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Thymbra L. and *Satureja* L. essential oils as rich sources of carvacrol, a food additive with health-promoting effects

Violetta Krisilia, Georgia Deli, Aikaterini Koutsaviti and Olga Tzakou

Abstract
Carvacrol, an oxygenated monoterpene, usually dominates the essential oil of aromatic plants of the Lamiaceae family, such as representatives of the genus *Origanum* L. (Lamiaceae), and other included genera commonly known as “oregano” spices. According to a significant number of studies, carvacrol exhibits an array of pharmacological and biological properties; it has also been approved by the Federal Drug Administration and Council of Europe as food additive and is considered generally safe for consumption. Nevertheless, not all “oregano” species are rich in carvacrol, depending on various factors and given chemotype. In the framework of our ongoing research on the chemistry and biological activities of aromatic plants found in the Mediterranean Basin and more specifically of Greek endemic species, we investigated the essential oils of *Thymbra calostachya* (Rech. fil.) Rech. fil., a Greek endemic species growing in Crete, along with *Thymbra capitata* (L.) Cav., as well as *Satureja thymbra* L., collected from natural populations in Greece, with the prospect of identifying new candidates for the production of carvacrol-rich cultivars. Apart from a single population, all investigated samples were characterized by the dominance of carvacrol [*T. calostachya* (Rech. fil.) Rech. fil. 73.6%-78.4%, *T. capitata* (L.) Cav. 50.4%-78.1%, *S. thymbra* L. 2.8%-65.2%].

Keywords *Satureja thymbra, Thymbra capitata, Thymbra calostachya,* essential oil, carvacrol, biological activities

1. Introduction

Carvacrol, an oxygenated monoterpene, is found in high abundance in the essential oil of aromatic plants of the Lamiaceae family, mainly in representatives of the genus *Origanum* L. (Lamiaceae), such as *O. vulgare* L. (Greek oregano), *O. dictammus* L. (Cretan dittany) and *O. majorana* L. (majoram), important culinary herbs widely used in Greek and Mediterranean diet. The term “oregano” comprises a number of genera and included taxa, characterized by the same distinguishing scent and flavor, such as *Thymbra* L. and *Satureja* L. (Lamiaceae). According to numerous studies carvacrol exhibits a plethora of pharmacological and biological properties, including antioxidant, antitumor, anti-inflammatory, hepatoprotective, anti-hyperlipidemic, antiplatelet, vasorelaxant, as well as antibacterial and antifungal [1]. Moreover, carvacrol has been approved by the Federal Drug Administration and Council of Europe as a food additive, namely as flavor improver and preservative, and is considered generally safe for consumption [1, 2, 3]. However, the chemical profile of these taxa often referred to as “oregano” can vary depending on various factors, producing different chemotypes within the same species; hence not all “oregano” species are rich in carvacrol. Moreover, some of these species can be often inaccurately identified because of their similar morphological characteristics, but most importantly because of their distinguishing oregano smell. *Satureja thymbra*, *Thymbra capitata* and *Thymbra calostachya* are also used as “oregano” spices, however *T. calostachya* (Lamiaceae) is not widely used due to its narrow geographic distribution [4]. *Satureja thymbra* is a multi-branched, usually grey-puberulent dwarf shrub 20-35cm, and can be found in south Aegean region and south coast of Sardinia [5]. *Thymbra capitata* is a dwarf shrub 20-50(-150) cm, with ascending to erect woody branches bearing axillary leaf-clusters (often the only leaves during the dry season). It grows in grounds rich in calcium in the Mediterranean Basin and in Portugal [6]. Both *S. thymbra* and *T. capitata* are aromatic plants that produce essential oils rich in monoterpene phenolic compounds. According to several reports on the essential oil composition of *S. thymbra* from the Mediterranean region, the oxygenated monoterpenes carvacrol, thymol or a mixture of both characterize the essential oil, along with *p*-cymene and γ-terpinene as the next in order major compounds. Similarly, the essential oil of *T. capitata* is characterized by a large amount of monoterpenes, which usually represent 90% of the essential oil. Also in this case, thymol and/or carvacrol dominate and they are always accompanied by *p*-cymene and γ-terpene. These four monoterpenes are biogenetically correlated [7]. *S. thymbra* and *T. capitata* have exhibited different chemotypes depending on the proportion of thymol, carvacrol, and thymol/carvacrol [4]. Furthermore, *S. thymbra* has been used in traditional medicine because of its stimulating carminative, antirheumatic, antispasmodic and antibacterial activity [8], while *T. capitata* is known for its antibacterial, antioxidant, antimycotic, and spasmolytic properties [9]. *T. calostachya* on the other hand, is endemic in eastern Crete (near Sitia) and grows in calcareous rocks. Its stems grow up to 40 cm, branches erect or ascending, densely puberulent or glabrescent [10]. *T. calostachya* essential oil is also characterized by a high percentage of carvacrol, followed by *p*-cymene and γ-terpinene [4]. However, due to the limited geographic distribution of *T. calostachya* there is no information about its biological activities, while there are only two references on the chemical composition of this species [4, 11]. In the framework of our ongoing research on the chemistry and biological activities of aromatic plants found in the Mediterranean Basin, and more specifically of Greek endemic species, we investigated the essential oils of ten different populations of *S. thymbra*, *T. capitata* and the endemic *T. calostachya* collected from natural populations in Greece, aiming at the comparison of their qualitative and quantitative differences, mainly in regard of their content in commercially valuable carvacrol, with the prospect of identifying new candidates for the production of carvacrol-rich cultivars. In addition, the present study covers a literature review on the chemical composition and the biological activities of *S. thymbra*, and *T. capitata* essential oils.

2. Materials and methods

2.1 Plant material

Aerial parts of the species *Satureja thymbra* L., *Thymbra capitata* (L.) Cav. and *Thymbra calostachya* (Rech. fil.) Rech. fil. were collected, during the flowering stage, from various localities in Greece (Table 1.). The identification of the samples was conducted by Assoc. Prof. T. Constandinidis and Dr. E. Kalpoutzakis (plant material collected in Athens, Attica, Karpathos, Kea, Peloponnese) and by Dr P. Petrakis (plant material collected in Crete).

