Pharmacological Effects of Mangiferin

WEI Zhi-quan[1], DENG Jia-gang[2*], YAN Li[3]

1. Graduate School, Guangxi Medical University, Nanning 530021, China
2. Guangxi Traditional Chinese Medical University, Nanning 530001, China
3. Faculty of Zhuang Medicine, Guangxi Traditional Chinese Medical University, Nanning 530001, China

Abstract: Mango leaves have been widely used in the clinical practice for thousands of years in traditional Chinese medicine. Mangiferin, an effective constituent in the mango leaves, has multiple pharmacological actions involved in some basic pathological processes, such as inflammation, oxidative injury, tumor growth, micro-organism infections, metabolic regulations, and immunological regulations. The pharmacological effects of mangiferin from some published data are reviewed in this article.

Key words: immunological regulations; mangiferin; mango leaves; pharmacology; metabolic regulations
DOI: 10.3969/j.issn.1674-6384.2011.04.006

Introduction

Mangiferin, (1,3,6,7-tetrahydroxyxanthone-C(2)-β-*D*-glucoside) (Fig. 1), existed in many food or medicinal plants, has some pharmacological effects on inflammation, oxidative injury, tumor growth, micro-organism infections, metabolic regulations, immune regulations, and radioprotection. This review summarized the seven effects with their potential mechanisms for further medical explorations (Wu *et al*, 2008).

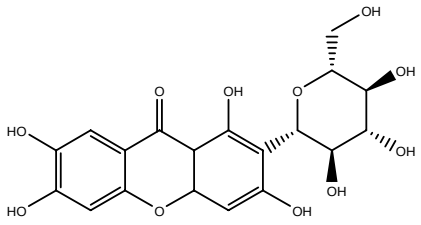

Fig. 1 Chemical structure of mangiferin

Pharmacological actions of mangiferin

Anti-inflammation

Mangiferin markedly inhibited acetic acid-induced intraperitoneal exudation (Deng, Zheng, and Zeng, 2002) and decreased xylene-induced swelling in mice (Garrido *et al*, 2006). It also relieved lipopoly-saccharide-induced fever in rabbits (Deng, Zheng, and Yang, 2006) and ligature-induced experimental periodontitis in rats (Carvalho *et al*, 2009). However, it has less effects on chronic systemic inflammation, such as rheumatic arthritis, recurrent asthma, obstructive bronchitis, and metabolic related arteritis (Prabhu, Narayan, and Devi, 2009).

The possible anti-inflammatory mechanisms of mangiferin include the balance between the overwhelming anti-inflammatory cytokines and proinflammatory mediators, inhibition of inflammatory cellular activations, regulations of inflammatory gene expressions, and enhancements of the cellular resistance against inflammatory injuries (Sánchez *et al*, 2000; Garrido *et al*, 2004; Carvalho *et al*, 2009). The sub-cellular targets of the anti-inflammatory effects located at the thermoregulatory neural centers for their reducing prostaglandin synthesis in fever (Bhatia *et al*, 2008), and the lysosomal membrane for its lowering hydrolase activity in isoprenaline-induced myocardial necrosis (Prabhu, Narayan, and Devi, 2009).

Anti-oxidative activity

The anti-oxidative activity of mangiferin has been

* Corresponding author: Deng JG Address: Guangxi Traditional Chinese Medical University, 179 Mingxiu Dong Road, Nanning 530001, China
Tel/ Fax: +86-0771-3137 555 E-mail: dengjg53@hotmail.com
First author: Wei ZQ Address: Graduate School, Guangxi Medical University, Nanning 530021, China E-mail: wzq01067@163.com
Received: August 1, 2010; Revised: March 28, 2011; Accepted: June 16, 2011
Fund: Natural Science Foundation of China (30973916)

