins, anti-inflammatory, endurance, energy homeostasis, exercise

BACKGROUND

The Mango tree originated in India more than 4,000 years ago. The fruit became popular due to its distinctive aroma, varying sour to sweet taste, and for being a particularly refreshing food during summer days in tropical climates [1-3]. During hot summer days, roasted mango sherbet or smoothies are common drinks for refreshment and hydration. Beneficial effects related to these drinks are increased vitality, vigor, strength, and endurance. Additionally, the baked mango smoothie is used as a novel and natural remedy against heat stroke, which is a life-threating inflammatory response [2-6]. Accordingly, Ayurvedic medicines used different parts of the mango tree, leaves, peels, kernel, flowers, pulp, twigs, branches, raw and ripe fruits, bark, and root for different nutritional, medicinal, and therapeutic benefits, in addition to effects against a broad spectrum of degenerative diseases and dysfunctions [4-10].

Research studies have established how different parts of the mango tree and fruits contain structurally diverse pharmacologically active beneficial and healthy bioactives and chemical constituents. These include structurally distinctive carbohydrates like glucose, galactose and arabinose, proteins, fats, polyalcohols such as xylitol, sorbitol and myoinositol, alkaloids, saponins, volatile constituents, fatty acids like estearic, linoleic, oleic, myristic and palmitic acids, polyunsaturated and dicarboxylic acid, vitamin B in the forms of niacin, riboflavin and thiamin, vitamins C, E, and ß-carotene, which are essential minerals and micronutrients that include calcium, iron, magnesium, manganese, potassium, zinc, copper, hydrolysable tannins, catechic and gallic tannins, bioflavonoids, polyphenolic antioxidants, leucoanthocyanins, anthocyanidins such as delphinidin, cyanidin, peonidin, catechic and gallic tannins, and finally mangiferin, which is extensively distributed in mango fruits, leaves, and throughout the entire tree [5, 6, 9, 10].

The chemical structure of the naturally occurring compound mangiferin, a glucoside of norathyriol, is 2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) [3, 6]. Mangiferin is widely distributed in different parts of the mango leaf, fruit, peel, seed, kernel, bark, root and

trunk. Mangiferin exhibits multiple medicinal and therapeutic benefits including improved antioxidant and anti-inflammatory effects, gastrointestinal health, regularity, focus, attention, vitality, vigor, and endurance. This review will demonstrate the extensive applications of the mango extract enriched in mangiferin in exercise, muscle building, endurance, focus, coordination, and attention [3, 6, 10].

As demonstrated previously, the mango is rich in vitamin B, vitamin C, β-carotene, and bioflavonoids like mangiferin [3, 6, 10]. These antioxidants play an important role in boosting the immune system, vitality, vigor, and energy [3, 10]. Accordingly, the mango has a potential role in focus and energy boosting [3, 10]. Incidentally, β-carotene stimulates the liver to boost metabolism and energy [11].

The ripe mango is a good source of energy and contains a variety of micronutrients and minerals. According to Ayurveda, sweet ripe mangoes balances all three *Doshas* namely Vata, Pitta and Kapha optimally [12]. *Dosas* are referred to as inherent sources of biological energies, which are believed to exist within the human body and mind. These three *Doshas* govern, regulate, and control the physical and mental processes of a living human being and provide an individual blueprint for health and fulfillment [12]. Mango enriched in mangiferin and other bioflavonoids, anthocyanins, β-carotene, essential B-, C-, and E vitamins, and trace minerals [3].

Phytochemical Constituents

Literature reveals how multiple scientists have extensively analyzed the mango tree, root, and fruit constituents using multiple chromatographic techniques including GC, GC-MS, HPLC, HPTLC, LC-MS, HPLC/APcI-MS, LC-(APcI(+))MS, ES-MS, and NMR, in addition to identifying numerous chemical constituents. Mangiferin, a xanthone glycoside, tannins, gallic acid and derivatives, catechins, quercetin, kaempferol, protocatechuic acid, ellagic acids, propyl and methyl gallate, rhamnetin, and anthocyanins are the major polyphenolic compounds in the mango [13-15]. Furthermore, structurally diverse flavonoids, and triterpenoids including friedelin, sesquiterpenes like elemene, in addition to minerals and micronutrients including Ca, Fe, Mg, Mn, K, Zn, and Cu are extensively distributed throughout the mango tree, leaves, and fruits [9, 10].

