

Phytochemical and pharmacological investigations on mangiferin

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Summary

Mangiferin, a C-glucopyranoside of 1, 3, 6, 7-tetrahydroxyxanthone, has been isolated from various parts of *Mangifera indica* (Anacardiaceae). The conclusive structure of mangiferin has been established by various researchers using a wide range of chemical and spectral analytical techniques. Mangiferin has been traditionally used in some parts of world as anti-inflammatory, analgesic, antipyretic, antioxidant, immunomodulator, anti-tumor, antiviral, and anthelmintic and in obesity treatment. The present article is an attempt to encompass various aspects and details related to the characterization of mangiferin and its subsequent pharmacological screening. The literature data on mangiferin has been comprehensively reviewed and evaluated by the authors and hence, the article contains brief description of phytochemical and pharmacological investigations conducted on mangiferin till now and thus may prove as a guiding force for further research in this particular area.

Key words: *Mangifera indica*, mangiferin

INTRODUCTION

Mangiferin is the major constituent obtained from *Mangifera indica* (Anacardiaceae). Both truly wild mango trees belong to *M. indica* and *M. sylvatica* genera.

***M. indica*: description**

M. indica is a large evergreen tree, 10–45 m high, bark thick, rough, dark grey; leaves linear-oblong or elliptic-lanceolate, 10–30 cm long and 2–9 cm wide, resinous odour; flowers tiny, reddish white or yellowish green, pungently odorous and melliferous; fruit forms a large drupe exceedingly variable in form and size: fruit skin thick or thin, leathery, green, yellowish or red, often dotted with numerous glands: flesh (mesocarp) whitish yellow, yellow or orange, firm, soft or juicy, sub-acid or sweet, richly aromatic: fibers throughout the flesh in some types, absent or very little in others; seed solitary, ovoid-oblique, encased in a hard compressed fibrous endocarp (stone).

***M. indica*: occurrence**

Mango occurs wild or semi-wild nearly throughout India, in tropical and subtropical hilly forests, particularly near nullahs and ravines. It is common in subtropical Himalayas, hills of western and Eastern Ghats and the forests of Central India, Bihar, Orissa, Assam and Andaman Island. It is now cultivated in southern China, Malaya, Indonesia, warmer parts of Australia, Philippines, Hawaii and West Indies, Madagascar and along the coast of tropical Africa. In N. America, it is grown to a limited extent in Florida and California.

***M. indica*: traditional use**

M. indica is commonly used in folk medicine for a wide variety of remedies. The root, bark, leaves, flowers, unripe and ripe fruit are acrid, cooling and astringent to the bowels and have been employed to cure “vata”, “pitta”, and “kapha” (Ayurvedic terminology). The parts of *M. indica* mentioned above have also been employed traditionally for treatment of leucorrhoea, bad blood; dysentery, piles, bronchitis, biliousness, urinary discharges, throat troubles, vaginal troubles, hiccough, ophthalmia, eruption, asthma and labouring under habitual constipation. It is also used as aphrodisiac, tonic, appetizer, beautifier of complexion, hiccough, laxative, diuretic, stomachic, antisyphilitic and for tanning purposes in various parts of the world.

Mangiferin

Mangiferin, $C_{19}H_{18}O_{11}$, a glucoxanthone (1,3,6,7-tetrahydroxyxanthone- C_2 - β -D-glucoside) (Fig. 1) has been reported to be present in various parts of *M. indica* (Anacardiaceae) and was encountered for the first time by Wiechowski [1]. The conclusive structure of mangiferin has been established as 2-C- β -D-gluco-pyranosyl-1,3,6,7-tetrahydroxyxanthone. Mangiferin occurs widely among angiosperms and has also been identified in ferns.

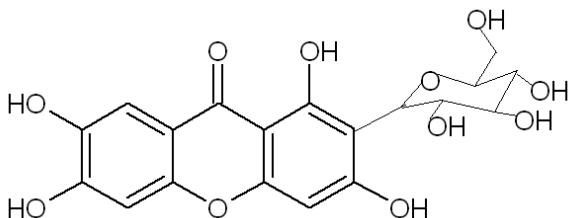


Figure 1. Structural formula of mangiferin

Mangiferin has been traditionally used as anti-inflammatory, analgesic, antioxidant, immunomodulator and in obesity treatment, particularly for diabetes type II. In Cuba and Sri Lanka it is sold under brand names Vimang® and Salaretin®, respectively.

