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Synopsis

Therapeutic Potential and Biotechnological Utilization of the Indigenous Biosynthetic Capacity of Artemisia alba Turra: A Review

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Abstract. Genus *Artemisia* is one of the largest in the Asteraceae family, consisting of ca. 500 representatives, known under the common names "mugwort", "wormwood" and "sagebrush". Traditionally many *Artemisia* species have been utilized as spices, aromatic agents, as well as for their medicinal and ornamental properties. The present review presents a summary of the pharmacological activity, based on secondary metabolites identified in different representatives of the *Artemisia* genus. The effect of plant extraction on the type of biologically active compounds has also been discussed. Special accent has been given to distribution of *Artemisia* species throughout Southeast Europe and essential oil bearing of *A. alba* Turra which is also characteristic for the flora of Bulgaria. Experience of our team on *A. alba* Turra as a model system for biotechnological development of different classes of secondary metabolites has been summarized. The established flexibility of plant secondary metabolism in relation to morphogenesis in this species might serve as a useful tool for obtaining plant material with desired secondary metabolite profile through modeling plant growth, development and morphogenesis and without the use of genetic modifications *in vitro*.

Key words: *Artemisia genus, Artemisia alba* Turra *in vitro,* essential oils, phenolic and flavonoid compounds, endogenous cytokinins.

General characteristics of the Artemisia genus

The *Artemisia* genus is one of the largest in the tribe Anthemideae of the Asteraceae family, comprising of ca. 500 species (Watson et al., 2002; Zhen et al., 2010 and references cited within). Its representatives are widely distributed in the Northern Hemisphere and rare in the Southern Hemisphere. Many of the representatives of the genus find ornamental, medicinal or economic application (Zhen et al., 2010 and references cited within).

The central Asian region is considered to be one of the centers of origin and specification of the genus, with over 180 taxa, 40 of which endemic (Kapustina et al., 2001). There are 174 *Artemisia* species in Russia, 150 - in Asia and China, about 50 in Japan

(Kurşat et al., 2015 and references cited within) and 35 in Iran (Nigam et al., 2019). According to Tutin & Persson (1976), there are 57 representatives of the genus in Europe. About 30 species are reported in Italy (Nigam et al., 2019). The flora of Turkey contains 22 species of the genus (Davis, 1975).

The region of South Eastern Europe represents a rich pool of *Artemisia* species with a great potential for investigations, with 37 *Artemisia* taxons on a subspecies level (Table 1).

Pharmacological application and phytochemical basis of the biological activities of representatives of the Artemisia genus

Probably the most widely studied species in the genus is *A. annua* L. (Sweet Wormwood) with the antimalarial sesquiterpene lactone artemisinin. The first mention of the plant in Traditional Chinese Medicinal records dates as far as 281–340 B.C. It was made by Hong Ge in the "Handbook of Prescriptions for Emergency Treatment" (Hou Bei Ji Fang) as a remedy to treat fever and chills (Efferth, 2017). Further official records are found in the "Compedium of Materia Medica" (Ben Cao Gang Mu) by Li Shizen in 1596 (Efferth, 2017).

A. annua L. and its main active constituent artemisin have been re-discovered for up-to-date medicinal application as a result of the secret 523 Project of the Chinese government launched on May 23, 1967. The project was initiated by the Chinese chairman Mao Zedong in response to the request of the Vietnamese government to cope with chloroquine-resistant malaria (Su & Miller, 2015). In January 1969, Professor Youyou Tu from the China Academy of Traditional Chinese Medicine was involved and assigned in the leadership of the project (NobelPrize, 2015). Upon her research within over 2000 ancient Chinese prescriptions for treatment of fever, she came upon *A. annua* as the most frequently occurring species. Then after variation of the plant part and extraction method used, finally on October 4, 1971, the biologically active preparation designated as "sample #191" was obtained. It was capable of inhibition of rodent and monkey malaria with 100% activity (Su & Miller, 2015). The results were announced on March 8, 1972 and followed by a broad research on structure elucidation of the active principle underlying this activity. Artemisinin was identified as an endoperoxide sesquiterpene lactone, in 1972, with its structure determined by X-ray analysis in 1979 (Dhingra et al., 2000). In 2015 professor Tu was assigned the Nobel Prize in Physiology or Medicine for the discovery of the team led by her (NobelPrize, 2015).

In addition to *A. annua* L. as the main artemisinin source, the compound has also been identified in low concentration in *A. apiacea* and *A. lancea* (Ferreira et al., 2010).

The years of intensive research on artemisinin have led to the identification of also other activities such as the prominent anti-inflammatory and immunoregulatory properties of this compound (Kim et al., 2019b). These activities have led to the clinical application of artemisinin in inflammatory and autoimmune conditions such as alcohol-induced liver damage, tubulointerstitial nephritis, and rheumatoid arthritis (Kim et al., 2019b and references cited within). The ability of artemisinin to alleviate inflammatory response is due to blocking pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1β (IL-1b), and IL-17) expression. The mechanisms underlying this are through reactive oxygen species generation, regulation of mitogen activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling pathways, and pathogenic Th17 responses (Li et al., 2006, Wang et al., 2008, and references cited within).

