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Ethnopharmacology of *Mangifera indica* L. Bark and Pharmacological Studies of its Main C-Glucosylxanthone, Mangiferin

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ABSTRACT

This review details the vernacular names, origin, distribution, taxonomy and variety of *Mangifera indica* L. (Anacardiaceae), a medicinal plant traditionally used in tropical regions. Mangiferin, a major C-glucosylxanthone from *M. indica* stem bark, leaves, heartwood, roots and fruits occurs widely among different angiosperm families and ferns. The reported pharmacological activities of mangiferin include antioxidant, radioprotective, antitumor, immunomodulatory, anti-allergic, anti-inflammatory, antidiabetic, lipolytic, antibone resorption, monoamine oxidase inhibiting, antiviral, antifungal antibacterial and antiparasitic properties, which may support the numerous traditional uses of the plant.

Keywords: cultivar, flavonoid, mango, medicinal plant constituent, phytochemistry

CONTENTS

INTRODUCTION

Ethnopharmacology has contributed to drug discovery since the 19th century (Heinrich and Gibbons 2001), but has had a relatively short history as a specifically designated field of research. The term was first used in 1967 and is nowadays much more broadly defined as the observation, identification, description and experimental investigation of the in-

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Invited Review

Fig. 1 Vegetative (left), flowering (center) and fruiting (right) stages of *Mangifera indica*, Conakry, Guinea. (Pictures by N. Wauthoz 2006).

gredients of indigenous drugs and their effects. This discipline implies a careful documentation of traditional knowledge about biologically active agents employed or observed by man and has become a truly interdisciplinary field of research in their scientific exploration (Bruhn and Holmstedt 1981). The ultimate aim of ethnopharmacology is the validation (or invalidation) of a medicinal plant through the isolation of active substances and/or pharmacotoxicological findings.

The present review details the vernacular names, origin, distribution, taxonomy and variety of *Mangifera indica* L., a medicinal plant widely distributed in tropical regions and used by indigenous cultures for millennia to cure a range of diseases. A long and sustained use of *M. indica*, based on a "trial and error" methodology, has selected the traditional uses of this medicinal plant. The xanthone C-glucoside mangiferin, the major component of *M. indica* bark aqueous extract, could be responsible for a lot of the reported activities, as discussed in this review.

MANGIFERA INDICA L.

Mangifera indica L. is a large evergreen tree, long living, 10-45 m high with a strong trunk and heavy crown (**Fig. 1**). Native from tropical Asia, it has been introduced wherever the climate is sufficiently warm and damp and is now completely naturalized in many parts of tropics and subtropics (Ross 1999).

Vernacular names

Brazil: Manga, Mango, Mangueira, Skin Mango; **Canary Islands**: Mango; **China**: An Lo Kuo, Mangguo, Mango; **Curação**: Mango; **Egypt**: Mango; **Fiji**: Aam, Mango; **France**: Abricotier de St. Domingue, Ambo, Loubi, Freycinet, Manguier de Saint Michel; **Germany**: Mango; **Guam**: Chamorro, Mangga, Mango; **Guatemala**: Mango; **Guyana**: Mango; **Haiti**: Mango; **India**: Aam, Alfonso mango, Alipriya, Am, Amm, Amra, Amva, Asm, Bhramavapriya, Bo-amb, Kamaphala, Kamayudha, Kamavallabha, Kokilavasa, Kires, Kokilananda, Maamidi, Mam-maram, Mango, Mango tree, Mangofruit, Mave, Oegkoti-tong, Pitavallabha; **Indonesia**: Pauh; **Italy**: Mango; **Ivory Coast**: Mango; **Japan**: マンゴ; **Mexico**: Mango; **Nepal**: Aamp, Aanp, Amp, Mango; **Nicaragua**: Mango, Mango dusa, Mangu, Mankro; **Oman**: Amba; **Pakistan**: Am, Mango; **Peru**: Mango; **Puerto Rico**: Mango; **Rarotonga**: Vi papaa; **Rodrigues Islands**: Mangue; **Senegal**: Bumango; **Sudan**: Mango; **Tanzania**: Embe, Mango, Mwembe; **Tonga**: Mango; **United States**: Bowen mango; **Venezuela**: Mango (Kirtikar and Basu 1993; Ross 1999).