Stem Bark

Dr. Nunez Selles et al. analyzed the mango stem bark, isolated, and elucidated seven phenolic antioxidants including gallic acid, 3,4-dihydroxy benzoic acid, gallic acid methyl ester, gallic acid propyl ester, mangiferin, (+)-catechin, (−)-epicatechin, and finally benzoic acid and benzoic acid propyl ester [16]. Khan et al. reported the presence of new saponins and other phytochemicals including indicoside A and B, manghopanal, mangoleanone, friedelin, cycloartan-3β-30-diol and derivatives, mangsterol, manglupenone, mangocoumarin, n-tetacosane, n-heneicosane, n-triacontane, and mangiferolic acid methyl ester from the stem bark [17]. Shankarnarayanan et al. confirmed the presence of mangostin, 29-hydroxy-mangiferonic acid, mangiferin, and other flavonoids in the stem bark [18]. Singh et al. (2015) reported the presence of 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester and 9,12-tetradecadiene-1-ol-acetate and 3-

chloro-N-(2-phenylethyl) propanamide in the stem bark [19]. Additionally, structurally diverse polyphenolic antioxidants, carbohydrates, and polyols were also reported elsewhere [3].

Bark

Scatezzini and Speroni reports that bark also contains protocatechuic acid, alanine, glycine, gama-aminobutyric acid, kinic acid, shikimic acid, 3 cycloart-24-en-3β,26diol, 3-ketodammar-24 (*E*)-en-20S,26-diol, C-24 epimers of cycloart-25 en-3β,24,27-triol, and cycloartan-3β,24,27-triol [20].

Flowers

Khan and Khan reported how mango flowers contain alkyl gallates including gallic acid, ethyl gallate, methyl gallate, n-propyl gallate, n-pentyl gallate, n-octyl gallate, 4-phenyl gallate, 6-phenyl-n-hexyl gallate, and dihydrogallic acid [21].

Root

Root contains chromones, 3-hydroxy-2-(4'-methylbenzoyl)-chromone and 3-methoxy-2-(4'-methyl benzoyl)-chromone [3].

Essential Oil in the Leaves and Fruit

Headspace solid phase microextraction (HS-SPME) and hydrodistillation techniques reported that immature mango leaves contain cyperene, E-caryophyllene, α-humulene, terpinolene, carotol, gualol and α-cadinol, while mature leaves contain cyperene, α-gurjunene, E-caryophyllene, α-cedrene and α-humulene [22]. The immuture fruit contains terpinolene, α-gurjunene, E-caryophyllene, α-humulene, and phenylpropanoid p-cymen-8-ol, while in the mature fruit contains terpinolene, α-gurjunene, E-caryophyllene and α-humulene. Shah et al. reported that flowers contain mainly essential oils including humulene, elemene, ocimene, linalool and nerol [3].

Fruit Pulp and Peel

Mango fruit pulp and peel contain vitamins A, C, E, α- and β-carotene, luteoxanthin, violaxanthin, neoxanthin, zeaxanthin, β-cryptoxanthin, xanthophylls, cis-9, and cis-15-octadecadienoic acid. Furthermore, these are rich in dietary fibers [3, 23, 24].

Leaves

In addition to the essential oils, mango leaves are enriched in micronutrients and beneficial trace minerals, carotenoids, vitamins B, C, and E, dehydroascorbic acid, mangiferin and other polyphenolic and phenolic compounds such as protocatechuic acid, gallic acid, hyperin, catechin, quercetin, kainic acid, ethyl digallate, ellagic acid, and shikimic acid. Amino acids including alanine, glycine, valine, tyrosine, leucine, and γ-aminobutyric acids, and terpenoids which involve α-pinene, β-pinene, δ-elemene, taraxerol, β-elemene, α–cubebene, camphene, γ–cadinene, lupeol, friedelin, linalool, β- bulnesene, α-guaiene, humulene, α-farnesene, myrcene, car3-ene, limonene, β-ocimene, γ–terpinene, and α-terpinolene, in addition to sterols including α, β, and γ-sitosterol.

Alcohols include methyl, ethyl, and isobutyl alcohols, while phenylpropenes include estragole, methyleugenol, and elemicin [3, 20, 25-28].

