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Phytochemical investigations on *Artemisia alba* Turra growing in the North-East of Italy

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ABSTRACT

Artemisia alba Turra (Asteraceae) is an Euro-Mediterranean plant used in Veneto (North-East of Italy) as traditional medicine for the treatment of various diseases. *A. alba* is a taxonomically problematic species, characterised by common polymorphism leading to a quite high variability in secondary metabolites content. Nonetheless, the phytochemical knowledge on its phytoconstituents, especially non-volatile components, is limited. In the present paper, the phytochemical composition of a tincture obtained from the aerial parts of *A. alba* growing in Veneto is presented. Extensive chromatographic separations led to the isolation of three new sesquiterpene derivatives, whose structures were elucidated by 1D and 2D NMR experiments and mass spectrometry. Furthermore, flavonoid composition and volatile constituents of the tincture of *A. alba* were preliminary studied by HPLC–MS^n and GC–MS, respectively.

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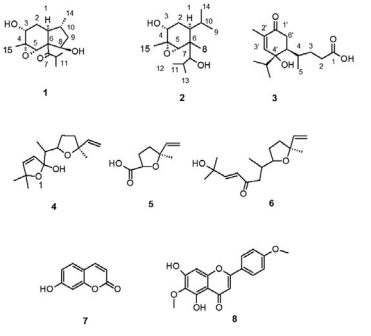

1. Introduction

The genus *Artemisia* (*Asteraceae)* consists of about 500 species and subspecies mainly distributed in the temperate zones of North America, Europe and Asia (Tan et al. 1998). Being included

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in the subclass Asteridae of Dicotyledones, *Artemisia* is considered one of the most evoluted genera in higher plants. This is reflected by the great morphological polymorphism and by the diversity in secondary metabolites content of its members. Various *Artemisia* species have been used in traditional medicine all over the world for the treatment of malaria, fever, hepatitis, helminthiasis, cardiac and digestive problems, neurodegenerative disorders, cancer, inflammation and infections by fungi, bacteria and viruses (Ling 1991; Guarrera 2005; Willcox 2009; Bora & Sharma 2011). Many papers have been published on phytochemical constituents of *Artemisia* species and the most abundant secondary metabolites resulted to be terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols and acetylenes (Bora & Sharma 2011).

The Italian Flora comprises 22 species included in the genus *Artemisia* (Conti et al. 2005) and among them, *Artemisia alba* Turra (syn. *A. intermedia* Host, *A. saxatilis* Waldst. Et Kit. Ex Willd.) was classified in 1764 by Antonio Turra using plants collected on Monte Baldo (Verona, Veneto, Italy). *A. alba* is an Euro-Mediterranean plant distributed in almost all Italian regions (Conti et al. 2005). The plant is shrubby, 20–40 cm tall, usually having camphoraceous odour and white-tomentose, 2–3 pinnatisect, laciniate leaves. Inflorescences are yellow capitula grouped in panicles, with hairy receptacle (Pignatti 1982). The plant grows on dry meadows and stony and rocky slopes up to 1300 m above sea level. In the traditional medicine, *A. alba* has been considered as a mineralising agent and its leaves decoction was used to heal burns and contusions (Tuttolomondo et al. 2014). Decoctions of aerial parts have been used as digestive and tonic (Rigat et al. 2007).

A. alba shows an important variability in morphology of the leaves, type and distribution of glandular trichomes, odour and habitat (Peruzzi et al. 2005). For these reasons, the *A. alba* group is considered as an example of problematic taxon (Tutin 1976; Pignatti 1982). Therefore, chemical analysis of secondary metabolites may represent an useful tool to understand the polymorphism of this species.

To the best of our knowledge, most of phytochemical studies on *A. alba* focused on its essential oil, revealing the presence of several chemotypes (Coassini Lokar et al. 1987; Ronse & De Pooter 1990; Mucciarelli et al. 1995; Perfumi et al. 1999; Radulovic & Blagojevic 2010; Maggio et al. 2012; Dordevic et al. 2013). Conversely, only few reports were published on non-volatile components. Furthermore, *A. alba* is believed to be devoid of sesquiterpene lactones, although they are considered as the chemotaxomic markers of the genus *Artemisia* (Todorova et al. 2015). Previous published papers reported that *A. alba* is characterised by irregular sesquiterpenes, acyclic nerolidol and davanone derivatives, coumarins, flavonoids and highly oxygenated sesquiterpenes (Appendino et al. 1985; Maggio et al. 2011, 2013; Dordevic et al. 2013; Todorova et al. 2015). As far as its biological properties are concerned, the plant ethanolic extract displayed anti-inflammatory effect, being able to inhibit the production of nitric oxide and TNFα synthesis in murine brain microvascular endothelial cells stimulated with LPS (Strzelecka et al. 2005).

