MINI-REVIEW

A mini-review of therapeutic potential of *Mangifera indica* L.

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Abstract: Among known species of 69 Mangifera, *Mangifera indica* L. is a medicinal plant being used in tropical regions by indigenous people. It has been a main plant species being used in Ayurvedic as well as indigenous medical systems form 4000 years. Components of *M. indica* are recurrently used as a traditional medicine system to cure numerous ailments. Active constituents are present in stem bark, leaves, heartwood, roots and fruit and have antioxidant, anti-inflammatory, radioprotective, antitumor, immune-modulatory, anti-allergic, anti-diabetic, anti-bone resorption, mono-amine oxidase inhibiting, anti-viral, anti-fungal, anti-bacterial, anti-spasmodic, antidiarrheal, anti-malarial, antiparasitic as well as lipolytic properties. In spite of essential progress in phyto-chemical and medicinal analysis of *M. indica*, more efforts are needed to explore *M. indica* active components and their application in pharmaceutical industry. In this review, we focus on recent information about chemical constituents and pharmacological uses of *M. indica*.

Keywords: *Mangifera indica,* pharmacology, mango bark active constituents, Mangiferin.

INTRODUCTION

Geographical distribution

Mangifera indica trees are tropical fruit bearing plants that is found wildly in Asia but cultivated varieties have also been found in world warmer regions. It is found in Pakistan in Sindh and Punjab areas (Ross 1999; Sairam *et al*. 2003).

Taxonomic hierarchy of M. indica

Division	Magnoliophyta
Class	Magnoliopsida
Sub Class	Rosidae
Order	Sapindales
Family	Anacardiaceae
Genus	*Mangifera*
Species	*indica*

Morphological description of M. indica

Mangifera indica belongs to family Anacardiaceae and is generally known as Aam in Pakistan. In other regions of world its common names are Manga (Brazil), Abricotier de St. Domingue, Ambo (France), Pauh (Indonsia),マンゴ (Japan), Aamp, Aanp, Amp (Nepal), Amba (Oman), Bumango (Senegal), Embe (Tanzania) (Wauthoz *et al*. 2007). *M. indica* is a tall, erect tree and grows about 15 to 30 m (fig. 1(a)); stem is upright, stout and woody whilst root is taproot type which reaches at a depth of 20 ft, while having profused and flourished root system. Leaves are simple alternate, leathery but oblong lanceolate, about 29 to 30 cm long and 3 to 5 cm in width. Young leaves of *M. indica* are reddish in color but older leaves are of dark green color with yellow and white venation (Rey *et al*. 2004). *M. indica* inflorescence is a panicle and about 4 mm bearing greenish white or pinkish flowers. Bisexual and male flowers are born on the same plant (fig. 1(b)). Fruit is an unevenly spherical shaped with a small compressed fleshy drupe which is about 8-12 cm long and mainly found at the broad ended pendulous stalk. Seeds are solitary, oval and oblong in shape which is encased in a hard, compact and fibrous endocarp (fig. 1(c)).

Active constituents of M. indica

Studies on chemical constituents of *M. indica* trace back to 20th century. Until now, many constituents have been isolated. Its active constituents are mainly polyphenolics, flavonoids and triterpenoids. Mangiferin is a xanthone glycoside as major bioactive constituent of *M. indica*. Bark of tree contains protocatechic acid, γ-aminobutyric acid, kinic acid, shikimic acid, catechin, mangiferin, alanine, glycine, and tetracyclic triterpenoids cycloart-24-en-3β,26diol, 3-ketodammar-24 (*E*)-en-20S,26-diol, C-24 epimers of cycloart-25 en 3β, 24, 27-triol and cycloartan-3β, 24, 27-triol (fig. 2 (a & b)) (Scartezzini & Speroni 2000). From bark and leaves of *M. indica* many scientists isolated indicoside A and B, mangoleanone, friedelin, manghopanal, cycloartan-3β-30-diol and its derivativants such as mangsterol, manglupenone, mangocoumarin, n-tetacosane, n-heneicosane, n-triacontane and mangiferolic acid methyl ester. Mangostin, 29-hydroxy mangiferonic

