MANGIFERIN FROM MANGIFERA INDICA LINN.: A PHARMACOLOGICAL STUDY

Article · July 2020

CITATION
1

READS
127

2 authors:

Jayanta Mistry
University of Kalyani
6 PUBLICATIONS **47** CITATIONS
SEE PROFILE

Maharaj Biswas
University of Kalyani
17 PUBLICATIONS **25** CITATIONS
SEE PROFILE

ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

MANGIFERIN FROM *MANGIFERA INDICA* LINN.: A PHARMACOLOGICAL STUDY

Jayanta Mistry, Maharaj Biswas*

Endocrinology laboratory, Department of Zoology, University of Kalyani, Kalyani, Nadia, West Bengal, India

**Corresponding author: mistryjayanta80.sm@gmail.com*

ABSTRACT

Natural remedies have been reported for centuries. The current review article is an attempt to discuss the pharmacological potential of Mangiferin, a water-soluble main bioactive compound (1,3,6,7-tetrahydroxyxanthone C2-β-D-glucoside) of mango tree although it is also found in many other plants, especially against various life-style disorders like diabetes mellitus, obesity, hyperlipidaemia, hypertension and other cardiovascular diseases (CVDs). Although numerous published pharmacological studies demonstrated many other activities of mangiferin: analgesic, antioxidant, antimicrobial, anti-tumourogenic, anti-inflammatory, anti-allergic, antisclerotic etc. This comprehensively analyzed and collectively summarized review work on primary pharmacological potentials of mangiferin may be helpful to support the future development of mangiferin as a novel therapeutic drug.

Keywords: Mangiferin, Diabetes, Hypertension, Hyperlipidemia, Antioxidant, CVDs.

1. INTRODUCTION

Mangiferin, a C-glucoside xanthone glucoside, is an active phytochemical present in various plants including *Mangifera indica* L. (Family: Anacardiaceae, Genus: *Mangifera*) [1]. The mangiferin [1,3,6,7-tetrahydroxyxanthone C2-β-D-glucoside; $C_{19}H_{18}O_{11}$; MW, 422.35; melting point (anhydrous)-271°C [2] has been reported in various parts of *M. indica i.e.* leaves [3], fruits [4], stem bark [4, 5], heartwood [6] and roots [7]. The plant which contains the mangiferin is used as phytomedicine. Mangiferin is a natural polyphenol distribution in the angiosperms occurring sporadically in 13 dicot and 6 monocot families [7-9]. Mangiferin possesses a wide range of pharmacological outcomes, including antitumor [10], antioxidant [11], antiviral [12-14], immunomodulatory [10, 15] and antidiabetic activities [14, 16-19].

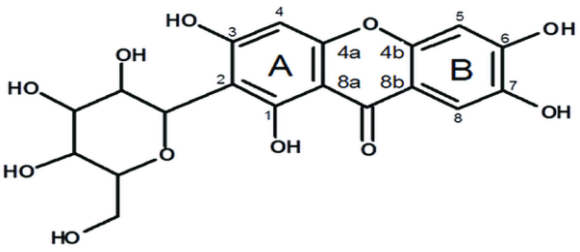

Fig. 1: Chemical structure of mangiferin (1,3,6,7-Tetrahydroxyxanthone C2-β-D-glucoside)

Mangifera indica L., a medicinal plant widely distributed in tropical areas in the world and used as ethnomedicine for millennia to cure various diseases. The mangiferin, a xanthone C-glucoside is the major component of *M. indica*, could be responsible for a lot of the reported activities for treatment of various diseases, as discussed in this review.

2. PHARMACOLOGICAL ACTIVITIES OF MANGIFERIN

The chemical constituents of the different parts of *M. indica* L. are reviewed in Ross [20] and Scartezzini and Speroni [21]. The various parts of *Mangifera indica* contain protocatechic acid, catechin, mangiferin, alanine, glycine, γ-amino-butyric acid, kinic acid, shikimic acid and various tetracyclic triterpenoids [21]. Mangiferin is the most active component and has been reported to have numerous pharmacological effects which are discussed below.

