Perspectives on Medicinal Properties of Mangiferin

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Abstract: Mango tree, *Mangifera indica*, has been cultivated in India and several other tropical countries for centuries, and it is a good source of compound 'mangiferin'. Mangiferin's xanthonoid structure with C-glucosyl linkage and polyhydroxy component is believed to be crucial for its free radical-scavenging ability leading to a potent antioxidant effect. A number of biological activities of mangiferin have been suggested, including antidiabetic and antiinflammatory abilities. These might be explained by its antioxidant ability as well as its ability to modulate several key inflammatory pathways. Mangiferin has also been shown to be an effective inhibitor of NF-κB signaling pathway. This partially explains its antiinflammatory ability and, additionally, points towards its anticancer potential. The anticancer effects of this compound are just beginning to emerge, and in this comprehensive review, we provide information on what we know about the chemistry and biological effects of mangiferin, which would likely create interest among researchers to design further mechanistic studies in order to better understand and exploit the biological activities of this compound.

Keywords: Anticancer, Antidiabetic, Antiinflammatory, Antioxidant, Mangiferin, NF-κB.

1. INTRODUCTION

It may be surprising to note that mango which is considered to be the undisputed king of all fruits and one of the most extensively exploited fruits for juice, pulp, flavor and fragrance, belongs to the family of highly poisonous plants such as cashews, poison oak and poison ivy,viz. Anacardiaceae. The fruit is indigenous to the Indian sub-continent, and other tropical areas around the globe, and grows on tropical fruiting tree, viz. *Mangifera indica* which has been cultivated in India for over 4000 years. It is thought to have reached East Asia between the 4th and 5th century BC and cultivated in East Africa and thereafter in Brazil, West Indies, China, United States, Carribean and Mexico, where the climate is conducive for its growth. There are over 20 million metric tons of mangoes grown throughout the tropical and sub-tropical regions. The leading mango producer country in the world is India, with very little export as most of the produce is consumed within the country. Mexico and China compete for the second place, followed by Pakistan and Indonesia. As briefly indicated that other cultivator countries include North, South and Central America, the Caribbean, South, West and Central Africa, Australia, Bangladesh and Southeast Asia.

The etymology of the name 'mango' suggests that it is derived from the Tamil word 'mangkay' or 'man-gay'. The Portuguese traders who settled in Western India adopted the name 'manga' which probably led to the word 'mango' used in English and Spanish. Some variations of the name exist in other languages: French (mangot, mangue, manguier), Portuguese (manga, manguiera) and Dutch (manja). In some parts of Africa it is referred to as mangou or mangoro. The wide usage of the variants of the name mango perhaps attests for its prevalence worldwide. The fruit is fleshy, variable in size and shape, with varying mixtures of green, yellow and red colors while leaves are evergreen, alternate and simple as well as long and broad. When the leaves are young they are orange and pink but rapidly transform into dark glossy red and then dark green as they mature. Mangoes, with their tangy sweet flesh, have contributed to many inventive dishes, especially in Indian and Southeast Asian cuisine including sweet and chewy fruit leathers and fiery hot and spicy mango pickle. A beverage called 'Lassi' made with mango, yogurt, sugar, ice and a touch of ground cardamom is typically featured in many Indian restaurants today. Probably the most well-known dish that employs the mango is 'Mango chutney' which is an Indian condiment made by using green mango, brown sugar, vinegar, hot peppers, and ginger.

A number of ancient Indian scriptures have highlighted nutritive and medicinal value of mango wherein different parts of mango have been converted into various types of therapeutic formulations. Many of the therapeutic uses attributed to mango tree extracts include antiviral, antiparasitic, antiseptic, antiasthmatic, cardiotonic, aphrodisiac and laxative. An extract of mango bark called 'Vimang' has been shown to possess cytoprotective antioxidant effects [1]. Dried flowers of mango contain 15% tannin and serve as astringents in case of diarrhea, chronic dysentery, catarrh of the bladder and chronic urethritis. Mango seeds have been found to be useful in treating diarrhea. The resinous gum obtained from the trunk is useful against skin cracking of feet. In some of the Caribbean islands, the leaf decoction is taken as a remedy for diarrhea, fever, chest complaints, diabetes and hypertension. Mango fruit and leaves contain polyphenols like quercetin, isoquercitin, gallic acid, methylgallate and a unique

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xanthone derivative, viz. mangiferin, all of which are powerful antioxidant compounds and potential therapeutic agents. In the present review, we aim to provide a summarized account of the therapeutic potential of mangiferin surveying literature available to-date.

2. PLANT SOURCES OF MANGIFERIN

The compound is found to be present in a variety of plant families in varying concentrations and it usually occurs as a glycoside. Some of the plant sources for Mangiferin include: *Anemmarhena asphodeloides* [2], *Aphloia theiformis* [3], *Arrabidaea patellifera*. [4], *Arrabidaea samydoides* [5], *Bersama abyssinica* [6], *Bombax ceiba* [7], *Bombax malabaricum* [8], *Cratoxylum cochinchinense* [9], *Cyclopia genistoides* [10], *Cyclopia subternata* [11], *Folium mangiferae* [12], *Folium pyrrosiae* [13], *Gentiana lutea* [14], *Gentianella nitida* [15], *Gnidia involucrata* [16], *Hypericum perforatum* [17], *Mahkota Dewa*[18], *Mangifera indica* [19], *Mangifera odorata* [20], *Phaleria cumingii* [21], *Phaleria macrocarpa* [22], *Mangifera Persiciformis* [23], *Polygala hongkongensis* [24], *Pyrrosia gralla* [25], *Rhizoma anemarrhenae* [26], *Rhizoma belamcandae* [27], *Salacia hainanensis* [28], *Salacia oblonga* [29], *Salacia reticulate* [30], *Swertia macrosperma* [31], *Swertia chirata* [32], *Swertia mussotii* [33], *Swertia punicea* [34], *Trichomanes reniforme* [35] and *Zizyphus cambodiana* [20]. However, the easiest source of mangiferin appears to be from mango and especially from mango tree leaves.

3. EXTRACTION, ISOLATION AND SPECTRO-SCOPIC CHARACTERIZATION

Mangifera indica is one of the chief sources of mangiferin. The secondary plant metabolites of this plant have been identified and quantitated by Baretto and co-workers [36] in solvent extracts of barks, kernels, peels, and old and young leaves. The method followed for the purpose included extraction of the plant material from *Mangifera indica* with hexane in a Soxhlet apparatus to remove lipids. After drying, the material was further extracted with methanol and the solutions were evaporated to dryness by rotavapor. The extracts were dissolved in methanol and analyzed by high-performance liquid chromatography (HPLC) and HPLC-electrospray ionization-mass spectro-metry (ESI-MS). Free radical scavenging activity of the solvent extracts was evaluated using a high-performance liquid chromatography-based hypoxanthine/xanthine oxidase assay which revealed dose-dependent antioxidant capacity in all extracts. The major phenolic compounds (mangiferin, penta-*O*-galloylglucoside gallic acid, and methyl gallate) detected in these extracts were also evaluated by additional *in vitro* assays such as oxygen radical absorbance capacity, 2,2-diphenyl-1-picrylhydrazyl, and ferric reducing ability of plasma. Mangiferin, in particular, is detected at high concentrations in young mango leaves (Coite) (172 g/kg), while present in moderate amounts in bark (Momika) (107 g/kg), and old leaves (Itamaraka) (94 g/kg), respectively. The compound exhibited exceptionally strong antioxidant properties [36].

