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Pharmacist's role in pharmacotherapeutic management of Alzheimer's disease

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ABSTRACT

Alzheimer Disease (AD) characterized by the progressive cognitive and functional impairment, is the most common form of dementia affecting people worldwide. In this study, we aimed to investigate the profile of patients with AD, the perception of caregivers about the disease and the role of pharmacist in the pharmacotherapy of AD by implementing a questionnaire for the caregivers of 44 patients with AD. 70% of the evaluated patients with AD is female gender and in 52% of the cases, hypertension co-exists with AD. The combination of memantine/donepezil (34%) was found the most commonly used pharmacological treatment in the patients which was associated with various adverse effects such as headache, insomnia, fatigue, and hallucinations. An average of 70% of the caregivers benefit from the pharmacists in regard to the use of drugs (94%), information about disease and side effects (48%) and drug-drug interactions (42%). Additionally, the 77% of caregivers who benefit from pharmacists were well satisfied with this support. In conclusion, patients with AD and their caregivers need a professional assistance regarding the use of drugs and modalities how to fight with the disease. Pharmacists play a significant role in both following the pharmacotherapy of AD patients and the education of caregivers. Thus, pharmacist's role in the management of rational pharmacotherapy should be strengthened by providing a continued educational support.

Keywords: Alzheimer Disease, pharmacist, pharmacotherapy applications, caregivers, donepezil

INTRODUCTION

Alzheimer's Disease (AD) is the most common form of dementia characterized by progressive cognitive and functional impairment involving memory loss, language impairment and disorientation as well as deterioration in their ability to carry out activities of daily living (Mucke 2009). As the rate of the aging population increases throughout the world, the number of patients with AD is also increasing in Turkey that was comparable with the rates in western countries (Gurvit et al. 2008). In Turkey, the latest ratio of the population aged over 65 was 8.2% in 2015 and as the rate of the aging population increases, the proportion of elderly people who lost their lives from AD was 4% in 2014, which was 2.7% in 2010 (Turkish Ministy of Health, Statistics 2015). Patients with AD show pathological changes including increased deposits of amyloid β peptide in the cerebral cortex, which eventually form extracellular senile plaques and intraneuronal fibrillary tangles consisting of tau protein (Zheng et al. 2002; Mucke, 2009; Graham et al. 2017). There is a progressive loss of neurons, especially cholinergic neurons in the brain areas related to memory and learning (Cummings and Cole 2002). The loss of cholinergic neurons results in a marked decrease of neurotransmitter acetylcholine (Ach) in the brain and thus, selective acetylcholine esterase inhibitors that increase Ach concentrations in the synaptic cleft by inhibiting its break down, are commonly used in the first line treatment of AD (Graham et al. 2017).

Pharmacists have been accepted as the most accessible, trusted and respected healthcare professionals and they play a critical role in the pharmacotherapy of AD (Tett et al. 1993; Wiens 2003). Pharmacists can play an active role in counselling of the patients, caregivers and clinicians on the rational use of drugs as well as alternative products, monitoring or identifiying drug-related problems such as adverse drug reactions, drug interactions, improper drug selection and inappropriate dosage form (Feinberg and Michocki 1998; Wiens 2003).

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AD is the major cause of nursing home admission because of the progressive cognitive and functional decline that directly affects families and caregivers. (Gaugler et al. 2007). Family caregivers play an essential role in optimal pharmacotherapy of these patients (Haley 1997). The present study was performed to determine the role of pharmacist in pharmacotherapy of patients with AD. Patients and their caregivers were surveyed to assess their socio-demographic characteristics, pharmacotherapy regimes of patients with AD, caregiver's attitudes to the patient and caregiver's perceptions about the the role of pharmacist in therapeutic management of AD.

MATERIALS AND METHODS

Subjects

This study was performed by administrating a questionnaire comprising 4 sections to a total number of 44 caregivers of patients with AD. Caregivers were selected through non-probability consecutive sampling among those who visited a community pharmacy to receive disease information and/or prescription drugs (n=20) and Turkish Alzheimer's Association Day Care Centre (n=24) in İstanbul (Turkey). The caregivers who live with the patients, were at least 18 years old, and those that were able to read and understand the questionnaire in Turkish and informed consent form were included in this study.

Procedure

The objectives of the study was explained on an individual basis and questionnaries were administrated to caregivers of patients with AD. The questionnaire consists of 4 sections regarding the socio-demographic characteristics of the patients and their caregivers (1), the pharmacotherapy (prescription drugs, adverse effects, alternative products, co-morbid diseases) (2), caregiver's approach to the patient (3) and perceptions about the the role of pharmacist in therapeutic management of AD (4).

Statistical analysis

Data were expressed as percentages. The diagnosis age of the patients with AD were expressed as means and standard deviations (SD) and assessed by the Student-*t* test. The statistical analysis was performed using Graph Pad (Prism 7) software. $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Sociodemographic characteristics of the patients with AD and their caregivers

This study was surveyed in 44 patients and their caregivers. The socio-demographic characteristics of the patients and their caregivers are shown on Table 1. The patient profile was 77 year-old whom diagnosed at age 69.6±2 for women and 73.7±2 for men ($p>0.05$) with a primary education. The caregiver profile was consistent with the 52-year-old first-degree relative (mostly daughters) with a retired working status (Table 1).

Table 1. Socio-demographic variables of patients with AD and their caregivers

Patients (n=44)		Caregivers (n=44)	
Variable	**n (%)**	**Variable**	**n (%)**
Sex		Sex	
Male	13 (30)	Male	10 (23)
Female	31 (70)	Female	34 (77)
Mean age (SD)	77 (7.6)	Mean age (SD)	52 (13.2)
Range (years)	58-94	Range (years)	24-83
Mean Age (SD)		**Relationship**	
(at the time of Diagnosis)		Daughter	19 (43)
Male	69.6 (2)	Wife	7 (16)
Female	73.7 (2)	Husband	4 (9)
		Son	5 (11)
		Grandchild	3 (7)
		Daughter-in law	3 (7)
		Son-in law	1 (2)
		Niece	1 (2)
		Nurse	1 (2)
Education level		**Working status**	
Primary	30 (68)	Working-full time	3 (7)
High School	7 (16)	Working-part time	4 (9)
Bachelor's Degree	6 (14)	Not-working	18 (41)
Master's Degree	1(2)	Retired	19 (43)

Pharmacotherapy of patients with AD

Among 44 patients, 15 (34%) were on memantine and donepezil combination therapy and they reported to have some side effects such as insomnia, hallucinations, urinary incontinence and fatigue (Table 2). Other therapies were memantine+rivastigmine combination therapy (n=8; 8%), memantine (n=7; 16%), donepezil (n=7; 16%), memantine+donepezil+ rivastigmine (n=4; 9%), rivastigmine only (n=2,5%) and donepezil+rivastigmine (n=1, 2%) and their reported side-effects were presented on Table 2. Only three of these 44 patients were using alternative products. These products were melatonin, fish oil and gingko biloba extract. Co-morbid diseases in patients with AD were hypertension (53%), depression (43%), diabetes (30%), heart disease (18%), hyperlipidemia (18%), osteoporosis (16%), vertigo (11%), epilepsy (9%) peptic ulcer (5%), Parkinson disease (5%) and prostate (2%).

Caregiver's attitudes to the patient

Caregiver's attitudes to the patient were reported as "always positive" for 52% (n=23) of caregivers and "sometimes nervous" for 48% (n=21) of caregivers. Only, 13 out of 44 (30%) caregivers reported to get psychological support for their own health, taking into account the challanges they are experiencing (Table 2). Twenty-three of remaining caregivers who did not receive (31) psychological support indicated that they would accept such support from a practitioner, while 8 refused to receive such support. Data related to the caregiver's approach is shown on Table 3.

Caregiver's perceptions about the the role of pharmacist in therapeutic management of AD

Among 44 caregivers 31 (70%) reported to get support from community pharmacy. 24 out of 31 patients who received support from pharmacists stated that support was sufficient, while 7 was stated as inadequate. Caregivers asked the pharmacist for information about drug usage (94%), the disease (48%), side-effects (48%), drug-drug interactions (42%) and psychological support (%32). While a large majority (70%) of

Table 2. Drug therapy and reported side effects in patients with AD

Side-effects	Drug theraphy						
	Memantin+ Donepezil (34%)	Donepezil (16%)	Memantin (16%)	Memantin+ Donepezil+ Rivastigmin (9%)	Memantin+ Rivastigmin (8%)	Rivastigmin (5%)	Donepezil+ Rivastigmin (2%)
Headache	6		1	3	2		
Dizziness	3	3		2	2	1	
Fatique	6	2	2	3	2		
İnsomnia	9	3	3	1	5	1	1
Loss of consciousness	2	1	3	1	2		
Excitement	4		1	3	2		
Extreme fear	5	1	2	2	4		
Halusination	8	3	1	3	5		
Urinary incontinence	5	4	3	3	4		
Nausea	4		1	2	2	1	
Vomitting	3			1	1		
Diarrhea	1	2			1		
Loss of appetite	3	1		1	3		
Sweeating	2		2	1			

Table 3. Caregivers approach to the patient with AD

Questions	Yes, n (%)	No, n (%)
Do you agree to receive training from an expert on Alzheimer's care?	37 (92)	7 (8)
Do you get psychological support for your own health, taking into account the challenges you are experiencing?	13 (30)	31(70)
If not, do you accept such pyhschological support from a practitioner?	23 (74)	8 (26)
Are you lean towards nursing home admission of the patient with AD?	12 (27)	32 (73)
Would you accept a new drug which being developed for the treatment the patient with AD?	24 (55)	20 (45)

caregivers reported that they received support from pharmacies, there were also those (%30) who did not receive any support as they feel more confident in their experience or believe in an insufficient knowledge of pharmacists about this disease.

In the present study, we surveyed the caregivers of the patients with AD to assess their socio-demographic characteristics, pharmacotherapy regimes of the patients with AD, caregiver's attitudes to the patient and perceptions about the the role of pharmacist in therapeutic management of AD.

The caregiver profile was consistent with the 52-year-old first-degree relative (mostly daughters) with a retired working status. The characteristics of caregivers were very similar to those found in other studies (Verez Cotelo et al. 2015; Yıkılkan et al. 2014) despite the small sample size of our group who lives in a spesific region (İstanbul).

N-methyl-D-aspartic acid antagonists (memantine) and cholinesterase inhibitors (ChEIs) are the only two approved classes of drugs to treat AD addressing respectively, the cholinergic and glutamatergic dysregulation which underlies the pathophysiology of AD (Mucke, 2009). The main ChEIs in use are donepezil, galantamine and rivastigmine. Among them donepezil was favored by caregivers in one study over other ChEIs particularly due to its ease of use (Sevilla et al. 2009). The combination therapy with memantine and donepezil in patients with moderate to severe AD have positive effects on both behaviour and cognition (Atri et al. 2008; Tariot et al. 2004). The outcomes of this survey also suggest the common use of memantine and donepezil combination therapy in patients with AD despite its anticholinergic side effects (Table 2). Diseases such as hypertension, diabetes, depression often co-exist since AD more commonly occurs in older age groups (Schubert et al. 2006).

Caring for patients with AD can lead physical, psychological, emotional, social and financial burdens (Novais et al. 2017). In Turkey, the caregivers (with the majority of women, often being daughter) had high prevelance of depressive and anxiety symptoms (Yıkılkan et al. 2014). The high percentage of caregivers who report their attitiues to the patient as "sometimes nervous" and accept a psychological support from a practitioner indicates a psychological burnout among these individuals. As supporting our findings, high percentage of Alzheimer's patient caregivers exhibited depressive symptoms (Papastavrou et al. 2007) and treated with anxiolytics and antidepressants (Verez Cotelo et al. 2015).

The survey revealed that 70% of caregivers benefit from pharmacists regarding the use of drugs (94%), the disease (48%), side effects (48%), drug-drug interactions (42%) and psychological support (32%). This finding is providing the pharma-

cist's role in both pharmacotherapy of patients with AD and the management of caregiver burden.

Pharmacist's roles in management of AD are described as: assesment of medications and prescriptions, counselling of patients and caregivers and surveillance or monitoring of medications (Wiens 2003). Donepezil consultation provided by hospital pharmacist for patients with AD and their caregivers lead better adherence to pharmacotherapy (Watanabe et al. 2012). Patients with AD particulary susceptible to risk of anticholinergic side effects with certain medications (Wiens 2003) and should be assisted by a pharmacists in selecting safe formulation such as over-the-counter (OTC) products. Pharmacists can also counsel patients and their caregivers on the safe use of herbal (alternative) products that high majorty of caregivers had requested relaxing plants and vitamins from the pharmacy for anxiety and insomnia (Verez Cotelo et al. 2015). As being one of the most accessible and regularly visited healthcare professionals in primary care (Patwardhan et al. 2012), pharmacists can also play a vital role in recognising the early symptoms of AD and may encourage patients to seek an early diagnosis (Rickles et al. 2014). While a large majority of caregivers benefit from pharmacists who make significant contribution to the management of AD, there were also those who did not receive any support as they feel more confident in their experience or believe in an insufficient knowledge of pharmacists about this disease. Supporting this, inadequate knowledge on risk factors, disease and its progression, caregiving issues and pharmacological management of AD has been recently reported in community pharmacists (Zerafa and Scerri 2016) and highlighted the need of training and educational support about AD (Skelton 2008).

Present results suggest that pharmacists play an active role in the pharmacotherapeutic management of AD and their involvement could improve clinical outcomes and caregiver's quality of life. In Turkey, with the expected increase in the number of patients diagnosed with AD in future, the pharmacist's involvement in AD management should be expanded by providing occupational training and continued educational support.

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Original Article

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Cytotoxicity and genotoxicity of fenoxaprop-p-ethyl and fluzifob-p-butyl herbicides

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ABSTRACT

Human populations are exposed to several toxic substances in the environment, including pesticides. Fenoxaprop-p-ethyl (FPE) and fluzifob-p-butyl (FPB) herbicides are extensively used in agricultural fields due to their high target selectivity and low non-target toxicity. They are known as aryloxyphenoxypropionate herbicides, and acetyl-CoA carboxylase inhibitor. In the study, we aimed to evaluate the toxic potentials of FPE and FPB herbicides. Cell viability was evaluated by MTT assay in the range of 15.6-500.0 µM exposure concentrations in mouse fibroblast (BALB/3T3) cell line. Also, we investigated their DNA damage potentials on BALB/3T3 cells by using alkaline Comet assay. The results indicated that FPE and FPB showed no evidence of DNA damage. And, the cell viability was more than 20% at 12.5-400 µM exposure concentrations. FPE and FPB might be safe according to our results and the previously studies, and there would be public health benefits from encouraging its use in the place of more toxic herbicide products.

Keywords: Fenoxaprop-p-ethyl, fluzifob-p-butyl, 3T3 cells

INTRODUCTION

Exposure to herbicides have become compulsory with increasing world population, is a global problem due to their toxic potentials although increasing the yield and quality of agricultural products. Herbicides are used for controlling several pests and weeds, even if they remain as residues in food, air, and water. There is a great deal of information that herbicides and their residues have negative effects on human and environmental health (Abd-Alrahman et al. 2014; Morrison et al. 1992; Saunders and Harper 1994). Herbicides The chemicals could affect human populations by direct exposure during production or application, or indirect exposure by oral ingestion of residues in cereals, vegetables and fruits or animal products (Betancourt and Reséndiz 2006).

FBE and FPB, members of aryloxy phenoxy propanoate herbicides, inhibit growth and lipid biosynthesis in grass species (Bakkali et al. 2007). The effect is related to the inhibition of acetyl-CoA carboxylase, a key enzyme in long-chain fatty acid biosynthesis (Shimabukuro and Hoffer 1995). FPE and FPB are mostly used as post-emergence to control grasses, although herbicides are attracting public attention (Hay 1981; Hongming et al. 2015; Yasin et al. 2013). FPE is a more recently formulated herbicide for weed control in wheat, rice, and broad-leafed crops due to its high target selectivity and low non-target toxicity (Bieringer et al. 1982; Tehranchian et al. 2016; Walia et al. 1998). Similarly, FPB is used to kill annual and perennial grasses, and does little or no harm to broad-leaved plants (Olszyk et al. 2013).

FPE inhibits the biosynthesis of fatty acids by affecting acetyl coenzyme A carboxylase.

FPE is found in plant chloroplasts and mammalian liver, and has produced reversible hepatic toxicity (Lin et al. 2007). FPE is rapidly absorbed after oral ingestion and metabolized to benzoxazol mercapturic acid and hydroxyphenoxy propionic acid (Zawahir et al. 2009). FPE is not considered carcinogenic or mutagenic and there are no reports indicating that it could be harmful to human

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fertility or reproduction (Casas et al. 2010; Peterson et al. 2011). However, Asshauer et al. (1990) indicate that FPE is harmful to aquatic organism.

FPB catalyzes the formation of malonyl-CoA during metabolism of lipids and/or of some secondary compounds (Horbowicz et al. 2013). FPB is of relatively low toxicity to birds and mammals, however, FPB is can be an irritant (eye, skin, respiratory passages, and skin sensitizer), and is toxic when to be inhaled. There are limited data about its toxicity. Tu et al. (2001) indicated FPB could be highly toxic to fish and aquatic invertebrates in aquatic systems. Also, it is thought that the weight loss in animals might be associated with reduction of the acetyl coenzyme carboxylase enzyme caused by FPB and its metabolites in mammalian studies (Ore and Olayinka 2016; Tong 2005).

In the present study, the toxic potential of FPE and FPB were investigated using MTT- cytotoxicity and Comet-genotoxicity assays because there are no reports indicating their cytotoxic and genotoxic effects on mouse fibroblast BALB/3T3 cell line.

MATERIALS AND METHODS

Chemicals

Cell culture medium (Dulbecco's Modified Eagle's Medium, DMEM), fetal bovine serum (FBS), phosphate buffered saline (PBS, 10X) and antibiotic solutions were purchased from Multi cell Wisent (Quebec, Canada). The herbicides standards, FPE and FPB were obtained from Riedel-de Haen (Seelze, Germany). MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) was obtained from Sigma Chemical Co. Ltd. (St. Louis, MO, USA). All other chemicals were obtained from Merck (NJ, USA). Stock standard solutions of 100 µM of FPE and FPB were prepared in DMSO.

Cell culture conditions

Mouse embryo fibroblast cell line BALB/3T3 (American Type Culture Collection ATCC® CRL163™, Rockville, MD, USA) was used. The cell was cultured in DMEM supplemented with 10% (v/v) FBS, 2 mM L-glutamine, 100 units/mL of penicillin, 100 µg/mL of streptomycin at 5% CO_2, 90% humidity, and 37°C for 24 h (70-80% confluence). The cell densities for each tests were in the range from $1x0^4$ to $1x10^7$ cells/mL for all assays (Abudayyak et al. 2017).

Cytotoxicity assay

Cytotoxic activities of FPE and FPB were determined by MTT (mitochondrial succinate dehydrogenase) assay. The cells were seeded in 96-well plates at a density of $1x10^4$ cells/well, and treated for 24 h with FPE and FPB in the concentration range of 15.6, 31.2, 62.6, 125, 250 and 500 µM. MTT is a water-soluble, yellow-colored salt reduced by the mitochondrial succinate dehydrogenase to insoluble purple formazan product. Mitochondrial succinate dehydrogenase is only active in viable cells. Therefore, in the MTT assay, color changes by activity of the enzyme are used as a cytotoxicity endpoint (Van Meerloo et al. 2011). Optical density (OD) values were read at 590 nm using a microplate spectrophotometer system (Epoch, Germany). In every assay, unexposed cells served as a negative control. DMSO was added to the negative control cells at a final concentration of 1% (v/v), which was related to the maximal concentration of the solvent compounds used in the experiment. The inhibition of enzyme activity observed in cells was calculated and compared to a negative control. The inhibitory concentration (IC) was then expressed as the concentration of sample causing percentage of inhibition of enzyme activity in cells.

Genotoxicity assay

Genotoxic activities of FPE and FPB were determined by Comet assay. The cells were seeded in 6-well plates at $2.5x10^5$ cells/well. After that, the cells were treated with FPE and FPB at 25, 50, 100, 200 and 400 µM concentrations in 1% DMSO during 24 h. The cells were washed with PBS, trypsinized, centrifuged at 250 g for 3 min and re-suspended into 1 mL fresh medium. 1% DMSO and 100 µM of hydrogen peroxide (H_2O_2) were used as solvent and positive controls. For positive control, the cells were incubated with H_2O_2 for 30 min.

The viability of cells was checked with trypan blue dye exclusion; cells viability was 80% in all concentrations. Briefly, 80 mL of cells was mixed with 180 mL of pre-warmed low-melting point agarose (0.65% in PBS), layered on conventional microscope slides precoated with normal-melting point agarose (1.5% in distilled water) and covered with cover slip. After solidification at 4°C, the cover slips were removed and slides were incubated for 1 h at 4°C in lysis solution (2.5 M NaCl, 100 mM EDTA, and 10 mM tris-HCl, pH 10), extemporarily added with 10% DMSO and 1% triton X-100. DNA was unwinded for 20 min in cold-fresh electrophoresis buffer (0.3 M NaOH, 1 mM EDTA, pH 13) at 4°C and electrophoresis was performed at 4°C for 20 min (20 V/300 mA) (Speit and Hartmann 1999). Then, the slides were neutralized with 0.4 M tris-HCl buffer (pH 7.5) 3 times for 5 min, and were fixed in absolute ethanol. DNA was stained with ethidium bromide (20 mg/mL) just before slide examination under a fluorescent microscope (Olympus, Japan) at 400 magnification by using an automated image analysis system (Comet Assay IV, Perceptive Instruments, UK). A total of 100 cells were scored per concentration and DNA damage to individual cells was expressed as a percentage of DNA in the Comet tail ($\%T_{DNA}$, tail intensity). Every step was performed under indirect light. Protocol was performed in triplicate to ensure reproducibility.

Statistical analysis

All experiments were done in triplicate and each assay was repeated twice. Data was expressed as mean ± standard deviation (SD). The significance of differences between unexposed and exposed cells with the herbicides was calculated by one-way ANOVA Dunnett t-test using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were selected as the levels of significance.

