

THE PHENOLIC COMPOUNDS, ANTIOXIDANT AND ANTICHOLINESTERASE ACTIVITIES OF *CYCLOTRICHIMUM ORIGANIFOLIUM* (LABILL.) MANDEN & SCHENG AND *THYMUS SIPYLEUS* BOISS TEAS FROM TURKEY

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ABSTRACT. In this study, phenolic compounds, antioxidant and anticholinesterase activities of *Cyclotrichium organifolium* (Labill.) Manden & Scheng and *Thymus sipyleus* Boiss teas were investigated. Two methods were used for the preparation of the teas: infusion and decoction. The quantitative amounts of the phenolic contents were determined by LC-MS/MS. Anticholinesterase activity was measured by Ellman method. Also, the antioxidant activity of the tea samples was determined by three methods: 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging, β -carotene linoleic acid and CUPRAC assays. Flavonoids and derivatives were the most abundant components of the *C. organifolium* and *T. sipyleus* teas. The infusion of *C. organifolium* and decoction of *T. sipyleus* were found to be rich in phenolics. The tea samples exhibited beneficial antioxidant and anticholinesterase activities. There is a useful relationship between the antioxidant capacity and polyphenolic composition of the decoction and infusion of *C. organifolium* and *T. sipyleus*. This study supported that *C. organifolium* and *T. sipyleus* used as tea traditionally, are source of natural antioxidant.

Keywords: *Cyclotrichium organifolium*; *Thymus sipyleus*; phenolics; anticholinesterase; antioxidant.

INTRODUCTION

For centuries, traditional plants have been presented as an alternative medicine. Herbal remedies are often consumed in the form of tea, which often prepared as decoction and infusion.

Lamiaceae (Labiatae) family is represented 45 genera and 546 species and totally 731 taxa in the Flora of Turkey [1, 2]. *Cyclotrichium* and *Thymus* species are a large genus belonging to the Lamiaceae family. In Turkey, *Cyclotrichium* is presented by 6 species [3]. Some members of this genus,

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especially *Cyclotrichium organifolium* (dağ nanesi), have been widely used as tea, flavoring agents in soups and salads in Eastern and Southern Anatolia [4]. *Thymus* is represented by 39 species with 64 taxa and has been used for a long time as spice or drugs. Members of this genus are called “kekik” in Turkish and used as herbal tea and condiments [5].

Many studies have been conducted to investigate the chemical essential oil content of *Cyclotrichium* and *Thymus* species [4, 6-18]. *C. organifolium* has rich essential oil content, dominated usually by pulegone which is monoterpene ketone and has various biological activities [4, 11, 12]. There are some reports about biological activities of essential oils and various extracts of *C. organifolium* [4, 6, 11, 17] and *T. sipyleus* [13, 14, 19]. The essential oil of *C. organifolium* and *T. sipyleus* were analyzed the first time by Baser *et al.* (Table 1) [12]. Apart from these studies, antioxidant flavonoids of hexane, ethyl acetate, and *n*-butanol extracts of *C. organifolium* have been reported [20]. Also, Tepe *et al.* reported that the amount of the total phenolics was highest in the dichloromethane extract. The lowest amount of total phenolics was recorded in deodorized hot water extract. Especially polar extracts exhibited stronger activity than non-polar ones [11]. There are many studies in the literature on the phenolics and biological activities of *Cyclotrichium* and *Thymus* extracts [5, 19-25]. (Table 1).

A correlation between the phenolic contents and antioxidant activity of plants have been demonstrated by several studies in medicinal plants. So there is an increasing interest about infusion and decoction of medicinal plants have been presented about phenolics and flavonoids which have strong antioxidant activity in the literature [26-28].

The aim of this study was to determine phenolic compounds, antioxidant and anticholinesterase activity of decoction and infusion of *C. organifolium* and *T. sipyleus*. To the best of our knowledge, in the literature, there is no study on the chemical composition and biological activities of teas prepared from *C. organifolium* (CO) and *T. sipyleus* (TS).