Nong *et al.* [37] utilized capillary zone electrophoresis (CZE) to develop an analytical method for mangiferin obtained from bark of *Mangifera indica* and leaves of *Mangifera persiciformis*. The isolation procedure for Mangiferin from leaves of *Mangifera persiciformis* involved extraction of the leaves with 95% ethanol for 24 h at room temperature and vacuum evaporation of the filtrate. The condensed residue was resuspended in distilled water and further processed with vacuum evaporation using petroleum ether (60–80^{0}C) and ethyl acetate consecutively when golden colored mangiferin (m.p. 271–273^{0}C) was obtained. The purity of the compound obtained in this manner was approximately 97.39%. daCruz *et al.* have reported single-crystal X-ray structure of mangiferin isolated and recrystallized from EtOH and water mixture [38]. Nunez Selles *et al.* [39] isolated several phenolic compounds from an aqueous decoction of the stem bark of *Mangifera indica*, including mangiferin which is the principal active compound amongst them. These molecules were quantitatively analyzed using HPLC. Schieber and co-workers isolated 14 flavonol and xanthone glycosides from peels of *Mangifera indica* and analyzed the compounds by HPLC-electrospray ionization mass spectrometry [40]. The analysis revealed seven quercetin O-glycosides, one kaempferol O-glycoside, and four xanthone C-glycosides. As per the fragmentation pattern of the mass spectra, the xanthone glycosides were found to be mangiferin, isomangiferin and their derivatives. Gowda and co-workers worked on the development and validation of a reversed-phase liquid chromatographic method for the determination of mangiferin in alcoholic extracts of *Mangifera indica*. Mangiferin was detected at 254 nm wavelength [41].

4. CHEMISTRY OF MANGIFERIN

Mangiferin (Fig. **1**) is a natural C-glucoside xanthone [2-C-β-Dgluco-pyranosyl-1,3,6,7-tetrahydroxyxanthone] with the molecular formula $C_{19}H_{18}O_{11}$ (Mw, 422.35) and melting point, anhydrous 271°C [42]. The compound is reported in various parts of *M. indica*: leaves [43], fruits [44], stem bark [45,46], heartwood [47] and roots [48]. The compound also forms among different angiosperm families and ferns [49-51] and is widely distributed in the Anacardiaceae and Gentianaceae families, especially in the leaves and bark [52]. The aglycone part is a phenolic compound that emerges from two different aromatization pathways, viz. shikimate (carbons C4b, C5, C6, C7, C8, C8a) and the ketate (carbons C1, C2, C3, C4, C4a, C8b), respectively. Xanthones are known natural constituents of plants and micro-organisms which have been extensively studied for their antioxidant, antiinflammatory and anticancer properties. Mangiferin's structure fulfils the four Lipinski's requisites reported to favor high bioavailability by oral administration [53]: molecular weight below 500 daltons, less than 5 donor functions for hydrogen bonds (4), less than 10 acceptor functions for hydrogen bonds (2) and favorable octanol/ water partition coefficient (logP mangiferin : + 2.73) [54].

5. REACTIONS OF MANGIFERIN

Wang and co-workers carried out regioselective acylation of mangiferin catalyzed by *Pseudomonas cepacea* lipase (PCL) with vinyl acetate as the acyl donor and DMSO as reaction solvent [55]. The reaction was conducted at 45 °C and the enzyme was loaded at 6 mg/ml. With a substrate

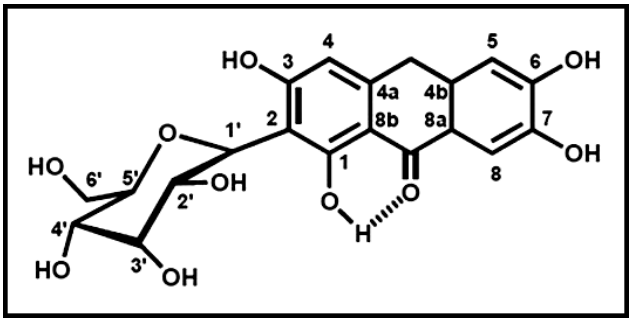

Fig. (1). Chemical structure of mangiferin.

ratio of 6:1 (vinyl acetate to mangiferin), the acylation yield was 84%. Faizi *et al.* obtained accurate assignments in NMR spectra for the acyl and methyl derivatives of mangiferin isolated from the leaves of *Bombax ceiba* [7]. The unstable acetates were transformed into the same penta-acetate at room temperature. NMR analysis revealed that H-4 exchanges with deuterium of the solvent molecule easily under acidic conditions, allowing facile electrophilic substitution reactions to take place at C-4 position. Wu and colleagues have synthesized mangiferin, isomangiferin and homomangiferin bringing about C-glycosylation of a xanthene derivative with perbenzylglucopyranosyl N-phenyltrifluoroacetimidate [56].

Yue *et al.* [57] demonstrated formation of a complex between mangiferin and human serum albumin (HSA) *via* hydrophobic interaction, by spectroscopy and molecular modeling . It was observed that the binding of mangiferin to HSA leads to changes in the conformation of HSA while the binding constant of mangiferin-HSA complex is affected by the presence of amino acids and metal ion. Pardo-Andreu *et al.* [58] reported the formation of a complex between mangiferin and ferric ions, and suggested that this complex prevents mitochondrial permeability transition (MPT) by protecting the mitochondrial membrane protein thiols and glutathione from oxidation. It has also been reported to increase the ability of mangiferin to scavenge the 2,2-diphenyl-1-picrylhydrazyl radical markedly and exhibit antioxidant action towards H_2O_2 production, mediated by antimycin A and mitochondrial membrane lipid peroxidation caused by t-butyl hydroperoxide. These researchers also demonstrated that a mixture of Vimang (*Mangifera indica* L. extract) and Fe(III) is an effective antioxidant and cytoprotective agent [59]. They showed the formation of a mangiferin:Fe(III) complex (2:1) with the help of changes in electronic spectra as well as by reduction of the anodic current peak in the voltammogram of the compound. The complex was found to be superior antioxidant than mangiferin alone which reacted rather easily with horseradish peroxidase/H_2O_2 as compared to mangiferin alone [59]. The above group has suggested the iron-complexing ability of mangiferin (10 μM) as the principal means of protection of rat liver mitochondria against lipid peroxidation mediated by $Fe^{(2+)}$-citrate (50 μM). The IC_{50} value was approximately 10 times less as compared to tert-butylhydroperoxide mitochondrial induction of thiobarbituric acid reactive substance formation. The formation of a transient charge transfer complex between $Fe^{(2+)}$ and mangiferin was also proposed on the basis of the absorption spectra accelerating $Fe^{(2+)}$ oxidation and formation of a more stable $Fe^{(3+)}$-mangiferin complex unable to participate in Fenton-type reaction and lipid peroxidation propagation phase [60].

