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PHYTOCHEMICAL AND CHEMOTAXONOMICAL INVESTIGATIONS OF LAMIACEAE FROM NORTH MACEDONIA

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The flora of North Macedonia and the entire Balkan Peninsula is very rich, hosting numerous species of Lamiaceae. To date, many Lamiaceae species have been studied from various perspectives, including phytochemistry, chemotaxonomy, biological activity, molecular phylogeny, pharmacology, ethnobotany, and more. This review summarizes the results of studies on the phytochemistry, chemotaxonomy, and biological activity of Lamiaceae, with a particular focus on those species that grow wild in North Macedonia. The findings suggest that this region is a rich source of plants that could be of interest for further research, both from fundamental and applied perspectives. Academician Vlado Matevski made significant contributions to the study of plants from North Macedonia and the broader Balkan Peninsula. His passion as a botanist and collaborative work with regional scientists led to the publication of numerous papers in national and international journals.

Key words: Lamiaceae; North Macedonia; phytochemistry; chemotaxonomy, biological activity

INTRODUCTION

Lamiaceae is one of the largest angiosperm families, with many species found in the Mediterranean region. For centuries, numerous species have been used in traditional medicine and as culinary herbs. Some genera, such as *Satureja* L., *Sideritis* L., *Thymus* L., and *Salvia* L., are frequently used in folk medicine in Mediterranean and Balkan countries due to the proven biological activities of their essential oils and extracts. Many members of the Lamiaceae family, particularly those from the Nepetoideae subfamily, are well-known aromatic plants. As a result, numerous native Lamiaceae species from North Macedonia have been subject to phytochemical investigations focusing on their chemical composition and biological activity, including chemotaxonomy. While most studies have concentrated on essential oils and flavonoids, some have also examined other specialized metabolites.

The aim of this study is: a) to review papers on the phytochemistry, biological activity, and chemotaxonomy of Lamiaceae species growing wild in North Macedonia and the Balkan Peninsula, and b) to highlight the contributions of Academician Vlado Matevski to these areas, as well as his collaborative work with scientists from international scientific institutions.

PHYTOCHEMICAL INVESTIGATIONS

Investigations of Lamiaceae species from North Macedonia have primarily focused on essential oils and flavonoids, though several studies have also explored other phenolics and nonvolatile terpenoids (such as diterpenes). Various aromatic plants from different genera have been studied for their essential oil composition, while most of the research on flavonoids has concentrated on two species from the genus *Sideritis*. Studies with applied phytochemistry, including chemotaxonomy

and bioactivity, will be discussed in other sections of this review. Here, we primarily focus on the fundamental phytochemical investigations of Lamiaceae species from North Macedonia.

Essential oils

Many aromatic plants grow in North Macedonia, the majority of which belong to the Lamiaceae family. Despite this, only a few aromatic species from Lamiaceae genera have been analyzed so far. Over the last 30 years, essential oils (EOs) have been extracted and characterized from species in genera such as *Micromeria* Benth., *Clinopodium* L., *Mentha* L., *Thymus* L., *Rosmarinus* L., *Melissa* L., *Origanum* L., *Ocimum* L., *Teucrium* L., and *Sideritis* L. In all cases, crude EOs were obtained by hydrodistillation using a Clevenger-type apparatus from dried plant material, then analyzed using gas chromatography (GC) equipped with MS and FID detectors. In most cases, oxygenated terpenes were the most abundant class of compounds in the essential oils, although in some samples, hydrocarbons predominated in the EO composition. The most commonly found terpenes are presented in Figure 1.

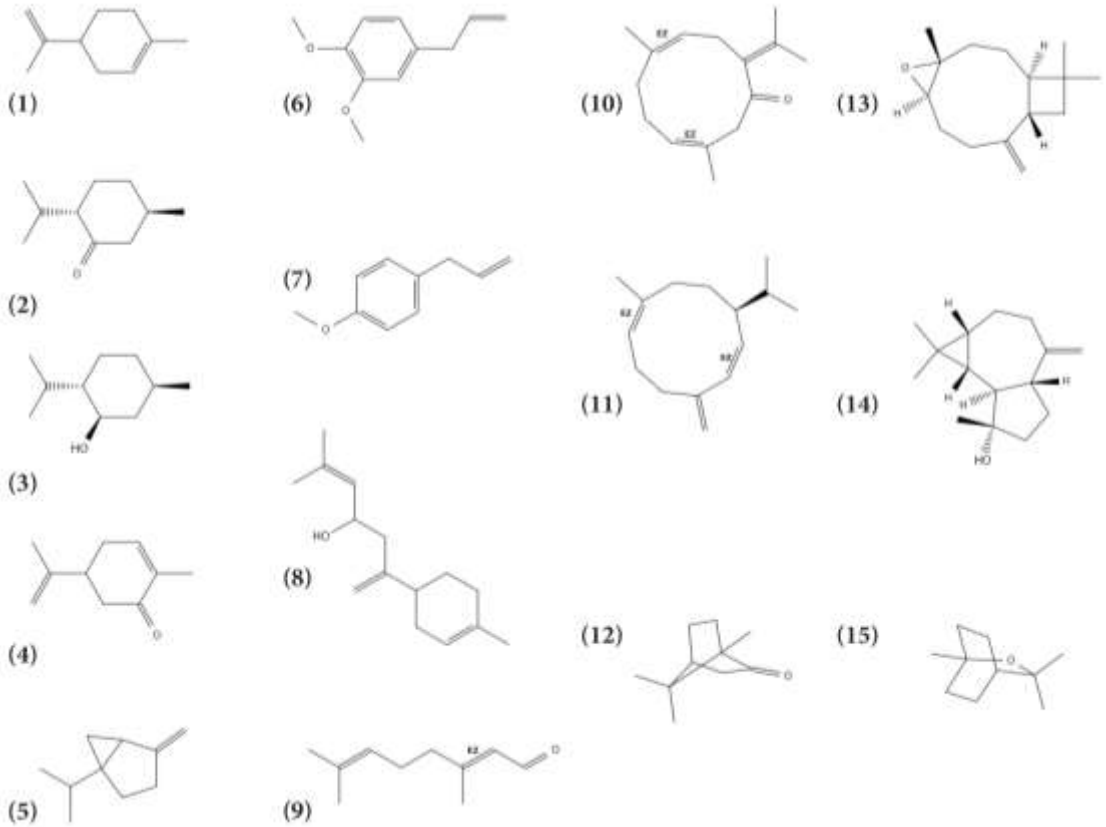

Figure 1. Structural formulae of some of the most commonly found terpenes in essential oils of Lamiaceae species from North Macedonia. (1) Limonene, (2) Menthone, (3) Menthol, (4) Carvone, (5) Sabinene, (6) Methyl eugenol, (7) Estragole, (8) β-Atlantol, (9) Geranial, (10) Germacron, (11) Germacrene D, (12) Camphor, (13) Caryophyllene oxide, (14) Spathulenol, (15) 1,8-Cineole.

Kostadinova et al. [1] analyzed EOs from two *Micromeria* species: *M. cristata* (Hampe) Griseb. (from Alshar) and *M. juliana* (L.) Benth. ex Rchb. (from Prilep). A total of 33 and 16 compounds were identified in the EOs of *M. cristata* and *M. juliana*, respectively. Oxygenated sesquiterpenes were the dominant class of compounds in both oils. In *M. cristata* EO, germacron and β-atlantol were the most abundant compounds, while the highest concentration in *M. juliana* EO was caryophyllene oxide. The chemical composition of both oils corresponded to reports in the literature for populations from the Balkan region. In contrast, the EO from *M. dalmatica* (now recognized as *Clinopodium dalmaticum* (Benth.) Bräuchler & Heubl) and a population of *M. cristata* collected from Bosnek (Bulgaria) had oxygenated monoterpenes as the dominant class of compounds. In a more recent study, Kremer et al. [2] investigated the chemical composition of the essential oil, as

well as the types and distribution of trichomes and pollen morphology, in two closely related species, *Micromeria kerneri* Murb. and *M. juliana* (L.) Benth. One of the analyzed populations was *M. juliana* from the Babuna River. A total of 37 compounds were identified in the EO. Oxygenated monoterpenes and sesquiterpenes together accounted for over 50% of the total oil composition. The two most abundant compounds were caryophyllene oxide and piperitone oxide. Caryophyllene oxide was the major component in the EO from all populations in the Balkans, except for North Macedonia, where piperitone oxide was also a significant component in the oil of the Macedonian population. This compound had not been previously reported in *M. juliana* from Macedonia, suggesting that the EO composition exhibits interpopulation diversity. Phenolic compounds such as thymol and carvacrol were found in the oils from all populations, except for the Macedonian locality, indicating a climate more similar to continental than Mediterranean conditions.