2.1. Antidiabetic Activity

Diabetes mellitus is a series of metabolic disorder with hyperglycaemia and caused by defects in insulin secretion or mechanism of insulin action. In type 1 diabetes, pancreatic Islet's β-cells are destroyed usually by auto-immune disorder while type 2 diabetes is associated with β-cells dysfunction and with insulin resistance [22]. As long as standing hyperglycaemia with diabetes mellitus

leads to the formation of various glycosylated end-products which are involved in the generation of ROS (reactive oxygen species), and responsible for oxidative damage, particularly to heart and kidneys [23]. Studies in laboratory animals reported that mangiferin treatments were beneficial in diabetes, lipid metabolism and lowering the atherogenic factors [24-27]. In streptozotocin (STZ)-induced diabetic mice with 40 mg/kg mangiferin for 30 days is beneficial in comparison to diabetic control mice, the level of blood glucose, aspartate aminotransferase (AST), glycosylated-hemoglobin, alkaline phosphatase (ALP) and alanine aminotransferase (ALT) were significantly reduced [28, 29]. Antidiabetic activity of mangiferin involves mechanisms other than insulin action [30, 31] like enhance of peripheral glucose utilization by glycolytic and glycogenic processes [32]. In mice model, mangiferin (30 mg/kg, once daily for 2 weeks) reduced the blood cholesterol and triglyceride levels [26] are beneficial on hyperglycaemia and hyperlipidemia in type 2 diabetes. Saleh, 2014 observed that mangiferin can improve insulin resistance, pancreatic β-cell function and liver glycogen content in a high-fat high fructose diet and STZ-induced diabetic insulin-resistant rat model.

2.2. Antioxidant Activity

Due to hyperglycemia, glucose converted into the glycosylated end-products and ultimately reactive oxygen species (ROS) are formed, a strong oxidizing effect and induce damage to biological molecules, including proteins, lipids and DNA, with related changes in their structure and function [33]. Reactive oxygen species (ROS) plays a crucial role in the pathogenesis of some serious diseases/disorders, such as cancer, liver cirrhosis, cardiovascular diseases, diabetes, and inflammation associated symptoms [34]. Extensive generation of ROS helps in reducing the levels of endogenous antioxidants, a condition named "oxidative stress" [35]. Studies showed that antioxidants, vitamin E, vitamin C and β-carotene, may be beneficial to prevent several chronic disorders [36]. The reaction of mangiferin with different oxidizing and reducing radicals, OH^-, N_3^- and CCl_3O_2, was investigated by Mishra *et al*. [37]. The protective antioxidant abilities of a *M. indica* stem bark extract and mangiferin were investigated in mice model [11]. Abundant research on the effects of mangiferin has revealed the antioxidant and anti-inflammatory properties, due to its C-glycosylxanthone structure [38]. The C-glucosyl linkage and polyhydroxy component in mangiferin contributes to its free radical-scavenging activity [39]. The treatment of mangiferin possessed antioxidant and anti-lipid-peroxidant activity by significant decreases of hydroperoxides production in the liver and kidney tissues of diabetic rats [40]. Glutathione protected the cellular system against toxic effects of lipid peroxidant. The level of reduced-glutathione was decreased in diabetes condition. The decrease in the level of glutathione in tissues increases in the utilization due to oxidative stress induced by diabetes. The mangiferin treated STZ-induced diabetic rats shows the increased level of glutathione (GSH) in liver and kidney tissues. These results suggested that the compound might increase the biosynthesis of GSH or reduce the oxidative stress or both [41]. In STZ-induced diabetic animal some toxic free radicals are produced and are eliminated by two scavenging enzyme named superoxide dismutase (SOD) and catalase (CAT). SOD converts the superoxide radicals into H_2O_2 and molecular oxygen. CAT protected the organ from highly reactive hydroxyl (OH^-) radical through catalyzing the reduction of hydrogen peroxides [42]. This is highly effective defensive mechanism against removal of O_2^- and OH^-. In STZ-induced diabetic rats, treated with mangiferin show an increase in the activities of SOD and CAT to near-normal in liver and kidneys. These results revealed that mangiferin may contain a free radical scavenging activity and prevent pathological alteration caused by O_2^- and OH^- [42].