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acid and Mangiferin have been isolated from the stem bark together with common flavonoids (Pott *et al*., 2003). Flower of *M. indica* has been reported to contain alkyl gallates such as gallic acid, ethyl gallate, methyl gallate, n-propyl gallate, n-pentyl gallate, n-octyl gallate, 4-phenyl gallate, 6-phenyl-n-hexyl gallate and dihydrogallic acid (Nunez *et al*., 2002). Roots of *M. indica* contain the chromones, 3-hydroxy-2-(4'-methylbenzoyl)-chromone and 3-methoxy-2-(4'-methyl benzoyl)-chromone. Essential oil such as elemene, ocimene, humulene, linalool and nerol are found in flower and leaf of *M. indica*. The pulp of fruit is containing vitamins A and C, β-carotenes as well as xanthophylls. Bark of stem contains phenolic compounds, free sugars and polyols. Chieli *et al*. (2009) characterized polyphenols by HPLC and GC-MS technique. Tharanathan *et al*. (2006)studies depicts that C-glucoside xanthone Mangiferin is found in its different parts such as leaves, fruits, bark of stem, heartwood and roots (Muruganandan *et al*. 2002; Yoshimi *et al*. 2001). Mangiferin aglycone is a phenolic compound that is formed by different pathways and its structure fulfills prerequisites to favor its bioavailability (Nuñez-Selles 2005) (fig. 3).

Fig. 1a: *M. indica* plant

Nutritional value of M. indica fruit

Mango fruit contains 0.5-1% protein and fruit pulp mainly contains carbohydrate (glucose, fructose, sucrose) (table 1) (Tharanathan *et al*., 2014).

Pharmacology of M. indica

M. indica has significant medicinal value and various active constituents have been isolated from different parts of plants such as mangiferin, alanine, glycine, γ-aminobutyric acid, kinic acid, shikimic acid, tetracyclic triterpenoids cycloart-24-en-3β, 26diol, 3-ketodammar-24 (*E*)-en-20S, 26-diol, C-24 epimers of cycloart-25 en 3β, 24, 27-triol and cycloartan-3β,24,27-triolare major compound (Nuänez-Selleäs *et al*. 2002). *M. indica* possess various bioactivities such as hepatoprotective and antioxidant activity (Pourahmad *et al*. 2010; Kim *et al*. 2010), antibacterial activity (Engels *et al*. 2012), antifungal activity (Kanwal *et al*., 2010), polyphenol oxidase activity (Arogba, 2000), anti diarrhoeal activity (Sairam *et al*. 2003), anticancerous activity (Abdullah *et al*., 2014), antihyperglycemic activity (Kemasari *et al*., 2011), lipolytic activity (Yoshikawa *et al*. 2002), antibone resorption (Li *et al*., 1998), antiviral activity (Guha *et al*. 1996), Inhibitory activities of carbohydrate metabolism enzyme (Yoshikawa *et al*. 2001), Monoamine oxidase-inhibiting activity (Bhattacharya *et al*., 1972), Immunomodulatory (Garcia *et al*., 2003), antitumor activity (Yoshimi *et al*., 2001), antidiabetic activity (Muruganandan *et al*., 2005) and Antiparasitic (Perrucci *et al.,* 2006).

Fig. 1b: *M. indica* floral parts.

Fig. 1c: *M. indica* fruit.

Antioxidant activity

Oxidative stress is a condition in which antioxidant status of cells is disturbed and this can results in cellular or tissue injury or death (Seifried *et al*., 2007). Reactive oxygen species have oxidizing power that could results in biological molecules damage. Oxidative stress leads to various diseases i.e. cancer, heart diseases, ischemic injury, sclerosis, hyperglycemia, rheumatoid arthritis and neurological disorders (Valko *et al*., 2007). Liver damage due to micro inflammatory hepatitis, cirrhosis and carcinoma has resulted in redox imbalance and oxidative