Kostik et al. [3] studied the EOs of *Mentha* × *piperita* L. and *M. spicata* L. from the Mavrovo region. Menthol, menthone, and carvone were the major constituents in both species, while 1,8-cineole and limonene were abundant in *M. spicata*. Essential oils from *M. longifolia* (L.) L. were also analyzed as part of an extensive study of medicinal plants from the Šara Mountain region by Hajdari et al. [4]. In the EOs obtained from the aerial parts of this species, 29 compounds were identified. Oxygenated monoterpenes were the most abundant class in the EO, with menthone representing the majority of the oil's composition.

In the study by Hajdari et al. [4], seven additional Lamiaceae taxa were analyzed: *Thymus* sp. (the original paper cites *T. serpyllum* L., but we consider this a misidentification of another thyme species, as the cited species does not grow in the mentioned region), *Rosmarinus officinalis* L. (now *Salvia rosmarinus* Spenn.), *Melissa officinalis* L., *Origanum vulgare* L., *Ocimum basilicum* L., *Teucrium chamaedrys* L., and *Sideritis scardica* Griseb. A total of 85 compounds were reported for each taxon. In *Melissa officinalis* L., 23 compounds were identified, predominantly belonging to the class of oxygenated sesquiterpenes and monoterpenes. The percentages of terpenic hydrocarbons and other aliphatic and aromatic hydrocarbons were low. The most abundant compounds in *Melissa officinalis* L. EO were geranial and spathulenol. In *Ocimum basilicum* EO, 56 compounds were identified, with phenylpropanoids being the principal compounds, making up the majority of the EO. Methyl chavicol (estragole) and methyl eugenol were the most prominent compounds. In the EO of *Rosmarinus officinalis*, 30 compounds were identified, with a high concentration of oxygenated monoterpenes, including 1,8-cineole and camphor as the most abundant compounds. In the EOs of *Teucrium chamaedrys*, 50 compounds were identified, with sesquiterpene hydrocarbons representing nearly half of the oil, and germacrene D being the dominant compound. The lowest number of compounds (22) was found in *Thymus* sp., where thyme oil was dominated by oxygenated monoterpenes, with linalool and linalyl acetate being the most abundant compounds.

Thirty-nine compounds were identified in *Origanum vulgare* EO, where the most abundant class were sesquiterpene hydrocarbons, and the most abundant compounds were germacrene D, sabinene, and (*E*)-caryophyllene [4]. Essential oil of *O. vulgare* was previously reported only by Lukas et al. [5] in a large pan-European study. EOs of 502 individual *O. vulgare* plants from 17 countries and 51 populations were analyzed. Three samples from North Macedonia, originating from the Ohrid, Kičevo, and Demir Hisar municipalities, were analyzed. These EOs were dominated by sesquiterpenes, a profile similar to populations from Serbia, Albania, and Bulgaria. Lukas et al. [5] identified three chemotypes based on the proportions of cymyl-compounds, sabinyl-compounds, and acyclic linalool/linalyl acetate. The cymyl- and acyclic pathways were typically active in plants from Mediterranean climates, while the sabinyl-pathway was characteristic of plants from continental climates. The plants from North Macedonia exhibited a chemical composition comparable to other non-coastal populations, with a sabinyl chemotype (the sum of sabinene, sabinene hydrate, and sabina ketone) at the population level. However, these percentages were lower than those found in true continental species, which aligns with the results obtained later by Hajdari et al. [4].

The last of the eight species studied by Hajdari and coworkers was *Sideritis scardica*. The essential oil of this species was the most complex, with 64 identified compounds. Fatty acids and other non-terpenic hydrocarbons were the principal components, with hexadecanoic acid and 13-epimanool being the most abundant compounds. Additionally, it is interesting to mention the study by Qazimi et al. [6], which investigated volatile organic compounds (VOCs) from hot water infusions of stems and rosette leaves of *Sideritis raeseri* Boiss. & Heldr. from three populations in North Macedonia. The hot water infusions were transferred to headspace vials, heated at 80°C, and ana-

lyzed using HS-GS/MS-FID for volatiles. Sixteen compounds were detected and identified in the volatiles from stem infusions, with α- and β-pinene representing over 60% of the volatiles. Only ten compounds were detected in the leaves from the rosette, but the overall composition was similar, with α- and β-pinene again accounting for over 60% of the VOCs. This is in stark contrast to the EOs obtained by hydrodistillation.

Flavonoids

Flavonoids were studied from a number of different species belonging to the genera *Mentha*, *Salvia*, *Sideritis*, *Stachys*, *Teucrium*, and *Thymus*. Depending on the study, different solvents were used (diethyl ether, acetone, methanol, and ethanol), and obtained extracts were analyzed using HPLC coupled with two detectors (DAD and MS^n). Some of the most commonly identified flavonoids are shown in Figure 2.

One of the earliest studies on flavonoids was conducted by Kulevanova et al. [7]. In this study, the flavonoid composition of *Thymus longidens* var. *lanicaulis* Ronn. and *T. longidens* var. *dassareticus* Ronn., growing wild in North Macedonia, was determined. The aglycones were extracted from the plant material using diethyl ether and analyzed via HPLC-DAD. Five aglycones were detected: eriodictyol, luteolin, naringenin, apigenin, and diosmetin. Apigenin was identified in both taxa, while luteolin was present in *T. longidens* var. *lanicaulis*. The principal flavone in *T. longidens* var. *dassareticus* was diosmetin. The flavanones naringenin and eriodictyol were found in both taxa.

A survey of twenty medicinal plants growing on Mount Jablanica (Gorna Belica) at altitudes ranging from 1,450 to 2,000 m a.s.l. included six species from the Lamiaceae family: *Mentha longifolia* L., *Salvia verticillata* L., *Sideritis raeseri*, *Stachys alpina* L., *S. jacquini* (Gren. & Godr.) Fritsch., and *S. sylvatica* L. [8 and references cited therein]. This preliminary study analyzed only the total phenolic and flavonoid contents of various plant parts, including leaves, stems, and flowers. The highest phenolic content in leaves was found in *Sideritis raeseri* and *Mentha longifolia*, while the lowest was observed in *Salvia verticillata*. The highest phenolic levels in stem extracts were detected in *Stachys jacquini*, with the lowest in *S. sylvatica*. The highest phenolic amounts in flower extracts were recorded in *Mentha longifolia* and *Sideritis raeseri*, while the lowest were found in *Stachys sylvatica*. Flavonoid content was similar across species and plant organs. However, flowers of *Mentha longifolia* and stems of *Stachys jacquini* had twice the concentration of flavonoids compared to other samples, while the lowest concentration was found in stems of *Salvia verticillata*.

Mitreski et al. [9] studied the polyphenolic profiles of *Teucrium chamaedrys*, *T. montanum* L., *T. polium* L., and *T. scordium* L. A total of 31 phenolic compounds were identified, quantified, and classified into four groups: hydroxycinnamic acid derivatives (2 compounds), phenylethanoid glycosides (12), flavonoid glycosides (11), and flavonoid aglycones (6). Most of the flavonoid glycosides contained luteolin as the flavonoid component, with various sugar moieties, and several of these compounds were found in higher concentrations. One quercetin, one kaempferol, two diosmetin, and four apigenin glycosides were detected, along with luteolin glycosides. Flavonoid aglycones were also present, including diosmetin, luteolin, apigenin, cirsiliol, and cirsimaritin.

Flavonoids have been extensively studied in two species of *Sideritis*: *S. scardica* and *S. raeseri*. Janeska et al. [10] identified isoscutellarein, chryseriol, and apigenin in acetone extracts. Additionally, a 4'-methyl ether derivative of isoscutellarein was found, along with hypolaetin and its methyl ether derivative. A wide variety of 8-OH flavones were found in *S. raeseri* (hypolaetin, isoscutellarein, 3'-OCH3 hypolaetin, apigenin, and 4'-OCH3 isoscutellarein), whereas only two (isoscutellarein and the 3'-methyl ether of hypolaetin) were found in *S. scardica*. Moreover, chryseriol was found only in the *S. scardica* extracts. Petreska et al. [11] expanded the study of *Sideritis* phenolics. They analyzed twenty-one samples of *Sideritis scardica*, *S. raeseri*, *S. taurica*, *S. syriaca*, and *S. perfoliata* from the Balkan Peninsula, including twelve populations of *S. scardica* and *S. raeseri* collected from North Macedonia. Twenty-four flavonoid glycosides were detected, constituting up to 50% of the phenolic composition. Most of the glycosides were derivatives of hypolaetin, isoscutellarein, apigenin, and luteolin. In a study by Ibraliu et al. [12], only one sample from North Macedonia was analyzed—*S. scardica* from Mt. Šara. Thirty flavonoids were identified in all the samples; however, only the following individual flavonoids were detected in every sample: 3'-O-methylhypolaetin, 7-O-[6‴-O-acetyl]-allosyl-(1→2) glucoside, 4'-O-methylhypolaetin, and 7-O-[6‴-O-acetyl]-allosyl-(1→2)-[6″-O-acetyl] glucoside. Other flavonoids varied depending on the species and locality studied (individual reports on each of the populations studied were not provided in this manuscript).