demonstrated as the health-keeper in food plants (Joubert *et al*, 2008), the free radical scavenger in medicinal plants (Rodriguez *et al*, 2006; Wu *et al*, 2008), and the anti-oxidant ingredients in the plants as traditional Chinese medicines (Tang *et al*, 2004; Martin *et al*, 2008). The polyphenolic moiety contributes to the protective effects, which has been confirmed in the oxidative stress process induced with various agents, e.g., $HgCl_2$ in HepG2 cell (Agarwala *et al*, 2010), 1-methyl-4-phenyl-pyridinium in neurons (Amazzal *et al*, 2007), carbon tetrachloride in hepatocytes (Dar *et al*, 2005; Yoshikawa *et al*, 2002), toxicants (tert-butyl hydroperoxide, ethanol, carbon tetrachloride, and lipopolysaccharide) in rat cultures hepatocytes (Rodeiro *et al*, 2008), isoproterenol in myocytes (Prabhu *et al*, 2006), hyperglycaemia in rat diabetic kidney or its mesangial cells (Li *et al*, 2010), and injury cytokins in infiltrative chronic inflammatory cells (Pardo-Andreu *et al*, 2006).

The possible anti-oxidative mechanisms of mangiferin were specialized with its iron-complexing ability in mitochondria (Andreu *et al*, 2005). Its free hydroxyl groups and catechol moiety were essential for its anti-oxidative activity, consequently cyclosporin A-sensitive mitochondrial swelling in the presence of Ca^{2+}, which confirmed that its iron-chelating properties account for its therapeutic actions in pathological iron overloads (Pardo-Andreu *et al*, 2007). In the atherosclerosis-prone hypercholesterolemic mouse with LDL receptor knockout, it prevented NADPH spontaneous oxidation and inhibited oxidative events in liver mitochondria and spleen lymphocytes (Pardo-Andreu *et al*, 2008). In a model of ischemic brain damage, its neuroprotective mechanisms included 1) to inhibit the production of reactive oxygen species, 2) to activate the enzymatic anti-oxidant system, 3) to restore the mitochondrial membrane potential, 4) to inhibit glutamate-induced activation of calpains, 5) to normalize the levels of phosphorylated Akt kinase and Erk1/2, 6) to inhibit AIF release from mitochondria, and 7) to regulate the nuclear translocation of NF-kappaB (Campos-Esparza, Sanchez-Gomez, and Matute 2009). In a model of scopolamine-induced cholinergic memory deficits in mice, it inhibited acetylcholinesterase activity in a dose-dependent manner due to the ability of improving long-term cholinergic memory deficits by AChE inhibition or cholinergic receptor stimulation and inhibition of NF-kappaB activation (Jung *et al*, 2009). In a model of isoproterenol-induced myocardial necrosis in rats, it protected lysosomal integrity through decreasing the inflammatory process (Prabhu, Narayan, and Devi, 2009). On the other hand, it was also involved in promoting new blood vessel growth (Daud *et al*, 2010).

Antitumor activity

Mangiferin was considered as a drug candidate for cancers because it could inhibit tumor cellular proliferation and activate the lymphocytes in cancer-bearing mice (Chattopadhyay *et al*, 1987). Its chemopreventive effect has been confirmed in the oncogenic process induced with various agents, e.g. azoxymethane in colonic mucosa (Yoshimi *et al*, 2001) and benzopyrene in lung carcinogenesis (Rajendran, Ekambaram, and Sakthisekaran, 2008).

The possible antitumor mechanisms of mangiferin included the antigenotoxic action on $CdCl_2$-induced toxicity in mice (Viswanadh, Rao, and Rao, 2010), the inhibition of the telomerase and the gene (Cheng *et al*, 2007), and the enhancement of the cellular apoptosis (Viswanadh, Rao, and Rao, 2010; Cheng *et al*, 2007; Peng *et al*, 2007). Mangiferin might inhibit the activity of the Fms-like tyrosine kinase 3 overactivated in malignant cells (Han and Chin, 2011) and block G_2/M phase in leukemia (Yao *et al*, 2010).

Antimicroorganism activity

Mangiferin was considered as an antiviral agent upon herpes simplex virus (Zheng and Lu, 1990; Zhu *et al*, 1993), HIV (Guha, Ghosal, and Chattopadhyay, 1996), hepatitis B virus (Zheng, Deng, and Yang, 2004; Deng *et al*, 2007). It has been used in the patients infected with influenza virus due to the inhibitory effect on the neuraminidase or isomerization (Ryu *et al*, 2009).

