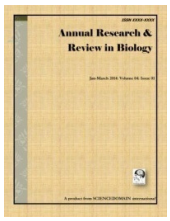

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Molecules of Interest – Mangiferin – A Review

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Mangiferin is a 1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside that has been reported to occur naturally in several genera. It exhibits a wide array of biological activities and also in several cases is responsible for the traditional use of its natural sources. It has been shown to exhibit various pharmacological activities, and thus has several possible applications in clinical research. This review presents a comprehensive literature search of different studies carried out on this secondary metabolite, especially its antidiabetic, anticancer, and antioxidant effects as well as, anti-inflammatory, antiviral, immunomodulatory and antimicrobial activities. The emphasis of the current review is on the chemistry and biological activity of mangiferin and its derivatives in addition to rational and ecologically acceptable methods for provision of this natural compound on a large scale. Therefore, further investigations may help in exploiting its properties and developing phyto-pharmaceuticals based on it.

Keywords: Mangiferin; xanthone; antidiabetic; anticancer; antioxidant; antimicrobial; antiviral; anti-inflammatory.

1. INTRODUCTION

For decades, natural products have played an important role in the development of drugs and drug leads. Mangiferin (1) is a xanthone derivative [1] widely distributed in higher plants like those of the *Anacardiaceae* [2], 23 species and three genera of *Gentianaceae* [3,4], 19

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species of *Podalyfrieae* [5] and 12 species of Hypericoideae families [6]. Some of these have been recommended as traditional medicinal plants. Mangiferin is a pharmacologically active phytochemical present in large amounts in the bark, fruits, roots and leaves of *Mangifera indica* (Family: *Anacardiaceae*). It is a reputed medicinal constituent recommended in the Indian system of medicine for the treatment of various diseases [2]. The traditional uses of the plants containing mangiferin in folk medicine are many. Some of these therapeutic effects have been confirmed by applied scientific experiments. New pharmacological activities of mangiferin have also been discovered after its isolation from medicinal plants based on folklore knowledge. Thousands of plants existing in nature are an enormous reservoir of bioactive molecules that can be developed as new chemical entities, analogs, derivatives, synthetic compounds with natural product derived pharmacophores or as natural product mimics [7]. The identification of right chemical entity is the only requirement. This review deals with the chemistry and pharmacology of mangiferin.

2. CHEMISTRY

Mangiferin, molecular formula: $C_{19}H_{18}O_{11}$, molecular weight: 422.35, melting point: anhydrous 271°C. It has bad solubility in most of the solvents, soluble in 60% aqueous ethanol, freely soluble in DMSO and DMF. The structural isomers are differing in substitution of glucoside ring at position 2 and 4 (Fig. 1).

2.1 IR *v* cm^{-1} (KBr Pellets)

3366.4 (O–H str.), 1649.4 (C=O str.), 1622.7 (aromatic C=C str.), 1199.3 (C–O str.), 1065.0 (Ar–O–Ar str.).

2.2 UV (Methanol) λ_{max} nm

237, 254, 268sh, 312, 364; +$AlCl_3$: 235, 268, 321sh, 350, 390; +$AlCl_3$ + HCl: 226, 259, 276sh, 316, 331, 398; +NaOH: 235, 268, 297sh, 340, 388; +NaOAc: 237, 263, 300sh, 334, 394.

2.3 ^{1}H NMR (500 MHz)

δ 13.76 (s, 1H, 1-OH), 10.55 (s, 2H, 6,7-OH), 9.86 (s, 1H, 3-OH), 4.86 (s, 2H, 3',4'-OH), 4.49 (s, 1H, 6'-OH), 3.87 (d, 1H, 2'-OH), 7.38 (s, 1H, 8-H), 6.86 (s, 1H, 5-H), 6.37 (s, 1H, 4-H), 4.60 (d, $^3J_{H1'/H2'}$ = 9.52, 1H, 1'-H), 4.05 (t, $^3J_{H2'/H3'}$ = 9.23 Hz, 1H, 2'-H), 3.69 (d, $^3J_{H6'/H5'}$ = 2.55 Hz, 1H, 6'-H), 3.41 (dd, $^3J_{H6'/H5'}$ = 5.22 Hz, 1H, 6'-H), 3.18 (m, $^3J_{H3'/H4'}$ = 9.19 Hz, $J_{H4'/H5'}$ = 9.17 Hz, 3H, 3', 4', 5'-H).