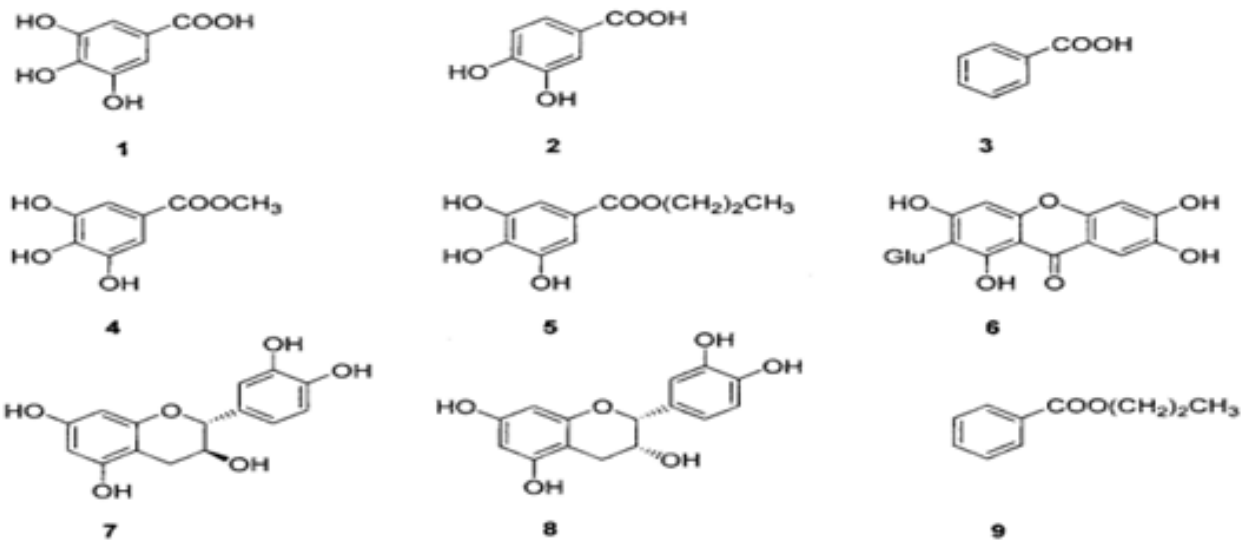

Fig. 2a: Compounds extracted from stem bark of *M. indica*; gallic acid (1), 3,4-dihydroxy benzoic acid (2), benzoic acid (3), methyl gallate (4), propyl gallate (5), mangiferin (6), (+)-catechin (7), (-)-epicatechin (8) propyl benzoate (9). Glc) *â*-D glucopyranosyl.

stress. Diplock *et al*. (1998) epidermal studies shown that nutritional antioxidants, vitamin E and C and β-carotene are useful against constant disorders. Mangiferin is characterized as an active compound against oxidative stress. Mishra *et al*. (2006) studied Mangiferin reaction with different oxidizing agents such as •OH, N3• and CCl_3O_2. They found Mangiferin reaction with free radicals as result Mangiferin was converted into 2 phenoxyl radicals. This is helpful against inter radical reactions and the other radical reacts to ascorbate and results in formation of mangiferin. Sanchez *et al*. (2000) studied *in vivo* antioxidant protective properties in *M. indica* stem bark extract and its mangiferin polyphenol found in OF1 mice. Pourahmad *et al*. (2010) findings proves that bark extract successfully prevent harmful effect of oxidative stress caused by cumene hydroperoxide in rat hepatocytes. Their finding confirmed that extract of mango has hepatoprotective as well as antioxidant components against CHP caused hepatotoxicity.

Antibacterial

Mango peels and kernels contain different phenolic compounds such as flavonols, xanthones and gallotannins and gallotannins antibacterial activities have been reported (Engels *et al*., 2009). Kabuki *et al*. (2001) demonstrated selective antimicrobial properties of hydrolysable tannins. Bacterial genera *Listeria, Bacillus, Clostridia,* and *Staphylococcus* are very sensitive to gallotannins, but lactic acid bacteria showed strong resistance. But gallotannins mode of antimicrobial action was still unclear (Engels *et al*., 2010). Mangiferin has antibacterial activity against several bacteria such as *Bacillus pumilus*, *S. citreus*, *Escherichia coli*, *B. cereus*, *Staphylococcus aureus*, *Salmonella agona* and *Klebsiella pneumonia* (Bbosa *et al*., 2007; Engels *et al*., 2011 & 2012).

Antifungal activity

Plants secondary metabolites such as Flavonoids are normally found in leaf epidermal cells vacuoles. Fungi are main group among heterotrophic organism that causes a lot of diseases. Antifungal activity of (-)-epicatechin-3-O-glucopyranoside (1), 5- hydroxy-3-(4-hydroxylphenyl) pyrano [3,2-g]chromene-4(8H)-one (2), 6-(phydroxybenzyl) taxifolin-7-O-D-glucoside (tricuspid) (3), quercetin-3-O-glucopyranosyl-(1-2)-D-glucopyranoside (4) and (–)-epicatechin(2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol was evaluated by Kanwal *et al*. (2010) against *Alternaria alternate, Aspergillus fumigatus, Aspergillus niger, Macrophomina phaseolina* and *Penicillium citrii* (fig. 3). Stoilova *et al*. (2005) explained that mango extract is effective against *Saccharomyces cerevisiae*, *Thermoascus aurantiacus*, *Trichoderma reesei*, *A. flavus* and *A. fumigatus*.

