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Article

Composition and Bioactivity of the Essential Oil of *Melissa officinalis* L. Growing Wild in Tajikistan

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Abstract: The chemical composition of the essential oil of *Melissa officinalis* L**.** from the aerial flowering parts were obtained by hydrodistillation and analyzed by Gas Chromatography – Mass Spectrometry. Thirty components representing 99.9% of the total oil were identified. The main constituents of the essential oils were geranial (43.2%), neral (31.5%), (*E*)-anethole (12.3%), (*E*)-caryophyllene (4.0%) and citronellal (2.8%). *Melissa officinalis* essential oil was cytotoxic to MCF-7 cells (IC_{50} = 61.6±5.5 μg/mL) and active in the brine shrimp lethality test (LC_{50} = 21.8±4.6 μg/mL), but showed only marginal antimicrobial activity to *Bacillus cereus* (MIC = 313 μg/mL) and *Aspergillus niger* (MIC = 625 μg/mL). A cluster analysis was carried out on the essential oil compositions of *Melissa officinalis.*

Keywords: *Melissa officinalis* L.; essential oil composition; geranial; neral; (*E*)-anethole; cytotoxic activity.

1. Introduction

Melissa officinalis L. (Lamiaceae), commonly referred to as "lemon balm", has been extensively studied. Lemon balm is native to southern Europe, the Mediterranean region and western

Asia (Meftahizade et al., 2010). The plant has been used as far back as the Middle Ages to reduce stress and anxiety, promote sleep, improve appetite, and ease pain and discomfort from indigestion. Lemon balm has traditionally been used as a tonic, antispasmodic, carminative, diaphoretic, and sedative-hypnotic for strengthening the memory (Blumenthal et al., 2000). In addition, it is currently used for the relief of stress-induced headaches and as an antiviral to improve the healing of herpes simplex cold sores. When mixed with St. John's wort, lemon balm is also a useful treatment for seasonal effective disorder (Kuhn and Winston, 2000). Other work has indicated that lemon balm may help improve cognitive function and decrease agitation in patients with Alzheimer's disease. The essential oil of lemon balm is used in aromatherapy and as an antitumor agent with the potential to remedy and prevent cancer (Janina, 2003). The plant is also used as an additive in food, for the production of many phytopharmaceutical preparations, fragrances and cosmetics (Dudchenko et al., 1989; Bruneton, 1999). *Melissa officinalis* essential oils have shown notable biological activities including antiviral, antibacterial, antioxidant, antimicrobial activities (Allahverdiyev et al., 2004; Friedman et al., 2004; Mazzanti et al., 2008; Mimica-Dukic et al., 2004; Munne-Bosch and Alegre, 2000; Schnitzler et al., 2008).

There have been some previous reports on the chemical constitutions of *Melissa officinalis g*rowing in Pakistan (Hussain et al., 2011), Iran (Norouzi et al., 2012; Adinee et al., 2008; Saeb and Gholamrezaee, 2012; Moradkhani et al., 2010), Turkey (Cosge et al., 2009; Sari and Ceylan, 2002), Kurdistan (Taherpour et al., 2012), Egypt (Aziz and El-Ashry, 2009), Greece (Basta et al., 2005), Romania (Hancianu et al., 2008), Slovakia (Ondrejovic et al., 2012; Toth et al., 2003), Russia (Stepanenko et al., 2007), Serbia (Anicic et al., 2005), Poland (Patora et al., 2003), Italy (Martino et al., 2009), and Brazil (da Silva et al., 2005). According to these studies, the major components of the essential oil of *Melissa officinalis* were geranial, neral, and citronellal (Moradkhani et al., 2010; Taherpour et al., 2012; Hancianu et al., 2008; Toth et al., 2003; Anicic et al., 2005; Patora et al., 2003; Martino et al., 2009; Silva et al., 2005), (*E*)-caryophyllene (Norouzi et al., 2012; Basta et al., 2005; Toth et al., 2003), caryophyllene oxide (Norouzi et al., 2012; Basta et al., 2005; Toth et al., 2003), linalool (Patora et al., 2003), geraniol (Hussain et al., 2011; Stepanenko et al., 2007), thymol (Cosge et al., 2009), α-pinene (Norouzi et al., 2012), β-pinene (Sari and Ceylan, 2002; Basta et al., 2005), carvacrol and *iso*-menthone (Martino et al., 2009), decadienal (Saeb and Gholamrezaee, 2012) and *trans*-carveol (Adinee et al., 2008).