In the attempt to provide new insights into the chemical polymorphism of the complex *A. alba* group, in this paper we report the phytochemical investigation of *A. alba* collected in Monte Baldo (North-East Italy). Extensive chromatographic separations of the alcoholic tincture obtained from *A. alba* aerial parts led to the isolation of three novel compounds as well as five known constituents, whose structures were elucidated by 1D, 2D NMR and high-resolution mass spectrometry (HR-MS). Furthermore, alcoholic tincture of *A. alba* was analysed for composition in flavonoids and volatile constituents by HPLC–MS^n and GC–MS, respectively.

2. Results and discussion

2.1. Structural elucidation of new constituents

Compound **1** was isolated as a pale solid. The HR-MS spectrum showed the pseudomolecular ion $[M + K]^+$ at *m/z* 307.1313, consistent with molecular formula $C_{15}H_{24}KO_4$ (Calculated 307.13007). The ^{1}H-NMR spectrum showed three doublets at δ 0.99 (J = 6.80), 1.15 (J = 6.65) and 1.17 (J = 6.70), each integrating for three protons and suggesting the presence of three secondary methyl groups. Furthermore, a singlet at δ 1.49 (3H) supported the presence of a tertiary methyl group. The HSQC-DEPT allowed the detection of two methylenes, at δ_H 1.84–1.80 δ_c 27.5 (C-2), and at δ_H 1.78–1.52 δ_c 33.5 (C-9), and six methynes, namely three at δ_H 2.08 δ_c 45.1 (C-1), δ_H 3.11 δ_c 36.4 (C-11), δ_H 1.57 δ_c 36.9 (C-10), and three linked to electron attractive groups at δ_H 3.96 δ_c 68.6 (C-8), δ_H 3.90 δ_c 67.9 (C-3) and δ_H 3.17 δ_c 66.7 (C-5). Diagnostic HMBC correlations from the methyl groups at δ 1.15 and 1.17 with carbon resonances at C-11, C-12, and with a keto group at δ_c 214.0 (C-7) allowed the identification of an isopropyl group and a vicinal keto function. Further diagnostic HMBC correlations were observed from methyl group 14 (δ 0.99) with C-1 (δ 45.05), C-10 (δ 36.9) and C-9 (δ 32.5). From the methyl group 15 (δ 1.49), HMBC correlations were observed with C-4 (δ 59.3), C-3 and C-5, supporting the presence of three electron attractive groups in these positions. Long-range H-C correlations were also observed from H-1 and C-9 (δ 32.5), C-6 (δ 50.8), C-3 (δ 67.9) and from H-5 (δ 3.17) with C-3, C-8 (δ 68.3), C-1 (δ 45.1) and C-7. All the spectral data are similar to those reported by Brown et al. (2003) for the 3α-hydroxy-4α,5α-epoxy-7-oxo-(8[7→6]-abeo)-amorphane. NOESY correlations were observed from 15-CH_3, H-3 and H-5, suggesting the same orientation for these groups. Further, NOESY interactions were observed from H-1 and 14-CH_3. The relative orientation of 8-OH group was assigned on the basis of the NOESY correlations observed from from H-8 and and isopropyl signals H-12 and 13. NMR data support the relative stereochemistry if position 1, 10, 4, 5 and 6 can be assigned as in compound 26 of the paper of Brown et al. (2003). The difference with compound **1** is the hydroxy group in position 8α; thus this structure was assigned to 3α,8α-dihydroxy-4α,5α-epoxy-7-oxo-(8[7→6]-abeo)-amorphane. As previously stated, these derivatives may originate from the amorphane skeleton by migration of C-8 from C-7 to C-6, resulting in a contraction of the B ring from six atoms to five (Brown et al. 2003).