6. BIOLOGICAL ACTIVTIES

Mangiferin has some very potent therapeutic activities but most of its biological activities remain to be explored. The compound has potent immunomodulatory properties and is believed to inhibit tumor growth in early as well as later stages. In addition, it can also counteract free radicals in various health disorders and diseases. For example, it has been reported that mangiferin has potent cytoprotective and antigenotoxic effects against $CdCl_2$- induced toxicity in HepG2 cells on the basis of absorption spectra, which are attributed to decrease the levels of reactive oxygen species [61]. The tender leaves of mango tree are considered useful in diabetes. Mangiferin could significantly prevent progression of diabetic nephropathy and improve renal function [62]. Another study has demonstrated that mangiferin possesses significant antidiabetic, antihyperlipidemic and antiatherogenic properties, suggesting that its beneficial effect in the treatment of diabetes is associated with hyperlipidemia and related cardiovascular complications [63]. Studies carried out by Lemus-Molina *et al.* have shown that *Mangifera indica* extract is an efficient neuroprotector in excitotoxic neuronal death indicating that it has therapeutic potential to treat neurodegenerative disorders [64]. Studies conducted by Rajendran *et al.* have confirmed the chemopreventive and chemotherapeutic effects of mangiferin [65]. Further literature reports have shown that mangiferin remarkably inhibits the proliferation of K562 leukemia cells *in vitro*, and induces apoptosis in K562 cell line [66]. Mangiferin-mediated down-regulation of NF-κB appears to be one of the molecular mechanisms in potentiating apoptosis, suggesting that mangiferin may be an important agent in combination therapy for the treatment of cancer using conventional therapeutics [67]. Considering that this compound can be extracted from a renewable source such as leaves of mango tree, it would be worthwhile to explore its medicinal properties in detail including assessment of the value of mangiferin in clinical trials in the future.

i. Antioxidant Activity

A recent review [68] highlights the antioxidant potential of polyphenolic compounds obtained from various dietary sources including anthocyanins (from berries), catechins and theaflavins (from tea), curcumin (from turmeric), resveratrol (from grapes and peanuts) and dihydrochalcones aspalathin and nothofagin (from rooibos). This article also discussed mangiferin from honeybush (*Cyclopia genistoides)* by reporting its neuroprotective effects in pre-clinical models of Alzheimer's disease. A comparative study between five varieties of mango (*Mangifera indica*) for their phenolic contents and antioxidant potential of the fruit pulp conducted by Manthey *et al.* [69] showed that the variety Ataulfo had the highest phenolic content and exhibited superior DPPH radical scavenging activity compared to other varieties. It was also observed that the country of origin and harvest

dates had far less influence on these parameters. The role of mangiferin in ameliorating oxidative stress, neuronal death and mitochondrial depolarization caused by overactivation of ionotropic glutamate receptors has been summarized by Lemus-Molina and co-workers [64].

The fundamental molecular mechanism of neuroprotection by mangiferin has been analyzed in an *in vitro* model of excitotoxic neuronal death related to NMDA receptor over-stimulation [70]. It was observed that the compound decreases formation of reactive oxygen species by triggering enzymatic antioxidant system and rejuvenating mitochondrial membrane potential. The antioxidant and radical scavenging activities of mangiferin, isomangiferin and 6 new derivatives isolated from the leaves of *Arrabidaea patellifera,* viz. 3'- O- p-hydroxybenzoylmangiferin, 3'- O- trans-coumaroylmangiferin, 6'- O- trans-coumaroylmangiferin, 3'- O- trans-cinnamoylmangiferin, 3'- O- trans-caffeoylmangiferin, and 3'- O-benzoylmangiferin, respectively have been described by Martin *et al.* [4]. Four of these compounds were also found to possess *in vitro* activity against *Plasmodium falciparum*. The influence of mangiferin on the antioxidant status of benzo (a) pyrene-induced lung carcinogenesis in mice was investigated by Rajendran's group. These researchers found that there was a significant increase in the levels of glycoproteins, membrane ATPases and membrane lipid peroxidation in animals with lung carcinoma. On administration of mangiferin, these changes were reverted back to near normal levels. The increased levels of glycoprotein components found in lung carcinoma were also significantly decreased in mangiferin-treated animals. It was concluded that the anticancer effects of mangiferin are more pronounced when used as a chemopreventive agent rather than as a chemotherapeutic agent against B(*a*)P-induced lung carcinogenesis [71].

Rodeiro *et al.* [72] investigated the effect of mangiferin on oxidative damages induced by toxicants in rat hepatocyte cultures. The compound also inhibited *in vitro* damages to rat hepatocytes. This hepatoprotective action was linked to the antioxidant property of mangiferin. In addition to antioxidant activity, Pardo-Andreu's group has shown that, mangiferin can be effective in atherosclerosis conditions [73]. The endogenous reducing equivalents (NADPH) in LDLr (-/-) mice mitochondria were spared by mangiferin subsequently correcting the lower antioxidant capacity and restoring the organelle redox homeostasis. Another study carried out by the same group suggested that mangiferin enhances the excretion of iron from liver and can therefore be useful in iron overload associated diseases [74]. Bertolini *et al.* evaluated the antioxidant potential of mangiferin along with several new chemical entities to prevent reactive oxygen species (ROS) associated loss of activity of proteins employing alkaline phosphatase (ALP) as model protein [75]. Another study [76] highlights the application of antioxidant activity of mangiferin in reducing the oxidative stress involved in neurodegenerative disorders such as Parkinson's disease. The study was conducted using murine neuroblastoma cell line N2A with MPP+- induced oxidative stress, which caused considerable cell death. The results indicated that mangiferin partially reversed this effect by quenching reactive oxygen intermediates. Prabhu *et al.* [77] studied the capacity of mangiferin related to its biochemical effects and antioxidant potential in isoproterenol-induced (ISPH) myocardial infarction (MI) in rats. It was observed that there was a change in the levels of antioxidant enzymes and non-enzymatic antioxidants in myocardial infarction rats whereas in the rats pre-treated intraperitoneally with mangiferin the antioxidant levels did not reduce. In a study carried out to investigate the effects of Vimang (an aqueous extract of *Mangifera indica*) on the degradation of 2-deoxyribose, brought about by Fe(III)-EDTA plus ascorbate or plus hypoxanthine/xanthine oxidase, Pardo-Andreu and group established that Vimang prevents the degradation of 2-deoxyribose [78]. It was concluded that the mechanism of action of Vimang on the degradation of 2-deoxyribose was not by hydroxyl radical trapping, but probably by the antioxidant action of complexing iron ions and thereby turning them inactive or inadequately active in the Fenton reaction.