Table 1: Collection data

Species	Sample Code	Collection site	Collection date	Yield (*v/w*)
Satureja thymbra L.	STH-1	Kea island[1]	June 2017	3.2%
Satureja thymbra L.	STH-2	Athens University Campus, Attica Prefecture [1]	May 2018	3.5%
Thymbra capitata (L.) Cav.	TCP-1	Zaritsi, Arcadia Prefecture, Peloponnese[1]	July 2016	3.6%
Thymbra capitata (L.) Cav.	TCP-2	Zaritsi, Arcadia Prefecture, Peloponnese[1]	July 2017	7.6%
Thymbra capitata (L.) Cav.	TCP-3	Athens University Campus, Attica Prefecture[1]	June 2017	2.8%
Thymbra capitata (L.) Cav.	TCP-4	Mt. Parnitha, Attica Prefecture[1]	June 2017	2.4%
Thymbra capitata (L.) Cav.	TCP-5	Karpathos island[1]	May 2018	0.7%
Thymbra calostachya (Rech. fil.) Rech. fil.	TCL-1	Monastery of Capsa, Lasithi Prefecture, Crete[1]	June 2018	1.9%
Thymbra calostachya (Rech. fil.) Rech. fil.	TCL-2	Monastery of Capsa, Lasithi Prefecture, Crete[1]	July 2018	6.0%
Thymbra calostachya (Rech. fil.) Rech. fil.	TCL-3	Mediterranean Agronomic Institute of Chania, Chania Prefecture, Crete[2]	June 2018	3.2%

[1] natural stand, [2] cultivated population

2.2 Extraction of the essential oils

Dried aerial parts of each sample were cut into small pieces and separately subjected to hydrodistillation for 3 h using a modified Clevenger-type apparatus with a water-cooled receiver, to reduce overheating artifacts, according to European Pharmacopoeia method [12]. The isolated essential oils were taken up in pentane, dried over anhydrous sodium sulfate and stored at 4 ºC until further analysis.

2.3 Gas chromatography and gas chromatography - mass spectrometry analysis

GC analyses for the percentage determination of components were carried out on a SRI (Brooks, Hatfield, PA, USA) 8610C gas chromatograph equipped with a DB-5 capillary column (30 m × 0.32 mm, film thickness 0.25 µm; J&W, CA, USA), and a FID detector. Injection and detection were performed at 280 °C in a split ratio 1:10, the carrier gas was helium at a flow rate of 1.2 mL/min. The oven temperature was 60 °C at the time of the injection, raised to 280 °C at a rate of 3 °C/min.

For the identification of components, GC–MS analyses were carried out using a Hewlett-Packard 6890 gas chromatograph equipped with a HP-5MS fused silica capillary column (30 m × 0.25 mm; film thickness 0.25 µm), and a Hewlett-Packard 5973 MS detector operating in electron ionization mode at 70 eV. Injection was performed at 200 °C in a split ratio 1:10, while detection was performed at 250 °C, the carrier gas was helium at a flow rate of 2 mL/min; the oven temperature was 60 °C at the time of the injection, raised to 300 °C at a rate of 3 °C/min and subsequently held at 300 °C for 10 min.

2.4 Identification of components

The identification of the chemical components was based on comparison of their relative retention times and mass spectra with those reported in the NIST/NBS and Wiley libraries and the literature [13].

3. Results & Discussion

3.1 Composition of the essential oils

The essential oils of *Satureja thymbra* collected in Kea island (STH-1) and in Athens University Campus (STH-2) were characterized by the presence of monoterpenes (94.0% and 93.8%, respectively). *S. thymbra* essential oil from Kea (STH-1) was dominated by oxygenated monoterpenes (66.3%) with carvacrol (65.2%) being the principal compound, followed by monoterpene hydrocarbons (27.7%), with γ-terpinene (14.9%) and *p*-cymene (6.0%) being the most important representatives. *S. thymbra* essential oil from Athens University Campus was richer in monoterpene hydrocarbons (53.1%) with γ-terpinene (27.3%) and *p*-cymene (11.1%) as major components. The oxygenated fraction (40.7%), although significantly abundant, came second in order.

Thymol (33.7%) instead of carvacrol was the major metabolite, while the latter appeared in a strikingly lower percentage (2.8%), compared to STH-1 sample. According to the above, the STH-2 sample probably features the thymol chemotype and the STH-1 sample the carvacrol chemotype, since *S. thymbra* populations are usually rich either in thymol or in carvacrol and more rarely in both phenolic monoterpenes [4]. The two samples are also characterized by the sesquiterpene hydrocarbon (*E*)-caryophyllene at analogous percentages (5.8%-4.5%).

The essential oils of five samples (TCP-1, TCP-2, TCP-3, TCP-4, TCP-5) of *Thymbra capitata*, which were collected in Zaritsi (the first two samples), Athens University Campus, Parnitha Mt and Karpathos island respectively, were rich in monoterpenes (93.8%-97.0%). The predominance of oxygenated monoterpenes (58.1%-80.0%) was remarkable, with carvacrol (50.4% -78.1%) as the main compound of the essential oils, followed by the monoterpene hydrocarbons γ-terpinene (3.6%-14.6%) and *p*-cymene (7.6%-12.8%). Thymol appeared only in the essential oil of TCP-4 in significant amount (14.4%), while in the essential oil of the other investigated populations was detected in significantly lower amounts (tr-0.7%). It is also noted that TCP-2 sample showed the highest percentage in oxygenated monoterpenes, especially in carvacrol (78.1%) and the lowest percentage of monoterpene hydrocarbons. With regard to sesquiterpenes, all samples were characterized by the presence of (*E*)-caryophyllene (2.9%-5.0%), while the oxygenated sesquiterpene caryophyllene oxide (0.4%-0.9%) appeared in all samples except TCP-2.

A high percentage of monoterpenes (98.1%, 98.6%, 92.7%) was identified in the essential oils of the dried aerial parts of the three samples of *Thymbra calostachya* (TCL-1, TCL-2, TCL-3). Oxygenated monoterpenes (80.1%, 76.2%, 80.7%) were also in this case the most abundant group of compounds, with carvacrol constantly being the predominant metabolite (76.0%, 73.6%, 78.4%). Thymol, on the other hand, appeared in traces. The monoterpene hydrocarbons (18.4%, 22.4%, 12.0%) followed in lower amounts, with *p*-cymene (8.0%, 8.4%, 5.8%) and γ-terpinene (3.1%, 5.0%, 1.8%) as main constituents. Furthermore, very small amounts of (*E*)-caryophyllene and caryophyllene oxide were present.