Mangiferin was also considered as an anti-microbial agent upon gram-positive, gram-negative bacteria and yeast *Candida albicans* (Savikin *et al*, 2009; Singh *et al*, 2009), and it was a helping agent for up-regulating the multidrug transporter of ABCB1/P-glycoprotein (Chieli *et al*, 2010).

Metabolic regulation

The metabolic regulation of mangiferin was confirmed for hyperglycemia (Miura *et al*, 2001a; 2001b), hyperlipidemia with therogenic risk

(Muruganandan, Lai, and Gupta, 2005), and the metabolic syndrome with both hyperglycemia and dyslipidemia (Ojewole, 2005). It also acted directly on liver cells and down-regulated the gluconeogenic pathway through regulation of fructose-1,6-bisphosphatase expression, thereby decreased fasting blood glucose levels (Im *et al*, 2009).

The possible metabolic mechanism of mangiferin was either the inhibition of carbohydrate-related enzymes, such as sucrase, isomaltase, and aldose reductase (Yoshikawa *et al*, 2001), or the modulation of the transcription of peroxisome proliferator-activated receptor isoforms from its metabolites (Wilkinson *et al*, 2008). Its antidiabetic effect by increasing GLUT4 expression and translocation in muscle cells was probably mediated through two independent pathways that are related to 5′-AMP-activated protein kinase and PPAR-gamma (Girón *et al*, 2009).

Immunoregulation

Mangiferin has been considered as a candidate for immunoregulators (Hamuro, 2005). As an immuno-stimulant, it rescued the cyclophosphamide-induced immunodeppression, such as the lymphoid organ atrophy, less cellular response, low antigen-specific IgM, more lipid peroxidation, and decreased superoxide dismutase activities (Muruganandan, Lai, and Gupta, 2005; Deng *et al*, 2007). It also increased remarkably the levels of serum hemolysis IgG and IgM in mice (Qin *et al*, 2007). As an immunosuppressant, it has no effect on mouse antibody responses, especially on the release of special IgM and IgG antibody (Garcia *et al*, 2003).

The possible immunostimulant mechanisms of mangiferin have been considered as its anti-oxidative action, since it inhibited the oxidative-stimulated activation of immunocytes, such as lymphocyte, neutrophil, and macrophage (Muruganandan, Lai, and Gupta, 2005). This was supported with both downregulations of inducible nitric oxide synthase with tumor necrosis factor-alpha and superoxide anion in rat macrophage stimulated with lipopolysaccharide (Leiro *et al*, 2003). Its immunomodulatory mechanisms might be related to the inhibition on activation-induced T cell death (Hernandez *et al*, 2007) and the cellular skeleton of the stimulated macrophage resulted in the cytoplasmic spread, long extensions and intercellular contacts (De and Chattopadhyay, 2009).

Radioprotective activity

The radioprotective actions of mangiferin have been confirmed on radiation-induced immunocytes without changing the susceptibility of malignant cells (Jagetia and Venkatesha, 2005; Jagetia and Baliga, 2005; Menkovic *et al*, 2010).

Others

The other effects of mangiferin have been reported as follows. It was used as a laxative (Kakino *et al*, 2010). It prevented osteoporosis (Ang *et al*, 2011), improved long-term object recognition memory (Pardo-Andreu *et al*, 2010), showed antiallergic effect (Lee *et al*, 2009), protected gastric injury induced with NSAIDs (Carvalho *et al*, 2007) and different experimental models (Severi *et al*, 2009), ameliorated scopolamine-induced learning deficits (Jung *et al*, 2009), protected cells against cadmium chloride induced toxicity, and showed neuroprotective action (Satish, Screedevi, and Nageshwar, 2009; Gottlieb *et al*, 2006).

Prospect of research strategy

Based on current studies on mangiferin, some critical sections might be deliberated at the level of research strategy.