2.4 ^{13}C NMR (100 MHz)

163.4 (C-1), 107.4 (C-2), 165.2 (C-3), 94.8 (C-4), 158.8, 155.5 (C-4a,b), 103.2 (C-5), 153.1 (C-6), 144.9 (C-7), 109.1 (C-8), 113.1, 103.2 (C-8a,b), 181.2 (C-9), 75.3 (C-1'), 70.7 (C-2'), 78.1 (C-3'), 70.2 (C-4'), 92.6 (C-5'), 62.7 (C-6').

2.5 Mass Spectrum

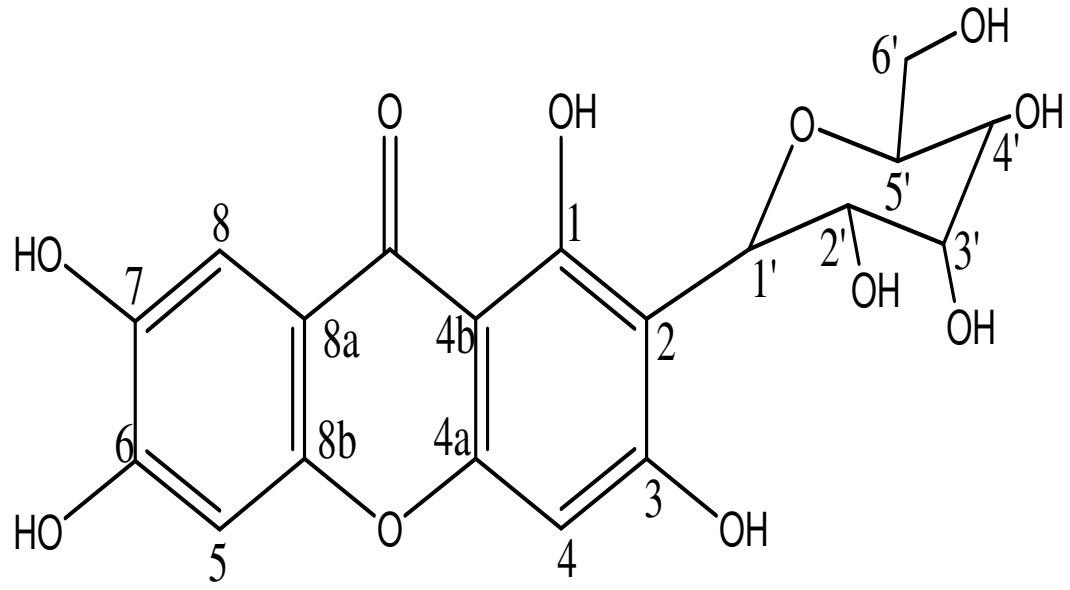
Molecular ion peak at m/z 423 (m+1), 405, 369, 357, 327, 303 and 273.

3. BIOSYNTHESIS OF MANGIFERIN FROM PHENYLALANINE

The biosynthesis of mangiferin has been investigated in *Anemarrhena asphodeloides* (Family: *Liliaceae*) with a result somewhat different from that found for the other xanthones [8]. In this plant, all the carbon atoms of phenylalanine (Fig. 2) as well as of cinnamic and coumaric acid are incorporated into the xanthone nucleus, and benzoic acid is apparently not on the pathway. Thus a pathway for the formation of mangiferin which is distinct from that of the normal xanthones was found out.

4. DISTRIBUTION OF MANGIFERIN

In a review on the distribution of the C-glycoxanthones known at that time, Richardson [9] found that mangiferin occurred more or less sporadically in 60 species, 18 genera, and 13 families of dicots (it is also present in monocots and in ferns). Of these, 23 species and three genera of Gentianaceae [3,4], 19 species of Cyclopia [5], 12 species of Hypericum [6]appeared to be the main centers of distribution for this compound. Table 1 gives a list of the different natural sources of mangiferin.



