A review on the pharmacological effects of vitexin and isovitexin

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Article history:
Received 13 June 2016
Received in revised form 14 September 2016
Accepted 26 September 2016
Available online 28 September 2016

Keywords:
Vitexin
Isovitexin
Pharmacological activities
Traditional Chinese medicine

ABSTRACT

Vitexin and isovitexin are active components of many traditional Chinese medicines, and were found in various medicinal plants. Vitexin (apigenin-8-C-glucoside) has recently received increased attention due to its wide range of pharmacological effects, including but not limited to anti-oxidant, anti-cancer, anti-inflammatory, anti-hyperalgesic, and neuroprotective effects. Isovitexin (apigenin-6-C-glucoside), an isomer of vitexin, generally purified together with vitexin, also exhibits diverse biological activities. Latest research has suggested that vitexin and isovitexin could be potential substitute medicines for diversity diseases, and may be adjuvants for stubborn diseases or health products. This review summarized recent findings on various pharmacological activities and associative signalling pathways of vitexin and isovitexin to provide a reference for future research and clinical applications.

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Chemical compounds referred in this article

Vitexin (PubChem CID: 5,280,441)

1. Introduction

Vitexin (apigenin-8-C-glucoside), referred to as ‘Mujingsu’ in Chinese, is an active component found in many traditional Chinese medicine. It is a c-glycosylated flavone (Fig. 1 A), and was found in various medicinal plants such as pearl millet [1], hawthorn [2], pigeon pea [3, 4], mung bean [5], mosses [6,7], Passiflora [8,9], bamboo [10,11], mimosa [12], wheat leaves [13], and chaste tree or chasteberry [14] in seeds [15], fruits [14,16], flowers [17], leaves [18], roots [19], etc. Since flavonoids tend to show multiple pharmacological activities [20], vitexin has recently received increased attention due to its wide range of pharmacological effects, including anti-cancer [21,22], anti-oxidant [23–25], anti-inflammatory [26–28], anti-nociceptive [24,29,30], anti-AD (AD, Alzheimer’s disease) [31], anti-hypertensive [32], anti-spasmodic [33,34], anti-hypoxia/ischemia injury [35], anti-depressant-like actions [36] and anti-viral [37,38] activities. The effects are linked to multiple systems such as the central nervous system, the heart and vascular system, the endocrine system, etc. For instance, vitexin exerts neuroprotective effect against pentylenetetrazole-induced seizures, scopalamine-induced memory impairment, and glutamate-induced neuronal excitotoxicity in vitro and in vivo [39–41].

Isovitexin (apigenin-6-C-glucoside), (Fig. 1 B), an isomer of vitexin, containing a 6-C-glycoside comparing to 8-C-glucoside in vitexin, is found in plants containing vitexin such as pigeon pea [3,4], Passiflora [8,9], bamboo [10], mimosa [12], wheat leaves [13], and screened as a bioactive integrant as well. Isovitexin has also been proved to have various activities, such as anti-oxidant [12], anti-inflammatory [42,43], anti-AD [31] effects and so on. According to the current knowledge, vitexin exerts similar pharmacological effects with vitexin, partly due to their similar chemical structure.

However, limited knowledge on their side-effects and metabolism process, as well as complicate pharmacological actions and molecular mechanisms, majority of the current research is still pre-clinical. This review provides a comprehensive summary of the pharmacological actions and mechanisms of vitexin and isovitexin, as well as a brief overview of their pharmacokinetic studies, to provide a reference for further clinical applications.

2. Phytochemical features of vitexin and isovitexin

2.1. Chemical features of vitexin and isovitexin

Flavones are a class of flavonoids, which name after their common yellow colour, that is, flavus. Flavones are based on the backbone of 2-phenylchromene-4-one (2-phenyl-1-benzopyran-4-one) (flavone). Apigenin (4’,5,7-trihydroxyflavone) is one of typical natural flavones.

Vitexin and isovitexin, whose structures are shown in Fig. 1, belong to the class of flavones and are as derivatives of apigenin with 8-/6-C-glucoside. Chemical properties of vitexin and isovitexin are similar. Vitexin is chemically known as 8-b-D-glucosyl-4’,5,7-trihydroxy-flavone, or apigenin-8-C-glucoside, with molecular formula C21H20O10, and molecular weight 342.3775 g/mol. Different from vitexin, isovitexin, as an isomer of vitexin, has a 6-C-glucosyl. In plants, such as Lemma minor, vitexin was found converting to isovitexin, rather than the reverse direction, demonstrating that a biosynthetic route to isovitexin is via vitexin [44]. As shown in Fig. 1, vitexin and isovitexin both totally have seven hydroxyls which may contribute to their bioactivities, especially the o-dihydroxyl structure in the A ring which was proven to contribute to the effective radical scavenger in flavonoids [45] and the stable radical order of hydroxyl in vitexin was found to be 4’-OH > 7-OH > 5-OH [46]. Investigated in gas phase using density functional theory (DFT) approach with B3LYP/6-311G(d,p) level of theory and analysed using bond dissociation enthalpy (BDE), the structural and molecular characteristics of vitexin was more comprehensible, and enrich the understanding of flavonoids [46]. Except for the common sense of flavones, the C-glucoside of vitexin, whose stability is higher than that of O-glycosiders, may also exert influence. Compared with apigenin, BDE for 4’-OH, 5-OH and 7-OH are lower for vitexin by 0.75 kcal/mol, 0.79 kcal/mol and 2.3 kcal/mol, which may due to its presence of C-8 glucoside via decreasing the negative charge on the oxygen atom at C-3. Consequently, enhance anti-oxidant potency of vitexin [46]. Except for theory studies, the conditions of chemical reactions need to be compared in respect of reaction rate, reaction temperature, yield and so on. Of concern is that anti-oxidant and anti-diabetes potential of C-glycosylflavonoids was showing higher than their corresponding O-glycosylflavonoids and aglycones in most cases [47], which points out one of the significance of researches on vitexin and isovitexin in a sense.

2.2. Plant resources distribution

Vitexin was found in various medicinal plants, such as pearl millet [1], hawthorn [2], pigeon pea [3,4], mung bean [5], mosses [6,7], Passiflora [8,9], bamboo [10,11], mimosa [12], wheat leaves [13], and chaste tree or chasteberry [14]. Mainly plant source of vitexin so far is hawthorn leaves [2,48], in which vitexin content is showing in Table 1, as well as concentration of isovitexin in some species.

3. Toxicity

As candidates of promising drugs, it is vital to examine safety of vitexin and isovitexin to human body. Until now, plenty of studies in vitro and in vivo have focused on the safety of vitexin, but very rare on isovitexin. Vitexin presents no cytotoxicity (IC50 > 200 μg/ml) in vitro [26]. In vivo, studies on Ficus deltoidea leaf extract, which contains high levels of vitexin and isovitexin, showed no significant acute and sub-chronic toxicity and genotoxicity [60]. Furthermore, regarding the liver and gastric mucosa injuries, even repeated treatment with high

![Fig. 1. Chemical structures of (A) vitexin, (B) isovitexin.](image-url)