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

Nathalie Wauthoz¹,²* • Aliou Balde² • Elhadj Saïdou Balde² • Marc Van Damme³ • Pierre Duez⁴

¹ Laboratory of Pharmacognosy and Biopharmaceutics, Institute of Pharmacy, Université Libre de Bruxelles (ULB), Boulevard du Triomphe CP 207, B-1050 Brussels, Belgium
² Centre de Recherche et de Valorisation des Plantes médicinales de Dubréka, BP 6411 Conakry, Guinea
³ Laboratory of Toxicology, Institute of Pharmacy, Université Libre de Bruxelles (ULB), Boulevard du Triomphe CP 205-01, B-1050 Brussels, Belgium
⁴ Laboratory of Pharmacognosy, Bromatology and Human Nutrition, Institute of Pharmacy, Université Libre de Bruxelles (ULB), Boulevard du Triomphe CP 205-9, B-1050 Brussels, Belgium

*Corresponding author: * Nathalie.Wauthoz@gmail.com

**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 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

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**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-
Vernacular names

**Brazil**: Mango, Mango, Mangueira, Skin Mango; **Canary Islands**: Mango; **China**: An Lo Kuo, Mangguo, Mango; **Curação**: Mango; **Egypt**: Mango; **Fiji**: Āám, 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**: Āâm, Alfonso mango, Alipiyya, Am, Anm, Amra, Amva, Asm, Bhramavapriya, Bo-am, Kamaphala, Kamayudha, Kamavallabha, Kokilavasa, Kires, Kokilananda, Mami, Mam-maram, Mango, Mango tree, Mangofruit, Mave, Oekkoti-tong, Pitavallabha; **Indonesia**: Pauh; **Italy**: Mango; **Ivory Coast**: Mango; **Japan**: マンゴ; **Mexico**: Mango; **Nepal**: Aamp, Aamp, Amp, Mango; **Nicaragua**: Mango, Mango dusa, Mango, 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; Kirtikar 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,...)
and Cuisse Madame); (iii) the Floridian varieties, also monoembyronic 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 Mangifera 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 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 protocatechric acid, catechin, mangiferin, alanine, glycine, and dermatological disorders, AIDS, cancer and asthma (Nuñez-Selles 2005).

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

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

**MANGIFERIN**

The natural C-glucoside xanthone mangiferin \(2-C-\beta-D\)-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 (Hostetmann 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 C1, C2, C3, C4, C4a, C8b) and the ketate (carbons C1, C2, C3, C4, C4a, C8b) pathways.

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

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*StB = Stem Bark; B = Bark; 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

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Table 3 Pharmacological activities of mangiferin.

<table>
<thead>
<tr>
<th>Pharmacological activities</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>Sanchez et al. 2000; Muruganandam et al. 2002; Leiro et al. 2003; Stoilova et al. 2005</td>
</tr>
<tr>
<td>Radioprotective</td>
<td>Jagetia and Baliga 2005; Jagetia and Venkatesha 2005</td>
</tr>
<tr>
<td>Anti-allergic</td>
<td>Rivera et al. 2006</td>
</tr>
<tr>
<td>Anti-inflammatory and anti-nociceptive</td>
<td>Beltran et al. 2004; Garuido et al. 2004</td>
</tr>
<tr>
<td>Antitumor</td>
<td>Guha et al. 1996; Yoshimi et al. 2001</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>Ichiki et al. 1998; Miura et al. 2001a, 2001b, 2001; Muruganandam et al. 2005</td>
</tr>
<tr>
<td>Inhibitory activities on carbohydrate metabolism enzyme</td>
<td>Yoshikawa et al. 2001</td>
</tr>
<tr>
<td>Lipolytic activity</td>
<td>Yoshikawa et al. 2002</td>
</tr>
<tr>
<td>Antibone resorption</td>
<td>Li et al. 1998</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Zheng et al. 1990, 1993; Guha et al. 1996</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>Srinivasan 1982; Stoilova et al. 2005</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Stoilova et al. 2005</td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>Perez et al. 2006</td>
</tr>
<tr>
<td>Monoamine oxidase-inhibiting activity</td>
<td>Bhattacharya et al. 1972</td>
</tr>
</tbody>
</table>