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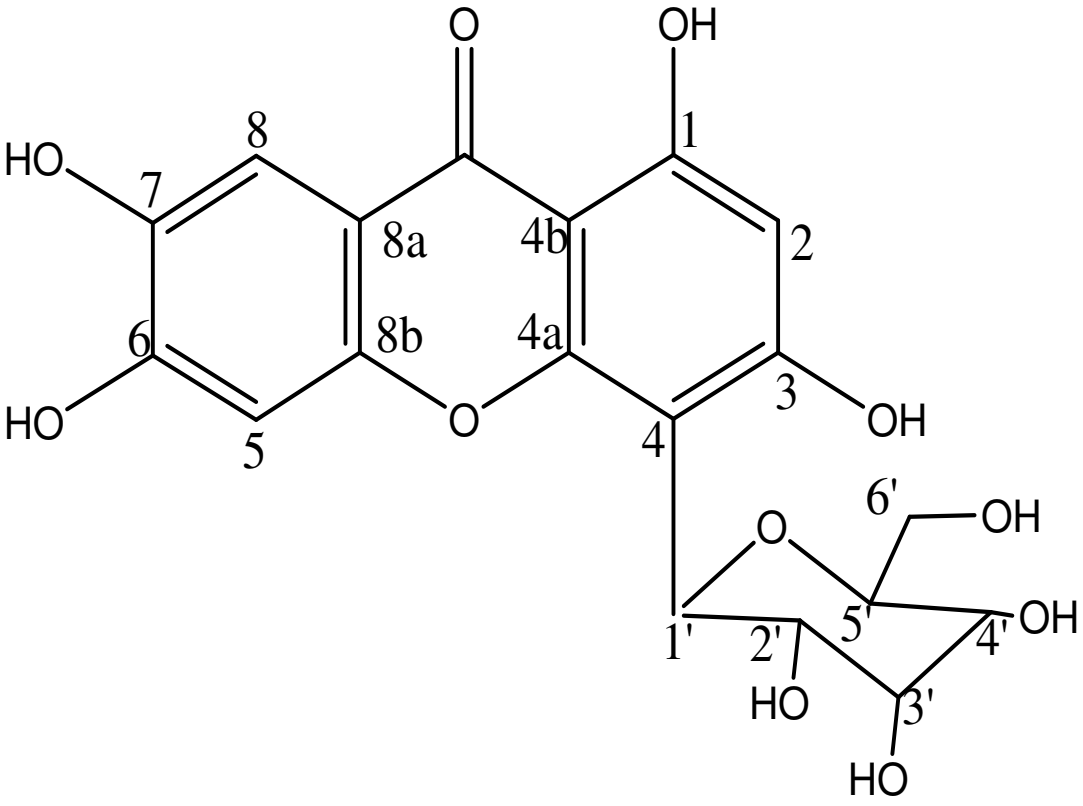

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Fig. 1. Structure of mangiferin (1) and iso mangiferin (2) [6]