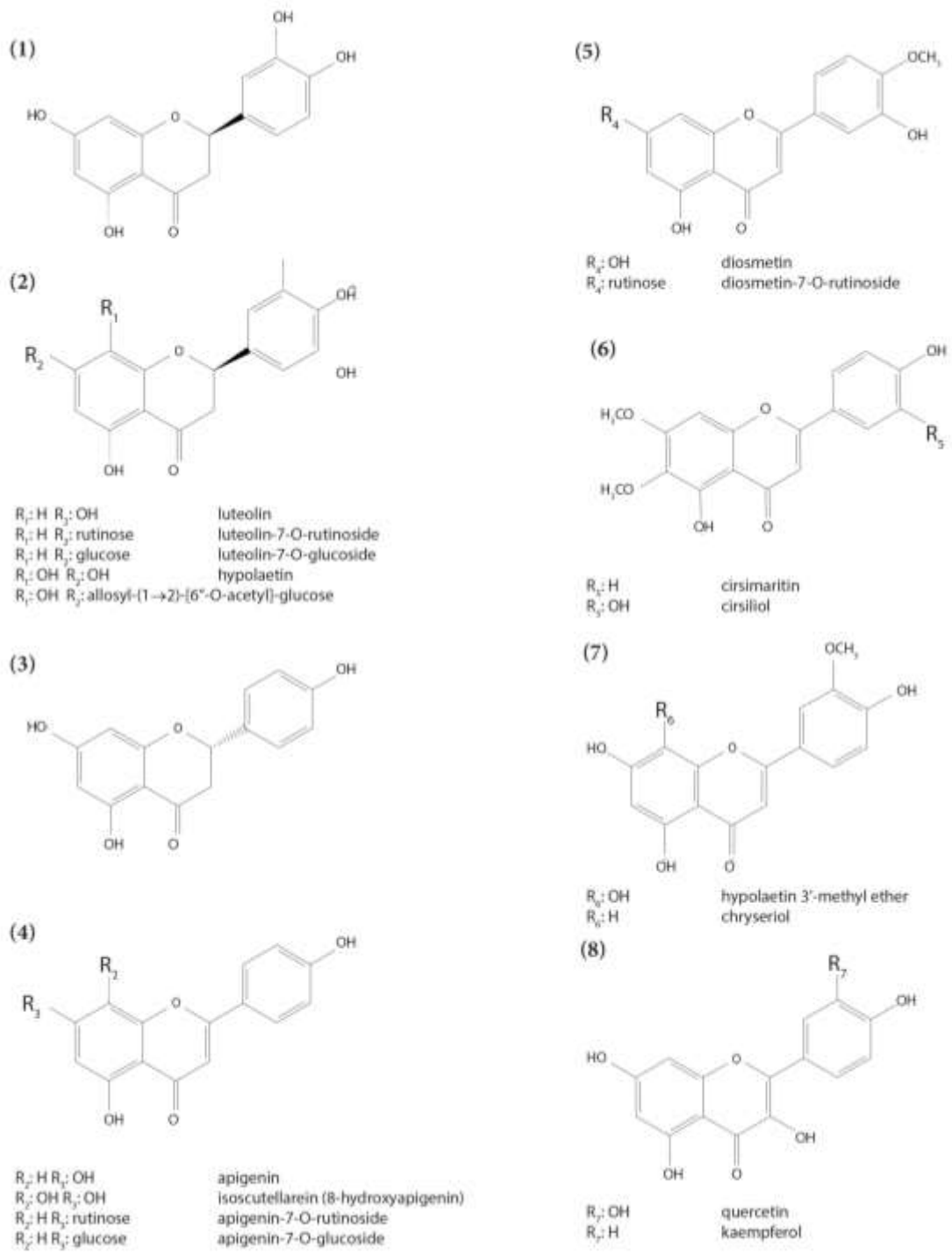

Figure 2. Structural formulae of some of the most commonly found flavonoids in Lamiaceae species from North Macedonia. (1) Eriodictyol, (2) luteolin and hypolaetin and their glycosides, (3) naringenin, (4) apigenin, isoscutellarein and glycosides, (5) diosmetin and diosmetin-7-*O*-rutinoside, (6) cirsimaritin and cirsiliol, (7) hypolaetin 3'-methylether and chryseriol, (8) quercetin and kaempferol.

Other compounds

Several other groups of compounds have also been reported from Lamiaceae species in North Macedonia. Here, we will focus on several papers that have not examined the chemical composition concerning applications, such as chemophenetics or bioactivity.

In a study by Mitreski et al. [9] on the polyphenolic profiles of *Teucrium*, other phenolics, aside from flavonoids, were also identified. 5-Caffeoylquinic acid was detected in all analyzed species, while caffeic acid was not found in *T. po-*

lium. Twelve phenylethanoid glycosides were detected, with varying distribution patterns. For example, forsythoside B was present in all taxa, but it was the most abundant compound in *T. chamaedrys*, while in *T. scordium*, verbascoside was also present in high concentrations. On the other hand, caerulescenoside was the second most abundant in *T. montanum*, while the most abundant glycoside in *T. polium* was samioside.

In their study of phenolics and diterpenes in *Sideritis* from the central Balkan region, Ibraliu et al. [12] used two solvents to obtain extracts with different chemical compositions. Plant material was pulverized and extracted using ethanol (for phenolics and flavonoids) or *n*-hexane (for diterpenes) with the aid of ultrasound. Only one sample (*S. scardica*) originated from North Macedonia (Mt. Šara), as mentioned earlier. In the ethanol extract, 48 compounds were detected and identified, of which eighteen were hydroxycinnamic acids and phenylethanoid glycosides, while the remainder were flavonoids. The following individual phenolics were detected in all the studied samples: 5-caffeoylquinic acid, lavandulfolioside, verbascoside, forsythoside A, isoverbascoside, leucoseptoside A, along with several flavonoids (as mentioned above). The results suggest that the geographic location where the samples were collected plays at least as significant a role in the phenolic qualitative profile as the species–*S. scardica* or *S. raeseri*. However, statistical analysis showed that wild species exhibit a species-specific phenolic profile, except for ex-situ grown specimens. The qualitative composition of diterpenes was almost identical across all *S. scardica* and *S. raeseri* samples, with the two major constituents being siderol and sideridiol. However, the ratio between these two compounds varied between species and localities.

Petreska et al. [11] also analyzed phenolics in two *Sideritis* species (*S. scardica* and *S. raeseri*). Three hydroxycinnamic derivatives – 5-caffeoylquinic acid, p-coumaric acid 4-O-glucoside, and feruloylquinic acid were present in both species. However, depending on the population, the levels of some of these compounds were too low to be detected. Eight phenylethanoid glycosides were detected at varying concentrations, with echinacoside, lavandulfolioside, and verbascoside often present in higher concentrations, while isoverbascoside was frequently absent.

Qazimi et al. [13] studied the chemical composition of n-hexane extracts of *Sideritis scardica* and *S. raeseri* using GC/FID/MS. The plant samples were collected from various locations in the western, central, and southern parts of Macedonia (nine localities), as well as the southern part of Albania, comprising twelve different samples of plant material. In the *n*-hexane extracts of *S. scardica* from seven localities and *S. raeseri* from two, over 100 different compounds were detected and identified. Mono- and sesquiterpenes were present in very small amounts, with a total of 25 components identified. In *S. scardica*, the sesquiterpene (*E*)-caryophyllene was the most abundant terpene, while, depending on the population, α- and β-pinene were more concentrated in *S. raeseri*. The fractions of fatty acids and fatty acid-ester compounds were more abundant, with methyl isopropyl hexadecanoate and hexadecanoic acid found in *S. scardica*, as well as octadecanoic acid methyl ester and hexadecanoic acid in *S. raeseri*. The largest fraction consisted of aliphatic hydrocarbons with long carbon chains (C25-C33). The most abundant components were *n*-C27, *n*-C29, *n*-C31, and *n*-C33. The second largest fraction was made up of diterpenes: kaur-15-en, 3a-hydroxy manool, manoyl oxide, and 7-ethenyl-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydro-1,1,4a,7-tetramethyl-2-phenanthrenol. Additionally, eight more components were tentatively identified as diterpenoids.