Origin and distribution

Native from Southern Asia, especially Eastern India, Burma and the Andaman Islands, *M. indica* has been cultivated, praised and even revered in its homeland since ancient times. Buddhist monks are believed to have taken the plant on voyages to Malaya and Eastern Asia in the 4th and 5th Centuries BC. Persians are said to have taken mangoes to East Africa around the 10th Century AD. The fruit was grown in the East Indies before the earliest visits of the Portuguese who apparently introduced it to West Africa and Brazil in the early 16th Century. *M. indica* was then carried to the West Indies, being first planted in Barbados about 1742 and later in the Dominican Republic; it reached Jamaica in about 1782 and, early in the 19th Century, reached Mexico from the Philippines and the West Indies (Morton 1987). In this day and age, *M. indica* resides in most tropical biotopes in India, Southeast Asia, Malaysia, Himalayan regions, Sri Lanka, Africa, America and Australia (Calabrese 1993; Kirtika and Basu 1993; Sahni 1998).

Taxonomy and variety

The genus *Mangifera* belongs to the order Sapindales, Anacardiaceae family (**Table 1**). Hundreds of *M. indica* cultivars are distributed throughout the world. The highest diversity occurs in Malaysia, particularly in peninsular Malaya, Borneo and Sumatra, representing the heart of the distribution range of the genus (Bompard and Schnell 1997). Asia and India present over 500 classified varieties of which 69 are mostly restricted to tropical regions. *M. indica* is one of the most widespread fruit trees in Western Africa, where 4 categories of mango varieties can be distinguished: (i) varieties of local or polyembryonic mangoes (mangots and Number One); (ii) first monoembryonic varieties propagated by grafting (Amélie, Julie, Sabot, Dijbelor

Table 1 Taxonomy of *Mangifera indica* Linn.

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

and Cuisse Madame); (iii) the Floridian varieties, also monoembryonic and propagated by grafting, introduced later and used either for export (Kent, Keitt, Palmer, Zill, Valencia, Smith, Irwin and Haden), or (iv) for the regional markets (Brooks, David-Haden, Miami Late, Springfels, Beverly, Eldon and Ruby) (Rey *et al*. 2004).

Ethnopharmacology of *M. indica* L. bark

In all the regions of *M. indica* distribution, one of main organs used is the bark; its medicinal uses throughout the world are reported in **Table 2**. Based on ethnopharmacological knowledge, a standardized aqueous extract of *M. indica* L. stem bark with antioxidant, anti-inflammatory and immunomodulatory properties has recently been developed in Cuba. This extract is proposed as both a nutritional supplement (antioxidant) and an anti-inflammatory, analgesic and immunomodulatory treatment to prevent disease progress or increase the patient's quality of life in gastric and dermatological disorders, AIDS, cancer and asthma (Nuñez-Selles 2005).

Phytochemistry

The chemical constituents of the different organs of *M. indica* L. are reviewed in Ross (1999) and Scartezzini and Speroni (2000). The bark is reported to contain protocatechic acid, catechin, mangiferin, alanine, glycine, γ-aminobutyric acid, kinic acid, shikimic acid and the 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 (Scartezzini and Speroni 2000).

MANGIFERIN

The natural C-glucoside xanthone mangiferin [2-C-β-$_D$-gluco-pyranosyl-1,3,6,7-tetrahydroxyxanthone; $C_{19}H_{18}O_{11;}$ Mw, 422.35; melting point, anhydrous 271°C (Muruganandan *et al*. 2002)] has been reported in various parts of *M. indica*: leaves (Desai *et al*. 1966), fruits (El Ansari *et al*. 1971), stem bark (Bhatia *et al*. 1967; El Ansari *et al*. 1967), heartwood (Ramanathan and Seshadri 1960) and roots (Nigam and Mitra 1964). This pharmacologically-active compound occurs among different angiosperm families and ferns (Hostettmann and Wagner 1977; Richardson 1983, 1984); it is widely distributed in the Anacardiaceae and Gentianaceae families, especially in the leaves and the bark (Yoshimi *et al*. 2001).

The mangiferin aglycone is a phenolic compound that arises from two different aromatization pathways, the shikimate (carbons C4b, C5, C6, C7, C8, C8a) and the ketate (carbons C1, C2, C3, C4, C4a, C8b) pathways.