The mechanism of the anti-inflammatory effect of artemisinin in uric acid induced inflammation was through suppression of the interaction between NEK7 and the NLRP3 inflammasome in uric acid-induced

inflammation. Thus, artemisinin was shown to suppress foot and ankle swelling in MSU crystal-induced arthritis mice (Kim et al., 2019b).

In addition the anti-viral, anti-parasitic, anti-fungal, anti-inflammatory and anticancer activities of artemisinin, as well as its derivatives were established (Ho et al., 2014).

Noteworthy, research has shown that besides the well-studied artemisinin, marked *in vitro* and *in vivo* anticancer activity was established for *A. annua* extract containing no detectable artemisinin (limit of detection=0.2 ng/mg). It was established that the main chemical constituents responsible for this activity were 6,7-dimethoxycoumarin, chrysosplenol D, casticin, arteanniun B, arteannuic acid (Table 1 and 2, Lang et al., 2019).

Prominent antihepatofibrotic, anti-inflammatory, choleretic, and hepatoprotective activities have been reported also for other biologically active compounds isolated from *Artemisia* species. Thus, *p*-hydroxyacetophenone, *β*-sitosterol, scoparone, cirsimaritin, quercetin, arcapillin, capillin, 6,7-dimethylesculetin, 6,7-dimethoxycoumarin, capillone, capillarin, 4'-methyl capillarisin, cirsilineol, cirsimaritin, and capillarisin, occurring in *A. capillaris,* as reviewed in Jang et al. (2015).

Table 2 and 3 contain a non-exclusive survey of literature of investigations performed in the last decade by different working groups on the pharmacological activities and identified phytochemical compounds in some *Artemisia* species.

Table 1. Distribution of *Artemisia* species throughout the region of Southeast Europe based on the online database of the Information resource for Euro-Mediterranean plant diversity (EuroMed PlantBase, 2020). *Legend:* Al – Albania, BH - Bosnia and Herzegovina, BG – Bulgaria, Cr – Croatia, Gr – Greece, Md - Moldova; Mn – Montenegro, NM – North Macedonia, RO – Romania, SKV – Serbia including Kosovo and Vojvodina, Sl – Slovenia, TEU - Turkey in Europe incl. Gökçeaga.

Taxa	Al	BH	BG	Cr	Gr	Md	Mn	NM	RO	SKV	Sl	TEU
A. abrotanum L.	+	+	+	+		+			+		+	
A. absinthium L.	+	+	+	+	+	+	+	+	+	+	+	+
A. alba Turra L.	+	+	+	+	+		+	+	+	+	+	
A. alpina Willd.			+						+			
A. annua L.	+	+	+	+	+	+	+	+	+	+	+	+
A. arborescens (Vaill.) L.				+	+		+					
A. argyi Lév. & Vaniot									+			
A. atrata Lam											+	
A. austriaca Jacq.		+	+	+		+			+	+		
A. caerulescens L.	+	+		+			+				+	
A. caerulescens L. ssp. *caerulescens*	+			+								
A. campestris L.	+	+	+	+	+	+	+	+	+	+	+	+
A. campestris ssp. *alpina* (DC.) Arcang.									+			
A. *campestris* L. ssp. *campestris*			+	+		+		+	+			+
A. *campestris* ssp. *inodora* Nyman			+			+			+			
A. *campestris* ssp. *lednicensis* (Spreng.) Greuter & Raab-Straube										+		+
A. chamaemelifolia Vill.			+									
A. codonocephala Diels									+			
A. dracunculus L.		+	+			+			+	+	+	
A. dzevanovskyi Leonova									+			

A. genipi Stechm.											+	
A. lancea Vaniot									+			
A. lerchiana Stechm			+		+				+			
A. nitida Bertol.											+	
A. pancicii Danihelka & Marhold										+		
A. pedemontana Balb.			+									
A. pontica L.			+			+			+	+	+	
A. santonicum L.			+	+	+	+		+	+	+		+
A. santonicum ssp. *patens* K. M. Perss.									+	+		
A. santonicum L. ssp. *santonicum*			+		+	+			+	+		+
A. scoparia Waldst. & Kit.	+	+	+	+	+	+	+	+	+	+	+	+
A. siversiana Willd.						+						
A. trautvetteriana Besser						+			+			
A. umbelliformis Lam.	+	+	+		+		+	+	+	+		
A. umbelliformis ssp. *eriantha* (Ten.) Vallès-Xirau & Oliva Brañas	+	+	+		+		+	+	+	+		
A. verlotiorum Lamotte				+	+						+	
A. vulgaris L.	+	+	+	+	+	+	+	+	+	+	+	+

Table 2. Pharmacological activities established for different preparations of some representatives of the *Artemisia* genus.