An extensive and recent literature survey has revealed that mangiferin has been isolated from various parts of *M. indica* and different methods have been employed to establish its chemical structure as well as its pharmacological activities through biological screening procedures.

PHYTOCHEMICAL INVESTIGATION OF MANGIFERIN

Initial research studies and the published work on extraction, isolation and chemical constitution of mangiferin indicated that it is a C-gluco-pyranoside of 1,3,6,7-tetrahydroxyxanthone. Although, the unresolved problem was concerned with the point of attachment of the glucose residue to the xanthone nucleus.

Ramanathan and Seshadri [3] isolated the crystalline mangiferin from the bark of *M. indica*. They further reported the constitution of mangiferin by synthesizing methyl ether derivatives of mangiferin and subsequent subjection to methods like methylation and periodic acid oxidation. They concluded that glucose was linked to the second position of xanthone nucleus of mangiferin.

El Siss and Saleh [4] quantitatively extracted mangiferin from the leaf material of *M. indica*. In the study on the constitution of mangiferin they used degradation studies and ultraviolet spectrophotometric analysis. The paper chromatographic analysis resulted in characteristic R_f values for mangiferin in different mobile phases. When sprayed with different spray agents, mangiferin gave distinct and cha-

racteristic colours like green with ferric chloride (1% alcoholic), yellow with lead acetate (1% aqueous) and yellow with ammonia. Sissi and co-workers reported maximum absorption on mangiferin and also reported characteristic bathochromic shift in the presence of aluminium chloride and sodium acetate. Phloroglucinol and 2,4,5-tri hydroxy benzoic acid were obtained as degradation products of mangiferin and KOH fusion at 260° for half an hour.

Haynes and Taylor [5] supported the constitution of mangiferin. As it was suggested by Ramanathan and Seshadri, the nuclear magnetic resonance studies and chemical degradation analysis of mangiferin confirmed it as 2- β -D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone.

Mangiferin was successfully isolated from the stem bark of *M. indica* along with other polyphenolic components by El Sissi and El Ansari [6]. They inferred that even in high concentration (10.1%), mangiferin had no influence on the amount of tannins absorbed by hide powder.

El Ansari et.al. [7] isolated and characterized mangiferin from the acetone extract of *M. indica*. The results were confirmed by paper chromatographic analysis and chemical degradation studies.

Bhatia, Ramanathan and Seshadri [8] isolated mangiferin from alcoholic extract of leaves and stem bark of *M. indica*. Further they confirmed the constitution of mangiferin through reductive hydrolysis with hydriodic acid and oxidation with ferric chloride. 1,3,6,7-tetrahydroxyxanthone and glucose were obtained as resultant products confirming the constitution of mangiferin as previously suggested by Ramanathan et. al. The position of linkage at C-2 was established by oxidizing the mangiferin tri and tetra methyl ethers with periodate to get corresponding α -hydroxy acetals of trimethoxy and tetramethoxy xanthenes. The results were further confirmed by UV and IR spectral analysis.

Nott and Roberts [2] isolated mangiferin from the bark of *M. indica*. They further suggested chemical methods of confirming the point of attachment of the glucose residue to the xanthone nucleus. The experimental work involved the alkali fusion of mangiferin and some of its derivatives.

Bhatia and Seshadri [9] for the first time chemically synthesized mangiferin by the reaction of 1,3,6,7-tetrahydroxyxanthone with tetra-O-acetyl- α -D-glucopyranosyl bromide. Through the synthesis of mangiferin, Bhatia V.K. et.al. Confirmed that the glucoside had the β -configuration.

In the attempt to confirm the linkage between sugar and aglycone of C-glycosyl compound, Prox [10] reported mass spectra of mangiferin. It was concluded by them that when the sugar is bound to the aromatic ring, the other substituents influence the fragmentation in a characteristic manner.

In another study, Chaudhuri and Ghosal [11] established the identity of mangiferin through chemical and mass spectral studies.

Mangiferin was isolated from the bark of *M. zeylanica* by Herath et.al. [12] the ethanolic extract yielded mangiferin, the paper chromatographic behavior and the spectrophotometric analysis of which were identical with recorded data for authentic mangiferin.