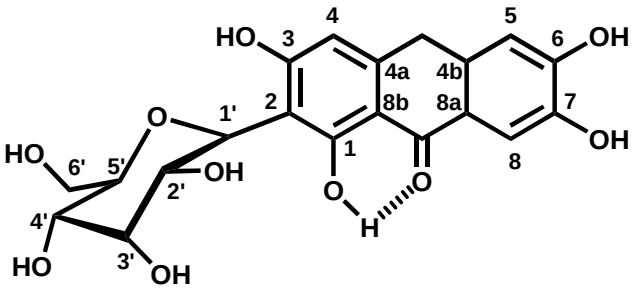

Fig. 2 The molecular structure of mangiferin described in Muruganandan *et al*. (2002).

Table 2 Medicinal uses of *Mangifera indica* L. bark in the world.

Country	Part(s) used [(a)]	Preparation [(b)]	Administration [(c)]	Medicinal use(s)	Reference(s)
Central African	StB	S	ER	Diarrhea	Ake Assi *et al*. 1978
Republic		D*	O	Cough	Ake Assi *et al*. 1978
Benin	StB	D	O	Anemia, hypotension	Adjanohoun *et al*. 1986
Brazil	StB	D	NR	Itch	Schemda and Rojas 1992
Caribbean	StB	I	NR	Diuretic, rheumatism	Grenard *et al*. 2004
Congo	B	D	NR	Cancer sore, gingivitis, diarrhea, dysentery	Boullard 2001
Cuba	StB	W	NR	Cancer, diabetes, asthma, infertility, lupus, prostatitis, prostatic hyperplasia, gastric disorders, arthralgies, mouth sores, tooth pain	Nuñez-Selles 2005
Fiji	DB	I	O	Syphilis	Ross 1999
Gabon	B	NR	NR	Emetic	Boullard 2001
Guyana	B	NR	NR	Diarrhea, gastric disorders	Grenard *et al*. 1987
Haiti	DB	I	O	Hepatic disorders	Weniger *et al*. 1986
Canary Islands	DB	I	O	Diarrhea	Ross 1999
India	DB	I	O	Leukorrhea, bleeding hemorrhoids, lung hemorrhage	Deka *et al*. 1983
	B	D	NR	Diabetes	Alam *et al*. 1990
	B	I	NR	Astringent, tonic	Maheshwari *et al*. 1975
	B	I	NR	Menorrhagia	Chopra 1933
	B	D	O or I	Jaundice	Singh *et al*. 1994
	StB	E	NR	Preventing conception	Ross 1999
	B	NR	NR	Melancholia, nervous debility	Chopra *et al*. 1956
Madagascar	B	NR	NR	Liver obstruction	Pernet *et al*. 1997
Mali	StB	NR	NR	Emetic	Boullard 2001
Nicaragua	IB	P/W	E	Wounds	Dennis 1988
Senegal	DB	I	O	Mouth sores, odontalgia, as a mouthwash for toothache, dysentery, diarrhea	Kerharo *et al*. 1974; Ross 1999
			E	Cutaneous affections	Ross 1999
Tonga	StB	DW	O	Dysmenorrhoea	Adjanohoun *et al*. 1986
Tanzania	StB	D	O	Toothache	Ross 1999
Democratic Republic of	StB	I	O	Diarrhea, chest pain, cough, anemia, urinary tract infusion, diabetes	Muanza *et al*. 1994
Congo (ex-Zaire)			E	Infected wounds, skin diseases	Muanza *et al*. 1994
			Oa	Dental caries	Muanza *et al*. 1994

[(a)] StB = Stem Bark; B = Bark; DB = Dried Bark; IB = inner Bark
[(b)] S = Soaking; D* = Decoction with salt and chili; D = Decoction; I = Infusion; W = aqueous extract; E = Powder in alcoholic wine; P/W = phenol/water extract; DW = decoction in wine; NR = not reported
[(c)] ER=Enema; E = External use; O = Oral; I = inhalation; Oa = oral application; NR = not reported

Table 3 Pharmacological activities of mangiferin.