In conclusion, the differences observed among the investigated essential oils were rather quantitative than qualitative, with high levels of oxygenated monoterpenes characterizing their chemical composition. Overall, *S. thymbra* essential oil was characterized by lower levels of oxygenated monoterpenes (40.7%-66.3%) compared to *T. capitata* (71.1%) and *T. calostachya* (79.0%). On the other hand, *S. thymbra* showed the highest percentage of monoterpene hydrocarbons (40.4%) among the investigated taxa (*T. capitata* 24.2%, *T. calostachya* 17.6%). Carvacrol was by far the most prevalent component in all essential oils, apart from a single sample of *S. thymbra* collected from Athens University Campus (STH-2), where thymol dominated instead and the monoterpene hydrocarbons γ-terpinene and *p*-cymene were next in order. Sesquiterpenes were the least abundant group of compounds, however *T. capitata* (2.9%-5.9%) and *S. thymbra* (5.8% and 6.1%) were richer in sesquiterpenes compared to *T. calostachya* (1.3%-2.6%). Comparison between the two species of the genus *Thymbra* showed some quantitative differences as well. Specifically, *T. capitata* showed a wider range in the amount of thymol (tr-14.4%), whereas in *T. calostachya* essential oils carvacrol was constantly dominating the essential oil analysis, and thymol was detected only in traces. Our results are generally in accordance with the literature. Major metabolites of *S. thymbra* essential oil are carvacrol or thymol, depending on the chemotype, followed by γ-terpinene and *p*-cymene [4]. In a study on the volatiles of *S. thymbra* from Sardinia γ-terpinene (27.0%-29.4%) was identified as the major component during all growing stages, followed by thymol (15.3%-22.2%), with carvacrol being present in a strikingly low percentage (1.0%-1.9%) [14]. Moreover, γ-terpinene dominated the essential oil of *S. thymbra* according to a number of studies [15, 16, 17]. Among the identified *T. capitata* chemotypes, the chemotype of thymol and of thymol-carvacrol have been encountered in limited studies in Greece and Italy [18, 19], while the chemotype of carvacrol predominates in other studies [20], a fact that stands in accordance with our results. According to the single published study on the volatiles of *T. calostachya* [4], carvacrol, γ-terpinene, *p*-cymene and β-bourbonene, are the main metabolites of the essential oil which are generally consistent with the present study, except from the presence β-bourbonene, which was not detected.

Table 2: Composition (%) of the essential oils from *Satureja thymbra*, *Thymbra capitata* and *Thymbra calostachya* samples

Compounds[a]	AI[b]	STH-1[c]	STH-2	TCP-1	TCP-2	TCP-3	TCP-4	TCP-5	TCL-1	TCL-2	TCL-3
α-Thujene	924	0.9	2.1	0.6	0.6	0.2	1.0	1.4	1.9	2.4	1.4
α-Pinene	932	1.4	2.1	1.0	1.0	1.0	1.6	1.0	1.0	1.0	0.8
Camphene	946	0.4	1.0	0.5	tr	0.2	0.6	0.8	0.1	0.2	tr
Sabinene	969	-	0.2	-	-	-	tr	tr	tr	0.1	tr
β-Pinene	974	0.6	1.2	0.3	-	0.2	0.7	0.5	0.3	0.3	tr
1-Octen-3-ol	975	-	-	tr	-	-	-	-	-	-	-
Myrcene	988	1.3	1.7	1.6	1.4	1.7	1.4	1.6	1.9	1.9	1.4
3-Octanol	988	tr	tr	tr	tr	tr	tr	-	-	-	-
α-Phellandrene	1002	tr	0.4	0.4	tr	0.4	0.3	tr	0.1	0.4	tr
δ-3-Carene	1008	-	-	-	-	tr	tr	-	tr	tr	tr
α-Terpinene	1014	2.2	3.9	2.4	1.7	1.4	2.2	3.0	1.2	1.8	0.8
p-Cymene	1020	6.0	11.1	9.0	7.6	8.9	8.1	12.8	8.0	8.4	5.8
Limonene	1024	tr	0.9	0.3	tr	0.3	0.3	tr	0.3	0.4	tr
β-Phellandrene	1025	tr	tr	0.3	tr	0.3	-	tr	0.3	0.3	tr
(*Z*)-β-Ocimene	1032	-	0.4	-	-	-	tr	-	-	-	-
(*E*)-β-Ocimene	1044	-	0.6	tr	-	tr	tr	tr	tr	0.1	-
γ-Terpinene	1054	14.9	27.3	6.4	4.7	3.6	10.5	14.6	3.1	5.0	1.8
cis-Sabinene hydrate	1065	-	0.2	tr	tr	-	tr	0.3	0.2	0.4	0.4
Terpinolene	1086	-	0.2	0.2	tr	0.2	tr	tr	0.2	0.1	tr

