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Research review paper

Verbascoside — A review of its occurrence, (bio)synthesis and pharmacological significance

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ABSTRACT

Phenylethanoid glycosides are naturally occurring water-soluble compounds with remarkable biological properties that are widely distributed in the plant kingdom. Verbascoside is a phenylethanoid glycoside that was first isolated from mullein but is also found in several other plant species. It has also been produced by *in vitro* plant culture systems, including genetically transformed roots (so-called 'hairy roots'). Verbascoside is hydrophilic in nature and possesses pharmacologically beneficial activities for human health, including antioxidant, anti-inflammatory and antineoplastic properties in addition to numerous wound-healing and neuroprotective properties. Recent advances with regard to the distribution, (bio)synthesis and bioproduction of verbascoside are summarised in this review. We also discuss its prominent pharmacological properties and outline future perspectives for its potential application.

Contents

Treasure from the garden: the discovery of verbascoside, and its occurrence and distribution

Phenylethanoid glycosides are naturally occurring water-soluble compounds that are widely distributed in the plant kingdom, most of which are isolated from medicinal plants. Structurally, they are characterised by cinnamic acid (C_6–C_3) and hydroxyphenylethyl (C_6–C_2) moieties that are attached to a β-glucopyranose (apiose, galactose, rhamnose, xylose, *etc.*) *via* a glycosidic bond (Dembitsky, 2005; Jimenez and Riguera, 1994). In recent years, interest has been growing regarding aromatic compounds, and phenylethanoid glycosides in particular, because of the significantly increasing volume of literature describing their evident role in the prevention and treatment of various human diseases and disorders.

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There are conflicting reports in the literature regarding the designation of verbascoside. In 1963, scientists from Italy reported the isolation of a phenylethanoid glycoside from mullein (*Verbascum sinuatum* L.; Scrophulariaceae), which they called verbascoside (Fig. 1; Scarpati and Monache, 1963). However, no data describing its structural elucidation was given. Several years later, the same compound was isolated from flowers of the common lilac (*Syringa vulgaris*, Oleaceae), and the structure was determined to be 2-(3, 4-dihydroxyphenyl)ethyl-1-*O*-α-L-rhamnopyranosyl-(1→3)-(4-*O*-*E*-caffeoyl)-β-D-glucopyranoside, which the authors named acteoside (Birkofer et al., 1968). Twenty years after the first report on verbascoside, Sakurai and Kato (1983) reported the isolation of a new phenylethanoid glycoside from the glory tree (*Clerodendron trichotomum* Thunb, Lamiaceae) that was named kusaginin by the authors. While isolating verbascoside from the greater broomrape (*Orobanche rapum-genistae*, Orobanchaceae), Andary et al. (1982) discovered that it is identical to the previously reported acteoside and recommended that this later name be no longer used. Currently, 50 years after the discovery of verbascoside, confusion still exists with regard to its name to a certain degree. A search of the Scopus database (accessed January 2014) pulled out 543 available hits under 'verbascoside' and 844 hits under "acteoside", while a search using the paired terms 'verbascoside AND acteoside' returned only 326 articles. To prevent any further confusion, we highly recommend that either verbascoside or acteoside be primarily used; however, the other name should also be supplied in the article's abstract or keyword list.

Verbascoside is among the most widespread of the disaccharide caffeoyl esters. To date, verbascoside has been mainly detected in the *Verbascum* species (Alipieva et al., 2014) but has also been found in more than 200 plant species (Deepak et al., 1999; Schlauer et al., 2004; Taskova et al., 2005) belonging to 23 plant families (Fig. 2) in addition to others that were recently reported, such as *Buddleja brasiliensis* (Filho et al., 2012), *Striga asiatica* (Huang et al., 2013), *Olea europea* (Quirantes-Piné et al., 2013b), *Paulownia tomentosa* var. *tomentosa* (Si et al., 2013), *Lippia javanica*, *Lantana camara* (Oyourou et al., 2013), and *Lippia citriodora* (Bilia et al., 2008; Funes et al., 2009; Quirantes-Piné et al., 2009).