Pharmacological activities	Reference(s)
Antioxidant	Sanchez *et al*. 2000; Muruganandan *et al*. 2002; Leiro *et al*. 2003; Stoilova *et al*. 2005
Radioprotective	Jagetia and Baliga 2005; Jagetia and Venkatesha 2005
Immunomodulatory	Chattopadhay *et al*. 1987; Guha *et al*. 1996; Moreira *et al*. 2001; Garcia *et al*. 2002, 2003; Leiro *et al*. 2003, 2004a, 2004b; Sarkar *et al*. 2004
Anti-allergic	Rivera *et al*. 2006
Anti-inflammatory and anti-nociceptive	Beltran *et al*. 2004; Garrido *et al*. 2004
Antitumor	Guha *et al*. 1996; Yoshimi *et al*. 2001
Antidiabetic	Ichiki *et al*. 1998; Miura *et al*. 2001a, 2001b, 2001; Muruganandan *et al*. 2005
Inhibitory activities on carbohydrate metabolism enzyme	Yoshikawa *et al*. 2001
Lipolytic activity	Yoshikawa *et al*. 2002
Antibone resorption	Li *et al*. 1998
Antiviral	Zheng *et al*. 1990, 1993; Guha *et al*. 1996
Antibacterial	Srinivasan 1982; Stoilova *et al*. 2005
Antifungal	Stoilova *et al*. 2005
Antiparasitic	Perrucci *et al*. 2006
Monoamine oxidase-inhibiting activity	Bhattacharya *et al*. 1972

Its structure (**Fig. 2**) fulfils the four requisites which have been reported to favor a high bioavailability by oral administration (Lipinski *et al*. 1997):

i. molecular weight below 500 daltons;
ii. less than 5 donor functions for hydrogen bonds (4);
iii. less than 10 acceptor functions for hydrogen bonds (2); favorable octanol/water partition coefficient ($\log P_{\text{mangiferin}}$: + 2.73; Nuñez-Selles 2005)

PHARMACOLOGICAL ACTIVITIES OF MANGIFERIN

Mangiferin has been reported to have multiple biological effects which are summarized in (**Table 3**) and commented hereunder.

Antioxidant activity

Reactive oxygen species (ROS) possess a strong oxidizing effect and induce damage to biological molecules, including proteins, lipids and DNA, with concomitant changes in their structure and function (Seifried *et al*. 2007). In a series of pathological conditions, an extensive generation of ROS appears to overwhelm natural defense mechanisms, dramatically reducing the levels of endogenous antioxidants, a condition named "oxidative stress" (McCord 2000); as epidemiological studies indicate that the major nutritional antioxidants, vitamin E, vitamin C and β-carotene, may be beneficial to prevent several chronic disorders (Diplock *et al*. 1998), considerable interest has arisen in the possible reinforcement of antioxidant defenses, both for chemoprevention and treatment purposes (Maxwell 1997). Two basic conditions must be fulfilled for an antioxidant; (i) the compound should be present in low concentrations relative to the substrate to be oxidized; and (ii) the species resulting from its oxidation must be stable through intramolecular hydrogen bonding stabilization (Halliwell 1990).

Mangiferin is characterized by 2 ionizable functions (pKa, 7.5 and 12.2, respectively) and its UV absorption spectrum significantly changes with pH; intense absorption bands are seen at pH 4 (λ_{max}, 317 and 364 nm) and 9 (λ_{max}, 390 nm). The reaction of mangiferin with different oxidizing and reducing radicals, $^{\bullet}OH$, $N_3^{\bullet}$ and $CCl_3O_2^{\bullet}$, was investigated by pulse radiolysis techniques. Upon reaction with these radicals (**Fig. 3**), mangiferin is converted into 2 phenoxyl radicals (λ_{max}, 390 and 470 nm, respectively) which decay by radical-radical reactions; the second radical reacts with ascorbate to regenerate mangiferin (Mishra *et al*. 2006).

The protective antioxidant abilities of a *M. indica* stem bark extract (Vimang®) and its main polyphenol mangiferin were investigated *in vivo* in OF1 mice (Sanchez *et al*. 2000). Vimang® (50, 110, 250 mg/kg), mangiferin (50 mg/kg), vitamin C (100 mg/kg), vitamin E (100 mg/kg), vitamin E plus vitamin C (100 mg/kg each) and β-carotene