p-Cymenene	1089	-	-	-	-	-	-	-	tr	tr	-
Linalool	1095	-	0.3	0.7	tr	1.3	1.3	1.5	tr	0.3	tr
trans-Sabinene hydrate	1098	-	0.2	-	-	-	-	-	-	-	-
cis-*p*-Menth-2-en-1-ol	1118	-	-	-	-	-	-	-	tr	tr	-
Borneol	1165	tr	1.2	1.2	1.1	tr	1.1	3.7	tr	tr	tr
Terpinen-4-ol	1174	tr	0.4	0.7	0.8	0.6	0.6	0.8	0.9	1.0	0.5
α-Terpineol	1186	-	-	-	-	-	-	-	tr	-	tr
Neral	1235	-	-	tr	-	tr	-	-	-	-	-
Carvone	1239	-	-	-	-	-	-	-	tr	tr	-
Carvacrol, methyl ether	1241	1.1	1.9	-	-	-	tr	-	-	-	-
Bornyl acetate	1287	-	-	-	-	-	-	tr	-	-	-
Thymol	1289	tr	33.7	tr	tr	tr	14.4	0.7	tr	tr	tr
Carvacrol	1298	65.2	2.8	69.3	78.1	75.2	50.4	50.8	76.0	73.6	78.4
Thymol acetate	1349	-	tr	-	-	-	-	-	-	-	-
Carvacrol acetate	1370	-	-	-	-	tr	0.4	0.3	3.0	0.9	1.4
(*E*)-Caryophyllene	1417	5.8	4.5	3.6	2.9	3.6	4.5	5.0	0.8	0.7	2.0
Aromadendrene	1439	-	-	-	-	-	tr	-	-	-	-
α-Humulene	1452	tr	0.2	tr	tr	tr	tr	tr	tr	tr	tr
γ-Muurolene	1478	-	-	-	-	-	-	tr	tr	-	-
Viridiflorene	1496	-	tr	-	-	-	-	-	-	-	
Bicyclogermacrene	1500	-	0.1	-	-	-	-	-	-	-	-
β-Bisabolene	1505	-	-	0.4	tr	tr	-	-	-	-	-
(*E*)-α-Bisabolene	1538	-	-	0.3	tr	tr	-	-	-	-	-
Caryophyllene oxide	1583	tr	1.3	0.7	-	0.8	0.4	0.9	0.6	0.6	0.6
Abietatriene	2055	-	-	tr	tr	tr	-	-	-	-	-
Total		99.8	99.9	99.9	99.9	99.9	99.8	99.7	99.9	99.9	95.3
Grouped components											
Monoterpene hydrocarbons		27.7	53.1	23.0	17.0	18.4	26.7	35.7	18.4	22.4	12.0
Oxygenated monoterpenes		66.3	40.7	71.9	80.0	77.1	68.2	58.1	80.1	76.2	80.7
Sesquiterpene hydrocarbons		5.8	4.8	4.3	2.9	3.6	4.5	5.0	0.8	0.7	2.0
Oxygenated sesquiterpenes		tr	1.3	0.7	-	0.8	0.4	0.9	0.6	0.6	0.6
Diterpene hydrocarbons		-	-	tr	tr	tr	-	-	-	-	-
Others		-	-	tr	tr	tr	tr	-	-	-	-

[a]Compounds listed in the order of elution on a HP-5MS column under the specifed chromatographic conditions; [b]Relative retention indices calculated from the retention times of the compounds in relation to those of a series of *n*-alkanes (C_8–C_{25}) analyzed under the same chromatographic conditions; [c]See sample code in Table 1.

3.2 Chemical profile of *Satureja thymbra* and *Thymbra capitata* essential oils

Tables 3 and 4 present the main essential oil components of *S. thymbra* and *T. capitata*, collected from various localities within their geographic distribution, including both wild and cultivated populations, according to reports, published until 2019

Table 3: Main components of *Satureja thymbra* essential oils based on the literature

Collection site	Plant material	Main components (%)					References
		carvacrol (%)	thymol (%)	*p*-cymene (%)	γ-terpinene (%)	other major compounds (%)	
Greece							
Karditsa	dried aerial parts[1]	32.4	0.3	13.7	32.4	β-myrcene (3.2), α-pinene (2.4)	[21]
	dried aerial parts[1]	34.3	0.3	13.3	29.9	myrcene (2.8), α-pinene (2.6)	[22]
Thessaloniki, Agricultural Research Centre of Northern Greece	dried leaves & flowers[2]	30.79-48.74	0.01-0.38	8.29-10.29	26.02-40.88	(*E*)-β-caryophyllene (6.41-7.56), α-terpinene (2.60-3.62)	[23]
	dried leaves[2]	30.8	0.05	9.28	40.9	(*E*)-β-caryophyllene (7.56), α-terpinene (3.62)	[17]
	dried inflorescences and the upper leaves[1]	3.00	33.8	11.8	30.8	α-terpinene (2.72), myrcene (2.38), (*E*)-β-caryophyllene (2.36)	[24]
Ikaria island	dried leaves and inflorescences[1]	46.53-58.00	-	5.32-6.42	16.04-24.36	(*E*)-β-caryophyllene (8.92-10.37)	[25]
	leaves and inflorescences[1]	41.71, 47.91	-	8.28, 6.96	29.47, 23.58	caryophyllene (7.06, 6.32)	[26]
Ikaria island (cultivated population)	leaves and inflorescences[1]	48.61, 44.02	-	6.01, 6.31	26.36, 28.69	caryophyllene (7.34, 6.75)	
Athens, Agricultural University of Athens (cultivated population)	leaves and inflorescences[1]	49.22, 47.17	-	5.63, 5.98	25.88, 27.52	caryophyllene (6.78, 5.99)	
Attiki	dried leaves and flowering tops[1]	48.5	-	9.6	23.2	*trans*-caryophyllene (3.1), α-terpinene (3.1)	[27]