An interesting study by Kitić et al. [14] is also worth mentioning. These authors examined the fatty acid composition of the aerial parts of four *Calamintha* Miller species, including *C. vardarensis* Šilić (= *Clinopodium vardarense* (Šilić) Govaerts), which originated from North Macedonia. The plant material (100 g) was extracted by maceration in chloroform/methanol (2:1). The obtained fatty acids and a 1% methanolic solution of H_2SO_4 were refluxed for 1.5 hours. Fatty acid methyl ester analysis was performed using GC-MS-FID. Oleic, palmitic, and linoleic acids were the main constituents in the chloroform–methanol extract of *C. vardarensis*. The unsaturated/saturated index was 1.1. The results were similar to those of other analyses of *Clinopodium* taxa.

Chemotaxonomical investigations

Essential oils

Many *Lamiaceae* species from this region have been investigated from chemical and chemotaxonomic perspectives. For example, Slavkovska et al. [15] studied the variability in the essential oil composition of *Satureja montana* L. They investigated both intra- and interpopulational variability within one population of ssp. *pisidica* (Wettst.) Šilić (now recognized as *S. montana* ssp. *macedonica* (Formánek) Baden) and two populations of ssp. *montana*. All samples were grouped according

to the dominant component in the EO. The results revealed significant individual variability in oil composition. Monoterpenes dominated in all samples, particularly oxygenated monoterpenes. The main constituents of ssp. *macedonica* were p-cymene, linalool, and carvacrol, while in ssp. *montana*, p-cymene, trans-sabinene hydrate, linalool, borneol, and p-cymen-8-ol were the dominant components. Based on the results presented, the authors concluded that populations of the same subspecies/variety exhibited similar profiles, as indicated by the presence of chemotypes and their frequency. Later, these authors investigated the variability in the essential oils of *Satureja montana* L. and *S. kitaibelii* Wierzb. ex Heuff. from the central part of the Balkan Peninsula [16]. The results of the EO composition confirmed that there were differences between populations within the same subspecies (ssp. *montana*), between subspecies (ssp. *montana* and ssp. *macedonica*), as well as between species (*S. montana* and *S. kitaibelii*). Additionally, the essential oil composition of *S. montana* ssp. *montana* was more similar to that of *S. montana* ssp. *macedonica* than to *S. kitaibelii*.

Very recent research conducted by our group aimed to study the variability in the essential oil composition of *S. montana* L. [17]. The study focused on individual plants from three *S. montana* subspecies (ssp. *montana*, ssp. *variegata*, and ssp. *macedonica*) collected from fourteen wild-growing populations in the western Balkans. Given the number of samples studied, this work represents the most extensive analysis of intra- and interpopulation variability of this species. The essential oil composition was dominated by monoterpenes, followed by sesquiterpenes, which is consistent with previous studies. Almost half of the individuals had carvacrol and thymol as the dominant constituents, while the others had p-cymene, linalool, geraniol, and cis-sabinene hydrate. This led to the identification of five chemotypes, each with a geography-specific distribution. The dominant chemotypes in coastal populations were phenolic in *S. montana* ssp. *variegata* and ssp. *montana*, while p-cymene, linalool, cis-sabinene hydrate, and geraniol were more common in continental populations, regardless of their intraspecific taxonomic status. This research confirmed a strong genetic control over chemical composition. Additionally, these findings could provide a solid foundation for selecting specific chemotypes with desired essential oil profiles, as the compounds mentioned above exhibit distinct biological activities [17].

Stachys L. has also been investigated by various authors. Radulović et al. [18] examined the chemotaxonomic significance of the volatiles in four Balkan representatives of this genus (*S. germanica* ssp. *heldreichii* (Boiss.) Hayek and *S. iva* Griseb. from North Macedonia; *S. plumosa* Griseb. and *S. scardica* (Griseb.) Hayek from Serbia). It is important to note that *Stachys* species are non-aromatic plants. The chemotaxonomic relationships within the genus, as well as with related Lamioideae, were discussed. Nuciferyl esters and volatile diterpenoids were identified as potential markers. The high degree of variation in the main constituents, particularly germacrene D and its congeners, was linked to possible rearrangements under hydrodistillation conditions. As a result, due to the potential artefactual origin of these compounds, they appear to be unreliable as chemotaxonomic markers [18].

The chemical composition of the EO was investigated in *Stachys iva* and *S. horvaticii* Micevski growing in North Macedonia [19]. The EO of *S. iva* was characterized by a high concentration of oxygenated sesquiterpenes, with caryophyllene oxide and spathulenol as the principal components. In contrast, hexadecanoic acid was a major component in *S. horvaticii* oil. Based on the EO composition, *S. iva* could be classified into the oxygenated sesquiterpenes group, while *S. horvaticii* was identified as the hydrocarbons chemotype [19]. Academician Matevski, an exceptional field botanist and taxonomist, contributed to the collection and identification of the investigated taxa in North Macedonia, as well as to the discussion of the obtained results.

Several papers have been published regarding *Clinopodium* L. and related genera. Dunkić et al. [20] investigated the micromorphological and phytochemical traits of four *Clinopodium* species. In total, 62 different EO compounds were identified: 21 from *C. dalmaticum*, 31 from *C. thymifolium* (Scop.) Kuntze, 36 from *C. serpyllifolium* (M. Bieb.) Kuntze, and 37 from *C. pulegium* (Rochel) Bräuchler. All species were characterized by a high content of oxygenated monoterpenes, with dominant menthane-type compounds such as menthone, pulegone, piperitenone, and piperitenone oxide. Based on the EO composition, the four investigated *Clinopodium* species could be grouped into the pulegone/piperitenone/piperitenone oxide chemotype.

A study of the phytochemical and molecular characteristics of *Micromeria* (*M. croatica* (Pers.) Schott, *M. cristata* ssp. *cristata* (Hampe) Griseb., *M. cristata* ssp. *kosaninii* Šilić, *M. graeca* ssp. *graeca* (L.) Benth. ex Rchb., *M. graeca* ssp. *fruticulosa* (Bertol.) Guinea, *M. juliana*, *M. longi-*

pedunculata Bräuchler, *M. microphylla* (d'Urv.) Benth.) and *Clinopodium* taxa (*C. dalmaticum*, *C. frivaldszkyanum* (Degen) Bräuchler & Heubl, *C. pulegium*, *C. thymifolium*, *C. serpyllifolium*) distributed across the Balkan Peninsula was carried out [21]. Each taxon was investigated across several populations. Some samples of the *Micromeria* taxa (*M. cristata* ssp. *cristata*, *M. cristata* ssp. *kosaninii*, *M. juliana*) were collected from various localities within North Macedonia. Essential oil composition and molecular data (AFLP) were used to study the taxonomic relationships among the taxa and the correlations between phytochemical and molecular results. The Mantel test revealed a significant correlation between the phytochemical and genetic data. Based on these results, the current taxonomic position of several of the studied taxa remains unresolved, and further studies are needed. Academician Matevski, as a coauthor, played an active role in the investigation, including plant collection, identification, and the discussion of the results.

Radulović and Blagojević (2010) [22] investigated the EO profile of *Calamintha vardarensis* Šilić, which, according to molecular phylogeny data, also belongs to the *Clinopodium* group (*Clinopodium vardarense* (Šilić) Govaerts).

Very recently, a chemometric analysis was conducted to examine the variability in the composition of essential oils in ten *Salvia* L. species (*S. aethiopis* L., *S. argentea* L., *S. candidissima* Vahl, *S. sclarea* L., *S. teddii* Turill, *S. ringens* Sm., *S. verticillata* L., *S. amplexicaulis* Lam., *S. pratensis* L., *S. virgata* Jacq.) from different taxonomic sections or phylogenetic clades [23]. Chemometric analysis was used to identify relationships between the samples based on their chemical classes, resulting in the classification of two distinct groups. This research highlighted two groups based on the chemical classes of the ten *Salvia* species from different taxonomic sections or phylogenetic clades, which were discernible both quantitatively and qualitatively. These findings can be further explored through classical or modern taxonomic studies on *Salvia* [23].