RESULTS AND DISCUSSION

In the present study, the effects of FPE and FPB on cell viability and DNA damage biomarkers in vitro conditions has been investigated because there are no reports related to their cytotoxic and genotoxic potentials. As it is well known, many commercial herbicide formulations are highly toxic; whereas the case fatality for the herbicide product containing FPE is relatively low (Dorn et al. 2009). Two groups claimed that FPE was not considered carcinogenic or mutagenic, or harmful to human

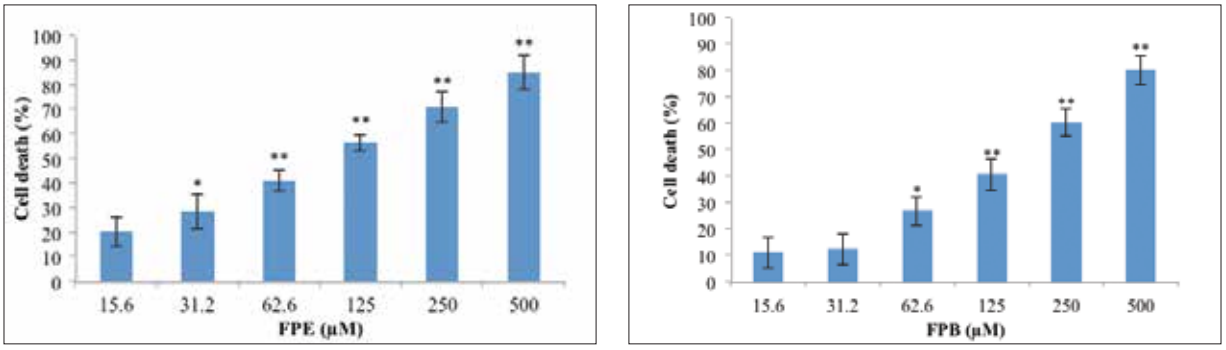

Figure 1. a, b. Effects of FPE (a) and FPB (b) on cell viability by MTT.

Values are expressed as mean ±SD; n=6 for each treatment group.
*Significantly different from DMSO control group (p←0.05).
**Significantly different from DMSO control group (p←0.001)

Table 1. Evaluation of genotoxic potentials of FPE and FPB by Comet assay.

	Mean tail intensity (%T_{DNA})±SE	
	FPB (µM)	FPE (µM)
PBS Control	0.54±0.10	0.54±0.10
H_2O_2 (100 µM)	56.09±0.84	56.09±0.02
12.5	1.12±0.09	0.70±0.22
25	0.41±0.00	1.92±0.58
50	0.80±0.38	1.96±0.55
100	1.93±0.41	2.64±0.96
200	1.60±0.68	1.62±0.72
400	1.70±0.48	3.43±0.72

All experiments were done in triplicates and each assay as repeated twice. The results were presented as mean tail intensity (%). NC mean negative controls, respectively.

fertility or reproduction (Casas et al. 2010; Peterson et al. 2011). Lin et al. (2007) indicated FPB was hepatotoxic in long-term study for mice. Kopec and Lembowicz (2002) observed the effect of herbicide FPB, on the early occurring changes in rat liver regarded as hepatic markers of peroxisome proliferators. Similarly, Kostka et al. (2002) indicated short term treatment of rats with FPB resulted in hepatomegaly due to time dependent proliferation of smooth endoplasmic reticulum and peroxisomes at 56 mg/kg body weight per day.

According to our results, all herbicides reduced the cell viability in a concentration-dependent manner. The cell viability at 37.12, 62.5, 125, and 250 and 500 µM concentrations of FPE and FPB on fibroblast cells were showed in Figure 1. IC_{50} (50% inhibition of enzyme activity) values of FPE and FPB were 392.88 and 231.37 mM, respectively.

Karadeniz et al. (2015) tested the viability and proliferation effects of FPE and FPB on human immortalized embryonic kidney HEK293 cells which examined with MTT and trypan-blue exclusion assays. They reported that herbicides did not affected the proliferation rate of the HEK293 cells but both induced cell death at high concentrations, as determined in our study.

According to data from Extoxnet (1996), FPB has shown very high to high toxicity in bluegill sunfish (LC_{50}=2.28 µM for 96 h) and rainbow trout (LC_{50}=5.9 µM for 96 h). Betancourt and Reséndiz (2006) observed with a computer-assisted semen analyzer that FPE was affected the sperm viability by being mediated at the level of the mitochondrion.

According to our Comet assay results, the genotoxic potentials of FPE and FPB were showed in Table 1. Based on our cytotoxicity results, the range of 12.5-400 µM concentration was selected as the exposure concentration for Comet assay in fibroblast cells. So, the cell viability was observed more than 40% compared to negative control in this concentration range. In positive controls (100 µM H_2O_2), the tail intensity ranged from 55.25-56.96%. The results revealed that FPE and FPB did not induce DNA damage. At the highest concentration of FPE (400 µM), tail intensities were 1.70%, which are approximately ≤1.631-fold of the negative control. Ore and Olayinka (2016) observed that FPB impaired renal and hepatic functions, and induced oxidative stress induced in treatment groups received FPB at 18.75-75 mg/kg body weight per day for 21 days by rat study. Also, they reported that FPB induced oxidative stress-mediated alteration of testicular functions in rat. We showed that FPE and FPB did not induce DNA damage. However, Ore et al. reported FPB is capable of causing testicular oxidative stress *in vivo*. Similarly, Karadeniz et al. (2015) showed that FPB and FPE possessed mutagenic and recombinogenic effects by using the somatic mutation and recombination test (SMART) in Drosophila wings. For the SMART assay, two different crosses were used: a standard (ST) and a high bioactivation (HB) cross. And, they observed that FPB and FPE did not increase the spot frequency in both ST and HB crosses.

All experiments were done in triplicates and each assay as repeated twice. The results were presented as mean tail intensity (%). NC mean negative controls, respectively.

In conclusion; we observed that FPE and FPB did not induce DNA damage. The findings should be supported with *in vivo* studies are needed to fully understand their toxicity mechanism. However, it shouldn't be ignored that FPE and FPB might be safe, and there would be public health benefits from encouraging its use in the place of more toxic herbicide products.

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Original Article

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Antioxidant potential of Cydonia oblonga Miller leaves

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ABSTRACT

Objective of this study was to determine the total polyphenol content, antioxidant activity properties of the methanolic, ethanolic and aqueous extracts of *Cydonia oblonga* Miller leaves. Quince leaves have been used as folk medicine in Turkey. Total polyphenol content was determined by Folin–Ciocalteu assay. The antioxidant capacity was determined by ferric ion reducing antioxidant power method (FRAP) and DPPH (2, 2-diphenyl-1 picryl hydrazyl) free radical scavenging method by spectrophotometry. The methanol extract had the highest total phenolic content and the highest antioxidant activity. The results demonstrated that the correlation between total polyphenol content and antioxidant activity which was measured by DPPH and FRAP assays was positive and quince leaves are cheap and natural sources of antioxidants.

Keywords: *Cydonia oblonga* Miller, quince leaves, Folin–Ciocalteu, DPPH

INTRODUCTION

Nowadays, it is commonly recognized that there is a positive relationship between a diet rich in herbal foods and a reduced incidence of degenerative diseases such as cancer and cardiovascular events. The protection provided against those illnesses has been attributed to a variety of antioxidant compounds, since free radicals present in human organism can cause oxidative damage to several molecules, such as lipids, proteins and nucleic acids, being involved in the initiation of those diseases (Pacifico et al., 2012). Hence, the search for new sources of natural antioxidants is currently of major interest to scientists. Health benefits of quince are known from ancient times. Quince (*Cydonia oblonga* Miller, Rosaceae family) is found especially in West Anatolia however it is cultivated widely in our country (Davis, 1972). The plant has been used in Turkish folk medicine for treatment of variety of diseases. The leaves are used as antitussive in the form of herbal tea and the fruits with high nutrient value are used for the treatment of diarrhea (Tuzlacı, 2006).

Study of Teleszko & Wojdylo, 2015 showed that, leaves of well-known crops and wild growing plants contain significantly higher polyphenol compounds than the fruits. In literature application of quince leaves was reported for wool fibers dyeing (Cerempei et al., 2016). There is great number of methods for determination of antioxidant capacity. The DPPH method is rapid, simple, accurate and inexpensive assay for measuring the ability of different compounds to act as free radical scavengers or hydrogen donors, and to evaluate the antioxidant activity of foods and beverages (Marinova & Batchvarov, 2011). In this study, leaves of the plant were extracted by using various solvents (water, methanol, ethanol) at 60°C and evaluated for their antioxidant activity using DPPH and FRAP modified methods. In addition, total phenolic content was determined by Folin–Ciocalteu reagent modified method (S. Ayaz Seyhan et al., 2013).

MATERIALS AND METHODS

Plant materials

The quince (*Cydonia oblonga* Miller) leaves were collected in İstanbul, Turkey. The plant has been identified by Dr. Gizem Bulut from Department of Pharmaceutical Botany, Faculty of Pharmacy, Marmara University. The voucher specimen is kept in Herbarium of the Faculty of Pharmacy, Marmara University (MARE 17527).

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Chemicals

1,1-Diphenyl-2-picrylhydrazyl radical (DPPH);6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox); 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ), Folin-Ciocalteu phenol reagent, gallic acid (GA), Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) were purchased from Sigma–Aldrich (Steinheim, Germany). The rest of chemicals, including sodium carbonate, sodium hydroxide, ferric chloride, methanol, hydrochloric acid, acetic acid were of analytical grade and obtained from Merck. Double distilled water was produced by a Milli-Q System (Millipore, Billerica, MA, USA).

Preparation of plant extracts

The quince (*Cydonia oblonga* Miller) leaves materials were dried at the room temperature and ground into fine powders using domestic blender. For antioxidant capacity methods, 1 g powdered quince leaves were subsequently extracted with three different solvents (methanol, ethanol and water) (solvent to leaf ratio 20:1) at 60°C for 1 hours and three cycles. Extract was filtered with Whatman blue band filter paper. All concentrations used in this study were calculated from dry weight (DW). The extracts prepared in this way were kept at 18°C until being tested.

Determination of total phenolic contents

Total phenolics of quince (*Cydonia oblonga* Miller) leaves extracts were determined with Folin–Ciocalteu reagent according to the method of Slinkard & Singleton (1977), with some modifications by using gallic acid as standard (S. Ayaz Seyhan et al., 2013). Sample solution was diluted with distilled water, Folin–Ciocalteu reagent was added. After vortexing and a 5 min incubation period at 30°C, Na_2CO_3 (6.0%) was added, and the mixture was vortexed and incubated for 30 min. at 30°C. The absorbance of the reaction mixture was read at 685-760 nm by spectrophotometer (Shimadzu, UV-1601). The total phenolic content was expressed as microgram of gallic acid equivalent (GAE) per mL sample by using a calibration graph gallic acid concentration range (Figure 1) (Karaçelik et al, 2015; Zengin et al., 2010).

Ferric reducing/antioxidant power (FRAP) assay

For ferric reducing/antioxidant power (FRAP) assay used in the determination of total antioxidant activities, the improved TPTZ (2,4,6-tris(2-pyridyl)-s-triazine) use is preferred (Benzie and Strain, 1999) with some modifications to accommodate aqueous as well as organic solvent extracts. Quince leaves extract was added to FRAP reagent and the reaction mixture incubated for 30 min. at 37˚C. The increase in the absorbance at 580-600 nm was measured. The antioxidant capacity based on the ability to reduce ferric ions of the extract was expressed as µmol trolox equivalents per sample by using a calibration graph Trolox concentration range of dry weight (DW) (Figure 2).

Scavenging activity on DPPH (2,2-diphenyl-1-picrylhydrazyl) radical

The free radical scavenging activity of plant extracts were determined by using modified DPPH method (S. Ayaz Seyhan et al., 2013). 0,1 mM solution of DPPH in methanol was prepared and the initial absorbance was measured at 515-528 nm. Quince leaves extract was added to DPPH solution and and the reaction mixture incubated for 30 min. at 37˚C. The change in the absorbance was measured. The antioxidant capacity based on the DPPH free radical scavenging ability of the extract was expressed as micromole of Trolox equivalents (TE) per gram sample by using a calibration graph Trolox concentration range of dry weight (DW) (Figure 3).

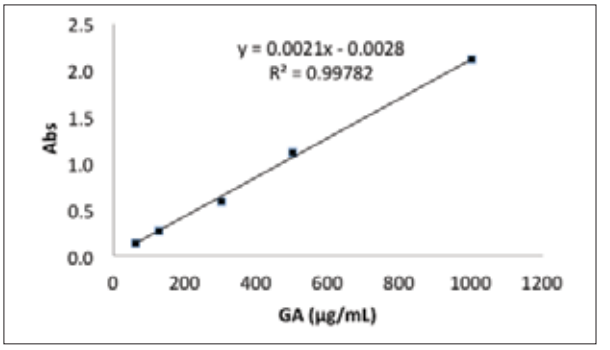

Figure 1. Calibration curve of Gallic acid equivalent by Folin-Ciocalteau Method

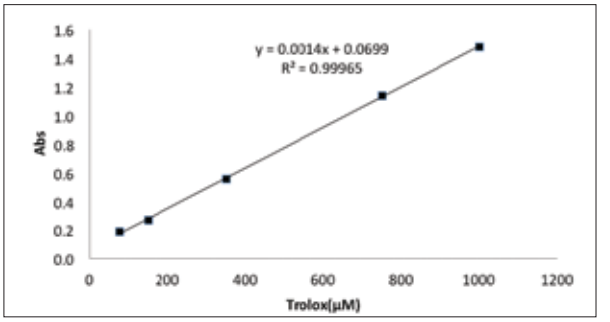

Figure 2. Calibration curve of Trolox equivalent by FRAP Method

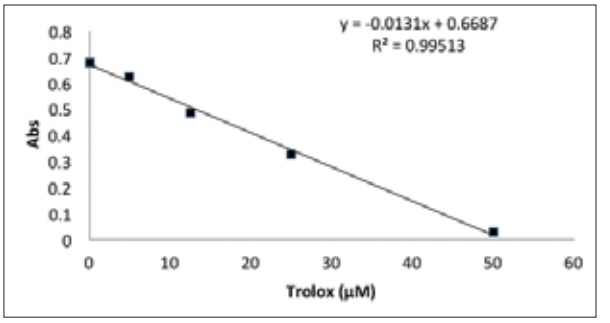

Figure 3. Calibration curve of Trolox equivalent by DPPH Method

RESULTS AND DISCUSSION

Total phenolic content

The total phenolic content was calculated using the calibration curve of gallic acid. The Folin-Ciocalteu assay is used to measure total phenolics by an oxidation/reduction (redox) reaction. The principle is based on the transfer of single electrons (SET) in alkaline medium from phenolic compounds to molybdenum to form a blue complex that can be monitored spectrophotometrically at 750-765 nm (Karadag, 2009). Total polyphenols were quantified in the extracts in order to compare the three solvents (methanol, ethanol and water) (Figure 4).

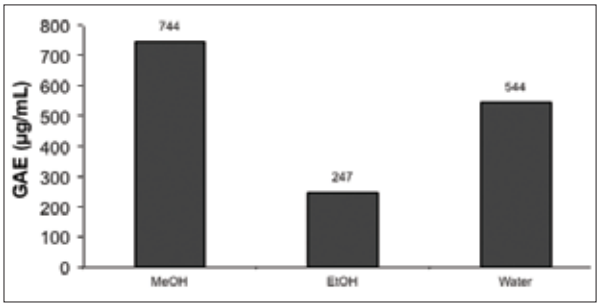

Figure 4. Total polyphenols contents determination of quince leaves extracts by Folin-Ciocalteau method

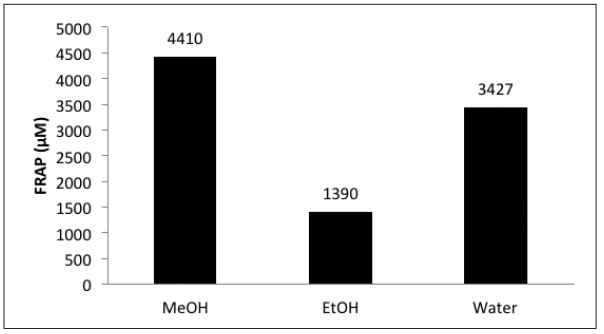

Figure 5. Ferric reducing antioxidant potential assay of quince leaves extracts

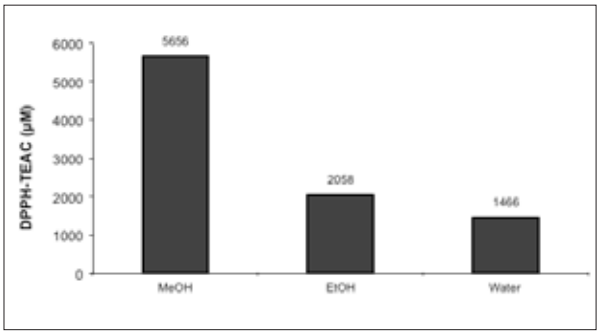

Figure 6. DPPH free radical scavenging assay of quince leaves extracts

The best polyphenol extraction was achieved using methanol. On the contrary, the lowest polyphenol amount was extracted using ethanol as solvent. As indicated in Figure 4, the total polyphenols values varied from 247-744 µg GAE /mL.

Antioxidant capacities

The antioxidant capacities of samples might be influenced by several factors, such as test system, and could not be fully described by one single method. In addition, most natural antioxidants are multifunctional. Therefore, a reliable antioxidant evaluation protocol requires to perform different antioxidant activity assessments to take into account various mechanisms of antioxidant action (Fu et al., 2011). In this study, the ferric reducing antioxidant power (FRAP) assay was used to evaluate antioxidant capacities of quince (*Cydonia oblonga* Miller) leaves. The FRAP assay is based on the ability of antioxidant to reduce ferric (III) ions to ferrous(II) ions, which is a simple and widely used method for the evaluation of antioxidant capacity (Karadag A, 2009). The FRAP values of different extraction samples are shown in Figure 5. The best antioxidant capacity was achieved using methanol. The lowest antioxidant capacity was extracted using ethanol as solvent. As indicated in Figure 5, the FRAP values varied from 1390-4410 µM Trolox/mL.

DPPH works in both electron transfer (SET) and hydrogen transfer (HAT) systems and allows the determination of a substance or a complex mixture that donate either hydrogen atoms or electrons in a homogeneous system. DPPH radical can only be dissolved in organic solvents (methanol, ethanol, acetone), which is a limitation when interpreting the role of hydrophilic antioxidants (Karadag et al., 2009). Several factors may affect the assay such as solvent, pH, sample concentration and reaction time. The DPPH values of difference extraction sample are shown in Figure 6. The best antioxidant capacity was achieved using methanol. On the contrary, the lowest antioxidant capacity was extracted using water as solvent. As indicated in Figure 6, the DPPH values varied from 1466-5656 µM Trolox/mL. DPPH can only be dissolved in organic media (especially in alcoholic media), not in aqueous media, which is an important limitation when interpreting the role of hydrophilic antioxidants. It was concluded that above a certain limit of water content of solvent, the antioxidant capacity decreased, since a part of the DPPH coagulates and it is not easily accessible to the reaction with antioxidants.

The results of this study indicated that methanolic extract of quince (*Cydonia oblonga* Miller) leaves have higher antioxidant properties compared to ethanolic and aqueous extract. Therefore, they could be considered as complementary raw material in fruit processing, enriching products (e.g. drinks) in bioactive compounds in the future. Further investigation needs to be performed for identification and quantification phenolic compounds present in the quince leaves.

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Original Article

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The local names of the plants in Kepsut and Savaştepe (Balıkesir, Turkey)

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ABSTRACT

Local plant names vary in Anatolia in every settlement. Ethnobotanical studies help to record local names of the used plants that may otherwise be lost to future generations. This study is the part of an ethnobotanical study which was conducted between 2012 and 2015 in order to determine wild plants used in Kepsut and Savaştepe (Balıkesir, Turkey). Kepsut and Savaştepe are the towns of Balıkesir province in the Marmara region of Turkey. As a result of the identification, the 509 local names of the 265 taxa, which are 12 of them are endemic, belonging to 72 families were recorded. According to the literature, among 509 local names, 338 local names were recorded for the first time in Balıkesir.

Keywords: Ethnobotany, local name, Savaştepe, Kepsut, Balıkesir, Turkey

INTRODUCTION

Ethnobotanical researches give information about relationships between public and plants which have important role in humans daily life. There is a rich ethnobotanical research collection in Turkey. Every ethnobotanical study in Turkey contains valuable information that records the cultural heritage, natural richness, traditions and customs of a different area, the life of the people. The value of the work done in the ethnobotanical field has increased more with the migration of rural populations to cities. The local people who have moved away from nature have also begun to forget the use of plants in everyday life. Therefore, listening to the valuable information of the elderly knowledgeable people living in the villages and recording the all information about used plants is also important in terms of protecting the very important values of our country. The local names of the plants are the part of our cultural heritage. The local names of the plants may differ in every settlements according to the various factors such as different uses of the same plants in every settlements and the traditions of the people living in settlements, the language used in the area and the geographic features of the area. This ethnobotanical study was planned to be carried out in villages of Savaştepe and Kepsut districts of Balıkesir (Özdemir Nath 2016). Kepsut and Savaştepe are the towns of Balıkesir province in the Marmara region of Turkey (Figure 1). Kepsut is in the eastern part of Balıkesir. It has an area of 894 km^2. The population is 24.180. Kepsut has 63 villages. As an individual Turkish ethnic group the Yoruks are distinguished by their language, customs and folkloric particularities and considering the contemporary way of life, their rather closed social community. Due to the different accent in local languages, the names of plants were different in yoruks villages. Karakeçili Yoruk communities live in 17 villages, Yağcıbedir Yoruk communities live in 9 villages. Savaştepe district has an area of 430 km^2. Its plant diversity is very rich because of its location where meeting point of 2 phytogeographic regions (Mediterranean, Euro-Siberian). The population is 20.201. Savaştepe has 44 villages. Karakeçili Yoruk communities live in 20 villages, Hardal yoruk communities live in 6 villages, Kubaş yoruk communities live in 10 villages, Kılaz yoruk communities live in 2 villages, Yüncü yoruk communities live in 1 village.

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Figure 1. Map of Kepsut and Savaştepe, Balıkesir and Turkey

Figure 2. An interview in Eyüpbükü village (Kepsut)

Figure 3. An interview in Işıklar village (Kepsut)

MATERIALS AND METHODS

This study was conducted between 2012 and 2015. The research area is a part of Balıkesir. During the field work, 107 villages (44 villages in Savaştepe and 63 villages in Kepsut) were visited in 59 days from May 2012 to October 2015 and 510 people were interviewed. After explaining the purpose of our study, questions were asked about local names of the plants and their usages. The plant samples were collected by the help of the local people (Figure 2, 3) and photographs of the plants were taken with Canon Powershot SX60. The collected specimens were identified by using "Flora of Turkey and the East Aegean Islands" (Davis, 1965–1985; Davis et al. 1988; Güner et al. 2000) and were compared with the specimens deposited at ISTE (Herbarium of Istanbul University, Faculty of Pharmacy). Plant names reviewed according to the literature (Güner et al. 2012, http://www.theplantlist.org). The collected plant materials were deposited as herbarium samples at ISTE. Some plant species deposited as a personel collection with the code of E.Ö.