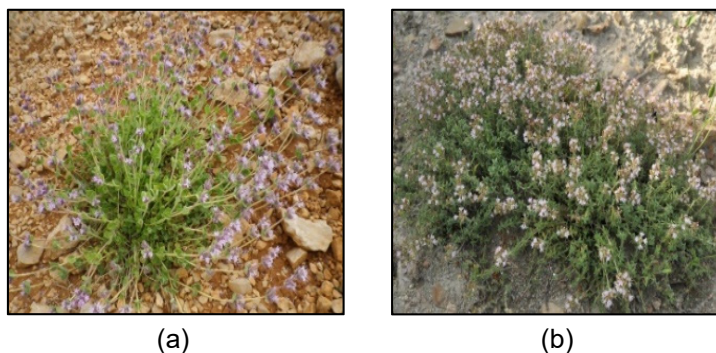


Figure 1. (a) *C. organifolium* and (b) *T. sipyleus*

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Table 1. Previous studies on *C. origanifolium* and *T. sipyleus*

	Main compounds of EO	Phenolics, Flavonoids and derivatives	Biological Activity
<i>C. origanifolium</i>	Pulegone, Cis-isopulegone Isomenthone, Isomenthol [12] Isopinocampone, β -pinene Limonene, Spathulenol [7] Bicyclo[3.1.1]hepten-3-one 2,6,6-trimethyl-, (1. α , 2. β , 5. α), pulegone 2-cyclohexen-1-ol 1-methyl-4-(1-methylethyl) [17] Pulegone, Menthone Limonene [11] Isopinacampone Menthone β -Pinene [6]	Isosakuranetin Eriodictyol Luteolin Naringenin Apigenin [20]	Antioxidant [11,20] Antimicrobial activities of extracts and EO [11,17] Antibacterial and Antifungal activity of EO [6].
<i>T. sipyleus</i>	Geranial, Neral Linalool, α -Terpineol [16] Borneol, α -Muurolol β -Caryophyllene Geranial Neral [13] Thymol, <i>p</i> -Cymene γ -Terpinene [14] 1,8-Cineol Linalool Borneol α -Pinen β -Pinen Carvone Camphor Carvacrol [18]	Chlorogenic acid Caffeic acid Rosmarinic acid Apigenin [5] Ursolic acid Rosmarinic acid Luteolin, Luteolin 7-O-(6"- feruloyl)- β - glucopyranoside Luteolin 5-O- β - glucopyranoside Luteolin 7-O- β - glucuronide [19]	Antioxidative activity of EO [13] Anti- inflammatory and antibacterial activities of EO [14]. Antioxidant activity of extracts [5,19]. Memory- vitalizing effect of extracts [25]

RESULTS AND DISCUSSION

The results of the studied phenolic compounds of decoction and infusion of CO and TS by LC-MS/MS are shown in Table 2. All the phenolic compounds of samples decoction and infusion were classified into three groups: flavonoids and derivatives, coumaric acids and derivatives and simple phenolics and others. Total 22 compounds, composed of 13 flavonoids

and derivatives, 4 coumaric acids and derivatives and 5 simple phenolics and others were determined in the decoction and infusion of CO and TS. Rutin (1143.27; 517.08 mg/kg dried herb), kaempferol (648.36; 552.11 mg/kg dried herb) and kaempferol-3-O-rutinoside (323.61; 205.92 mg/kg dried herb) were found to be the main phenolic compounds in infusion sample of CO (COI) and decoction sample of CO (COD), respectively. Rosmarinic acid (992.18 mg/kg dried herb), fumaric acid (669.64 mg/kg dried herb) and quercetin (399.12 mg/kg dried herb) were found to be the main phenolic compounds in decoction sample of TS (TSD), whereas fumaric acid (682.17 mg/kg dried herb), rosmarinic acid (643.43 mg/kg dried herb) and kaempferol (255.24 mg/kg dried herb) were found to be the main phenolic compounds in infusion sample of TS (TSI).