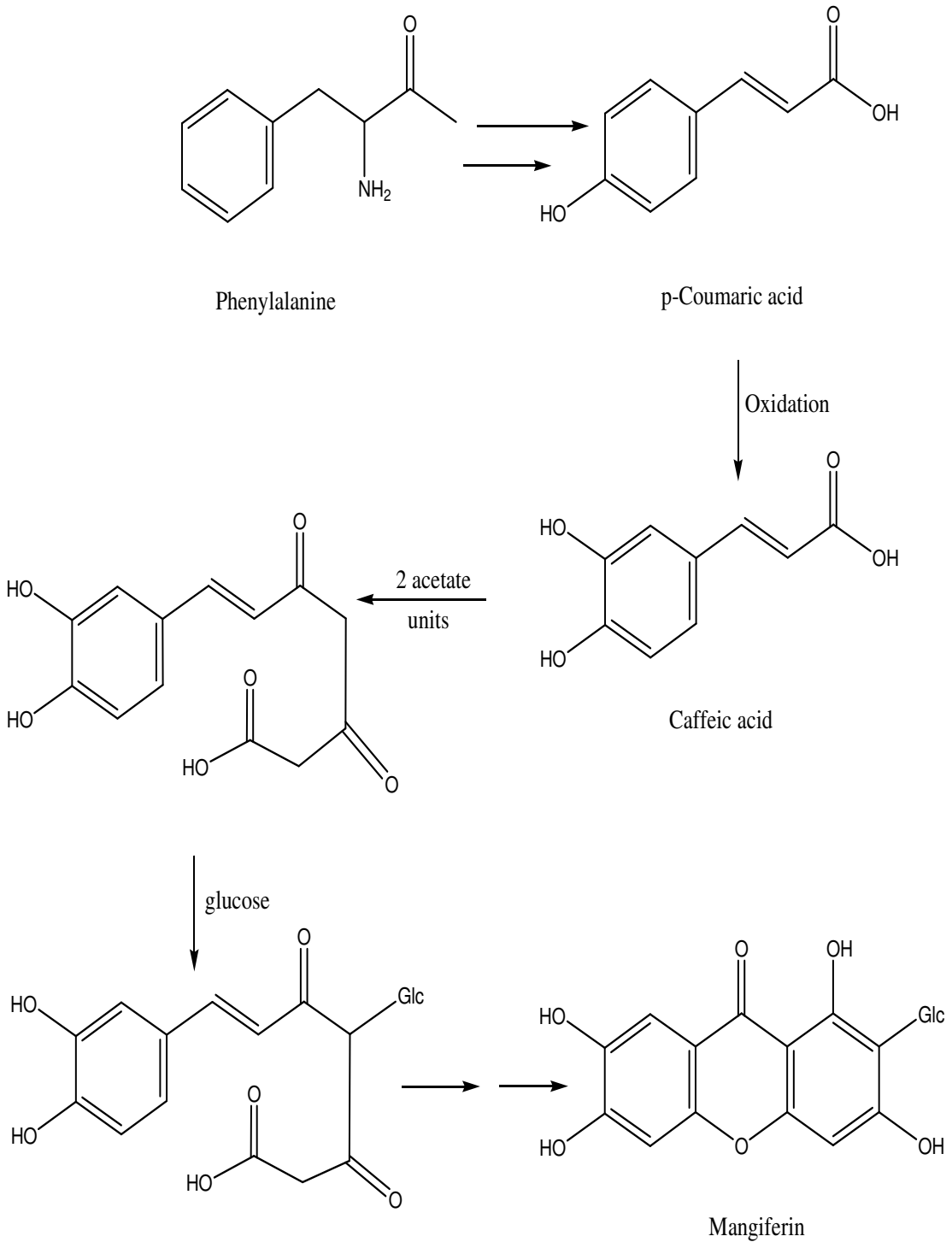

Fig. 2. Proposed biosynthetic route for mangiferin (Fujita and Inoue, 1980)

Table 1. Different plant sources of mangiferin

Name of the plant	Family	Reference
Canscora decussate, Fagraea blumei, Gentiana asclepiadea, G. campestris, G. corymbifera, G. cruciata, G. favrati, G. karelinii, G. lacteal, G. lutea, G. marcailhouana, G. nivalis, G. orbicularis, G. pneumonanthe, G. schistocalyx, G. utriculosa, G. verna, Gentianella campestris, G. caucasica, G. germanica, G. ramose, G. serotina, G. stenocalyx, Hoppea dichotoma, Swertia calycina, S. chirata, S. connata, S. cordata, S. dilatata S. elongate, S. franchetiana, S. gracilescens, S. macrosperma, S. mussotii, Salacia oblonga, S. perennis, S. perfoliata, S. randaiensis, S. speciosa, S. swertopsis, S. tosaensis, S. japonica, Tripterospermum lanceolatum, Tripterospermum taiwanense.	*Gentianaceae*	[3,4]
Hypericum androsaemum, H. maculatum, H. sampsonii, H. perforatum, H. undulatum, H. barbatum, H. rumeliacum, H. rochelii, H. boissieri, H. humifusum, H. aucheri, H. linarifolium.	Hypericoideae	[6]
Cyclopia spp, C. aurescens, C. bolusii, C. bowieana, C. burtonii, C. buxifolia, C. dregeana, C. falcate, C. galioides, C. genistoides, C. intermedia, C. latifolia, C. longifolia, C. maculate, C. Montana, C. plicata, C. pubescens, C. sessiliflora, C. subternata.	Podalyfrieae	[5]
Mangifera indica, M. odorata, M. persiciformis	*Anacardiaceae*	[10,11,12]
Bombax ceiba	*Bombacaceae*	[13]
Anemarrhena asphodeloides	*Liliaceae*	[14]
Phaleria macrocarpa, Mahkota dewa, Gnidia involucrata	*Thymelaeaceae*	[15,16,17]
Polygala tenuifolia, P. hongkongensis	*Polygalaceae*	[18,19]
Zizyphus cambodiana	*Rhamnaceae*	[18]
Bersama engleriana	*Melianthaceae*	[20]
Arrabidaea patellifera	*Bignoniaceae*	[21]
Belamcanda chinensis	*Iridaceae*	[22]
Salacia oblonga, S. hainanensis	*Celastraceae*	[23,24]
Salacia reticulata	Hippocrateacaea	[25]
Trichomanes reniforme	*Hymenophyllaceae*	[26]
Bersama abyssinia	*Melianthaceae*	[27]
Cratoxylum cochinchinense	*Clusiaceae*	[28]

5. MEDICINAL USES OF PLANTS CONTAINING MANGIFERIN

Some members of the genus such as *Swertia japonica, S. chirata, S. hookeri, S. macrosperma, S. petiolata* and *S. calycina* belongs to the family *Gentianaceae*, have been used in traditional medicine of the Far East for many years. Among their active principles xanthones (mostly 1,3,7,8- and 1,3,5,8-tetraoxygenated) occupy an important role, exhibiting antidepressant, antileukaemic, antitumor, antitubercular, choleretic, diuretic, antimicrobial, antifungal, antiinflammatory, antiviral, cardiotonic, hypoglycaemic and other activities [29,30].

