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RESEARCH PAPER

Some Important Plants for Epilepsy Treatment: Antioxidant Activity and Flavonoid Compositions

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Abstract

Epilepsy, a disorder of the brain, is a major health problem that the widespread availability and use of herbal medicines raise the potential for adverse effects in the epilepsy population. Although many synthetic antiepileptic drugs are available in operation, their efficiency does not verify with the all population suffering from this disorder because of the major restrictions such as side effects and the drug interactions in its clinical utility. This paper is concerned with antioxidant activity, total phenolic and flavonoid contents and flavonoid composition of the 14 plants for three different solvents (water, ethanol and hexane). For this reason, FRAP, DPPH free radical scavenging, metal-chelate and H_2O_2 scavenging activities were investigated. In addition, total phenolic and flavonoid contents of extracts were determined via spectroscopic techniques. Lastly, composition of catechin, epicatechin, rutin, naringin, myricetin, luteolin, naringenin and apigenin was found with normal-phase HPLC in the obtained extracts. Extracts of fourteen plants taxa foreseen in having antioxidant and antiepileptic features were obtained with soxhlet extraction using different solvents, i.e., water, ethanol and hexane in this study. The extracts of 14 plant taxa were acquired: French lavender (*Lavandula stoechas* L.—inflorescence), Valerian (*Valeriana officinalis* L.—herb), Syrian rue (*Peganum harmala* L.—seeds), Liquorice (*Glycyrrhiza glabra* L.—roots), Boxwood (*Buxus sempervirens* L.—leaves), Chicory (*Cichorium intybus* L.—herb), Marjoram (*Origanum majorana* L.—leaves), Lemon balm (*Melissa officinalis* L.—leaves), Prickly juniper (*Juniperus oxycedrus* L.—fruits), Wild camomile (*Anthemis cotula* L.—flowers), Oats (*Avena sativa* L.—herb), Coriander (*Coriandrum sativum* L.—seeds), Flax (*Linum usitatissimum* L.—seeds) and Marijuana (*Cannabis sativa* L.—seeds)". The antioxidant capacities of plant extracts were assayed with four different assays including FRAP, metal chelating, H_2O_2, DPPH scavenging because the antioxidant capacity cannot be fully described by a single method. The determined flavonoid amounts are between 3.85 and 694-47 (catechin), 2.70 and 2045.49 (epicatechin), 0.12 and 47.11 (rutin), 0.02 and 24.99 (naringin), 0.80 and 153.19 (myricetin), 0.03 and 7.80 (luteolin), 0.02 and 4.75 (naringenin) and 0.38 and 2.73 (apigenin) as μg g^{-1} plant. These plant materials and their flavonoid components via gamma-aminobutyric acid (GABA) and $GABA_A$ receptors can be therapeutical due to their different mechanism on treatment of epilepsy.

Keywords Epilepsy · Medicinal plants · Phenolic · Flavonoid · HPLC · Antioxidant

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1 Introduction

Epilepsy is one of the most serious brain disorders and affects about 40 million people. In the future, about 100 million will be affected at some time in their life. It accounts for 1% of rate of diseases in the world and the prevalence rate is reported at 2% in the literature. In addition, the absence seizures are highest in infants and children (Vyawahare et al. 2007). Almost 40 recognized epileptic syndrome types can be classified as partial and generalized. Partial seizures occur within localized brain regions, whereas generalized seizures appear in the entire forebrain (Lutz 2004). A lot of plant species have pharmacologic properties as treatment and prevention of epilepsy and convulsions or sedations (Jäger et al. 2006).

Despite the traditional medicine limitations, it is crucial for the health care needs of millions of people worldwide. Discovery of modern drugs from folk remedies and their usage are better safety and efficacy profiles. Phytomedicines can potentially play an important role in the development of new antiepileptic drugs and may be effective in combating or preventing disease due to their antioxidant effect. Drugs obtained from phytomedicines are commonly used in many parts of the world by the people for managing various forms of epilepsies (Diniz et al. 2015).

Antioxidant defense system declines, so free radicals increase in the brain during the absence seizure, which further induces the oxidative stress. Free radicals, having one or more unpaired electrons, bring about lipid peroxidation, brain edema, and epilepsy including coma and death. Oxidative stress can be decreased by flavonoids in the brain. This function results from several flavonoids binding to the benzodiazepine site in the $GABA_A$-receptor, which caused anticonvulsive effects in the central nervous system (Diniz et al. 2015; Onbaşılı et al. 2015).

Flavonoids are a broad class of low molecular weight, secondary plant phenolics characterized by the flavan nucleus as carbon framework C6–C3–C6 (Rice-Evans et al. 1996). In the literature, it has been mentioned about 10,000 flavonoids known (Bligh et al. 2013). The subclass occurs by the substitutions some groups to the core structure such as flavonol, flavone, flavonol, flavanone, isoflavone and anthocyanidin (Heim et al. 2002).

It is well known that about 2% of the materials formed by photosynthesis in the plant body are transformed to flavonoids. Flavonoids are present in roots, stalks, leaves, fruits, and anywhere in green plants. The role of flavonoids in the plant body is to protect itself from ultraviolet lights and bacteria. A flavonoid called "chalcone" is formed first in the plant body, and is transformed to various flavonoids such as flavanone, flavone, flavonol, catechin, and epicatechin. Many natural flavonoids exist in glycosides because glycosides are chemically more stable and more soluble in water, and easier to be stored in the aqueous space of the plant cell (Cheong et al. 2005).