The active mechanisms of mangiferin which we poorly understand seem to be seriously concerned by most of researchers. It also seems to be involved in many aspects, but the actually comparative dominance is usually lacked in most of research directions. It is self-evident to clarify the mechanism of action by appropriate method, and fully understand the reasons why the efficacy or the reverse reaction appears. Thus, it will be available to enhance the efficacy and decrease the reverse reaction (Wang and Zhu, 2006). Mangiferin will be identified as a potentially valuable leading compound in a very long term until the action mechanisms are clarified.

It is important to establish a series of experimental methods for the pharmacological research. A series of unified experimental methods and normative means of drug effectiveness are proper as the system core of pharmacological researches and drug quality assurance (Xie, 2006). An essential point is that mangiferin should be studied and assessed according to current

national principles of drug screening and evaluation, and taken as a normal drug. Furthermore, the dose-effect and time-effect relationship which are necessary for developing a successful drug ought to be appeared in research.

System biology ideas and techniques, as revolutionary advances in pharmacologicals research due to modern sciences, should be introduced into the pharmacologicals research of mangiferin. While entering into the human or animal bodies to play a role, it will be certain for mangiferin to take a series of changes in structure and function from genetic information to algometric function achievement at the molecules, cells, tissues, organs, and whole body levels. It is gene as the material base to modulate these structures and functions, and protein as the material carrier, and metabolite as the ultimate reflect product. The method based on the genomics, proteomics and metabolomics idea and skills are applicable for the research on the multi-target drug effect (Wen and Han, 2004).

Conclusion

Theory and practice have proved that natural products are still the optimal source of new drugs. Mangiferin is of them with rich resource. The pharmacological activities of mangiferin have been proved by a lot of studies. Mangiferin could be a leading compound for the development of new drugs used in dozens of diseases. On the basis of the natural structure-based activity of mangiferin, the guidance of the systematic research on the relationship of structure and activity/toxicity can be summarized and turned into a basis to design the new drug target compounds. It should be the foremost strategy and method for the pharmacological research of mangiferin.

References

Amazzal L, Lapôtre A, Quignon F, Bagrel D, 2007. Mangiferin protects against 1-methyl-4-phenylpyridinium toxicity mediated by oxidative stress in N2A cells. *Neurosci Lett* 418: 159-164.

Andreu GP, Delgado R, Velho JA, Curti C, Vercesi AE, 2005. Iron complexing activity of mangiferin, a naturally occurring glucosylxanthone, inhibits mitochondrial lipid peroxidation induced by Fe^{2+}-citrate. *Eur J Pharmacol* 513: 47-55.

Ang E, Liu Q, Qi M, Liu HG, Yang X, Chen H, Zheng MH, Xu J, 2011. Mangiferin attenuates osteoclastogenesis, bone resorption and RANKL-induced activation of NF-kappaB and ERK. *J Cell Biochem* 112: 89-97.

Bhatia HS, Candelario-Jalil E, de Oliveira AC, Olajide OA, Martínez-Sánchez G, Fiebich BL, 2008. Mangiferin inhibits cyclooxygenase-2 expression and prostaglandin E_2 production in activated rat microglial cells. *Arch Biochem Biophys* 477: 253-258.

Campos-Esparza MR, Sanchez-Gomez MV, Matute C, 2009. Molecular mechanisms of neuroprotection by two natural anti-oxidant polyphenols. *Cell Calcium* 45: 358-368.

Carvalho AC, Guedes MM, de Souza AL, Trevisan MT, Lima AF, Santos FA, Rao VS, 2007. Gastroprotective effect of mangiferin, a xanthonoid from *Mangifera indica*, against gastric injury induced by ethanol and indomethacin in rodents. *Planta Med* 73: 1372-1376.

Carvalho RR, Pellizzon CH, Justulin LJr, Felisbino SL, Vilegas W, Bruni F, Lopes-Ferreira M, Hiruma-Lima CA, 2009. Effect of mangiferin on the development of periodontal disease: Involvement of lipoxin A4, anti-chemotaxic action in leukocyte rolling. *Chem Biol Inter* 179: 344-350.

Chattopadhyay U, Das S, Guha S, Ghosal S, 1987. Activation of lymphocytes of normal and tumor bearing mice by mangiferin, a naturally occurring glucosylxanthone. *Cancer Lett* 37: 293-299.