RESULTS AND DISCUSSION

This study allowed us to collect information about the local names of used plants in Savaştepe and Kepsut (Balıkesir, Turkey) for the first time. As a result of the identification, the 509 local names of the 265 taxa (12 of them are endemic) belonging to 72 families were recorded (Table 1). According to the literature, among 509 local names, 338 local names were recorded for the first time in Balıkesir (Baytop 2007, Tuzlacı 2011). Edremit, Gönen, Bandırma are the towns of Balıkesir province in the Marmara region of Turkey and close to our study area. However, the local names of some plants used in these areas are different. The local names used in Savaştepe and Kepsut for *Dracunculus vulgare* are El kabartan, Gavurotu, Kabarcık, Yılancık, Yılan bıçağı, Yılan burçağı, Yılan kaması, Yılan kavcığı, Yılan pürçeği, Yılan yastığı, on the other hand the local names of the same plant are Yılan bırçağı, Köpeksiyen in Edremit gulf (Polat and Satıl 2012). The local names used in Savaştepe and Kepsut for *Asphodelus aestivus* are At otu, Kirişlik, Yabani pırasa however the local name of the same plant is Hıdırellez kamçısı in Gönen (Tuzlacı and Aymaz Eryaşar 2001). The local names used in Savaştepe and Kepsut for *Sambucus ebulus* are Kokar otu, Yılan otu on the other hand the local name of the same plant is Sultan otu in Bandırma (Onar 2006). The local name of Sultan otu is used for *Verbena officinalis* in Savaştepe. The local name of Altın otu is used for *Polypodium vulgare* in Edremit but the same name is used for *Ceterach officinarum* in Kepsut and Savaştepe. The local names may change in every settlements. Local plant names do not give us sufficient and safe information about the collection of plants from the nature and consumption for medical or food purposes. If the local people collect and use the medicinal plants or edible plants from the nature only according to the local name, they may use the wrong plants and instead of curing the disease, undesirable results may occur.

Table 1. List of plants investigated with their local names. The local names which are different from the literature are indicated as underlined and the local names of the plants which are not found in the literature are indicated with bold color.

Pteridophyta	
Aspleniaceae	**Local Name**
Ceterach officinarum Willd. (ISTE 109566)	Altınbaş otu, Altın otu, Altın yaldız otu, Kısa mahmut, Kısa mamza, Mahmutçuk otu
Equisetaceae	
Equisetum arvense L. (ISTE 109971, E.Ö.1)	Eklemeli ot, Eklice otu, Kırkkilit, Kilitotu, Mide otu
Equisetum ramosissimum Desf. (ISTE 109972)	Eklemeli otu, Mide otu
Hypolepidaceae	
Pteridium aquilinum (L.) Kuhn (ISTE 109726)	Eğrelti
Spermatophyta-Gymnospermae	
Cupressaceae	
Cupressus sempervirens L. (E.Ö.2)	Selvi, Servi
Juniperus oxycedrus L. (ISTE 109615)	Ardıç
Pinaceae	
Pinus brutia Ten. (ISTE 109873)	Çam
Spermatophyta-Angiospermae	
Adoxaceae	
Sambucus ebulus L. (ISTE 109531)	Kokar otu, Yılan otu
Sambucus nigra L. (ISTE 109530)	Mürver
Viburnum opulus L. (ISTE 109529)	**Kartopu**
Amaranthaceae	
Amaranthus retroflexus L. (ISTE 109534, 109533)	Sirken
Beta vulgaris L. (E.Ö.3)	Pancar
Chenopodium murale L. (ISTE 109535)	Deli Kazayağı, Ekşigüney, Gırya tosbası, Kazayağı, Tavuk otu, Sirken
Amaryllidaceae	
Allium paniculatum L. (ISTE 109756, 109758)	Yoğurtçuk otu
Anacardiaceae	
Pistacia terebinthus L. (ISTE 10536, 109537)	Çertlemik, Çetek, Çetlemik, Çetmik, Çitlembik, Menengiç, Şimşir
Rhus coriaria L. (ISTE 109538, 109540, 109539)	Somak, Somak otu, Sumak
Apiaceae	
Anethum graveolens L. (ISTE 109551)	Arapsaçı, Çarşır, Kırca, Tere
Anthriscus nemorosa (M.Bieb.) Spreng. (ISTE 109543)	Kazayağı
Apium nodiflorum (L.) Lag. (ISTE 109544)	Gereviz, Kereviz
Conium maculatum L. (ISTE 109547, 109548)	Baldıran
Ferulago aucheri Boiss. (ISTE 109546) **Endemic**	**Çağşır otu, Çarşır otu**
Ferulago macrosciadia Boiss. & Balansa (ISTE 109541) **Endemic**	Mide otu
Foeniculum vulgare Mill. (E.Ö.6)	Arap saçı, Rezene
Heptaptera triquetra (Vent.) Tutin (ISTE 109549)	**Öksürük otu**
Hippomarathrum cristatum (DC.) Boiss.(ISTE 109553)	Tarhana otu
Laser trilobum (L.) Borkh. (ISTE 109552)	Yabani kimyon

Table 1. List of plants investigated with their local names. The local names which are different from the literature are indicated as underlined and the local names of the plants which are not found in the literature are indicated with bold color (continued)

Oenanthe pimpinelloides L. (E.Ö.7, ISTE 109542)	Kazayağı
Petroselinum crispum (Mill.) Fuss (E.Ö.8)	Maydanoz
Smyrnium rotundifolium Mill. (ISTE 109545)	Maydanoz
Araceae	
Arum elongatum Steven (E.Ö.10)	El kabartan, Gavurotu, Kabarcık, Kabarağı, Yılancık, Yılan bıçağı, Yılan burçağı, Yılan dili, Yılan kaması, Yılan kavçığı, Yılan pürçeği, Yılan yastığı
Dracunculus vulgaris Schott (ISTE 109558)	El kabartan, Gavurotu, Kabarcık, Yılancık, Yılan bıçağı, Yılan burçağı, Yılan kaması, Yılan kavcığı, Yılan pürçeği, Yılan yastığı
Aristolochiaceae	
Aristolochia sempervirens L. (ISTE 109561)	**Mayasıl otu**
Asparagaceae	
Polygonatum orientale Desf. (ISTE 109565)	Afrodizyak otu, Süleyman otu, Tahir otu
Ruscus aculeatus L. (ISTE 109562)	Değirmen boncuğu, Deve çöküren, Deve tomurcuğu, Kalp otu, Köpek üzümü, Mercan, Sidikkesen otu, Tavşan bubusu, Tavşan memesi, Tavşan otu, Tavşan topu, Tavşan üzümü, Tilki üzümü, Yandak
Betulaceae	
Alnus glutinosa (L.) Gaertn. (E.Ö.20)	Karaağaç, Kızılçınar
Carpinus betulus L. (ISTE 109574)	Gürgen, Karaağaç
Boraginaceae	
Alkanna tubulosa Boiss. (ISTE 109578)	**Kökboya**
Anchusa undulata L. subsp. *hybrida* (Ten.) Cout. (ISTE 109583)	Bal otu, Emme otu, Sütlüce
Echium italicaum L. (ISTE 109579)	Bal otu
Echium plantagineum L. (ISTE 109580)	Engerek otu, Tüylü ot
Onosma armenum DC. (ISTE 109575) **Endemic**	Sarı çiçek
Onosma aucherana DC. (ISTE 109577)	Emme otu
Symphytum orientale L. (ISTE 109581)	**Yara otu**
Brassicaceae	
Alyssum murale Waldst. & Kit. (ISTE 109605)	Sünnetlice
Brassica oleracea L.	Karnabahar, Kelem, Lahana
Brassica nigra (L.) K.Koch (ISTE 109608)	Hardala
Brassica rapa L. (ISTE 109601)	Şalgam otu
Calepina irregularis (Asso) Thell. (ISTE 109610)	Develik
Capsella bursa-pastoris (L.) Medik. (ISTE 109606)	Çoban çantası
Lepidium spinosum Ard. (E.Ö.24)	Muşurat
Nasturtium officinale R.Br. (ISTE 109602, 109603)	Deli kereviz, Gerdeme, Gereviz, Su kazayağı
Raphanus sativus L. (E.Ö.25)	Kara turp
Raphanus raphanistrum L. (ISTE 109611)	Eşek turbu, Hardala, Turp otu
Rapistrum rugosum (L.) All. (ISTE 109600)	Hardala, Hardal otu
Thlaspi perfoliatum L. (ISTE 109607)	Kuşkuşotu
Cactaceae	
Opuntia ficus-indica (L.) Mill. (E.Ö.22.)	Eşek dikeni, Kaynana dili

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Campanulaceae	
Campanula lyrata Lam. (ISTE 109584) **Endemic**	Çanotu
Caryophyllaceae	
Silene gallica L. (ISTE 109585)	Pembe çiçek
Cistaceae	
Cistus creticus L. (ISTE 109588)	Pamuklar
Cistus laurifolius L. (ISTE 109625, 109587)	Murt, Murtotu, Tavşanak, Tavşanaki, Tavşan pıynarı
Cistus salviifolius L. (ISTE 109626, 109591, 109592)	Pamuklar, Pamuk otu
Helianthemum nummularium (L.) Mill. (ISTE 109590) Endemic	**Çay otu**
Colchicaceae	
Colchicum bivonae Guss. (ISTE 109764)	**Çiğdem**
Compositae	
Achillea arabica Kotschy (ISTE 109618)	Ayvadana, Kurtotu, Populca
Achillea nobilis L. subsp. *neilreichii* (A.Kern.) Velen. (ISTE 109654, 109624, 109655, 109656)	Ayvadana, Kurtotu
Achillea setacea Waldst. & Kit. (ISTE 109623)	Kurtotu, Ülser otu
Aetheorhiza bulbosa (L.) Cass. (ISTE 109632)	Mayasıl otu
Anthemis cotula L. (ISTE 109647, 109645, 109646)	Bopatça
Anthemis cretica L. subsp. *absinthifolia* (Boiss.) Grierson (E.Ö.11)	Papatya
Anthemis pseudocotula Boiss. (ISTE 109666, 109648)	Bopatça
Anthemis wiedemanniana Fisch. & C.A.Mey. (ISTE 109665) **Endemic**	Papatya
Artemisia annua L. (ISTE 109622)	Kabe süpürgeliği, Pelinotu
Calendula officinalis L. (E.Ö.12)	Aynısefa otu, Portakal nergisi
Cardopatium corymbosum (L.) Pers. (ISTE 109642)	Çoban çırası, Diken
Carduus nutans L. (ISTE 109620)	Deve dikeni
Carduus pycnocephalus L. subsp. *albidus* (M.Bieb.) Kazmi (ISTE 109628)	Çakır dikeni
Carthamus lanatus L. (ISTE 109640)	Dikenli afın, Dikenli afyon
Centaurea iberica Trevir. ex Spreng. (ISTE 109649)	Çakır dikeni
Centaurea solstitialis L. (E.Ö.13, ISTE 109650)	Çakır dikeni, Oyun dikeni
Chondrilla juncea L. (E.Ö.14, ISTE 109638)	Sakızlık
Chrysanthemum segetum L. (ISTE 109643)	Karanfil
Cnicus benedictus L. (ISTE 109616)	Acı dürlek, Diken, Diken otu, Mayasıl otu, Sancı dikeni, Sancı otu, Şevketi bostan, Yer dikeni
Cota tinctoria (L.) J.Gay (ISTE 109661, 109664)	Akıllı papatya, Bopatça, Gömeç
Helianthus annuus L. (E.Ö.15)	Günebakan
Hieracium marmoricola P.D.Sell & C.West (ISTE 109653, 109652) **Endemic**	**Mercangümüş**
Lactuca serriola L. (E.Ö.16)	Helvacık
Leontodon tuberosus L. (ISTE 109636, 109637, 109635)	Hindibağ, Karahindibağ

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Matricaria chamomilla L. (ISTE 109644)	Bopatça, Bubatçe, Papatça, Papatya, Keloğlan çiçeği
Pallenis spinosa (L.) Cass. (ISTE 109651)	Altınyıldız otu
Silybum marianum (L.) Gaertn. (ISTE 109639)	Çıtırgan, Deve dikeni, Kenger, Sarıkız
Sonchus asper (L.) Hill subsp. *glaucescens* (Jord.) Ball ex Ball (ISTE 109634, 109627)	Diken otu, Eşek dikeni, Eşek helvası, Helvacık, Helvacık otu, Radika
Taraxacum gracilens Dahlst. (ISTE 109619)	**Karahindibağ**
Taraxacum hybernum Steven (ISTE 109641)	Karahindibağ, Radika, Üfleme otu
Tripleurospermum conoclinium Boiss. & Balansa) Hayek (ISTE 109659, E.Ö.17) **Endemic**	Uzun papatya
Urospermum picroides (L.) Scop. ex F.W.Schmidt (ISTE 109629)	Helvacık
Xanthium strumarium L. (E.Ö.18)	Büyük pıtrak, Domuz pıtrağı
Xeranthemum cylindraceum Sm. (E.Ö.19)	**Duman otu**
Convolvulaceae	
Convolvulus arvensis L. (ISTE 109670, 109669)	Filiz, Sarmaşık
Convolvulus cantabrica L. (ISTE 109667)	Pembe sarmaşık
Convolvulus scammonia L. (ISTE 109668)	Sarmaşık
Cornaceae	
Cornus mas L. (ISTE 109595, 109594)	Kızılcık, Küren
Crassulaceae	
Sedum album L. (ISTE 109599)	İsilik otu
Sedum pallidum M.Bieb. (ISTE 109598, 109597)	İsilik otu, Taş koruğu
Umbilicus rupestris (Salisb.) Dandy (ISTE 109596)	Kaplık otu
Cucurbitaceae	
Ecballium elaterium (L.) A.Rich. (ISTE 109613, 109612)	Acı bostan, Acı dülek, Acı dürlek, Acı kavun, Acı kelek, Deli kelek, Deve daşağı, Kabarağı, Mayasıl otu, Şeytan keleği, Yer dikeni
Lagenaria siceraria (Molina) Standl. (E.Ö.28)	Su kabağı
Momordica charantia L. (E.Ö.29)	Akçakız, Kah kah kabağı, Kudret Narı, Şevketibostan
Cyperaceae	
Cyperus rotundus L. (ISTE 109671)	Topalak otu
Scirpoides holoschoenus (L.) Soják (ISTE 109672)	Kovalık otu
Dioscoreaceae	
Dioscorea communis (L.) Caddick & Wilkin (ISTE 109676, 109673, 109674)	Acı filiz, Acı ot, Adem otu, Akıllı sarmaşık, Çıtırga filizi, Domuz helvası, Filiz, Köpek üzümü, Mayasıl otu, Sarmaşık, Yakı otu, Yel otu
Elaeagnaceae	
Elaeagnus angustifolia L. (E.Ö.31)	İğde
Ericaceae	
Arbutus andrachne L. (ISTE 109679)	Ağaç çileği, Ayı üzümü, Dağ çileği, Davulgu
Arbutus unedo L. (ISTE 109681)	Davulgu
Erica arborea L. (ISTE 109680)	Pien, Piren, Piyen
Euphorbiaceae	
Euphorbia helioscopia L. (ISTE 109682)	Sütligen

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Euphorbia oblongata Griseb. (ISTE 109684)	Sütleğen
Euphorbia rigida M.Bieb.(ISTE 109683)	Sütleğen
Fagaceae	
Quercus cerris L. (ISTE 109687)	Ak gobak, Çalı kobağı, Gobak, Meşe, Karakubak, Kara kombalak, Kızılmeşe, Kobak, Kobar çalısı, Kombalak, Kubak, Kubar
Quercus infectoria G.Olivier (ISTE 109693, 109694, 109692)	Akgobak, Akmeşe, Akpıynar, Çalı kobağı, Gobak, Kasnak, Meşe, Pelit, Palamut, Sartal
Quercus ithaburensis Decne. subsp. *macrolepis* (Kotschy) Hedge & Yalt. (ISTE 109686)	Meşe, Kırmızı pelit
Quercus petraea (Matt.) Liebl. subsp. iberica (Steven ex M.Bieb.) Krassiln. (ISTE 109689)	Meşe
Gentianaceae	
Centaurium erythraea Rafn (ISTE 109695)	Kırmızı kantaron
Geraniaceae	
Erodium ciconium (L.) L'Hér. (ISTE 109701)	İğnelik
Erodium cicutarium (L.) L'Hér. (ISTE 109700)	Kocakarı iğnesi
Erodium leucanthum Boiss. (ISTE 109699, 109697)	İğnelik
Erodium moschatum (L.) L'Hér. (ISTE 109702)	Leylek kakması
Geranium asphodeloides Burm.f. (ISTE 109698)	Hıdır otu, Mor çiçek
Grossulariaceae	
Ribes rubrum L. (ISTE 109709, ISTE 109708)	Kanser otu
Hypericaceae	
Hypericum atomarium Boiss. (ISTE 109723)	Kantoron otu
Hypericum calycinum L. (ISTE 109720, 109719)	Hayırsız otu
Hypericum montbretii Spach (ISTE 109718, 109721)	Kantaron, Kantarot
Hypericum perforatum L. (ISTE 109710, 109717, 109712)	Boyalık otu, Çayotu, Kantarot, Kantaron, Kantar otu, Katırcı otu, Sarı kantaron
Hypericum triquetrifolium Turra (ISTE 109713, 109716)	Kantaron, Şeytan evi
Juncaceae	
Juncus inflexus L. (ISTE 109727)	Kovalık otu
Lamiaceae	
Ballota nigra L. (ISTE 109820)	Çay otu, Kanser otu
Clinopodium vulgare L. (ISTE 109854, 109853)	Ballıbaba
Lavandula stoechas L. (ISTE 109852, 109826)	Karabaş otu, Kocabaşotu, Lavanta
Marrubium vulgare L. (ISTE 109830, 109847, 109848, 109849, 109850)	Bertik otu, Eşek otu, Konyalı otu, Koyun otu, Mayasıl otu
Melissa officinalis L. (ISTE 109802)	İliman, Limon otu, Oğulotu
Mentha longifolia (L.) L. subsp. *typhoides* (Briq.) Harley (ISTE 109834)	Dere nanesi, Köpek nanesi
Mentha pulegium L.(E.Ö.36)	Nana, Nane
Micromeria myrtifolia (L.) Benth. ex Rchb. (ISTE 109809)	Ayaklı kekik
Ocimum basilicum L. (E.Ö.37)	Fesleğen, Reyhan

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Origanum vulgare L. subsp. *hirtum* (Link) Ietsw. (ISTE 109829, 109813)	Akkekik, Ayaklı kekik, Dal kekiği, Dağ kekiği, Ege kekiği, Gır kekiği, Güve otu, İnce kekik, Kekik, Keklik, Mercan köşk, Nuzla, Orman kekiği, Uzun kekik.
Phlomis russeliana (Sims) Lag. ex Benth. (ISTE 109833) **Endemic**	**Sorkuç**
Prunella laciniata (L.) L. (ISTE 109841, 109840)	**Horoz ibiği**
Prunella vulgaris L. (ISTE 109843)	Siğil otu
Rosmarinus officinalis L. (ISTE 109838, 109839)	Akıl otu, Biberiye
Salvia aethiopis L. (ISTE 109808)	Yünlü adaçayı
Salvia argentea L. (ISTE 109824)	**Beyaz şabla**
Salvia fruticosa Mill. (ISTE 109807)	Adaçayı, Boş, Boşotu, Boşapla, Muşapla, Moşapla, Puşapla, Şapla, Yakıotu
Salvia napifolia Jacq. (ISTE 109795)	Çay otu
Salvia tomentosa Mill. (ISTE 109804)	Adaçayı, Muşapla
Salvia verbenaca L. (ISTE 109797)	Böbrek otu
Salvia virgata Jacq. (ISTE 109799, 109794)	Kanser otu
Salvia viridis L. (ISTE 109801, 109800)	Grip çayı
Scutellaria rubicunda Hornem. (ISTE 109791)	**Mantar otu**
Sideritis montana L. subsp. *remota* (d'Urv.) P.W.Ball (ISTE 109823)	**Dağ çayı**
Stachys cretica L. subsp. *anatolica* Rech. fil. (ISTE 109811) **Endemic**	Beyaz şabla, Karabaş otu
Stachys obliqua Waldst. & Kit. (ISTE 109787)	Dağ çayı
Stachys thirkei K.Koch (ISTE 109788)	Minare otu, Tavşanak otu
Teucrium chamaedrys L. (ISTE 109831, 109786, 109784, 109785)	Bodur mahmut, Bodur otu, Kebir, Kısa mahmut
Teucrium polium L. (ISTE 109782,109781)	Şeker otu
Thymbra spicata L. (ISTE 109827, 109780, 109779, 109777)	Bayır kekiği, Havai kekik, Karabaş otu, Karakülef, Kaya kekiği, Kekik, Mercanköşk, Şeker otu
Thymus longicaulis C.Presl subsp. *chaubardii* (Rchb.f.) Jalas (ISTE 109832)	Akbaşlı ot, Güve otu, Kekik, Nuzla, Nuzlot, Yer kekiği
Thymus zygioides Griseb. (ISTE 109818, 109817)	Bayır çayı, Kaya kekiği, Kekik, Kır kekiği, Nuzla otu, Şeker otu, Taş kekiği, Toğga
Vitex agnus-castus L. (ISTE 109828, 109774, 109773)	Hayıt
Leguminosae	
Astragalus angustifolius Lam. (ISTE 109729)	Diken otu, Dikenli ot, Top diken
Astragalus hamosus L. (ISTE 109754)	Pıtrak
Bituminaria bituminosa (L.) C.H.Stirt. (ISTE 109736)	Yağlı ot
Cercis siliquastrum L. (ISTE 109733)	Erguvan, Keçi gevişi, Yabani keçiboynuzu
Dorycnium graecum (L.) Ser. (ISTE 109737)	Yonca
Genista anatolica Boiss. (ISTE 109743)	Diken otu, Mayasıl dikeni
Hymenocarpos circinnatus (L.) Savi (ISTE 109744)	**Tandır otu**
Melilotus indica (L.) All. (ISTE 109730)	Sarı yonca
Pisum sativum L. subsp. *elatius* (M.Bieb.) Asch. & Graebn. (ISTE 109745)	Yabani bezelye
Securigera securidaca (L.) Degen & Dorfl. (ISTE 109739, 109741)	**Sinameki**
Spartium junceum L. (ISTE 109752)	Katır kuyruğu, Katır tırnağı, Piren, Poruk