Edible and nonedible plants include flavonoids which are rather bioactive compounds. Flavonoids are extracted with polar solvents such as water, methyl and ethyl alcohol, acetone or their mixture using soxhlet extraction method (Khoddami et al. 2013).

Flavonoids have beneficial health effects owing to their antioxidant and chelating capacities. These protective activities are seen in living organisms as metal-chelating, antioxidant enzyme activation, reduction α-tocopherol radicals and inhibition oxidase enzymes (Heim et al. 2002; Ateş et al. 2016).

Recently, many studies have been carried out by the researchers because of the antioxidant activities of these polyphenolic compounds. Functional hydroxyl groups of flavonoids bring about free radical scavenging and/or metal-chelating activities. Especially, metal-chelating capacity can be important for prevention of radical generation which damages target biomolecules. Consuming flavonoids as a dietary component are crucial due to their health-promoting properties. In addition, flavonoids show effective stimulation activity for human protective enzyme systems (Kumar and Pandey 2013).

The solubility of a flavonoid is a crucial factor in controlling its interaction with the mobile phase in HPLC. Therefore, choosing mobile phase for an effective separation is important because of the properties of flavonoids such as hydrophobicity, dipole moment, hydrogen bonding, ionization, and steric effects (Bligh et al. 2013).

This paper is concerned with antioxidant activity, total phenolic and flavonoid contents and flavonoid composition of the 14 plants for three different solvents (water, ethanol and hexane). For this reason, FRAP, DPPH free radical scavenging, metal-chelate and H_2O_2 scavenging activities were investigated. In addition, total phenolic and flavonoid contents of extracts were determined via spectroscopic techniques. Lastly, composition of catechin, epicatechin, rutin, naringin, myricetin, luteolin, naringenin and apigenin was found with normal-phase HPLC in the obtained extracts.

2 Materials and Methods

2.1 Plant Samples

Valeriana officinalis L., *G. glabra* L, *O. majorana* L., *A. sativa* L., *C. sativum* L., *C. sativa* L. were obtained from Özşen Lokman Hekim Company located in Ankara/Turkey, Gimat at 2016. *Peganum harmala* L., *L. stoechas* L., *B. sempervirens* L., *C. intybus* L., *M. officinalis* L., *J.*

oxycedrus L., *A. cotula* L., *L. usitatissimum* L. were collected from eight different localities in Muğla, Karabük, Kastamonu and Konya (Table 1). Plant materials were dried at room temperature and on draft for three weeks. All the plants were identified by Assist. Prof. Dr. Kerim GÜNEY, Department of Forest Engineering, Faculty of Forestry, Kastamonu University.

2.2 Extraction Method

The plants were washed thoroughly 2–3 times with water, and then they were air dried under shade. Afterwards, the dried plant materials were grinded in a mixer, and the powder was kept in the brown glass bottle with paper labeling. Between the range of 10–30 g, grinded materials were extracted with 250 mL of distilled water, ethanol or in a soxhlet apparatus by continuous heat extraction for 24 h. All extract solutions were filtered through Whatman No. 1 paper. Then, filtrates were evaporated with rotary evaporator. The filtrates were concentrated to a small volume under reduced pressure and evaporated to dryness. The extracts were stored in refrigerator at about 4 °C after sealed with paraffin in order to use in further studies. The soxhlet extraction conditions and the used plants and solvents are summarized in Table 2.

2.3 Determination of Antioxidant Activities

2.3.1 Ferric Reducing Antioxidant Power (FRAP) Assay

The reducing capability of samples was investigated using a ferric ion with minor modifications (Güder et al. 2014). 2.0 mL of samples (50 μg mL^{-1}) was mixed with PBS (phosphate buffer solution) (2.0 mL, 0.2 mol L^{-1}, pH 6.6) and potassium ferricyanide (2.0 mL, 1.0%). The mixture was incubated at 50 °C for 20 min and trichloroacetic acid (2.0 mL, 10%) was added to the mixture. Then, 2.0 mL of this solution was mixed with distilled water (2.0 mL) and $FeCl_3$ (0.5 mL, 0.1%). The Fe^{3+}/Fe^{2+} transformation was determined due to the presence of samples at 700 nm.

$$\text{FRAP}(\%) = (A_s/A_c) \times 100,$$

where A_c was the absorbance of control, and A_s was the absorbance of samples or standards.

2.3.2 Ferrous Ions Chelating Activity (FICA) Assay

Ferrous ion (Fe^{2+}) chelating activity was evaluated according to the previous method (Temel et al. 2015). In this experiment, metal-chelating activity was monitored by way of absorbance of the Fe^{2+}-ferrozine complex at 562 nm. Briefly, samples (3.75 mL) were added to $FeCl_2$ solution (0.05 mL, 2.0 mmol L^{-1}). The reaction was started by the addition of 0.2 mL ferrozine (5.0 mmol L^{-1}). Then, the mixtures were stirred using a vortex and kept at R.T. for 10 min. The absorbance was measured at 562 nm.

$$\text{FICA}(\%) = [1 - (A_s/A_c)] \times 100,$$

where A_c is the absorbance of the control, and A_s is the absorbance of the samples and standards.