Flavonoids and derivatives were the dominant group (2640.01 mg/kg) in the COI with rutin (1143.27 mg/kg), kaempferol (648.36 mg/kg) and kaempferol-3-O-rutinoside (323.61 mg/kg), luteolin (166.82 mg/kg) and penduletin (136.04 mg/kg). Coumaric acids and derivatives were represented with 152.87 mg/kg with rosmarinic acid (85.04 mg/kg), chlorogenic acid (50.79 mg/kg) and caffeic acid (17.04 mg/kg). While simple phenolics and others were detected in scarce amounts (119.91 mg/kg) with fumaric acid (114.24 mg/kg) and syringic acid (5.67 mg/kg).

Similarly, phenolic compounds of COD were characterized by the presence of flavonoids and derivatives (1654.31 mg/kg), with kaempferol (552.11 mg/kg), rutin (517.08 mg/kg) and kaempferol-3-O-rutinoside (205.92 mg/kg). Coumaric acids and derivatives were represented with 175.24 mg/kg. Simple phenolics and others were detected in scarce amounts (73.84 mg/kg) as compared to the flavonoids and derivatives.

Flavonoids and derivatives were the dominant group in the TSD (1506.23 mg/kg) with quercetin (339.12 mg/kg), kaempferol (366.27 mg/kg), luteolin-5-O-glucoside (179.38 mg/kg) and luteolin (178.39 mg/kg). Coumaric acids and derivatives were represented with 1163.88 mg/kg and rosmarinic acid (992.18 mg/kg) was the dominant compound in decoction *T. sipyleus*. While simple phenolics and others were represented with 737.26 mg/kg with fumaric acid (669.64 mg/kg).

On the contrary, In TSI, flavonoids and derivatives (872.92 mg/kg), coumaric acids and derivatives (771.44 mg/kg) and simple phenolics and others (707.36 mg/kg) were detected in equal amounts. Kaempferol (255.24 mg/kg) was detected as main flavonoid, rosmarinic acid (643.43 mg/kg) was detected as main coumaric acid derivative and fumaric acid (682.17 mg/kg) was detected as main simple phenolic.

The antioxidant activities were determined with three methods: DPPH, β -carotene linoleic acid and CUPRAC. Butylated hydroxytoluene (BHT) and

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butylated hydroxyanisole (BHA) were used as standard compounds in DPPH and β -carotene linoleic acid assays. DPPH and β -carotene analyzes were performed at four concentrations: at 10, 25, 50 and 100 μ g/mL.

Table 2. Phenolic contents of CO and TS decoction and infusion

	COD	COI	TSD	TSI
Flavonoids and derivatives				
Pelargonin (1)	42.89 \pm 4.36	82.21 \pm 4.18	117.51 \pm 11.96	117.51 \pm 11.96
Penduletin (2)	106.11 \pm 10.76	136.04 \pm 13.79	35.13 \pm 3.56	35.13 \pm 3.56
Luteolin (3)	39.48 \pm 10.14	166.82 \pm 21.43	178.39 \pm 45.82	178.39 \pm 45.82
Apigenin (4)	32.64 \pm 2.63	56.87 \pm 4.58	72.46 \pm 5.84	4.49 \pm 0.36
Quercitin (5)	-	-	399.12\pm25.47	208.5 \pm 13.3
Quercetagenin-3,6-dimethylether (6)	112.3 \pm 21.03	12.26 \pm 2.3	-	-
Luteolin-7-O-glucoside (7)	11.22 \pm 1.14	30.81 \pm 1.57	115.16 \pm 11.72	67.79 \pm 3.45
Luteolin-5-O-glucoside (8)	6.81 \pm 0.44	11.04 \pm 0.71	179.38 \pm 11.54	160.57 \pm 10.33
Kaempferol (9)	552.11\pm38.97	648.36\pm45.76	366.27 \pm 25.85	255.24\pm18.02
Rutin (10)	517.08\pm33.87	1143.27\pm74.88	18.36 \pm 1.2	62.08 \pm 4.07
Kaempferol-3-O-rutinoside (11)	205.92\pm18.61	323.61\pm29.25	8.73 \pm 0.79	9.39 \pm 0.85
Salvigenin (12)	12.8 \pm 0.87	14.65 \pm 1.00	-	-
Isoquercetin (13)	14.95 \pm 4.29	14.07 \pm 4.04	15.72 \pm 4.51	22.023 \pm 6.38
Total (mg/kg dried herb)	1654.31	2640.01	1506.23	872.97
Coumaric acids and derivatives				
Caffeic acid (14)	28.29 \pm 5.6	17.04 \pm 3.37	153.97 \pm 30.47	98.86 \pm 19.56
Chlorogenic acid (15)	27.86 \pm 3.86	50.79 \pm 7.03	9.12 \pm 1.26	21.36 \pm 2.96
t-Ferulic acid (16)	-	-	8.61 \pm 0.6	7.79 \pm 0.54
Rosmarinic acid (17)	119.09 \pm 9.13	85.04 \pm 6.52	992.18\pm76.08	643.43\pm49.34
Total (mg/kg dried herb)	175.24	152.87	1163.88	771.44
Simple phenolics and others				
Syringic acid (18)	18.12 \pm 1.22	5.67 \pm 0.38	11.49 \pm 0.77	2.66 \pm 0.18
Fumaric acid (19)	55.72\pm3.86	114.24\pm7.92	669.64\pm46.44	682.17\pm47.31
Gallic acid (20)	-	-	4.59 \pm 0.32	4.76 \pm 0.33
Pyrogallol (21)	-	-	16.24 \pm 1.08	17.77 \pm 1.18
Ellagic acid (22)	-	-	35.3 \pm 2.36	-
Total (mg/kg dried herb)	73.84	119.91	737.26	707.36
Curcumin*				
	1903.39	2912.79	3407.37	2351.77
* Used as internal standard				

