Pharmacological Effects of Mangiferin

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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

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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 ligation-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
Ca2+, which confirmed that its iron-chelating properties and antioxidative activity, consequently cyclosporin hydroxyl groups and catechol moiety were essential for its ability in mitochondria (Andreu et al., 2006). Infiltrative chronic inflammatory cells (Pardo-Andreu et al., 2005; Yoshikawa et al., 2005; Yoshikawa et al., 2008), 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 Ca2+, 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 Sakhthisekaran, 2008).

The possible antitumor mechanisms of mangiferin included the antigenotoxic action on CdCl2-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 G2/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 (Ghosal, Chattopadhyay, and Guha, 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 antimicrobial 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 immunostimulant, it rescued the cyclophosphamide-induced immunodepression, 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