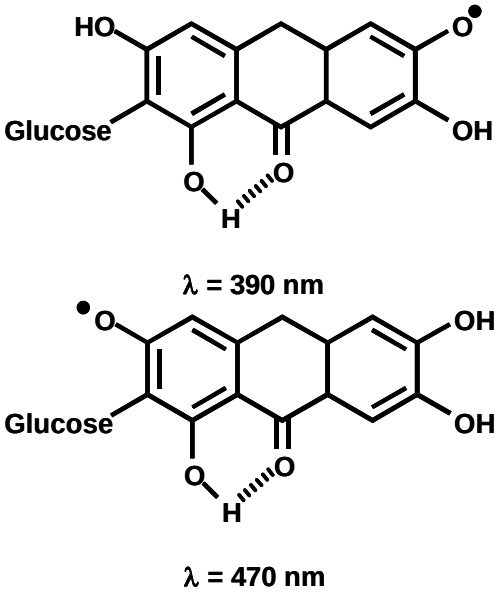

Fig. 3 Phenoxyl radicals observed after the reaction between mangiferin and $N_3^{\bullet}$ in Mishra *et al*. (2006).

(50 mg/kg) were orally administered once a day for 7 consecutive days; 12-*O*-tetradecanoylphorbol-13-acetate (TPA), an inductor of oxidative damage in serum, liver and brain and a stimulator of ROS production by peritoneal macrophages, was administered (0.1 µg, i.p.) on the eighth day, 2 h after the antioxidant treatment. Considering a series of biomarkers ((i) the activity of the major antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx); (ii) a marker for protein oxidation, total sulfhydryl group protein content (TSH); (iii) markers for lipid peroxidation (LP), malondialdehyde (MDA) and 4-hydroxyalkenals (4-HA); (iv) fragmentation of nuclear DNA; and (v) cytochrome c reduction and H_2O_2 levels), Vimang® was either comparable or superior (GPx, TSH, LP, DNA fragmentation, cytochrome c reduction and H_2O_2 levels) to the nutritional antioxidants in protecting mice from oxidative stress; the effect was dose-dependent. Mangiferin showed the same pattern of effect as Vimang® except for GPx (no restoration of GPx levels) (Sanchez *et al*. 2000).

Radioprotective effect

A protection of mangiferin against radiation-induced micronuclei formation in cultured human peripheral blood lymphocytes and in DBAxC57BL mice was shown by Jagetia and Venkatesha (2005) and by Jagetia and Baliga (2005).

Immunomodulatory effect

Most of the genes overexpressed in inflammation, such as those encoding proinflammatory cytokines, chemokines, adhesion molecules and inflammatory enzymes, contain κB sites within their promoter suggesting that these genes are controlled predominantly by the nuclear factor kappa B (NF-κB) (Christman *et al*. 2000; Aggarwal *et al*. 2006). The activation of NF-κB and its associated kinases as IκBα kinase (IKK) depends in most cases on the production of ROS (Manna *et al*. 1998; Kumar and Aggarwal 1999).

Mangiferin mediates the down-regulation of NF-κB, suppresses NF-κB activation induced by inflammatory agents, including tumor nuclear factor (TNF), increases the intracellular glutathione (GSH) levels and potentiates chemotherapeutic agent-mediated cell death; this suggests a possible role in combination therapy for cancer (Sarkar *et al*. 2004). It is likely that these effects are mediated through mangiferin ROS quenching and GSH rising; increased intracellular (GSH) levels are indeed known to inhibit the TNF-induced activation of NF-κB (Manna *et al*. 1999).

Leiro *et al*. (2004a) characterized *in vivo* the immunomodulatory activity of mangiferin on thioglycollate-elicited mouse macrophages which were stimulated with lipopolysaccharide (LPS) and gamma interferon (IFN-γ). The expression of cytokines synthesis and of 96 genes involved in the NF-κB signal transduction pathway was investigated by microarray.

Mangiferin at 10µM significantly (i) hinders NF-κB activation by LPS, TNF, and interleukin 1 (IL-1) at the level of TNF receptor-associated factor 6; (ii) inhibits NF-κB mediated signal transduction (inhibition of two genes of the Rel/ NF-κB/ IκB family, RelA and RelB); (iii) inhibits toll-like receptor proteins, including Jun N-terminal Kinase 1 and 2 (JNK1 and JNK2); (iv) inhibits proteins involved in response to TNF and in apoptotic pathways triggered by DNA damage; (v) inhibits a series of pro-inflammatory cytokines (IL-1α, IL-1, IL-6, IL-12, TNF-α, granulocyte and macrophage colony-stimulating factors, A2) and various intracellular and vascular adhesion molecules (VCAM-1) (Leiro *et al*. 2004a).