In DPPH-free radical scavenging activity assay, CO and TS teas at all concentrations (10, 25, 50 and 100 μ g/mL) showed very high activity (up to 60%). In the literature, aqueous extracts of *C. niveum* and *T. praecox*

subsp. *caucasicus* var. *caucasicus* had weak scavenging ability 9.96% and 11.36% at 2.0 mg/mL, respectively [23]. Also, the percentage inhibition of free radical scavenging activity by 15 µg/mL concentration of *C. niveum* (Boiss.) Manden and Scheng water extract was found as 31.8% [21]. In view of these tea samples are rich in flavonoids, it can be said that these compounds to be high antioxidant capacity (Figure 2).

Furthermore, β -carotene linoleic acid assay, for all concentrations, COD, COI and TSD showed good activity results while TSI had relatively lower activity (Figure 3). The TSI has showed best inhibition result at a concentration of 100 µg/mL (67.44%). Especially, the richest of the phenolic compounds, the TSD and COI have had good activity values like as the standard compounds (BHA and BHT). For the CUPRAC method, the tea samples showed good activity. Especially, TSD were showed higher activity (3.20 mmol TR g⁻¹), while the lowest activity was showed by COD (1.15 mmol TR g⁻¹), which is the lowest tea sample in terms of phenolic compounds. Curcumin was used as a standard compound (0.9 mmol TR g⁻¹). The results are given in the Figure 4.

The acetyl-cholinesterase (AChE) and butyryl-cholinesterase (BChE) activities of decoction and infusion of CO and TS were determined at 200 µg/mL concentration, for which galanthamine was used as a standard compound. The best inhibition values against AChE and BChE enzymes were shown by COI (58.40% and 60.73%, respectively) and TSD (56.65% and 48.76%, respectively) as compared to galanthamine. The results are given in the Table 3. The aqueous extract of *C. niveum* were also tested for their inhibitory effect against AChE and was reported to have 9.68% at 2.0 mg/mL [23]. In the another study, *T. serpyllum* water extract was found to have a low AChE inhibition [29].

The amount of phenolics extracted in TSD and COI are very high comparison with TSI and COD (3407.37 and 2912.79 mg/kg dried herb, respectively). In DPPH, β -carotene linoleic acid and CUPRAC assays, the high antioxidant capacity of the TSD and COI is associated with the amount of phenolic compounds.

Considering that decoction sample of TS, rosmarinic acid and fumaric acid were determined as the main compounds, it can be said that these compounds are responsible for the significant antioxidant activity of the tea. Rosmarinic acid, which has antiviral, antibacterial, antiinflammatory and antioxidant activities, is very important phenolic compound [5, 30]. The presence of rosmarinic acid in medicinal plants, herbs and spices has beneficial and health promoting effects.

