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SHORT COMMUNICATION

Secondary metabolites from the aerial parts of *Sideritis germanicopolitana* and their *in vitro* enzyme inhibitory activities

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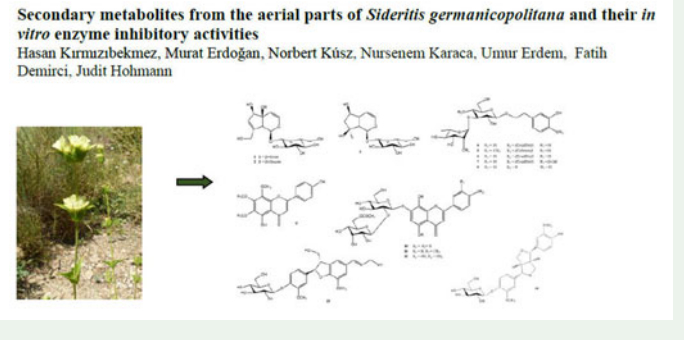
ABSTRACT

Three iridoid glycosides, 5-allosyloxy-aucubine (**1**), melittoside (**2**), ajugol (**3**), five phenylethanoid glycosides, verbascoside (**4**), martynoside (**5**), leucoseptoside A (**6**), lamalboside (**7**), decaffeoyl-verbascoside (**8**), four flavonoids, xanthomicrol (**9**), isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (**10**), 4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (**11**), 3′-hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (**12**), and two lignan glycosides dehydrodiconiferylalcohol 4-*O*-β-D-glucopyranose (**13**) and pinoresinol 4′-*O*-β-glucopyranoside (**14**) were isolated from the aerial parts of *Sideritis germanicopolitana*. Their structures were determined on the basis of detailed NMR and HRESIMS analyses. To our knowledge, all compounds are being reported for the first time from *S. germanicopolitana*, while the isolated lignans (**13** and **14**) are new for the genus *Sideritis*. *In vitro* evaluation of AChE, BChE and LOX inhibitory effects of all the tested compounds (**1**–**14**) resulted in low to moderate activities.



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1. Introduction

The genus *Sideritis* (Lamiaceae) contains around 150 aromatic species distributed mainly in the Mediterranean basin (Huber-Morath 1982; Fraga 2012). The aerial parts of some *Sideritis* species are used to prepare infusions and decoctions for the treatment of gastritis, gastric ulcer, inflammations of mucous membrane as well as against common cold and flu in the traditional medicines of Mediterranean countries, including Turkey, Spain and Greece (González-Burgos et al. 2011; Sağır et al. 2017). Previous bioactivity studies on the extracts or secondary metabolites of several *Sideritis* species revealed their antioxidant, antiulcerogenic, antiproliferative, antimicrobial, analgesic, anti-inflammatory, antinociceptive and anticholinesterase activities (Güvenç et al. 2010; González-Burgos et al. 2011; Halfon et al. 2013; Tóth et al. 2017). The phytochemical composition of the genus is mainly represented by flavonoids, phenylethanoid glycosides, iridoid glycosides, diterpenes and volatile principles (González-Burgos et al. 2011; Fraga 2012; Kırmızıbekmez et al. 2012; Garzoli et al. 2018). Comprised by 46 *Sideritis* species and a relatively high endemism rate, Turkey is considered to be one of the gene centers of this genus (Huber-Morath 1982; González-Burgos et al. 2011). *S. germanicopolitana* Bornm., an endemic species to Turkey, is a perennial herb which is distributed in Inner and Northern Anatolia (Huber-Morath 1982). It has only been investigated for its essential oil composition (Kırımer et al. 1992). In the continuation of our studies on the isolation of bioactive secondary metabolites from *Sideritis* species, we herein report the isolation and structure elucidation of the secondary metabolites from the aerial parts of *S. germanicopolitana*. Furthermore, the *in vitro* inhibitory effects on lipoxygenase (LOX), acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes associated with inflammatory and Alzheimer's diseases, respectively were evaluated for the pure compounds.

2. Results and discussion

Phytochemical studies on the MeOH extract of *S. germanicopolitana* yielded 14 secondary metabolites belonging to iridoid glycosides (**1**–**3**), phenylethanoid glycosides (**4**–**8**), flavonoids (**9**–**12**) and lignans (**13** and **14**). The structures of the isolates were characterized as 5-allosyloxy-aucubine (**1**), melittoside (**2**), ajugol (**3**), verbascoside (**4**), martynoside (**5**), leucoseptoside A (**6**), lamalboside (**7**), decaffeoylverbascoside (**8**), xanthomicrol (**9**), isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (**10**), 4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (11), 3′-hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside (**12**), dehydrodiconiferylalcohol 4-*O*-β-D-glucopyranose (**13**) and pinoresinol 4′-*O*-β-glucopyranoside (**14**) (Figure 1). The structures were determined based on extensive 1 D and 2 D NMR experiments as well as HRESIMS analysis. To the best of our knowledge, all purified and characterized constituents are reported for the first time from *S. germanicopolitana*, while lignan glycosides (**13** and **14**) are new for the genus *Sideritis*.