2.3. Effect on Lipid Metabolism

Mangiferin, showed a significant lipolytic effect on rat epididymal fat-derived cultured adipocytes and reduced 35% triglycerides [43]. Muruganandan *et al.* [24] and Saleh *et al.,* [44] administered mangiferin to streptozotocin-diabetic rats resulted in significant decreases in plasma total cholesterol (TC), triglycerides (TG), and LDL - cholesterol with elevations in HDL - cholesterol, liver TG, TC content and liver glycogen. These consequences validated the anti-hyperlipidemic and anti-atherogenic events of the mangiferin. The triglycerides lowering property of mangiferin could indirectly contribute to the overall antihyperglycemic activity through a mechanism of so-called glucose-fatty acid cycle [45]. Guo *et al.* [46] discovered that mangiferin (50 and 150 mg/kg) ameliorates hypertriglyceridemia by modulating the expression of genes involved in lipid oxidation and lipogenesis. Na *et al.* [47] conducted a 12-week double-blind randomized clinical trial to evaluate the effects of mangiferin (150 mg/day) on blood

lipid profiles in overweight patients with hyperlipidemia. Mangiferin noticeably increases the serum levels of high-density lipoprotein cholesterol, L-carnitine, β-hydroxybutyrate and acetoacetate, and increases lipoprotein lipase activity. Apontes *et al.* [48] administered mangiferin (400 mg/kg) and a high fat diet (HFD) to mice for 16 weeks, demonstrating that mangiferin protects against HFD-induced weight gain, promotes aerobic mitochondrial capacity and increases thermogenesis. In addition, treatment with mangiferin in overweight patients with hyperlipidemia stimulated carbohydrate oxidation and improved glucose and insulin profiles.

2.4. Antitumor Activity

Dietary nutrients act as a promising approach to cancer control, prevent carcinogenesis or revert tumor promotion, are known as chemo-preventive agents [49]. Mangiferin has been demonstrated to have direct and auxiliary roles in tumor control. Mangiferin inhibits tumor cell cycle progression. Yoshimi *et al*. [50] examined the chemo-defensive effects of mangiferin for both the initiation and post-initiation phases of azoxymethane-induced colon carcinogenesis in rats. The primary mechanisms are still indistinct but the chemo-preventive effect may be due to quenching of azoxymethane by the xanthone; the inhibitory effect on cell proliferation may come from the release of proapoptotic cytokines [51] by mangiferin-triggered lymphocytes [52]. Remarkably, mangiferin has been reinforced to trigger G2/M phase cell cycle arrest via regulation of the CDK1-cyclin B1 signaling pathway [53-55]. In colorectal cancer HT29 cells and cervical cancer HeLa cells treatment with mangiferin causes delay of DNA synthesis the S phase of the cell cycle [56]. Mangiferin brings apoptosis in tumor cells. Kim *et al*. [57] detected that antitumor efficacy and primary mechanisms of mangiferin in human cervical carcinoma HeLa cells established that the protein expression of BH3 interacting domain death agonist, Bcl-2 and pro-caspase-3 and -8 is downregulated in response to mangiferin treatment, which results in the activation of caspase-3, -7, -8 and -9, in due course leading to apoptosis. Nuclear factor-κB (NF-κB) is a transcription factor that induces the proliferation of cancer cells [58] by inhibiting the expression of RelA and RelB genes [59-61]. Mangiferin shows anti-neoplastic properties, arrest cell cycle G2/M phase via downregulation of the cyclin-dependent kinase 1-cyclin B1 signaling pathway and inducing apoptotic cell death in human lung carcinoma A549 cells, by inhibiting the PKC-NF-κB pathway [60]. Caspase activation serves a critical role in apoptosis, particularly via the mitochondria-initiated pathway [62]. *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 [63]. Pan *et al.* [64] demonstrated that through regulation of Bcl-2, apoptosis regulator (Bcl-2) and Bcl-2 associated X, apoptosis regulator (Bax) expression, mangiferin potently inhibits tumor cell proliferation and induces apoptosis in nasopharyngeal carcinoma cells. Lv *et al.* [65] and Zou *et al.* [66] studies contributed to the understanding of the primary molecular mechanism of mangiferin in tumor treatment. In human breast carcinoma MCF-7 cells, mangiferin downregulates the cyclin-dependent kinase 1-cyclin Bl signaling pathway and induces G2/M phase cell-cycle arrest to inhibit tumor cell growth.