Mangifera indica, commonly known as mango, is consumed worldwide as a fruit, culinary and flavoring agent. The fruits, barks and leaves of *M. indica* have been reported to possess diverse medicinal properties in the traditional Indian system of medicine, the Ayurveda, and are widely used in several medicinal preparations [31,32]. The plant has been reported to contain antidiabetic, antiviral, antibacterial, antiamoebic, antidiarrhoeal, immunostimulant, immunomodulatory, analgesic and antiinflammatory properties [10,33,34,35,36,37,38]. The extract of *M. indica* has been reported to be an antioxidant and a potent scavenger of hydroxyl radicals and hypochlorous acid. It has also been found to chelate iron, inhibit lipid peroxidation and DNA damage *in vitro* [39].

6. BIOLOGICAL ACTIVITIES OF MANGIFERIN

6.1 Antimicrobial Activity

Mangiferin possesses antibacterial activity *in vivo* against specific periodontal pathogens such as *Prevotella intermedia* and *Porphyromonas gingivalis* [35]. The solution of mangiferin in polyethylene glycol-400 was found to exert superior activity against seven bacterial and five fungal species - *Bacillus pumilus, Bacillus cereus, Staphylococcus aureus, Staphylococcus citreus, Escherichia coli, Salmonella agona, Klebsiella pneumoniae*, *Saccharomyces cerevisiae, Thermoascus aurantiacus, Trichoderma reesei, Aspergillus flavus* and *Aspergillus fumigatus*. It was more effective against Gram-positive microorganisms and the species most sensitive was *Bacillus pumilus*. Among the Gram-negative organisms, most sensitive to mangiferin was *Salmonella agona*. Mangiferin did not show any activity with regard to *Pseudomonas aeruginosa* [40].

6.2 Antiviral Activity

Antiviral effect of mangiferin and isomangiferin against type I herpes simplex virus, HSV-I was studied. The effect of isomangiferin somewhat exceeded such control drugs as acyclovir, idoxuridine and cyclocytidine. The average plaque reduction rates of mangiferin and isomangiferin were 56.8% and 69.5%, respectively. The antiviral effect of mangiferin and isomangiferin was presumably due to their capability of inhibiting virus replication within cells.

In a follow-up study [10] the effect of mangiferin, against herpes simplex virus type 2 (HSV-2) *in vitro* was assessed. The 50% effective concentration of it against HSV-2 plaque formation in HeLa cells was 111.7 µg/ml, and at the concentrations of 33 and 80 µg/ml reduced the virus replicative yields by 90% (EC_{90}) and 99% (EC_{99}), respectively. The therapeutic index (IC_{50}/EC_{50}) was 8.1. Mangiferin did not directly inactivate HSV-2. The results of the drug addition and removal tests suggest that mangiferin inhibits the late event in HSV-2 replication.

6.3 Antioxidant Activity

Studies have been demonstrated that mango stem bark extract is useful in preventing the hyper production of reactive oxygen species (ROS) and their oxidative tissue damage *in vivo* was more active than vitamin C, vitamin E and β-carotene [2,39]. Hence mangiferin was studied both *in vitro* and *in vivo* for its possible antioxidant effects. It has shown potential antioxidant activity against DPPH [13,41,42,43] hydroxyl radicals and reductive activity of Fe^{3+} (Wu et al.) [19], antimycin A-induced H_2O_2 production [44] and t-butyl hydroperoxide-promoted membrane lipid peroxidation [45]. The antioxidant activity in linoleic acid/water emulsion system, determined by the thiobarbituric acid reactive substances (TBARS) indicated its higher activity than quercetin [40].

It also significantly enhanced erythrocyte resistance to H_2O_2 induced reactive oxygen species production [46]. Several mechanistic studies were carried out and it was postulated that mangiferin works mainly by a mechanism different from the classical hydroxyl radical scavengers, keeping iron in its ferric form, by

complexing Fe^{3+}or stimulating Fe^{2+}autoxidation [47]. *In vitro* antioxidant activity of mangiferin is also related to its iron-chelating properties and not merely due to the scavenging activity of free radicals [48]. Ca^{2+} increases levels of mitochondria-generated reactive oxygen species, which reacts with mangiferin producing quinoid derivatives, which in turn react with the most accessible mitochondrial thiol groups, thus triggering mitochondrial permeability transition. It seems probable that the free radical scavenging activity of mangiferin shifts its anti-oxidant protection to the thiol arylation [49].