In this report, we present the chemical composition and biological activity screening of the essential oil of *Melissa officinalis* L. collected from south-central Tajikistan. To our knowledge, no previous work on *Melissa officinalis* from Tajikistan has been reported, and so this work extends our understanding of the phytochemistry of this important medicinal plant.

2. Materials and Methods

2.1. Plant Material

The aerial parts of *Melissa officinalis* were collected on 28 May 2012 from the Shahrchai Akademiki, Shohmansur region of Dushanbe city, Tajikistan, (38.3316 N, 68.5122 E, 1000 m above sea level) and identified by F. Sharopov. A voucher specimen (N7304) has been deposited in the herbarium of the Institute of Botany, Plant Physiology and Genetics of the Tajikistan Academy of Sciences. The fresh samples were used and hydrodistilled for 2 h to give the essential oils, 0.3-0.4% yield.

2.2. Gas Chromatographic – Mass Spectral (GC-MS) Analysis

The essential oil of *Melissa officinalis* was analyzed by GC-MS using an Agilent 6890 GC with Agilent 5973 mass selective detector [MSD, operated in the EI mode (electron energy = 70 eV), scan range = 40-400 amu, and scan rate = 3.99 scans/sec], and an Agilent ChemStation data system. The GC column was an HP-5ms fused silica capillary with a (5% phenyl)-polymethylsiloxane stationary phase, film thickness of 0.25 μm, a length of 30 m, and an internal diameter of 0.25 mm. The carrier gas was helium with a column head pressure of 48.7 kPa and a flow rate of 1.0 mL/min. Inlet temperature was 200°C and interface temperature was 280°C. The GC oven temperature program was used as follows: 40°C initial temperature, hold for 10 min; increased at 3°C/min to 200°C; increased 2°C/min to 220°C. A 1 % w/v solution of the sample in CH_2Cl_2 was prepared and 1 μL was injected using a 10:1 split ratio.

Identification of the oil components was based on their retention indices determined by reference to a homologous series of *n*-alkanes, and by comparison of their mass spectral fragmentation patterns with those reported in the literature (Adams, 2007) and stored on the MS library [NIST database (G1036A, revision D.01.00)/ChemStation data system (G1701CA, version C.00.01.080]. The percentages of each component are reported as averages of three replicates, based on total ion current without standardization. The essential oil composition of *Melissa officinalis* is summarized in Table 1.

2.3. Numerical Cluster Analysis

Thirty *Melissa officinalis* samples were treated as operational taxonomic units (OTUs). The percentage composition of the 15 major essential oil components [geraniol, geranial, citronellal, neral, caryophyllene oxide, (*E*)-caryophyllene, linalool, geranyl acetate, germacrene D, citronellol, γ-terpinene, α-pinene, β-pinene, carvacrol, and methyl citronellate] was used to determine the chemical relationship between the different *Melissa officinalis* essential oil samples by cluster analysis using the

NTSYSpc software, version 2.2 (Rohlf, 2005). Correlation was selected as a measure of similarity, and the unweighted pairgroup method with arithmetic average (UPGMA) was used for cluster definition.