2.5. Antimicrobial Activity

In addition to its antioxidative, antidiabetic and antitumor properties, the antibacterial and antiviral effects of mangiferin are also prominent [67]. In an *in vitro* agar diffusion technique, mangiferin exhibited activity counter to 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*) [68]. Maji *et al.* [69] observed that mangiferin exert antibacterial activity against two bacterial species: *Staphylococcus aureus* (Gram positive) and *Salmonella typhi* (Gram negative). Zhu *et al.* [13] deliberate *in vitro* the effect of mangiferin counter to Herpes simplex virus type 2; mangiferin does not directly inactivate HSV-2 but prevents the late phase in HSV-2 replication. *In vitro* mangiferin was also able to upset the cytopathic effects of HIV [10].

2.6. Other Effects

Leiro *et al.* [15] studied the immunomodulatory activity of mangiferin on thioglycollate-elicited mouse macrophages which were stimulated with lipopolysaccharide (LPS) and gamma interferon (IFN-γ). Mangiferin significantly reduces IgE levels and inhibits the lymphocyte proliferative response in ovalbumin-immunized mice; reduces histamine-induced cutaneous

reaction; inhibits passive anaphylactic reactions; decreases the compound 48/80-induced histamine release from rat mast cells [70]. Jagetia and Venkatesha [71] studied that mangiferin can protect against radiation-induced micronuclei formation in cultured human peripheral blood lymphocytes. Mangiferin (50 mg/kg oral dose) overwhelms the growth of helminths *Trichinella spiralis* throughout the parasitic life cycle, by inhibiting mast cell degranulation, decreasing the serum levels of specific anti-*Trichinella* IgE and reducing the number of parasitic larvae [72].

3. CONCLUSION

Many different pharmacological activities like antioxidant, antitumor, antidiabetic, lipolytic, radioprotective, antimicrobial, anti-inflammatory, antiparasitic, immunomodulatory, anti-allergic have been reported for mangiferin. Based on the information of the many properties of mangiferin, phytomedicines should be adequately standardized regarding this active compound. The *M. indica* long history of use has been validated by many researches; modern phytomedicines based on its active ingredients are worthy of further investigation to exhaustive their major fields of use. Mangiferin appears to have varied pharmacological effects. However, additional clinical investigation into the pharmacology and pharmacokinetics of mangiferin is required, as most of these effects have only been demonstrated in *in vivo* and *in vitro* experiments.

4. ACKNOWLEDGEMENT

This study was partially supported by the DST PURSE II Programme, University of Kalyani, Kalyani, Nadia, W. B, India.