2.3.3 Hydrogen Peroxide Scavenging Activity (HPSA) Assay

The hydrogen peroxide scavenging activity of the samples was determined with regard to Ruch et al. method (Ruch et al. 1989). For this reason, 3.0 mL of sample solutions was added to 1.0 mL of hydrogen peroxide solution (40 mmol L^{-1}, in 0.1 mol L^{-1} PBS, pH 7.4). Hydrogen

Table 1 Location, studied part, Latin and English name of used plants in the study

Latin name	English name	Used part	Location
Valeriana officinalis L.	Valerian	Herb	Location Bursa (Ozsen Company, Ankara, Turkey)
Glycyrrhiza glabra L.	Liquorice	Roots	Location Adıyaman (Ozsen Company, Ankara, Turkey)
Origanum majorana L.	Marjoram	Leaves	Location İzmir (Ozsen Company, Ankara, Turkey)
Avena sativa L	Oats	Herb	Location Konya (Ozsen Company, Ankara, Turkey)
Coriandrum sativum L.	Coriander	Seeds	Location Konya (Ozsen Company, Ankara, Turkey)
Cannabis sativa L.	Marijuana	Seeds	Location Tekirdağ (Ozsen Company, Ankara, Turkey)
Peganum harmala L.	Syrian rue	Seeds	Konya, 39°8′6.76″K, 33°20′42.61″D
Lavandula stoechas L.	French lavender	Inflorescence	Muğla, 37°18′13.43″K, 27°53′20.36″D
Buxus sempervirens L.	Boxwood	Leaves	Kastamonu, 41°39′14.19″K, 33° 8′29.03″D
Cichorium intybus L.	Chicory	Herb	Kastamonu, 41°29′23.82″K, 33°59′27.85″D
Melissa officinalis L.	Lemon balm	Leaves	Karabük, 41°9′2.52″K, 32°17′49.98″D
Juniperus oxycedrus L.	Prickly juniper	Fruits	Kastamonu, 41°25′35.43″K, 33°46′16.40″D
Anthemis cotula L.	Wild camomile	Flowers	Kastamonu, 41°29′59.23″K, 33°26′27.29″D
Linum usitatissimum L.	Flax	Seeds	Kastamonu, 41°16′26.03″K, 33°17′10.53″D

Table 2 Information of plant materials and extraction process

Plant name	Amount (g)	Extract amount (g)	Product label	Plant name	Amount (g)	Extract amount (g)	Product label
Juniperus oxycedrus	15	4.5792	1W	*Origanum majorana*	10	4.1124	8W
	15	6.061	1E		10	1.6232	8E
	15	1.2202	1H		10	0.874	8H
Cannabis sativa	25	2.3327	2W	*Glycyrrhiza glabra*	20	3.2184	9W
	25	0.4894	2E		20	1.6167	9E
	25	8.2836	2H		20	0.4848	9H
Cichorium intybus	15	1.9175	3W	*Melissa officinalis*	20	2.392	10W
	15	0.8553	3E		20	1.8793	10E
	15	0.3818	3H		20	1.2601	10H
Lavandula stoechas	5	0.6453	4W	*Anthemis cotula*	15	3.3144	11W
	5	0.8899	4E		15	2.8634	11E
	5	0.5963	4H		15	0.8671	11H
Valeriana officinalis	30	2.0327	5W	*Buxus sempervirens*	15	4.5841	12W
	30	7.5594	5E		15	2.9868	12E
	30	0.5448	5H		15	0.7031	12H
Linum usitatissimum	25	2.0956	6W	*Peganum harmala*	30	2.1107	13W
	25	1.5414	6E		30	1.652	13E
	25	8.7694	6H		30	1.2466	13H
Coriandrum sativum	15	2.9864	7W	*Avena sativa*	10	1.8536	14W
	15	2.9373	7E		10	1.2927	14E
	15	1.2759	7H		10	0.5729	14H

W, E and H capitals indicate distilled water, ethanol and hexane, respectively. Each solvent was used as 250 mL

peroxide concentration was determined after 10 min against a blank solution (only contains PBS) with measurement of absorbance at 230 nm. The results were expressed as SC_{50} (μg mL^{-1}) by linear regression analysis using four different concentrations in triplicate and represent mean of the data.

2.3.4 DPPH Free Radical Scavenging Activity (FRSA) Assay

The free radical scavenging activity of samples was measured using 1,1-diphenyl-2-picryl-hydrazyl (DPPH·) (Shimada et al. 1992). DPPH· solution (0.1 mmol L^{-1}) was prepared in ethanol. Then, 1.0 mL of this solution was added to 3.0 mL of sample solutions. The mixtures were stirred using vortex and incubated at R.T. for 30 min. Then, the absorbance was monitored at 517 nm. The results were expressed as SC_{50} (μg mL^{-1}) by linear regression analysis using four different concentrations in triplicate and represent mean of the data.

2.3.5 Determination of Total Phenolic Contents (TPC)

The total phenolic contents of samples were analyzed by the FC (Folin and Ciocalteu's) colorimetric method with minor modifications (Ateş et al. 2015). Each extract solution (0.5 mL) was mixed with 7.0 mL of distilled water and subsequently with FC reagent (0.5 mL). After 3 min, Na_2CO_3 solution (2.0 mL, 2.0%) was added into the mixture. The reaction was advanced during 120 min and the absorbance was measured at 760 nm. Gallic acid was used as the standard and the total phenolic content was expressed as microgram of gallic acid equivalent using an equation that was obtained from the standard gallic acid graph ($R^2 = 0.9981$).

2.3.6 Determination of Total Flavonoid Contents (TFC)

The total flavonoids contents of the samples were evaluated by using a colorimetric method with minor modification (Ateş et al. 2015). Extract solutions (0.5 mL) were added to a tube containing 1.5 mL of absolute ethanol. To the mixture, subsequently $AlCl_3{\cdot}6H_2O$ solution (0.1 mL, 10.0%) and potassium acetate (0.1 mL, 1.0 mol L^{-1}) were added. Distilled water was added to bring the total volume to 5.0 mL and the absorbance was read after 30 min at 415 nm. The total flavonoid contents were expressed as microgram of catechin equivalent that was obtained from standard graph ($R^2 = 0.9986$).