COI consisted of rutin and kaempferol as main compounds. The effective antioxidant and anticholinesterase activities of COI might be due to the high level of those phenolic compounds. According to previous studies,

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rutin and kaempferol had antioxidant, antimicrobial, diabetic, anti-inflammation, antiproliferative, antibacterial, anticancer, antidiabetic, anticarcinogenic, antitumor and antiglycation activities [31, 32]. These results are consistent with the literature.

Previous studies have been showed that, CO solvent extracts were rich in flavonoids (isosakuranetin, eriodictyol, luteolin, naringenin, apigenin) [20] and TS solvent extracts were rich in triterpenic acid (ursolic acid), phenolic acid (rosmarinic acid, chorogenic acid, caffeic acid), and flavonoids (luteolin, luteolin 7-O-(6''-feruloyl)- β -glucopyranoside, luteolin 5-O- β -glucopyranoside, and luteolin 7-O- β -glucuronide, apigenin) [5, 19].

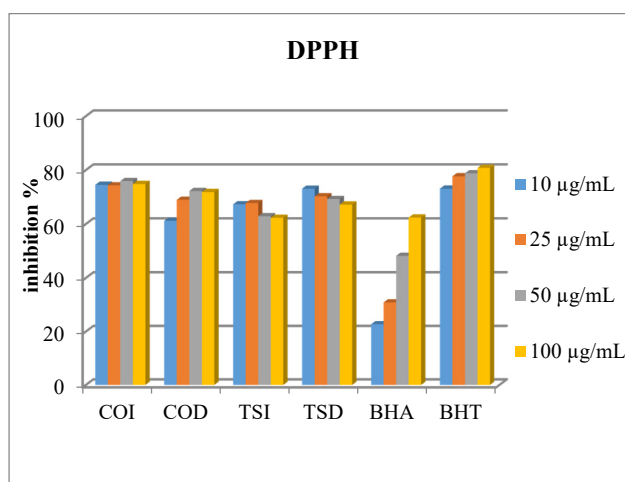


Figure 2. DPPH results of CO and TS.

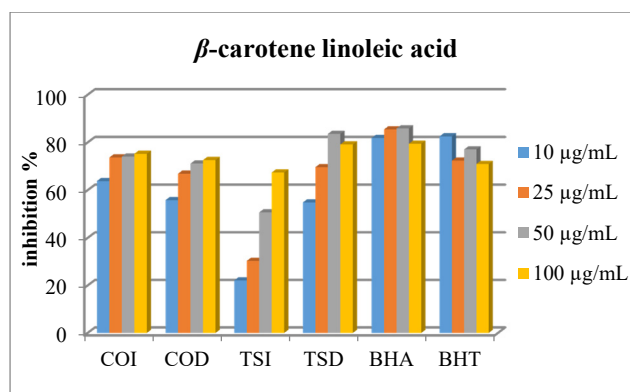


Figure 3. β -carotene-linoleic acid assay results of CO and TS.

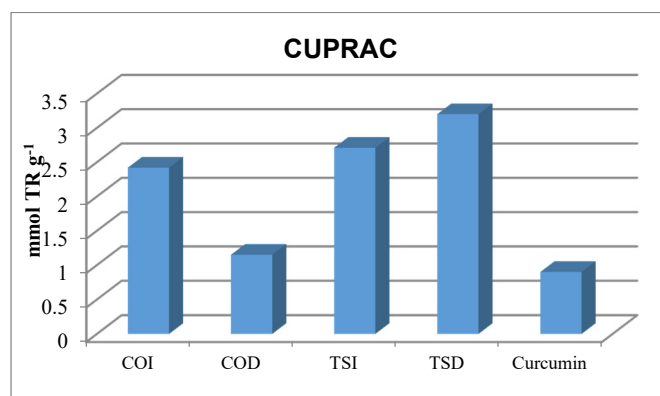


Figure 4. CUPRAC assay results of CO and TS.