***Artemisia* species**	**Pharmacological activity**	**Parts used/method of preparation**	**References**
A. absinthium L.	Antifungal (*Fusarium moniliforme*, *F. oxysporum fs. lycopersici* (Scheldt) and *F. solani*) and antiparasitic (*Leishmania infantum* PB75 strain) activities	Essential oils obtained by Clevenger distillation	Bailen et al., 2013
A. absinthium L.	Neuroprotective against disturbances induced by cerebral ischemia and reperfusion injury in rats	Methanol extract of the aerial parts	Bora & Sharma, 2010
A. absinthium L.	*In vitro* and *in vivo* alleviation of acute inflammation, induced by *Montivipera xanthine* viper venom	Methanol extract of the aerial parts	Nalbantsoy et al., 2013
A. annua L.	*In vivo* and *in vitro* anticancer activity	Commercial extract, MoMundo GmbH capsules (Bad Emstal, Germany)	Lang et al., 2019
A. capillaris Thunb.	Antioxidant, antisteatotic, anti-inflammatory, antiviral, choleretic, antifibrotic, antitumor activities in diverse *in vitro* and *in vivo* hepatic experimental models.	Aqueous extracts of the aerial parts	Jang et al., 2015
A. capillaris Thunb., *A. iwayomogi* Kitam. and *A. annua* L.	Antioxidant and anti-fibrotic activity in Hepatic stellate T6 (HSC-T6) cells	Aqueous extracts of the aerial parts	Saravanakumar et al., 2019
A. iwayomogi Kitam.	Lowering of gene expression of pro-inflammatory cytokines, reduction of visceral fat accumulation and obesity-related biomarkers in mice fed on a high-fat diet	Ethanol extract	Choi et al., 2013

A. iwayomogi Kitam.	Protective effect of against hypertriglyceridemia induced by a high-fat diet (HFD) in mice	Ethanol extract	Lee et al., 2017
A. iwayomogi Kitam.	DPPH and superoxide radical scavenging; anti-age potential due to tyrosinase, elastase and collagenase inhibition activity	Ethyl acetate and water fractions of the ethanol extract	Kim et al., 2019a
A. rutifolia Spreng	Antioxidant and antimicrobial (*Escherichia coli*, *Pasteurella multocida*, *Bacillus subtilis*, *Staphylococcus aureus*, *Aspergillus flavus*, *Aspergillus niger*, *Fusarium solani* and *Rhizoctonia solani*)	Comparative study of the hexane, chloroform and methanol extract of the aerial parts	Ashraf et al., 2017
A. anethifolia Poljakov, *A. commutate* Besser, *A. desertorum* Spreng, *A. integrifolia* Richards, *A. latifolia* Ledeb, *A. leucophylla* Turcz. ex Besser, *A. macrocephala* Jacquem. ex Besser, *A. messerschmidtiana* Besser, *A. palustris* L., *A. sericea* Weber ex Stehm., *A. tanacetifolia* L., *A. umbrosa* (Besser) Pamp.	*α*-glucosidase and *α*-amylase inhibitory activity.	SPE fractionation of 60 % Ethanol extract	Olennikov et al., 2018
A. vulgaris L.	Concentration-dependent genotoxicity (in human peripheral blood lymphocytes, PBLs) when applied alone; concentration dependent genoprotective effect upon mitomycin C co-treatment. No cytotoxicicty in individual application. Moderate cytotoxic effect in co-treatment with mitomycin C after long-term exposure (against SW-480 human colon cancer cells). Low cytotoxicity in control human periodontal ligament stem cells (PDLSCs).	Methanol extract of the aerial parts	Jakovljević et al., 2020

Table 3. Biologically active chemical constituents identified in some representatives of the *Artemisia* genus.

***Artemisia* species**	**Phytochemical constituents identified**	**Parts used/method of preparation**	**References**
A. annua L.	Arteannuin B, casticin, chrysosplenol D, arteannuic acid; 6,7-dimethoxycoumarin	Momundo *Artemisia annua* acetonitrile extract, MoMundo GmbH commercial capsules (Bad Emstal, Germany)	Lang et al., 2019
A. iwayomogi Kitam.	Major components scopolin, acetophenone glycoside and	Ethanol extract	Choi et al., 2013

	scopoletin		
A. iwayomogi Kitam.	3,5-dicaffeoylquinic, 5-O-caffeoylquinic and 3,4-dicaffeoylquinic acids; scopolin, scopoletin and patuletin-3-O-glucoside	Ethanol extract	Lee et al., 2017
A. iwayomogi Kitam.	Scopolin , 2,4-dihydroxy-6-methoxy-acetophenone-4-O-ß-D-glucopyranoside, scopoletin, kaempferol-3-O-methyl ether and luteolin	Ethyl acetate and water fractions of the ethanol extract	Kim et al., 2019a
A. rutifolia Spreng	Gallic acid, caffeic acid, chlorogenic acid, syringic acid, sinapic acid, p-coumaric acid, m-coumaric acid, ferulic acid, vanillic acid, myricetin, and quercetin	Methanol extract of the aerial parts	Ashraf et al., 2017
A. anethifolia Poljakov, *A. commutate* Besser, *A. desertorum* Spreng, *A. integrifolia* Richards, *A. latifolia* Ledeb, *A. leucophylla* Turcz. ex Besser, *A. macrocephala* Jacquem. ex Besser, *A. messerschmidtiana* Besser, *A. palustris* L., *A. sericea* Weber ex Stehm., *A. tanacetifolia* L., *A. umbrosa* (Besser) Pamp.	Caffeoylquinic acids, Flavonoids,	SPE fractionation of 60 % Ethanol extract	Olennikov et al., 2018
A. vulgaris L.	Domination of chlorogenic acid, quercetin-3-O-glucopyranoside, syringic, trans-cinnamic and p-coumaric acids, presence of fisetin and syringing.	Methanol extract of the aerial parts	Jakovljević et al., 2020

