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SHORT COMMUNICATION



## Madeira moneywort (*Sibthorpia peregrina* L.) as a new source of verbascoside and its derivatives with potential phyto-pharmaceutical applications

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### ABSTRACT

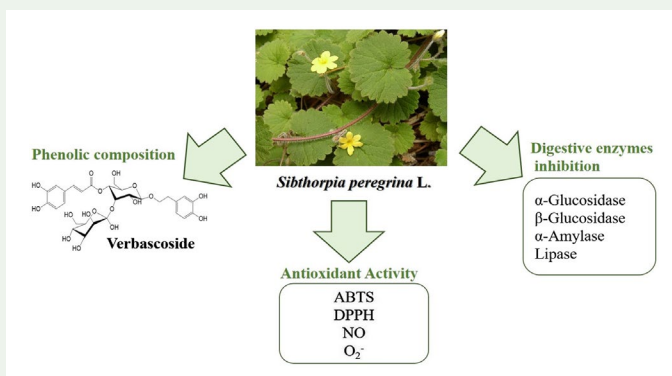
The qualitative and quantitative characterization of Madeira moneywort (*Sibthorpia peregrina* L.) compounds was investigated for the first time. The antioxidant activity and the effect of the methanolic extract on digestive enzymes activity linked to type-2 diabetes and obesity were also determined by *in vitro* assays. A total of 56 components were characterized in *S. peregrina*. Phenylethanoids glycosides (PhEGs) represented the main classes of compounds (95.23 mg g<sup>-1</sup> of dry extract), almost all verbascoside and its derivatives (up to 98.85% of the total individual phenolic content). The analysed sample was active against ABTS, DPPH, nitric oxide and superoxide radicals, suggesting a potential beneficial effect against oxidative stress. In addition, the methanolic extract was able to inhibit the catalytic activity of  $\alpha$ -,  $\beta$ -glucosidases,  $\alpha$ -amylase and pancreatic lipase. Overall, *S. peregrina* showed good perspectives to be explored as a rich source of verbascoside and its derivatives for nutraceutical/ pharmaceutical products.

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## 1. Introduction

Verbascoside (also known as acteoside or kusagin) (Figure S1) has been shown to possess extensive beneficial effects on human health, namely antioxidant, anti-inflammatory and antimicrobial in addition to wound-healing, photo-, hepato- and neuroprotective properties (He et al. 2011; Alpieva et al. 2014). Due to its low side effects and toxicity, this molecule is very promising for development of phyto-pharmaceuticals (Funes et al. 2009; He et al. 2011).

Madeira moneywort (*Sibthorpia peregrina* L.; Plantaginaceae) locally known as 'erva terrestre' or 'erva redonda' it is a low creeping perennial herb endemic to Madeira archipelago (Portugal). Hot infusions and decoction of its leaves were used in folk medicine for relieving cough and as an expectorant (Rivera and Obón 1995). Despite its medicinal use, its phytochemical composition remains unknown. Verbascoside has been reported as the main compound in the *Sibthorpia* genera (Taskova et al. 2006). Therefore, the main goal of this work was to determine the polyphenolic profile of *S. peregrina* leaves. Additionally, the *in vitro* antioxidant and digestive enzymes inhibitory activities of methanolic extract were assessed.

## 2. Results and discussion

### 2.1. Phytochemical characterization

Among the 56 compounds identified by HPLC-ESI/MS<sup>n</sup>, there were 34 phenylethanoid glycosides (PheGs) (in particular verbascoside derivatives), 10 phenolic acids, 3 flavonoids and 8 other phytochemicals (lignans, fatty acids, and saccharides) (Table S1 and Figure S2).