Table 3. Anticholinesterase activity of CO and TS (200 µg/mL)

Tea samples	AChE*	BChE*
COI	58.40±1.12	35.21±0.99
COD	40.94±2.52	60.73±4.70
TSI	56.65±5.36	22.93±0.64
TSD	52.82±3.15	48.76±2.64
Galantamine**	86.73±5.25	77.13±4.31

* % inhibition of 200 µg/mL concentration of tea samples
 ** Galantamine was used as a standard.

CONCLUSIONS

In conclusion, we examined and reported the main phenolic components, antioxidant and anticholinesterase activity of decoction and infusion of CO and TS. The decoction and infusion of the samples were found to be a rich source of phenolics, while rutin and kaempferol were found to be the major units of the composition in CO. Also, rosmarinic acid and fumaric acid were found to be the major units of the composition in TS. Considering the antioxidant capacity determination assays, such as DPPH, β -carotene linoleic acid, and CUPRAC methods, there is a good relationship between the antioxidant capacity and polyphenolic composition of the decoction and infusion. This study supports that *C. origanifolium* and *T. sipyleus*, used in tea, food, pharmaceutical and cosmetic industry, are a source of natural antioxidant.

EXPERIMENTAL SECTION

Plant material

The aerial parts of *C. organifolium* were collected from Antalya, Alanya, Mahmutlar-Hadim road, rocky slopes, (36°34'36.30"N, 32°22'12.05"E, 1298 m) during the full-flowering season in July 2016, Turkey (Herbarium number SV 1543).

The aerial parts of *T. sipyleus* were collected from Balıkesir, Kazdağları, Sarıkız location, rocky slope, (39°42'12.39"N, 26°50'6.55"E, 1648 m), during the full-flowering season in July 2016, Turkey (Herbarium number SV 2466).

The species were identified by Assoc. Prof. Dr. Selami Selvi at Balıkesir University. Voucher specimens were deposited at the Herbarium of the Altınoluk Vocational School, Balıkesir University, Balıkesir, Turkey. The plant samples were allowed to dry in the shade.

Preparation of decoction and infusion samples

4 g of aerial parts of the plant, dried (30 °C) in the shade and chopped into small pieces. The teas were prepared as following two methods; infusion and decoction.

Infusion; 2 g of the plant were added to 98 mL of distilled boiling water and allowed to stay for 15 minutes.

Decoction; 2 g of the plant were added to 98 mL of distilled water and heated together in a steel kettle and allowed to stay for 15 minutes after boiled.

The teas were filtered with an ashless filter paper. The filtrates were diluted with 25 mL of distilled water. Phenolic compounds were determined by LC-MS/MS. Infusion samples were named as **COI** and **TSI**, decoction was **COD** and **TSD**.

Liquid chromatography-mass spectrometry

LC-MS/MS experiments were performed by a Zivak® HPLC and Zivak® Tandem Gold Triple quadrupole (Istanbul, Turkey) mass spectrometry equipped with a Synergy Max C18 column (250 x 2 mm i.d., 5µm particle size). The mobile phase was composed of water (A, 0.1% formic acid) in methanol (B, 0.1% formic acid), the gradient programme of which was 0-1.00 minute 55% A and 45% B, 1.01-20.00 minutes 100% B and finally 20.01-23.00 55% A and 45% B. The flow rate of the mobile phase was 0.25 mL/min, and the column temperature was set to 30 °C. The injection volume was 10 µL.

The detailed information on preparation of test solution and evaluation of uncertainty has been reported in the literature [33, 34].

Antioxidant activities

The antioxidant activities were measured based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity [33-38], β -carotene linoleic acid assays [33, 34, 37] and cupric (Cu^{2+}) ion reducing power assay (CUPRAC) [33, 34, 39, 40]. The detailed experimental procedure was given in the "Supplementary data".

Anticholinesterase activity

Inhibitory activities of acetyl- and butyrylcholinesterase were measured by a slightly modified spectrophotometric method, developed by Ellman, Courtney, Andres and Featherston [41-44]. Acetylthiocholine iodide and butyryl thiocholine iodide were used as substrates of the reaction, and DTNB method was applied for the measurement of the anticholinesterase activity [41, 42]. Detailed procedure was given in "Supplementary data".

Supplementary Supporting information will be provided by the author upon request.

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