An impressive number of works have been performed regarding the phytochemical richness of the genus. Studies have shown the presence of triterpenes, steroids, hydrocarbons, polyacetylenes, flavonoids, coumarins, mono and sesquiterpenoids with a wide range of biological activities such as antimalarial, cytotoxic, antihepatotoxic, anti-bacterial, antifungal and antioxidant properties (Maggio et al., 2012 and references cited within).

The broad research on pharmacological activity of *Artemisia* species is based on the long-lived knowledge and practices of the indigenous population in many regions of the world. Thus, the traditional utilization of representatives of the genus for treatment of malaria, hepatitis, cancer, inflammation, as well as against fungi, bacteria, and viruses has been documented (Willcox, 2009; Abad et al., 2012; Nigam et al., 2019). Thus, *A. abrotanum* L. ("southernwood") has been traditionally used in the treatment of upper

respiratory tract diseases and applied nowadays for culinary and cosmetic purposes (Abad et al., 2012). *A. absinthium* L. ("wormwood") is distributed throughout Europe and Siberia and utilized as antiparasitic and for treatment of anorexia and as a digestive. Its properties are the reason for its broad inclusion in digestive herbal preparations, dietary supplements and it is especially known as an additive in alcoholic beverages, such as the Absinth, known all over the world (Lachenmeier, 2010). *A. iwayomogi* Kitamura ("hanin-jin" or "dowijigi" in Korean) growing in Korea has been known for its traditional application in treating liver ailments, includingly hepatitis (Park, 1999). *A. vulgaris* L. ("mugwort") occurring in Asia, Europe and North America is widely used in the Philippines (locally known as "herbaka") for its antihypertensive properties. Its traditional application as anti-inflammatory, antispasmodic, carminative and anthelmintic remedy has also been reported, as well as its effect in the treatment of painful menstruation and in the induction of labour or miscarriage (Quisumbing, 1978).

Phytochemical research has shown the scientific basis of the activities recorded for many of the *Artemisia* species. As seen by the works surveyed in Tables 2. and 3, in addition to the sesquiterpene lactones, responsible for the characteristic bitterness of *Artemisia* species, terpenoids in their essential oils, as well as phenolic compounds in their extractable preparations attribute for the wide array of pharmacological activities in the different species.

Artemisia alba Turra – general outline and phytochemicals with therapeutic potential

A. alba Turra is a fragrant shrub species with an Euro-Mediterranean distribution widespread in the South Eastern parts of Europe.

According to some literature sources, its morphological variability attributes to its botanical placement to different subgenera of the *Artemisia* genus (Maggio et al., 2012). Throughout the years it has been placed in subgenera *Absinthium* (Fiori, 1927), *Abrotanum* (Greger et al., 1982) or *Artemisia* (Tutin & Perron, 1976). Due to this complexity, for example the Sicilian population has been classified both as *A. camphorata* Vill. var. *subcanescens* Ten. and *A. alba* var. *incanescens* (Jord.) Fiori (Maggio et al., 2012 and references cited within).

According to other sources, the species could be placed in the *Artemisia* subgenus *Seriphidium* Less. Heterotypic synonyms of the species name are *A. achilleifolia* Ten., *A. alba* ssp. *camphorata* (Vill.) P. Fourn., *A. alba* ssp. *canescens* Priszter & Soó, *A. alba* ssp. *lobelia* (All.) Hegi, *A. alba* ssp. *saxatilis* (Willd.) P. Fourn., *A. alba* ssp. *suavis* (Jord.) P. Fourn., *A. biasolettiana* Vis., *A. camphorata* Vill., *A. camphorata* var. *canescens* DC., *A. fruticosa* Asso, *A. humilis* Wulfen, *A. incanescens* Godr., *A. lobelia* All., *A. saxatilis* Willd., *A. suavis* Jord. and *A. subcanescens* Willd. (Greuter, 2006).

Traditionally, the decoction of the plant has been used in the Mediterranean region as a stomach digestive (Rigat et al., 2007). Research, been performed on the biological activity and secondary metabolites of the species are summarized in Tables 4 and 5.