Ibarretxe *et al.* [79] have reviewed the distinctive oxidative stress after excitotoxic insult in oligodendrocytes and neurons, and assessed the role of natural polyphenols like mangiferin and morin in treating this condition. Over-stimulation of the 3-amino-5-hydroxy-4-methylisoxazole propionic acid (AMPA) receptors and the kainite receptors has different effects on oligodendrocytes. The authors suggest that mangiferin and morin, in nanomolar concentrations, can protect cell types from mild AMPA-induced insult and can therefore be used in pathological conditions in which oligodendrocytes and neurons are lost. Remirez and colleagues have demonstrated that Vimang (an aqueous extract of *Mangifera indica*) has an inhibitory effect on oxidative stress in rat hepatocytes [80]. The study revealed that Vimang could arrest glucose-glucose oxidase mediated ROS formation. Simultaneously, it also prevented cumene hydroperoxide-induced hepatocyte cytotoxicity as well as lipid peroxidation in a time and dose-dependent manner. Additionally, it prevented generation of superoxide radicals caused by xanthone oxidase and hypoxanthine. Dar and co-workers obtained mangiferin from the methanolic extract of *Bombax ceiba* leaves and evaluated its antioxidant activity with EC_{50} value of 5.8±0.96 µg/ml or 13.74 mM in DPPH assay [81]. Further, mangiferin exhibited *in vivo* hepatoprotective activity in CCl_4-induced liver injury. It also exhibited analgesic activity evaluated in acetic acid induced writhing and hot plate method in mice. Tang *et al.* [9] showed that a semi-purified extract of *Cratoxylum cochinchinense* can cause cell death which has some similarity to apoptosis. Mangiferin is one of the major constituents of this extract, which displays selective toxicity to particular cell types. In this study, Jurkat T cells were used and the mechanism of toxicity was outlined using flow cytometric analysis. It was observed that the extract initially induces intense oxidative stress and an increase in cytosolic Ca^{2+}, subsequently leading to increase in mitochondrial Ca^{2+}, release of cytochrome c, collapse of DeltaPsi(m), decrease in ATP levels, and finally leading to cell death. Since cell death is prevented by potassium ferricyanide the authors derive that the mechanism of oxidative stress may be associated with a plasma membrane redox system.

Tang and co-workers obtained extracts from 33 traditional Chinese medicines and evaluated their antioxidant potential [82]. Of these, extracts from *Cratoxylum cochinchinense, Cortex magnoliae officinalis, Psoralea corylifolia* L*, Curculigo orchioides Gaertn,* and *Glycyrrhiza uralensis* showed significant activity and were further evaluated. These tests revealed that *Cratoxylum cochinchinense* has a superior action in majority of the assays except phospholipid peroxidation inhibition, in which *P. corylifolia* L displayed better activity. The extract from *C. cochinchinense* markedly showed antiglycation capacity as well as inhibition of DNA damage, caused by hypochlorous acid. Sarkar *et al.* [67] have shown that mangiferin blocks tumor necrosis factor (TNF)-induced NF-κB activation and NF-κB-dependent genes like ICAM-1 and COX-2. These effects were found to be mediated through inhibition of IKK activation and blockade of phosphorylation and degradation of IkB-α. Mangiferin displayed enhanced glutathione levels which are known to modulate NF-κB levels along with decreased─levels of GSSG and increase in activity of catalase. Depletion of GSH by buthionine sulfoximine led to a significant reversal of mangiferin effect. Pauletti and group isolated mangiferin from stems of *Arrabidaea samydoides* and evaluated its antioxidant activity in the DPPH assay. Mangiferin exhibited moderate free radical scavenging activity along with redox properties proving its antioxidant potential [5]. Yoshikawa *et al.* [83] examined the hepatoprotective effects of methanolic (SRM) extracts from the roots and stems of *Salacia reticulata* against CCl_4-induced liver injury in mice. The IC_{50} values of the extracts were found to be less than 10 μg/ml while mangiferin showed potent scavenging activity with IC_{50} value of 5.9 μM against 40 μM DPPH radicals. These results suggest that the antioxidant activity of the principal phenolic compounds is involved in the hepatoprotective activity of *S. reticulata*.

Martinez *et al.* [84] have explored the antioxidant role of a stem bark extract of *Mangifera indica* L. in hydroxyl-mediated oxidation of bovine serum albumin (BSA) and in a hepatic microsome system. The extract was found to be effective in reducing the oxidation of BSA with IC_{50} value of 0.0049% w/v for the inhibition of carbonyl group formation and lower than 0.0025% w/v for the inhibition of sulfhydryl group loss. Its inhibition of lipid peroxidation was initiated enzymatically by reduced nicotinamide adenine dinucleotide phosphate (NADPH). The results suggest that the extract has an antioxidant activity, probably due to its ability to scavenge free radicals involved in microsome lipid peroxidation. Sánchez and co-workers have conducted a comparative study on the protective role of *Mangifera indica* L. extract against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative damage and peritoneal macrophage activation [85]. The extracts reduced the TPA-mediated production of ROS by the peritoneal macrophages in a dose-dependent manner. In the hepatic tissues, Vimang, mangiferin, vitamin C plus E and β-carotene decreased TPA-induced DNA fragmentation to a great extent which also suggests that Vimang has bioavailability for some vital target organs, including liver, brain tissues, peritoneal exudate cells and serum. Hsu and co-workers found that norathyriol, which is an aglycone of mangiferin isolated from *Tripterospermum lanceolatum*, inhibits formylmethionyl-leucyl-phenylalanine-induced respiratory burst in rat neutrophils in a concentration-dependent manner [86]. It was observed that norathyriol inhibited the O_2^- generation during dihydroxyfumaric acid (DHF) autoxidation and in hypoxanthine-xanthine oxidase system. It also suppressed the neutrophil cytosolic phospholipase C (PLC). Based on these results the authors proposed that norathyriol contributes to the reduction of generated ROS, attenuates protein tyrosine phosphorylation, as well as suppresses NADPH oxidase through the interruption of electrons transport. Barreto and co-workers characterized and quantified the polyphenolic compounds in bark, leaves, and peels of *Mangifera indica* L., which showed variations in the profiles of secondary plant substances but consistency across cultivars [36]. The free radical scavenging activity of the solvent extracts, using HPLC method, revealed a dose-dependent antioxidant capacity in all extracts.

On the basis of all these reports, it appears that there is ample evidence in support of a very potent antioxidant activity of mangiferin and extracts from *Mangifera indica*. Although a number of targets for such antioxidant activity have been proposed, as discussed above, the primary antioxidant mechanism of mangiferin seems to be mediated through scavenging of reactive oxygen species or free radicals, inhibition of lipid peroxidation as well as modulation of mitochondrial membrane potential (Table **1**).