Verbascoside has been detected in both underground (*e.g.*, primary and secondary roots) and above-ground (*e.g.*, stems, leaves and flowers) parts of plants but at widely varying levels. For example, the roots of *Sideritis trojana* accumulate verbascoside at 0.002% (Kirmizibekmez et al., 2012), while in the aerial parts of *Verbascum xanthophoeniceum* its concentration is much higher (0.25%; Georgiev et al., 2011a). In a recent nuclear magnetic resonance (NMR)-based metabolomics study, it was found that verbascoside content varies within the plant species of the same genus; from 0.2% in *V. phoeniceum* up to 3% in *Verbascum nigrum* (Georgiev et al., 2011b). On the other hand, verbascoside content in roots (0.9%) and inflorescences (0.8%) was comparable (Gómez-Aguirre et al., 2012). Another potentially valuable source of verbascoside includes industrial by-products. For example, olive mill waste that was obtained as a by-product from the processing of olive fruit was found to contain abundant amounts of verbascoside in addition to several other phenolic compounds (*e.g.*, oleuropein, hydroxytyrosol, caffeic acid and some flavonoids; Obied et al., 2007). Verbascoside was reported to be abundant in olive mill wastewater (De Marco et al., 2007). Although more detailed research is needed, olive mill wastewater could be considered to be a potential source of verbascoside (and concomitant bioactive molecules) that are suitable for applications involving dietary supplements and food (Cardinali et al., 2012).

Biological effects of verbascoside underlying its potential clinical utility

Traditionally, plants with high concentrations of verbascoside have been used in folk medicine to treat inflammation and microbial infections (Georgiev et al., 2012). Therefore, investigations into its anti-microbial and anti-fungal activities have been conducted over the course of many years. In general, these studies may be regarded as purely observational because they lack any mechanistic approaches (Arruda et al., 2011; Avila et al., 1999; Pendota et al., 2013). Recent studies of seven compounds that were isolated from the *Lippia* species have confirmed the very high anti-*Cryptococcus neoformans* activities of verbascoside, which the authors interpreted to be promising for new selective anti-fungal verbascoside-containing drugs (Funari et al., 2012). The combination of anti-bacterial, anti-inflammatory and anti-androgen effects of pure verbascoside and plant extracts with their high concentrations (*Camellia sinensis* and *Commiphora mukul*) show promise in the development of pharmacological treatments for acne vulgaris (Azimi et al., 2012).

Mechanisms of anti-inflammatory effects of verbascoside on skin, endothelium, intestine and lungs

Early reports describing the anti-inflammatory effects of verbascoside have focused on the inhibition of histamine and arachidonic acid release from mast cells (Lee et al., 2006a). The inhibitory activity of verbascoside depends on the presence of Ca^{2+} and correlates with the verbascoside-associated inhibition of phospholipase A2 (Song et al., 2012). Mechanistic studies have been carried out recently, revealing that verbascoside down-regulates Ca^{2+}-dependent MAPK signalling in basophilic cells (Motojima et al., 2013). It appears to become involved in the inhibition of type I allergies. Glycosylated phenylethanoids, which are constituents of *Anisomeles indica*, exhibit profound anti-inflammatory activities towards macrophages that are stimulated by LPS and IFN-γ. In particular, 40 μM verbascoside has been shown to strongly inhibit NO, TNF-α and IL-12 production (Rao et al., 2009). The anti-inflammatory and anti-irritant activities of verbascoside from *Kigelia africana* have been attributed to its ability to inhibit inducible nitric oxide synthase (iNOS) and NO release from macrophages as stimulated by bacterial lipopolysaccharides (Picerno et al., 2005). The inhibition of iNOS *in vitro* and *in vivo* by a water-soluble extract of *Wendita calysina* leaves was attributed to

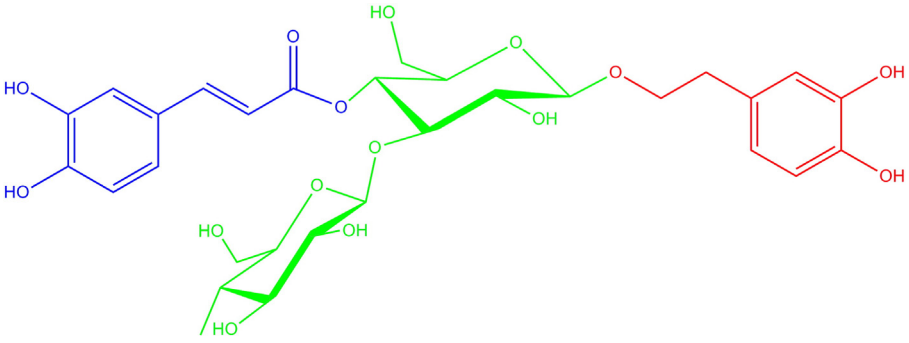

Fig. 1. Chemical structure of verbascoside. Phenylethanoid (in red) and caffeic acid (in blue) moieties attached to α-rhamnopyranosyl-β-glucopyranose (in green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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