These results indicate that, in addition to ROS-scavenging properties, mangiferin modulates the expression of a large number of genes critical for the regulation of apoptosis, viral replication, tumorogenesis, inflammation and various autoimmune diseases. They suggest that mangiferin, protecting cells against oxidative damage and mutagenesis, may be of value in the treatment and prevention of inflammatory diseases and/or cancer.

Anti-allergic activity

Type I allergic response is mainly mediated by mast cells activated through the interaction of their surface receptors (FcεRI) with specific molecules such as an IgE-bound antigen. These interactions initiate a series of biochemical events resulting in the release of biologically active mediators that cause allergic reaction (Chang and Shiung 2006); other cells, notably basophils, eosinophils, B and Th2 lymphocytes and neutrophils, are also involved in the allergic response. In animal models of allergy, mangiferin significantly (i) reduces IgE levels in ovoalbumin-immunized mice; (ii) inhibits passive anaphylactic reactions; (iii) reduces histamine-induced cutaneous reaction; (iv) decreases the compound 48/80-induced histamine release from rat mast cells; and (v) inhibits the lymphocyte proliferative response to ovoalbumin stimulation (Rivera *et al.* 2006).

Anti-inflammatory activity

Inflammatory processes involve a broad spectrum of chemical mediators; these include nitric oxide (NO) and prostanoids synthesized by inducible isoforms of NO synthase (iNOS) and cyclooxygenase (COX-2), respectively. Vascular events associated with an inflammatory reaction include dilatation of the small arterioles, resulting in increased blood flow and permeability (Briones *et al*. 2002; Garcia and Stein 2006; Zeilhofer 2007).

Beltran *et al*. investigated the effects of Vimang® and mangiferin on COX-2 and iNOS expression and noradrenaline-induced vasoconstriction in vascular smooth muscle cells from mesenteric arteries of normotensive (WKY) and spontaneously hypertensive (SHR) rats, with and without stimulation by interleukin-1β (1 ng/ml; 24 h). In both strains, in the absence of IL-1β, Vimang® (0.5 mg/ml) and mangiferin (0.025 mg/ml) had no effect by themselves on iNos nor COX-2 vascular expression; they could however prevent the 2 enzymes induction by IL-1β, suggesting a potent anti-inflammatory action. In agreement with these data, mangiferin was found to decrease NO production and iNOS mRNA levels in activated macrophages (Garcia *et al*. 2002; Leiro *et al*. 2003). As NF-κB plays an important role in the induction of the promoter for both cyclooxygenase-2 and iNOS genes, the inhibition of NF-κB activation (cd § 4.3) appears to be involved in the anti-inflammatory mechanisms of action (Aggarwal *et al*. 2006).

Both in WKY and SHR rats, Vimang® (1, 0.5 and 0.25 mg/ml), but not mangiferin (0.05 mg/ml), induces a reduction of the contractions elicited by noradrenalin (0.1-30 µM).

This suggests that the inhibitory effect of Vimang® on vasoconstrictor responses and on COX-2 and iNOS expression would be mediated by different compounds.

Antitumor activity

Minor dietary constituents, apparently important to prevent carcinogenesis or revert tumor promotion, are known as chemopreventive agents, a very promising approach to cancer control (Chen and Kong 2005). Yoshimi *et al*. (2001) examined in rats the chemopreventive effects of mangiferin for both the initiation and post-initiation phases of azoxymethane (AOM; alkylant, 15 mg/kg body weight, s.c., once a week for 3 weeks) - induced colon carcinogenesis. In a short-term assay (5 weeks, development of AOM-induced preneoplastic lesions), mangiferin (0.1% in the basal diet for 5 weeks) significantly inhibited the aberrant crypt foci development in AOM-treated rats (~40% less). In a long-term assay (40 weeks), the group treated with mangiferin during the AOM initiation phase had significantly lower incidence and multiplicity of intestinal neoplasms (>40% reduction) with reduced colonic mucosa cell proliferation (65-85% decrease). The underlying mechanisms are still unclear but the chemopreventive effect may be due to quenching of AOM by the xanthone; the inhibitory effect on cell proliferation may come from the release of pro-apoptotic cytokines (Hara *et al*. 1997) by mangiferin-activated lymphocytes (Chattopadhyay *et al*. 1987). *In vitro*, mangiferin dose- and time-dependently inhibited the proliferation of K562 leukemia cells and induced apoptosis in K563 cells line, probably through down-regulation of bcr/ abl gene expression (Peng *et al*. 2004). These results suggest that mangiferin has a potential as a naturally-occurring chemopreventive agent (Yoshimi *et al*. 2001).