A key factor in cancer genesis is the process of chronic and repeated inflammation, affecting tissue homeostasis and repair (Rakoff-Nahoum, 2006). The functional relationship between inflammation and cancer is not new. In 1863, Virchow hypothesized that the origin of cancer was at sites of chronic inflammation, in part based on his hypothesis that some classes of irritants, together with the tissue injury and ensuing inflammation they cause, enhance cell proliferation (Balkwill & Mantovani 2001). Thus it has been considered a challenging perspective in anti-cancer therapy to normalize the inflammatory network in order to recover the normal host response of the patient which would lead to decreasing the tumour-promoting properties of the infiltrating cells (i.e. pro-inflammatory cytokines) while increasing their tumour-suppressing properties, such as anti-inflammatory cytokines (Coussens & Werb,

2002). The established results of the significant toxicity on SW-480 colon cancer cells when applied alone, and the significant increase of the antiproliferative activity and decreased the required concentration (IC50) of the chemotherapeutic agent Mitomycin C (MMC), together with the obtained results of the anti-radical and anti-inflammatory effect of preparations of the species demonstrate the potential of *A. alba* as a dietary food supplement or as a supplement to chemotherapy (references summarized in Table 4).

Literature sources of volatile and non-volatile phytochemical constituents of preparations of the species are summarized in Table 5.

Noteworthy are the results obtained in the literature on the marked variability of the terpenoid profile of the essential oil of the species, as well as the effect of external factors on their mono : sesquiterpenoids ratio (Table 5).

This motivated our further research to develop biotechnologically the species in order to study the factors affecting *in vitro* production of essential oils and polyphenolics in *A. alba* Turra.

Biotechnological development of the species

Based on the obtained variability of essential oil production discussed in literature, as well as the phytotherapeutic potential of the phenolic compounds established in the species, biotechnological development of *A. alba* Turra was performed. The effect of modification of *in vitro* morphogenesis on the terpenoid profile of essential oils as well as total phenolic and flavonoid compounds was performed. Dependencies were established with the endogenous cytokinin pools of the plant.

Shoot cultures of *A. alba* Turra were initiated from the surface sterilized stem explants of the aerial parts of the plant kindly provided by Assoc. Prof. Ljuba Evstatieva from the collection of the Institute of Biodiversity and Ecosystem Research-BAS (Danova et al., 2012). Stock shoots were maintained in plant growth regulators (PGR)-free culture medium. In order to modify plant growth and development, auxin (indole-3-butyric acid, IBA) and benzyl adenine (BA) treatments were applied.

Two main *in vitro* morphotypes of the plant were obtained (Fig. 1). The PGR-free control, as well as 0.5 mg/l IBA and 1.0 mg/l IBA treated plants (designated as GAIP_0, GAIP_1 and GAIP_2, respectively), were characterized by the formation of both aerial and root parts (Danova et al., 2012). Plants, treated with auxin and cytokinin combination - 0.5 and 1.0 mg/l IBA together with 0.2 mg/l BA (GAIP_3 and GAIP_4, respectively) were characterized with inhibition of root development. Extensive callusogenesis at the plantlets' base was recorded instead, with only up to 15 % of indirect rooting through callus.

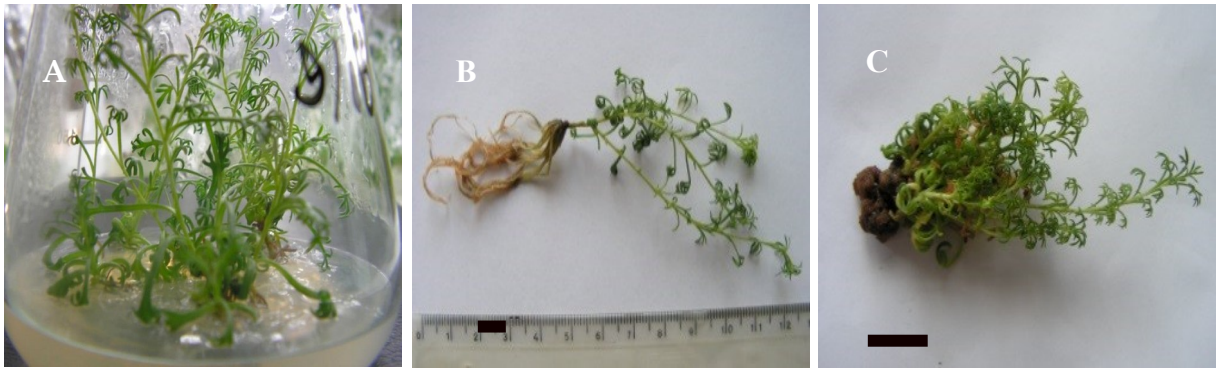

Fig. 1. Morphoregulatory effect of PGR on *A. alba* shoot cultures. Stock shoots cultivated in PGR-free medium (A); rooting moprhotype, illustrated by *A. alba* Turra cultivated in GAIP_1 - 0.5 mg/l IBA supplemented medium (B); non-rooting morphotype, illustrated by the plant grown in GAIP_3 - 0.5 mg/l IBA + 0.2 mg/l BA medium (C). *Space bar = 1 cm.*

Table 4. Investigations on biological activity established for different preparations of *A. alba* Turra.