Aritomi and Kawasaki [13] isolated a new xanthone C-glycoside named homomangiferin, coexisting with mangiferin. On the basis of chemical and spectral data it was formulated as 2-C- β -D-glucopyranosyl-3-methoxy-1,6,7-trihydroxyxanthone i.e. 3-O-methylmangiferin. Later on, they also isolated isomangiferin from aerial parts of *Anemarrhena asphodeloides*. On the basis of chemical and spectral data the structure, 4-C- β -D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone was assigned.

Researching polyphenolics of *M. indica*, El Ansari et.al. [14] simultaneously isolated 3 xanthenes-mangiferin, isomangiferin and homomangiferin from *M. indica* and identified these phenolic component using UV spectral analysis, acid hydrolysis, chromatographic analysis etc.

Frahm and Chaudhuri [15] presented an analyzed ^{13}C NMR chemical shifts of mangiferin. The additivity data provided by them could be applied for the structural elucidation of naturally occurring polysubstituted xanthenes.

Tanaka et.al. [16] isolated mangiferin from the leaves of *M. indica* and characterized its structure on the basis of chemical and spectroscopic evidences. Furthermore, they isolated a new xanthone C-glucoside gallate which was characterized as mangiferin-6'-O-gallate.

Berardini et.al. [17] isolated four xanthone C-glycosides from *M. indica*. These xanthone C-glycosides were subjected to high-performance liquid chromatography-electrospray ionization/mass spectrometry. On the basis of fragmentation pattern were identified as mangiferin and isomangiferin as well as their galloyl derivatives.

Rojas-Hernandez et.al. [18] tried to contribute to subsequent pharmacokinetic studies of mangiferin and also to understand its biological effects by subjecting mangiferin to UV and NMR spectral analysis and stability study in aqueous solution involving pka value determination of mangiferin.

PHARMACOLOGICAL INVESTIGATION OF MANGIFERIN

Immunomodulatory effect

Mangiferin was assessed for its immunomodulatory potential by Chattopadhyay et.al, [19] who observed the suppression of the proliferative response of murine splenocytes and thymocytes with higher doses of mangiferin. When used with concanavalin a (lectin), mangiferin produced additive stimulatory effect and induced heightened DNA synthesis of normal and advanced tumor bearers' splenocytes.

Ghosal et.al. [20] observed that mangiferin was effective in activating murine peritoneal macrophages. The mangiferin-elicited as well as *in vitro* mangiferin-treated macrophages showing increased lysosomal enzyme acid phosphatase activity and enhanced cytotoxicity as well as phagocytosis against ascitic fibrosarcoma (AFS) cells. The *in vivo* effect of mangiferin in activating macrophages was of short duration.

Bodhankar et. al. [21] investigated the immunomodulatory activity of alcoholic extract of *M. indica* containing mangiferin for its effect on cell mediated and humoral components of the immune system in mice. Mangiferin produced increase in humoral antibody (HA) titre and delayed type hypersensitivity (DTH) in mice confirming its promising immunostimulant properties.

In a research study, Leiro et.al. [22] investigated the effects of orally administered mangiferin on mouse antibody responses induced by inoculation with spores of microsporidian parasites. Mangiferin did not affect either IgM or IgG2a, but significantly enhanced production of IgG1 and IgG2b. Although, it did not enhance specific antibody secretion by splenic plasma cells from mice inoculated with microsporidian spores. Inoculation with spores induced splenomegally was significantly enhanced by mangiferin. These results suggested that components of *M. indica* extracts (mangiferin) might be of potential value for modulating the humoral response in different immunopathological disorders.

Garrido et.al. [23] explained some of biological activities at the molecular level attributed to the aqueous stem bark extract of *M. indica* (mangiferin). They investigated that mangiferin inhibited early and late events in T cell activation, including CD25 cell surface expression, progression to the S-phase of the cell cycle and proliferation in response to T cell receptor (TCR) stimulation. It also prevented TNF-induced with IB degradation and the binding of nuclear transcription factor, NF-B to the DNA.

Leiro et.al. [24] described the inhibitory effects of mangiferin (a C-glucosyl-xanthone present in the *M. indica* extract) on rat macrophage functions including phagocytic activity and the respiratory burst. They suggested that mangiferin had depressor effects on the phagocytic and ROS production activities of rat macrophages. Thus, it might be of value in treatment of diseases of immunopathological origin characterized by the hyperactivation of phagocytic cells such as certain autoimmune disorders.