Free Radical Scavenging and Antioxidant Efficacy

We need to emphasize how oxidative stress is lower in athletes compared to more sedentary individuals [29]. Research has demonstrated there is lower oxidative response in athletes compared to control subjects, who are at rest. Malondialdhehyde (MDA), protein carbonyls, and 8-hydroxy-deoxyguanosine (8-OH-dG) are lower, while superoxide dismutase (SOD) is higher in trained athletes compared to control subjects without exercise and physical activities [29]. Significantly, mango contains notable amounts of vitamin B1, B2, B4, C, and E, dehydroascorbic acid, phenolic and polyphenolic antioxidants that include quercetin, mangiferin, and many others [3].

Together vitamin C and E have cumulative synergistic antioxidant efficacy in the heart and skeletal muscle, in addition to pronounced anti-inflammatory activities [30]. The bright yellow portion of *Mangifera Indica* fruit peel and flesh is due to the presence of carotenoids, which are remarkable free radical scavengers [31-34]. Quercetin and other polyphenolic flavonoids increase mitochondrial biogenesis and endurance in skeletal muscle and brain. Administration of quercetin (500 mg bid) increased VO2max and endurance capacity in untrained individuals [33-35]. Polyphenolic flavonoids in mango also improve glucose homeostasis, antioxidant capacity, and microcirculatory parameters in male elite triathletes [35, 36]. Mangiferin is a potent antioxidant, a remarkable iron chelator, and an effective free radical scavenger due to the C-glucosyl linkage and four hydroxyl groups in its structural moiety, and the antioxidant potential is tremendously amplified under pro-inflammatory and inflammatory conditions [37]. Mangiferin has comparable free radical scavenging ability similar to the flavonoid rutin. Moreover, the antioxidant efficacy of mangiferin is stronger compared to cinnamon [38]. In other investigations, mangiferin helped prevent noxious hydroxyl radicals and UV radiation and protected against H_2O_2-induced elevated lipid peroxidation in human peripheral blood lymphocyte cells [39].

H_2O_2-induced oxidative injury and apoptosis in osteoblast-like cultured MC3T3-E1 cells was protected by mangiferin via modulation of ERK5/Nrf2 signaling and the researchers indicated mangiferin may demonstrate marvelous promise in the treatment of osteoporosis. Eventually, mangiferin has the ability to make the bone stronger for exercise [40].

Mangiferin also demonstrated to compensate against iron-induced free radical injury, Fe^{2+} accumulation, and iron-mediated toxicity [41]. In another experiment in rat hepatic mitochondria, Fe^{2+} citrate-induced lipid peroxidation was remarkably protected by mangiferin through its iron chelating ability [42]. Furthermore, carbon tetrachloride-induced hepatic injury was protected by mangiferin in rats [43]. In another parallel investigation, arsenic-induced hepatic injury was significantly inhibited by mangiferin [44].

Immuno-Modulatory and Anti-Inflammatory Potential

Bioflavoinds and polyphenolic antioxidants including mangiferin, quercetin, and others caused the reduction of arachidonic acid metabolizing enzymes (phospholipase A2, cyclooxygenase, lipoxygenase), inhibition of pro-inflammatory cytokines (IL-1 β, IL-2, IL-6, TNFα), and modulation of nitric oxide synthase (NOS) [32].

Mangiferin can act as an immunomodulatory agent with little or no side effects [45]. Mangiferin inhibits the proliferation of T cells and NF- κβ transcription factors in *in vitro* and *in vivo* studies.

Mangiferin exhibited anti-inflammatory efficacy in diverse models of hepatoprotection and cardioprotection [36, 46]. Mangiferin protected against lipopolysaccharide and D-galactosamine-induced acute liver injury and inflammation. Increases in serum ALT, AST, IL-1β, TNF-α, MCP-1, and RANTES (regulated on activation, normal T cell expressed and secreted) in addition to hepatic lipid peroxidation and oxidative stress were significantly protected by mangiferin [47]. Upregulation of Nrf2 and HO-1 was observed following incubation with mangiferin in a dose-dependent manner [47]. Mangiferin inhibited hepatic NLRP3, ASC, caspase-1, IL-1β, and TNF-α expression. Overall, hepatic injury was remarkably inhibited by mangiferin by activating the Nrf2 pathway and regulating NLRP3 inflammasome activation [47].