Compound **2** was isolated as a pale solid. The HR-MS spectrum showed the pseudomolecular ion $[M + H]^+$ at *m/z* 257.2110, consistent with molecular formula $C_{15}H_{29}O_3$ (Calculated 257.2117). The ^{1}H NMR spectrum was characterised by the presence of two series of doublets at δ 1.00 (J = 6.3, 3H), 0.99 (J = 6.8, 3H), 0.90 (J = 6.6 3H) and 0.92 (J = 6.6, 3H) suggesting the presence of two different isopropyl groups, and two singlets at δ 1.51 and 1.02 supporting the presence of two quaternary methyl groups. HSQC-DEPT showed the presence of six methyl groups at δ_H 0.90 δ_c 19.6, δ_H 0.92 δ_c 19.4, δ_H 0.99 δ_c 16.0, δ_H 1.00 δ_c 15.7, δ_H 1.02 δ_c 14.5 and δ_H 1.51 δ_c 18.7, one aliphatic CH_2 at δ_H 1.84–1.57 δ_c 32.9, and six CH, namely three aliphatic (δ_H 1.48 δ_c 28.1, δ_H 2.00 δ_c 32.7, δ_H 2.21 δ_c 40.6) and three aliphatic bearing electron attractive groups (δ_H 3.16 δ_c 66.8, δ_H 3.95 δ_c 67.2, δ_H 4.04 δ_c 74.1). Diagnostic HMBC correlations were observed from the methyl at δ 1.00 and 0.99 (C-12 and 13) with carbon resonances at δ 32.7 (C-11) and 74.1 (C-7), and from singlet at 1.02 (C-8) with C-6 (δ 45.9) and C-7. From H-1 (δ 2.21) long range H-C correlations were observed with C-2 (δ 32.9), C-6 and C-5 (δ 66.8) and HMBC correlations were also observed from C-15 (δ 1.51) with C-3 (δ 67.2), C-4 (δ 59.2) and C-5 (δ 66.8). Finally, the COSY interaction between H-3 (δ 3.95) with H-2 (δ 1.84–1.57)

allowed to determine the presence of the oxabicyclo[4.1.0]heptanol moiety, similar to the six member ring of compound **1**. Further HMBC correlations allowed to locate isopropyl substituent in position 1 due to the long-range correlations observed from CH_3-9 and -14 (δ 0.92 and 0.90) with resonance at δ 40.6 (C-1). A methyl group and the 2-methylpropanol chain were linked to position C-6 due to HMBC correlations observed from singlet at δ 1.02 (CH_3-8) with C-6 (δ 45.9) and C-7 (δ 74.1). NOESY correlations were observed from H-3 with H-10 and CH_3-15 and from H-1 and methyl group 8. The structure of the compound could be related to the 3α-hydroxy-4α,5α-epoxy-7-oxo-(8[7->6]-abeo-amorphane) originating from the opening of the five member ring and reduction of the keto group to alcohol (Brown et al. 2003). Relative stereochemistry of positions 1, 3, 4, 6 and 5 was assumed to be the same as in the above-mentioned derivative, while orientation of hydroxyl group in position 7 was not assigned. Compound **2** is a new natural product and the presence of such derivative has not been previously reported in the genus *Artemisia* or in other botanical species.

Compound **3** was isolated as a pale solid. The HR-MS spectrum showed the pseudomolecular ion $[M + Na]^+$ at *m/z* 291.3369, consistent with molecular formula $C_{15}H_{24}NaO_4$ (Calculated 291.3378). The ^{1}H NMR spectrum showed three doublets at δ 0.90 (J = 6.6), 1.02 (J = 6.7) and 0.99 (J = 6.7) integrating three protons each. A narrow doublet at 1.80 (J = 0.90, 3H) was assigned to a methyl group. A signal at δ 6.46 (q, J = 0.9; 1H) was assigned to a sp^2 methyne (H-3′). The HSQC-DEPT revealed the presence of three aliphatic CH_2 and two CH, confirming the presence of the sp^2 CH and the four methyl groups. Diagnostic HMBC were observed from the methyl group at δ 1.80 (CH_3-4′) with carbon resonances at 136.8 (C-4′), 142.9 (C-3′) and 198.5 (C-5′), the latter suggesting the presence of a keto group conjugated with a double bond. Further long-range correlations were observed from H-3′ (δ 6.49) with C-5′, C-1′ (δ 40.08), C-2′ (δ 74.6) and CH_3-4′ (δ 15.2) and from the CH_2-6′ (δ 2.78–2.38) with C-4′, C-1′ and C-2′ (δ 74.6). Those data support the presence of a cyclohexenone moiety. The linkage of an isopropyl group was assigned to position 2′ on the basis of the HMBC correlations observed from the methyl groups (δ 0.99 and 1.00) with resonances at δ 32.1 and 74.6 (C-2′) and confirmed by NOESY cross peaks observable from H-3′ and proton signals at δ 0.99, 1.00 and 1.97 assigned to the isopropyl moiety. The presence of a second substituent linked to position C-1′ was deduced on the basis of HMBC correlation observed from the doublet at δ 0.90 (C-5) and carbon resonance at δ 40.1 (C-1′) and due to the NOESY interaction observed from the methyl group 5 with the isopropyl signals. Further HMBC correlations were observed from the triplet at δ 2.35 (H-2) and carbon signals at δ 176.2 suggesting the presence of a carboxyl function, and with CH_2 at δ 24.6 (C-3) and 28.0 (C-4). On the basis of the spectral data, compound **3** was established as 4-[2-hydroxy-4-methyl-5-oxo-2-(propan-2-yl)cyclohex-3-en-1-yl]pentanoic acid. We consider this derivative as an unusual seco-eudesmane derived by ring opening, oxidation to carboxylic function of C-1, oxidation to keto function of C-10 and migration of methyl 14 to position 9.