6.4 Analgesic and Antipyretic Activity

Analgesic activity of mangiferin was studied using acetic acid induced writhing in mice at three dose levels 0.42, 4.2 and 42.2 given i.p significant (P = 0.05) and dose dependent activity was observed. In hot plate test confirmed the analgesic activity of mangiferin. Mechanistic studies indicated the involvement of opioid receptors [13].

6.5 Anti-Inflammatory Activity

Mangiferin at 100 mg/kg failed to exhibit detectable anti-inflammatory activity when subjected to carrageenan-induced rat paw edema [50]. The mangiferin aglycon (norathyriol) was tested *in vitro* as an inhibitor of the formylmethionyl-leucyl-phenylalanine induced respiratory burst in rat neutrophils. The results suggested that norathyriol inhibited both cyclooxygenase and 5-lypoxigenase (LOX) pathway, and that this action probably accounts for its anti-inflammatory effects. However marked reduction on the phagocytic production of rat macrophages by mangiferin tested at 50-250 mg/kg given intra peritoneally revealed that anti-inflammatory response is detectable but after the onset of the immunological response [37].

In other studies mangiferin blocks tumor necrosis factor (TNF)-induced NF-kappaB activation and NF-kappaB-dependent genes like ICAM1 (Inter-Cellular Adhesion Molecule 1) and COX2, increased the intracellular GSH levels indicating its potency for anti-inflammatory therapy [51,52].

6.6 Anticancer Activity

Mangiferin enhances tumor cell cytotoxicity of lymphocytes and macrophages and antagonizes *in vitro* the cytopathic effect of HIV [53]. These activities are slightly similar to other chemopreventive agents such as 1-acetoxy chavicol acetate. Hence mangiferin was studied both *in vitro* and *in vivo* for its possible anticancer effects. The antiproliferation effects of mangiferin on K562 leukemia cells [54] were tested by tetrazolium salt (MTT) method.

Supplementation of mangiferin (100 mg/kg) enhanced the detoxification enzymes and reduced DNA damage as determined by single cell electrophoresis. Furthermore, the DNA-protein cross links which was found to be high in lung cancer bearing animals was also modulated upon supplementation with mangiferin. This results was explained the unique association between the anti-oxidant effect of mangiferin and ultimately the capability of mangiferin to prevent cancer [55]. Recent studies in which the modulatory effect of mangiferin on mitochondrial lipid peroxidation (LPO), tricarboxylic acid (TCA) cycle key enzymes and electron transport chain complexes was investigated against lung carcinogenesis induced by benzo(a)pyrene (50 mg/kg) in Swiss albino mice. Decreased activities of electron transport chain complexes and TCA cycle key enzymes such as isocitrate dehydrogenase (ICDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH) and alpha-ketoglutarate dehydrogenase (alpha-KGDH), in lung cancer bearing animals were observed. Pre- and post-treatment with mangiferin (100 mg/kg) for 18 weeks, prevented the above biochemical changes, which were inclined towards normal control animal values. This study was confirmed the chemopreventive and chemotherapeutic effect of mangiferin [55,56].

6.7 Gastroprotection Activity

In search of novel gastroprotective agents, mangiferin, a naturally occurring glucosylxanthone from *Mangifera indica*, was evaluated in mice on gastric injury induced by ethanol and indomethacin. The effects of mangiferin on gastric mucosal damage were assessed by determination of changes in mean gastric lesion area or ulcer score in mice and on gastric secretory volume and total acidity in 4-h pylorus-ligated rats [57]. These findings provide evidence that mangiferin affords gastroprotection against gastric injury induced by ethanol and indomethacin most possibly through the antisecretory and antioxidant mechanisms of action.

6.8 Cardioprotective Effect

Mangiferin possess cardioprotective and hypolipidemic effect on experimentally induced cardiotoxic myocardial infarcted rats [58]. The recent findings [59] suggest that the protective effect of mangiferin can be attributed to its reducing effect on oxidative damage and activation of mitochondrial energy metabolism. These results were useful to study and understand the cellular events involved in this cardioprotective mechanism of mangiferin.

6.9 Anticryptosporidial Activity

The inhibitory activity of mangiferin (50 mg/kg/die and 100 mg/kg/die) on *Cryptosporidium parvum* was evaluated in a neonatal mouse model and its activity was compared with that of paromomycin (100 mg/kg/die). Mangiferin at 100 mg/kg has a significant anticryptosporidial activity and that its activity is similar to that showed by the same dose (100 mg/kg) of paromomycin. However, both mangiferin and paromomycin were not able to completely inhibit intestinal colonization of *C. parvum* but only to reduce it. This reduction was calculated at over 80% for both mangiferin and paromomycin with respect to the untreated control. A significant activity was found also for mangiferin at 50 mg/kg only after the end of treatment [60].