Table 1. Targets for Antioxidant Activity of Mangiferin

Target	Study
Reactive Oxygen Species / Free Radicals	Campos-Esparza *et al*. [70], Rajendran *et al*. [71], Pardo-Andreu *et al*. [73], Bertolini *et al*. [75], Amazzal *et al*. [76], Pardo-Andreu *et al*. [78], Remirez *et al*. [80], Dar *et al*. [81], Sarkar *et al*. [67], Yoshikawa *et al*. [83], Sanchez *et al*. [85], Hsu *et al*. [86], Barreto *et al*. [36], Leiro *et al*. [97], Viswanadh *et al*. [19], Hernandez *et al*. [125]
Mitochondrial Membrane Potential	Lemus-Molina *et al*. [64], Campos-Esparza *et al*. [70], Pardo-Andreu *et al*. [73], Ibarretxe *et al*. [79], Tang *et al*. [9], Pardo-Andreu *et al*. [102]
Glutathione	Rajendran *et al*. [71], Rodeiro *et al*. [72], Pardo-Andreu *et al*. [74], Amazzal *et al*. [76], Prabhu *et al*. [77], Sarkar *et al*. [67], Viswanadh *et al*. [19]
Lipid Oxidation	Rodeiro *et al*. [72], Pardo-Andreu *et al*. [73], Pardo-Andreu *et al*. [74], Remirez *et al*. [80], Martinez *et al*. [84], Viswanadh *et al*. [19]

ii. Antiinflammatory Activity

Prabhu and co-workers have studied the mechanism of protective action of mangiferin on the suppression of inflammatory response, lysosomal instability and TNF-α production during isoproterenol-induced myocardial necrosis in rats [87]. The study revealed a significant increase in plasma TNF-α production and serum and heart lysosomal hydrolases activity. The compound also reduced stability of the membranes and lowered cathepsin-D and β-glucuronidase in mitochondrial, nuclear, lysosomal and microsomal fractions. This study demonstrated that mangiferin can preserve lysosomal integrity through decreasing the inflammatory process confirming the cardioprotective effect of the compound. Bhatia *et al.* [88] reported that mangiferin inhibits cyclooxygenase-2 expression and prostaglandin E2 production. Rat microglial cells were stimulated with 10 ng/ml of lipopolysaccharide LPS in the presence or absence of different concentrations (1-50 μM) of mangiferin. It was found that mangiferin markedly reduces LPS-induced prostaglandin synthesis and formation of 8-iso-prostaglandin F(2 α) (8-iso-PGF2 α). However, it did not modify LPS-mediated phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) nor did it have any effects on LPS-induced expression of inducible nitric oxide synthase (iNOS) or TNF-α production.

Garrido and co-workers investigated the protective effects of the Vimang from *Mangifera indica* L. against mouse ear edemas and its inhibition of eicosanoid production in J774 murine macrophages [89]. Vimang, when administered orally, reduced ear edema induced by arachidonic acid (AA) and phorbol myristate acetate (PMA) in mice and myeloperoxidase (MPO) activity. The extract also inhibited the induction of prostaglandin PGE (2) and leukotriene LTB (4) with IC_{50} values of 21.7 and 26.0 μg/ml, respectively. Ojewole *et al.* [90] evaluated antiinflammatory, analgesic and antidiabetic properties of the stem-bark aqueous extract of *Mangifera indica* L. The analgesic effect was investigated by hot-plate and acetic acid test models of pain in mice with morphine as the reference standard The antiinflammatory and antidiabetic effects were also studied in rats, using fresh egg albumin-induced paw edema, and streptozotocin (STZ)-induced diabetes, respectively, with diclofenac and chlorpropamide as respective references. The extract, administered i.p., exhibited dose-dependent, marked analgesic activity against thermal and chemical nociceptive pain stimuli in mice. It also significantly inhibited paw edema and hypoglycemic effects in rats.

Beltran and co-workers have studied the vascular effects of the *Mangifera indica* L. extract Vimang on the inducible isoforms of cyclooxygenase (cyclooxygenase-2) and nitric oxide synthase (iNOS) expression in Wistar Kyoto (WKY) and spontaneously hypertensive (SHR) rats [91]. It was observed that Vimang (0.5-0.1 mg/ml) and mangiferin (0.025 mg/ml) inhibited the interleukin-1β-induced iNOS expression more in SHR than in WKY, and cyclooxygenase-2 expression more in WKY than in SHR, respectively. It was concluded that antiinflammatory action of Vimang may be associated with inhibition of iNOS and cyclooxygenase-2 expression, but had no effect on vasoconstrictor responses. Leiro and co-workers found that mangiferin and other phenolic components of Vimang produce strong anti-inflammatory effects by modulation of inflammation-related gene expression undermining macrophage activation [92]. It was observed that *in vitro* treatment with Vimang at 4 μg/ml reduced levels of NOS-2 mRNA and NOS-2, whereas treatment at 40 μg/ml also reduced levels of COX-2 mRNA, COX-2 and PGE_2. It has been suggested that mangiferin could be partially responsible for the inhibition of TNF-α production. Further, it was observed that Vimang, at 4 μg/ml concentration, decreased the mRNA levels of NF-κB but did not affect expression of the NF-κB inhibitor, IkappaB. Garrido *et al.* investigated the role of Vimang and mangiferin in protection against septic shock and suppression of TNFα and nitric oxide (NO) production on macrophages and microglia [93]. *In vivo* studies were conducted on TNFα in a murine model of endotoxic shock, using Balb/c mice pre-treated with lipopolysaccharide (LPS). The results suggested that mangiferin may be associated with inhibition of TNFα and NO production. This group also showed that topical administration of Vimang reduced arachidonic acid (AA) and phorbol myristate acetate-induced ear edema as well as myeloperoxidase (MPO) activity [94]. Leiro and co-workers used a DNA hybridization array containing 96 NF-κB-related genes and reported that mangiferin modifies the expression profiles of genes involved in the mouse NF-κ B signal transduction pathway [95].

Kumar and group investigated the effect of aqueous extract of *Swertia chirayita* stem, containing amerogentin and mangiferin, on the elevated pro- and antiinflammatory cytokines balance in primary joint synovium of arthritic mice [96]. Although administration of the extract in varying oral doses did not affect the proinflammatory cytokines on day 2, a dose-dependent reduction of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-β), interferon-gamma (IFN-γ) and elevation of Interleukin-10 (IL-10) were observed in the joint homogenates by the 12^{th} day. Leiro *et al.* demonstrated the O_2 scavenging activity of mangiferin, its inhibition of expression of iNOS and TNF-α genes, and proposed its prospective role in the treatment of inflammatory and/or neurodegenerative disorders [97]. Further, it was also found that mangiferin augments TGF-β expression, and thus the possible role of mangiferin in cancer prevention, autoimmune disorders, atherosclerosis as well as coronary heart disease is highlighted.

iii. Anticancer Activity

Viswanadh and co-workers have evaluated the protective effect of mangiferin against $CdCl_2$-induced toxicity in mice [19]. The compound was administered in a single intra-peritoneal dose of 2.5 mg/kg body weight prior to treatment with various concentrations of $CdCl_2$. In the control group, LD_{50} was found to be 8.5 mg/kg body weight, while it was increased to 9.77 mg/kg after mangiferin treatment. In the $CdCl_2$-treated mice, a dose-dependent increase in the frequency of micronucleated polychromatic (MnPCE) and normochromatic erythrocytes (MnNCE) was also observed concomitantly, with corresponding decrease in the polychromatic/normochromatic erythrocyte ratio (PCE/NCE ratio). Chieli *et al.* [98] evaluated effects of stem bark extract of *Mangifera indica* L. and related phenols (mangiferin,

norathyriol, catechin, quercetin and gallic acid) on P-gp activity in HK-2 proximal tubule cell line, constitutively expressing P-gp, and in a Caco-2 cell sub-line selected by resistance to vincristine (Caco-2/VCR) and over-expressing P-gp, by using rhodamine-123 accumulation as well as by the Calcein-AM assays. The effects on esterase activity were tested by Calcein-AM test. All compounds, except for catechin and gallic acid, inhibited P-gp activity in HK-2 cells and mangiferin was found to be the most potent compound.