2.4 HPLC Analysis

HPLC analysis was carried out using an Agilent Eclipse XDB C18 5 μm with 4.6 × 250 mm column and studied at the column temperature of 30 °C. Flavonoid measurements were determined at 280 nm after 20 μL injection volume. Standard solvents were prepared in the ethanol-distilled water (65–35) mixture. For HPLC analysis, mobile phase A [containing water–10% formic acid (95–5)] and mobile phase B [containing acetonitrile–10% formic acid (5–95)] were used. Mobile phases have been flowed for 39 min. For this reason, 0–25 min (95% A, 5% B), 25–35 min (57% A, 43% B), 35–37 min (45% A, 55% B) and 37–39 min (95% A, 5% B) have been used as mobile phases.

Identification of the flavonoids was carried out by comparing their retention times to those of standards. The retention times of flavonoid standards were determined at 5.736 (catechin), 8.149 (epicatechin), 12.128 (rutin), 14.093 (naringin), 14.958 (myricetin), 19.608 (luteolin), 21.443 (naringenin), 23.049 (apigenin) under HPLC analysis conditions as described above.

2.5 Statistical Analysis

The experiment results of plant extracts were analyzed using one-way analysis of variance (ANOVA) with IBM SPSS 21.0 for determining differences between the plant extracts. The effects of independent parameters followed the comparison of means performed by Duncan test.

3 Result and Discussion

The antioxidant capacities of plant extracts were assayed with four different assays including FRAP, metal chelating, H_2O_2, and DPPH scavenging because the antioxidant capacity cannot be fully described by a single method (Table 3).

The ferric reducing antioxidant power (FRAP) method is important for the evaluation of antioxidants. FRAP was associated with antioxidant potential of extracts to confirm its level (Pohanka et al. 2009). In this assay, the Fe^{3+}/Fe^{2+} transformation was investigated in the presence of samples and the absorbance values were measured at 700 nm. It was found that FRAP activity of the plant extracts had significant variation, ranged from 38.41 to 66.57%. In addition, FRAP activity of the different solvent extracts had significant variation, ranged from 10.28 to 82.68%. According to these results, we can say that especially ethanol extracts have higher FRAP activity than the others. On the other hand, *G. glabra* demonstrates more efficient activity than the others. Contribution of them FRAP activity is water and ethanol extracts which detected as 91.68 and 89.42%, respectively.

As excess free irons have been implicated in the induction and formation of free radicals in biological systems, we tested our medicinal plant extracts in a metal-chelating assay (Wong et al. 2014). Iron and other transition metals such as copper, chromium, cobalt, vanadium, cadmium, arsenic, and nickel support oxidation owing to their catalyst properties on free radical reactions. These transition metals donate single electrons during redox reaction between them. When some compounds chelate metals, their pro-oxidant activity diminishes by reducing their redox potentials and stabilizing the oxidized form of the metal (Huang et al. 2012). Metal chelating of the plant had statistically significant variation, ranging from 60.63 to 81.32%. While hexane extracts have the highest metal-chelating activity, water extracts have the lowest activity. Besides, ethanol extracts show very efficient activity as the hexane extracts. When we investigate the extracts results, water extracts show the very low chelating activity, especially *A. cotula* (3.87%). Metal chelating of the different solvent extracts had statistically significant variation, ranging from 40.45 to 91.82%.

Reactive oxygen species (ROS), i.e., hydrogen peroxide, singlet oxygen, hydroxyl and superoxide radicals, have crucial acts such as in energy production, phagocytosis, intercellular signal transfer, cell growth regulation and important biological compounds synthesis (Shastri and Potdar 2014). Furthermore, there is currently great interest in the possible role of ROS in causing DNA damage that leads to cancer and spontaneous mutations (Hemnani and Parihar 1998). Although hydrogen peroxide is not very reactive; it can show toxic property to cell due to their transformation hydroxyl radical in the cells. By this way, H_2O_2 scavenging activity is very important for antioxidant defense in cell or food systems (Güder and Korkmaz 2012). H_2O_2 activity showed statistically significant variation, ranging from 278.50 to 616.59 μg mL^{-1}. *Buxus sempervirens* demonstrates the best activity. *Glycyrrhiza glabra* and *L. usitatissimum* have the similar activity as statistically. On the other hand, extraction solvent is very important for the hydrogen peroxide scavenging activity like investigated in the other tests. H_2O_2 activity of different solvent showed statistically significant variation, ranging from 388.25 to 500.50 μg mL^{-1}.