Flavonoids

Phytochemical, chemotaxonomic, and micromorphological aspects of *Micromeria* and related genera (*Satureja*, *Calamintha*, *Acinos*, and *Clinopodium*) of the tribe *Satureineae* Benth. from the Central Balkan region were investigated by Marin [24]. Some species were collected from North Macedonia, such as *Micromeria juliana*, *Acinos suaveolens* (Sm.) G. Don, *A. hungaricus* (Simonk.) Šilić, and *Clinopodium vulgare* L. Surface (lipophilic) and vacuolar flavonoids were examined from a chemotaxonomic perspective. In later collaborative work with Spanish phytochemists, external and vacuolar flavonoids of some *Micromeria* species were also studied [25]. The presented results suggested the possibility of separating the studied species into two well-defined groups. The first group (*M. albanica* (Griseb. ex K. Malý) Šilić, *M. dalmatica* Benth., and *M. thymifolia* (Scop.) Fritsch) was characterized by the accumulation of significant amounts of external flavonoids of the 5,6-dihydroxy-7-methoxy type and acacetin glycosides, while the second group (*M. juliana* and *M. graeca*) was characterized by a minimal amount of external flavonoids (mostly luteolin and apigenin) and by luteolin and apigenin glycosides as major constituents. This separation aligns with newer systematics that have transferred species from section *Pseudomelissa* sensu Boissier into the genus *Clinopodium*. A later chemotaxonomic study of vacuolar flavonoids in some Balkan *Micromeria* Benth. species further demonstrated the usefulness of these metabolites in the taxonomy of this intriguing group [26].

Marin et al. [27] also investigated external flavonoids from *Satureja cuneifolia* Ten. and *S. adamovicii* Šilić, a very complex taxa from a taxonomic perspective. Specimens of *S. adamovicii* were collected in the gorge of the Raicka River (North Macedonia). The main external methoxylated flavone was gardenin-B. Salvigenin and xanthomicrol were also present in high concentrations, while cirsimaritin was found in slightly lower amounts. In addition to the external methylated flavones, two flavanones, eriodictyol and naringenin, were also present in this species. Samples of *S. cuneifolia* were gathered from Pelješac (Croatia). In the leaves of *S. cuneifolia*, four methylated flavones were identified: 5-desmethylnobiletin (the main compound), xanthomicrol, 5,6,4'-trihydroxy-7,3'-dimethoxyflavone, gardenin-B, thymonin, and 5,6-dihydroxy-7,8,3',4'-tetramethoxyflavone. The flavanone eriodictyol was also present in the *S. cuneifolia* extract. These two related species share the dominance of 5-hydroxy-6,7,8-trimethoxyflavones (xanthomicrol, 5-desmethyl nobiletin, and gardenin-B). However, they differ in the presence of other flavones and flavanones identified. The taxonomic significance of the external flavonoid profiles in these related taxa is discussed.

External flavonoids of 40 Macedonian *Thymus* L. species and infraspecific taxa, belonging to the sections *Marginati*, *Pseudothymbra*, and *Ser-*

pyllum, were studied using HPLC combined with diode array detection and atmospheric pressure chemical ionization mass spectrometry [28]. Nineteen different flavones were identified, with the most common and abundant compound being 5,6-dihydroxy-7,3,4-trimethoxyflavone. Most species also produce surface flavanones, including eriodictyol, naringenin, and isosakuranetin. Despite correlations with geography, the profiles of surface flavones and flavanones found in this survey of Macedonian *Thymus* taxa may provide valuable additional taxonomic markers at the subspecific, specific, and sometimes subsectional and sectional levels of this genus. The contribution of Academician Matevski, a coauthor of this paper and a well-known expert in the taxonomy and chorology of the *Thymus* genus, was exceptional. His expertise was crucial in the discussion of the flavonoid profile within the investigated taxa.

Recently, the chemical profiling of six *Stachys* taxa from the Balkan Peninsula – *S. recta* L. subsp. *nitens* (Janka) Chrtek, *S. atherocalyx* K. Koch, *S. beckeana* Dörfl. & Hayek, *S. zepcensis* Formánek (all four belonging to the *S. recta* group), *S. alpina* ssp. *dinarica* Murb., and *S. plumosa* – was conducted using the HPLC-DAD-ESI-MS technique [29]. Samples of *S. atherocalyx* K. Koch were collected from North Macedonia. In total, 44 phenolic compounds were detected, categorized into three main classes: phenolic acids, phenylethanol glycosides, and flavonoids. The results of this study confirmed the significance of flavone 7-O-allosylglucosides at the sectional level of the *Stachys* genus.

Macedonian and Bulgarian scientists have investigated the polyphenolic profiles of Balkan *Sideritis* L. species. Stanoeva et al. [30] examined forty-two samples from five *Sideritis* species (*S. scardica*, *S. raeseri*, *S. syriaca* L., *S. taurica* Stephan ex Willd., and *S. lanata* Jacq.) to establish a correlation between taxonomy and geography regarding the phenolic compound content. Several samples of *S. raeseri* and *S. scardica* were collected from various localities in North Macedonia. The study revealed distinct differentiation between *S. lanata* (sect. *Hesiodia*) and *S. scardica*, *S. syriaca*, and *S. raeseri* (sect. *Empedoclia*), primarily due to the high content of 5-caffeoylquinic acid and the relatively low amounts of phenylethanoid glycosides and flavonoid glycosides in *S. lanata*. The results also showed significant similarity between *S. scardica*, *S. raeseri*, and Bulgarian *S. syriaca*, suggesting that the latter may be closely related to Turkish *S. taurica*, and indicating the need for further investigation into its taxonomic status [30].

Other metabolites

Various authors have also investigated other metabolites in addition to essential oils and flavonoids. Marin [24] examined the chemotaxonomic significance of nutlet fatty acids in *Micromeria* and related genera (*Satureja*, *Calamintha*, *Acinos*, and *Clinopodium*) from the Balkan Peninsula.

Dodoš et al. [31] investigated the leaf *n*-alkanes of three *Satureja montana* L. subspecies from the Balkan Peninsula, focusing on ecological and taxonomic aspects. The epicuticular leaf *n*-alkane composition of natural populations of the three subspecies (ssp. *macedonica*, ssp. *montana*, and ssp. *variegata*) from central and western areas of the Balkan Peninsula was characterized using modern techniques. Samples from four populations of ssp. *variegata* were collected from various localities in Slovenia and Croatia, while samples from nine populations of ssp. *variegata* came from Croatia, Bosnia-Herzegovina, and Montenegro. One population of ssp. *macedonica* was collected from Mount Galičica (North Macedonia). The study found differences in the contents of three dominant *n*-alkanes, which allowed for the separation of coastal and continental populations. The diversity and variability of the epicuticular alkane patterns, as well as their relation to geographic and bioclimatic parameters, were analyzed using several statistical methods. All tests showed a strong correlation between the leaf *n*-alkane patterns and the geographical distribution of the investigated populations, confirming the differentiation between *Satureja montana* ssp. *macedonica* and the other two subspecies. Populations of ssp. *variegata* and ssp. *montana* are geographically closer, and while there was some indication of differentiation between them, it was not clear-cut based on the leaf n-alkane patterns. Additionally, most of the bioclimatic parameters related to temperature were strongly correlated with the differentiation between coastal and continental populations [31]. As a coauthor of this paper, Academician Matevski made significant contributions to the identification of the studied taxa and the discussion of the results.

Investigations of biological activities

Plants are considered an inexhaustible source for isolating pharmacologically active compounds and have long been used in traditional medicine as herbal remedies [32]. The first step in drug discovery is to evaluate the potential of medicinal plants by studying their biological activities both *in vitro* and *in vivo*. In recent decades, the

bioactivities of various plant species have been intensively studied worldwide, with numerous studies focusing on the biological effects of Lamiaceae species native to North Macedonia.

The species of the genus *Salvia*, particularly *S. officinalis* L., have been used as medicinal plants for centuries due to their antimicrobial, antioxidant, anti-inflammatory, antidiabetic, cytotoxic, astringent, antihypertensive, neuroprotective, and cardioprotective effects [33]. The genus *Salvia* is represented by fifteen species in the flora of North Macedonia [34], with *S. jurisicii* Košanin being an endemic species from the central part of the country. *S. jurisicii*, *S. amplexicaulis*, and *S. ringens* have been studied in detail by Alimpić et al. [35–40]. The plant material of these three *Salvia* species was collected during their flowering period from natural populations near Štip, Pletvar, and Krivolak in North Macedonia. Academician Matevski, with his extensive knowledge of the flora of North Macedonia, played a key role in the field research of these *Salvia* taxa in these localities. As a co-author of publications [35–40], he also made significant contributions to the discussion of the results.

