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Review

Neuroprotective effects of chrysin: From chemistry to medicine

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ABSTRACT

The World Health Organization estimated that the proportion of older people (over 60 years) will increase from 11% to 22% during next 40 years throughout the world. With respect to this, the morbidity and mortality rates of age-related diseases will increase. Mental diseases are the most common and important health problems among elderly people. Therefore, much attention has been paid to the discovery of neuroprotective drugs with high efficacy and negligible adverse effects. A growing body of scientific evidence has shown that phytochemicals possess neuroprotective effects and also mitigate neurodegeneration under both *in vivo* and *in vitro* conditions. Polyphenolic compounds, especially flavonoids, are known as most common chemical class of phytochemicals which possess a multiple range of health promoting effects. Chrysin, belonging to the flavone class, is one of the most important bioactive constituents of different fruits, vegetables and even mushrooms. Chrysin possesses potent neuroprotective effects and suppress neuroinflammation. In addition, chrysin improves cognitive decline and possesses a potent anti-amyloidogenic and neurotrophic effects. Furthermore, beneficial effects of chrysin on both depression and epilepsy have been reported. The present paper aimed to critically review the available literature data regarding the neuroprotective effects of chrysin as well as its chemistry, sources and bioavailability.

Contents

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1. Introduction

Flavonoids are the largest group of plant secondary metabolites with immense biological activities desired for human health. The research on flavonoids has been going on with growing interest as they act through physiological mechanisms and a large number of signalling pathways involved in many diseases. It has been estimated that the dietary flavonoid intake varies between 50 and 800 mg per day or greater, if dietary supplements are administered (Pietta, 2000). Among them, chrysin is a hydroxylated flavone derivative mainly found in honey, propolis and many plant species e.g. *Pelargonium crispum* (P.J. Bergius) L Her., *Passiflora incarnata* L., *Oroxylum indicum* (L.) Vent., *Scutellaria immaculata* Nevski ex Juz., *Scutellaria ramosissima* M. Pop., *Desmos cochinchinensis* Lour., *Cytisus multiflorus* (L'Her. Ex Aiton) Sweet., *Centaurea omphalotricha* (Batt.) Willk., *Lactarius deliciosus* (L. ex Fr.) S.F. Gray., *Suillus bellinii* (Inzenga) Watling., *Passiflora caerulea* L. (Bajgai et al., 2011; Escuredo et al., 2012; Mamadalieva et al., 2011; Mouffok et al., 2012; Pasini et al., 2013; Pereira et al., 2012; Sobočanec et al., 2006; Sulaiman et al., 2011; Williams et al., 1997; Yan et al., 2011). Previous studies have evaluated the concentrations of chrysin in several honeys. The chrysin content is 0.10 mg/kg in honeydew honey, and 5.3 mg/kg in forest honeys (Hadjmohammadi et al., 2010). Another study showed that the chrysin content in propolis is as high as 28 g/L (Pichichero et al., 2010). Individual chrysin content in a variety of mushrooms from the island of Lesvos, Greece ranged between 0.17 mg/kg in L. deliciosus to 0.34 mg/kg in *S. bellinii* (Kalogeropoulos et al., 2013).