There are a lot of assays for evaluation of the radical scavenging effects of antioxidants. Fast, easy, reliable and stabile synthetic free radical DPPH is mostly used by the researchers to determine radical scavenging activity. The free radical scavenging activities of extracts depend on the ability of antioxidant compounds to lose hydrogen and the structural conformation of these components (Aksoy et al. 2013). DPPH results were found and ranged from 120.12 to 1167.13 μg mL^{-1} ($P < 0.01$). While *V. officinalis* exhibits the very efficient scavenging activity, *G. glabra* presents

Table 3 Antioxidant activity, total phenolic and flavonoid contents of extracts

Product label	FRAP (%)	FICA (%)	TPC (μg mL^{-1})	TFC (μg mL^{-1})	HPSA (SC_{50} μg mL^{-1})	FRSA (SC_{50} μg mL^{-1})
1W	63.82	86.88	11.87	4.02	287.36	148.28
1E	86.66	46.37	20.19	6.77	368.19	108.84
1H	7.42	91.20	9.11	0.22	286.70	320.20
2W	40.95	92.65	3.56	1.06	397.46	126.06
2E	91.71	26.81	42.04	8.48	791.14	108.93
2H	4.08	91.36	1.59	0.22	361.27	272.55
3W	71.63	87.14	16.20	5.38	398.72	147.69
3E	80.97	57.59	21.46	10.80	395.57	120.38
3H	12.39	92.30	15.54	0.30	358.68	206.06
4W	82.00	82.79	37.62	3.97	285.71	130.28
4E	94.58	44.96	38.73	5.88	358.68	114.50
4H	5.84	92.49	4.32	0.21	692.52	327.44
5W	52.68	91.36	8.62	1.37	287.36	115.09
5E	82.58	39.28	31.23	7.39	389.41	115.15
5H	17.26	92.94	14.95	0.21	766.87	130.11
6W	55.47	91.23	6.18	2.14	791.14	119.65
6E	76.50	20.37	5.66	8.56	673.85	159.29
6H	4.42	91.62	2.57	0.19	383.44	261.37
7W	64.76	86.59	14.90	4.05	287.36	139.33
7E	68.76	65.87	5.16	6.23	803.86	125.25
7H	5.29	91.49	8.74	0.19	366.57	243.49
8W	84.42	80.60	46.66	8.40	397.46	144.84
8E	94.58	42.31	88.68	10.80	386.40	133.46
8H	13.00	91.72	10.54	0.64	366.57	251.95
9W	91.68	73.77	21.35	10.95	398.72	3246.75
9E	89.42	59.10	91.41	10.95	786.16	139.24
9H	18.61	92.33	2.49	0.20	664.89	115.41
10W	75.24	77.38	68.10	8.00	380.52	139.70
10E	94.58	62.26	61.19	7.22	383.44	126.39
10H	9.16	91.40	5.10	0.35	394.32	281.69
11W	80.97	85.79	25.10	8.43	287.36	139.43
11E	91.71	3.87	48.49	11.11	755.29	112.51
11H	17.63	92.23	8.36	0.36	389.41	245.22
12W	72.08	87.17	21.26	9.91	271.15	123.66
12E	88.42	27.94	19.14	10.67	284.09	115.58
12H	14.68	89.59	11.82	0.44	280.27	179.47
13W	49.82	94.36	7.83	8.74	692.52	118.98
13E	58.39	37.16	11.32	9.91	361.27	123.29
13H	7.03	92.85	4.06	0.29	287.36	140.94
14W	58.18	89.78	6.88	2.72	272.63	123.61
14E	58.61	32.39	29.98	3.85	269.69	121.42
14H	7.18	91.88	17.40	0.20	368.19	347.10

the lowest activity. All samples except for the *G. glabra* have the nearly activity so water extract of this plant demonstrates very low value when compared to others. DPPH results were found and ranged from 123.16 to 354.52 μg mL^{-1} ($P < 0.01$).

The quantity of catechin, epicatechin, rutin, naringin, myricetin, luteolin, naringenin and apigenin flavonoids has been investigated in the studied plant extract with HPLC analysis. HPLC results are summarized in Table 4. The used flavonoids are situated in the following sub-

Table 4 HPLC analyses results of flavonoids (μg g^{-1} plant)

Samples	Catechin	Epicatechin	Rutin	Naringin	Myricetin	Luteolin	Naringenin	Apigenin
1W	694.47	–	9.37	–	–	–	–	–
1E	1.57	1.74	–	1.43	–	0.13	8.82	8.32
1H	–	–	–	–	–	–	–	–
2W	3.85	–	0.33	–	0.83	0.54	–	1.06
2E	–	0.33	–	–	1.61	0.08	0.88	18.72
2H	–	–	–	–	39.34	–	–	6.99
3W	–	100.04	23.15	1.69	–	0.31	–	–
3E	–	3.57	5.23	–	2.87	35.37	2.31	1.19
3H	–	–	–	–	–	–	–	0.48
4W	48.56	–	3.39	24.99	29.62	4.18	–	–
4E	–	–	–	30.40	–	–	53.17	10.41
4H	1.89	0.68	1.74	0.47	5.78	0.04	0.48	0.43
5W	48.69	2.70	–	0.02	0.80	0.03	0.02	0.38
5E	–	572.41	93.53	84.07	8.56	–	25.20	0.22
5H	0.07	0.03	0.03	0.001	–	–	0.03	–
6W	–	2.90	0.12	0.11	–	0.80	1.49	–
6E	0.60	–	0.06	0.05	0.12	0.009	0.09	0.07
6H	–	–	–	–	–	–	0.20	–
7W	49.21	372.61	5.53	1.06	–	–	3.64	–
7E	–	–	0.20	0.21	0.61	0.21	0.13	–
7H	0.6	–	–	–	–	–	0.06	0.6
8W	179.52	2045.49	–	–	22.02	4.42	–	1.04
8E	–	271.74	20.60	223.22	23.40	4.66	77.12	8.53
8H	–	–	0.56	0.004	0.24	–	–	0.34
9W	–	396.70	1.76	9.21	60.63	7.80	–	2.73
9E	–	–	–	0.05	36.03	0.89	1.33	0.46
9H	–	–	–	–	–	–	–	–
10W	360.36	102.20	33.01	–	153.19	–	–	–
10E	–	4.40	0.22	128.96	10.09	20.51	–	13.66
10H	–	0.59	0.76	0.19	1.10	–	0.20	0.05
11W	–	–	47.11	–	103.96	–	–	–
11E	568.16	–	253.94	9.23	206.45	0.93	50.56	78.94
11H	–	–	0.08	0.12	–	–	0.3	12.72
12W	18.55	1375.88	–	2.28	53.98	6.03	4.75	2.61
12E	–	6.75	–	1.01	1.28	1.91	5.13	0.76
12H	–	–	0.16	–	–	–	–	–
13W	–	67.34	–	0.17	–	0.12	0.58	–
13E	–	9.41	–	–	–	–	–	–
13H	1.32	–	–	–	–	0.2	0.38	–
14W	11.31	10.86	1.49	1.53	7.07	1.85	–	–
14E	–	–	4.28	–	30.43	3.20	–	17.83
14H	–	–	–	–	–	–	–	–