Rajendran *et al.* [65] reported mangiferin as a potential chemopreventive and chemotherapeutic source in benzopyrene-induced lung carcinogenesis in experimental Swiss albino mice through its modulatory effect on increased mitochondrial lipid peroxidation (LPO), tricarboxylic acid (TCA) and electron transport chain complexes. Their findings indicate that animals pre-and post-treated with mangiferin for 18 weeks did not show any changes in these biochemical factors and the animals resembled those of the control group. Rodeiro and co-workers evaluated Cuban traditional medicine, which is a mixture of extracts from *Mangifera indica* L., *Thalassia testudinum*, *Erythroxylum minutifolium* and *confusum,* for its cytotoxic effects and alterations in the CYP450 system, using rat hepatocytes [99]. The results showed *in vitro* effects of these natural products on P450 systems. Cheng and co-workers found that mangiferin inhibited telomerase activity of K562 cells in a time-and-concentration-dependent manner and that it could induce apoptosis and up-regulate the levels of Fas in K562 cells [100]. It was concluded that the probable mechanism may be related to apoptosis induction and expression of Fas protein. Rodeiro *et al.* [101] examined the genotoxicity potential of Vimang, using Ames, comet and micronucleus assays. Genotoxic effects were evaluated in blood peripheral lymphocytes of NMRI mice of both sexes, which were treated for two days with intraperitoneal doses of *M. indica* L. extract. The results suggested that the extract showed evidences of light cytotoxic activity but did not induce mutagenic or genotoxic effects. Pardo-Andreu *et al.* [102] have demonstrated that *Mangifera indica* L. extract, in the presence of 20 μM $Ca^{(2+)}$, induced mitochondrial permeability transition (MPT) in isolated rat liver mitochondria (assessed as CsA-sensitive mitochondrial swelling) closely reproducing effects similar to mangiferin. It was concluded that Vimang-induced MPT closely reproduced mangiferin effects, and it was proposed that mangiferin is the main agent responsible for the extract's MPT inducing ability.

Peng and co-workers have investigated the *in vitro* antiproliferative effect of mangiferin on chronic myeloid leukemia K562 cells using MTT assay, cell morphology, DNA gel electrophoresis and flow cytometry [66]. The results revealed that mangiferin (25 - 200 μmol/L) inhibited proliferation of K562 cells in a dose-dependent and time-dependent manner, leading to apoptosis in K562 cell line. Guha and group evaluated mangiferin for its antitumor, immunomodulatory and anti-HIV effects wherein growth-inhibitory activity against ascitic fibrosarcoma in Swiss mice was observed along with enhanced tumor cell cytotoxicity of the splenic cells and peritoneal macrophages of normal and tumor-bearing mice [103]. Chattopadhyay and co-workers have assessed mangiferin for its immunomodulatory potential through *in vitro* proliferation of murine splenocytes and thymocytes at the doses of 5-40 μg/ ml [104]. Higher doses of mangiferin exhibited suppression of the proliferative response. Yoshimi and co-workers examined the effects of mangiferin in rat colon carcinogenesis, induced by the chemical carcinogen, viz. azoxymethane [52]. The study investigated the effects of mangiferin on development of pre-neoplastic lesions by azoxymethane, aberrant crypt foci, and influence of mangiferin on tumorigenesis induced by azoxymethane. It was observed that mangiferin significantly inhibited the aberrant crypt foci development in rats treated with azoxymethane. In addition, the cell proliferation in colonic mucosa was reduced in rats treated with mangiferin. These results clearly suggested that mangiferin has potential as a naturally-occuring chemopreventive agent.

Percival and group have evaluated *mangifera indica* extract for *in vitro* antioxidant and anticancer activity [105]. Anticancer activity was measured by examining the effect on cell cycle kinetics and the ability to inhibit chemically induced neoplastic transformation of mammalian cell lines. Incubation of HL-60 cells with extract resulted in an inhibition of the cell cycle in the G0/G1 phase. Whole mango juice was effective in reducing the number of transformed foci in the neoplastic transformation assay in a dose-dependent manner. Recently, Garcia-Rivera and co-workers evaluated the antiproliferative activity of Vimang against metastatic breast cancer cell line MDA-MB-231, by MTT assay [106]. The inhibition of cell growth was dose dependent, with IC_{50} values of 259 μg/ml. Similar results were observed in case of Caco-2 colon and HT1080 fibrosarcoma cancer cells in the presence of Vimang, but with lower efficacy. Furthermore, Vimang could successfully inhibit the activation of marker genes involved in inflammation (COX2), metastasis (CXCR4), angiogenesis (VEGF), inhibition of apoptosis (XIAP, bcl2) and, most importantly, NF-κB. Norrato *et al.* [107] studied the anticancer properties of polyphenolic extracts from several varieties of mango (Francis, Kent, Ataulfo, Tommy Atkins and Haden) in cancer cell lines, including Molt-4 leukemia, A-549 lung, MDA-MB-231 breast, LNCaP prostate, and SW-480 colon cancer cells. In SW-480 colon carcinoma cells, Ataulfo and Haden demonstrated superior efficacy, followed by Kent, Francis and Tommy Atkins. Overall, it was observed that the extracts exerted anticancer effects against variety of cancer cells with great efficacy.

In summary, the reports on anticancer activity of mangiferin are beginning to emerge (Table **2**). This is not surprising, considering the amount of information on its antioxidant activity. It is now widely accepted that the antioxidant activity of plant-derived compounds is a good indicator of their potent anticancer ability [108] although there is evidence to connect prooxidant activity with the anticancer ability of such compounds as well [109-111]. Thus, the ability to influence production of reactive oxygen species is crucial to the chemopreventive effect of natural compounds. The potent antioxidant activity of mangiferin clearly indicates that more mechanistic studies need to be designed to fully elucidate its anti-cancer potential.