Antitumor activity

Chemo-preventive agents are dietary constituents which prevent or reverts carcinogenesis and tumor promotion (Chen & Kong 2005). Mangiferin chemo-protective were effects examined in rats for once a week for three weeks initiation and post-initiation phases of azoxymethane induce colon cancer (Yoshimi *et al*., 2001). Mangiferin were tested in long term assay of about 40 weeks, during which rats were treated with mangiferin at the AOM initiation phase and resulted in considerably lower division of intestinal neoplasms while colonic mucosa cell proliferation reduces. Mangiferin mechanism of action is not clearly understood but chemoprotective ability might

be due to AOM up taking by the xanthone and retardation of cell proliferation may be that due to proapoptotic cytokines. Peng *et al*. (2004) demonstrate through in vitro experiment that mangiferin depend on time and dose and inhibit K562 leukemia cells proliferation and enhance cell death in K563 cells line, perhaps gene show expression through bcr/abl. Mangiferin is suggested as potential component as a naturally occurring chemoprotective component (Yoshimi *et al*. 2001). Abdullah *et al*. (2014) findings proved that *M. indica* extract considered being more cytoxic for estrogen by having both types of breast cancer cell lines (positive and negative) than to normal breast cells. So *M. indica* extract has anticancer activity against breast cancer cell lines.

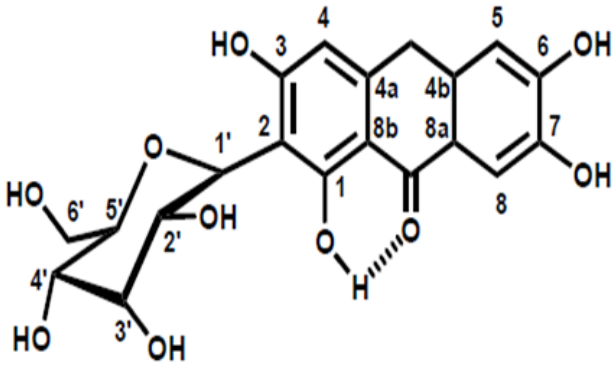

Fig. 2b: Mangiferin

Anti-diabetic activity

Metabolic condition associated with hyperglycaemia is known as diabetes mellitus and this is caused by irregular insulin secretion or insulin action. In recent studies, scientist found prolongs hyperglycaemia results in glycosylated products formation and these products are results in ROS formation which leads to oxidative damage mostly to heart and kidney (Rolo & Palmeira 2006; Rajesh 2013). Effects of mangiferin in hyperglycaemia, atherogenicity and oxidative stress to heart and kidney tissues in streptozotocin induced diabetic rats were studied by Muruganandan *et al*. (2002) and Muruganandan *et al*. (2005). In 30 days experiment Mangiferin or insulin was given to diabetic rats daily. As a result of STZ treatment (i) catalase as well as SOD kidney activities have decreased significantly, heart increase and do not created change in red blood cells; (ii) a remarkable MDA increase occurred in glycosylated haemoglobin, blood glucose, triglycerides, creatine phosphokinase, low density lipoprotein cholesterol and total cholesterol while decrease of high-density lipoprotein cholesterol (HDL-C) (Muruganadan *et al*. 2005). When STZ induced rats were repeatedly injected with mangiferin or insulin 28 days there was drastically reduction in the tissue MDA levels, decreased in the glycosylated haemoglobin and creatine phosphokinase levels. Jouad *et al*. (2000) explained that mangiferin antidiabetic activity induce some mechanism as compared to pancreatic β-cell insulin production. Bwititi *et al*. (2000) demonstrated that these extra pancreatic actions consist of peripheral glucose utilization stimulation (Saxena & Vikram 2004). Muruganandan *et al*. (2005) did experiment with glucose treated healthy rats; while mangiferin induce a significant betterment in orally taken glucose tolerance but with no change in plasma glucose levels. Gupta and Gupta (2011) studied hypoglycemic potency of seed kernel of mango. Plant extract was applied as an anti-diabetic agent in diabetic rats (Miura *et al*., 2001; Kemasari 2011).