Antiallergic activity

Leiro et.al. [28] observed antiallergic effect of mangiferin in mice infected with the nematode, *T. spiralis*. Treatment with mangiferin led to a significant decline in serum levels of specific anti-*Trichinella* IgE, throughout the parasite life cycle. Finally, oral treatment of rats with mangiferin inhibited mast cell degranulation as evaluated by the passive cutaneous anaphylaxis test. Since IgE plays a key role in the pathogenesis of allergic diseases, these results suggested that mangiferin might be useful in such diseases treatment.

Bronchodilatory effect

Gbeassor et.al. [29] studied the effect of *M. indica* stem bark aqueous extract (mangiferin) on rat trachea contracted by acetylcholine and histamine. The rat

trachea was previously incubated in presence of indomethacin, propranolol and atropine. The strips of trachea were suspended for isometric tension recorded at 37°C. *M. indica* aqueous extract at 2 mg/ml impair the contraction induced both by histamine and acetylcholine in all three experimental conditions. These experiments suggested that the aqueous extract of *M. indica* (mangiferin) could block both the histaminic and muscarinic receptors on rat trachea and thus suggesting its potential use in the treatment of asthma.

Antidiabetic activity

Ye Wu et.al. [30] confirmed significant antidiabetic activity of mangiferin by establishing its protein tyrosine phosphatase 1B (PTP1B) inhibitory activity. They synthesized some derivatives of mangiferin and evaluated their PTP1B inhibitory activity. PTP1B plays vital role in the potential treatment of diabetes mellitus.

An *in-vitro* study was carried out by Prashanth et.al. [31] established α -glucosidase inhibitory activity of ethanolic extract of *M. indica* (mangiferin) and suggested the potential usefulness of mangiferin in obesity and diabetes.

It has been suggested by Yoshikawa et.al. [32] that mangiferin inhibits the glucosidase enzymes (such as sucrase, isomaltase and maltase) in rats. These enzymes are involved in the digestion of carbohydrates into simple sugars in the gut leading to delay or inhibition of carbohydrate breakdown and subsequent slower glucose absorption from the intestine. Thus, mangiferin reduces blood glucose levels by inhibiting the glucose absorption from the intestine and hence possesses both pancreatic and extrapancreatic mechanisms in its antidiabetic action. Such apparent dual actions of mangiferin enhance its efficiency. They also found that mangiferin inhibited body weight gain in experimental rats. The results of this study indicate the possible utilization of mangiferin in food products for special dietary needs like with obese people.

Antioxidant activity

Andreu et.al. [34] reported for the first time, the iron-complexing ability of mangiferin as a primary mechanism for protection of rat liver mitochondria against Fe^{2+} -citrate induced lipid peroxidation. It also inhibited the iron citrate induction of mitochondrial antimycin A-insensitive oxygen consumption, stimulated oxygen consumption due to Fe^{2+} autoxidation and prevented Fe^{3+} ascorbate reduction. They concluded that *in vitro* antioxidant activity of mangiferin could be related to its iron-chelating properties and not merely due to the scavenging activity of free radicals. These results were of significant pharmacological relevance, since mangiferin could be potential candidate for chelation therapy in diseases related to abnormal intracellular iron distribution or iron overload.

Rajendran et.al. [35] reported that mangiferin decreased activities of electron transport chain complexes and TCA cycle key enzymes such as isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase and alpha-ketoglutarate dehydrogenase in lung cancer bearing animals. The results of the study and the modulatory effect of mangiferin in preventing biochemical changes further confirms the chemopreventive and chemotherapeutic effect of mangiferin particularly against cancer, in which oxidative stress plays an important causative role.

Nishigaki et.al. [36] performed an *in vitro* study to evaluate the protective effect of mangiferin on human umbilical vein endothelial cells against glycated protein-iron chelate induced toxicity. Mangiferin exerted protective effect by enhancing the level of antioxidant enzymes and reducing the amount of lipid peroxidases. The results confirm the significant role of mangiferin in preventing the development of vascular complications induced by glycated protein-iron chelate.