This research provides a comprehensive evaluation of the antioxidant, antimicrobial, cytotoxic, and antineurodegenerative effects of extracts with varying polarity obtained from three *Salvia* species, as well as the essential oil of *S. ringens*. The results from four antioxidant assays indicated that the ethanolic and aqueous extracts of the aerial parts particularly the leaves of *S. amplexicaulis* and *S. ringens* exhibited antioxidant activity comparable to that of standard antioxidants. Furthermore, deodorized extracts derived from the distillation waste of all three species, especially *S. amplexicaulis*, demonstrated high polyphenol content and exhibited strong antioxidant and antineurodegenerative potential [39]. Additionally, the ethanolic and aqueous extracts of all the tested species effectively inhibited the growth of various bacteria and micromycetes, with *Staphylococcus aureus*, *Micrococcus flavus*, *Bacillus cereus*, and *Trichophyton mentagrophytes* being the most sensitive [37, 38, 40]. The ethanolic and aqueous extracts of *S. ringens* exhibited cytotoxic effects against the HCT-116 colorectal carcinoma cell line [38], while the aqueous extract of *S. amplexicaulis* demonstrated the highest efficacy against the K562 myeloid leukemia cell line [36]. The antineurodegenerative potential was evaluated based on the inhibition of acetylcholinesterase (AChE) and tyrosinase. Extracts from all three species, especially *S. amplexicaulis* and *S. ringens*, were potent inhibitors of AChE, though they were less effective than the positive control, galantamine. On the other hand, these extracts exhibited stronger inhibition of tyrosinase compared to the commercially used kojic acid, while deodorized extracts showed relatively lower inhibitory activity [37-40].

In a study on the antioxidant capacity of various medicinal plants collected from Galičica Mountain, Tusevski et al. [41] found that hydromethanolic extracts of *S. ringens* exhibited higher antioxidant potential compared to *S. nemorosa* and *S. sclarea* across five complementary antioxidant assays. Other species identified as valuable sources of polyphenols with significant antioxidant potential in this study included *Melissa officinalis* and *Origanum vulgare*. The antioxidant potential of extracts from different plant parts of *S. verticillata*, collected from Jablanica Mountain, varied significantly, with the following hierarchy: flowers > stem > leaves [8].

In the review article published by Ćavar Zeljković et al. [42], the largest number of *Thymus* species analyzed comes from North Macedonia (18 in total). The official *Thymi aetheroleum* is commonly used in natural remedies to treat mouth and throat inflammation, which is why 90 % of studies on *Thymus* species have focused on the antimicrobial activity of their essential oils [43]. Kulevanova et al. [43] demonstrated strong antibacterial effects of the essential oils obtained from four varieties of *Thymus tosevii* Velen. (now recognized as *Thymus sibthorpii* Benth.) from natural populations in North Macedonia. These oils were effective against eleven bacterial strains and also exhibited antifungal activity against *Candida albicans*. The antimicrobial effects are attributed to the high content of thymol, carvacrol, geraniol, and linalool [43], with thymol and carvacrol also showing notable antioxidant properties [42]. In contrast to the EO, Tusevski et al. [41] found that the hydromethanolic extract of *Th. tosevii* collected from Galičica Mountain exhibited moderate antioxidant potential when compared to other Lamiaceae species analyzed.

Kostik et al. [44] investigated the antifungal potential of EOs from the leaves of wild *Mentha* × *piperita* and *M. spicata*, both collected from the Mariovo region in North Macedonia. The study, using the disc diffusion method and MIC testing, found that the essential oil of *M. spicata* exhibited the strongest antifungal activity against all tested plant pathogenic fungi. Among the main components of the essential oil, menthol demonstrated excellent antifungal activity, followed by menthone and carvone. Additionally, the antioxidant

activity of methanolic extracts from various parts of *M. longifolia*, collected from Jablanica Mountain, was found to be highest in the flowers, followed by the leaves and stems [8].

In the Balkan countries, tea made from the dried inflorescences of certain *Sideritis* species, commonly referred to as "mountain tea" or "Šarplaninski čaj," is traditionally used to treat ailments such as coughs, bronchitis, asthma, and gastrointestinal diseases [45]. *Sideritis scardica* is particularly popular in traditional medicine for treating conditions like bronchitis, bronchial asthma, and the common cold [46]. Additionally, Tasheva et al. [47] demonstrated that *S. scardica* can be efficiently micropropagated under laboratory conditions, and that the plants cultivated in vitro exhibit significant antioxidant and cytotoxic effects. *Sideritis raeseri* spp. *raeseri* is another well-known culinary and medicinal plant in the Mediterranean region. Its decoction is used in folk medicine for its anti-inflammatory, carminative, analgesic, antitussive, stomachic, and antimicrobial properties. The antioxidant potential and polyphenol content of the methanolic extract of *Sideritis raeseri* were moderate compared to other species collected from the Jablanica and Galičica Mountains and analyzed by Tusevski et al. [8, 41]. However, the antioxidant capacity of different plant parts of *S. raeseri* from Jablanica Mountain was found to be highest in the flowers, followed by the leaves and stems [8]. A study by Branković et al. [48] demonstrated the spasmolytic effect of the ethanolic extract of mountain tea, showing that it reduced both spontaneous and spasmogen-induced contractions in the ileum of experimental rats, which supports its use in treating gastrointestinal disorders. Additionally, Petreska et al. [45] identified 24 potentially bioactive phenolic compounds in the methanolic and aqueous extracts of *S. scardica* (collected from Shar Mountain near Gostivar, NW Macedonia) and *S. raeseri* (Galičica Mountain, SW Macedonia), primarily phenolic acids and flavonoids.

Among other non-aromatic species of the Lamiaceae family, Kadifkova Panovska et al. [49] investigated the antioxidant capacity of various extracts from *Teucrium* species (*T. chamaedrys*, *T. montanum*, and *T. polium*) collected from the Lazaropole district and Belasica Mountain using three complementary in vitro tests. The extracts from *T. montanum* and *T. chamaedrys* demonstrated stronger antioxidant effects in two of the three assays, which were attributed to the higher flavonoid content in the samples. Harlev et al. [50] included *T. polium* ssp. *capitatum* (L.) Arcang. in the list of desert and steppe plants with significant antidiabetic potential. Traditionally used in North Macedonia for the treatment of diabetes, *T. polium* was studied by Stefkov et al. [51], who showed that the hydroethanolic extract of this plant, collected from Belasica Mountain, contains flavonoids such as luteolin, apigenin, cirsiliol, diosmetin, cirsimaritin, and cirsilineol, all of which possess insulinotropic and antihyperglycaemic activity. The study revealed that the hydroethanolic extract of *T. polium* at 0.5 mg/mL had a significant insulinotropic effect on INS-1E cells. Intragastric administration of the extract reduced blood glucose levels by 35% in both normal and hyperglycaemic rats, with the effect being comparable to that of the antidiabetic drug glibenclamide after 10 days of treatment.

Other, less aromatic species of the Lamiaceae family, such as those from the genus *Stachys*, also exhibit significant bioactivity. Tusevski et al. [8] reported on the antioxidant potential of *S. alpina*, *S. jacquinii*, and *S. sylvatica* from Jablanica Mountain. Methanolic extracts of the flowers of *S. alpina* demonstrated strong antioxidant effects, comparable to those of well-known medicinal plants like *Achillea millefolium* L. (Asteraceae), which were also collected from the same locality [8].

CONCLUSIONS

A number of Lamiaceae species native to the territory of North Macedonia have been studied from various phytochemical, chemotaxonomical, and biological activity perspectives. Based on the available literature, it can be concluded that this region is a rich source of plants, offering great potential for further investigation, both from fundamental research and applied aspects. Decades of research by Academician Vlado Matevski on the flora of North Macedonia have laid the foundation for many of these investigations, particularly those focusing on endemic, rare, and taxonomically complex species. His contributions to both fundamental and applied research on numerous Macedonian plant species are significant. As an expert in the Lamiaceae family, he played an instrumental role in the phytochemical and other studies of genera such as *Thymus*, *Clinopodium*, *Micromeria*, *Salvia*, *Satureja*, *Stachys*, and *Sideritis*. Although he was not a coauthor in all the cited publications, it is important to note that many of these papers resulted from his collaborative work with scientists in the region. His extensive knowledge of Balkan flora, his unrelenting curiosity, and his openness to sharing ideas earned him recognition as a leading botanist, both in North Macedonia and across Eu-

rope. The findings highlighted in this review encourage further collaborative, interdisciplinary work, paving the way for new publications that will continue to showcase the richness and significance of Macedonian and Balkan flora.