Iridoids are well-known for their chemotaxonomic values. Allose-containing iridoids, particularly diglycosidic iridoids are rarely encountered in plant species. Only two allose-bearing iridoid diglycosides namely 5-allosyl-aucubin (**1**) and allobetonicoside

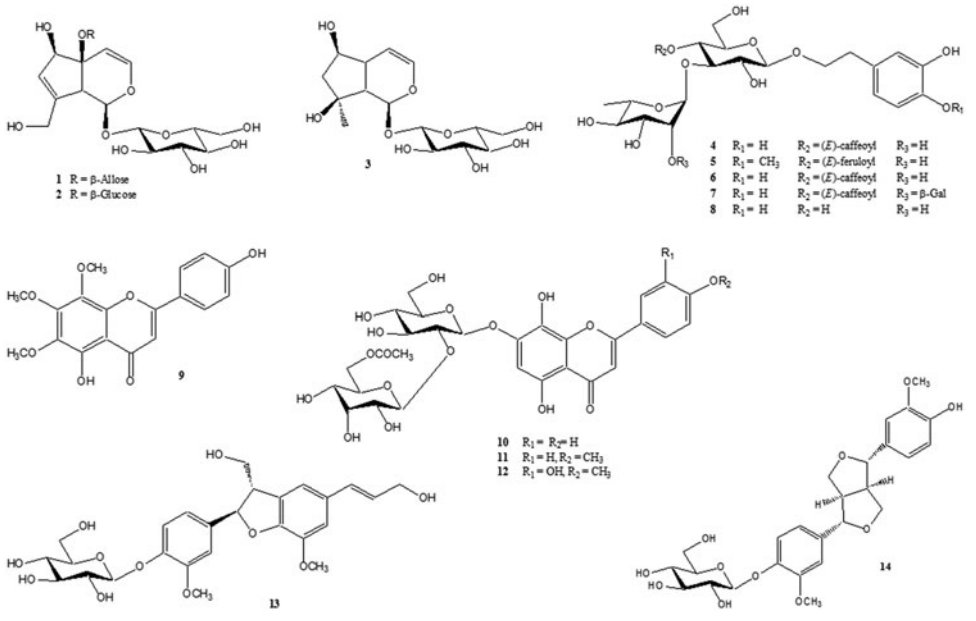

Figure 1. Chemical structures of compounds (**1**–**14**) isolated from *S. germanicopolitana*.

have been reported from nature up till now. Both structures were previously isolated from the genera *Stachys* and *Sideritis* implying the close proximity between them (Serrilli et al. 2006; Venditti et al. 2013; 2016; 2017). The chemotaxonomic relationship between *Sideritis* and *Stachys* was also supported by allose-containing 8-hydroxyflavone (isoscutellarein) derivatives (**10**–**12**) as these compounds were reported several times from many species of both genera (Serrilli et al. 2005; Kırmızıbekmez et al. 2012; Venditti et al. 2016).

All the isolates (**1**–**14**) were evaluated for their potential *in vitro* inhibitory activities on the AChE, BChE and LOX enzymes that are associated with Alzheimer's diseases and inflammation, respectively (Table S1). Tested compounds displayed moderate inhibition percentages on AChE enzyme in the range of 18.35–27.90% when compared to reference drugs, being the most active ones were **11** and **4**. Similarly, all compounds also showed inhibitory activities against BChE enzyme, where they were found to be relatively less inhibitory (10.51–19.41%), when compared to their effects on AChE. Unfortunately, only a few compounds showed relatively weak inhibitory effects against LOX enzyme compared to positive control nordihydroguaiaretic acid (NDGA).

3. Conclusion

Phytochemical investigation of *S. germanicopolitana* yielded 14 secondary metabolites belonging to iridoid glycosides, phenylethanoid glycosides, flavonoids and lignan glycosides. Compounds showed moderate *in vitro* inhibitory activities on the AChE and BChE enzymes while ony a few compounds displayed weak activity against LOX enzyme.

Disclosure statement

The authors declare that there is no potential conflict of interest referring to this article.

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