Cheng P, Peng ZG, Yang J, Song SJ, 2007. The effect of mangiferin on telomerase activity and apoptosis in leukemic K562 cells. *J Chin Med Mater* 30: 306-309.

Chieli E, Romiti N, Rodeiro I, Garrido G, 2010. *In vitro* modulation of ABCB1/P-glycoprotein expression by polyphenols from *Mangifera indica*. *Chem Biol Inter* 186: 287-294.

Dar A, Faizi S, Naqvi S, Roome T, Zikr-ur-Rehman S, Ali M, Firdous S, Moin ST, 2005. Analgesic and anti-oxidant activity of mangiferin and its derivatives: The structure activity relationship. *Biol Pharm Bull* 28: 596-600.

Daud NH, Aung CS, Hewavitharana AK, Wilkinson AS, Pierson JT, Roberts-Thomson SJ, Shaw PN, Monteith GR, Gidley MJ, Parat MO, 2010. Mango extracts and the mango component mangiferin promote endothelial cell migration. *J Agric Food Chem* 58: 5181-5186.

De A, Chattopadhyay S, 2009. The variation in cytoplasmic distribution of mouse peritoneal macrophage during phagocytosis modulated by mangiferin, an immunomodulator. *Immunobiology* 214: 367-376.

Deng JG, Yang K, Zheng ZW, Zhou XX, 2007. Inhibitory effect of mangiferin on duck hepatitis B virus (DHBV) DNA *in vivo*. *J Guangxi Tradit Chin Med Univ* 10: 1-3.

Deng JG, Zheng ZW, Yang K, 2006. Effect of mangiferin on the fever mediated by lipopolysaccharide in rabbits. *Chin J Exp Tradit Med Form* 12: 72-73.

Deng JG, Zheng ZW, Zeng CH, 2002. Pharmacological studies on mangiferin. *Chin Arch Tradit Chin Med* 20: 371-372.

Garcia D, Leiro J, Delgado R, Sanmartín ML, Ubeira FM, 2003. *Mangifera indica* L. extract (Vimang) and mangiferin modulate mouse humoral immune responses. *Phytother Res* 17: 1182-1187.

Garrido G, Delgado R, Lemus Y, Rodríguez J, García D, Núñez-Sellés AJ, 2004. Protection against septic shock and suppression of tumor necrosis factor alpha and nitric oxide production on macrophages and microglia by a standard aqueous extract of *Mangifera indica* L. (VIMANG). Role of mangiferin isolated from the extract. *Pharm Res* 50: 165-172.

Garrido G, Gonzalez D, Lemus Y, Delporte C, Delgado R, 2006.

Protective effects of a standard extract of *Mangifera indica* L. (VIMANG) against mouse ear edemas and its inhibition of eicosanoid production in J774 murine macrophages. *Phytomedicine* 13: 412-418.

Girón MD, Sevillano N, Salto R, Haidour A, Manzano M, Jiménez ML, Rueda R, López-Pedrosa JM, 2009. *Salacia oblonga* extract increases glucose transporter 4-mediated glucose uptake in L6 rat myotubes: Role of mangiferin. *Clin Nutr* 28: 565-574.

Gottlieb M, Leal-Campanario R, Campos-Esparza MR, Sánchez-Gómez MV, Alberdi E, Arranz A, Delgado-García JM, Gruart A, Matute C, 2006. Neuroprotection by two polyphenols following excitotoxicity and experimental ischemia. *Neurobiol Dis* 23: 374-386.

Guha S, Ghosal S, Chattopadhyay U, 1996. Antitumor, immuno-modulatory and anti-HIV effect of mangiferin, a naturally occurring glucosylxanthone. *Chemotherapy* 42: 443-451.

Hamuro J, 2005. Anticancer immunotherapy with perorally effective lentinan. *Jpn J Cancer Chemother* 32: 1209-1215.

Han SY, Chin YW, 2011. A FLT3-inhibitory constituent from the rhizomes of *Anemarrhena asphodeloides*. *J Enzyme Inhib Med Chem* 26: 445-448.