Parts used/method of preparation	Pharmacological activity	References
Lyophilized ethanol extract	Anti-inflammatory effect through inhibition of NF-κB and AP-1 transcription factors in human hepatoma (HepG2) and human umbilical vein endothelial cells (HUVEC).	Stalińska et al., 2005
Ethanol extract	Anti-inflammatory through suppression of nitric oxide and TNFα (tumor necrosis factor α) synthesis in cells of monocyte origin	Strzelecka et al., 2005
Essential oil of the aerials of the plant (under the name of *A. lobelii* All.	Antimicrobial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*	Stojanovic et al., 2000
Essential oil of the aerial parts of *A. alba* Turra	Antioxidant activity (FRAP assay 0.023 ± 0.00 mmol Fe2 +/g; DPPH assay, EC_{50} = 14.08 ± 1.09 mg/ml). Antimicrobial activity (Gram (+) bacteria: *Micrococcus luteus*, *Micrococcus flavus*, *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis* and *Bacillus subtilis*; Gram (-) bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*; two standard strains of the *Candida albicans* yeast).	Dordević et al., 2013
70 % Ethanol extract of the aerial parts of *A. alba* Turra	Antioxidant activity (FRAP assay 1.6 ± 0.08 mmol $^{Fe2+}$/g; DPPH assay IC_{50} = 0.032 ± 0.002 mg/ml). Antimicrobial activity (Gram (+) bacteria: *Micrococcus luteus*, *Micrococcus flavus*, *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis* and *Bacillus subtilis*; Gram (-) bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*; two standard strains of the *Candida albicans* yeast). Activity of the extract showed to be higher than the one of the essential oil.	Dordević et al., 2013
Ethyl acetate extract of the aerial parts	Induction of early stage apoptosis in SW-480 colon cancer cells.	Jakovljević et al., 2019
Methanol extract of the aerial parts of *A. alba* Turra	Concentration-dependent genotoxicity (in human peripheral blood lymphocytes (PBLs)) when applied alone; concentration dependent genoprotective effect upon mitomycin C co-treatment. Significant cytotoxic effect against SW-480 human colon cancer cells. Low cytotoxicity in human periodontal ligament stem cells (PDLSCs) as normal control.	Jakovljević et al., 2020

Table 5. Volatile and non-volatile phytochemical constituents identified in different *A. alba* Turra preparations.

Parts used/method of preparation	Phytochemical constituents identified	References
	Volatile constituents	
Aerial parts of *A. alba* of Calabrian origin	Five oxygenated nerolidol derivatives	Appendino et al., 1985
Essential oil from inflorescences of *A. alba* Turra collected at different location of the Adriatic area of NE Italy	Thermophytic plant communities - domination of sesquiterpene hydrocarbons; mesophytic plant communities - domination of oxygenated monoterpenes	Coassini Lokar et al., 1987
Essential oil of the aerials of the plant (under the name of *A. lobelii* All.	Major constituents camphor (33.2-36.8%), 1,8–cineole (15.2-21.1%) and artemisia ketone (6.0-24.2%)	Stojanovic et al., 2000
Essential oil of the aerials of the plant originating from contrasting serpentine (*A. alba* var. *saxatillis*) and calcareous (*A. alba*) habitats in Serbia	Germacrene D (38.3%) - major constituent in the accession of the serpentine habitat; spathulenol (11.8%), artemisia ketone (10.1%), camphor (7.5%) and 1,8-cineole (7.4%) in the samples of the calcareous habitat. Overall ca. 73 % sesquiterpenes and ca. 60 % monoterpens, in the first and latter samples, respectively. Four times lower yield in the *saxatillis* var.	Radulović & Blagojević, 2010
Essential oil of the aerial parts of *A. alba* Turra, obtained by Clevenger distillation	Major constituents: camphor (23.7%), artemisia ketone (15.2 %) 1,8-cineole (14.1%) and trans-chrysanthenol (8.6%), followed by camphene (3.2%), silphiperfol-5-en-3-one A (6.4%) and α-bisabolol (6.1%). Mono- towards sesquiterpenoids ratio 3:1.	Dordević et al., 2013
Volatile fraction obtained from 70 % Ethanol extract of the aerial parts of *A. alba* Turra	49 components, among which scopoletin (14.0%), corymbolone (10.3%), trans-chrysanthenol (7.4%), umbelliferone (4.9%), camphor (4.3%), 1,8-cineole (5.9%) and artemisia ketone (2.9%)	Dordević et al., 2013
Comparative analysis of the essential oils of *A. alba* Turra from four different locations in Italy, obtained by hydrodistillation	Variability in the oil yield (from 0.03% up to 1.5 % w/w). Generally high levels of camphor and isopinocamphone. Domination of sesquiterpenes (60 %) in one of the oils, comparable levels of mono- and sesquiterpenes in the remaining three samples (with mono- towards sesquiterpenes ratio varying from 0.38 up to 0.95).	Maggio et al., 2012
Hydrodistillation from the aerial parts of *A. lobelia* All. from Serbia	Dominating components: camphor (41.94 %), 1,8-cineole (13.8 %), syn-anti-antiHelifolen-12-al A(10.2 %), camphene (8.89 %), borneol (3.38 %). Domination of oxygenated monoterpenes (61.4 %) with mono-sesquiterpenoid ratio 3.08.	Janaćković et al., 2019
	Non-volatile constituents	
Dichloromethane extract of the aerial parts of *A. alba* Turra from Sicily	Artalbic acid - sesquiterpene with unusual skeleton.	Maggio et al., 2011
70 % Ethanol extract of the aerial parts of *A. alba* Turra	In the non-volatile fraction of the extract: kaempferol 3-O-(6"-O-malonylglucoside)-	Dordević et al., 2013