5. REFERENCES

1. Matkowski A, Kuś P, Góralska E, Woźniak D. *Mini Rev. Med. Chem*, 2013; **13**:439-455.
2. Muruganandan S, Gupta S, Kataria M *et al*. *Toxicology*, 2002; **176**:165-173.
3. Desai PD, Ganguly AK, Govindachari TR, Joshi BS *et al. Indian Journal of Chemistry*, 1966; **4**:457-549.
4. El Ansari MA, Rajadurai S, Nayudamma Y. *Leather Science,* 1967; **14**:247-251.
5. Bhatia VK, Ramanathan JD, Seshadri TR. *Tetrahedron*, 1967; **23**:1363-1368.
6. Ramanathan JD, Seshadri TR. *Curr Sci,* 1960; **29**:131-2.
7. Nigam SK, Mitra CR. *Indian Journal of Chemistry*, 1964; **2**:378-379.
8. Richardson PM, Thaddeus E. *Journal of natural products*, 1983; **46**:747-749.
9. Jensen SR, J. Schripsema. Chemotaxonomy and pharmacology of Gentianaceae. In: Gentianaceae, Systematics and Natural History. L. Struwe& V. Albert (eds.), Cambridge University Press, Cambridge; 2002. pp 573-631.
10. Guha S, Ghosal S, Chattopadhyay U. *Chemotherapy*, 1996; **42:**443-451.
11. Sanchez GM, Re L, Giuliani A, Nunez-Selles AJ *et al*. *Pharmacological Research*, 2000; **42**:565-573.
12. Zheng MS, Lu ZY. *Chinese Medical Journal,* 1990; **103**:160-165.
13. Zhu XM, Song JX, Huang ZZ, Whu YM *et al*. *Zhongguo Yaoli Xuebao*, 1993; **14**:452-454.
14. Yoosook C, Bunyapraphatsara N, Boonyakiat Y, Kantasuk C. *Phytomedicine,* 2000; **6**:411-419.
15. Leiro J, Arranz JA, Yanez M, Ubeira FM *et al*. *International Immunopharmacology*, 2004; **4**:63-77.
16. Aderibigbe AO, Emudianughe TS, Lowal BA. *Phytotherapy Research*, 1999; **13**:504-507.
17. Aderibigbe AO, Emudianughe TS, Lowal BA. *Phytotherapy Research*, 2001; **15**:456-458.
18. Periyar SS, Arulselvan P, Balu PM, Murugesan K. *Asian Pacific Journal of Tropical Biomedicine,* 2012; **2**: 1583-1587.
19. Huang M, Deng SH, Han QQ, Zhao P, Zhou Q, Zheng SJ. *Front. Pharmacol,* 2016; **7**:288. doi: 10.3389/fphar.2016.00288
20. Ross IA. Medicinal Plants of the world, Chemical constituents, Tradi-tional and Modern Medicinal Uses, Humana Press, Totowa;1999. pp 197-205.
21. Scartezzini P, Speroni E. *Journal of Ethnopharmacology*, 2000; **71**:23-43.
22. Dinneen SF. *Medicine*, 2006; **34**:45-46.
23. Rolo AP, Palmeira CM. *Toxicology and Applied Pharmacology*, 2006; **212**:167-178.
24. Muruganandan S, Srinivasan K, Gupta S. *J Ethnopharmacol*, 2005; **97**:497-501.
25. Miura T, Iwamoto N, Kato M, Ichiki H *et al*. *Biol Pharm Bull*, 2001a; **24**:1091-1092.
26. Miura T, Ichiki H, Hashimoto I, Iwamoto N *et al*. *Phytomedicine*, 2001b; **8**:85-87.
27. Kumar SR, Ray MI, Ujwala M, Borde MK, Deshmukh YA. *Diabetes MetabSyndrObes*, 2016;**9**: 261-272.