Hernandez P, Rodriguez PC, Delgado R, Walczak H, 2007. Protective effect of *Mangifera indica* L. polyphenols on human T lymphocytes against activation-induced cell death. *Pharm Res* 55: 167-173.

Im R, Mano H, Matsuura T, Nakatani S, Shimizu J, Wada M, 2009. Mechanisms of blood glucose-lowering effect of aqueous extract from stems of *Kothala himbutu* (*Salacia reticulata*) in the mouse. *J Ethnopharmacol* 121: 234-240.

Jagetia GC, Baliga MS, 2005. Radioprotection by mangiferin in DBAxC57BL mice: A preliminary study. *Phytomedicine* 12: 209-215.

Jagetia GC, Venkatesha VA, 2005. Effect of mangiferin on radiation-induced micronucleus formation in cultured human peripheral blood lymphocytes. *Environ Mol Mutagen* 46: 12-21.

Joubert E, Richards ES, Merwe JD, De Beer D, Manley M, Gelderblom WC, 2008. Effect of species variation and processing on phenolic composition and *in vitro* anti-oxidation activity of aqueous extracts of *Cyclopia* spp. (Honeybush Tea). *J Agric Food Chem* 56: 954-963.

Jung K, Lee B, Han SJ, Ryu JH, Kim DH, 2009. Mangiferin ameliorates scopolamine-induced learning deficits in mice. *Biol Pharm Bull* 32: 242-246.

Kakino M, Izuta H, Ito T, Tsuruma K, Araki Y, Shimazawa M, Oyama M, Iinuma M, Hara H, 2010. Agarwood induced laxative effects *via* acetylcholine receptors on loperamide-induced constipation in mice. *Biosci Biotechnol Biochem* 74: 1550-1555.

Lee B, Trung Trinh H, Bae EA, Jung K, Kim DH, 2009. Mangiferin inhibits passive cutaneous anaphylaxis reaction and pruritus in mice. *Planta Med* 75: 1415-1417.

Leiro JM, Alvarez E, Arranz JA, Siso IG, Orallo F, 2003. *In vitro* effects of mangiferin on superoxide concentrations and expression of the inducible nitric oxide synthase, tumour necrosis factor-alpha and transforming growth factor-beta genes. *Biochem Pharmacol* 65: 1361-1371.

Li X, Cui X, Sun X, Li X, Zhu Q, Li W, 2010. Mangiferin prevents diabetic nephropathy progression in streptozotocin-induced diabetic rats. *Phytother Res* 24: 893-899.

Martin F, Hay AE, Cressend D, Reist M, Vivas L, Gupta MP, Carrupt PA, Hostettmann K, 2008. Anti-oxidant *C*-glucosylxanthones from the leaves of *Arrabidaea patellifera*. *J Nat Prod* 71: 1887-1890.

Menkovic N, Juranic Z, Stanojkovic T, Raonic-Stevanovic T, Savikin K, Zdunić G, Borojevic N, 2010. Radioprotective activity of *Gentiana lutea* extract and mangiferin. *Phytother Res* 24: 1693-1696.

Miura T, Ichiki H, Hashimoto I, Iwamoto N, Kao M, 2001a. Antidiabetic activity of a xanthone compound mangiferin. *Phytomedicine* 8: 85-87.

Miura T, Ichiki H, Iwamoto N, Kato M, Kubo M, Sasaki H, Okada M, Ishida T, Seino Y, Tanigawa K, 2001b. Antidiabetic activity of the rhizoma of *Anemarrhena asphodeloides* and active components, mangiferin and its glucoside. *Biol Pharm Bull* 24: 1009-1011.

Muruganandan S, Lai J, Gupta PK, 2005. Immunotherapeutic effects of mangiferin mediated by the inhibition of oxidative stress to activated lymphocytes, neutrophils and macrophages. *Toxicology* 215: 57-68.

Ojewole JA, 2005. Anti-inflammatory, analgesic and hypoglycemic effects of *Mangifera indica* Linn. (Anacardiaceae) stem-bark aqueous extract. *Methods Find Exp Clin Pharmacol* 27: 547-554.