Chrysin has been shown to be a very active flavonoid exerting a vast number of pharmacological properties such as anti-inflammatory activity *via* blocking histamine release and pro-inflammatory cytokine expression (Bae et al., 2011), anti-asthmatic activity through suppression of inducible nitric oxide synthase (iNOS) and nuclear factor-κB (NF-κB) (Wadibhasme et al., 2011), anticancer activity by endorsing the cell death induced by tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and increasing TRAIL-induced degradation of caspases 3 and 8 (Li et al., 2011), inhibition of histone deacetylase (Sun et al., 2012) and DNA topoisomerases (Russo et al., 2012), suppressive effect on vascular endothelial growth factor (VEGF)-induced angiogenesis (Tian et al., 2014), preventing metastatic progression in breast cancer cells (Lirdprapamongkol et al., 2013), inhibition of TNF-α and interleukin (IL)-1β (Bai et al., 2013), anti-hypercholesterolemic activity (Anandhi et al., 2013), cardioprotective activity *via* improving post-ischaemic functional recovery (Testai et al., 2013), prevention of osteoporosis by activation of estrogen receptor (ER)/mitogen activated protein kinase (MAPK) (Zeng et al., 2013), and renoprotective activity by glucose-induced renal tubular cell migration with diminishing matrix metalloproteinase (MMP)-2 activity (Kang et al., 2015). In addition to all these pharmacological effectiveness of chrysin, it has also been shown to possess neuroprotective activity acting through various mechanisms. However, unlike other flavonoids, the therapeutic benefits of chrysin remains nascent in current literature due to issues with bioavailability and absorption. Consequently, the target of the current review is to articulate neurological potential of chrysin particularly referring to neuroinflammation, antidepressant, anti-epileptic, anti-amyloidogenic, anti-atherogenic effects as well as its chemistry and bioavailability.

2. Chemistry & occurrence

Chrysin (5,7-dihydroxyflavone or 5,7-dihydroxy-2-phenyl-4H-chromen-4-one) belongs to the flavone class of the ubiquitous 15-carbon skeleton natural polyphenolic compounds collectively called flavonoids. The characteristic feature of flavones as evidenced in chrysin is the presence C2-C3 double bond in ring C and the lack of oxygenation at C-3 (Fig. 1). Unlike many flavonoids that possess either one (most commonly at C-4′) or two hydroxy (C3′,C4′-diortho hydroxyl) functional group in ring-B, chrysin lacks oxygenation in this ring. Other natural derivatives of chrysin arise due to diversity in ring-A oxygenation as exemplified by the common natural biologically important flavonoids such as wogonin, oroxylin A and baicalein (Fig. 1).

Fruits and vegetables are the main dietary sources of flavonoids. Due to the presence of these compounds, health benefits are ascribed to vegetable foods when they are consumed on regular basis. Flavonoids are also present in many medicinal plants and account for the different pharmacological benefits reported to date. Chrysin and its derivatives have been shown to be the principal constituents of the well-known medicinal plant, *Radix scutellariae* (Tong et al., 2012). Other common sources of chrysin, which attracted much scientific attention in recent years from the pharmacological point of view, are propolis and/or honey (Bertoncelj et al., 2011; Sobočanec et al., 2006; Volpi and Bergonzini, 2006). Moreover, many fruits (Chen et al., 2014), passion flowers such as *P. caerulea* L (Wolfman et al., 1994) and even mushrooms (e.g. oyster mushroom, *Pleurotus ostreatus*; Anandhi et al., 2013) are known to be good sources of chrysin. While chrysin-containing plants have been widely used for medicinal purposes, synthetic chrysin is used for large scale uses. The range of different methods for chrysin synthesis has been growing over recent years (e.g. Man et al. (Liu et al., 2014)) and gram quantities of this compound can be purchased from commercial sources at a reasonable price.

3. Structure-activity relationships

The chemical properties of chrysin, due to B and C-ring lack of oxygenation, are associated with a number of pharmacological activities that range from antioxidant to anticancer effects (Habtemariam, 1997). However, differences in the chemical structure of flavones has been shown to influence the antioxidant activity, and the inhibitory effect on the expression of the pro-inflammatory enzyme cyclooxygenase-2 (Cox-2). For instance, luteolin, an equally important flavone, demonstrated greater Cox-2 inhibition than chrysin (Harris et al., 2006). This has been attributed to chrysin's lack of 3′,4′ hydroxylation on the “B” ring. Ko et al. showed that 2′ or 4′ B ring hydroxylation was necessary for the inhibition of phorbol ester-induced Cox-2 expression by flavanones (Ko et al., 2002). Similarly, Hou et al. demonstrated that an ortho-hydroxyl group is a requirement for the inhibition of LPS-induced Cox-2 expression in RAW 264.7 cells by anthocyanins (Hou et al., 2005).

As well, luteolin, which possesses 3′,4′ hydroxylation exhibits