Anti-diabetic activity

Diabetes mellitus represents a series of metabolic conditions associated with hyperglycaemia and caused by defects in insulin secretion and/or insulin action. In type 1 diabetes, pancreatic β-cells are destroyed, usually by autoimmune inflammatory mechanisms; type 2 diabetes is a complex metabolic disorder associated with β-cells dysfunction and with varying degrees of insulin resistance (Dinneen 2006). Recently, it has been reported that long standing hyperglycaemia with diabetes mellitus leads to the formation of advanced glycosylated end-products which are involved in the generation of ROS, leading to oxidative damage, particularly to heart and kidney (Rolo and Palmeira 2006).

Effect on type 1 diabetes

Muruganandan *et al*. (2002) and Muruganandan *et al*. (2005) investigated the effects of mangiferin on hyperglycaemia, atherogenicity and oxidative damage to cardiac and renal tissues in streptozotocin-induced diabetic rats (STZ destroys pancreatic β cells and causes persistent hyperglycaemia; 55 mg/kg body weight i.v..); after 30 days, diabetic rats were administered mangiferin or insulin (positive control) daily for 28 days. As expected, STZ treatment resulted in (i) catalase (CAT) and SOD activities significantly reduced in kidney, increased in heart (possibly through a compensatory mechanism) and unaltered in erythrocytes; (ii) a significant increase of MDA in all tissues, of glycosylated haemoglobin, creatine phosphokinase (CPK), glucose, triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C) and decrease of high-density lipoprotein cholesterol (HDL-C) (Muruganadan *et al*. 2002, 2005). In STZ-induced rats, repeated i.p. injections of insulin (6 U/kg) or mangiferin (10 or 20 mg/kg) for 28 days significantly reduced the tissue MDA levels, improved the alterations in cardiac and renal antioxidant enzyme activities, decreased the glycosylated haemoglobin and CPK levels. This antidiabetic activity of mangiferin could involve mechanisms other than pancreatic β-cell insulin release/secretion; these extrapancreatic actions (Bwititi *et al*. 2000; Jouad *et al*. 2000) could consist of (i) a stimulation of peripheral glucose utilization; (ii) an enhancement of glycolytic and glycogenic processes (Saxena and Vikram 2004); and/or (iii) a glycaemia reduction through the inhibition of glucose intake. The last hypothesis could be supported by the recent finding that mangiferin isolated from roots of *Salacia reticulata* inhibits α-glucosidases (sucrase, isomaltase and maltase; IC50 values of 87, 216 and 1.4 µg/ml, respectively) (Yoshikawa *et al*. 2001). Treatment with mangiferin resulted in a potent antihyperlipidemic and antiatherogenic activities in diabetic rats (strong and significant reduction in atherogenic index, total cholesterol, TG, LDL-C associated with concomitant significant increase in HDL-C) (Muruganandan *et al*. 2005). In glucose-loaded normal rats, mangiferin induces a significant improvement in oral glucose tolerance but without alteration of basal plasma glucose levels (Muruganandan *et al*. 2005). These studies show that mangiferin (10 and 20 mg/kg, i.p.) exhibits potent antidiabetic, antihyperlipidemic, antiatherogenic and antioxidant properties without causing hypoglycaemia; mangiferin would then offer a greater therapeutic benefit for the management of diabetes mellitus and diabetic complications associated with abnormalities in lipid profiles.

Effect on type 2 diabetes

Therapy of type 2 diabetes resides principally in exercise and diet; in second line, therapeutic agents to stimulate insulin secretion are used. In KK-A^y mice, an animal model of type 2 diabetes, mangiferin (90 mg/kg), 7 h after oral administration, decreased the baseline glucose level by 56% (Miura *et al*. 2001a). In the same model, mangiferin (30 mg/kg, p.o., once daily followed 30 min later by exercise (120 min motorized treadmill) for 2 weeks) reduced the blood cholesterol (~40%) and triglyceride levels (~70%) (Miura *et al*. 2001b). Mangiferin or exercise alone did not influence cholesterol but significantly decreased triglycerides (Miura *et al*. 2001b). Mangiferin is certainly worthy of further investigation for these beneficial effects on hyperglycaemia and hyperlipidemia in type 2 diabetes.