	dried leaves and flowering tops[1]	48.5	-	9.6	23.2	α-terpinene (3.1)	[28]
	dried plant material[1]	44.6	0.3	11.9	25.5	β-caryophyllene (2.7), α-terpinene (2.6)	[4]
	dried plant material[1]	3.2	35.5	10.4	27.6	β-caryophyllene (5.3), terpinen-4-ol (4.6)	
	stems and leaves[1]	4.16-12.80	20.21-27.88	12.18-18.20	14.91-25.12	β-caryophyllene (5.24-8.05)	[29]
	stems, leaves and flowers[1]	39.10-29.88	12.59-17.22	8.83-10.89	10.61-12.45	β-caryophyllene (4.29-6.88)	
	fresh stems, leaves and flowers[1]	1.39	41.0	11.80	22.2	(*E*)-β-caryophyllene (5.92), thymol methyl ether (3.02)	[30]
	fresh stems and leaves[2]	2.27	42.15	10.39	20.12	β-caryophyllene (5.47), thymol methyl ether (4.12)	[31]
Crete Mt Dikti	fresh stems, leaves and flowers[2]	30.39	24.32	9.19	14.64	*β*-caryophyllene (4.89), thymol methyl ether (4.34)	
Several locations (Crete)	dried aerial parts[1]	5.2-66.5	0.1-65.6	5.5-15.0	4.4-22.6	-	[18]
Mt Taygetus	dried aerial parts[1]	3.12	34.72	26.76	13.86	β-caryophyllene (3.82), α-pinene (3.80)	[32]
Nisyros island	dried aerial parts[1]	53.6	0.1	13.7	18.0	β-caryophyllene (4.3)	[33]
Italy							
Cagliari, Sardinia	branches, leaves and apeces[1]	1.03-1.92	15.33-22.16	8.76-8.94	26.98-29.39	β-caryophyllene (2.52-7.27), α-pinene (2.38-5.69), α-terpinene (2.69-2.83)	[14]
Turkey							
commercial product	dried leaves[1]	42.7	-	-	4.22	*o*-cymene (17.98), linalool (9.65), caryophyllene oxide (5.25),	[34]
Aydin	dried aerial parts[1]	17.50	13.13	12.73	40.99	β-caryophyllene (3.15)	[15]
commercial product	dried aerial parts[3]	38.72	17.15	12.26	4.51	borneol (2.82)	[35]
	dried aerial parts[1]	34.03	14.36	18.32	8.81	(*Z*)- b-ocimene (2.16)	
commercial product	dried aerial parts[1]	34.6	12.8	13.0	22.9	thymol methyl ether (4.4)	[36]
Mersin	dried leaves[1]	53.68	12.96	10.05	17.55	myrcene (2.32)	[37]
Cesme-Izmir	leaves[1]	40.15	13.16	16.39	26.56	α-terpinene (1.07)	[38]
	branches[1]	24.35	24.3	17.16	21.13	caryophyllene oxide (14.56), β-caryophyllene (5.19)	
Izmir-Kiraz-Sarigöl	dried aerial parts[1]	39.0	0.3	10.2	29.0	β-caryophyllene (6.3), α-pinene (2.4)	[39]
Mediterranean regions of Turkey	dried leaf and flower parts[1]	52.60	26.45	0.94	8.92	caryophyllene (7.28)	[40]
	herb	44-45	-	7-13	18-25	-	[41]
	leaves	30-40	-	14-16	23-25	-	
	dried plant material[1]	41.6	-	7.7	34.0	-	[42]
Israel							
cultivated from wild populations	fresh flowering plants[1]	0.5-22.3	1.0-44.9	10.1-13.2	26.7-48.9	α-terpinene (3.3-5.3), α-pinene (3.9-5.1)	[43]
Lebanon							
Nahr Ibrahim	dried aerial parts[1]	6.15	54.30	10.70	8.87	caryophyllene oxide (3.80)	[44]
	flowering tops[1]	5.3	44.5	21.7	11.1	caryophyllene oxide (2.0)	[45]
	dried aerial parts[1]	23.07	18.82	7.58	34.06	caryophyllene (3.96), α-terpinene (3.53)	[8]
Ayoun-kourkoush	fresh leaves[1]	4.98	9.92	10.76	7.56	sabinene (8.64), *trans* caryophyllene (3.67), δ-cadinene (3.11), β-pinene (2.90), linalool (2.81)	[46]
Libya							
Bayda	dried aerial parts (wooden parts removed)	4.18	25.16	7.17	39.26	carvacrol methyl ether (3.33), α-terpinene (3.26), β-caryophyllene (2.76)	[16]

Essential oil obtained by: [1]hydrodistillation; [2] steam distillation; [3] microwave extraction

Table 4: Main components of *Thymbra capitata* essential oils based on the literature

Collection site	Plant material	Main components (%)					References
		carvacrol (%)	thymol (%)	*p*-cymene (%)	γ-terpinene (%)	other major compounds (%)	
Greece							
Mt Ochi, Euboea	fresh aerial parts (leaves, stems and flowers)[1]	74.3	-	7.1	7.0	(*E*)-β-caryophyllene (2.6), α-terpinene (2.0)	[47]
Ikaria island	air-dried leaves and inflorescences[1]	66.58, 75.69	-	9.45, 7.22	9.84, 6.35	caryophyllene (4.67, 2.89)	[26]
Ikaria island (cultivated population)	air-dried leaves and inflorescences[1]	73.54, 72.03	-	8.52, 8.47	6.67, 7.19	caryophyllene (3.60, 3.19)	
Agricultural University of	air-dried leaves and	77.78, 76.62	-	5.42, 6.27	4.30, 4.84	caryophyllene (4.14, 4.33)	