Pardo-Andreu GL, Cavalheiro RA, Dorta DJ, Naal Z, Delgado R, Vercesi AE, Curti C, 2007. Fe(III) shifts the mitochondria permeability transition-eliciting capacity of mangiferin to protection of organelle. *J Pharmacol Exp Ther* 320: 646-653.

Pardo-Andreu GL, Maurmann N, Reolon GK, de Farias CB, Schwartsmann G, Delgado R, Roesler R, 2010. Mangiferin, a naturally occurring glucoxilxanthone improves long-term object recognition memory in rats. *Eur J Pharmacol* 635: 124-128.

Pardo-Andreu GL, Paim BA, Castilho RF, Velho JA, Delgado R, Vercesi AE, Oliveira HC, 2008. *Mangifera indica* L. extract (Vimang) and its main polyphenol mangiferin prevent mitochondrial oxidative stress in atherosclerosis-prone hyper-cholesterolemic mouse. *Pharm Res* 57: 332-338.

Pardo-Andreu GL, Sanchez-Baldoquin C, Avila-Gonzalez R, Yamamoto ET, Revilla A, Uyemura SA, Naal Z, Delgado R, Curti C, 2006. Interaction of Vimang (*Mangifera indica* L. extract) with Fe (III) improves its anti-oxidant and cytoprotecting activity. *Pharm Res* 54: 389-395.

Peng ZG, Luo J, Lai YR, Song SJ, 2007. Apoptotic mechanism of leukemic K562 cells induced by mangiferin. *Chin Tradit Herb Drugs* 38(5): 715-719.

Prabhu S, Jainu M, Sabitha KE, Devi CS, 2006. Role of mangiferin on biochemical alterations and anti-oxidant status in isoproterenol-induced myocardial infarction in rats. *J Ethnopharmacol* 107: 126-133.

Prabhu S, Narayan S, Devi CS, 2009. Mechanism of protective action of mangiferin on suppression of inflammatory response and lysosomal instability in rat model of myocardial infarction. *Phytother Res* 23: 756-760.

Qin HZ, Wang ML, Zhao ZW, Li LH, Deng JP, Qu YZ, Shi HY, Gao L, Gao GD, 2007. Preliminary study on effects of mangiferin on immunologic function in mice. *Chin J Clin Pharm Ther* 12: 931-934.

Rajendran P, Ekambaram G, Sakthisekaran D, 2008. Effect of mangiferin on benzo(a)pyrene induced lung carcinogenesis in experimental Swiss albino mice. *Nat Prod Res* 22: 672-680.

Rodeiro I, Donato MT, Martínez I, Hernández I, Garrido G, González-Lavaut JA, Menéndez R, Laguna A, Castell JV, Gómez-Lechón MJ, 2008. Potential hepatoprotective effects of new Cuban natural products in rat hepatocytes culture. *Toxicol in Vitro* 22: 1242-1249.

Rodríguez J, Di Pierro D, Gioia M, Monaco S, Delgado R, Coletta M, Marini S, 2006. Effects of a natural extract from *Mangifera indica* L., and its active compound, mangiferin, on energy state and lipid peroxidation of red blood cells. *Biochim Biophys Acta* 1760: 1333-1342.

Ryu YB, Curtis-Long MJ, Lee JW, Kim JH, Kim JY, Kang KY, Lee WS, Park KH, 2009. Characteristic of neuraminidase inhibitory xanthones from *Cudrania tricuspidata*. *Bioorg Med Chem* 17: 2744-2750.

Sánchez GM, Re L, Giuliani A, Núñez-Sellésd AJ, Davisona GP, León-Fernández OS, 2000. Protective effects of *Mangifera indica* L. extract mangiferin and selected anti-oxidants against TPA-induced biomolecules oxidation and peritoneal macrophage activation in mice. *Pharm Res* 42: 565-573.

Satish RBS, Sreedevi MV, Nageshwar RB, 2009. Cytoprotective and antigenotoxic potential of mangiferin, a glucosylxanthone against cadmium chloride induced toxicity in $HepG_2$ cells. *Food Chem Toxicol* 47: 592-600.