REFERENCES

[1] E. Kostadinova, K. Alipieva, M. Stefova, T. Stafilov, D. Antonova, L. Evstatieva, V. Matevski, S. Kulevanova, G. Stefkov, V. Bankova, Chemical composition of the essential oils of three *Micromeria* species growing in Macedonia and Bulgaria, *Maced. J. Chem. Chem. Eng.*, **26** (2007), pp. 3–7.

[2] D. Kremer, V. Dunkić, M. Ruščić, V. Matevski, D. Ballian, F. Bogunić, E. Eleftheriadou, D. Stešević, I. Kosalec, N. Bezić, Micromorphological traits and essential oil contents of *Micromeria kerneri* Murb. and *M. juliana* (L.) Benth. (*Lamiaceae*), *Phytochemistry*, **98** (2014), pp. 128–136.

[3] V. Kostik, B. Bauer, Chemical composition of essential oils of wild-growing *Mentha piperita* L and *Mentha spicata* L from the Mariovo region, Republic of Macedonia, *Second Mediterr. Symp. Med. Aromat. Plants Book Abstr.*, (2015), p.185.

[4] A. Hajdari, B. Mustafa, L. Hyseni, A. Bajrami, G. Mustafa, C. L. Quave, D. Nebija, Phytochemical study of eight medicinal plants of the Lamiaceae family traditionally used as tea in the Sharri Mountains region of the Balkans, *Sci. World J.*, **2020** (2020), pp.1–9.

[5] B. Lukas, C. Schmiderer, J. Novak, Essential oil diversity of European *Origanum vulgare* L. (*Lamiaceae*), *Phytochemistry*, **119** (2015), pp. 32–40.

[6] B. Qazimi, G. Stefkov, M. Karapandzova, I. Cvetkovikj, S. Kulevanova, Volatile aroma compounds in infusions of stems and rosette leaves of *Sideritis raeseri* Boiss. & Heldr. from R. Macedonia, Albania and Greece, *Maced. Pharm. Bull.*, **60** (2014), pp. 27–33.

[7] S. Kulevanova, T. Stafilov, M. Ristić, D. Brkić, Isolation and identification of flavonoid from *Thymus longidens* var. *lanicaulis* and *T. longidens* var. *dassareticus* (*Lamiaceae*), *Acta Pharm.*, **47** (1997), pp. 281–286.

[8] O. Tusevski, M. Trpevski, I. Lozanovska, A. Talevska, D. Ugurovska, S. Gadzovska-Simic, Antioxidant activity of phenolic compounds in methanolic extracts of some Macedonian medicinal plants collected on Jablanica Mountain, *Bull. Biol. Stud. Res. Soc.*, **4** (2010), pp. 103–111.

[9] I. Mitreski, J. P. Stanoeva, M. Stefova, G. Stefkov, S. Kulevanova, Polyphenols in Representative *Teucrium* Species in the Flora of R. Macedonia: LC/DAD/ESI-MS^n Profile and Content, *Nat. Prod. Commun.*, **9** (2014), 1934578X1400900.

[10] B. Janeska, M. Stefova, K. Alipieva, Assay of flavonoid aglycones from species of the genus *Sideritis* (*Lamiaceae*) from Macedonia with HPLC UV DAD, *Acta Pharm.*, **57** (2007), pp. 371–377.

[11] J. Petreska, G. Stefkov, S. Kulevanova, K. Alipieva, V. Bankova, M. Stefova, Phenolic Compounds of Mountain Tea from the Balkans: LC/DAD/ESI/MS^n Profile and Content, *Nat. Prod. Commun.*, **6** (2011), 1934578X1100600107.

[12] A. Ibraliu, A. Trendafilova, B. Andjelković, B. Qazimi, D. Godjevac, E. Bebeci, G. Stefkov, G. Zdunic, I. Aneva, I. Pasho, Comparative Study of Balkan *Sideritis* Species from Albania, Bulgaria and Macedonia, *Eur. J. Med. Plants*, **5** (2015), pp. 328–340.

[13] B. Qazimi, M. Karapandzova, G. Stefkov, S. Kulevanova, Chemical composition of ultrasonic-assisted *n*-hexane extracts of *Sideritis scardica* Griseb. and *Sideritis raeseri* Boiss. & Heldr. (*Lamiaceae*) from Macedonia and Albania, *Maced Pharm Bull*, **56** (2010), pp. 45–56.

[14] D. Kitić, B. Zlatković, R. Palić, T. Jovanović, M. Ristić, Fatty acids of some plants of the genus *Calamintha*, *Chem. Nat. Compd.*, **45** (2009), pp. 231–233.

[15] V. Slavkovska, R. Jančić, S. Milosavljević, D. Djoković, Variability of the essential oil composition of the species *Satureja montana* L. (*Lamiaceae*), *J. Essent. Oil Res.*, **9** (1997), pp. 629–634.

[16] V. Slavkovska, R. Jančić, S. Bojović, S. Milosavljević, D. Djoković, Variability of essential oils of *Satureja montana* L. and *Satureja kitaibelii* Wierzb. ex Heuff. from the central part of the Balkan peninsula, *Phytochemistry*, **57** (2001), pp. 71–76.

[17] T. Dodoš, J. Novaković, L. Vujisić, P. D. Marin, N. Rajčević, Geographic variability of winter savory essential oil, *Ind. Crops Prod.*, **210** (2024), 118167.

[18] N. Radulović, J. Lazarević, N. Ristić, R. Palić, Chemotaxonomic significance of the volatiles in the genus *Stachys* (*Lamiaceae*): Essential oil composition of four Balkan *Stachys* species, *Biochem. Syst. Ecol.*, **35** (2007), pp. 196–208.

[19] D. Kremer, V. Matevski, V. Dunkić, N. Bezić, E. Stabentheiner, Essential oil contents and micromorphological traits of *Stachys iva* Griseb. and *S. horvaticii* Micevski (*Lamiaceae*), *Rec. Nat. Prod.*, **10** (2016), pp. 228–239.

[20] V. Dunkić, D. Kremer, R. J. Grubešić, J. V. Rodríguez, D. Ballian, F. Bogunić, D. Stešević, I. Kosalec, N. Bezić, E. Stabentheiner, Micromorphological and phytochemical traits of four *Clinopodium* L. species (*Lamiaceae*), *South Afr. J. Bot.*, **111** (2017), pp. 232–241.

[21] D. Kremer, V. Dunkić, I. Radosavljević, F. Bogunić, D. Ivanova, D. Ballian, D. Stešević, V. Matevski, V. Ranđelović, E. Eleftheriadou, Phy-

tochemicals and their correlation with molecular data in *Micromeria* and *Clinopodium* (*Lamiaceae*) taxa, *Plants*, **11** (2022), 3407.

[22] N. S. Radulović, P. D. Blagojević, Plant Volatiles Providing Additional Evidences to the Occurence of a Wild-Growing Population of *Calamintha vardarensis* (Greuter et Burdet) Šilić Outside of Its Natural Habitat, *Chem. Biodivers.*, **7** (2010), pp. 2856–2868.

[23] E.-M. Tomou, P. Fraskou, K. Dimakopoulou, E. Dariotis, N. Krigas, H. Skaltsa, Chemometric Analysis Evidencing the Variability in the Composition of Essential Oils in 10 *Salvia* Species from Different Taxonomic Sections or Phylogenetic Clades, *Molecules*, **29** (2024), 1547.

[24] P. D. Marin, Hemotaksonomska i mikromorfološka studija roda *Micromeria* Benth. i srodnih rodova iz tribusa Satureineae (*Lamiaceae*), Doktorska disertacija, Biološki fakultet, Univerzitet u Beogradu, (1989), pp. 1–11.

[25] F. A. Tomas-Barberan, M. I. Gil, P. D. Marin, F. Tomas-Lorente, Flavonoids from some Yugoslavian *Micromeria* species: Chemotaxonomical aspects, *Biochem. Syst. Ecol.*, **19** (1991), pp.697–698.

[26] P. D. Marin, A chemotaxonomic study of vacuolar flavonoids from some Balkan *Micromeria* Benth. species (*Lamiaceae*), *Arch. Biol. Sci.*, **48** (1996), pp. 49–55.