Its structure (Fig. 2) fulfills 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 (logP 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 et al. 1998); 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 (λmax, 317 and 364 nm) and 9 (λmax, 390 nm). The reaction of mangiferin with different oxidizing and reducing radicals, •OH, •N3 and CCl3O2•, was investigated by pulse radiolysis techniques. Upon reaction with these radicals (Fig. 3), mangiferin is converted into 2 phenoxy radicals (λmax 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 (50 mg/kg) were orally administered once a day for 7 consecutive days; 12-O-tetradecanoylphorbol-13-acetate (TPA), an inducer 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 (ii) 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-hydroxynonenals (4-HA); (iv) fragmentation of nuclear DNA; and (v) cytochrome c reduction and H2O2 levels, Vimang® was either comparable or superior (GPx, TSH, LP, DNA fragmentation, cytochrome c reduction and H2O2 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 cytokites, chemokines, adhesion molecules and inflammatory enzymes, contain NFκB sites within their promoter suggesting that these genes are controlled predominantly by the nuclear factor kappa B (NFκB) (Christman et al. 2000; Aggarwal et al. 2006). The activation of NFκB and its associated kinases as IkB 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 NFκB, suppresses NFκB 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 NFκB (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 (IFNγ). The expression of cytokines synthesis and of 96 genes involved in the NFκB signal transduction pathway was investigated by microarray.

Mangiferin at 10µM significantly (i) hinders NFκB activation by LPS, TNF, and interleukin 1 (IL-1) at the level of TNF receptor-associated factor 6; (ii) inhibits NFκB mediated signal transduction (inhibition of two genes of the Rel/NFκB/ IκκB 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 Shiu 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 ovalbumin-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 ovalbumin 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; Zeihofer 2007).

Beltrán 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 NFκB plays an important role in the induction of the promoter for both cyclooxygenase-2 and iNOS genes, the inhibition of NFκB 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 noradrenaline (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 bcl/ 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 by auto-immune inflammatory mechanisms; type 2 diabetes is a complex metabolic disorder associated with β-cells dysfunction and with varying degrees of insulin resistance (Dimreen 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

Murugananand et al. (2002) and Murugananand 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 (~70%); 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) (Murugananad 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 (Bwiiti 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 (Satxena and Vikram 2004); and/or (iii) a glycema 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 antatherogenic activities in diabetic rats (strong and significant reduction in atherogenic index, total cholesterol, TG, LDL-C associated with concomitant significant increase in HDL-C) (Murugananand 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 (Murugananand et al. 2005). These studies show that mangiferin (10 and 20 mg/kg, i.p.) exhibits potent antidiabetic, antihyperlipidemic, antatherogenic 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-Ay mice, an animal model and diet; in second line, therapeutic agents to stimulate in insulin secretion are used. In KK-Ay mice, an animal model and diet; in second line, therapeutic agents to stimulate in oral glucose tolerance but without altering the blood 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) reduces 35% triglycerides in these adipocytes (Yoshikawa et al. 2002).

Antibiotic 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 (Zhu et al. 1990) and to antagonize the cytotoxic 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. ce- reus, 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. fumi- gatus) (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-inhibiting activity

The monoamine oxidase-inhibiting activity was investigated on adult albino rats and mice. Mangiferin (100 mg/kg, i.p.) (i) significantly potentiates hexobarbitone (100 mg/kg, i.p. 30 min after mangiferin) narcosis by nearly 80% (sleeping time); (ii) markedly antagonizes the ptois and reverses the sedation induced by reserpine; (iii) potentiates amphetamine (25 mg/kg, i.p. 60 min after mangiferin) toxicity in aggregated rats (750% increase in mortality); (iv) potentiates DOPA-induced (100 mg/kg, i.p. 60 min after mangiferin) piloerection, salivation, motor activity and aggressiveness; (v) potentiates the typical head-twitch response of 5-HTP (50 mg/kg, i.p. 60 min after mangiferin); and (vi) potentiates the analgesic effect of subanalgic 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 phytoecinmes based on its bark are worthy of further investigation to precise their major fields of use. The present extent of diabetes in deve-
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