Pardo-Andreu et al. demonstrated that mangiferin dose-dependently inhibited inflammatory cytokines, TNFα, NO, and NF-κβ in both *in vitro* and *in vivo* models [32-35, 38, 41]. In two independent studies Saha et al. demonstrated that mangiferin successfully modulated transcription factors including NF-κB and Nrf-2, in addition to TNF-α and COX-2, which are pro-inflammatory signaling molecules. The study further demonstrated the anti-inflammatory benefits of mangiferin [37, 44].

Mangiferin exhibited protective abilities against doxorubicin (DOX)-induced cardiotoxicity, cardiac inflammation, and apoptosis via down-regulation of proapoptotic and proinflammatory gene expressions, upregulation of SERCA2a gene expression, and normalization of cytosolic calcium level [46].

In a renal ischemia-reperfusion model of inflammation in mice, mangiferin protected against oxidative stress and inflammatory response by significantly improving kidney function, enhancing adenosine production, increasing CD73 expression in the kidneys, and inhibiting pro-inflammatory responses and tubular apoptosis [48].

Mangiferin (30 and 100 mg/kg body weight doses) demonstrated dose-dependent ability to protect colon tissues against 2,4,6-trinitrobenzensulfonic acid-induced colitis. At a 100 mg/kg body weight dose in rodents, it also reduced macro and microscopic injury, inflammatory manifestations and colitis, lipid peroxidation, TNF-α and IL-17 levels, and increased SOD activity in colon tissues [49].

Gong et al. demonstrated that mangiferin was able to reduce systemic and pulmonary inflammation by decreasing cecal ligation and puncture-induced mortality, acute lung injury, and multiple pro-inflammatory mediators including MAPK and NFκβ in septic mice. It was concluded that mangiferin attenuated sepsis by up-regulation of HO-1, which protects against sepsis-induced acute lung injury by modulating inflammatory mediators [50].

Cardiovascular Health, ATP and Mitochondrial Energy Homeostasis

ATP is the most widely propagated high energy compound in the human body. The ultimate source of energy for constructing ATP are appropriate food sources. Moreover, ATP is simply the carrier and regulation storage unit of energy. ATP is also used for numerous cell functions including transportation of vital molecules across cell membrane. ATP is used for supplying energy needed

for muscle contraction and blood circulation in the heart and skeletal muscles for exercise and other activities including gross movement of the body [51].

Miura et al. demonstrated that mangiferin (0, 10, 30, 90 mg/kg body weight) administration in conjunction with exercise reduced blood cholesterol, triglyceride, and blood lipid levels in KK-Ay diabetic mice by attenuating metabolism. The study noted that the blood triglyceride level was reduced only in the mangiferin-administered exercise group. Miura et al. interpreted that this hypo-triglycemic effect following the administration of mangiferin in conjunction with exercise is a synergistic effect. Antidiabetic efficacy was also observed following oral administration of 30 mg and 90 mg of mangiferin/kg body weight [52].

Prabhu et al. examined the cardiac energy metabolism in isoproterenol-induced myocardial infarction and energy metabolism in rats. Isoproterenol caused a significant decrease in TCA cycle enzymes and antioxidant defense enzymes activities, while the cardiac mitochondrial lipid peroxidation significantly increased. Furthermore, ATP level and oxidation of succinate in state 3 and 4 significantly decreased in the cardiac mitochondria. The cardiac integrity was protected by mangiferin, which also reduced isoproterenol-induced oxidative injury and activated the mitochondrial energy metabolism with ATP production while restoring TCA enzyme cycle [53].

In another study, Rodriguez et al. (2006) investigated the protective effect of a Mangifera indica extract enriched in Mangiferin and epigallocatechin gallate on energy metabolism, energy state, and MDA production against H_2O_2-induced cellular injury in red blood cell system. Mangiferin exerted marvelous protection with concomitant increase in energy charge potential, ATP and GTP levels, in addition to a significant decrease in MDA level [54]. Mangiferin has been investigated by a number of researchers and shown to be effective in isoproterenol hydrochloride-induced myocardial infarction in rats. Pretreatment with mangiferin over a period of 28 days attenuated isoproterenol hydrochloride-induced lipid peroxidation and significantly reduced total cholesterol, triglyceride, and the free fatty acid level, in addition to increasing phospholipids level in the serum and heart tissues of myocardial infarcted rats. Mangiferin also increased the antioxidant enzymes SOD, catalase, and glutathione-S-transferase levels. The beneficial effects of mangiferin can be attributed to its free radical scavenging effect, hypolipidemic effect, and activation of mitochondrial energy metabolism [55-57].