(–) Flavonoid was undetected

classifications: catechin and epicatechin in flavanol, rutin, luteolin and apigenin in flavone, naringin and naringenin in flavanone, myricetin in flavonol.

As seen in the Table 4 in HPLC analysis, some flavonoid compositions were done. The determined flavonoid amounts are between 3.85 and 694-47 (catechin), 2.70 and 2045.49 (epicatechin), 0.12 and 47.11 (rutin), 0.02 and 24.99 (naringin), 0.80 and 153.19 (myricetin), 0.03 and 7.80 (luteolin), 0.02 and 4.75 (naringenin) and 0.38 and 2.73 (apigenin) as μg g^{-1} plant, and also small amounts of eight flavonoids were determined in the 4H sample.

The most quantities of flavonoids are determined as follows: catechin (694.47 μg g^{-1} plant, 1W), epicatechin (2045.49 μg g^{-1} plant, 8W; 1375.88 μg g^{-1} plant, 12W; 572.41 μg g^{-1} plant, 5E; 396.70 μg g^{-1} plant, 9W; 372.61 μg g^{-1} plant, 7W; 271.74 μg g^{-1} plant, 8E), rutin (253.94 μg g^{-1} plant, 11E), naringin, (223.22 μg g^{-1} plant, 8E; 128.96 μg g^{-1} plant, 10E), myricetin (206.45 μg g^{-1} plant, 11E; 153.19 μg g^{-1} plant, 10W) (Table 5).

For analysis *L. stoechas* L. extracts in our study, the rutin compound in water and hexane extract (3.39 and 1.74 as μg mL^{-1}, respectively) was determined, and not determined in ethanol extract. In addition, catechin, naringin, myricetin, luteolin in water extract, naringin, naringenin and apigenin in ethanol extract, eight flavonoids in hexane extract were determined.

Fernández et al. in a study (2006) about flavonoid glycosides isolated from *V. officinalis* L., the pharmacological properties of the flavonoid glycosides were studied and they were determined sedative action of the flavonoid glycosides and aglycones. The compounds of rutin and naringenin in our study and were investigated as routine glycosides and naringenin aglycones in their studies. Other compounds were not same with their studied flavonoids.

Sharaf et al. (1997) were investigated four flavonoid glycosides in methanolic extract from *P. harmala*. These flavonoids are acacetin 7-*O*-rhamnoside, acacetin 7-*O*-[6″-*O*-glucosyl-2″-*O*-(3‴-acetylrhamnosyl)]glucoside, acacetin 7-*O*-(2‴-*O*-rhamnosyl-2″-*O*-glucosylglucoside), and the glycoflavone 2‴-*O*-rhamnosyl-2″-*O*-glucosylcytisoside.

Morsi et al. (2008) reported that the ethanol extract of *G. glabra* included some flavonoid compounds. Some detected compounds are as follows: Resorcinol, protocatechuic acid, hydroxybenzoic acid, phenol, vanillin, *p*-coumaric, ferulic acid, rutin, myrcetin, apignin, cinnamic acid, kaempherol.

In a study, named "Flavonoids of *C. intybus* (Dem'yanenko and Dranik 1973)", the presence of the following flavonoids was mentioned: apigenin, luteolin *O*-7-fl-D-glucopyranoside, quercitrin, hyperin, apigenin *O*-7-L-arabinoside.

Roby et al. (2013) determined two flavonoids such as the quantity of apigenin, luteolin-7-*o*-rutinose in methanol extract of *O. majorana*.

A study on *M. officinalis*, the determined major flavonoid compound, was luteolin-7-*O*-glucoside (Carnat et al. 1998). In another study about *M. officinalis*, luteolin 3′-*O*-β-D-glucuronide compound was isolated (Heitz et al. 2000).

In a research about fruits of *J. oxycedrus* L. subsp. *oxycedrus* and *J. oxycedrus* L. subsp. *macrocarpa*, it was found that rutin, hypolaetin-7-pentoside, apigenin, cupressoflavone, amentoflavone, biflavone and metil-biflavone were included (Taviano et al. 2013).

Popovici et al. (1977) isolated some compounds from *A. Sativa* belonging to sub-flavonoids such as apigenin, luteolin and tricin type flavones. In a more recent study on *A. sativa*, fifteen chemical constituents were isolated such as kaempferol 3-*O*-(2″,3″-di-E-*p*-coumaroyl)-α-L-rhamnopyranoside, kaempferol 3-*O*-(3″-E-*p*-coumaroyl)-α-L-rhamnopyranoside, kaempferol 3-*O*-(2″-*O*-E-*p*-coumaroyl)-β-D-glucopyranoside, kaempferol 3-*O*-β-D-glucopyranoside, kaempferol 7-*O*-α-L-rhamnopyranoside, linarin, tilianin, myricitrin, quercitrin, kaempferol 3-*O*-rutinoside, rutin, tricin 7-*O*-β-D-glucopyranoside, tricin, kaempferol, and luteolin (Wei-Ku et al. 2012).