Savikin K, Menković N, Zdunić G, Stević T, Radanović D, Janković T, 2009. Antimicrobial activity of *Gentiana lutea* L. extracts. *Z Naturforsch C* 64: 339-342.

Severi JA, Lima ZP, Kushima H, Brito AR, Santos LC, Vilegas W, Hiruma-Lima CA, 2009. Polyphenols with anti-ulcerogenic action from aqueous decoction of mango leaves (*Mangifera indica* L.). *Molecules* 14: 1098-1100.

Singh SK, Kumar Y, Kumar SS, Sharma VK, Dua K, Samad A, 2009. Antimicrobial evaluation of mangiferin analogues. *Indian J Pharm Sci* 71: 328-331.

Tang SY, Whiteman M, Peng ZF, Jenner A, Yong EL, Halliwell B, 2004. Characterization of anti-oxidant and antiglycation properties and isolation of active ingredients from traditional Chinese medicines. *Free Radic Biol Med* 36: 1575-1587.

Viswanadh EK, Rao BN, Rao BS, 2010. Antigenotoxic effect of mangiferin and changes in anti-oxidant enzyme levels of Swiss albino mice treated with cadmium chloride. *Hum Exp Toxicol* 29: 409-418.

Wang ST, Zhu QZ, 2006. The development and applied progression of TCM fingerprinting. *Health Vocat Educ* 24: 153-155.

Wen JK, Han M, 2004. Application of genomics and proteomics in study of traditional Chinese medicine. *J Chin Integr Med* 2: 323-325.

Wilkinson AS, Monteith GR, Shaw PN, Lin CN, Gidley MJ, Roberts-Thomson SJ, 2008. Effects of the mango components mangiferin and quercetin and the putative mangiferin metabolite norathyriol on the transactivation of peroxisome proliferator-activated receptor isoforms. *J Agric Food Chem* 56: 3037-3042.

Wu JF, Chen SB, Gao JC, Song HL, Wu LJ, Chen SL, Tu PF, 2008. Xanthone glycosides from herbs of *Polygala hongkongensis* Hemsl and their anti-oxidant activities. *J Asian Nat Prod Res* 10: 673-678.

Xie PS, 2006. Based on classical modernization of TCM and quality assessment inheritance and innovation. *World Sci Technol Mod Tradit Chin Med* 8: 8-13.

Yao YB, Peng ZG, Liu ZF, Yang J, Luo J, 2010. Effects of mangiferin on cell cycle status and CDC2/CyclinB1 expression of HL-60 cells. *J Chin Med Mater* 33: 81-85.

Yoshikawa M, Ninomiya K, Shimoda H, Nishida N, Matsuda H, 2002. Hepatoprotective and anti-oxidative properties of *Salacia reticulata*: Preventive effects of phenolic constituents on CCl_4-induced liver injury in mice. *Biol Pharm Bull* 25: 72-76.

Yoshikawa M, Nishida N, Shimoda H, Takada M, Kawahara Y, Matsuda H, 2001. Polyphenol constituents from *Salacia* species: Quantitative analysis of mangiferin with alpha-glucosidase and aldose reductase inhibitory activities. *J Pharm Soc Jpn* 121: 371-378.

Yoshimi N, Matsunaga K, Katayama M, Yamada Y, Kuno T, Qiao Z, Hara A, Yamahara J, Mori H, 2001. The inhibitory effects of mangiferin, a naturally occurring glucosylxanthone, in bowel carcinogenesis of male F344 rats. *Cancer Lett* 163: 163-170.

Zheng MS, Lu ZY, 1990. Antiviral effect of mangiferin and isomangiferin on herpes simplex virus. *Chin Med J* (*Eng Ed*) 103: 160-165.

Zheng ZW, Deng JG, Yang K, 2004. The effect of mangiferin on HBsAg and HBeAg secretion in HBV. *Chin Arch Tradit Chin Med* 22: 1645-1646.

Zhu XM, Song JX, Huang ZZ, Wu YM, Yu MJ, 1993. Antiviral activity of mangiferin against herpes simplex virus type 2 *in vitro*. *Acta Pharmacol Sin* 14: 452-454.