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Trifolium angustifolium L. (ISTE 109750)	Trifil
Trifolium nigrescens Viv. (ISTE 109732)	Trifil, Yonca
Trifolium purpureum Loisel. (ISTE 109734)	Tirfil
Vicia grandiflora Scop. (ISTE 109746)	Deli bakla, Fi, Trifil, Yerli Fi
Vicia tetrasperma (L.) Schreb. (ISTE 109751)	**Mavi kantaron**
Vicia villosa Roth (ISTE 109749)	Bağla otu, Deli bakla, Fi, Yabani bezelye
Liliaceae	
Asparagus acutifolius L. (ISTE 109763)	Çıtır dikeni
Asparagus aphyllus L. subsp. *orientalis* (Baker) P.H.Davis (ISTE 109762)	Ciğer otu, Kalp otu
Lilium candidum L. (ISTE 109761)	Beyaz zambak
Lythraceae	
Lythrum salicaria L. (ISTE 109765)	Egzama otu
Malvaceae	
Alcea pisidica Hub.-Mor. (ISTE 109770) **Endemic**	**Fatmagül, Hatmi**
Malva sylvestris L. (ISTE 109767, 109769, 109768)	Develik otu, Ebegümeci, Evelik, Gömeç
Oleaceae	
Jasminum fruticans L. (ISTE 109861, 109857)	Çeltik, Çingirlik
Phillyrea latifolia L. (ISTE 109858, 109860, 109859)	Akçakesme, Pınar
Paeoniaceae	
Paeonia peregrina Mill. (ISTE 109864)	Abaç, Ay gülü, Ayı gülü, Beşparmak, Dolaman, Dülbent, Garga basması, Geyik göbeği, Geyik lalesi, Kaba dülbent lalesi, Kaba dülber, Kafire, Kame, Lale, Tombak lale, Top lale
Papaveraceae	
Fumaria officinalis L. (ISTE 109868)	Şahteren
Glaucium corniculatum (L.) Curtis (ISTE 109872)	Gelincik
Papaver rhoeas L. (ISTE 109869, 109866)	Gelincik, Gelineli
Plantaginaceae	
Plantago lanceolata L. (ISTE 109874)	Damarlı ot, Kılınç otu
Plantago major L. (ISTE 109876)	Kırkdamar otu, Sinirli ot
Plantago major L. subsp. *intermedia* (Gilib.) Lange (ISTE 109875)	Beşparmak otu, Damarlı ot
Poaceae	
Briza maxima L. (ISTE 109705)	Günebakan, Şıngırdak otu
Cynodon dactylon (L.) Pers. (ISTE 109707)	Ayrık otu, Bıcırgan, Eklem otu
Sorghum halepense (L.) Pers. (ISTE 109706)	Kanyaş, Kıynaş, Süpürgelik
Polygonaceae	
Polygonum alpinum All. (ISTE 109885)	Ekşigünek otu
Polygonum cognatum Meisn. (ISTE 109880)	Madımak, Tavuk otu
Rumex acetosella L. (E.Ö.44)	Acı kulak, Ekşi kulak, Epelek, Ilıbada, Kızılbacak, Kuzukulak, Kuzukulağı, Labada
Rumex crispus L. (ISTE 109883, 109884)	Alabardağı, Ebe kuzulağı, Eşek alabadası, Labada

Table 1. List of plants investigated with their local names. The local names which are different from the literature are indicated as underlined and the local names of the plants which are not found in the literature are indicated with bold color (continued)

Rumex cristatus DC. (ISTE 109882)	Kuzukulak
Rumex obtusifolius L. (ISTE 109879)	Alabardak
Rumex patientia L. (E.Ö.45)	Labada otu, Pazı
Rumex tuberosus L. (ISTE 109881)	Ekşi kulak, Kuzukulağı
Portulacaceae	
Portulaca oleracea L. (E.Ö.49)	Semizlik otu, Temizlik otu
Primulaceae	
Primula vulgaris Huds. subsp. *rubra* (Sm.) Arcang. (ISTE 109887)	Dağ marulu, Dere çiçeği, Karga basması, Karga yaşmağı, Marul
Ranunculaceae	
Delphinium peregrinum L. (ISTE 109888)	Bit otu
Helleborus orientalis Lam. (E.Ö.50)	Karacakökü, Karacaot, Kökboyası
Ranunculus arvensis L. (ISTE 109889)	Bağdırnağı, Ellik pıtrağı, Pıtrak, Sarı pıtrak
Ranunculus repens L. (ISTE 109892, 109891)	Bağdırnağı, Yağlı lale, Yakı otu
Rhamnaceae	
Paliurus spina-christi Mill. (ISTE 109893, 109894, 109895)	Çaltı, Çaltı güllüğü, Çaltı pulu, Karaçaltı
Rosaceae	
Cotoneaster morulus Pojark. (ISTE 109910)	**Geyik elması**
Crataegus microphylla K.Koch (ISTE 109914)	Alıç
Crataegus monogyna Jacq. (ISTE 109915, 109917)	Alıç, Alıç gülü, yemişen
Crataegus orientalis Pall. ex M.Bieb. subsp. *szovitsii* (Pojark.) K.I.Chr. (ISTE 109913)	Alıç, Yemişen
Filipendula vulgaris Moench (ISTE 109912)	Keçisakalı
Malus sylvestris (L.) Mill. (ISTE 109922)	Bayır elması
Potentilla recta L. (ISTE 109921)	Aslan pençesi, Yaraotu
Prunus divaricata A. Sav. subsp. *divaricata* (E.Ö.54)	Dağ eriği, Erik
Prunus dulcis (Mill.) D.A.Webb	Badem, Çağla
(ISTE 109934)	
Prunus laurocerasus L. (ISTE 109932)	Tahlan, Taflan, Taflana
Prunus spinosa L. (ISTE 109909)	Çakal eriği, Deli erik, Domuz eriği, Güvem, Karagüvem, Likapa, Mamık, Yabani erik
Pyrus amygdaliformis Vill. (ISTE 109936)	Deli armut
Pyrus elaeagnifolia Pall. (ISTE 109923, 109933)	Ahlat, Aflat, Alfat, Çakal armudu, Geyik elması, Üvez, Yabani armut
Rosa canina L. (ISTE 109938, 109931)	Bayırgülü, Iprım, İtgülü, Kuşbaşı, Kuşburnu, Öküzgötü, Yabangülü, Yabani gül
Rosa phoenicia Boiss. (ISTE 109904, 109924)	Kuşburnu
Rosa sempervirens L. (ISTE 109902)	Kuşburnu, İtgülü, Öküzgötü
Rubus canescens DC. (ISTE 109926)	Böğürtlen, Karamık, Karantı, Kırantı
Rubus idaeus L. (ISTE 109898, 109897, 109903)	Karantı
Rubus sanctus Schreb. (ISTE 109900)	Böğürtlen, Kırıntı
Rubus ulmifolius Schott (ISTE 109927)	Karantı
Sarcopoterium spinosum (L.) Spach (E.Ö.56)	Çıtırdak, Çıtırgan, Çıtırık, Çıtırgı dikeni, Çıtır pıtır

Table 1. List of plants investigated with their local names. The local names which are different from the literature are indicated as underlined and the local names of the plants which are not found in the literature are indicated with bold color (continued)

Sorbus torminalis (L.) Crantz (ISTE 109918)	Geyik elması
Rubiaceae	
Galium aparine L. (ISTE 109946, 109948, 109943)	Dil kanatan otu, Kedi taşağı, Yapışkan ot
Galium verum L. (ISTE 109947)	Sünnetlice otu, Yoğurt otu
Rubia tinctorum L. (ISTE 109945)	Boyalık otu, Kökboya, Yapışkan ot
Salicaceae	
Populus nigra L. (E.Ö.59)	Deli kavak, Kavak, Telli kavak
Salix alba L. (ISTE 109949)	Söğüt
Santalaceae	
Osyris alba L. (E.Ö.60)	Poruk otu
Viscum album L. subsp. *album* (E.Ö.61)	Aflat burcu, Ahlat, Ahlat burcu, Ahlat hurcu, Ahlat pürçüğü, Alfat, Ardıç burcu, Ardıç pürçüğü, Armut burcu, Burç, Hurç, Ökse otu
Viscum album L. subsp. *austriacum* (Wiesb.) Vollm. (E.Ö.62)	Burç, Çam burcu, Hurç, Ökse otu
Scrophulariaceae	
Scrophularia scopolii Hoppe ex Pers. (ISTE 109953)	Basur otu
Verbascum lasianthum Boiss. ex Benth. (ISTE 109954)	Eşek kulağı, Mayasıl otu, Sığır kuyruğu, Sığır sidiği
Verbascum mucronatum Lam. (ISTE 109951)	Balık otu, Mayasıl otu, Sığır kuyruğu, Süpürgelik otu
Verbascum simavicum Hub.-Mor. (ISTE 109950, 109952, E.Ö.63) **Endemic**	**Eşek kulağı, Sığır kuyruğu, Sığır sidiği**
Veronica pectinata L. (ISTE 109956, 109955)	**Bodur mahmut**
Solanaceae	
Datura stramonium L. (ISTE 109959)	Hardalotu, Tatala
Hyoscyamus niger L. (ISTE 109958, 109957)	Diş otu
Tiliaceae	
Tilia argentea Desf. ex DC. (ISTE 109961)	Ihlamur
Tilia rubra DC. subsp. *caucasica* (Rupr.) V.Engl. (E.Ö.67)	Ihlamur
Urticaceae	
Urtica dioica L. (ISTE 109962, E.Ö.68)	Bıcırgan, Gıcırgan, Gidişken, Isırgan, Kabarcık
Urtica membranacea Poir. ex Savigny (ISTE 109964)	Isırgan
Urtica pilulifera L. (ISTE 109963)	Gidişken
Verbenaceae	
Verbena officinalis L. (ISTE 109965)	Sultan otu
Violaceae	
Viola sieheana W.Becker (ISTE 109967)	Mor menekşe
Viola tricolor L. (ISTE 109966)	Yabani menekşe
Xanthorrhoeaceae	
Asphodeline lutea L. (ISTE 109966)	Köpek şilşili, Lüllük, Nünü, Yabani pırasa
Asphodelus aestivus Brot. (E.Ö.70, ISTE 109969)	At otu, Kirişlik, Yabani pırasa
Zygophyllaceae	
Tribulus terrestris L. (E.Ö.71)	Çoban çökerten, Deve çökerten, Domuz pıtrağı, Pıtrak otu, Sarı pıtrak

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Review

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Drug and Herb induced liver injury: a short review

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ABSTRACT

Chemical induced liver injury is a pathological condition caused by diver's medications and other xenobiotics, leading to deficiencies in liver functions with the elimination of other diagnosis. Liver injury is prevalent in the world and can result in serious clinical outcome and has possibly fatal outcome. Chemical induced liver injury has an estimated annual incidence 10-15 per 10,000-100,000 patients received several prescription medications. The kind of liver injury are almost 10% cases with acute hepatitis, and is the most common cause of acute liver failure in the United States. Also, liver injury appeared after approval for marketing has restricted the use of many drugs (e.g., isoniazid, labetalol, and felbamate). Therefore, especially drug-induced liver injury is currently the major reason for discontinuation of a new compound in development or for withdrawal of a successfully launched drug from the market. In this review, we researched that mechanisms of liver injury with drugs and herbal preparations, and potential risks have been reported.

Keywords: Liver injury, hepatotoxicity, drug withdrawal

INTRODUCTION

Chemical induced liver injury is a pathological condition caused by several drugs, herbal and dietary supplements, and other xenobiotics, leading to deficiencies in liver functions after the elimination of other diagnosis (Suk and Kim 2012). Drug-induced liver injury is rare; however, is one of the commonest causes of failed drug approval from regulatory authorities, adverse drug reactions, withdrawal of medications from the market and acute liver failure. As it is well known, pharmaceutical preparations contains drugs approved by regulative authorities, and they still are often the main cause of the adverse liver reactions (Clinical 2009; Temple 2006).

Several retrospective and prospective studies have been reported the incidence and risk factors for chemical-induced liver injury in the medical literatures. In the world, the estimated annual incidence rate of liver injury is 13.9-24.0 per 100,000 people (Oh et al. 2015; Suk and Kim 2012). The annual incidence rate of liver injury has varied from 1.27 to 14 cases per 10^5 inhabitants in reported studies from Europe (Dağ et al 2014; Hussaini and Farrington 2014; Sgro et al. 2002). In the United States, drugs are related to over 50% of acute liver failure cases that circa 2000 annually reported (Korth 2014). Available data from Turkey about chemical-induced liver injury are very limited. Published data about liver injury from our country consist of case reports and experimental studies. In a large retrospective analysis from Ankara, antibiotics were the most common causative agents in 84 of 170 patients with drug-induced liver injury (Dağ et al. 2014).

THE ETIOLOGY OF LIVER INJURY

Most researchers agree that the etiology of liver injury can be commonly separated into two categories. Firstly, a cause of direct hepatotoxicity or liver injury is the drug itself or its metabolite as is the case with acetaminophen overdose. Several other drugs

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can cause dose-related hepatotoxicity as in bromfenac, cyclophosphamide, methotrexate *etc*. Second category is commonly described as idiosyncratic. A majority of liver injury cases arise from idiosyncratic metabolic responses or unexpected medication reactions, and the pathogenesis of reactions is uncertain (Njoku 2014; Suk and Kim 2012).

Biotransformation takes important stage in the development of chemical induced liver injury through the formation of directly toxic or reactive metabolites (Figure 1). The metabolites could effectuate direct injury to the hepatocyte by interaction with important cellular functions. For example; bioactivation of acetaminophen by CYP2E1 leads to the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). The metabolite has an affinity to intracellular organelles including the mitochondria. Further information about mechanism could be achieved by the sources (Njoku 2014). Direct toxic or reactive metabolites could also raise sensitization of hepatocytes to cytokine-induced damage such as in bacterial endotoxins represented by lipopolysaccharide via TNF-α, in some cases, from sensitization to injury in liver (Njoku 2014). In third way, drug and reactive metabolites process through haptenization including covalent conversion of native cellular proteins, which subsequently altered and organize immune recognition. In a susceptible host, the last process initiates a cascade of cytokine driven immune reactions be the result of hepatotoxicity (Njoku 2014; Garcia-Cortes et al. 2011).

RISK FACTORS FOR LIVER INJURY

Up to present many studies with liver injury and its risk factors are poorly understood. The susceptibility to chemical-induced liver injury is dependent on aging and gender, genetic factors, pre-existing liver disease, oxidative and mitochondrial damage, and social factors (Boelsterli and Lim 2007; Chen et al. 2015; Gómez-Lechón et al. 2015; Hussaini and Farrington 2014).

Aging: Decreased in renal function and reduced conjugation reactions in hepatic metabolism by age affects drugs pharmacokinetics. The general hypothesis suggested that older age probably increases chemical-induced liver injury susceptibility. In the Spanish Drug-Induced Liver Injury Registry, 46% of patients with liver injury were ≥60 years of age. United States Drug-Induced Liver Injury Network (DILIN) reported 18.5% of patients with liver injury to be 65 years or older (Chen et al. 2015). Liver injury is rare in children, which are related with the accidental exposure and overdose (Korth, 2014). In Korea, the age distribution was varied with the age groups <20, 20-29, 30-39, 40-49, 50-59, and ≥60 representing 1.3, 8.1, 16.4, 27.5,

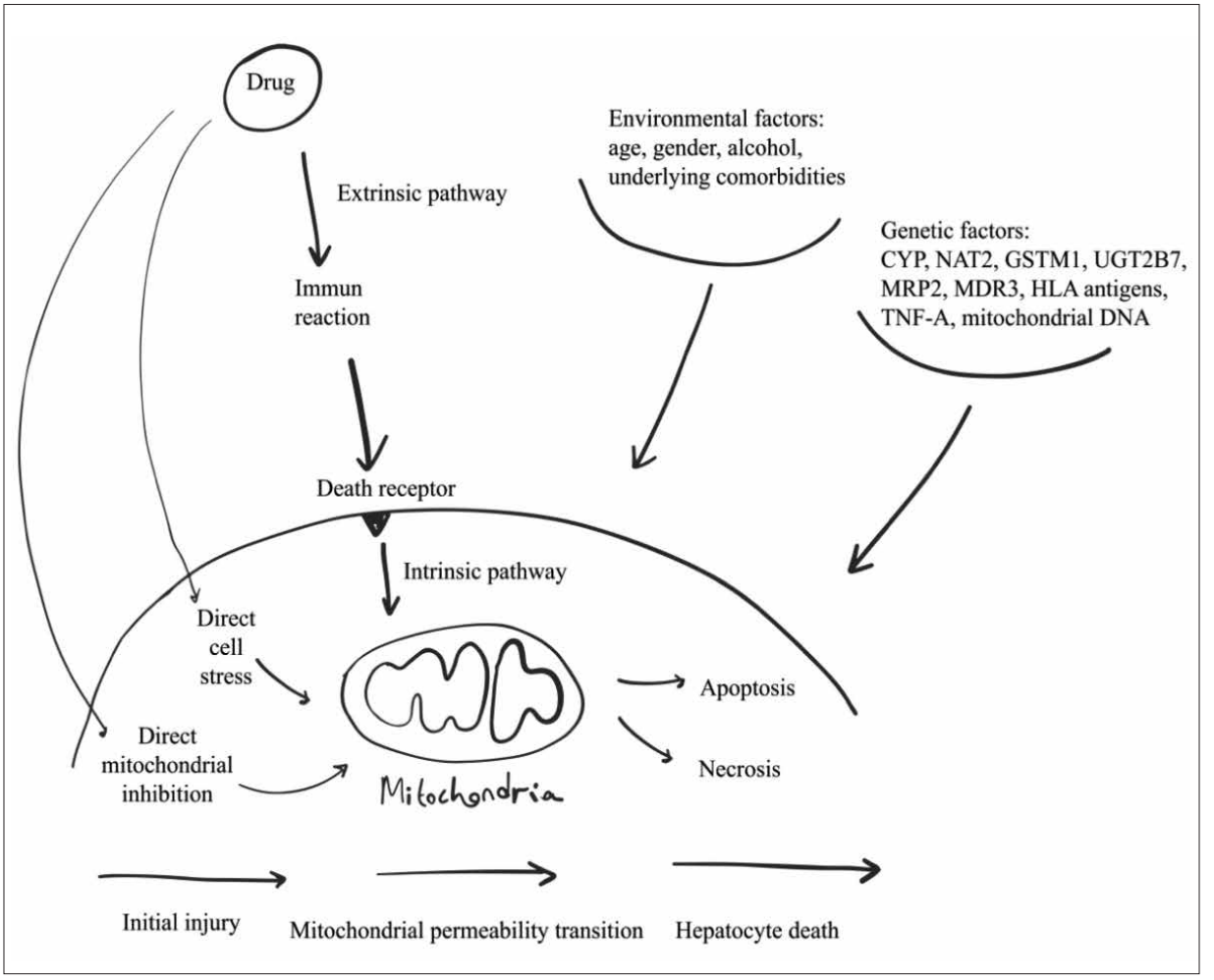

Figure 1. Three possible ways in the development of DILI (The figure was modified by Suk and Kim 2012)

21.8, and 24.8% of cases, respectively. There was no significant difference between age groups (Suk and Kim 2012).

Gender: Pubertal development, sex hormones, pregnancy and growth hormone levels also affects drug metabolizing enzymes. In males CYP3A4, one of the main drug metabolizing enzymes, has a higher expression rate related to clearance ,of acetaminophen in comparison with females (Chen et al. 2015). In a retrospective study of the United Network for Organ Sharing (UNOS) conducted in 1990-2002 by Russo et al. (2004), it was reported 270 patients with liver transplantation possessed drug-induced liver injury, and it was observed 76% of recipients were female (Hussaini and Farrington 2014). The DILIN network reported that the incidence in women of drug-induced liver injury was 65%, significantly greater than a rate of 35% in men (Chalasani et al. 2008). An another liver injury model showed that severe hepatitis and antibody production in females are more than in males with the higher level of pro-inflammatory hepatic cytokines. In halothane-induced liver injury, estrogens reduced liver injury in mice while progesterone aggravated the damage possibly by inducing inflammation and immune response (Chen et al. 2015).

Genetics: There is limited research about the issue in literature. However, genetics could be an important factor in the susceptibility to liver injury. Some drug metabolizing genes coding for CYPs, N-acetyltransferase (NAT), glutathione-S-transferase (GST) have been associated with racial differences in liver injury caused by anti-tuberculosis, non-steroidal anti-inflammation and antibacterial drugs. Patients with variations in these genes have an increased risk of developing liver injury (Stepan et al. 2011; Chen et al. 2015). CYP2E1*1A variant has been associated with the generation of a toxic metabolite of anti-tuberculosis drugs, also improving of reactive oxygen species. CYP2C8 has been related with liver injury following the generation of toxic metabolites of diclofenac (Njoku 2014). For diclofenac, several possible reactive intermediates have been postulated, including the 2,5- and 2,4′-quinone imines and both the parent and 4′-hydroxy-diclofenac acyl-glucuronides. This metabolites may result from combined metabolism involving CYP2C8 and uridine-5′-diphosphate glucuronosyl tranferase (UGT) 2B7, and, in fact, the CYP2C8*4 and UGT2B7*2 variants were found to be associated with diclofenac induced liver injury (Stepan et al. 2011; Njoku 2014). Isoniazid has two reactive metabolites, which are acetylhydrazine and hydrazine. The metabolites are known to be hepatotoxic and metabolized by NAT-2. In addition to detoxification by NAT-2, GST has a key role in neutralization of reactive oxygen species and in detoxification of reactive metabolites from isoniazid (Njoku 2014).