[27] P. D. Marin, R. J. Grayer, P. Janacković, External flavonoids from *Satureja cuneifolia* and *S. adamovicii*, *Second International Balkan Botanical Congress*, Sarajevo, 2003, Book of Abstracts p. 296.

[28] P. D. Marin, R. J. Grayer, G. C. Kite, V. Matevski, External leaf flavonoids of *Thymus* species from Macedonia, *Biochem. Syst. Ecol.*, **31** (2003), pp. 1291–1307.

[29] A. Karioti, J. Kukić-Marković, A. R. Bilia, M. Niketić, S. Petrović, Chemical profiling of six *Stachys* taxa from Balkan Peninsula, *Biochem. Syst. Ecol.*, **104** (2022), 104482.

[30] J. P. Stanoeva, M. Stefova, G. Stefkov, S. Kulevanova, K. Alipieva, V. Bankova, I. Aneva, L. N. Evstatieva, Chemotaxonomic contribution to the *Sideritis species* dilemma on the Balkans, *Biochem. Syst. Ecol.*, **61** (2015), pp. 477–487.

[31] T. Dodoš, N. Rajčević, V. Tešević, V. Matevski, P. Janaćković, P. D. Marin, Composition of Leaf *n*-Alkanes in Three *Satureja montana* L. Subspecies from the Balkan Peninsula: Ecological and Taxonomic Aspects, *Chem. Biodivers.*, **12** (2015), pp. 157–169.

[32] F. Les, G. Cásedas, V. López, Bioactivity of medicinal plants and extracts, *Biology*, **10** (2021), p. 634.

[33] M. Nikolova, I. Aneva, European Species of Genus *Salvia*: Distribution, Chemodiversity and Biological Activity, in: V. Georgiev, A. Pavlov (Eds.), *Salvia Biotechnology*, Springer International Publishing, Cham, 2017, pp. 1–30.

[34] V. Matevski, *Salvia* L., in: *Flora na RS Makedonija*, G. Jovanovski (ed), tom II, sv. 2, Makedonska akademija na naukite i umetnostite, Skopje, 2021, pp. 397–416.

[35] A. Alimpić, M. Oaldje, V. Matevski, P. Marin, S. Duletić-Laušević, Antioxidant activity and total phenolic and flavonoid contents of *Salvia amplexicaulis* Lam. Extracts, *Arch. Biol. Sci.*, **66** (2014), pp. 307–316.

[36] A. Z. Alimpić, N. Kotur, B. Stanković, P. D. Marin, V. Matevski, N. Al Sheef, S. Duletić-Laušević, The in vitro antioxidative and cytotoxic effects of selected *Salvia* species water extracts, *J. Appl. Bot. Food Qual.*, **88** (2015), pp. 115–119.

[37] A. Alimpić, A. Knežević, M. Milutinović, T. Stević, K. Šavikin, M. Stajić, S. Marković, P.D. Marin, V. Matevski, S. Duletić-Laušević, Biological activities and chemical composition of *Salvia amplexicaulis* Lam. extracts, *Ind. Crop. Prod.*, **105** (2017), pp. 1–9.

[38] A. Alimpić, D. Pljevljakušić, K. Šavikin, A. Knežević, M. Ćurčić, D. Veličković, T. Stević, G. Petrović, V. Matevski, J. Vukojević, Composition and biological effects of *Salvia ringens* (*Lamiaceae*) essential oil and extracts, *Ind. Crops Prod.*, **76** (2015), pp. 702–709.

[39] A. Alimpić, K. Šavikin, D. Pljevljakušić, V. Matevski, P. D. Marin, I. Petrović, S. Duletić-Laušević, Polyphenolic Content and Biological Activities of Post-Distillation Waste of Three Sage Species from the Republic of Macedonia, *Agroznanje*, **18** (2017), pp. 27–36.

[40] A. Alimpić, A. Knežević, K. Šavikin, M. Ćurčić, D. Veličković, T. Stević, V. Matevski, M. Stajić, S. Marković, P. D. Marin, S. Duletić-Laušević, Composition and biological activities of different extracts of *Salvia jurisicii*, a rare and endemic Macedonian species, *Plant Biosyst. – Int. J. Deal. Asp. Plant Biol.*, **151** (2017), pp. 1002–1011.

[41] O. Tusevski, A. Kostovska, A. Iloska, L. Trajkovska, S. G. Simic, Phenolic production and antioxidant properties of some Macedonian medicinal plants, *Centr. Eur. J. Biol.*, **9** (2014), pp. 888–900.

[42] S. Ćavar Zeljković, M. Maksimović, Chemical composition and bioactivity of essential oil from *Thymus* species in Balkan Peninsula, *Phytochem. Rev.*, **14** (2015), pp. 335–352.

[43] S. Kulevanova, A. Kaftandzieva, A. Dimitrovska, G. Stefkov, N. Panovski, Potential antimicrobial activity of the essential oil of some Macedonian *Thymus tosevii* Vel. (*Lamiaceae*) varieties, *Acta Pharm.*, **52** (2002), pp. 305–311.

[44] V. Kostik, B. Gjorgjeska, S. Petkovska, *Mentha* L. essential oils composition and *in vitro* antifungal activity, *IOSR J. Pharm.*, **5** (2015), pp. 1–7.

[45] J. Petreska, M. Stefova, F. Ferreres, D. A. Moreno, F. A. Tomás-Barberán, G. Stefkov, S. Kulevanova, A. Gil-Izquierdo, Potential bioactive phenolics of Macedonian *Sideritis* species used for medicinal "Mountain Tea", *Food Chem.*, **125** (2011), pp. 13–20.

[46] M. Todorova, A. Trendafilova, *Sideritis scardica* Griseb., an endemic species of Balkan peninsula: Traditional uses, cultivation, chemical composition, biological activity, *J. Ethnopharmacol.*, **152** (2014), pp. 256–265.

[47] K. Tasheva, A. Georgieva, P. Denev, L. Dimitrova, M. Dimitrova, S. Misheva, P. Petkova-Kirova, M. Lazarova, M. Petrova, Antioxidant and Antitumor Potential of Micropropagated Balkan Endemic *Sideritis scardica* Griseb, *Plants*, **12** (2023), 3924.

[48] S. Branković, D. Kitić, M. Radenković, S. Veljković, T. Janković, K. Savikin, G. Zdunić, Spasmolytic Activity of the Ethanol Extract of *Sideritis raeseri* ssp. *raeseri* Boiss. & Heldr. on the Isolated Rat Ileum Contractions, *J. Med. Food*, **14** (2011), pp. 495–498.

[49] T. Kadifkova Panovska, S. Kulevanova, M. Stefova, *In vitro* antioxidant activity of some *Teucrium* species (*Lamiaceae*), *Acta Pharm.*, **55** (2005), pp. 207–214.

[50] E. Harlev, E. Nevo, N. Mirsky, R. Ofir, Antidiabetic Attributes of Desert and Steppic Plants: A Review, *Planta Med.*, **79** (2013), pp. 425–436.

[51] G. Stefkov, S. Kulevanova, B. Miova, S. Dinevska-Kjovkarovska, P. Mølgaard, A. K. Jäger, K. Josefsen, Effects of *Teucrium polium* ssp. *capitatum* flavonoids on the lipid and carbohydrate metabolism in rats, *Pharm. Biol.*, **49** (2011), pp. 885–892.

ФИТОХЕМИСКИ И ХЕМОТАКСОНОМСКИ ИСТРАЖУВАЊА НА LAMIACEAE ОД СЕВЕРНА МАКЕДОНИЈА

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Флората на Северна Македонија и на целиот Балкански Полуостров е многу богата, каде што се присутни и бројни видови од фам. Lamiaceae. Многу видови од оваа фамилија се проучувани од различни аспекти, вклучувајќи фитохемија, хемотаксономија, биолошка активност, молекуларна филогенија, фармакологија, етноботаника и многу други. Со овој преглед се сумирани резултатите од студиите за фитохемијата, хемотаксономијата и биолошката активност на претставници од фам. *Lamiaceae*, со посебен фокус на оние видови кои се автохтони во Северна Македонија. Наодите сугерираат дека овој регион е богат извор на растенија кои би можеле да бидат од интерес за понатамошни истражувања, како од фундаментална, така и од применета перспектива.

Академик Владо Матевски даде значаен придонес во проучувањето на растенијата од Северна Македонија и од поширокиот Балкански Полуостров. Неговата страст како ботаничар и соработката со регионалните научници доведе до објавување на бројни трудови во национални и во меѓународни списанија.

Клучни зборови: Lamiaceae; Северна Македонија; фитохемија; хемотаксономија; биолошка активност