### 2.2. Quantification of main polyphenols

Results showed that PhEGs were the dominant phenolic group (99.19% of TIPC) of *S. peregrina*, adding up to 96 mg. g<sup>-1</sup> DE, mainly verbascoside I (84.89% of TIPC) (Table 1 and Supplementary Material). By comparison, *Penstemon barbatus* and *Plantago* spp. (Plantaginaceae) and *S. europaea* showed lower verbascoside contents (6 – 27.49 mg g<sup>-1</sup> DE) (Taskova et al. 2006; Xie et al. 2012; Gonçalves et al. 2015). *S. africana* had superior amounts of verbascoside (540 mg g<sup>-1</sup> DE) (Taskova et al. 2006), but it only corresponded to 18% of polyphenolic contents. So, *S. peregrina* emerges as an interesting alternative source for extraction of verbascoside and its derivatives, since the high percentage of these compounds ( $\approx$  99% of TIPC) in the analysed extract facilitates the process of isolation and purification from the mixture.

### 2.3. In vitro antioxidant activities

*S. peregrina* extract showed interesting antiradical activities (Table 2). In fact, it was more effective than two well-known verbascoside-rich plants, *Plantago* spp. (0.27 – 0.78 mmol TE g<sup>-1</sup> DE) (Gonçalves et al. 2015) and *Lippia citrodora* (1.15 mmol TE g<sup>-1</sup> DE) (Funes et al. 2009) towards ABTS and DPPH radicals, respectively. This could be due to their lower verbascoside contents which, in both cases is a small percentage of complex mixtures (Supplementary Material). The inhibition of NO and O<sub>2</sub><sup>-</sup> (Table 2) is more biologically relevant than that of non-biological radicals, being indicative of the potential of *S. peregrina* to prevent oxidative damage (Harput et al. 2012). The obtained results (Table 2) are assumedly due to the high

**Table 1.** Quantification (mg g<sup>-1</sup> of dry extract) of main polyphenols present in *S. peregrina* methanolic extract by HPLC-DAD.

No.	[M-H] <sup>-</sup>	Assigned identification	Content
<i>Hydroxycinnamic acids</i>			
2	353	Caffeoylisocitrate	0.15 ± 0.01
7	487	Caffeic acid- <i>O</i> -rutinoside	0.27 ± 0.01
8	493	Coumaric acid derivative	0.08 ± 0.01
9	353	4- <i>O</i> -Caffeoylquinic acid	0.05 ± 0.01
Total			<b>0.55 ± 0.01</b>
<i>Flavones</i>			
17	593	Vicenin-2	0.22 ± 0.01
Total			<b>0.22 ± 0.01</b>
<i>Phenylethanoids</i>			
6	643	Verbascoside derivative	0.07 ± 0.01
15	641	Verbascoside derivative	0.08 ± 0.01
20	639	β-Hydroxyverbascoside	0.88 ± 0.01
21	639	β-Hydroxyverbascoside	0.80 ± 0.03
23	785	Echinacoside II	0.16 ± 0.01
28	653	Campneoside	0.32 ± 0.01
29	769	Poliumoside I	7.81 ± 0.07
30	623	Verbascoside I	81.50 ± 0.70
37	623	Verbascoside IV	1.98 ± 0.04
38	753	Forsythoside B I	0.42 ± 0.01
44	637	Eukovoside I	0.35 ± 0.01
50	667	Verbascoside derivative	0.06 ± 0.01
55	623	Verbascoside VI	0.50 ± 0.01
56	623	Verbascoside VII	0.29 ± 0.01
Total			95.23 ± 0.89
<b>TIPC</b>			<b>96.01 ± 0.67</b>

Notes: Data represent the mean ± standard deviation ( $n = 3$ ). Bold values represent the sum of each type of components.

**Table 2.** *In vitro* antioxidant and digestive enzymes inhibitory activities of *S. peregrina*.

Antioxidant activity <sup>a</sup>	ABTS <sup>+</sup>	DPPH	NO	O <sub>2</sub>
<i>S. peregrina</i>	3.74 ± 0.13	0.93 ± 0.03	0.49 ± 0.02	0.40 ± 0.01
Enzyme inhibition <sup>**</sup>	α-Glucosidase	β-glucosidase	α-Amylase	Lipase
<i>S. peregrina</i>	1.56 ± 0.06 <sup>c</sup>	1.15 ± 0.05 <sup>b</sup>	4.79 ± 0.14 <sup>b</sup>	2.31 ± 0.13 <sup>b</sup>
Acarbose	0.12 ± 0.01 <sup>b</sup>	–	0.02 ± 0.01 <sup>a</sup>	–
1-Deoxynojirimycin	0.01 ± 0.01 <sup>a</sup>	0.45 ± 0.02 <sup>a</sup>	–	–
Conduritol B epoxide	–	8.94 ± 0.19 <sup>c</sup>	–	–
Orlistat	–	–	–	0.47 ± 0.02 <sup>a</sup>

Notes: Data represent the mean ± standard deviation ( $n = 3$ ).