Table 5 Classification of extracts according to flavonoids

Flavonoids	Samples (flavonoids: determined)	Samples (flavonoids: undetermined)
Catechin	1 (W, E), 2 (W), 4 (W, H), 5 (W, H), 6 (E), 7 (W, H), 8 (W), 10 (W), 11 (E), 12 (W), 13 (H), 14 (W)	3 and 9
Epicatechin	1 (E), 2 (E),3 (W, E), 4 (H), 5 (W, E H), 6 (W), 7(W), 8 (W, E), 9 (W), 10 (W E H), 12 (W, E), 13 (W, E), 14 (W)	11
Rutin	1 (W), 2 (W), 3 (W, E), 4 (W, H), 5 (E, H), 6 (W, E), 7 (W, E), 8 (E, H), 9 (W), 10 (W, E, H), 11 (W, E, H), 12 (H), 14 (W)	13
Naringin	1 (E), 3 (W), 4 (W, E, H), 5 (W, E, H), 6 (W, E), 7 (W, E), 8 (E, H), 9 (W, E), 10 (E, H), 11 (E, H), 12 (W, E), 13 (W), 14 (W)	2
Myricetin	2 (W, E, H), 3 (E), 4 (W, H), 5 (W, E), 6 (E), 7 (E), 8 (W, E, H), 9 (W, E), 10 (W, E, H), 11 (W, E), 12 (W, E), 14 (W, E)	1 and 13
Luteolin	Of 1 (E), 2 (W, E), 3 (W, E), 4 (W, H), 5 (W), 6 (W, E), 7 (E), 8 (W, E), 9 (W, E), 10 (E), 11 (E), 12 (W, E), 13 (W, H), 14 (W, E)	–
Naringenin	1 (E), 2 (E), 3 (E), 4 (E, H), 5 (W, E, H), 6 (W, E, H), 7 (W, E, H), 8 (E), 9 (E), 10 (H), 11 (E, H), 12 (W, E), 13 (W, H)	14
Apigenin	1 (E), 2 (W, E, H), 3 (E, H), 4 (E, H), 5 (W, E), 6 (E), 7 (H), 8 (W, E, H), 9 (W, E), 10 (E, H), 11 (E, H), 12 (W, E), 14 (E)	13

Rahman et al. (1988) isolated four flavones from *B. sempervirens* of Turkish origin and they suggested that these flavones have not been isolated from Buxus species previously.

Ross et al. (2005) isolated two flavonol glycosides such as kaempferol 3-*O*-sophoroside and quercetin 3-*O*-sophoroside from male plants of *C. sativa* L. They characterized structures of isolated flavonols using high-field two-dimensional NMR spectroscopy, GC-FID and GC–MS analyses.

Rajeshwari and Andallu (2011) detected some flavonoids in the methanolic and ethanolic extracts of *C. sativum* L. seeds using RP-HPLC. In their study, rutin, quercetin, chlorogenic acid and caffeic acid were identified and quantified in the multi-component methanolic and ethanolic extracts by comparing with the respective standards using the method of RP-HPLC.

Yassine et al. (2016) studied on the phytochemical screening in hydro-ethanolic extracts of *L. stoechas* L. from Morocco. El-Beltagi et al. (2007) studied on the evaluation of fatty acids profile and determination of total flavonoids, tocopherols and phenolics in the extracts from *L. usitatissimum* L.

As shown in Table 6, the plant type has statistically significant factor on FRAP, metal chelating, H_2O_2, DPPH activities and TPC, TFC results. Additionally, solvent type has significant factor on FRAP, metal chelating, H_2O_2, DPPH activities and TPC, TFC results ($P < 0.01$). Also, interactions of plant type and solvent have significantly affected the all antioxidant activities and chemical content results ($P < 0.01$).

As can be seen from Table 7, the highest FRAP (66.57%), metal chelating (81.32%), H_2O_2 (616.59 μg mL^{-1}) and DPPH scavenging activity (1167.13 μg mL^{-1}) were found in *G. glabra*, *C. sativum*, *G. glabra* and *G. glabra*, respectively.

Phenolic and flavonoid compounds, antioxidants and free radical scavengers are widely components in plant kingdom (Baba and Malik 2015). Also, these important components show anti-mutagenic, anti-cancerogenic, cardioprotective, anti-inflammatory and antimicrobial properties (Stanojević et al. 2008). However, we do not have sufficient knowledge and data about the practical usefulness of most of them. Several fruits, vegetables and herbs including secondary plant metabolites, antioxidant phenolics, and flavonoids provide a fruitful defence against oxidative stress from oxidizing agents and free radicals (Hossain and Shah 2015). Of the 14 plants detected, the total phenolic content of the plants had significant variation between 4.80 and 48.63 μg mL^{-1} ($P < 0.01$). *Origanum majorana* contained the most phenolic compounds 48.62 followed by *M. officinalis* (44.80) as μg gallic acid equivalent (GAE) mL^{-1}. Total flavonoid content of the plants had significant variation ranging from 2.26 to 7.37 μg mL^{-1} ($P < 0.01$). *Glycyrrhiza glabra* contained the most flavonoid compounds 7.37 μg mL^{-1} followed by *B. sempervirens* (7.01 μg mL^{-1}). *Linum usitatissimum* and *A. sativa* include the lowest total phenolic and flavonoid contents, respectively. Generally, the total phenolic contents of hexane extracts are lower than the water and ethanol extracts. Similarly, the total flavonoid contents of them are lower than the other extracts. If we compare with the ethanol and water extracts with respect to total phenolic contents, ethanol extracts generally have the highest value except for *L. usitatissimum*, *C. sativum*, *M. officinalis* and *B. sempervirens* (Table 7).