Stoilova et.al. [37] studied the antioxidant properties of alcohol solutions of mangiferin in linoleic acid/water emulsion system by the thiobarbituric acid reactive substances and by inhibiting conjugated dienes formation. Mangiferin also inhibited the hydroxyl radicals. The result of the study suggests that mangiferin can be a promising antioxidant agent.

Analgesic and anti-inflammatory activity

Gabino G. et.al. [38] investigated analgesic and anti-inflammatory effects of *M. indica* extract (Vimang a formulation which majorly contains mangiferin). Analgesia was produced by using acetic acid-induced abdominal constriction and formalin-induced licking. Inflammation was produced by carrageenan- and formalin-induced oedema. *M. indica* extract exhibited a potent and dose-dependent antinociceptive effect against acetic acid test in mice. It significantly inhibited oedema formation of both carrageenan- and formalin-induced oedema in rat, guinea-pigs and mice (maximal inhibitions: 39.5, 45.0 and 48.6, respectively). The inhibitions were similar to those produced by indomethacin and sodium naproxen. The antinociceptive and antiinflammatory actions were reported by them for the first time.

Bhatia et.al. [39] examined the ability of mangiferin to reduce prostaglandin E(2) (PGE(2)) and 8-iso-prostaglandin F(2 α) (8-iso-PGF(2 α)) production by lipopolysaccharide (LPS)-activated primary rat microglia. Mangiferin potently reduced LPS-induced PGE(2) synthesis and the formation of 8-iso-PGF(2 α). It also reduced LPS-induced COX-2 protein synthesis in a dose-dependent manner without modifying COX-2 transcription. It can be inferred from the study that mangiferin limits microglial activation and thus may play vital role in the mechanism of cerebral protection.

ANTITUMOR/ANTIVIRAL ACTIVITY

Zleng et. al. [25] studied *in vitro* the effect of mangiferin against *Herpes simplex* virus type 2. Mangiferin does not directly inactivate HSV-2 but inhibits the late event in HSV-2 replication.

Chattopadhyay et.al. [26] investigated the potential of mangiferin as a potent biological response modifier with antitumor and antiviral effect. They reported that mangiferin had *in vivo* growth-inhibitory activity against ascitic fibrosarcoma in Swiss mice. Mangiferin was found to induce antitumor effect irrespective of the size of tumor inoculum. It was also observed to have cytotoxic effect on tumor cells.

Mangiferin was also found to antagonize *in vitro* the cytopathic effect of HIV in MT-2 cells and prevented cell death. This anti-HIV effect of mangiferin might be associated with its effect as an interferon inducer.

Yoshimi et.al. [27] examined the effects of mangiferin in rat colon carcinogenesis induced by chemical carcinogen and azoxymethane. The cell proliferation in colonic mucosa was reduced in rats treated with mangiferin. The study supports the potential role of mangiferin as a naturally-occurring chemopreventive agent. It also suggests that mangiferin, a minor dietary constituent, can be used to prevent carcinogenesis or revert tumor promotion, a very promising approach to cancer control.

Anthelmintic activity

The anthelmintic property of mangiferin was investigated by Leiro et.al. [28] in mice experimentally infected with the nematode, *Trichinella spiralis*. The oral administration of mangiferin throughout the parasite life cycle led to a significant decline in the number of parasite larvae encysted in the musculature.

Antiplasmodial activity

Awe et.al. [40] evaluated antiplasmodial activity of the stem bark extract (mangiferin) of *M. indica* against *Plasmodium yoelii nigeriensis*. A marked respiratory activity and schizontocidal effect during early infection were observed by them.

Antiamoebic activity

During research study on plant extracts having antiamoebic activity, Cimanga et.al [33] reported *in vitro* antiamoebic activity of extract (mangiferin) from stem bark of *M. indica*. Metronidazole was used as a reference drug. The results provided a rational evidence to justify the traditional use of mangiferin for the treatment of amoebiasis.

Antipyretic activity

Awe et.al. [40] reported antipyretic activity of the stem bark extract (mangiferin) of *M. indica* in mice. A reduction in yeast-induced hyperpyrexia was also produced by it. The results validated the folklore use of *M. indica*.

Cardioprotective effect

Shyamala Devi et.al. [41] investigated the effect of mangiferin on the isoproterenol-induced myocardial infarction in rats. Mangiferin was found to ameliorate the effect of isoproterenol-induced pathological changes, reduced the lipid peroxide formation and retained the myocardial marker enzyme activities at near normal level. The above results indicate the cardioprotective effect of mangiferin.