6.10 Neuroprotectant Activity

Brain ischemia induces neuronal loss which is caused in part by excitotoxicity and free radical formation. Gottlieb et al. [61] reported that mangiferin are neuroprotective in both *in vitro* and *in vivo* models of ischemia. Cell death caused by glutamate in neuronal cultures was decreased in the presence of submicromolar concentrations of mangiferin which in turn attenuated receptor-mediated calcium influx, oxidative stress as well as apoptosis. In addition, it was diminished the generation of free radicals and neuronal loss in the hippocampal CA1 region due to transient forebrain ischemia in rats when administered after the insult. Importantly, neuroprotection by this antioxidants was functionally relevant since treated-ischemic rats performed significantly better in three hippocampal-dependent behavioral tests. Together, these results indicate that mangiferin have potent neuroprotectant activity [61] which may be of therapeutic value for the treatment of acute neuronal damage and disability.

6.11 Antidiabetic Activity

Many active compounds associated with antidiabetic activity have been discovered, including triterpenoid glucoside, a steroidal glucoside, a iridoidal glucoside [62]. It is therefore interesting that mangiferin have a significant antidiabetic activity and it was studied. Mangiferin has beneficial effects on hyperlipidemia in type 2 diabetes [63]. In addition, mangiferin improved hyperinsulinemia and, on insulin tolerance test, reduced blood glucose levels of KK-Ay mice. From these findings, it seems likely that mangiferin exerts its antidiabetic activity by decreasing insulin resistance [62,63]. Mangiferin were tested for their antidiabetic activity in KK-Ay mice, an animal model of non-insulin-dependent diabetes mellitus (NIDDM). Mangiferin lowered the blood glucose level of KK-Ay mice after oral administration. However, no affect on the blood glucose level in normal mice was seen, indicating that MF is useful in treating NIDDM [64].

Mangiferin was found to inhibit sucrase, isomaltase, and aldose reductase from rat with IC_{50} values of 87, 216 and 1.4 µg/ml, respectively. The inhibitory activities of mangiferin are competitive for sucrase and isomaltase with inhibitor constant (Ki) 55 µg/ml and 70 µg/ml, respectively [65,66].

Repeated intraperitoneal injections of mangiferin (10 and 20 mg/kg) and insulin (6 U/kg) controlled STZ-induced lipid peroxidation and significantly protected the animals against cardiac as well as renal damage [67]. In a follow-up study [66,67,68] the effect of mangiferin on the atherogenic potential of streptozotocin (STZ)-diabetes was investigated. In addition, the effect of mangiferin on oral glucose tolerance in glucose-loaded normal rats was also determined. Further, mangiferin (10 and 20 mg/kg, i.p.) showed significant antihyperlipidemic and antiatherogenic activities as evidenced by significant decrease in plasma total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) levels coupled together with elevation of high-density lipoprotein cholesterol (HDL-C) level and diminution of atherogenic index in diabetic rats. In addition, the chronic administration of mangiferin (10 and 20 mg/kg, i.p.) for 14 days significantly as well as markedly improved oral glucose tolerance in glucose-loaded normal rats suggesting its potent antihyperglycemic activity.

6.12 Radioprotective Effect

Irradiation causes a variety of lesions in important biomolecules of the cell through generation of free radicals leading to genomic instability. DNA strand breaks, acentric fragments, or defective kinetochores are manifested as micronuclei after the first cell division. Chemicals that can trap free radicals may reduce the deleterious effects of ionizing radiation. Mangiferin, a glucosylxanthone derived from *Mangifera indica*, was investigated for its ability to reduce the frequency of radiation-induced micronucleated binucleate cells (MNBNCs) in cultured human peripheral blood lymphocytes (HPBLs) [69]. HPBL cultures were pretreated with 0, 5, 10, 20, 50, and 100 µg/ml of mangiferin for 30 min before exposure to 3 Gy of (60) Co gamma-radiation. The maximum decline in radiation-induced micronuclei was observed at a concentration of 50 µg/ml mangiferin.

The radioprotective effect of various concentrations of mangiferin was also studied in the DBAxC_{57}BL mice whole body exposed to 10 Gy of γ-irradiation [69]. Treatment of mice with different doses of mangiferin, one hour before irradiation reduced the symptoms of radiation sickness and delayed the onset of mortality when compared with the non-drug treated irradiated controls. The radioprotective action of mangiferin increased in a dose dependent manner up to 2mg/kg and declined thereafter. The highest radioprotective effect was observed at 2mg/kg mangiferin, where greatest number of animals survived against the radiation-induced mortality. The administration of 0.5, 1, 2, 5, 10 and 17.5 mg/kg mangiferin reduced the radiation-induced gastrointestinal death as evident by a greater number of survivors up to 10 days in this group when compared with the DDW + 10 Gy irradiation group. A similar effect of mangiferin was observed for the radiation-induced bone marrow deaths also.