Table 2. Model Cancer Systems where Anticancer Activity of Mangiferin has been Demonstrated

Cancer	Reference
Breast	Garcia-Rivera *et al*. [106], Noratto *et al*. [107]
Colon	Noratto *et al*. [107], Chieli *et al*. [98]
Leukemia	Cheng *et al*. [100], Peng *et al*. [66], Percival *et al*. [105], Noratto *et al*. [107]
Lung	Rajendran *et al*. [71], Noratto *et al*. [107]
Prostate	Noratto *et al*. [107]

iv. Antidiabetic Activity

Lin *et al.* [112] have studied the interaction of mangiferin with insulin and glucagon in ternary system in the presence and absence of another peptide, by optical spectroscopy. It was revealed in the fluorescence titration experiments that mangiferin quenched the intrinsic fluorescence of insulin and glucagon by static quenching. The ratios of binding constants of glucagon-mangiferin to insulin-mangiferin at different temperatures were calculated in pure and ternary system respectively, which showed that the peptides bind competitively to mangiferin. It was established by the values of the thermodynamic parameters and pH effect that hydrocarbon interactions were the key interacting forces between mangiferin and the peptides. Furthermore, it was revealed that there was a change in the conformation of insulin and glucagon after addition of mangiferin. Another study also investigated the interaction between mangiferin and BSA in aqueous solution by spectroscopic methods. It was observed that secondary structures of the protein changed after the interaction of mangiferin with BSA [113]. Li and his group have reported on the role of mangiferin in the prevention of diabetic nephropathy progression in streptozotocin-induced diabetic rats. It was observed that mangiferin markedly reduced the serum-advanced glycation end-products, malonaldehyde levels, sorbitol concentration of red blood cell and 24 h albuminuria excretion while it increased the activity of serum superoxide dismutase and glutathione peroxidase and creatinine clearance rate. The compound did not have any effect on blood glucose level. The glomerular extracellular matrix expansion and accumulation and transforming growth factor-beta 1 over-expression in glomeruli of diabetic nephropathy rats were distinctly inhibited by mangiferin. In addition, the study showed that mangiferin inhibited high glucose-mediated proliferation of mesangial cells and the advanced glycation end products-induced over-expression of collagen type IV of mesangial cells [62].

Girón *et al.* [114] have reported that mangiferin exhibits antidiabetic activity which is mediated by inhibiting intestinal α-glycosidases as well as by enhancing glucose transport in muscle and adipose cells. It was concluded that mangiferin exerts its antidiabetic effects by increasing GLUT4 expression and translocation in muscle cells which was probably mediated through two independent pathways that are related to 5'-AMP-activated protein kinase and PPAR-gamma. Ojewole *et al.* [90] evaluated antidiabetic properties of the stem-bark aqueous extract of *Mangifera indica* L. in STZ-induced diabetes mellitus. The extract (MIE, 50-800 mg/kg i.p.) exhibited significant hypoglycemic effects in rats. Huang and co-workers observed that oral administration of aqueous extract of the root of *Salacia oblonga* to Zucker diabetic fatty rats lowered plasma triglyceride and total cholesterol (TC) levels while increasing the plasma high-density lipoprotein levels, and reduced liver contents of triglyceride, non-esterified fatty acids and ratio of fatty droplets to total tissue [115]. The study proved that the extract improved postprandial hyperlipidemia and hepatic steatosis in rats by activation of peroxisome proliferator-activated receptor (PPAR)-alpha. However, the extract had no effect on plasma triglyceride and TC levels in fasted rats. *In vitro*, the extract and its major constituent mangiferin activated PPAR-alpha luciferase activity in human embryonic kidney 293 cells and lipoprotein lipase mRNA expression and enzyme activity in THP-1 differentiated macrophages. Muruganandan and co-workers also noted antidiabetic, antihyperlipidemic and antiathero-genic properties of mangiferin (isolated from the leaves of *Mangifera indica*) and indicated its use in diabetes mellitus related to hyperlipidemia and cardiovascular complications [63]. Yoshikawa and group have established that mangiferin inhibits sucrase, isomaltase and aldose reductase in rats [116]. These activities of mangiferin were found to be competitive for sucrase and isomaltase with inhibitor constant (Ki) 55 μg/ml and 70 μg /ml, respectively. Ichiki and co-workers have established that mangiferin and its glucosides (mangiferin-7-O-beta-glucoside) exhibit antidia-betic activity in KK-Ay mice (an animal model of type-2 diabetes) by increasing insulin sensitivity [117].

v. Miscellaneous Activities

Daud *et al.* have suggested that mangiferin may have health promoting activity in diseases related to the impaired formation of new blood vessels by increasing endothelial cell migration [118]. It was observed that this effect was not associated with any modification in the production of matrix metalloproteases-2 or 9 by the endothelial cells or due to effect on cell proliferation. Pardo Andreu and group have reported that mangiferin improves long-term object recognition memory in rats *via* increase in neurotrophin and cytokine levels [119]. The study also reported that mangiferin did not affect locomotion or motivation. Savikin and co-workers investigated the antimicrobial activity of mangiferin, isogentisin and gentiopicrin, isolated from methanolic extracts of flowers and leaves of *Gentiana lutea* L., on various gram-positive and gram-negative bacteria as well as the yeast *Candida albicans* with MIC values ranging from 0.12-0.31 mg/ml [120]. Yoshikawa and group have evaluated the lipolytic effects exhibited by mangiferin at 100 mg/L ($P < 0.01$) and concluded that it may be involved in the antiobesity effects of *Salacia reticulata* in rats by inhibition of fat metabolizing enzymes (pancreatic lipase, lipoprotein lipase and glycerophosphate dehydrogenase) and enhanced lipolysis [121]. These workers proposed that the hepatopro-tective activity of mangiferin, obtained from *S. reticulata*, is associated with its antioxidant mechanism. [83].

Lee and group have demonstrated that mangiferin isolated from the rhizome of *Anemarrhena asphodeloides* Bunge (family Liliaceae) inhibited IgE-antigen complex mediated passive cutaneous anaphylaxis reaction and induced pruritus in mice [2]. It was also found that mangiferin inhibited the expression of the pro-inflammatory cytokine TNF-α and the IgE-switching cytokine IL-4 along with transcription factor NF-κB activation in RBL-2H3 cells stimulated by IgE-antigen complex. Severi *et al.* have evaluated the gastroprotective effects of decoction from *M. indica* leaves in rodents. It was found that a dose of 5 g/kg markedly decreased the severity of gastric damage, induced in several gastro-protective models, with no symptoms of toxicity [122]. Carvalho *et al.* [123] have investigated the potential role of mangiferin in the prevention and treatment of periodontitis induced in Wistar rats. The compound reduced alveolar bone loss and inhibited COX-2 expression and adhesion of leukocytes while maintaining normal lipoxin A(4) levels. Bairy and group explored *in vivo* anti-bacterial property of mangiferin against periodontal pathogens like *P. intermedia* and *P. gingivalis* [124].