Athens (cultivated population)	inflorescences[1]						
Crete	air-dried aerial parts[1]	8.3-75.7	0.2-62.8	6.1-12.9	1.2-12.5	-	[18]
	dry plant material[1]	62.6	0.4	13.5	7.4	terpinen-4-ol (3.5)	[4]
	dry plant material[1]	5.1	34.0	19.6	13.7	β-caryophyllene (5.4),	
Italy							
S. Apulia	dry biomass[1]	24.82	48.91	4.89	5.43	borneol (3.10)	[19]
	dry leaves[1]	6.7-6.9	60.9-67.5	6.7-8.3	5.9-12.1	β-caryophyllene (2.6-3.0)	[48]
	dry biomass[1]	24.35	49.33	4.90	5.46	borneol (3.10)	[49]
Sicily	air dried aerial parts[1]	67.40-79.58	nd-0.21	5.37-10.01	2.5-7.8	β-caryophyllene (1.44-4.24), α-terpinene (1.16-2.02)	[50]
	air dried aerial parts[1]	65.26-81.27	0.14-0.39	4.63-11.45	2.10-9.09	β-caryophyllene (1.34-4.25)	[51]
	air-dried aerial parts[1]	69.4-83.2	0.1-8.1	3.5-19.1	1.9-10.0	β-caryophyllene (1.3-2.5)	[7]
	air-dried aerial parts[1]	2.7	16.1	40.4	10.4	borneol (4.0)	
	air-dried aerial parts[1]	76.0-81.1	0.1-0.4	3.8-5.9	0.3-6.6	β-caryophyllene (1.3-2.8), *trans*-β-ocimene (0.1-4.3)	
Spain							
Carmona, (Sevilla)	fresh aerial parts	91.56	-	1.69	-	-	[52]
Badajoz	dried flowers[1]	75.51	nd	7.29	4.83	linalool (3.38)	[53]
	dried fruits[1]	74.27	nd	9.10	4.14	linalool (3.25)	
cultivated population	aerial parts[1]	72.7	0.1	7.5	5.8	myrcene (2.0)	[54]
cultivated population	dried plant material[1]	66.2-75.2	t-0.1	7.3-8.4	3.4-11.2	linalool (1.4-2.6)	[20]
	dried plant material[1]	74.3-78.3	t-0.3	3.5-9.2	3.4-7.1	linalool (1.1-3.1)	
Portugal							
Algarve	fresh aerial parts[1]	73.1	0.4	5.8	7.5	β-myrcene (2.1), β-caryophyllene (2.1)	[55]
	fresh aerial parts[1]	68.0	-	-	11.0	-	[56]
	fresh aerial parts[1]	72.0	0.4	10.6	1.4	β-caryophyllene (2.4)	[57]
	air-dried aerial parts[1]	75.0	0.2	5.0	5.1	linalool (2.0)	[58]
Nave do Borao (Algarve)	dried plant material[1]	78.6	-	6.7	3.0	β-caryophyllene (2.2)	[59]
Direcção Regional de Agri-cultura e Pescas do Algarve	dried aerial parts[1]	68.1	0.1	12.7	6.1	myrcene (3.0), α-terpinene (2.2)	[60]
Direcção Regional de Agri-cultura do Algarve (cultivated population)	dried aerial parts[1]	78.0	0.2	-	5.4	*trans*-ocimene (4.8)	[61]
samples from Algavre and Estremadura	air-dried aerial parts[1]	60.6-65.8	0.1-0.3	6.0-7.5	8.5-9.5	linalool (2.1-2.9), (E)-caryophyllene (2.0-2.5)	[62]
Algarvian Barrocal	air-dried aerial parts[1]	58.4, 51.7	11.7, 10.4	8.7, 10.1	9.1, 5.5	β-caryophyllene (1.3, 1.9)	[63]
Estremadura: (Setúbal district)	air-dried aerial parts[1]	59.3-65.6	8.2-21.4	5.0-11.1	2.3-7.7	β-caryophyllene (2.1, 4.4)	
Estremadura (Lisbon district)	air-dried aerial parts[1]	76.6	15.3	2.2	1.4	β-caryophyllene (3.5)	
Gambelas	fresh aerial parts[1]	71.4	0.4	8.8	5.9	β-myrcene (2.5)	[64]
Faro	fresh aerial parts[1]	75.0	0.2	5.6	6.7	β-myrcene (2.4)	[65]
Croatia							
island Hvar	air-dried aerial parts[1]	82.56, 75.90	0.29-0.41	-	-	1,8-cineole (5.16, 7.63), limonene (3.37, 5.71)	[66]
Lebanon							
Nakoura	dried aerial parts[1]	37.19	28.40	9.72	3.06	β-caryophyllene (2.10)	[44]
Anfeh	flowering tops	41.5	29.3	9.0	4.0	β-caryophyllene (1.8)	[45]
	dried flowering tops[1]	47.0	19.9	5.7	6.3	β-caryophyllene (2.6)	[67]
Tunisia							
14 sites in Tunisia	fresh leaves[2]	51.1-75.9	0.1-0.8	3.7-15.0	1.4-11.9	*trans*-β-caryophyllene (2.9-4.6), myrcene (0.5-3.0)	[9]

Essential oil obtained by [1]hydrodistillation; [2]maceration in hexane

Literature survey suggested that carvacrol was one of the most abundant constituents in the essential oils of *S. thymbra*. However, in some cases thymol was the major compound [4, 29, 30, 31, 32] while in other samples carvacrol and thymol co-dominated [18, 29, 31]. In many of the essential oils, γ-terpinene followed as the next in order major compound, while in some cases this monoterpene hydrocarbon dominated in the analysis [17, 23, 29]. A study also showed that γ- terpinene was the main component of Italian *S. thymbra* essential oil regardless of the collection period [14]. Carvacrol was the most important constituent in the essential oils from Greece [4, 21, 22, 25, 26, 27, 28, 29] and Turkey as well [34-42]. In the majority of the samples where carvacrol prevailed, there was a notable but lower amount of thymol or γ-terpinene [35, 36, 38, 39]. In Israel both carvacrol and thymol chemotypes were identified [43]. In Lebanon in some studies thymol predominates [44, 45], however in another study γ-terpinene prevailed [8], or *p*-cymene and thymol were equally abundant [46]. Finally, Libyan *S. thymbra* essential oil was dominated by γ-terpinene and thymol followed also with a remarkable percentage, while carvacrol was identified in strikingly lower amount [16].

Carvacrol was the metabolite with the highest abundance in *T. capitata* essential oils in most of the samples according to the literature. More specifically, carvacrol was the principle component of the essential oils originating from Greece [4, 18, 26, 47] apart from a few samples from Crete which were richer in thymol [4, 18]. Carvacrol was found to dominate the samples from Sicily, Italy [7, 50, 51], however thymol was the principle component in the samples from Apulia [19, 48, 49]. Interestingly, in one sample from Val Demona (Sicily), *p*-cymene was the main constituent [7]. In the essential oils originating from Spain, Portugal, Croatia and Tunisia carvacrol was the major metabolite. In most cases, *p*-cymene and γ-terpinene were next in order of abundance. In Spanish samples, carvacrol was followed by *p*-cymene in all the cases, except from two samples where γ-terpinene was the second most important component [20]. In Portuguese samples, the second most important constituent was γ-terpinene [55, 56, 58, 61, 62, 65] or *p*-cymene [57, 59, 60, 64] or thymol [63], whereas 1,8-cineole was the second principle component in Croatian samples [66]; the samples from Tunisia showed *p*-cymene as second major constituent [9]. Also in the essential oils from Lebanon carvacrol was the most abundant compound [44, 45, 67], however thymol was the second most important metabolite of the analysis possessing a relatively high amount.

3.3 Pharmacological activities of the essential oil of *Satureja thymbra* and *Thymbra capitata*

The essential oils of both species have been evaluated mainly as antibacterial and antifungal agents exhibiting also a high potency against the tested pathogens as shown in Tables 5 and 6. Additionally, the essential oils of *S. thymbra* and *T. capitata* have shown also important antioxidant, insecticidal and other properties.