6.13 Antiallergic Activities

Oral treatment of rats with mangiferin, daily for 50 days (50 mg/kg bodyweight/day), inhibited mast cell degranulation as evaluated by the passive cutaneous anaphylaxis test (sensitization with infected mouse serum with a high IgE titre, then stimulation with the cytosolic fraction of *T. spiralis* muscle larvae). Since IgE plays a key role in the pathogenesis of allergic diseases [70]. Recent study, mangiferin showed a significant dose-dependent inhibition of IgE production in mice and anaphylaxis reaction in rats, histamine-induced vascular permeability and the histamine release induced by compound 48/80 from rat mast cells, and of lymphocyte proliferative response as evidence of the reduction of the amount of B and T lymphocytes able to contribute to allergic response [71].

6.14 Other Activities

The effective bioavailability of mangiferin makes them suitable antioxidants with potential use in atherosclerosis susceptible conditions [72]. It is also a significant neuraminidase inhibitor [11]. Mangiferin could be a useful compound in therapies for degenerative diseases, including Parkinson's disease, in which oxidative stress plays a crucial role [73].

In vitro experiments showed that pretreatment of lymphocytes with mangiferin protected from the toxicity induced by H_2O_2, further confirming the *in vivo* findings. From this study, it is evident that mangiferin exhibits an immunoprotective role mediated through the inhibition of reactive intermediate-induced oxidative stress in lymphocytes, neutrophils and macrophages [68]. Mangiferin on mouse antibody responses induced by inoculation with spores of microsporidian parasites. Inoculation induced specific antibody production with an exponential timecourse, peaking after about one month. Mangiferin did no affect either IgM or IgG2a, but significantly enhanced production of IgG1 and IgG2b. This result suggests that mangiferin may be of potential value for modulating the humoral response in different immunopathological disorders [74].

7. SYNTHESIS OF MANGIFERIN DERIVATIVES AND ITS STRUCTURE ACTIVITY RELATIONSHIP

The many functional groups of mangiferin make the molecule a good target for structural modification. Antioxidant activity appeared in mangiferin, while acetyl and cinnamoyl derivatives of mangiferin possessed reduced activity in DPPH method. The methyl and its acetyl derivative found to be inactive [13].

Substitutional benzyl derivatives of mangiferin demonstrated moderate to good PTP1B inhibitory activity at 4 µg/ml concentration. Compounds m-chloro benzyl mangiferin, dichloro benzyl mangiferin and p-fluoro benzyl mangiferin displayed 24.1%, 37.6% and 40.9% inhibition

against PTP1B. It was evident that mangiferin is a weak PTP1B inhibitor, whereas some derivates were found to show good inhibition. The structure–activity relationship study showed the substitution of free hydroxyl at C-3, C-6, and C-7 of mangiferin remarkably enhanced the activity, and the benzylated derivates with mono or di-chloro atom were of better inhibitory activity than other groups. Comparing to someother substitutional benyl derivatives with dichloro benzyl mangiferin and p-fluoro benzyl mangiferin, it could be seen that the para position of the benzyl was a better place for introducing substituent than meta and ortho position [75].

8. CONCLUSION

Xanthone glucosides are important group of compounds in nature. During the recent decades a large number of pharmacological studies have been carried out to indicate the beneficial effects of xanthones including mangiferin [76,77]. Thus, from the present review it can be concluded that although its full potential has not been fully explored, mangiferin shows possible applications in clinical research and seems to be a potential phytotherapeutic agent especially as an antidiabetic, anticancer, anti-inflammatory and an antioxidant. It is present in abundant yields in various parts of *Mangifera indica* (*Anacardiaceae*) which can be used as good sources of mangiferin [2]. In order for further studies to be feasible it is vital to find economical and ecologically acceptable ways of producing mangiferin. Further development of synthetic or tissue culture methods could prove valuable and advances in molecular biology will hopefully lead to acquisition potential through recombinant DNA techniques. Further investigations may, therefore, help in exploiting its properties and developing phyto-pharmaceuticals based on it. In the future, more mechanistic oriented basic research is needed to elucidate the mechanisms of actions. Mangiferin with highly interesting biological effects is worth to be studied more carefully considering the folklore uses of the plants possessing this active ingredient.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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