It was found out that human leukocyte antigen (HLA) variants are related with each other on the subject of hepatoxicity. The relation between the mechanism of liver injury and HLA is still unclear. Genome-Wide Association (GWA) studies have assembled a wide variety of genetic markers in the major histocompatibility complex (MHC) region. The strongest associations have been found with especially HLA class I and II genes. However, there is no found direct evidence. So, the gene products are causal although the main drug or metabolite either might interact direct with specific HLA class I or II proteins in an antigen presentation reaction to T cells or might produce a covalent complex with intracellular proteins (Daly 2012). It was declared person with HLA-DRB1*1501-DRB5,*0101-DQB1*0602 haplotype had almost more than 10 times risk in developing hepatotoxicity following amoxicillin clavulanate with GWAS (Njoku 2014). The whole HLA association for lumiracoxib-related liver injury was less strong than that for flucloxacillin-related liver injury. Clinicians should avoid typing the prescription including lumiracoxib to the 34% of Europeans positive to a HLA allele (DQA1*0102) in linkage disequilibrium with DRB1*1501 (Daly 2012). HLA-DRB1*1501-DQB1*0602-DQA1*0102 haplotype have been detected for both amoxicillin-clavulanate and lumiracoxib-related liver injury. The association between HLA-B*5701 and flucloxacillin related liver injury is observed in abacavir-induced hypersensitivity reactions that ordinarily have not affect on the liver, but the positive predictive value for HLA-B*5701 in abacavir hypersensitivity is substantially higher than that for flucloxacillin-related liver injury (Daly 2012).

Pre-existing Liver Disease: The presence of fatty liver disease or chronic viral hepatitis might increase the risk of chemical-induced liver injury. Compared to a normal liver, the fatty liver is more susceptible to oxidative stress, endotoxin, cytokine-mediated injury and ischemia (Hussaini and Farrington 2014). Immune renewal from human immunodeficiency virus (HIV) treatment might aggravate the liver injury of pre-existing hepatitis C virus (HCV) viral hepatitis causing immune mediated liver injury (Kramer et al. 2005). Alternatively, the mitochondrial toxicity associated with antiretroviral therapy can produce hepatic steatosis, which raise fulminant hepatic failure (Spengler et al. 2002). Furthermore, HCV may increase mitochondrial toxicity by impairing mitochondrial DNA (mtDNA) (Spengler et al. 2002).

Oxidative and Mitochondrial Damage: Oxidative stress could be occurred following drug metabolism or directly be generated in mitochondria subsequently leading to inflammatory cell response by damage hepatocytes, which cause oxidative damage in the liver. When drugs taken, disable respiratory-chain enzymes or DNA, oxidative stress results with subsequent anaerobic metabolism, lactic acidosis, and triglyceride accumulation (Lee, 2003). Cellular and mitochondrial damage could induce activation of diverse signal transduction pathways regulating cell death and survival. The c-Jun kinase (JNK) signalling pathway is a significant cellular stress component leading activation to cell death. JNK triggers mitochondrial permeability transition and releasing of apoptotic factors such as cytochrome c (*e.g.,* acetaminophen hepatotoxicity). In animal models, it was observed that glutathione depletion and covalent binding of NAPQI were insufficient to cause hepatocyte death with hepatotoxic doses of acetaminophen, but JNK was required to actively induce programmed necrosis (Garcie-Cortes et al. 2014).

In the pathogenesis of liver injury, one of the critical underlying factors is mitochondrial dysfunction, which generates alteration of metabolic pathways and mitochondrial damage

(Jaeschke et al. 2012). Drugs (*e.g.*,stavudine and amiodarone) could produce steatosis/steatohepatitis by seriously chancing mitochondrial function (Boelsterli and Lim, 2007). Mitochondrial injury could initiate necrosis and/or apoptosis in liver, leading to activation of cell death signalling pathways, which is exceeded in the mitochondrial death threshold (Han et al. 2013). Age-related regression of mitochondrial function might also hazard energy provide for cellular metabolism and tissue renewal (Chen et al. 2015).

In particular, drugs could damage mitochondrial respiration and/or β-oxidation leading to mitochondrial membrane degradation, which affects mtDNA (Chen et al. 2015). On the other hand, mitochondrial aging, partially due to accumulated oxidative DNA damage, might be affected by host factors including over-nutrition (*e.g.,* obesity, insulin resistance) and alcohol consumption (Stewart et al. 2010).

Social Factors: Alcohol and high fat diets could induce CYP2E1 and CYP4A. Alcohol induces CYP2E1 associated with an enhanced risk of acetaminophen-induced liver injury (Chen et al. 2015). Factors, lowering glutathione stores such as fasting, malnutrition and AIDS, could have an influence on the susceptibility to drug reactions (Korth 2014).

Drugs causing liver injury

Recently, some studies indicate that macrophages could have an important role in solving the liver injury. Chemokines act locally joint with cytokines and cells as idiosyncratic liver injury (Njoku 2014). Alternatively activated macrophages reduce inflammation, and stimulate hepatic regeneration and repair. And, activated macrophages simulated by interleukins (IL-10, IL-4) or tumour growth factors (TGF-β). Additionally, prior studies demonstrated that stem cell-derived tyrosine kinase receptor signalling on macrophages might down regulate inflammation through alternative activation of macrophages (Njoku 2014). In the mechanisms, IL-4 can organize immune responses to diclofenac metabolites that results in diclofenac hepatotoxicity, while IL-6 and IL-10 appease anti-inflammatory responses that may inhibit hepatotoxicity induced diclofenac (Njoku 2014).

The bile salt export pump (BSEP) is a selective bile salts transporter. Certain drugs can block BSEP activity even though BSEP is not directly involved in drug transport. Enhanced hepatocyte exposure to toxic bile salts due to drug-mediated BSEP inhibition raises the risk of idiosyncratic liver injury (Garcia-Cortes et al. 2011).

Drugs affecting transport proteins located at the canalicular membrane could cease bile flow. Specific drugs bind to or disable the bile salt export protein, which causes cholestasis. However, this is little cell injury (Lee 2003). An inhibition of BSEP function causes the accumulation of cytotoxic bile acids in hepatocytes, which induce oxidative stress and/or apoptosis and necrosis by FAS-mediated pathways. Aleo et al. (2014) showed that drugs carrying an important liver injury risk affect both BSEP and mitochondrial activities. Mitochondrial dysfunction could result in decayed ATP production, and in encountering with BSEP inhibition, and the issue might explain the synergistic connection between mitochondria and ATP-dependent transporters such as BSEP in liver injury (Wu et al. 2011). Multidrug resistance protein (MRP) family, one of hepatobiliary transporters, are also involved in the releasing of conjugated organic anions, bilirubin and drug metabolites (Köck et al. 2014). MRP2/3/4 inhibition could increase the risk in liver injury as compared with BSEP inhibition alone (Köck et al. 2014). As it is well known, bile acids salts are anionic detergents and highly toxic to the cells. In bile, mixed micelle formation with cholesterol, phospholipids, bile pigments, proteins, and inorganic electrolytes protects cholangiocytes from the toxic detergent effect of bile acid salts. Dysfunction of MDR3/ABCB4 has been associated with cholestasis, presumably via inhibition of micelle formation, releasing free bile acids salts in bile (Vree et al. 1998; Chen et al. 2015).

Amoxicillin-clavulanate is the most commonly mentioned medications in liver injury. Also, azathioprine and infliximab are shown to be associated with the highest risk of liver injury (Björnsson and Hoofnagle 2016). In the most studies in DILIN project, antimicrobials, containing antibacterial agents and antituberculosis agents, were approximately 46% of all cases with liver injury (Fontana et al. 2009).

HERBALS AND DIETARY SUPPLEMENTS CAUSING LIVER INJURY

Herbal supplements used for curing disease exist as both raw and commercial preparations. Raw herbal supplements are more frequently used in less developed countries. They are sometimes formulated as a mixture (*i.e.* Chinese herbal medicine), where frequently all ingredients are not known and may include unhealthy contaminants, such as heavy metals, and pesticides. Herbal supplements such as tablets or capsules are mostly used in developed countries. They frequently change in ingredients and concentration of chemical constituents from batch to-batch and also come from different producers (Bunchorntavakul and Reddy 2013).

Some factors increasing use of herbal products such as safety, validity, availability (Abdualmjid and Sergi 2013). Patients with herb-induced liver injury usually have a good prognosis, but acute liver failure with a lethal outcome or the requirement for a liver transplant rarely may occur (Teschke et al. 2013). Some pyrrolizidine alkaloids containing plants such as *Crotalaria*, *Ilexparaguarensis*, *Symphytum*, *Senecio*, *Heliotropium* and *Compositae species* can cause herb-induced liver injury (Teschke and Eickhoff 2015). The pathogenesis of pyrrolizidine alkaloid induced hepatotoxicity has been elucidated in experimental studies, which showed the involvement of CYPs in the activation of pyrrolizidine alkaloids (Larrey and Faure 2011). In a report related with alkaloid poisoning in Afghanistan, more than 2000 people, in which alkaloids were ingested as medicinal herbs or as weed contaminants within cereal grains, have seen liver injury (Korth 2014). Kava is a perennial plant, indigenous to the South Pacific Islands, most frequently used in Western countries as an herbal medicine for the remedy of anxiety and insomnia. In 2005, 55 case reports of kava associated liver injury had been collected by World Health Organization (WHO) (Korth

2014). *Teucrium chamaedrys L.*, known as wall germander, is a small herbaceous, perennial and aromatic plant (Abdualmjid and Sergi 2013). Germander have been used for thousands of years for various disorders, such as dyspepsia, hypertension, gout, diabetes and obesity (Bunchorntavakul and Reddy 2013). Germander includes various ingredients such as saponins and flavonoids. Furan including diterpenoids is well-known to be cytotoxic and carcinogenic. In the studies, the constituents are reported as oxidant via CYP3A4 to reactive metabolites binding to proteins, which deplete cellular glutathione and protein thiols, and ultimately stimulate membrane disruption and hepatocyte apoptosis (Bunchorntavakul and Reddy 2013; Korth 2014; Larrey et al. 1992; Larrey and Faure 2011).

Herbals and dietary products may cause liver injury and are consumed by nearly half of the population in United State and represent excessive amount of trade in worldwide (Navarro and Lucena 2014). Herbalife products (Los Angeles, CA, USA) are distributed via online marketing and through independent sale agents. They are in the form of drinks, tablets, capsules and energy bars for weight control, cosmetics, nutritional support and improvement in well-being. Since 2007, more than 34 cases were reported of herbal life hepatotoxicity from different countries. Hydroxycut is a popular dietary supplement claimed to increase weight loss. Hydroxycut Hard Core include also White Willow extract and Yohimbine (Dara et al. 2008). Several cases were reported of hydroxycut products liver injury. In May 2009, Food and Drug Administration (FDA) issued a warning to stop using hydroxycut products and recalled its products by the manufacturer (Bunchorntavakul and Reddy 2013). Lipokinetix is as dietary supplement for weight loss. Also, lipokinetix marketed by Syntrax Innovations. The supplement includes norephedrine, caffeine, yohimbine, diiodothyronine, and sodium usniate. FDA is warning consumers to immediately stop use of the product lipokinetix. FDA has received multiple reports of persons who developed hepatotoxicity while using lipokinetix (Federal Register 2012). Usnic acid used as a component in weight-loss products. Usnic acid is known to uncouple membrane potential, and stimulates oxidative stress and cell injury. Hepatotoxic cases, resulting in liver transplantation, led to elimination of some usnic acid containing products from the market (Navarro and Lucena 2014). Products provided as mixtures may be particularly dangerous because all components may not be known (Korth 2014).

Nutritional insufficiencies cause epigenetic alterations, which possibly change individual susceptibility in liver injury. Insufficiencies of folic acids, vitamin B_{12}, and choline stimulate methyl donor depletion, which contributes to hypomethylation in the genes in cellular metabolism and hepatocyte differentiation (Chen et al. 2015). Hepatotoxicity resulting from androgenic anabolic steroids causes the typical cholestatic hepatitis. Many reports of products used for body-building and muscle enhancement as a suspected cause for hepatotoxicity have been published (Navarro and Lucena 2014). Vitamin A, cause dose-dependent hepatotoxicity, the spectrum of hepatotoxicity can range from mild liver test elevations with steatosis, to necrosis. Injury usually occurs after exceeding 50,000 IU/day (Navarro and Lucena 2014).

Previous studies show that drugs cause injuries in liver seriously. For that reason some approved drugs were withdrawn. On the other hand some herbal products, which ingredients may not be known, can be particularly dangerous. High and good quality of scientific studies is needed to understand herbal drug-induced hepatotoxicity. The adverse effects of herbs, herbal drugs and herbal supplements should be fully reported to reduce the adverse effects of herbs and herbal products. In this review we compiled that etiologies and risk factors of liver injury, drugs and herbals cause DILI.

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Review

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Check-list of additional taxa to the supplement flora of Turkey VIII

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ABSTRACT

The eighth check-list of the series entitled "Check-list of Additional taxa to the Flora of Turkey" comprises a total of 152 taxa based on the data given in 133 papers published the period between December 2014-December 2016. Additionally taxa which have not been recorded neither in the 11 volumes of the Flora of Turkey nor in the seven previously published supplementary check-lists. With this paper the following are added to the Turkish flora: 127 taxa new to science and 25 taxa new records.

Keywords: Additional taxa, Turkish flora, new species, new records

INTRODUCTION

Turkey is one of the most important temperature countries on earth in terms of plant diversity. The diversity of vascular plants of the country has been documented in the Flora of Turkey and the Eastern Aegean Islands edited by Prof. Peter H. Davis and published in nine volumes between 1965 and 1985. With the publication of this flora, so interest in Turkey's rich plant diversity has been brought to the attention of Turkish and foreign botanists, and subsequent study has greatly increased our knowledge of the flora resulting in the addition of many new taxa.

The identification of these additional taxa has necessitated the publication of the supplementary volumes to the Flora of Turkey vol. 10 in 1988 (Davis et al. 1988) with the eleventh supplemental volume in 2000 (Güner et al. 2000). The flora of Turkey continues to grow following publication of the 11th volume, and an additional 1196 new species were added either as a new species or new records in the periods up to December 2016. These check list have been published in a series paper by Özhatay et al. as Check list III, IV, V, VI VII and VIII (Özhatay and Kültür, 2006; Özhatay et al. 2009; 2011; 2013; 2015).

Since 2000 (vol. 11) 853 papers about the flora of Turkey have been published and 1196 additional taxa have been recorded which were either new to science (888 taxa) or new to the Turkish flora (308 taxa). According to these data almost 74 taxa is added to the Turkish flora for each year. The all original publication of these taxa was subsequently drawn together by the authors as a collection housed in the library of the Department of Pharmaceutical Botany, Istanbul University. The aim of this paper is to present all published taxa added to the flora of Turkey during 2015 to 2017 with the missing records (14 papers with 24 taxa) in earlier check-lists. Since 1994 have been published eight check-list of additional taxa to the Turkish flora respectively (Table 1).

The present list contains a total of 152 taxa, of which 127 taxa were added as new taxa to science (comprising 110 species, 12 subspecies, 3 varieties and 2 hybrid), whilst a further 25 known taxa have previously been unrecorded from Turkey (21 species, 2 subspecies and 2 hybrid). The genus *Psylliostachys* (Jaub. & Spach) Nevski (Plumbaginaceae) is new for Turkish flora. The four genera which have been recorded with the most taxa to the flora of Turkey are *Centaurea* (with 13 taxa), *Crocus* (with 8 taxa), *Sanguisorba* (with 7 taxa) and *Allium* (with 6 taxa) respectively (Figure 2).

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Table 1. Statistical table of summary data of additional taxa for the checklists (N: new taxa for science, R: new record for Turkey. N: 1121, R: 405, Total: 1526)

	Check-list I (1994)		Check-list II (1999)		Check-list III (2006)		Check-list IV (2009)		Check-list V (2011)		Check-list VI (2013)		Check-list VII (2015)		Check-list VIII	
	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Sp.	96	36	77	42	154	75	85	40	158	53	141	32	76	19	110	21
Subsp	16	8	26	4	12	16	23	13	20	4	29	5	1	2	12	2
Var.	11	2	5	4	15	13	9	1	9	3	8	4	-	-	3	-
Hyb.	1	-	1	1	8	2	3	-	1	-	8	1	1		2	2
Total	124	46	109	51	189	106	120	54	188	60	186	42	78	21	127	25

Vol. 11 (2000) based on Check-list I & II

Güner et al. (2012)

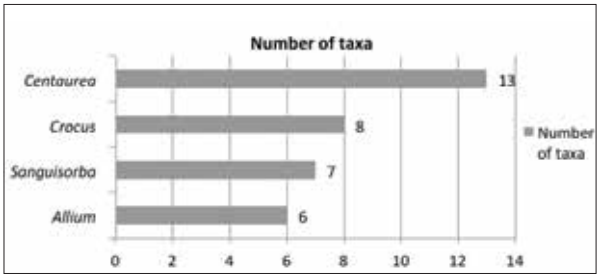

Figure 1. The four genera which have been recorded with the most taxa in Check-list VIII

The list of additional taxa

The list of the additional taxa is arranged in alphabetical order within families, genera, and species under two main systematic groups: Dicotyledonae and Monocotyledonae. The format is in accordance with that in Davis' Flora of Turkey and references to original papers appear in angled brackets at the end of the taxon name. It is hoped that this list will provide useful information for researchers currently working on the Turkish flora. We have endeavoured to trace all additional taxa to the flora published until December 2016. Although we are certain that further taxa remain unreported either in Davis Flora of Turkey or in our supplementary check-lists, then accordingly we invite all additions or comments for future issues in the series.

e: endemic species; *new record for Turkish flora; **new taxon for science; ■ new genus for Turkish flora

DICOTYLEDONES

AMARANTHACEAE

Amaranthus L. (2:340)

A. palmeri S. Watson in Proc. Amer. Acad. Arts 12: 274 (1877) [Eren et al. 2016]

Examined specimens: Turkey. İzmir: İzmir-Çanakkale main road, between Menemen and Yeni Foça, Helvacı village, 16 m, margin of cornfields, populations with male and female plants, 20 Sep 2015, Doğan 23/2015 & al. [pistillate specimen] (AYDN); ibid., 20 Sep 2015, Doğan 24/2015 & al. [staminate specimen] (AYDN); ibid., Buruncuk village, 13 m, roadsides, 20 Sep 2015, Doğan & al. (obs.); Adana: Ceyhan, Mustafabeyli village, 25 m, 22 Jul 2014, Doğan 36/2014 & al. [pistillate specimen] (AYDN); ibid., 22 Jul 2014, Doğan 37/2014 & al. [staminate specimen] (AYDN); Osmaniye: Toprakkale, 120 m, roadside, 23 Jul 2014, Doğan & al. (obs.); Hatay: Erzin, 160 m, field margins, 19 Aug 2014, Doğan & al. (obs.).

Atriplex L. (2:305)

A. oblongifolia Waldst. & Kit., Descr. Icon. Pl. Rar. Hung. 3: 278 (1812). [Başköse and Yaprak 2016]

Examined specimens: Turkey. A1 Kırklareli: Pınarhisar, Pınarhisar-Demirkoy yolu, Poyralı köyü çıkışı, tarla ve yol kenarları, 225 m, 02.10.2013, K 041°37.775' - D 026°35.893', Başköse-2325; Pınarhisar, Pınarhisar'a 5 km kala yol ve tarla kenarları, 150 m, 09.09.2014, K 041°36.268'-D 027°27.396' Başköse-2672; Pınarhisar, Pınarhisar-Demirkoy yolu, Poyralı köyü çıkışı, tarla ve yol kenarları, 225 m, 09.09.2014, K 041°37.775'-D 026°35.893', Başköse-2673; Pınarhisar, Hamzabey köyü girişi, tarla ve yol kenarları, 115 m, 22.08.2015, K 041°31' 33.40"-D 027°55'13.34", Başköse-2929; Pınarhisar, Ceylanköy girişi, tarla ve yol kenarları, 120 m, 22.08.2015, K 041°32'49.61"-D 027°25'54.76", Başköse-2930; A1 Edirne: Sarayakpınar, Suakacağı köyü, Tunca nehri kenarları, 55 m, 10.09.2014, K 041°50.659'-D 026°35.110', Başköse-2687.

APOCYNACEAE

Vinca L. (6:161)

e**V. ispartensis*** Koyuncu & Ekşi in Ann Bot. Fennici 52: 340-344 (2015). [Koyuncu et al. 2015]

Holotype: Turkey**.** Isparta: Şarkikarağaç, Kızıldağ Milli Parkı, stony slopes, 1300-1700 m a.s.l., 28 April 2013 (flowering), Kadir Terzioğlu & Faruk Canız (AEF 26342).

BORAGINACEAE

Cynoglossum L. (6:306)

e***C. brandii* Sutorý in Edinburgh Journal of Botany 73 (3): 265–275 (2016). [Sutorý 2016]

Type: Turkey. Antalya province, on the road between Anamur and Ermenek, in the summit region of mountains, 36°17′15″N, 32°54′33″W, 1700 m, 23 vi 1977, K. Sutorý s.n. (BRNM 707463) (holo BRNM; iso B, BRNM, E, K, W).

Onosma L. (6:326)

e***O. anatolica* Binzet in PhytoKeys 69: 39–49 (2016). [Binzet 2016b]

Type: Turkey, C5 Niğde: Çamardı, 2 km South of Demirkazık village, subalpine community with dwarf shrub and thorn-cushion, 1760 m, limestone, 22 June 2015, 37°50′47″N, 35°05′32″E, Binzet 201501 (holotype: ANK; isotype: GAZI).

e***O. demirizii* Kaynak, Tarımcılar & Yılmaz in Bangladesh J. Bot. 44(2): 261-265 (2015) [Tarımcılar et al. 2015]

Type: Turkey. B6 Kayseri: Pınarbaşı, 38°43´N, 36°23´E, 1540 m, 24.v.2013, G. Kaynak, Ö. Yılmaz s.n. (BULU 35011).

e***O. juliae* L.Cecchi & Selvi in Phytotaxa 288 (3): 201–213 (2016). [Cecchi et al. 2016]

Type: Turkey. Karaman: Ermenek district, 5 km from Ermenek to Anamur, garrigue on calcareous rocks ["Turchia, Karaman, distretto di Ermenek, 5 km da Ermenek verso Anamur, gariga e rocce calcaree assolate"], 1200 m ca., 36°37′ N, 32°55′ E, 4 June 2013, L. Cecchi, M. Nepi, D. Nocentini & F. Selvi, no. 13.37 (holotype FI, isotypes GZU and Herb. Cecchi no. 2500).

e***O. malatyana* Binzet in Turk J Bot 40: 194-200 (2016). [Binzet 2016a]

Type: Turkey. B7 Malatya: Arapgir-Malatya, 19 km to Malatya, roadside and field area, 31.V.2011, 38°53′44″N, 38°35′26″E, 1275 m, Binzet 201117 (holotype: ANK; isotype: GAZI).