Table 5: Biological activities of *Satureja thymbra*

Biological activity evaluated	Short description	References
antimicrobial	The EO was effective against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Listeria monocytogenes*, *Salmonella Enteritidis*, *Salmonella Typhimurium*, *Pseudomonas fragi*, *Saccharomyces cerevisiae* and *Aspergillus niger*. In contrast, EtOAc and EtOH extracts were active only against the bacterial strains, but not against *S. cerevisiae* and *A. niger*, while no antimicrobial activity was observed for Aq extract.	[68]
antimicrobial	The EO showed very strong antimicrobial activity against *Bacillus subtilis*, *Candida albicans*, *Enterococcus faecalis*, *Enterobacter aerogenes*, *Enterococcus durans*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Listeria innocua*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescence*, *Salmonella infantis*, *Salmonella kentucky*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Staphylococcus epidermidis*.	[34]
antimicrobial	The EO was able to inhibit the growth of *Escherichia coli*, *Enterococcus faecalis*, and *Bacillus subtilis* subsp *spizizenii*, *Pseudomonas aeruginosa* and *Salmonella enteritidis*.	[44]
antibacterial	The EO was found highly effective on *Aeromonas salmonicida* FC43 and FC29 strains	[69]
antimicrobial	EO showed growth inhibition of *Listeria monocytogenes* Scott A and *Salmonella* ser. *Enteritidis* PT4.	[70]
antimicrobial	The EO demonstrated activity against *Bacillus cereus*, while the most resistant bacterial strains were *Listeria monocytogenes*, *Enterococcus faecalis* and *Escherichia coli*. In the cases of *B. cereus* and *L. monocytogenes*, the EO was more effective than the commercial drug streptomycin.	[24]
antimicrobial	The EO and the hydrosol exhibited strong antimicrobial activity against *Listeria monocytogenes*, *Pseudomonas putida*, *Staphylococcus simulans* and *Lactobacillus fermentum* and *Salmonella enteric*, as well as against mixed-culture biofilms formed on stainless steel. The decoction was less effective.	[71]
antimicrobial	The EOs were highly active against the resistant strains such as *Stenotrophomonas maltophilia* MU 64, *S. maltophilia* MU 99 and *Chryseomonas luteola* MU 65. The maximum antimicrobial activities of the essential oils were against *Bacillus subtilis*. *Pseudomonas aeruginosa* and *Pseudomonas fluorescens* were resistant to this essential oil.	[72]
antibacterial	The EO was highly effective on spoilage strains (*Pseudomonas fragi*, *Escherichia coli*) and *Staphylococcus equorum*, moderately effective on *Staphylococcus aureus* and *Listeria monocytogenes*, and ineffective on *Staphylococcus succinus* and *Lactobacillus sakei*.	[73]
antibacterial	The EO showed higher activity against the Gram-positive bacterial strain of *Listeria monocytogenes* Scott A in comparison with the Gram-negative strain *Salmonella* serovar *Enteritidis* PT4. The EO, obtained during the full flowering stage, showed the lowest MIC and NIC values against the pathogens tested.	[29]
antibacterial, antifungal	*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Candida albicans*, *Penicillium clavigerum*, *Mucor hiemalis* and *Absidia glauca* were inhibited by the EO of *S. thymbra*. *E. coli* and *P. aeruginosa* showed higher sensitivity, while *S. aureus* was more resistant.	[39]
antibacterial	The EO showed antibacterial activity against a panel of five foodborne bacteria: *Escherichia coli*, *Salmonella enteritidis*, *Staphylococcus aureus*, *Listeria monocytogenes* ScottA, and *Bacillus cereus*.	[30]
antimicrobial	The EO showed antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Shigella sonnei* and was found to be highly active against *Candida albicans*. The strongest activity was observed against *C. albicans* and *S. typhimurium*. The ethanolic extract did not inhibit the growth of any of the organisms tested.	[38]
antimicrobial	The EO was found to possess potent antimicrobial activity against *Erwinia carotovora* strains and bacteria isolated from the surface of potato tubers.	[74]
antifungal	The EO of *S. thymbra* exhibited activity against *Saprolegnia parasitica*.	[40]
antifungal	The EOs isolated from *S. thymbra* inhibited the growth of *Aspergillus fumigatus* and *Paecilomyces variotii*.	[75]
antifungal	The EO has completely inhibited mycelial growth of *Aspergillus parasiticus* compared with control.	[76]
antifungal	The EO possessed very good antifungal properties. The least sensitive fungal strains were *Trichoderma viride*, *Penicillium ochrochloron* and *Penicillium funiculosum*, while *Cladosporium cladosporioides*, *Phomopsis helianthi*, *Trichophyton metagrophytes*, *Microsporum canis*, *Epidermophyton foccosum* were the most sensitive ones.	[27]
antifungal	The EO caused complete inhibition of *Exserohilum turcicum* and reduced growth of *Fusarium oxysporum*.	[77]
antifungal	The EO was proven to be fungistatic against *Penicillium citrinum* spores in soil and the mycelial growth of *Mucor hermalis* in liquid culture.	[78]
antiviral	The ethanol extract showed high selectivity index (SI) against *Herpes simplex* virus type 1 (HSV-1). The EO showed no antiviral activity against Severe Acute Respiratory Syndrome-Corona Virus (SARS-CoV).	[79]