Means in the same column not sharing the same letter are significantly different at  $p < 0.05$  probability level.

<sup>a</sup>Results expressed as mmol TE g<sup>-1</sup> of dry extract.

<sup>\*\*</sup>Results expressed as the IC<sub>50</sub> value (mg mL<sup>-1</sup>).

content of verbascoside and its derivatives. Previous works (Funes et al. 2009; Harput et al. 2012; Timóteo et al. 2015; Mihailovic et al. 2016) had similar observations. Several *in vitro* and *in vivo* studies have demonstrated the powerful antioxidant effects of verbascoside by scavenging of biological free radicals, metal chelation activities, cellular protection against oxidizing agents, inhibition of lipid peroxidation and hemolysis of erythrocytes, and enhancement of endogenous antioxidant defenses (Funes et al. 2009; He et al. 2011; Cardinali et al. 2012; Alipieva et al. 2014; Gonçalves et al. 2015; Mihailovic et al. 2016). The four hydroxyls at the *ortho* position (catechol groups) in the two aromatic rings of verbascoside are the main responsible for its remarkable antioxidant activities (Alipieva et al. 2014).

## 2.4. *In vitro* digestive enzymes inhibition assays

Inhibition of intestinal digestive enzymes, linked to sugar and fat metabolism, is recognized as an efficient therapeutic strategy to prevent diabetic complications and weight gain (Liu et al. 2014; Wu et al. 2014). Previously (Liu et al. 2014; Wu et al. 2014, 2017), verbascoside and other PhEGs were described as effective inhibitory agents of  $\alpha$ -glucosidase and pancreatic lipase (PL). Therefore, the inhibitory potential of *S. peregrina* against key digestive enzymes linked to type-2 diabetes and obesity was evaluated. *S. peregrina* effectively inhibited targeted enzymes (Table 2), although positive controls displayed higher activities ( $p < 0.05$ ). Caffeic and chlorogenic acids are strong glucosidases inhibitors (Xiao et al. 2013). Considering the verbascoside structure (Figure S1), it can be inferred that the presence of a caffeic acid moiety has a key role in the obtained results (Table 2). Structure–activity studies showed also that the presence of two catechol groups in verbascoside (Figure S1) is determinant for its strong binding affinities and inhibition for PL (Wu et al. 2014, 2017). In fact, increasing the number of phenolic groups in PhEGs remarkably improves the binding with PL (Wu et al. 2017). The hydrogen bonding interactions (non-covalent) between the catechol groups of verbascoside and the polar groups of PL are important for protein conformational change, thus affecting the enzyme catalytic activity (Wu et al. 2014, 2017). These results demonstrate the potential hypoglycemic and hypolipidemic effects of verbascoside-rich plant extracts and their application in the prevention/control of type II diabetes and obesity.

## 3. Experimental

The methodologies used in this work are described in detail in Supplementary Material.

## 4. Conclusions

The present work demonstrated that verbascoside and its derivatives are the most abundant compounds of *S. peregrina* extract. Based on the displayed *in vitro* antiradical scavenging properties, *S. peregrina* might potentially prevent chronic pathologies associated with oxidative stress. In addition, the methanolic extract exhibited moderate inhibitory effects against digestive enzymes linked to sugars and fats metabolism. These results provide a valuable foundation for further research on this species as potential novel source of easily purifiable verbascoside with pharmacologic perspectives. Nevertheless, the effects of *S. peregrina* in cell-based models and animal experiments need further research in order to validate its potential bioactivities.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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