Hernandez and group have demonstrated that the main constituents isolated from stem bark of *Mangifera indica* L reduce intracellular ROS and free $Ca^{(2+)}$ induced by T cell receptor triggering. [125]. Prabhu *et al.* [126] studied the effect of mangiferin on mitochondrial energy production in experimentally induced myocardial infarcted rats. The study revealed that pre-treatment with mangiferin (100 mg/kg b.w. i.p.) for 28 days prevented mitochondrial alterations, oxidation as well as restored the TCA cycle enzyme

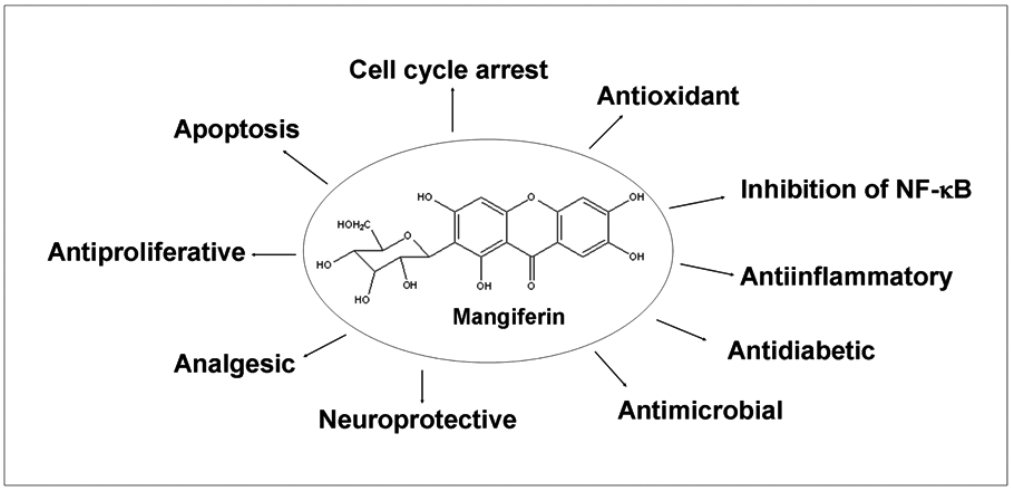

Fig. (2). A summary of reported biological effects of mangiferin.

Table 3. Reported Biological Activities of Mangiferin

Study	Activity
Dar *et al*. [81], Ojewole *et al*. [90]	Analgesic
Ojewole *et al*. [90], Lin *et al*. [112], Li *et al*. [62], Giron *et al*. [114], Huang *et al*. [115], Muruganandan *et al*. [63], Ichiki *et al*. [117]	Antidiabetic
Sarkar *et al*. [67], Prabhu *et al*. [87], Bhatia *et al*. [88], Garrido *et al*. [89], Ojewole *et al*. [90], Beltrán *et al*. [91], Leiro *et al*. [92], Garrido *et al*. [93], Garrido *et al*. [94], Leiro *et al*. [95], Kumar *et al*. [96], Leiro *et al*. [97], Lee *et al*. [2], Carvalho *et al*. [123]	Antiinflammatory
Guha *et al*. [103]	Antiviral
Savikin *et al*. [120]	Antimicrobial
Pardo-Andreu *et al*. [73]	Anti-atherosclerosis
Ang *et al*. [127]	Protection against Bone diseases
Prabhu *et al*. [77]	Cardioprotective
Percival *et al*. [105]	Cell cycle arrest
Severi *et al*. [122]	Gastroprotective
Yoshikawa *et al*. [83]	Hepatoprotective
Lemus-Molina *et al*. [64], Amazzal *et al*. [76]	Neuroprotective

activities to near normal values post-ISPH administration and it also protected the structural integrity of the heart in ISPH administered rats. Osteolytic bone diseases such as osteoporosis have a common pathological feature in which osteoclastic bone resorption outstrips bone synthesis. Osteoclast formation and activation are regulated by receptor activator of NF-κB ligand. In a recent study, Ang and co-workers showed that mangiferin inhibits osteoclast formation and bone resorption by attenuating RANKL-induced signaling [127]. Mangiferin diminished the expression of osteoclast marker genes, including cathepsin K, calcitonin receptor, DC-STAMP, and V-ATPase d2. Mechanistic studies revealed that mangiferin inhibits RANKL-induced activation of NF-κB, concomitant with the inhibition of IκB-α degradation and p65 nuclear translocation. This study also revealed that mangiferin exhibits antiresorptive properties, suggesting potential application of mangiferin for the treatment and prevention of bone diseases involving excessive osteoclastic bone resorption, which may also be important for bone metastasis of human malignancies.

CONCLUSIONS

From above literature review, it is quite evident that mangiferin exhibits wide ranging pharmacological and physiological activities, amongst which antioxidant (Table **1**) and anticancer (Table **2**) stand out as the prominent ones. Other biological activities (Fig. **2**) include antimicrobial, antidiabetic, antiinflammatory and several other unrelated effects, as summarized in Table **3**. Most of the mangiferin-activities are thought to emerge from its xanthonoid structure with C-glucosyl linkage and polyhydroxy component of the molecule, although mechanistic explanation of this still largely remains unexplored. In cancer research, the property of mangiferin appears to be particularly appealing because of its ability to modulate multiple molecular targets (Fig. **3**), including NF-κB signaling. For many years our laboratory has been interested in elucidating the molecular mechanism(s) of modulation of NF-κB signaling pathway as a determinant of anticancer potential of novel anticancer agents. Our investigations have revealed that inhibition of NF-κB signaling pathway is a major molecular event associated with the activity of most of the known chemopreventive natural compounds [128-135]. NF-κB signaling is known to play a key role in the proliferation, invasion and metastasis of cancer cells; it is involved in crosstalk with several other known oncogenic pathways, and therefore, it is an attractive target for anticancer therapeutics [136-140].

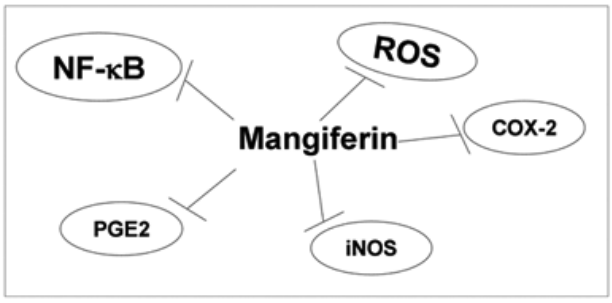

Fig. (3). Molecular targets of mangiferin.

As it is evident from the survey of the literature, the anticancer potential of mangiferin is just beginning to be elucidated. The connection between anticancer and antioxidant/antiinflammatory/ antidiabetic properties is now well understood [139,141] and, hopefully, it is just a matter of time before innovative reports on the mechanism of anticancer effects of mangiferin will emerge. The plant *Mangifera indica,* from which mangiferin is extracted, has traditionally been cultivated for the commercial value of the mango fruit, which is considered as the undisputed king of all fruits; however, the extraction of mangiferin from mango leaves will provide a rich source of the supply of mangiferin provided it becomes cost-effective compared to synthetic mangiferin in the future. The available literature on the biological activity indicates that the plant is a good source not only for its fruit but also for the medicinal properties exhibited by its extracts, which have been used from ancient times for the treatment of various diseases. The present review should thus motivate researchers to explore novel pharmacological and medicinal properties of mangiferin.

CONFLICT OF INTEREST

None declared.

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None declared.

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