Other isolated constituents were characterised comparing the obtained spectral data with those reported in the literature. They were hemiacetale derivatives of davana ether 2,6,10-trimethyl-2,5:7,10-dioxido-dodeca-3,11-dien-5-ol (**4**) (Thomas & Dubini 1974), hydroxydavanone (**5**), 6,10-dimethyl-7,10-epoxyocta-11-enoic acid (**6**) (Maggio et al. 2013), 7-hydroxy-coumarin (**7**) and pectolinarigenin (**8**). The structures of the isolated compounds are summarised in Figure 1.

The structures of the new compounds confirm that *A. alba* is a problematic taxon deserving further studies in order to understand if there is a possible link between the

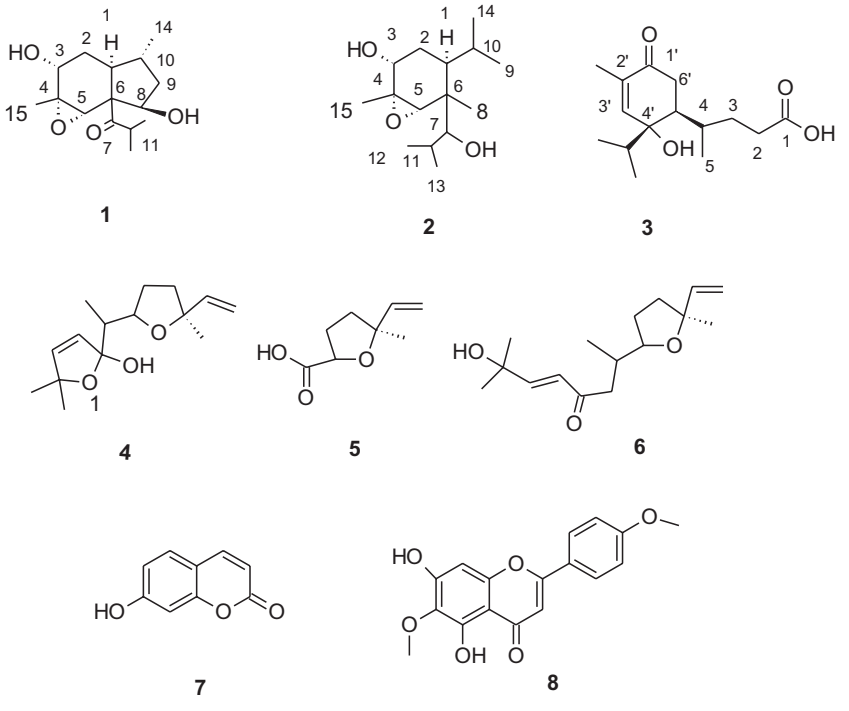

Figure 1. Structure of isolated compounds.

morphological variability exhibited by several populations (Peruzzi et al. 2005) and the presence of specific ecotypes and chemotypes. Finally, this work confirmed the absence of sesquiterpene lactones that are instead marker compounds of other members of the genus *Artemisia* (Kelsey & Shafizadeh 1979).

2.2. HPLC–MS^n analysis of ethanolic extract from plant aerial parts

Phenolic constituents were tentatively identified in the ethanolic tincture of *A. alba* by HPLC-MS^n, comparing fragmentation pathways with the literature (Fabre et al. 2001; Clifford et al. 2003; Felipe et al. 2014). Structures of **9**, **10**, **11**, **13**, **17** and **18** were confirmed by co-injection with reference compounds as indicated in Table 1. The total amount of flavonoid was 0.78 mg/mL while large amounts of chlorogenic acid were observed (4.66 mg/mL).

2.3. Volatile constituents of the tincture

In order to analyse the volatile constituents occurring in the tincture of *A. alba*, a liquid–liquid partition with petroleum ether was used and the main constituents were identified by GC–MS using the combination of linear retention indices (RI) and mass spectra (MS). A total of 32 volatile components were identified in the tincture, mainly monoterpenoids and sesquiterpenoids (Table 2). Among them, artemisia alcohol, borneol, camphor and davana ether were representative compounds detected by several authors in the *A. alba* essential oil (Mucciarelli et al. 1995; Perfumi et al. 1999; Maggio et al. 2012; Dordevic et al. 2013). Furthermore, the

Table 1. Phenolic compounds detected in the tincture of *A. alba*.