Table 1: Nutritional value of 100 gm ripe *M. indica* fruit

Total Calories	62.1–63.7 Cal
Moisture	62.1–63.7 Cal
Fat	0.36–0.40 g
Protein	0.30–0.53 g
Carbohydrate	16.20–17.18 g
Fiber	0.85–1.06 g
Ash	0.34–0.52 g
Calcium	6.1–12.8 mg
Iron	0.2–0.6 mg
Vitamin A	0.135–1.872 mg
Methionine	4 mg
Ascorbic Acid	7.8–172.0 mg
Tryptophan	3–6 mg
Lysine	32–37 mg

Anti-bone resorption

Simvastatin and atorvastatin are used current as lipid lowering agents however expensive and caused adverse effects on liver and muscle. In cholesterol induced hyperlipidemic model of rats *M. indica* leaf extract showes significant antihyperlipidemic activity (Kaliora *et al*. 2006). Mango leaves extract help in more inhibition of intestinal absorption of cholesterol, increase in expression of hepatic LDL receptors and their protection. Hypo-lipidemic activity of *M. indica* is mainly due to presence of flavonoids, Saponins, glycosides, tannins, phenolics in different parts of plant (Shah *et al*., 2010). Li *et al*. (1998) findings demonstrate that water extracts have negative effect on bone resorption that is due to parathyroid hormone in neonatal mouse's parietal bones organ culture. Mangiferin has extracted and tested over living organisms which have a considerable inhibitory effect.

Radio protective effect

Radio protectors are important interest for tumor therapy but nontoxic radio protectors also considerable important and regular air traveller's exposure from cosmic radiation (Turner *et al*. 2002). Jagetia & Baliga (2005) findings demonstrate that Mangiferin help against the sickness and mortality caused by radiation. The dose of 2 mg/kg is optimum as it is protective and safe to toxicity induced by drug, as it is 1/200 of the LD_{50} dose at 400 mg/kg by weight. Mangiferin provide protection against radiation

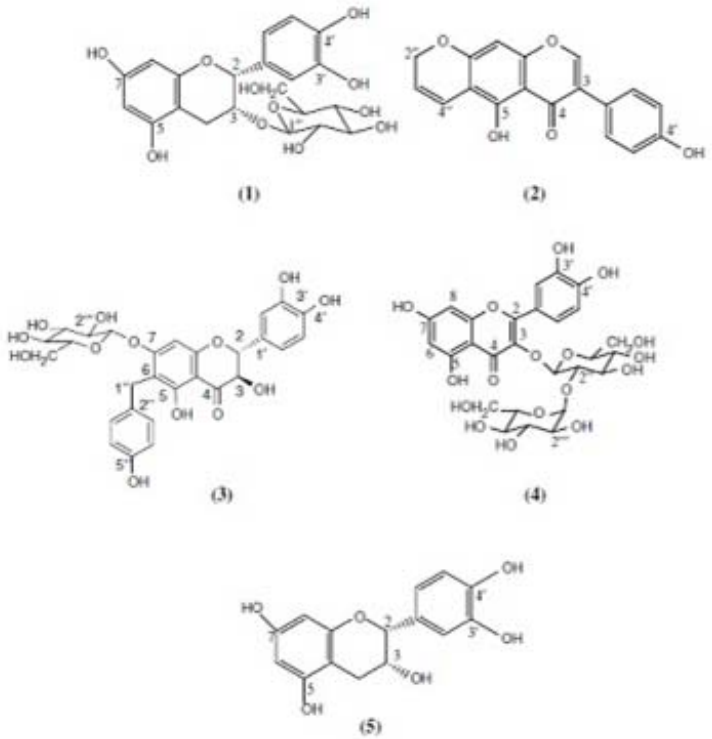

Fig. 3: Structure of antifungal Flavonoids isolated from Mango leaves (Kanwal *et al*., 2010).

induced micronuclei formation in mice DBAxC57BL and in human peripheral blood lymphocytes culture. *M. indica* has shown to a potent scavenger of hydroxyl radicals and hypochlorous acid. It is an iron chilator, lipid per oxidation inhibitor and damage of DNA within cell (Martinez *et al*., 2001).

Antiparasitic activity

Results of Perrucci *et al*. (2006) studies explain that mangiferin has a comparable negative effect on activity of *Cryptosporidium parvum* as same dose of paromomycin in neonatal mouse model (Rajakumar *et al*. 2014). Gehad *et al*. (2013) finding should that unripe mango has fruit anthelmintic activity and aqueous extract of unripe fruit showed 100% inhibition larval growth of *strongyloides stercoralis*.

Antiprogesteronic and Estrogenic activity

Ngokere *et al*. (2014) demonstrated that extract of mango plant applied in Chinchilla rabbit's ovaries alters female sex hormones and *M. indica* extract has potential to alter serum concentration of female sex hormones.