Table 1. Chemical composition of *Melissa officinalis* essential oil from Tajikistan

RI[a]	Compound	%[b]
982	1-Octen-3-ol	0.2±0.1
989	6-Methyl-5-hepten-2-one	0.3±0.1
993	Myrcene	0.2±0.1
1005	α-Phellandrene	1.0±0.0
1025	*p*-Cymene	0.6±0.2
1029	Limonene	0.1±0.0
1059	γ-Terpinene	0.3±0.1
1105	*cis*-Thujone (= α-Thujone)	0.1±0.1
1116	*trans*-Thujone (= β-Thujone)	0.6±0.2
1155	Citronellal	2.8±0.5
1166	(*Z*)-Isocitral	0.3±0.2
1182	(*E*)-Isocitral	0.5±0.2
1198	Methyl chavicol	0.1±0.1
1229	Nerol	0.1±0.1
1243	Neral (= (*Z*)-Citral)	31.5±0.6
1249	Anisaldehyde	0.1±0.0
1252	Geraniol	0.2±0.1
1260	Methyl citronellate	0.1±0.1
1274	Geranial (= (*E*)-Citral)	43.2±2.4
1285	(*E*)-Anethole	12.3±0.3
1322	Methyl geranate	0.1±0.0
1358	Ethyl nerolate	0.1±0.1
1382	Geranyl acetate	1.2±0.3
1420	(*E*)-Caryophyllene	4.0±0.3
1454	α-Humulene	0.1±0.0
1467	(2*E*)-Dodecenal	0.1±0.0
1482	Germacrene D	0.6±0.2
1497	(*E*,*E*)-α-Farnesene	0.1±0.1
1525	δ-Cadinene	Trace
1584	Caryophyllene oxide	0.4±0.1
	Total Identified	99.9

[a] RI = Retention Index determined with respect to a series of *n*-alkanes on an HP-5ms column.

[b] Percent composition is an average of three runs (± standard deviations).

2.4. Bioactivity Screening

Melissa officinalis essential oil was screened for *in-vitro* cytotoxic activity against MCF-7 human breast adenocarcinoma cells using the MTT assay as described previously (Moriarity et al.,

2007). The essential oil was screened for antibacterial activity against *Bacillus cereus* (ATCC No. 14579), *Staphylococcus aureus* (ATCC No. 29213), *Escherichia coli* (ATCC No. 10798), and *Pseudomonas aeruginosa* (ATCC No. 27853), and antifungal activity against *Aspergillus niger* (ATCC No. 16888) using the microbroth dilution technique as earlier reported (Satyal et al., 2012). *Melissa officinalis* oil was tested for brine shrimp (*Artemia salina*) lethality as previously described (Jones et al., 2012).

3. Results and Discussion

3.1. Essential Oil Composition

The chemical composition of the essential oil of *Melissa officinalis* from the aerial parts were obtained by hydrodistillation and analyzed by gas chromatography – mass spectrometry. Thirty components representing 99.9% of the total oil were identified. The oil was characterized with high relative concentration of monoterpenoids. The principal components of essential oil of the aerial parts of *Melissa officinalis* were geranial (43.2±2.4 %), neral (31.5±0.6 %), (*E*)-anethole (12.3±0.3 %), (*E*)-caryophyllene (4.0±0.3 %) and citronellal (2.8±0.5 %).

The chemical composition of *Melissa officinalis* oil from Tajikistan is qualitatively similar to several earlier reports, indicating the main components to be the citral isomers geranial and neral (Sari et al., 2011; Silva et al., 2005; Patora et al., 2003; Taherpour et al., 2012; Masakova et al., 1979; Carnat et al., 1998). Sari and co-workers (2011) investigated *Melissa officinalis* oils from two different locations in Turkey (Menemen and Bozdag). The major components of the oils from Menemen were geranial (38.1%) and neral (12.2%), and the concentrations of other components were as follows: β-pinene 11.7%, citronellal 5.9%, geraniol 5.0%, α-pinene 2.9%, linalool 2.7%, and borneol 0.6%. These previous results are in agreement with this current study except that pinene, linalool, and borneol were not detected in the oil from Tajikistan while the oil from Tajikistan had a large concentration of (*E*)-anethole, not previously reported in *Melissa officinalis* oils. By comparing the composition of *Melissa officinalis* oil from Turkey to that of Europe, Sari and co-workers (2011) concluded that the populations originating from Turkey had higher β-pinene concentrations than did the other populations.