Paracaryum (DC.) Boiss. (6:282)

e** ***P. bingoelianum*** Behçet & İlçim in Turk J Bot 39: 334-340, (2015). [Behçet and İlçim 2015]

Type: Turkey. B8 Bingöl: SE of Genç, Şamdağı, NW rocky slopes, 1950–2000 m. 11.vii.2012, L. Behçet 8606 (in flower) (Holotype: Mustafa Kemal Univ. Herb. Isotypes: ANK, Bingöl Univ. Herb.)

BRASSICACEAE

Alyssum L. (1:362)

e***A. amasianum* Karabacak & A.Duran in Turk J Bot 40: 402-411 (2016). [Karabacak et al. 2016]

Type: Turkey. A5 Amasya: Taşova, Borabay village to Başyurt Yayla, 9 km, 1382 m, serpentine slopes, roadsides, 16.08.2013, 40°48′011″N 36°07′005″E, A.Duran 9733 & O.Karabacak (holotype: KNYA; isotypes: GAZI, ANK).

CAMPANULACEAE

Campanula L. (6:2)

e***C. malatyaensis* Mutlu & Karakuş in Phytotaxa 234 (3): 287–293 (2015) [Mutlu and Karakuş 2015a]

Type: Turkey. Malatya: Hekimhan, Zürbehan Hill, 2000 m, 30 vi 2012, Ş.Karakuş 2476 & B.Mutlu (holotype INU (INU 12528-2013)).

******C. raddeana* Trautv. in Bull. Acad. Imp. Sci. Saint-Pétersbourg, sér. 3, 10: 395 (1866) [Yıldırım et al. 2016]

Examined specimens: Turkey. A9 Ardahan: Çıldır, on the way from Çıldır lake to Mazeret pass, Karaçay valley, on volcanic rock cliffs, 41°09′39″N, 43°08′19.2″E, 2100 m, 24.07.2014, H.Yıldırım 3125 (EGE); Çıldır, Karaçay valley, near Şeytan castle, on volcanic rock cracks, 41°08′45.45″N, 43°07′45.05″E, 1941 m, 10.09.2015, H.Yıldırım 3699

CAPRIFOLIACEAE

Cephalaria Schrader ex Roemer & Schultes (4:585)

e***C. anamurensis* Göktürk & Sümbül in PhytoKeys 65: 25–33 (2016). [Göktürk and Sümbül 2016]

Type: Turkey. Mersin: Anamur, Anamur to Kazancı, Kırkkuyu, Bıçkıcı boğazı, 36°28′35″N; 032°44′11″E, 1784 m, steppe and stony places, 24 July 2015 Göktürk 8018, Sümbül & Çıngay (holotype: Akdeniz University Herbarium 3446; isotypes: ANK, GAZI, HUB, NGBB).

CARYOPHYLLACEAE

Bolanthus (Ser.) Reichb. (2:171)

e***B. turcicus* Koç & Hamzaoğlu in PhytoKeys 52: 81-88 (2015). [Koç and Hamzaoğlu 2015]

Type: Turkey. Aksaray province, Hasan Mountain above Karkın town, Hamcaoğlu 7110 and Koç (holo GAZI, iso GAZI, ANK, Dept of Bozok Univ., Herbarium of Biology), 1950 m, volcanic stony slopes and alpine steppe, 18 June 2014.

Dianthus L. (2:99)

e***D. aticii* Hamzaoğlu in PhytoKeys 48: 21–28 (2015) [Hamzaoğlu et al. 2015]

Type: Turkey. Bilecik: Bilecik highway exit towards Eskişehir, 40°06′27″N, 29°59′47′E, 330 m, stony slopes and steppes, 16 June 2013 (fl , fr), E. Hamzaoğlu et al. 6743 (holotype: GAZI; isotypes: GAZI, ANK)

e***D. burdurensis* Hamzaoğlu & Koç in Phytotaxa 233 (2): 196-200 (2015). [Hamzaoğlu and Koç 2015]

Type: Turkey. Burdur: Between Yeşilova and Salda village, N slopes of Eşeler Mountain, small dry meadows in forest clearings, 37°29′08″N, 29°39′09″E, 1590 m a.s.l., 23 August 2014, Koç & Hamzaoğlu 7170 (holotype GAZI, isotypes GAZI, ANK, HUB).

e***D. macroflorus* Hamzaoğlu in Systematic Botany 40(1): 208-213 (2015). [Hamzaoğlu et al. 2015]

Type: Turkey. Antalya: Manavgat, between Taşağıl and Beşkonak, 65 m, macchie, 28 jul 2012, Hamzaoğlu 6545, Aksoy & M. Koç (holotype: GAZI, isotypes: GAZI, ANK, HUB).

e***D. multiflorus* Deniz & Aykurt in PhytoKeys 63: 1–12 (2016). [Deniz et al. 2016]

Type: Turkey. Antalya: Gazipaşa, from Akoluk Village to Akkaya Hill of Taşeli Plateau, c. 3. km, stony sliding slopes and serpentine soils in clearings of *Pinus brutia* forest, 1075 m a.s.l., 05 July 2015, İ.G. Deniz, C. Aykurt, 6195 (holotype: Akdeniz University Herbarium 3823).

******D. purpureoluteus* Velen., Fl. Bulg. 72 (1891). [Hamzaoğlu et al. 2015]

Examined specimens: Turkey. Kırklareli: between villages of Kofçaz and Kocayazı, 685 m, 7 Aug. 2012, *Quercus* forest opening, Hamzaoğlu 6593, Aksoy & M Koç (GAZI); between Kırklareli and Kofçaz, seventh km, 5 Nov 1975, A. Baytop & N. Özhatay s.n.(ISTE 34061)

Eremogone Fenzl

e***E. ali-gulii* Koç & Hamzaoğlu, in PhytoKeys 61: 93–99 (2016). [Koç and Hamzaoğlu 2016]

Type: Turkey. Erzurum province, between Bayburt and Aşkale, Kop mountain, 40°00'N-040°32'E, 2150 m, serpentine stony slopes, 24 June 2014, Koç 1723 & Hamzaoğlu (holotype ANK, isotype Bozok Univ. Herb., ANK, GAZI).

Gypsophila L. (2:149)

e***G. munzurensis* Armağan in Phytotaxa 275(2): 175-180 (2016). [Armağan, 2016]

Type: Turkey. Tunceli: Ovacık, Munzur Valley, 30. Km from Tunceli to Ovacık, oak forest openings and eroded slopes, 39°17'01.1"N, 39°26'10.2"E, 1080 m, 24 July 2014, Armağan & Özel 5645 (holotype VANF-165058, isotype W).

Silene L. (2:179)

e***S. bilgilii* E. Doğan & H. Duman in Phytotaxa 246 (4): 293–299 (2016). [Doğan-Güner and Duman 2016]

Type: Turkey. Balıkesir: Bigadiç, South of Bozbük village, 1280 m, on the metamorphic rocks, 35 S 632832 E, 4356941 N, 29 July 2015, Duman & Çakır 10385 (holotype GAZI, isotype AN K).

e***S. ertekinii* Aydın & Oxelman in Phytotaxa 178(2): 98-112 (2014). [Aydın et al. 2014]

Type: Turkey. Antalya: Road from Antalya to Altınyaka, 1160 m a.s.l., 36 74 N, 30.45 E, 13 May 2009, Aydın 28 (holotype: GB-0128343, isotypes: DUF, ANK).

e***S. kemahensis* Aytaç & Kandemir in Bağbahçe Bilim Dergisi 32(1): 7-42 (2015). [Aytaç et al. 2015]

Type: Turkey. Erzincan: Kemah, Yücebelen köyü, Sohmarik Yayla yolu, serpantin, 1816 m,01.07.2014, Kandemir 10566, (holotip/holotype: GAZI; isotip/isotype: ANK).

e***S. konuralpii* Fırat & K.Yıldız in Phytotaxa 288 (3): 214-236 (2016). [Fırat and Yıldız 2016a]

Type: Turkey. B9 Ağrı: Eleşkirt district, Heyrangol village, humid slopes steppe, 2396 m, 39°45'29"N, 42°24'00"E, 15.vi.2016, Fırat 32740 (holotype VANF; isotypes ANK, E, herb. M.Fırat, herb. Manisa Celal Bayar University)

e***S. miksensis* Fırat & K. Yıldız in Phytotaxa 273(4): 283-292 (2016). [Fırat and Yıldız 2016b]

Type: Turkey. B9 Van: Miks (Bahçesaray) district, Çıravis Mountains (Çiyayê Çirawîs), limestone and rocky slopes, 3343 m,38°09 ' 44" N, 42°54'04" E, 10 August 2011, Fırat 27345 (holotype VANF, isotypes ANK, E, herb. M. Fırat).

COMPOSITAE

Achillea L. (5:224)

e***A. adenii* Aytaç & M.Ekici in Turk J Bot 40: 373-379 (2016). [Aytaç et al. 2016]

Type: Turkey. C2 Muğla, Fethiye, Babadağ, calcareous rocks, 1600–1650 m, 23.07.2011, Aytaç 10429 & M. Ekici (holotype: GAZI; isotypes: ANK, HUB, and Yıldırımlı).

e***A. baltai* H.Duman & Aytaç in Turk J Bot 40: 373-379 (2016). [Aytaç et al. 2016]

Type: Turkey. C6 Niğde: Pozantı Dağı, Sivri tepe, 2050–2100 m, 08.06.2013, calcareous rocks, Duman 10321 & T. Balta, holotype: GAZI; isotypes: ANK, HUB, Yıldırımlı.

Artemisia L. (5:311)

**e *****A. bashkalensis* Kurşat & Civelek in Turk J Bot 88-95 (2015). [Kurşat et al. 2015]

Type: Turkey. C10 Hakkâri: 58 km from Hakkâri to Van, roadside, slopes, steppe, 20.09.2007, 1805 m, 37°47.817'N, 44°05.156'E, M. Kurşat & Ş. Civelek 1057 (FUH).

******A. fragrans* Willd. in Sp. Pl. 3 (1804) 1835 [Kürşat et al. 2014]

Examined specimens: Turkey. B9 Van: Kuzgun gate, peak, 2142 m, 19.9.2007, Ş. Civelek, M. Kürşat 1049, ibid, 9.1.2010, Ş. Civelek, M. Kürşat & P. Yılmaz 5001 and (FUH); Van Kuzgun Koran gate, 1 km landing, 2161 m, 26.11.2010, Ş. Civelek, M. Kürşat & P. Yılmaz 5011; Van, Akdamar between Gürpınar and Bahçesaray, 1 km after the fork, crop edges, 1714 m, 9.10.2010, Ş. Civelek, M. Kürşat & P. Yılmaz 5012 (FUH); Van-Muradiye, waterfall role, 1778 m, 10.10.2010, Ş. Civelek, M. Kürşat & P. Yılmaz 5005 (FUH); Muş, Malazgirt-Aktuzla break, around Nurettin village, road side, hillsides, 1728 m, 26.11.2010, Ş. Civelek, M. Kürşat & P. Yılmaz; Muş, Aktuzla to 5.5 km, Ant valley, road upper slopes, 1555 m, 26.11.2010, Ş. Civelek, M. Kürşat & P. Yılmaz 5020 (FUH).

******A. oliveriana* J.Gay ex Besser, Prodr. 6:101 (1837). [Fırat 2015a]

Examined specimen: Turkey. C9 Hakkari, from Karadağ Mountains to Berçelan Plateau, step, near road, 1927 m, 37°35'464"N, 043°43'883"E, 04.x.2014, M.Fırat 31325, VANF

Centaurea L. (5:465)

e***C. amanosensis* M. Bona in Plant Biosystems 150(5): 1083-1086 (2016) [Bona 2016]

Type: Turkey. Hatay: Antakya, Amanos Mountains, between Kisecik and Hacı Ahmetli villages, 1410 m, 17.06.2014, M. Bona, ISTE 102723.

e***C. goksivriensis* M. Bona in Phytotaxa 203 (1): 063–068 (2015) [Bona 2015]

Type: Turkey. Prov. Hatay; Samandağ, Teknepinar, Musa Mountain, Göksivri Hill, 1200 m, 22.06.2014, M. Bona (holotype ISTE 102727).

e*****C. malatyensis*** Ş. Kültür & M. Bona in Phytotaxa 247 (1): 085–091 (2016). [Kültür et al. 2016]

Type: Turkey. Malatya: Doğanşehir-Eskiköy, Aşipınar area, rocky places, 1960 m, 10.07.2012, Ş. Kültür et al. (holotype: ISTE 98931).

e***C. mersinensis* Uysal & Hamzaoğlu in Biosystems (2016). [Uysal & Hamzaoğlu 2016]

Type: Turkey. C4 Mersin, Aydıncık-Yenikaş köyü üstü, *Pinus brutia* orman açıklıkları, kireçli yamaçlar, 36°08'38''N, 33°15'18''E, 520 m, 3.6.2014, Hamzaoğlu 7009 (Holotype: GAZI, isotypes; KNYA, ANK, HUB, GAZI).

e***C. nallihanense* Uysal & Hamzaoğlu in Phytotaxa 275 (2): 149–158 (2016) [Uysal et al. 2016]

Type: Turkey. B2 Ankara: Nallihan, Osmanköy–Yenice arası, Taşlı yamaçlar, Meşe açıklıkları 395 m, 40º04'39" N, 30º53'41" E, 10 July 2011, Hamzaoğlu 6120 (holotype KNYA).

e***C. raimondoi* Bancheva & Kaya in Fl. Medit. 25: 305-310 (2015) [Bancheva and Kaya 2015]

Holotype: Turkey. A3 Bolu: between the cities of Mengen and Pazarköy, on rocky places, N 40°55'25" N, E 32°8'12", 13 June 2012, coll. S. Bancheva & Z. Kaya, SOM-171075, Isotype PAL

e***C. sakariyaensis* Uysal & Dural in Plant Biosystems DOI: 10.1080/11263504.2015.1108940 (2015). [Uysal et al. 2015]

Type: Turkey. A2 Sakarya: Sakarya-Bilecik yolu, Mekece, Cambazkaya civarı, Kayalık yamaçlar, 96 m., 40" 25' 059 N, 30" 02' 045 E, 02.07.2012, T. Uysal 2763 & H. Dural (Holotip KNYA).

e***C. sennikoviana* Negaresh & Kaya in Ann Bot Fennici 52: 321-327 (2015). [Negaresh et al. 2015]

Type: Turkey. C5 Niğde: Çamardi, Nazımlı, high platean foat, (without collector) 495 (holotype ISTE, isotype HUI).

******C. sintenisiana* Gand., Bull. Soc. Bot. France 65: 37 (1918). [Pınar 2016]

Examined specimen: Turkey. C10 Hakkari: Yüksekova, 13. km from Yüksekova to Esendere, around of Dereiçi village, valley slopes, step, 2200 m, 26.08.2014, M.Pınar 5101 (VANF).

******C. verutum* L. Cent. Pl. 1:30 (1755). [Duran et al. 2014]

Examined specimens: Turkey. C6 Gaziantep: between Gaziantep-Kilis, after Gahinbey monument, 712 m, 15.05.2010, 36°52'510"N, 37° 21'020"E, M.Öztürk 1539 & A.Duran (KNYA); C6 Gaziantep: between Gaziantep-Kilis, after ġahinbey monument, 712 m, 02.06.2012, 36°52'510"N, 37° 21'020"E, A.Duran 9366, Ö.Çetin & M.Çelik (KNYA, ANK, GAZI, HUB).

e***C. ziganensis* Yüzb., M. Bona & İ. Genç in PhytoKeys 53: 27-38 (2015). [Yüzbaşıoğlu et al. 2015]

Type: Turkey. Gümüşhane: Zigana pass-Gümüşhane road, c. 5. Km, rocky places, 1450 m a.s.l., 20 Aug, 2014, S. Yüzbaşıoğlu 4117 (holotype: ISTE 104470, isotype: ANK).

Cirsium Miller (5:370)

******C.* × *prativagum* Petr. Věstn., Tiflissk. Bot. Sada 19: 22 (1911) [Yıldız et al. 2016]

(*Cirsium obvallatum* M.Bieb. × *C. pseudopersonata* Boiss. & Balansa subsp. *kusnezovianum* (Sommier& Levier) Petr.)

Examined specimen: Turkey. A9 Artvin: Şavsat, 10 km from Pınarlı village to Arsiyan hamlet, 2400 m, 02.09.2008, Dirmenci 2646 & Akçiçek (hb. Yıldız).

******C.* × *woronowii* Petr., Věstn. Tiflissk. Bot. Sada 19: 19 (1911). [Yıldız et al. 2016]

(*Cirsium hypoleucum* DC × *C. obvallatum* M.Bieb)

Examined specimen: Turkey. A9 Artvin: Şavşat, between Sahara and Karaköy, 1800 m, 20.09.2007, Yıldız 16739 & Arabacı (hb. Yıldız).

Galatella Cass. (5:122)

******G. cretica* Gand. in Fl. Cret. 59, No. 1044 (1916); et in Bull. Soc. Bot. France, 1916, ixiii. 235 (1919) [Yıldırım et al. 2016]

Examined specimens: Turkey. C1 Muğla: Marmaris, Söğüt village, on the Taşlıca road, 150 m, 07.11.2015, H.Yıldırım 3756 (EGE); Between Datça and Aktur, 1 km before Aktur, 10 m, in maquis, serpentine soil, 4.12.2014, R.Gül 2650a (EGE); Datça, on solid waste center way, in maquis, 200 m, calcareous soil, 4.12.2014, R.Gül 2651(EGE)

Gundelia L. (5:325)

e***G. vitekii* Armağan in Ann. Naturhist. Mus. Wien, B, 118: 129-134 (2016). [Armağan 2016]

Type: Turkey. Tunceli (Dersim), Tunceli Merkez, c. 8 km N of Tunceli, mountain slope NW of Tüllük Bucağı, 39°10'32"N 39°32'04"E, 1745 m s.m., 2015-05-31, E. Vitek, M. Armağan & M. Özel 15-0042 (holotype VANF, isotype W 2015-11168).

Hieracium L. (5:696)

e***H. altinozlui* Yıld. in Ot 21(1): 15-20 (2014) [Yıldırımlı 2014a]

Type: Turkey. C6 Osmaniye: Zorkun, Mitis, along stream, mixed forest, serpentinous places, 135-1400 m, 05.09.2008, Ş.Yıldırımlı 35241, H.Işıl Yıldırımlı (Holo. Hb. Yıldırımlı, iso. GAZI, HUB)

e***H. kazdaghensis* Keskin & Özyiğit in Kasmera 43(2): 12-20(2015). [Keskin et al. 2015a]

Type: Turkey. Balıkesir, Mount Ida, through the Sarıkız Peak, Yayla location, 840 m, 21.vii.2012, 39 40.580 N/26 56.646 E, M. Keskin 5833, İ.İ. Özyiğit, Z. Severoğlu (ISTE 99103).

e***H. tortumense* Gottschl. & Pils in Wulfenia 23: 52–56 (2016) [Gottschlich and Pils 2016]

Type: Turkey. Tortum, Yeşiltepe deresi (valley), between Esendurak and Alapinar, alt. ca. 1600 m.s.m, 40°19'27"N, 41°25'40"E, 8.7.2001, G.Pils 4785 (holo. KL)

Klasea Cass.

e***K. yunus-emrei* B. Dogan, Ocak & A. Duran in Plant Biosystems 149: 1010-1014 (2015). [Dogan et al. 2015]

Type: Turkey. B3 Eskişehir: Alpu, plantation area of Bozan, calcareous soils, 935 m, a.s.l., N 39 48.255, E 31 08.528, 26.05.2012, OUFE 17594 (holotype: KNYA, isotype: GAZI).

Pilosella Hill (5:747)

e***P. ilgazensis* Vladimirov, Coşkunçelebi & Kit Tan in Turk J Bot 39: 70-75 (2015). [Vladimirov et al. 2015]

Type: Turkey. A4 Cankırı: Ilgaz mountain, by tower left (west) of the pass from Ilgaz to Kastamonu, subalpine vegetation on W-exposed slope, c. 2050 m, 41°03'13"N, 33°42'49"E, 12.07.2007, K. Coşkunçelebi 659 & V. Vladimirov (holotype: KTUB; isotypes: C, KTUB, SOM (163493).

Psephellus Cass. (5:466)

e***P. vanensis* A.Duran, Behçet & B.Doga in PhytoKeys 48: 11–19, (2015). [Dogan et al. 2015]

Type: Turkey. Van: Başkale, Çaldıran village, steppe fields, 2000–2050 m a.s.l., 17 Jun 2009, Behçet & D. Avlamaz 1603 (holotype: KNYA, isotypes: GAZI, ANK, HUB, Bingöl Univ. Herb.)

Rhaponticoides Vaill.

******R. ruthenica* (Lam.) M.V.Agab & Greuter Willdenowia 33:61 (2003) [Duran et al. 2014]

Examined specimens: Turkey. B9 Ağrı: Patnos, Karakuyu village road, 1681 m, 08.08.2009, 39°20'040"N, 42°44'521"E, A.Duran 8730 & B.Doğan (KNYA); B9 Ağrı: Patnos, Beydamarlı village road, 1675 m, 19.07.2009, 39°20'656"N, 42°43'928"E, A.Duran 8619 & M.Öztürk (KNYA, ANK, GAZI, HUB).

Tanacetum L. (5:256)

e***T. erzincanense* Korkmaz, Kandemir & İlhan in Turk J Bot 39: 96-104 (2015). [Korkmaz et al. 2015]

Type: Turkey. B7 Erzincan: Çayırlı, between Mantarlı and Akyurt villages, 39°43'709"N, 40°10'118"E, 1622 m, 02.07.2012, steppe, M. Korkmaz & V. İlhan 3249 (holotype: GAZI, isotypes: NGBB, ANK).

Tragopogon L. (5:657)

e***T. turcicus* Coşkunç., M. Gultepe & Makbul in Nordic Journal of Botany 33: 540-547 (2015). [Gültepe et al. 2015]

Type: Turkey. B3/C3: Isparta: Şarkikaraağaç, Kızıldağ National Park, 1400 m, a.s.l., 14 jul 2012, Coşkunçelebi and M. Gültepe 403 (holotype: KTUB, isotypes: KTUB, RUB, ANK).

e***T. artvinensis* Makbul, M. Gultepe & Coşkunç in Nordic Journal of Botany 34: 529–537. [Gültepe et al. 2016]

Type: Turkey. A8 Artvin: Yusufeli, between Yaylalar and Körahmet, 2122 m a.s.l., 4 Aug 2010, Coşkunçelebi and M. Gültepe 155 (holotype: KTUB; isotypes: KTUB, RUB, KATO, ANK).

e***T. vanensis* M. Gultepe, Coşkunç.& Makbul in Nordic Journal of Botany 34: 529–537. [Gültepe et al. 2016]

Type: Turkey. B9 Van: between Başkale and Van, 2052 m a.s.l., Coşkunçelebi and M. Gültepe 267 (holotype: KTUB, isotypes: KTUB, RUB, KATO, ANK).