Monoamine oxidase inhibition activity

When deficiency of monoamine neurotransmitters occurs in brain it can cause depression (Fišar *et al*., 2010). Mangiferin act as antidepressants by inhibiting activity enzyme that degrades monoamine neurotransmitters (Bhattacharya *et al*., 1972; Wauthoz *et al*., 2007).

Antiviral activity

Mangiferin is effective against *Herpes simplex* virus but Mangiferin have not shown a direct inhibition of HSV-2 but delay replication in HSV-2 (Zhu *et al*., 1993). Guha *et al*. (1996) findings show that in vitro mangiferin inhibited HSV-1 virus replication *in vivo* and antagonized the cytopathic effects of HIV (Zheng *et al*., 1990).

Immunomodulatory effect

Aggarwal *et al*. (2006) demonstrated that some genes are over expressed in inflammation, which may include genes coding for proinflammatory cytokines, chemokines, adhesion molecules, inflammatory enzymes and NF-κB (nuclear factor kappa B) (Kumar and Aggarwal 1999; Christman *et al*., 2000). Experiment by Sarkar *et al*., (2004) with mango plant extract, showed that mangiferin initiate NF-κB down regulation, which suppresses NF-κB activation caused by inflammatory agents. This may increase the cell's glutathione levels and potential chemotherapeutic agent that mediate apoptosis. It shows a possible role in cancer therapy and it happens through Mangiferin, which quench ROS and increase glutathione levels (Christman *et al*., 2000; Leiro *et al*., 2004). Number of scientist findings depict that mangiferin alter expression of genes which are essential for the viral replication, regulation of apoptosis and tumorogenesis. It was recommended that Mangiferin has a potential to provide protection to cells from oxidative stress and mutations in the treatment and decrease in inflammatory or cancer diseases.

Anti allergic activity

Allergic reactions are mostly caused by mast cells and that activate via surface receptors interaction with molecules i.e., an antigen bounded to IgE. Notably blood

cells including basophils, eosinophils, B and Th2 lymphocytes and neutrophils are having role in allergic reaction. Such interactions began a series of biochemical reactions including release of active components that induce allergic reactions (Chang & Shiung 2006). Mangiferin in ovo albumin immunized mice reduces IgE levels, stops passive anaphylactic reactions and decreases histamine caused skin reaction (Rivera *et al.,* 2006).

Anti-malarial and antispasmodic activity

Asase *et al*. (2010) demonstrated that *M. indica* leaves extract are effective against malarial parasites. For this purpose, they recommend to boiled leaves with cut fruits of *Citrus aurantifolia* for an hour and to take orally this decoction three thrice a day until recovered. Bidle *et al*. (2004) conducted *in vitro experiment to evaluate* antimalarial activity by chloroform and methanol extract of *M. indica*. Significant activity on P. *falciparum* extract is shown *in vitro. Malann et al.* (2013) results depicts that *M. indica* leaf extract have activity against *Plasmodium berghei*.

Anti-diarrheal activity

M. indica seed is considered to cure against nausea, vomiting, dysentery and burning sensation in chest. In traditional medicine decoction of mango plant kernel or in combination with its seed is usually given to cure diarrhea (Ansari *et al*., 2000). Sairam *et al*. (2003) conducted experiment in which they evaluated potential of *M. indica* seeds by methanolic and aqueous extracts against diarrhoea, by castor seed oil and $MgSO_4$ in mice. Their results illustrated that extracts of *M. indica* has remarkable anti-diarrhoeal activity.

Anti-inflammatory activity

Zeilhofer (2007) demonstrated the inflammation over a broad ranged chemical such as nitric oxide, prostanoids and inflammatory reaction associated with dilation of the arterioles, increased in blood flow and permeability (Garcia & Stein 2006;). Mangiferin has potential to reduce NO formation and iNOS in activated macrophages in mRNA levels (Leiro *et al*., 2003).

CONCLUSION

These above mention results are very hopeful and reveal that this plant need to be more extensively studied to confirm its antioxidant, antibone resorption, radio protective activity, immunomodulatory reactions, anti-allergic properties, anti-inflammatory, antitumor, monoamine oxidase-inhibiting, antidiabetic, lipolytic, antimicrobial and antiparasitic activites. All part of plant useful but *Mangifera indica* bark could be play major role. Based on its various properties, its phytomedicines shall need to be standardized regarding this active compound.

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