There have been several reports on *Melissa officinalis* essential oils showing an absence of both geranial and neral (Adinee et al., 2008; Norouzi et al., 2012; Saeb and Gholamrezaee, 2012; Basta et al., 2005; Martino et al., 2009). Of these, the major components were citronellol (Adinee et al., 2008), α-pinene and caryophyllene oxide (Norouzi et al., 2012; Basta et al., 2005), geraniol (Saeb et al., 2012), or citronellal (Martino et al., 2009). Up until now, however, distinct chemotypes of *Melissa officinalis* have not been delineated.

3.2. Numerical Cluster Analysis

Because of the wide variation in chemical profiles for *Melissa officinalis* collected from different geographical locations, a numerical cluster analysis has been carried out based on the chemical compositions of *Melissa officinalis* essential oils published in the literature (Figure 1) in order to assess the differences and similarities in the oils. There is an apparent geranial/neral cluster that includes samples from Tajikistan (this work), Turkey (Sari et al., 2011), Romania (Hancianu et al., 2008), Serbia (Anicic et al., 2005), Poland (Patora et al., 2003), Brazil (Silva et al., 2005), and Kurdistan (Taherpour et al., 2012). Two samples from Iran (Saeb and Gholamrezaee, 2012) form a geranol/caryophyllene oxide chemotype, while samples from Egypt (Aziz et al., 2009), Turkey (Cosge et al., 2009), and Italy (Martino et al., 2009) were largely dominated by citronellal. Two additional clusters, samples from Iran, dominated by α-pinene and caryophyllene oxide (Norouzi et al., 2012), and Greece, caryophyllene-oxide/β-caryophyllene/β-pinene (Basta et al., 2005), formed mixed chemotypes. The other samples from the literature represented individual chemotypes: Greece #1, β-pinene (Basta et al., 2005), Iran #2, citronellol (Adinee et al., 2008), Iran #7, carvacrol/methyl citronellate (Saeb and Gholamrezaee, 2012), Egypt #1, citronellal/geranial/geranyl acetate (Aziz et al., 2009), Iran #1, neral/β-caryophyllene (Moradkhani et al., 2010), and Russia, geraniol (Stepanenko et al., 2007). It is important to note the wide variation in chemical composition of these *Melissa officinalis* essential oils, particularly with respect to their use in traditional medicine, flavoring, and fragrances.

3.3. Bioactivity

In this study, the essential oil was screened for antimicrobial activity against a panel of bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*) as well as the mold *Aspergillus niger*. The essential oil was not appreciably antimicrobial, however. It was inactive against *S. aureus*, *E. coli*, and *P. aeruginosa* (MIC > 2500 μg/mL), and only marginally active against *B. cereus* (MIC = 313 μg/mL) and *A. niger* (MIC = 625 μg/mL).

The oil was also tested for *in-vitro* cytotoxic activity against the human mammary adenocarcinoma, MCF-7, cell line and did prove to be cytotoxic (IC_{50} = 61.6±5.5 μg/mL) on this cell line. The cytotoxicity is most likely due to the major aldehyde components geranial and neral. Citral, a mixture of geranial and neral, has been shown to be cytotoxic to MCF-7 (Wright et al., 2007) as well as other cell lines (Setzer et al., 2005). Consistent with the cytotoxic activity, *Melissa officinalis* oil also demonstrated notable brine shrimp lethality (LC_{50} = 21.8±4.6 μg/mL).