Tripleurospermum Schultz Bip. (5:295)

e***T. insularum* Inceer & Hayırlıoglu-Ayaz in in Ann. Bot. Fennici 51: 49-53 (2014) [İnceer and Hayırlıoğlu-Ayaz 2014]

Type: Turkey. Çanakkale: Gökçeada, 30 m a.s.l., 17.4.2009, İnceer 717 (holo. KTUB; iso. ANK, GAZI, E).

CRUCIFERAE

Aubrieta Adanson (1:444)

e***A. ekimii* Yüzb., Al-Shehbaz and M.A.Koch in Plant Syst Evol 301: 2043-2055 (2015). [Yüzbaşıoğlu et al. 2015]

Type: Turkey. A2(A) Kocaeli, Yuvacık, Soğuksu, Menekşe yaylası patikası, Şahin kaya, 870 m, kaya üstü, 26 May 2013, S. Yüzbaşıoğlu3861 (holotype, ISTE 99694; isotypes, ANK, NGBB).

Barbarea R.Br. (1:433)

******B. bracteosa* Guss. Fl. Sic. Prodr. 2:257 (1828) [Akkemik and Yılmaz 2016]

Examined specimen: Turkey. A2 İstanbul: Elmalı Dam Basin, 110 m asl., within open area and road sides in the forest, ISTO 36729, 36730

Hesperis L. (1:452)

e***H. tosyaensis* A. Duran in Turk J Bot 40: 87-96 (2016). [Duran and Çetin 2016]

Type: Turkey. A5 Kastamonu: between Tosya-Sekiler village, 7 km, 1000 m, under an open *Quercus* forest, 40 55. 62 N, 34

02.06 E, 12.5.2001, A. Duran 5657 & Hamzaoğlu (holotype: KNYA, isotypes: GAZI, ANK, ISTE, ISTF, E, K).

Sisymbrium L. (1:481)

e***S. malatyanum* Mutlu & Karakuş in Turk J Bot 39: 325-333 (2015). [Mutlu and Karakuş 2015b]

Type: Turkey. B7 Malatya: Akçadağ, Bayramuşağı village, İnikayası Hill, outside of cave, 1804 m, 09 v 2013, 38 20 158 N, 37 52 046 E, Ş.Karakuş 3919 (in flower) (holotype INU; isotypes INU, ANK, ISTE, HUB). 30 v 2013, Ş. Karakuş 4187 & B. Mutlu (in fruit).

EUPHORBIACEAE

Euphorbia L. (7:571)

e***E. akmanii* İ.Genç & Kültür in Phytotaxa 265(2): 112-120 (2016) [Genç and Kültür 2016]

Type: Turkey. Osmaniye: Zorkun Yaylası, Gürgen orman altı, Amanos Dağ, ca.850 m, 4.vi.1968, Y. Akman 22 (holotype ANK, isotype ISTE)

ISOETACEAE

Isoetes L. (1:37)

e***I. vanensis* Keskin & G.Zare in Phytotaxa 269(4): 294–300 (2016) [Zare et al. 2016]

Type: Turkey. Van: Gevaş, Artos Mountain, Aşağınarlıca Village, 38°12′17″N, 43°04′40″E, 2013 m, 24 June 2015. G. Zare 1103 with A.D. Koca, M. Armağan and M. Fidan (holotype HUB., isotypes ANK, ISTE, NGBB).

LABIATAE

Clinopodium L. (7:329)

e***C. serpyllifolium* subsp. ***sirnakense*** Fırat & Akçiçek in Phytotaxa 201(2): 131-139 (2015). [Fırat et al. 2015]

Type: Turkey. C9 Şırnak: Cizre, the intersection of Cudi and Gabar Mountains, Kasrik pass, rock crevices, 423 m, 37°23′46.09″ N, 42°10′35.77″ E, 20 October 2013, M. Fırat. 30493 (holotype GAZI, isotypes ISTE, M, VANF, Balıkesir Univ. Herb.)

Marrubium L. (7:165)

e***M. cephalanthum* Boiss &Noë subsp. ***montanum*** Akgül & Ketenoğlu in Ot 21(1): 21-28 (2014) [Akgül and Ketenoğlu 2014]

Type: Turkey. A5 Amasya: Between Direkli and Yassıçal villages, above Direkli, Nalbant hill, rocky slopes, 1350-1400 m, 30.6.2007, G. Akgül 2562 (holo. ANK)

******M. eriocephalum* Seybold in Stuttgarter Beitr. Naturk., A 310: 25. 1978 [Fırat 2016]

Examined specimens: Turkey. B9 Van; Başkale, İspiriz Mountains West, Serpantine rocks, 3259 m, 38°04′17″N, 43°56′23″E, 11.09.2013, M. Fırat 30289 & E. Hamzaoğlu (in flower), VANF; ibid M. Fırat 30335 (in fruit) VANF; B9 Van; Başkale, İspiriz Mountains East, Mobile limestone screes, near serpentine rocks, 3419 m, 38°05′04″N, 43°57′26″E, 15.09.2014, M. Fırat 31010 (in flower), VANF.

e***M. yildirimlii* Akgül & B. Selvi in Ot 21(2): 15-22 (2014) [Akgül and Selvi 2014]

Type: Turkey. C3 Isparta: Yalvaç, Aşağı Tistor village, from Alicinler towards the summit, 1205-1900 m, 14.6.2002, stony and rocky creeks, hills, *Q. coccifera* forest, B. Selvi 2823 (holo. Yıldırımlı otluk'u, iso. HUB)

Salvia L. (7:400)

e***S. hasankeyfense* Dirmenci, Celep & O. Guner in Phytotaxa 227 (3): 289-294 (2015). [Celep et al. 2015]

Type: Turkey. Batman: Hasankeyf, Hasankeyf to Karaköy, ca. 1 km from the main road to Karaköy, in valley, rocky cracks, 655 m, 37°42′7,855" N, 41°26′14,059″ E, 20 June 2015, F. Celep 3782 (holotype GAZI, isotypes ANK, E).

Stachys L. (7:199)

e***S. gaziantepensis* M. Dinç & S. Doğu in Proc. Natl. Acad. Sci.İndia, Sect. B Biol.Sci. [Dinç and Doğu 2015]

Type: Turkey. C6 Gaziantep: Şehitkamil, Yeşilce Köyü, Sof Dağı, Kayalık yamaçlar, 1060 m, 12.05.2012, M. Dinç 3467 and S. Doğu (holotype KNYA 26860, isotypes GAZI 3630, HUB 45843, Yıldırımlı Herb. 20426).

e***S. hakkariensis* Akçiçek & Fırat in Phytotaxa 257(2): 167-173 (2016). [Akçiçek et al. 2016]

Type: Turkey. C9 Hakkari: between Şine and Marinus, rocky slopes, eroded slopes, 37°29′53″N, 43°27′47″E, 1200 m, 7.vii.2015, M. Fırat 32600 (holotype GAZI, isotypes ISTE, VANF, Hb. Akçiçek, Hb. M.Fırat

******S. megalodonta* Hausskn. & Bornm. ex P.H.Davis subsp. ***megalodonta*** in Notes Roy. Bot. Gard. Edinburgh 21: 46 1951. [Güner and Akçiçek 2015]

Examined specimens: Türkiye, Şırnak: Uludere-Çukurca arası, Taşdelen köyü, Rüştem mahallesi, kayalık alanlar, 37° 23´ 512» K / 42° 51´ 907» D, 1236 m, 10.06.2013, Akçiçek, Dirmenci & Ö. Güner 2343; ibid, 03.06.2015, Akçiçek, Dirmenci & Ö. Güner 2528; Uludere-Çukurca arası 60. km, kayalık yamaçlar, 37 22 701 K / 042 55 066 D, 1097 m, 03.06.2015, Akçiçek, Dirmenci & Ö. Güner 2529 (Herb. E. Akçiçek).

Satureja L. (7:314)

******S. avromanica* Maroofi in Iranian J. Bot. 16: 79 (2010). [Fırat 2015b]

Examined specimens: Turkey. C9 Şırnak: Cudi Mountain and Gabar Mountain. Siirt: Botan River. October 2013, 2014.

Teucrium L. (7:53)

e***T. aladagense* Vural & H.Duman in Turk J Bot 39: 318-324 (2015). [Vural et al. 2015]

Type: Turkey. Adana: Aladağ/Pozantı: Kamışlı, between Hamidiye (Pozantı district) and Büyüksofulu (Aladağ district) villages, 1200 m, *Pinus brutia* Ten. forest, serpentine, rocky slopes, 23.06.2007. Vural (10030) & H. Duman (holotype: GAZI, isotype: ANK, HUB, ISTE, EGE, NGBB).

e***T. pruinosum* Boiss. **var.** ***aksarayense*** M. Dinç & S. Doğu in Modern Phytomorphology 9: 13-17 (2016). [Dinç and Doğu 2016]

Type: Turkey. B5 Aksaray: Hasan Dağı etekleri, Karkın köyü civarı, steppe, 1350 m, 17.07.2010, M. Dinç 3333 & S. Doğu (Holotype: KNYA, Isotypes: GAZI, HUB, Yıldırımlı Herb.)

e***T. sarikizensis* Keskin & Özyiğit in Kasmera 43(2):2-11 (2015). [Keskin et al. 2015b]

Type: Turkey. B1 Balıkesir: Mount Ida, Sarıkız Peak, 1780 m, 07.viii.1996, N. Özhatay, E. Özhatay, S. Saçlı, E. Akalın (holotype ISTE 72496).

e***T. sirnakense* Özcan & Dirmenci in Turk J Bot 39: 310-317 (2015). [Özcan et al. 2015]

Type: Turkey. C9 Şırnak: between Çukurca and Şırnak, 47 km from junction of Şırnak road, Taşdelen village, rocky slopes, 37°23'36"N, 042°51'882"E, 1037 m, 10.06.2013, Dirmenci 3892, Akçiçek & Ö.Güner. (Holotype: GAZI, isotypes: ANK, HUB, ISTE, NGBB, VANF).

LEGUMINOSAE

Astragalus L. (3:49)

e***A. topalanense* Behçet & İlçim in Turk J Bot 40:74-80 (2016). [İlçim and Behçet 2016]

Type: Turkey. B8 Bingöl: Between Topalan and Çirişli villages, in *Quercus petraea* (Matt.) Liebl. subsp. *pinnatiloba* (K.Koch) Menitsky and *Q. libani* G. Olivier forest clearings, 1700-1750 m, 01.05.2013, L. Behçet 8605. (holotype: Bingöl Univ. Herb., isotypes: Mustafa Kemal Univ. Herb., Bingöl Univ. Herb. ANK).

e***A. unalii* Çeçen, Aytaç and Mısırdalı in Turk J Bot 40:81-86 (2016). [Çeçen et al. 2016]

Type: Turkey. C4 Karaman: 19 km North of Karaman, Karadağ Mountain, southwest of Davda Hill, steppe, 1140-1345 m, 03.05.2013, Ö. Çeçen 1941, Unal and Mısırdalı (holotype: GAZI, isotypes: HUB, Yıldırımlı, KNYA, and ANK).

e***A. yukselii* Karaman & Aytaç in Turk J Bot 37: 836-840 (2013). [Karaman-Erkul and Aytaç 2013]

Type: Turkey. C4 Konya: Hadim, 3 km from Hadim to Taşkent, steppe, 1580 m, 11.06.2011, S.Karaman 2620 & Y.Karaman (holotype: GAZI, isotypes: ANK, GAZI).

Dorycnium Miller (3:512)

******D. pentaphyllum* Scop. subsp. ***pentaphyylum*** in Fl. Carniol., ed. 2. 2: 87 (1772) [Aybeke 2016]

Examined specimen: A1(E) Edirne: Centre, Budakdoğanca village, in hilly environment of Taşkaynak Deresi, 41.758849°N, 26.367967°E, 06.06.2015, coll. & det. M. Aybeke (EDTU 15003).

MALVACEAE

Kitaibelia Willd. (2:404)

******K. vitifolia* Willd. in Neue Schriften Ges. Naturf. Freunde Berlin 2: 107 (1799). [Ertuğrul et al. 2016]

Examined specimen: Turkey. C6 Osmaniye: Amanos Mountains, clearings of pine forest, 1400 m, 26.vii.2014, O. Tugay 10.138 (KNYA).

ONAGRACEAE

Chamaenerion Adanson (4:183)

e***C. angustifolium* var. ***karsianum*** Tzvelev in Novosti Sist. Vyssh. Rast. 45: 46. (2014) [Tzvelev 2014]

Type: Turkey. Kars: in monte Surb-Chacz, 4.viii.1909, T. Roop. LE

e***C. bordzilovskyi* Tzvelev in Novosti Sist. Vyssh. Rast. 45: 47. (2014) [Tzvelev 2014]

Type: Armenia rossica, distr. Kagyzman, in schistosis in monte Kecza-czi, 31.VII.1910, leg. T. Roop. (LE). (a region of Turkey adjacent to Armenia).

PLUMBAGINACEAE

■ **Psylliostachys** (Jaub. & Spach) Nevski

******P. spicata* (Willd.) Nevski in Trudy Bot. Inst. Akad. Nauk SSSR, Ser. 1, IV: 314 (1937) [Celep et al. 2016]

Examined specimens: Turkey. B9 Siirt: Akdoğmuş köyü, tuzcul alan, 03.05.2013, 37°51'618"N, 042°03'119"E, 617 m, O.Karabacak 8834 (GAZI, ANK); ibid, 01.07.2013, O.Karabacak 8849 (GAZI); Eruh, Gölgelikonak köyü, tuzcul alan, 31.05.2014, 37°46'348"N, 042°06'883"E, 763 m, M. Fidan 1874 (GAZI); Eruh, Üzümlük köyü, tuzcul alan, 31.05.2014, 37°46'699"N, 042°45'743"E, 730 m, M. Fidan 1880 (GAZI).

POLYGALACEAE

Polygala L. (1:533)

e***P. turcica* Dönmez & Uğurlu in Novon 45(3): 429-434 (2015). [Dönmez et al. 2015b]

Holotype: Turkey. A9 Kars, Kağızman-Karakurt road, 5 km from Kuloğlu village to Karakurt, 40 0380 N, 42 51 69 E, 1314 m, stony slopes along Aras river, 14 May 2009, Dönmez 15242 (HUB; isotypes: HUB, W).

PRIMULACEAE

Lysimachia L. ()

e***L. savranii* Başköse & A.Keskin in Phytotaxa 267(3): 228–232 (2016). [Başköse et al. 2016]

Type: Turkey. Adana: Karaisalı district, Kızıldağ Plateau, north side of Susuz Mountain, Koyun Kırkacağı mevkii, 1500–1550 m, 37º24'34"N–35º04'34"E, 18 June 2014, A. Savran, İ. Başköse, K. Gurbanov, and A. Keskin 1071 (holotype ANK, Isotype ANK and Nigde University Herbarium).

RANUNCULACEAE

Nigella L. (1:98)

e***N. koyuncui* Dönmez & Uğurlu in Novon 23(4): 411-415 (2015). [Dönmez et al. 2015a]

Type: Turkey. Sinop: Boyabat, Uzunçay village, 41 38 N 034 36 E, 442 m, 7 july 2009, A. A. Dönmez & Z. Uğurlu 15801 (holotype, HUB, isotypes, AEF, HUB, MO).

RUBIACEAE

Galium L. (7:767)

e***G. bingoelense* Yıldırımlı & Ö.Kılıç in Ot 21 (2): 1-14 (2014) [Yıldırımlı and Kılıç 2014]

Type: Turkey. B8 Bingöl: Solhan, HAzarşah köyü, Aksakal Göl mezrası, derenin volkanik taşlı yamaçları, 1700 m, 22.6.2014, Şinasi Yıldırımlı 40313 & Ömer Kılıç (holo. Hb. Yıldırımlı, iso. BİN, GAZI, HUB, Hb. Yıldırımlı)

e***G. shinasii* Yıldırım in PhytoKeys 75: 19–29 (2016) [Şık et al. 2016]

Type: Turkey. B7 Malatya: Akçadağ district, Levent Canyon, on marlstone rocky cliffs 1390 m, 26.06.2011, H.Yıldırım 2128 (holotype: EGE42431, isotypes: EGE42432, NGBB, ANK).

ROSACEAE

Rubus L. (4:30)

e***R. sivasicus* Yıldırımlı & Ö.Kılıç in Ot 21 (2): 1-14 (2014) [Yıldırımlı and Kılıç 2014]

Type: Turkey. B6 Sivas: Zara, Halkalı ve Korkut köyleri karşısı, bozkır, jipzizli dere, tepe, bayır, karışık orman ve açıklığı, 1385-1500 m, 19.6.2014, Şinasi Yıldırımlı 40086 & Ömer Kılıç (holo. Hb. Yıldırımlı, iso. BİN)

Rosa L. (4:106)

e***R.* × *ozcelikii* Korkmaz & Kandemir in Phytotaxa 245 (3): 207-215 (2016). [Korkmaz et al. 2016]

(*R. villosa* L. subsp. *mollis* (Sm.) Hook.f. × *R. hemisphaerica* Herrm.)

Type: Turkey. B7 Erzincan: Çayırlı District, between Verimli and Balıklı villages, about 15 km to Çayırlı district, field side, 1641 m, 39° 52′ 418″ N, 39° 55′ 644″ E, 2 June 2014, Korkmaz 4081 (holotype: ANK, isotypes: GAZI, NGBB, GUL).

Sanguisorba L. (4:77)

e***S. durui* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014b]

Type: Turkey. B1 Manisa: Soma, Madenci çeşmesi, yol kenarı, c.600 m, 12.05.1977, Özcan Seçmen 886 (holo. HUB, iso EGE)

e***S. magnolii* (Spach) Rothn. & P.Silva subsp. *bicakcii* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. C3 Antalya: Kemer, Beldibi, Seagull otelden Göynük deresi ağzına, kumul, kızılçam ormanı altı, 1-5 m, 21.04.2007, Ş. Yıldırımlı 33549 (holo. Yıldırımlı Otluk'u)

e***S. magnolii* (Spach) Rothn. & P.Silva subsp. *goekhanii* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. C2 Muğla: Fethiye, Kelebekler kepezi (vadisi), kayalık, taşlık, ağaçlık, maki, orman, çağlayana dek izlek ile, 1-150 m, 22.04.2012, Ş. Yıldırımlı 38216 (holo. Yıldırımlı Otluk'u, iso. EGE, HUB, Yıldırımlı Otluk'u).

e***S. magnolii* (Spach) Rothn. & P.Silva subsp. *magnolii* var. *koruklii* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. C3 Antalya: Kemer, Olimpos ören yeri, kayalık, duvar, su kıyısı, kumul, 1-5 m, 24.04.2010, Ş. Yıldırımlı 36691 (holo. Yıldırımlı Otluk'u, iso. ANK, EDTU, EGE, GAZI, HUB, ISTE, Yıldırımlı Otluk'u)

e***S. minor* Scop. subsp. *kucukodukii* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. C3 Konya: Beyşehir, göl kıyısı, kamış birliği, kumlu ve nemli yerler, 1220 m, 01.06.2008, Ş. Yıldırımlı 34900 & Görkem Yıldırımlı (holo. Yıldırımlı Otluk'u)

e***S. muricata* Franch subsp. *mushensis* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. B8 Muş: Meslek yüksek okulu çevresi, ova, 1300 m, 4.6.1999, Ş. Yıldırımlı 23856 (holo. Yıldırımlı Otluk'u, iso HUB)

e***S. sirnakia* Yıldırımlı in Ot 21 (2): 23-48 (2014) [Yıldırımlı 2014]

Type: Turkey. C9 Şırnak: Cudi dağı, kuzey eteği, Gümüş tepesi, korunmuş alan, kömür kumullu, meşelik, 1100-1200 m, 20.6.2005, Ş. Yıldırımlı 30048 (holo. Yıldırımlı Otluk'u, iso HUB)

Sorbus L. (4:147)

***S.* ×*latifolia** (Lam.) Pers. in Syn. Pl. [Persoon] 2(1): 38. 1806 [Zieliński and Vladimirov 2013]

Examined specimen: Turkey. Prov. Kastamonu, Daday to Azdavay, 35 km from Daday, on the banks in Abietum, 1000 m, 30.07.1962, coll. Coode & Yaltirik in: Davis 38662 (KOR 19958; E: barcode E00408672

SCROPHULARIACEAE

Scrophularia L. (6:603)

e***S. lucidaifolia* Uzunh. & E. Doğan in Phytotaxa 204 (1): 095–098 (2015) [Uzunhisarcıklı et al. 2015]

Type: Turkey. C5 Mersin: Gözne, Işıktepe-çukurkeşli, stony slopes, 612 m, 7 May 2014, E. Uzunhisarcıklı 2501 & E.D. Güner (holotype GAZI; isotypes ANK, HUB).

Verbascum L. (6:461)

e***V. ibrahim-belenlii* Karavel. in Phytotaxa 212 (3): 246-248 (2015). [Karavelioğulları 2015b]

Type: Turkey. Kars: Tuzluca-Kağızman 10 km, 1300-1400m, riverside, meadows, 2 june 2002, F. A. Karavelioğulları 3267., M. Ekici & Alkan (holotype GAZI, isotype ANK).

e***V.* × *ersin-yücelii* Karavel. in Biodicon 8/1: 78-82 (2015). [Karavelioğulları, 2015a]

(=*V. heterobarbatum* Hub.-Mor. x *V. caudatum* Freyn & Bornm.)

Type: Turkey. A4 Ankara: Kalecik, nr. Çukur köy, Kılınç 1975 (Holotype ANK).

e***V. kurdistanicum* Fırat in PhytoKeys 52: 89-94 (2015). [Fırat, 2015c]

Type: Turkey. C9 Hakkari: Berçelan Plateau, 37 40 57 N, 043 43 21 E, 2600-2800 m, limestone rocks and steppe, 21 July 2011, M. Fırat 27584. (Holotype: VANF, isotype: ANK, GAZI, HUB, VANF, E).

e***V. mecit-vuralii* Karavel. in Biodicon 8/1: 78-82 (2015). [Karavelioğulları, 2015a]

Type: Turkey. A8 Trabzon: Hamsiköy, 650-700 m, 15 june 2009, FAK 3875. (Holotype; ANK, Isotype: GAZI).

e***V. misirdalianum* Karavel. Çeçen and Ünal in Phytotaxa 217 (1): 96-99 (2015). [Çeçen et al. 2015]

Type: Turkey. C4 Karaman: 40 km North of Karaman, Çakırdağı Mountain, southwest of Yalnızdağ Hill, steppe, 1100-1300 m, 3 May 2013, Ö. Çeçen 700, A. Ünal & H. Mısırdalı (holotype: KNYA, isotypes: HUB, Yıldırımlı, KNYA, and ANK).