It has been well established that the main causes of hyperglycemia include inefficient or impaired glucose utilization by skeletal muscle, which can be exacerbated by chronic high caloric intake. Apontes et al. demonstrated how mangiferin protected against high-fat diet-induced weight gain, increased aerobic mitochondrial capacity, thermogenesis, and improved glucose and insulin parameters. Mangiferin also demonstrated a substantial shift in respiratory quotient from fatty acid toward carbohydrate utilization and significantly increased glucose oxidation in the muscles without altering fatty acid oxidation. In cultured C2C12 myotubes, mangiferin increased glucose and pyruvate oxidation, and ATP production without affecting fatty acid oxidation, thereby supporting the validity of both *in vivo* and *ex vivo* models. Mangiferin inhibited anaerobic metabolism of pyruvate to lactate but enhanced pyruvate oxidation. The above study demonstrated how mangiferin has the therapeutic potential to integrate carbohydrate utilization in correcting metabolic syndrome and can elicit fuel-switching effects [58].

In continuation from the earlier study, the same research group conducted targeted metabolomics and transcriptomics studies of glycolyic and mitochondrial bioenergetics pathways in skeletal muscle. Mangiferin increased the formation of α-ketoglutarate and fumarate metabolites in the tricarboxylic acid cycle, in addition to increasing ATP production. Furthermore, mangiferin induced mRNAs of mitochondrial genes and their transcriptional factors and upregulated mitochondrial oxidative capacity, which in turn accelerated glycolysis flux [59].

CONCLUSION

The physiological accumulation of energy, strength, vitality, and vigor adaption in conjunction with integrated and personalized nutrition and exercise program should be appropriately designed according to the requirement of individual athletes for their maximum performance [60]. A well-balanced food habit along with a well-designed dietary supplement is essential to promote ATP level, an important physiological macromolecule for energy levels and athletic performance. ATP is a complex nano-machine and a well-recognized energy coin, which serves as the primary energy currency of living organisms [60].

A significant number of research studies have established how mangiferin is a novel antioxidant and a free radical scavenger [3, 61]. A large number of studies established the immunomodulatory and anti-inflammatory potential of mangiferin [6, 61]. Significantly, mangiferin at different doses increased ATP levels, which can thereby intensify strength, stamina, vitality, and vigor [3, 61-63]. Overall, mango leaf extract enriched in mangiferin may have tremendous potential in mitochondrial energy homeostasis, endurance, and exercise performance.

List of Abbreviations: 8-OH-dG, 8-hydroxy-deoxyguanosine; ALT, Alanine Aminotransferase; APcI-MS, Atmospheric pressure chemical ionization-mass spectrometry; ASC, Apoptosis-associated Speck-like protein containing a caspase-recruitment domain; AST, Aspartate aminotransferase; ATP, Adenosine triphosphate; C2C12, An immortalized mouse myoblast cell line; CD73, Cluster of differentiation 73; COX-2, Cyclooxygenase-2; DOX, Doxorubicin; EC-MS, Electrochemistry/mass spectrometry; ERK5, Extracellular-signal-regulated kinase 5; GC-MS, Gas chromatography-mass spectrometry; GTP, Guanosine-5'-triphosphate; HO-1, Hemeoxygenase-1; HPLC, High performance liquid chromatography; HPTLC, High performance thin layer chromatography; IL-1 β, Interleukin-1beta; IL-2, Interleukin 2; IL-6, Interleukin 6; IL-17, Interleukin 17; LC-(APcI(+))MS, Liquid chromatography - Atmospheric pressure chemical ionization-mass spectrometry; LC-MS, Liquid chromatography–mass spectrometry; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte Chemoattractant Protein-1; MDA, Malondialdehyde; NF-κβ, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NMR, Nuclear magnetic resonance; NO, Nitric oxide; NOS, Nitric oxide synthase; Nrf2, Nuclear factor erythroid 2–related factor 2; RANTES, Regulated on activation, normal T cell expressed and secreted; SERCA2a, Cardiac isoform of sarcoplasmic reticulum calcium ATPase; SOD, Superoxide dismutase; TCA cycle, Tricarboxylic acid cycle; TNFα, Tumor necrosis factor alpha;VO2max, Maximal oxygen uptake.

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