When only we take into account the extraction solvents, FRAP activity, H_2O_2 activity and TPC, TFC values of ethanol extracts are higher than those of water and hexane extracts ($P < 0.01$). Metal-chelating values of hexane extracts are higher than those of water and ethanol extracts ($P < 0.01$). DPPH activity of water extracts is higher than that of ethanol and hexane extracts ($P < 0.01$) (Table 8).

Table 6 ANOVA results of the experiment factors (*significant at $P < 0.01$)

Experiments	Plant type (A)	Solvent (B)	A × B
FRAP	*	*	*
Metal chelating activity	*	*	*
H_2O_2 scavenging activity	*	*	*
DPPH scavenging activity	*	*	*
Total phenolic contents	*	*	*
Total flavonoid contents	*	*	*

4 Conclusion

The different extracts of some antiepileptic plants are tested in this study. They have effective antioxidant capacity and high phenolic and flavonoid contents. HPLC analysis was carried out with the presence of eight flavonoid compounds: catechin, epicatechin, rutin, naringin, myricetin, luteolin, naringenin and apigenin. In this assay, 11W, 8W, 11E, 8E, 11E, 3E, 8E and 11E include the highest catechin, epicatechin, rutin, naringin, myricetin, luteolin, naringenin and apigenin, respectively. For this reason, investigated plant material extracts especially 11E have the highest total flavonoid contents and relatively higher total phenolic contents. Moreover, it can be used as an easily accessible source of natural antioxidants. In the future work, we advise in vivo studies for these plant materials and their flavonoid components via gamma-aminobutyric acid (GABA) and $GABA_A$ receptors because of its activity of

Table 7 Comparison plant results of Duncan test for antioxidant activity and chemical content

Plant name	FRAP (%)	Metal chelating (%)	H_2O_2 (μg mL^{-1})	DPPH (μg mL^{-1})	TPC (μg mL^{-1})	TFC (μg mL^{-1})
Juniperus oxycedrus	52.63^{E}	74.82^{F}	314.08^{C}	192.44^{K}	13.72^{D}	3.67^{B}
Cannabis sativa	45.58^{C}	70.27^{C}	516.62^{K}	169.18^{F}	15.73^{E}	3.25^{B}
Cichorium intybus	54.99^{F}	79.01^{H}	384.32^{D}	158.04^{D}	17.73^{F}	5.49^{CD}
Lavandula stoechas	60.80^{I}	73.41^{E}	445.64^{F}	190.74^{J}	26.89^{G}	3.35^{B}
Valeriana officinalis	50.84^{D}	74.53^{F}	481.21^{I}	120.12^{A}	18.27^{F}	2.99^{AB}
Linum usitatissimum	45.46^{C}	67.74^{B}	**616.14^{L}**	180.10^{H}	4.80^{A}	3.63^{B}
Coriandrum sativum	46.27^{C}	**81.32^{I}**	485.93^{J}	169.36^{F}	9.60^{C}	3.49^{B}
Origanum majorana	63.43^{J}	71.54^{D}	383.48^{D}	176.75^{G}	**48.63^{J}**	6.61^{EF}
Glycyrrhiza glabra	**66.57^{K}**	75.07^{F}	**616.59^{L}**	**1167.13^{M}**	38.42^{H}	**7.37^{F}**
Melissa officinalis	59.66^{H}	77.01^{G}	386.09^{E}	182.59^{I}	44.80^{I}	5.19^{C}
Anthemis cotula	63.43^{J}	60.63^{A}	477.35^{H}	165.72^{E}	27.32^{G}	6.63^{EF}
Buxus sempervirens	55.00^{G}	68.23^{B}	278.50^{A}	139.57^{C}	17.41^{F}	7.01^{EF}
Peganum harmala	38.41^{A}	74.79^{F}	447.05^{G}	127.74^{B}	7.74^{B}	6.31^{DE}
Avena sativa	41.32^{B}	71.35^{D}	303.50^{B}	197.38^{L}	18.09^{F}	2.26^{A}

Same column with different letters indicates significant difference ($P < 0.05$)

Bold fonts indicate the highest values for related assays

Table 8 Comparison solvent type results of Duncan test for antioxidant activity and chemical content

Solvent	FRAP (%)	Metal chelating (%)	H_2O_2 (μg mL^{-1})	DPPH (μg mL^{-1})	TPC (μg mL^{-1})	TFC (μg mL^{-1})
Water	67.41^{B}	86.25^{B}	388.25^{A}	**354.52^{C}**	21.15^{B}	5.65^{B}
Ethanol	**82.68^{C}**	40.45^{A}	**500.50^{C}**	123.16^{A}	**36.76^{C}**	**8.47^{C}**
Hexane	10.28^{A}	**91.81^{C}**	426.22^{B}	237.36^{B}	8.33^{A}	0.29^{A}

Same column with different letters indicates significant difference

Bold fonts indicate the highest values for related assays

the different mechanism on treatment of epilepsy (Treiman 2001).

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