Compound	R.T., min	Identification	$[M-H]^-$, *m/z*	MS^2, *m/z*	MS^3, *m/z*	mg/mL
1	5.5	Chlorogenic acid[a]	353	191	173	4.66 ± 0.02
2	7.5	Rutin[a]	609	301		0.282 ± 0.02
3	8.5	Quercetin-3-O-glucoside[a]	463	301		0.031 ± 0.02
4	8.5	Isorhamnetin-3-O-rutinoside[a]	623	315	300	0.157 ± 0.01
5	8.5	Kaempferol-3-O-glucopyranoside[a]	447	285	175	0.022 ± 0.01
6	9.0	Isorhamnetin-3-O-glucopyranoside[a]	477	315	300	0.025 ± 0.01
7	10.0	Quercetin-dihexoside	625	463, 301	301	0.025 ± 0.02
8	11.0	Isorhamnetin-dihexoside	639	315	300	0.038 ± 0.02
9	12.5	Kaempferol[a]	285	175		0.094 ± 0.01
10	13.5	Isorhamnetin[a]	315	300		0.107 ± 0.02

[a]Compared with reference compounds.

Table 2. Volatile components from the tincture of *A. alba*.

Component[a]	Experimental KI[b]	Reference KI[b]	%
α-pinene	924	931	0,34
3,3,6-trimethyl-1,4-heptadien-6-ol	940	999	0,22
Benzyl alcohol	991	1006	0,07
p-cymene	1010	1011	0,16
1,8-cineole	1020	1023	1,74
γ-vinyl-*γ*-valerolactone	1032	1046	0,22
Artemisia alcohol	1070	1068	0,26
2-decyne	1076	1064	0,21
cis-verbenol	1117	1136	0,05
trans-pinocarveol	1121	1143	0,08
Borneol	1128	1148	1,89
Pinocarvone	1136	1114	0,5
Camphor	1147	1146	2,83
cis-*β*-terpineol	1157	1158	0,07
Myrtenol	1167	1174	0,14
8-oxo-*cis*-ocimene	1175	1164	0,19
cis-*p*-mentha-1(7), 8-dien-2-ol	1193	1185	0,1
Lilac aldehyde A	1204	1197	0,16
Piperitone	1238	1228	2,76
trans-chrysanthenyl acetate	1245	1239	0,18
Thymol	1283	1266	0,29
β-ylangene	1410	1418	0,15
Aromadendrene oxide	1443	1462	0,08
β-copaene	1457	1437	0,18
Davana ether	1507	1487	0,11
Methyl *p*-methoxycinnamate	1545	1544	0,34
Spathulenol	1568	1572	0,27
6-*epi*-shyobunol	1578	1555	7,55
Caryophyllene oxide	1588	1583	0,25
Methyl *p*-hydroxycinnamate	1625	1673	0,5
(*E*)-ethyl ferulate	1894	1916	0,3
Ethyl *α*-linolenate	2198	2201	4,26

[a]Compounds are listed in order of their elution from a DB-5MS column.
[b]Linear retention index experimentally determined using homologous series of C_8-C_{30} alkanes.

oxygenated sesquiterpene 6-epi-shyobunol and the fatty acid ester ethyl α-linolenate were found as major volatile components of the tincture.

3. Conclusions

Two new amorphane derivatives (**1**, **2**) and one modified seco-eudesmane (**3**) were isolated from *A. alba* and their structure elucidated by spectral techniques. Rutin and chlorogenic

acid were the most abundant phenolic constituents, whereas 6-*epi*-shyobunol, ethyl α-linolenate and camphor were the most abundant compounds in the volatile fraction. The presence of irregular mono and sesquiterpene in *Artemisia* spp. is not unusual (Bora & Sharma 2011). So, our data confirm the chemical polymorphism in this species, with significant variability among populations of different geographic origin. Published papers on Turkish (Todorova et al. 2015) and Sicilian (Maggio et al. 2013) samples showed the presence of other unusual derivatives, notably highly oxygenated germacrane, eudesmane, guaiane and oplopane (Todorova et al. 2015), and other irregular sesquiterpenes (Maggio et al. 2013). Therefore, further studies on other populations are needed in order to deeply understand the possible chemotaxonomical role of such constituents.

Disclosure statement

No potential conflict of interest was reported by the authors.

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