	7-O-rhamnoside, chlorogenic acid and rutin (16.1%, 11.4% and 9.5%, respectively), followed by kaempferol 3,7-O-diglucoside (8.4 %), luteolin 5-O-(6"-O-malonylglucoside) (7.7 %), apigenin (3.8 %), luteolin (3.4 %), genkwanin 5-O-glucoside, kaempferol 7-O-rhamnoside (1.9 %), luteolin 5-O-glucoside (1.2 %) and gallic acid (0.3 %).	
Chloroform extract of the aerial parts of *A. alba* Turra	11 highly oxygenated sesquiterpenoids: 2β,5α,12-trihydroxygermacra-1(10),4(15),11(13)-triene, 12-acetoxy-1α,10β-epoxy-5α-hydroperoxy-2β-hydroxygermacra-4(15),11(13)-diene, 1β,10β-epoxy-2β,5α,12-trihydroxygermacra-4(15),11(13)-diene, 5α,10α-Epoxy-1α,2β,12-trihydroxygermacra-4(15),11(13)-diene, 12-acetoxy-5α,10α-epoxy-1α,2β-dihydroxygermacra-4(15),11(13)-diene, 9β-Acetoxy-1β,3β,4β-trihydroxygermacra-5,10(14)-diene, 9β-Acetoxy-1β-hydroperoxy -3β,4β-dihydroxygermacra -5,10(14)-diene, 1α,2β,12-trihydroxyeudesma-4(15),11(13)-diene, 12-acetoxy-2α,4α,10α-trihydroxyguai-11(13)-ene, 7β-acetoxy-2β-hydroxyoplopenone, 7β-acetoxy-2α-hydroxyoplopenone, and 7-hydroxycadin-4-en-3-one 2 flavonoids: centaureidin and axillarin	Todorova et al., 2015
Methanol extract of the aerial parts of *A. alba* Turra	chlorogenic acid, 3,5- and 4,5- dicaffeoylquinic acids, scopoletin, umbeliferone, luteolin, nepetin, quercetin 3-methyl ether, axillarin, apigenin, hispidulin, diosmetin, chrysoeriol, desmethoxycentaureidin, jaceosidin, quercetin-3,3'-dimethylether, centaureidin and rutin were isolated from the methanol extract. UHPLC-PDA-MS confirmed the presence of additional 11 compounds : phenolic acids and flavonoids	Trendafilova et al., 2018
Ethyl acetate extract of the aerial parts of *A. alba* Turra	Phenolic acids (gallic, p-coumaric, vanillic, and ferulic acids) and flavonoids (rutin, myricetin, luteolin, quercetin, and apigenin)	Jakovljević et al., 2019
Methanol extract of the aerial parts of *A. alba* Turra	Domination of chlorogenic acid, quercetin-3-O-glucopyranoside, 2,5-dihydroxybenzoic, trans-cinnamic and p-coumaric acids. Presence of ferulic acid, quercetin, 3,5-dihydroxybenzoic acid, rutin, syringin, protocatechuic acid, vanillic acid and fisetin.	Jakovljević et al., 2020

The essential oil of the plantlets was obtained by micro steam distillation-extraction of the fresh shoots of the in vitro grown plants in a modified Lickens-Nickerson apparatus for 2.5 h using diethyl ether as a solvent (Sandra & Bicchi,1987). The essential oil of the five *A. alba* Turra treatments was characterized based on up to 34 terpenoid components. The mono- towards sesquiterpenoids (M/S) ratio of the essential oils was shown to be dependent on the morphotype of *A. alba* Turra *in vitro.* Thus, while its value was 5.2 for the rooting morphotype, its value dropped to 2 - 2.5 for the non-rooting *A. alba* Turra (Danova et al., 2012). Interestingly, the reverse dependencies were obtained from the underground parts of the plants. Thus, while in the rooting morphotype the M/S ratio of the oils of the underground parts was 0.01 -

0.02, and for the non-rooting morphotype it was 0.09 - 0.17, showing the generally strong predominance of sesquiterpenoids in the underground samples (Krumova et al., 2013). The qualitative analysis of the oils showed that the chemical composition of the sesquiterpenods in the aerial and underground samples differed, excluding the option of root-to-shoot translocation as a factor affection the terpenoid profile in the two morphotypes (Danova et al., 2018).