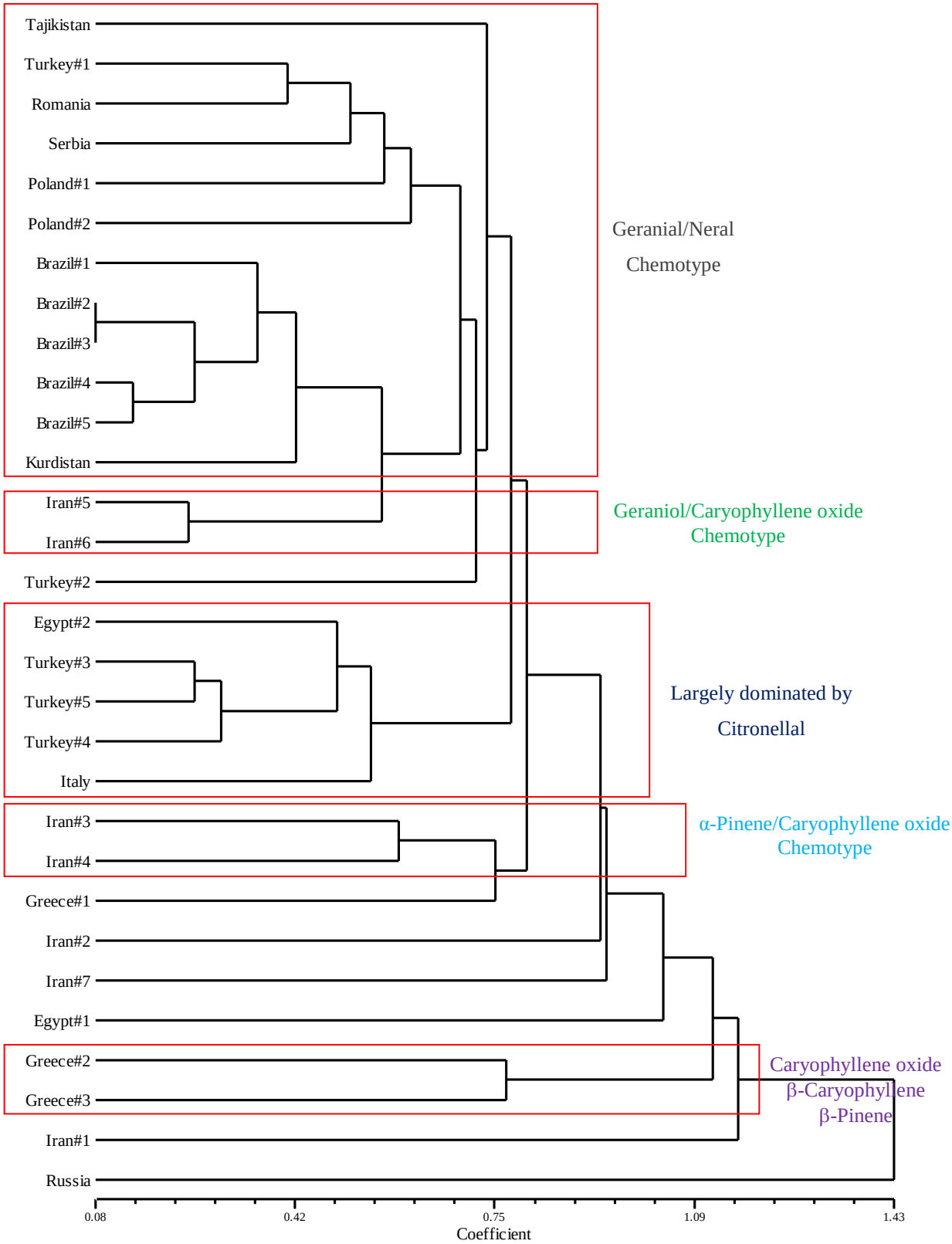

Figure 1. Dendrogram obtained by cluster analysis based on *Melissa officinalis* essential oil compositions

4. Conclusions

Melissa officinalis is regarded as a valuable medicinal plant and it has been traditionally used for different medicinal purposes and in aromatherapy (Blumenthal et al., 2000; Janina, 2003). The essential oil of *Melissa officinalis* from Tajikistan was found to be rich in geranial and neral, similar to several other samples reported previously, and represents the most common chemotype of this plant. The medicinal and pharmaceutical attributes of lemon balm are likely due to the monoterpenoid aldehydes geranial, neral, and citronellal (Allahverdiyev et al., 2003). The chemical composition of this plant does, however, show a wide range of variation, so the utility and efficacy would be expected to vary as well.

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