28. Sellamuthu PS, Muniappan BP, Perumal SM, Kandasamy M. *J Health Sci*, 2009; **55**:206-214.
29. Sellamuthu PS, Arulselvan P, Fakurazi S, Kandasamy M. *Pak J Pharm Sc,* 2014; **27**:161-167.
30. Bwititi P, Musabayane CT, Nhachi CFB. *Journal of Ethnopharmacology*, 2000; **69**:247-252.
31. Jouad H, Eddouks M, Dubois MA, Lyoussi B. *Journal of Ethnopharmacology*, 2000; **71**:169-177.
32. Saxena A, Vikram NK. *The Journal of Alternative and Complementary Medicine*, 2004; **10**:369-378.
33. Seifried HE, Anderson DE, Fisher EI, Milner JA. *J NutrBiochem,* 2007; **18**(**9**):567-579.
34. Halliwell B. *Free Radical Research Communications*, 1990; **9**:1-32.
35. McCord JM. *Ameri-can Journal of Medicine*, 2000; **108**: 652-659.
36. Diplock AT, Charleux JL, Crozier-Willi G, Kok FG*et al*. *British Journal of Nutrition*, 1998; **80 (Suppl. 1):** 77-112.
37. Mishra B, Indira Priyadarsini K, Sudheerkumar M, Unnikrishhnan MK*et al*. *Radiation Physics and Chemistry*, 2006; **75:** 70-77.
38. Saha S, Sadhukhan P, Sil PC. *Biofactors*, 2016; **42**: 459-474.
39. Bera S, Chaudhuri S, Dutta D. *Indian J Biotechnol*, 2015;**14**: 179-185.
40. Matkovics M, Kotorman IS, Varga D, Quy Hai, Varga C. *Acta Physiologica Hungarica,*1998; **85**:29-38.
41. Sellamuthu PS, Arulselvan P, Kamalraj S, Fakurazi S, and Kandasamy M. *ISRN Pharmacology*, 2013; **2013**: 1-10.
42. Omotayo EO, Gurtu S, Sulaiman SA, Wahab MSA *et al*. *International Journal for Vitamin and Nutrition Research*, 2010; **80**:74-82.
43. Yoshikawa M, Shimoda H, Nishida N, Takada M *et al*. *The Journal of Nutrition,* 2002; **132**:1819-1824.
44. Saleh S, El-Maraghy N, Reda E, Barakat W. *An Acad Bras Cienc*, 2014; **86**:1935-1948.
45. Randle PJ, Garland PB, Hales CN, Newsholme EA. *Lancet,*1963; **1**:785-789.
46. Guo F, Huang C, Liao X, Wang Y *et al*. *Mol Nutr Food Res*, 2011; **55**:1809-1818.
47. Na L, Zhang Q, Jiang S, Du S *et al*. *Sci Rep*, 2015; **5**: 10344.
48. Apontes P, Liu Z, Su K, Benard O *et al*. *Diabetes*, 2014; **63**:3626-3636.
49. Chen C, Kong T. *Trends in Pharmacological Sciences*, 2005; **26**:318-326.
50. Yoshimi N, Matsunaga K, Katayama M, Yamada Y *et al*. *Cancer Letters,* 2001; **163**:163-170.
51. Hara A, Yoshimi N, Niwa M, Ino N *et al*. *Japanese Journal of Cancer Research*, 1997; **88**:600-604.
52. Chattopadhyay U, Das S, Guha S, Ghosal S. *Cancer Letters,*1987; **37**:293-299.
53. Hu X and Moscinski LC. *Cell Prolif*, 2011; **44**:205-211.
54. Peng ZG, Yao YB, Yang J, Tang YL, Huang X. *Genet Mol Res*, 2015; **14**:4989-5002.
55. Yao YB, Peng ZG, Liu ZF, Yang J, Luo J. *Zhong Yao Cai,* 2010; **33**:81-85.
56. du Plessis-Stoman D, du Preez J, van de Venter M. *Afr J Tradit Complement Altern Med*, 2011; **8**:177-184.
57. Kim H, Kim H, Mosaddik A, Gyawali R *et al*. *Food Chem*, 2012; **133**:416-422.
58. Dolcet X, Llobet D, Pallares J, Matias-Guiu X. *Virchows Archiv*, 2005; **446**:475-382.
59. García-Rivera D, Delgado R, Bougarne N, Haegeman G, Berghe WV. *Cancer Lett*, 2011; **305**:21-31.
60. Shi W, Deng J, Tong R, Yang Y *et al*. *Mol Med Rep*, 2016; **13**:3423-3432.
61. Telang M, Dhulap S, Mandhare A, Hirwani R. *Expert Opin Ther Pat,* 2013; **23**:1561-1580.
62. Budihardjo I, Oliver H, Lutter M, Luo X, Wang X. *Annu Rev Cell Dev Biol*, 1999; **15**:269-290.
63. Peng Z, Luo J, Xia L, Chen Y, Song S. *Zhongguo Shiyan Xueyexue Zazhi*, 2004; **12**:590-594.
64. Pan LL, Wang AY, Huang YQ, Luo Y, Ling M. *Asian Pac J Cancer Prev*, 2014;**15**: 7065-7068.
65. Lv J, Wang Z, Zhang L, Wang HL *et al*. *J Anim Vet Adv*, 2013; **12**:352-359.
66. Zou B, Wang H, Liu Y, Qi P*et al*. *Oncol Rep,* 2017; **38**:1431-1441.
67. Kim CY, Ahn MJ, Kim J. *J Liq Chromatogr Relat Technol*, 2006; **29**:869-875.
68. Stoilova I, Gargova S, Stoyanova A, Ho L. *Herbal Polonica,* 2005; **51**:37-44.
69. Maji HS, Maji S, Roy R, Sen A, Biswas T. *JPA*, 2015; **4**:49-56.
70. Rivera DG, Balmaseda IH, Leon AA, Hernandez BC *et al*. *Journal of Pharmacy and Pharmacology*, 2006; **58**:385-392.
71. Jagetia GC, Venkatesha VA. *International Congress Series*, 2005; **1276**:195-196.
72. García D, Escalante M, Delgado R, Ubeira FM, Leiro J. *Phytother Res*, 2003; **17**:1203-1208.