Radioprotective effect

A protection of mangiferin against radiation-induced micronuclei formation in cultured human peripheral blood lymphocytes and in DBAxC57BL mice was shown by Jagetia et.al. [42].

Lipolytic effect

Yoshikawa et.al. [43] isolated mangiferin from the roots of *Salacia reticulata*. Mangiferin showed a significant lipolytic effect on rat epididymal fat-derived cultured adipocytes. Mangiferin also reduced triglycerides in these adipocytes.

Muruganandan et.al. [44] found that the mangiferin significantly reduce plasma total cholesterol, triglycerides, and LDL-C associated with a concomitant increase in HDL-C levels and a decrease in atherogenic index in diabetic rats indicating its potential antihyperlipidemic and antiatherogenic activity.

Antibacterial and antifungal activities

Stoilova et.al. [45] investigated an *in vitro* agar diffusion technique. Mangiferin showed activity against seven bacterial species: *Bacillus pumilus*, *Bacillus cereus*, *Staphylococcus aureus*, *Staphylococcus citreus*, *Escherichia coli*, *Salmonella agona*, *Klebsiella pneumoniae*, one yeast, *Saccharomyces cerevisiae* and four fungi: *Thermoascus aurantiacus*, *Trichoderma reesei*, *Aspergillus flavus* and *Aspergillus fumigatus*.

CONCLUSIVE REMARK

The available literature on phytochemical investigation of mangiferin reveals that the conclusive structure of mangiferin ($C_{19}H_{18}O_{11}$) can be established as 2-C- β -D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone. The point of attachment of glucose to the xanthone nucleus of mangiferin was regarded as an unresolved problem for quite a long period of time. It has been inferred and confirmed by various researchers that glucose is linked to the second position of xanthone nucleus of mangiferin. Most of phytochemical studies conducted with regard to the structural elucidation and characterization of mangiferin involve chemical methods like degradation studies as well as spectrophotometric analytical techniques like UV, IR, NMR, mass spectroscopy.

The authors are of the opinion that there exists a good correlation between traditional and folklore use of mangiferin and the results of the recent research studies on the same.

The pharmacological evaluation of the research studies conducted on mangiferin as well as plant extract of *M. indica* reveals the fact that mangiferin being major chemical and representative constituent of *M. indica* exhibits similar pharmacological activities to that exhibited by the plant extract of *M. indica*.

Mangiferin has prominent pharmacological actions corroborated by numerous research studies. Potential anti-inflammatory, analgesic, antipyretic, antioxidant, immunomodulator, antitumor, antiviral, anthelmintic, antiallergic, antihistaminic, cardioprotective, anticholinergic, antiamebic and antidiabetic effects have been found to be exerted by mangiferin.

Though, considerable research has been and are being done on mangiferin and its plant source. Yet, the potential therapeutic effects of mangiferin have not been fully exploited till now. There is an ample scope for researchers to work further in this area.

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BADANIA FITOCHEMICZNE I FARMAKOLOGICZNE MANGIFERYNY

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Streszczenie

Mangiferyna, C-glukopiranozyd 1,3,6,7-tetrahydroksyksantonu, izolowano z różnych części *Mangifera indica* (Anacardiaceae). Ostateczna struktura mangiferyny została ustalona przez kilku badaczy przy użyciu szerokiej gamy technik chemicznych i analizy spektralnej. Mangiferyny używa się tradycyjnie w kilku częściach świata jako środka przeciwzapalnego, przeciwbólowego, przeciwgorączkowego, przeciwutleniającego, regulującego procesy odpornościowe, przeciwrakowego, przeciwwirusowego, a także w leczeniu chorób pasożytniczych i otyłości. Niniejsza praca jest próbą przedstawienia cech charakterystycznych mangiferyny oraz wynikającego z tego przeglądu działań farmakologicznych. Przeprowadzono analizę porównawczą danych pochodzących z dostępnej literatury przedmiotu. Artykuł zawiera krótki opis przeprowadzonych do tej pory badań fitochemicznych i farmakologicznych nad mangiferyną i może stać się przewodnikiem dla kolejnych badań z tego zakresu.

Słowa kluczowe: *Mangifera indica*, mangiferyna