Lipolytic

Constituents isolated from the roots of *Salacia reticulate*, including its main xanthone, mangiferin, showed a significant lipolytic effect on rat epididymal fat-derived cultured adipocytes. Mangiferin (100 mg/l) reduced 35% triglycerides in these adipocytes (Yoshikawa *et al*. 2002).

Antibone resorption

Four water extracts of *Kampo* formulae were screened for their inhibitory effect on bone resorption induced by parathyroid hormone in organ culture of neonatal mouse parietal bones. Mangiferin isolated and tested *in vitro* showed a significant inhibitory effect on this model (Li *et al*. 1998).

Antimicrobial

Antiviral activity

Zhu *et al*. studied *in vitro* the effect of mangiferin against *Herpes simplex* virus type 2; mangiferin does not directly inactivate HSV-2 but inhibits the late event in HSV-2 replication (Zhu *et al*.1993). *In vitro* mangiferin was also able to inhibit HSV-1 virus replication within cells (Zheng *et al*. 1990) and to antagonize the cytopathic effects of HIV (Guha *et al*. 1996).

Antibacterial and antifungal activities

In an *in vitro* agar diffusion technique, mangiferin showed activity against 7 bacterial species, *Bacillus pumilus*, *B. cereus*, *Staphylococcus aureus*, *S. citreus*, *Escherichia coli*, *Salmonella agona*, *Klebsiella pneumoniae*, 1 yeast (*Saccharomyces cerevisiae*) and 4 fungi (*Thermoascus aurantiacus*, *Trichoderma reesei*, *Aspergillus flavus* and *A. fumigatus*) (Stoilova *et al*. 2005).

Antiparasitic activity

In a neonatal mouse model, mangiferin at 100 mg/kg has a similar inhibitory activity on *Cryptosporidium parvum* than the same dose (100 mg/kg) of an active drug, paromomycin (Perrucci *et al*. 2006).

Monoamine oxidase-inhibition activity

The monoamine oxidase-inhibiting activity was investigated on adult albino rats and mice. Mangiferin (100 mg/kg, i.p.) (i) significantly potentates hexobarbitone (100 mg/kg, i.p. 30 min after mangiferin) narcosis by nearly 80% (sleeping time); (ii) markedly antagonizes the ptosis and reverses the sedation induced by reserpine; (iii) potentates amphetamine (25 mg/kg, i.p. 60 min after mangiferin) toxicity in aggregated rats (750% increase in mortality); (iv) potentates DOPA-induced (100 mg/kg, i.p. 60 min after mangiferin) piloerection, salivation, motor activity and aggressiveness; (v) potentates the typical head-twitch response of 5-HTP (50 mg/kg, i.p. 60 min after mangiferin); and (vi) potentates the analgesic effect of subanalgesic doses of morphine (2 mg/kg, i.p. 60 min after mangiferin) by nearly 100% (increase in tail flick time), when administered 60 min before morphine.

Although mangiferin induced a positive response on all these techniques accepted for detecting monoamine oxidase-inhibiting activity *in vivo*, the dose required to produce an inhibition was fairly large (100 mg/kg versus a LD50 of 365 mg/kg) (Bhattacharya *et al*. 1972).

CONCLUSION

Many different pharmacological activities, antioxidant, radioprotective, immunomodulatory, anti-allergic, anti-inflammatory, antitumor, antidiabetic, lipolytic, antibone resorption, monoamine oxidase-inhibiting, antimicrobial and antiparasitic, have been reported for mangiferin. All these studies indicate that a wide part of activities acknowledged to preparation based on *Mangifera indica* bark could be attributed to this C-glucosyl-xanthone.

The *M. indica* long history of use has been substantiated by many researches; modern phytomedicines based on its bark are worthy of further investigation to precise their major fields of use. The present extent of diabetes in deve-

loping countries (so-called *coca-colonization…*) makes it a choice preparation to develop. Based on the knowledge of the many properties of mangiferin, phytomedicines should be adequately standardized regarding this active compound.

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