Rooting is a key feature in cytokinin biogenesis and translocation. The biosynthesis of free cytokinins occurs mainly in root apical meristems (Sakakibara, 2006). In order to establish the possible dependencies, endogenous cytokinin pools of the *A. alba* Turra samples were studied by HPLC coupled to hybrid triple quadrupole/linear ion trap mass spectrometer with internal standards (Djilianov et al., 2013, Žižková et al., 2015).

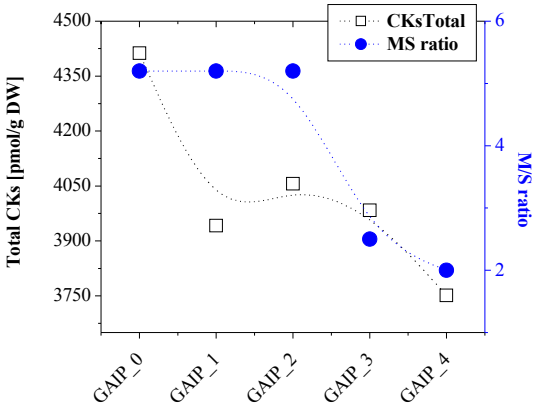

Fig. 2. Comparative representation of the content of total cytokinins and the mono- towards sesquiterpenoids (M/S) ratio in the different *A. alba* Turra PGR treatments *in vitro*.

The graphical representation of the dependencies obtained is given in Figs. 2 and 3. The relations between the M/S ratio and the total cytokinins, and bioactive cytokinins (representing the sums of cytokinin free bases and ribosides), Figs. 2 and 3, respectively showed that rooting of the plant influenced by the exogenous PGR treatments plays a major role in both terpenoid biogenesis and status of endogenous cytokinin pools of the plant.

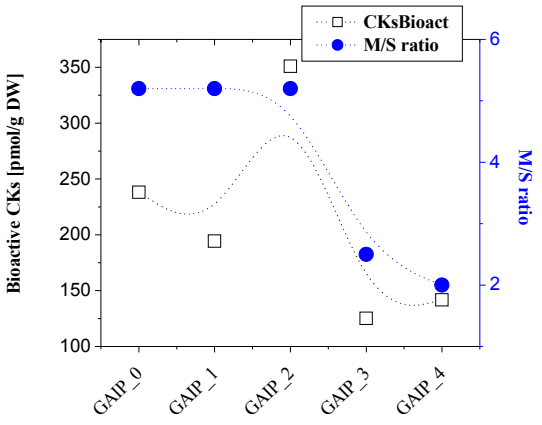

Fig. 3. Comparative representation of the content of bioactive cytokinins (sum of free bases and ribosides) and the mono- towards sesquiterpenoids (M/S) ratio in the different *A. alba* Turra PGR treatments *in vitro*.

The levels of total phenolic and flavonoid compounds were also studied spectrophotometrically (Koleva et al., 2015).

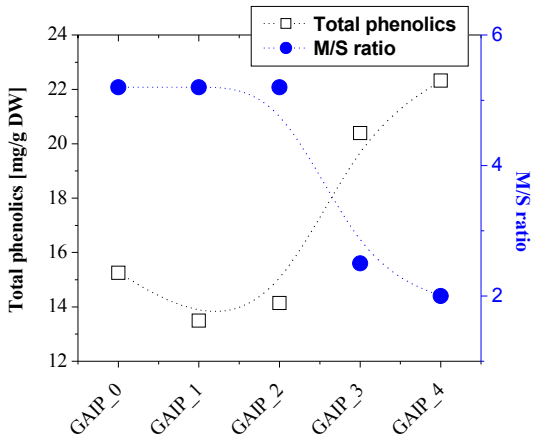

Fig. 4. Comparative representation of the content of total phenolic compounds and the mono- towards sesquiterpenoids (M/S) ratio in the different *A. alba* Turra PGR treatments *in vitro*.

It was established that the levels of both phenolic (Fig. 4) and flavonoid (Fig. 5) compounds were related to the *A. alba* Turra morphotypes obtained.

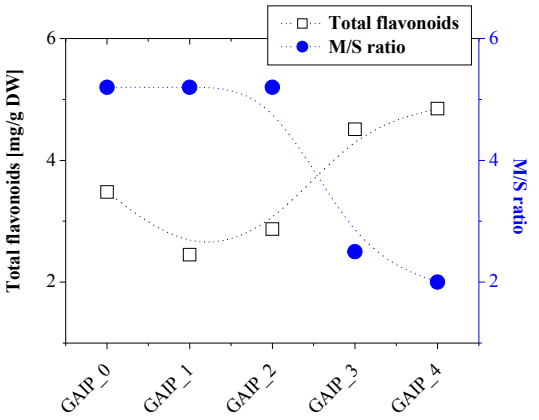

Fig. 5. Comparative representation of the content of total flavonoid compounds and the mono- towards sesquiterpenoids (M/S) ratio in the different *A. alba* Turra PGR treatments *in vitro*.

The biotechnological development of *A. alba* Turra and the dependencies obtained by this experimental design provide clues of the possibilities to target terpenoid and phenolic compounds biogenesis by means of inducing morphological changes of the *in vitro* cultivated plants without performing genetic manipulations.

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