UMBELLIFERAE

Angelica L. (4:431)

e***A. turcica* Hamzaoglu & Koc in Phytotaxa 245(1): 66-70 (2016). [Hamzaoğlu and Koç 2016]

Type: Turkey. Kastamonu: Between Devrekani and Bozkurt, S. of Mamatlar village, above Koru Yaylası, Yaralıgöz Mountains, 145 m, 22.viii.2014 (flower and immature fruit), Hamzaoğlu 7193 & Koç (holotype GAZI, isotypes ANK, GAZI, HUB)

Anthriscus Pers. (4:321)

e***A. lamprocarpa* Boiss. subsp. ***chelikii*** Tekin & Civelek in Phytotaxa 253(4): 275–284 (2016). [Tekin and Civelek 2016]

Type: Turkey. C4 Mersin: Mut to Ermenek, 38. km, Adras Mountain, 1158 m, 36°34′50.3″N, 33°13′07.3″E, with flowers and fruits, 25 May 2011, M. Tekin 1092 (holotype CUFH).

Dichoropetalum Fenzl (4:635)

e***D. alanyensis* Bilgili, Sağıroğlu & H. Duman in Turk J Bot 40: 201-208 (2016). [Bilgili et al. 2016]

Type: Turkey. C3 Antalya: Alanya-Gökbel plateau, rocky slopes, 1650 m, 06.07.2006, B.Bilgili 2416 & M. Sağıroğlu (holotype: GAZI, isotype: ANK, HUB).

e***D. vuralii* Özbek & Arslan in Phytotaxa 278 (2): 153-162 (2016). [Özbek et al. 2016]

Type: Turkey. C3 Isparta: Yenişarbademli, Dedegöl Mountains, above Melikler pastures, transition to alpine zone from Pinus nigra subsp. pallasiana and Quercus vulcanica stand, 1700-1820 m, 24.viii.2012, U. Özbek 2852 & M.Arslan (holotype: GAZI, isotype: ANK).

Grammosciadium DC. (4:318)

e***G. macrodon* Boiss. subsp. ***nezaketae*** B.Bani in Phytotaxa 224(3): 267-275 (2015). [Bani and Koch, 2015]

Type: Turkey. C9 Van: Çatak, around of Dalbastı village, clearing of oak woodland, 1450 m, x: 42.935397; y: 37.910315, 10 June 2012, B. Bani 6832 (holotype GAZI, isotype ANK).

Pastinaca L. (4:481)

e***P. erzincanensis* Menemen & Kandemir in Ann Bot Fennici 53(5-6):373-382 (2016). [Menemen et al. 2016]

Type: Turkey. B7 Erzincan: Tatlısu köyünün güney batısı, Mercan suyu yolu, hareketli taşlı yamaçlar, (UTM) 37 S 553556E, 437848 N, 2165 m a.s.l., 25.6.2013, Kandemir 10426 (holo ADO, iso ADO, NGBB).

Pimpinella L. (4:352)

e***P. enguezekensis* Yıldırım, Akalın & Yeşil in Phytotaxa 289 (3): 237–246 (2016) [Yeşil et al. 2016]

Type: Turkey. B6 Malatya: Darende District, Ergü road, Kilise location, gypsum-marl soils, 1420 m elevation, 22 July 2015, H.Yıldırım HY3492 (holotype: EGE 42433, isotype: EGE 42434, ISTE, NGBB, ANK).

e***P. ibradiensis* Çinbilgel, Eren, H. Duman & Gökçeoğlu in Phytotaxa 217 (2): 164-172 (2015). [Çinbilgel et al. 2015]

Type: Turkey. C3 Antalya: İbradı, Toka yayla, in Trifolio-Polygonetalia community on flat or gently sloping stony places with plentiful fine soil and good water supply, limestone, 37 13 253 N, 31 22 503 E, 1527 m, 02 July 2011, Çinbilgel 7975 & Eren (holotype GAZI, isotypes ANK, AYDIN, Herbarium of Akdeniz University, HUB).

Prangos Lindley (4:382)

e***P. abieticola* Aytaç & H.Duman in Edinburgh Journal of Botany 73(1): 125-131 (2016) [Aytaç and Duman 2016]

Type: Turkey. C3 Antalya: Akseki–Seydi ş ehir, 38th km, 1600 m, in open forest of *Abies cilicica* and *Pinus nigra*, calcareous rocks, 23 vii 2010, H. Duman 10209 (holo GAZI; iso ANK, HUB).

Seseli L. (4:367)

e_S. gummiferum_** Pall. ex Sm. subsp. ***ilgazense*** A. Duran, Ö. Çetin & M. Öztürk in PhytoKeys 56: 99-110 (2015). [Çetin et al. 2015]

Type: Turkey. A4 Kastamonu: Ilgaz Mountain Natural Park, Kastamonu road, from Çatören village to Büyük Hacet Hill, 6 km, in open *Pinus sylvestris* L. and *Abies nordmanniana* (Stev.) Spach. Mixed forest, serpentine stony slopes, 41 06 344 N, 3348 628 E, 1465 m, 22 August 2008, A. Duran 8135, Ö. Çetin & M. Öztürk (holotype KNYA, isotypes ANK, GAZI, HUB).

URTICACEAE

Parietaria L. (7:636)

e_P. semispeluncaria_** Yıldırım in Phytotaxa 226 (3): 281-287 (2015). [Yıldırım 2015b]

Type: Turkey. Malatya: Akçadağ district, Levent Canyon, on marlstone cliffs, 38 23 31.03 N, 37 54 36.26 E, 1390 m, 16 June 2014, H. Yıldırım 2896 (holotype: EGE, ANK, GAZI, NGBB).

VALERIANACEAE

Valerianella Miller (4:559)

e_V. turcica_** A. Doğru-Koca & G. Zare in Phytotaxa 272 (2): 157-164 (2016) [Doğru-Koca et al. 2016]

Type: Turkey. Karaman: North of Çakırdağı, between the villages of Beydili and Akçaşehir, around Fahrettin's sheep pen, protected area, steppe, 1069 m, 16.v.2015, ADK4385 with GZ & Ö. Çeçen (holo. HUB)

VIOLACEAE

Viola L. (1:524)

e_V. barhalensis_** Knoche & Marcussen in Phytotaxa 275(1): 14-22 (2016). [Knoche and Marcussen, 2016]

Holotype: Turkey. A8 Artvin: southern slope of the Kaçkar Mountains, Barhal River Valley, along road from Barhal/ Altıparmak to Yaylalar, 1700 m, 40°51'58.51"N 41°19'13.65"E, 06 May 2014, G. Knoche K 14/9 (holotype W).

MONOCOTYLEDONS

ARACEAE

Arum L. (8:43)

***_A. sintenisii_** (Engl.) P.C.Boyce, Ann. Mus. Goulandris 9: 33 (1995) [Yıldırım and Altıoğlu 2016b]

Examined specimens: Turkey. Muğla: Fethiye, Kayaköyü, Kınalı mevkii, tarla içi, 50 m, 21.03.2015, H.Yıldırım 3160 (EGE); Fethiye, Kayaköyü, Kınalı Mahallesi, tarla içi, 50 m, 18.04.2015, H.Yıldırım 3175 (EGE).

Biarum Schott (8:55)

***_B. aleppicum_** J.Thiébaut, Bull. Soc. Bot. France 95: 21 (1948) [Yıldırım et al, 2016]

Examined specimens: Turkey. Şanlıurfa: Şanlıurfa-Birecik karayolu Bentbahçesi yol ayrımı 1. km, 20.09.2005, 480 m, step, M.M.Balos 1530 (Harran Üniv. Herbaryumu); Şanlıurfa-Birecik karayolu Mezra köyü, Akarçay yolu, Akarçay'a 1 km kala, 23.04.2015, 480 m, step, H.Yıldırım 3186 (EGE). Suriye: Alep, Fr. Louis s.n. (lektotip: P00733219).

e_B. rifatii_** Yıldırım & Altıoğlu in Bağbahçe Bilim Dergisi 3(2): 12-19 (2016) [Yıldırım and Altıoğlu 2016a]

Type: Turkey. Antalya: Kaş, Palamut Köyü, Ağaçlı Akgedik Yaylası ile Rahat Yaylası arası, açık dağ yamaçları, 1800-2000 m, 20.vi.2016, H. Yıldırım (holotip: EGE-42437, izotip: EGE-42438, NGBB, ANK).

GRAMINEAE

Agropyron Gaertner (9:204)

***_A. pinifolium_** Nevski, Trudy Sredne- Aziatsk. Gosud. Univ., Ser. 8b, Bot. 17: 57 1934. [Cabi et al. 2015]

Examined specimen: Kırklareli: Vize to Kıyıköy, about 5 km from Vize, calcareous stony places, 41° 59257 N 27° 82273 E, 400 m, 16 june 2013, E. Cabi & E. Karabacak.

Bellardiochloa Chiov. (9:442)

e_B. doganiana_** Cabi & Soreng in Phytotaxa 205 (2): 123-128 (2015) [Cabi et al. 2015]

Type: Turkey. Konya: Bozkır, Palaz Dağları, step slopes on northwest side of pass to Hacıobası, 2015 m, 37.04410 N, 32.09117 E, 25.vii.2014, R.J. Soreng 8861, E. Cabi & B. Çıngay (holotype US, isotype ANK, B, CAN, E, G, HAOC, ISTE, K, KNYA, LE, NAKU, W)

Poa L. (9:470)

***_P. eigii_** Feinbrun in Bull. Misc. Inform. Kew 1940: 280 (1941). [Cabi and Soreng 2016]

Examined specimens: C1 Aydın: Aydın Mountains. Along road to the summit from Aydın, near the summit. 37°57'11.3" N, 27°53'53.2" E, 1615m; 20 Jun 2011; Open, calcareous rock, rocky and dry; L. Gillespie, E. Cabi, R. Soreng, and K. Boudko, s.n.(CAN, NAKU, US).

P. pratensis** subsp. ***irrigata (Lindm.) H. Lindb. Sched. in Pl. Finl. Exs. 2: 20 (1916). [Cabi and Soreng 2016]

Examined specimens: A2(A) Bursa Uludağ, 1659 m, under Abies and Carpinus sp., 24 Jun 2014 E. Cabi s.n. (NAKU); B2 Kütahya Simav, Simav mount. around summit, clearings and under *Pinus nigra* forest, E. Cabi, F. Celep s.n. (NAKU, US); B4 Ankara, METU Campus, around Tennis court, 2 Jun 2007, E. Cabi s.n. (NAKU).

Pseudophleum M.Doğan (9:397)

e_P. anatolicum_** Doğan, Behçet & A.Sinan in Systematic Botany 40(2):454-460 (2015). [Doğan et al. 2015]

Type: Turkey. B8 Bingöl: West of Bingöl, 4-5 km from the city cemetery on the road to Aşağı Köy, 1150-1200 m, 25.v.2013, L. Behçet 8703 (holotype: ANK, isotype: GAZI)

IRIDACEAE

Crocus L. (8:413)

e***C. ancyrensis* subsp. ***guneri*** in Phytotaxa 266 (3): 219-225 (2016) [Yüzbaşıoğlu and Celep 2016]

Type: Turkey. A5 Amasya. Göynücek, Bekdemir köyü çevresi, 505 m, bozkır yamaçlar, 2 March 2007, A. Güner (14380), F. Tezcan, M. Öztekin (holotype NGBB 1864).

e***C. antalyensioides* Rukšāns in International Rock Gardener 64 (2015) [Rukšāns 2015]

Type: Ex culturae in horto Jānis Rukšāns. (Plants from NW Turkey, Bursa province, near the road from İnegöl to Domaniç). Cultivated plants collected on 26-02-2011 (TULA-024). Holotype: GAT, Isotype GB.

e***C. dilekyarensis* Rukšāns in International Rock Gardener 64 (2015) [Rukšāns 2015]

Type: Ex culturae in horto Jānis Rukšāns. (Plants from W Turkey, Aydın prov., Dilek Yar, W of the ruins of Priene, alt. ~ 190m). Collected on 14-03-2008 (R2CV-018). Holotype: GAT.

e***C. kofudagensis* Rukšāns in International Rock Gardener 64 (2015) [Rukšāns 2015]

Type: Ex culturae in horto Jānis Rukšāns. (Plants from SW Turkey, W Antalya province, after the turn to Kaş from the road to Kalkan-Elmali). Cultivated plants collected on 01-11-2009 (JJJ-024). Holotype: GAT, Isotype GB.

e***C. musagecitii* Erol & Yıldırım, in Phytotaxa 239: 223-232 (2015). [Erol et al. 2015]

Type: Turkey. Artuklu, Mardin province, 950 m, 4 january 2014, Musa Geçit (holotype ISTF 41070, isotype EGE 42337).

e***C. sozenii* Rukšāns in International Rock Gardener 64 (2015) [Rukšāns 2015]

Type: Ex culturae in horto Jānis Rukšāns. (Plants from NW Turkey, Manisa province, Simav Dağları, altitude 1370m, at the edge of a Pinus forest). Collected 15-03-2013 (13TUS-028). Holotype: GAT.

e***C. thracicus* Yüzb. & Aslan in Phytotaxa 197(3): 207–214 (2015) [Yüzbaşıoğlu et al. 2015]

Type: Turkey. A1(E) Kırklareli: Vize, Saray-Vize yolu, c. 10 km, Quercus sp. & Paliurus spina-christi Mill. açıklıkları, 170 m, 8 February 2014, S. Yüzbaşıoğlu 3920, S. Aslan, İ. Sözen, F. Canız (holotype ISTE 102922, isotype DUOF 5630).

e***C. yakarianus* Yıldırım & O. Erol in Nordic Journal of Botany 31: 426-429 (2013). [Yıldırım and Erol 2013]

Type: Turkey. B6/7 Malatya: Doğanşehir, mountain slopes, 1900 m a.s.l., 12 Apr. 2012, H. Yıldırım 2265 (holotype: EGE: 40802, isotype: ISTF 40841).

LILIACEAE

Allium L. (8:98)

e***A. bingoelense* Yıldırımlı & Ö.Kılıç in Ot 21 (2): 1-14 (2014) [Yıldırımlı and Kılıç 2014]

Type: Turkey. B8 Bingöl: Merkez, Dikme köyü, volkanik kayalık ve taşlık, meşelik ve açıklığı, 1750-2000 m, 21.6.2014, Şinasi Yıldırımlı 40265 & Ömer Kılıç (holo. Hb. Yıldırımlı, iso. BİN, HUB)

e***A. dumanii* Koyuncu & Koçyiğit in Willdenowia 46: 113 – 119 (2016). [Koçyiğit et al. 2016]

Holotype: Turkey. C6 Kahramanmaraş, Engizek Mountain, Küçükyeşil area, 2300 m, 19 Jul 1986, H. Duman 1987 (AEF; isotypes: GAZI, ISTE).

e***A. ekimianum* Ekşi, Koyuncu & Özkan in PhytoKeys 62: 83–93 (2016). [Ekşi et al. 2016]

Type: Turkey. Elazığ: Fırat University, steppe, c. 1150 m, 02.07.1983, Koyuncu 7847 (holotype: AEF, isotype: GAZI).

e***A. phanerantherum* subsp. ***involucratum*** Ekşi, Koyuncu & M. Bona in Bangladesh J. Plant Taxon. 22(2): 143-146 (2015) [Ekşi et al. 2015]

Holotype: Turkey. Hatay: Antakya, above Kisecik, trackside, c. 900 m, 22 Aug 2013, G. Ekşi & M. Bona (AEF26318).

e***A. undulatipetalum* İ. Genç & N. Özhatay in Phytotaxa 212(4): 283-292 (2015). [Deniz et al. 2015]

Type: Turkey. C3 Antalya: Akseki, Çaltılıçukur village, Salamut Plateau, calcareous stony and grassy slopes close to *Cedrus libani* forests, 36 53 N, 31 55 E, 1600 m, 9 May 1982, T. Ekim M. Koyuncu s.n. (holotype ISTE 54419; isotypes AEF).

e***A. urusakiorum* Özhatay, Seregin & N.Friesen in Phytotaxa 275 (3): 228–242 (2016). [Koçyiğit et al. 2016]

Type: Turkey. A1 (E) Kırklareli: Demirköy, Mahya Mt, Sarpdere village, 358 m, 3 October 2009, E. Akalın Urusak & Y. Yeşil (holotype, ISTE 92497).

Bellevalia Lapeyr. (8:264)

e***B. behcetii* Pınar, Eroğlu & Fidan in Phytotaxa 270(2): 127-136 (2016). [Pınar et al. 2016]

Type: Turkey. C9 Şırnak: Balveren, Gavur Mountain (Ermeni Mountain), around of Yamyam Cave, 37°30′02″N, 42°32′51″E, oakland yards, stony-rocky slopes, 1780 m, 26 April 2015, M.Pınar 5563 (holotype VANF, isotypes GAZI, ANK).

e***B. chrisii* Yıldırım & B. Şahin in Nordic Journal of Botany 33: 45–49 (2015) [Yıldırım et al. 2015]

Type: Turkey. C6 Malatya: Pötürge, Pötürge-Nemrut mountain road, Kubbe passing, mountain steppe, 1900 m a.s.l., 28 May 2012, H. Yıldırım 2358 (holotype: EGE, isotype: EGE).

e***B. koyuncui* Karabacak & Yıldırım in Phytotaxa 203 (1): 081-084 (2015). [Karabacak et al. 2015]

Type: Turkey. B9 Siirt: Şirvan, Nallıkaya köyüne 5 km kala, step, 1286 m, 13 April 2014, O. Karabacak 9040 (holotype EGE; isotype GAZI, ANK).

e***B. vuralii* B.Şahin & Aslan in Turk J Bot 40: 394-401 (2016). [Şahin et al. 2016]

Type: Turkey. Siirt: Siirt-Eruh yolu, Sağlarca köyü, bozkır, 463 m, 14.04.2009, S. Aslan 3148 & B. Şahin; (holotype: DUOF 5750, paratypes: ANK, GAZI, DUOF).

Fritillaria L. (8:284)

e***F. asumaniae* R. Wallis, R. B.Wallis & N. Özhatay in Flora Mediterranea 25: 199-208 (2015) [Özhatay et al. 2015]

Type: Turkey. C3 Antalya. Kemer, west of Göynük, forest in deep leaf soil amongst limestone rocks under tall pine woodland, 250 m. 29.III.2012, N. Özhatay and A. Kavgacı (Holotype: ISTE 106610).

Gagea Salisb. (8:312)

******G. minima* (L.) Ker Gawl. Quart. J. Roy. Inst. 1: 180 (1816). [Tekşen et al. 2015]

Examined specimen: Türkiye. Van: Güzelsu- Başkale arası, Güzeldere Geçidi, taşlık yamaçlar, 2700 m, 11.v.2014, İ. Eker 3892, S. Aslan & M. Bozdoğan (AIBU, DUOF 6071).

Muscari Mill. (8:245)

e***M. atillae* Yıldırım in Phytotaxa 213(3): 291-295 (2015). [Yıldırım 2015a]

Type: Turkey. B7 Malatya: Akçadağ district, Levent Canyon, west of Çayözü village, on marlstone-calcareous slopes, 1185 m of elevation, 10 April 2014, H. Yıldırım 2800 (holotype EGE, isotypes ANK, EGE, GAZI, NGBB).

e***M. elmasii* Yıldırım in Turk J Bot 40: 380-387 (2016). [Yıldırım 2016]

Type: Turkey. C2 Muğla: Fethiye, Çaldağı, açık Serpantin yamaçlar, 1275 m, 19.05.2014, H.Yıldırım 2825 (holotype: EGE, isotypes: EGE, ANK, herbarium NGBB).

e***M. serpenticum* Yıldırım, Altıoğlu & Pirhan in OT Sistematik Botanik Dergisi 20(1): 1-14 (2014). [Pirhan et al. 2014]

Type: Turkey. C2 Muğla: Köyceğiz, Sandras mountain, Sandras tapleland, on serpentine soil slopes, 1460 m, 04.04.2008, H. Yıldırım 1295 (holo. EGE, iso. EGE, Hb. Yıldırımlı).

Prospero Salisb.

e***P. cudidaghense* Fırat & Yıldırım in Turk J Bot 40: 388-393 (2016). [Fırat and Yıldırım 2016]

Type: Turkey. C9 Şırnak, Silopi, Cudi Dağı Güney yamacı, Kireç kayası bloklarının çatlağında, 700 m, 37°23'31"N, 42°20'21"E, 02.05.2014, M.Fırat 30575 (holotype: EGE, isotypes: EGE).

Scilla L. (8:214)

e***S. alinihatiana* Aslan & Yıldırım in Bağbahçe Bilim Dergisi 2(2): 33-41 (2015). [Yıldırım and Aslan 2015]

Type: Türkiye. Artvin: Yusufeli, Sarıgöl, Yüksekoba Köyü, Marsis Dağı, Salikvan Yaylası civarı, yüksek dağ çayırlıkları, 2250 m, 21.06.2014, H. Yıldırım 2936 (holotype: DUOF, isotypes: EGE, NGBB).

Tulipa L. (8:302)

e***T. cinnabarina* K.Perss. subsp. ***toprakii*** Yıldırım & Eker in PhytoKeys 69: 65–70 (2016) [Eker et al. 2016]

Type: Turkey. Muğla: Milas, on the road of Milas to Akgedik Dam, near Yusufça Village, open slopes and in olive orchard, 457 m, 37°20'7"N; 27°52'6"E, 02 April 2016, H.Yıldırım 3750 & Y. Altıoğlu (holotype EGE, isotypes AIBU, NGBB).

ORCHIDACEAE

Ophrys L. (8:476)

******O. apollonae* Paulus & M. Hirth in J. Eur. Orch. 41(3-4): 647 (2009). [Bozkurt and Yıldırım 2015]

Examined specimens: Türkiye. İzmir: Çeşme, deniz kenarı yamaçlarda Frigana içleri, 13.02.2013, H. Yıldırım 2204 & N. Bozkurt (EGE). Muğla: Datça, eski Datça mevkii, çayır alanlar, 01.02.2015, N. Bozkurt (EGE).

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