antiviral	The ethanol extract showed activity against *Herpes simplex* virus type 1 (HSV-1).	[80]
antiplasmodial insecticidal	The EO of *S. thymbra*, was effective against *Plasmodium falciparum* with an inhibitory activity independent from the time of collection. Thymol-enriched fractions were the most active on both strains and thymol was identified as the compound mainly responsible for this activity. The EO of *S. thymbra* showed also larvicidal and adulticidal activities.	[81]
larvicidal, repellent	EO from *S. thymbra* had acceptable larvidical effect (LC_{50}=53.3 mg/L) and exerted strong repellent activity with less than ten landings per 5 min of exposure against *Aedes albopictus*.	[21]
insecticidal	The EO of *Satureja thymbra* showed insecticidal activity against 3rd instar nymphs and female adults of *Planococcus ficus*.	[22]
insecticidal	The EO showed insecticidal activity against *Ephestia kuehniella*, *Plodia interpunctella* and *Acanthoscelides obtectus* adults.	[37]
insecticidal, genotoxic	The EO of *Satureja thymbra* was found to be effective as an insecticide against *Drosophila melanogaster*, without mutagenic or recombinagenic activity.	[32]
acaricidal	The EO exhibited acaricidal activity against *Hyalomma marginatum* adults.	[85]
ovicidal	The EO showed mortality for *Ephestia kuehniella* and *Plodia interpunctella* eggs.	[84]
fumigant	*S. thymbra* EO caused 100% mortality to the adults of *Scatopse* spp.	[82]
fumigant	Increasing doses of EO decreased eclosion from treated eggs of *Ephestia kuehniella*. The most prominent decrease (35%) was observed at the highest concentration of the EO. Also the EO of *S.thymbra* did not produce any lethal effect at 3h exposure time on adult moths (*E. kuehniella*).	[83]
antioxidant antiproliferative	The EO showed antioxidant and antiproliferative activity on mammary adenocarcinoma MCF-7 cells.	[86]
antioxidant, antimicrobial	The EO possessed antioxidant activity and antimicrobial activity against eight bacterial strains (*Escherichia coli, Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Proteus mirabilis*, *Listeria monocytogenes*, *Bacillus cereus*, *Micrococcus flavus*, *Staphylococcus aureus*) and eight fungal species (*Aspergillus flavus*, *A. fumigatus*, *A. niger*, *A. ochraceus*, *Penicillium funiculosum*, *P. ochrochloron*, *Trichoderma viride*, *Candida albicans*).	[16]
anticholinesterase, antioxidant	The EO showed acetylcholinesterase and butyrylcholinesterase inhibitory activities. In contrast, the methanol extract exhibited weak activity, particularly against acetylcholinesterase enzyme. The EO and the methanol extract proved to have antioxidant activity. Both the extract and the oil exhibited a good lipid peroxidation inhibitory activity.	[36]
antinociceptive, anti-inflammatory	*S. thymbra* EO did not exert any anti-inflammatory effect. It may have central analgesic activity in mice and rats.	[15]

EO: Essential Oil; SI: Selective Index

Table 6: Biological activities of *Thymbra capitata*

Biological activity evaluated	Short description	References
antimicrobial	The EO showed strong antimicrobial activity and was assayed as a potential natural sanitizing solution (SAN) for food contact surfaces.	[52]
antibacterial	The EO and carvacrol exhibited a potent antibacterial activity against *Gardnerella vaginalis* cells. Antibiofilm activity was more evident with the EO than carvacrol. Vaginal lactobacilli were significantly more resistant to the EO.	[87]
antimicrobial	The hydrosol was active against *Salmonella enterica* Serovar, *Typhimurium* biofilms and planktonic cells, whereas a 200-times-higher concentration of benzalkonium chloride was needed to achieve the same effect against biofilm compared to planktonic cells.	[88]
antibacterial	Inhibitory activity against three bacterial strains of *Erwinia carotovora* ssp. *carotovora* isolated from cyclamen, calla and *Erwinia carotovora* ssp. *atroseptica* isolated from potato.	[74]
antifungal	*T. capitata* EO and chitosan (TCCH hydrogel) exhibited an acidic nature, compatible with the vaginal pH. The association of both natural products revealed a synergistic effect against *Candida* and TCCH hydrogel proved to be active against both *Candida* planktonic cells and biofilm.	[89]
antifungal	The EO reduced biofilm biomass and metabolic activity of all tested *Candida* species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*) up to 50% at MIC values. The effect was more pronounced at double MIC values, achieving >80% reduction, except for *Candida albicans* that presented a more resistant profile (62%).	[58]
antifungal	The EO exhibited antifungal activity for 7 clinical isolates and 3 ATCC type *Candida* strains, 5 clinical isolates, 2 CECT and 2 ATCC type *Aspergillus* strains and 5 dermatophyta clinical strains.	[62]
antilisterial, antioxidant	The EO had higher antilisterial activity compared to chloramphenicol. It also showed also antioxidant activity.	[59]
fumigant	The EO exhibited remarkable activity against *Sitophilus oryzae*.	[47]
insecticide	The effects of the EO were observed on *Ceratitis capitata* adults. After 2 days, the mortality rate was 33.3%, after 3 days it was 43.3% and after 4 days it reached 50%.	[90]
antiprotozoal	*T. capitata* EO exhibited antiprotozoal activity against *Trypanosoma brucei brucei*.	[91]
antiprotozoal	The EO proved to be active in inhibiting the growth of *Giardia lamblia*.	[92]
nematicidal	The EO showed activity in tests against *Meloidogyne chitwoodi* hatching. Fractions rich in oxygenated compounds were found to exhibit higher inhibitory effect.	[56]
nematicidal	Among 84 samples analyzed for their activity against *Bursaphelenchus xylophilus*, *T. capitata*'s EO caused mortality higher than 96%.	[93]
antioxidant	The EO exhibited similar capacity of preventing the lipid oxidation compared to butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).	[61]
antioxidant	Lower indices of oxidation were observed in gilthead seabreams (*Sparus aurata*) that were administered with feeds supplemented with *Thymbra capitata* EO, rich in carvacrol.	[94]

antioxidant	The EO was able to prevent meat oxidation even after one month of storage and showed a dose-dependent activity.	[95]
antiproliferative	The EO exhibited dose-dependent decrease in THP-1 leukemia cell line viability.	[64]
enzyme inhibition	The EO exhibited inhibition of the enzyme 5-lipoxygenase. The EO showed strong inhibition of the enzyme acetylcholinesterase, This is partly due to the high content of EO in carvacrol, as some studies have shown that this monoterpene is a potent inhibitor of acetylcholinesterase.	[60]

EO: Essential Oil

4. Conclusions

In conclusion, the essential oil composition of ten populations of three species characterized as “oregano” spices was investigated, characterized by a profound abundance in carvacrol, a biologically important oxygenated monoterpene with commercial value. Nine out of ten of the investigated populations were dominated by carvacrol, thus samples from these selected populations could be employed as candidates for the production of new cultivars, with a constant and high content in this biologically and commercially valuable metabolite or mother plants for propagation. In this context, it is worth noting that all three investigated populations of *T. calostachya*, an under investigated so far Greek endemic taxon, were proven to be the richest in carvacrol. Apart from the comparative chemical study of the essential oils of these taxa, a literature review on the chemical composition and pharmacological activities of the essential oil of *Satureja thymbra* and *Thymbra capitata* was presented.

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