Vitamins & Minerals
ISSN: 2376-1318

Editorial Open Access

Mangiferin - A Nutraceutical with Clinical Implications

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Natural remedies have been used for centuries. A lasting appeal of such remedies seems embedded in the human nature that instinctively associates a human being with other living systems, most often conceived as plants. Worldwide aging of societies also seems to give a boost for search of new potential natural medicines to prevent or slow down the aging process and thus to increase quality of life. Mangiferin, a natural polyphenol, comes in handy at this juncture. Mangiferin is a nutraceutical, a polyphenolic ingredient extracted from the stem bark and leaves of Mango tree (*Mangifera indica* L.), a tropical fruit-bearing plant, with a spate of purported beneficial health effects [1]. It is widely used in Latin America and the Caribbean region for protection against chronic disorders and treatment of acute ailments. Reported benefits of mangiferin range from antioxidant, antiinfectious, antidiabetic, antiatherosclerotic, and cardiovascular effects to enhanced cognitive brain function. No wonder that such a diverse range of conditions is lately reflected in the increasing number of studies being performed on aspects of therapeutic advantages of mangiferin. Since mangiferin has been suggested as a potential neuropharmacotherapeutic [2], we have deemed it worthwhile to investigate its ability to traverse the blood-brain barrier after systemic administration; an issue that was not yet dealt with in the literature. Employing thin-layered chromatography and spectrophotometry we found no traces of mangiferin in brain homogenates obtained from rats after an intraperitoneal injection of a loading dose of 300 mg/kg [3]. Nonetheless, in other studies we found physiological effects of mangiferin, which, albeit pertaining mostly to its peripheral action, may also have to do with central neural effects or integration of peripheral afferent neural inputs. Mangiferin decreases resting respiration and the ventilatory responses to hypoxia that is generated at the sensory organ of the carotid body [4]. Interestingly, this action is evident in the healthy condition, but when the hypoxic ventilatory response is diminished, for instance, in streptozotocin-induced diabetes in the rat, it is reverted back toward the healthy level by mangiferin. Increased respiration is essential for the control of diabetes, as it improves tissue oxygenation hampered by diabetic stagnant hypoxia. Other experimental studies also show antidiabetic activity of mangiferin in that it mitigates hyperglycemia and insulin resistance [5,6].

The predominant mechanism of mangiferin action is its antioxidant and free radical scavenging activity. The antioxidant activity is traceable already in the healthy condition, but it is strikingly amplified in the inflammatory and infectious, including diabetes, states [7,8]. In our studies, mangiferin decreased diabetic-enhanced lipid peroxidation products - thiobarbituric acid reactive substances (TBARS) formed as degradation products of fats - down to the healthy level. Scavenging of reactive oxygen species (ROS) also has to do with mangiferin's iron-chelating property. ROS foster the presence of the biologically active, ferrous Fe^{2+}. Thus, antioxidant activity of mangiferin would counteract the iron-induced free radical formation, Fe^{2+} accumulation and toxicity [8]. Mangiferin shows exceptional antioxidant activity, stronger than cinnamon, and hepatoprotective activity against free radical-induced liver injury in the mouse *in vivo* [4]. It also dose-dependently inhibits inflammatory cytokines, tumor necrosis factor alpha (TNFα), nitric oxide (NO), and NF-κBin *in vitro* and *in vivo* experiments in the mouse [9], which suggests this is the mechanism of anti-inflammatory effects of *M. indica* extracts. Finally, mangiferin shows antiapoptoticaction that protects against glutaminergicexcitotoxicity leading to neuronal death [9,10]. The central effects of mangiferin include the antagonism of sedation induced by reserpine [2], which may explain the time proven traditional use of mangiferin containing extracts as a mood enhancer. It is baffling, however, how mangiferin exerts its central effects, not being able to directly penetrate into the brain. It is tempting to suggest that there are ways, still to be unraveled, of a central functional reflection, for instance due to altered brain metabolism, of peripheral changes induced by redox or chelating properties of a compound.

It is an interesting feature of vitamin and supplement compounds, particularly of the antioxidant genre, that they seem therapeutically inert in the healthy condition. Actually, there is no convincing evidence that such compounds prevent the appearance of diseases in humans, increase longevity and health span, or rejuvenate. However, they assume dedicated beneficial effects in diseased conditions, even not linked to their insufficient level. Vitamin C, an archetype antioxidant, is a case in point, For instance, it inhibits exercise-induced bronchoconstriction [11]. Coenzyme Q10 is of benefit in cardiomyopathy [12]; the examples are many. Mangiferin is here no exception. It has negligible influence on respiration in health, but we found it improved dampened respiration in diabetes and thus may positively affect arterial blood oxygenation. Likewise, mangiferin does not alter normal blood glucose level, but lowers hyperglycemia in diabetes. Such dichotomous effects of antioxidant compounds are not readily explainable. In case of the carotid body-generated hypoxic respiration, the clue may lie in mitochondrial ROS production and their influence on stabilization of hypoxia inducible factor (HIF-1α). ROS are presumed to facilitate HIF-1α stabilization in hypoxia and augment the hypoxic response, which implies a reducing effect on this response of antioxidants. The reversal, in diabetes, may likely have to do with altered mitochondrial metabolism and changes in ROS-HIF-1α interaction, an area of limited understanding.

A note of caution is in place concerning the medicinal use of antioxidant vitamins and nutraceuticals to combat enhanced ROS production. As above mentioned, antioxidants have no conclusively proven preventive or therapeutic effects, but ROS, in certain situations, do have it. Physical exercise that transiently increases ROS formation is one such example, with its proven benefits on muscle metabolism or glucose control. Moreover, evidence accumulates that antioxidants may actually mitigate these positive ROS-involving effects.

Antioxidant nutraceuticals should just be used judiciously, not to oppose the advantageous influence expected. In this regard, mangiferin is lucky, as it enjoys the benefit of no known toxicity, for the time being

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Received October 15, 2013; **Accepted** October 24, 2013; **Published** October 27, 2013

Citation: Pokorski M (2013) Mangiferin - A Nutraceutical with Clinical Implications. Vitam Miner 3: e122.

that is, let alone tastes very good if consumed in the form of Mango fruit.

Mangiferin has got a clear pharmacological potential. Understanding the underlying mechanisms of mangiferin action offers opportunities for the rational development of new preventive and therapeutic interventions. Mangiferin holds promise to this end and deserves further scientific scrutiny.

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