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The Studies on The endemic Hypericum Species from Turkey

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ABSTRACT

The genus *Hypericum* (Hypericaceae), inclusive about 450 species, has spread in various parts of the world. The members of this species have been used for centuries as traditional medicinal plants. Turkey is an important gene center for the genus *Hypericum* which represented by nearly 100 taxa grouped under 19 sections. Among them, 45 species are endemic. The genus is known as “sari kantaron, kantaron, binbirdelik otu, mayasil otu” and used the treatment of burns, wounds, haemorroids, diarrhorea and ulcers in Turkish traditional medicine.

Thanks to this study was collected together the studies on endemic *Hypericum* species in Turkey.

Key words: *Hypericum L.,* Endemic, Turkey, Phenolic contents, Essential oil

Türkiye’den Endemik Hypericum Türleri Üzerinde Çalışmalar

ÖZ

Yaklaşık 450 tür içeren Hypericum (Hypericaceae) cinsi, dünyanın çeşitli bölgelerine yayılmıştır. Bu türün üyeleri yüzyıllardır geleneksel şifalı bitkiler olarak kullanılmaktadır. Türkiye, 19 bölüm altında gruplanmış yaklaşık 100 taksonun temsil ettiği Hypericum (Hypericaceae) cinsi için önemli bir gen merkezidir. Bunlar arasında 45 tür endemiktir. Bu bitki cinsi, “sari kantaron, kantaron, binbirdelik otu, mayasil otu” olarak bilinir ve Türk geleneksel tıbbında yanıklar, yaralar, hemorroidler, diyare ve ülserlerin tedavisinde kullanılır.

Bu çalışma sayesinde Türkiye'deki endemik Hypericum türleri ile ilgili çalışmalar bir araya toplanmıştır.

Anahtar Kelimeler: Hypericum L., Endemik, Türkiye, Fenolik içerik, Temel yağlar

1. INTRODUCTION

The *Hypericum* L. (Hypericaceae) has grown in a several of habitats in different regions of world and have a wide distribution. This genus comprising about 484 species on the World (Meseguer and Sanmartín, 2012). Turkey is an considerable gene centre of *Hypericum* species. The most recent revision showed that the *Hypericum* genus there are a total of 96 species in the flora of Turkey and 46 of which are endemic (Guner et al., 2012).

Hypericum perforatum is the most well-known in the world and is the most studied among these species. *H. perforatum* has been used mostly on the depression therapy (Solomon et al., 2013). The studies on the this species revealed that have several activities, namely, antidepressant, anti-inflammatory, antimicrobial, antiviral, antinociceptive, wound healing (Müller et al., 2003), neuroprotection (Genovese et al., 2006) and antitumor properties (Tala et al., 2013). These activities are shown by the high value bioactive constituents that *Hypericums* including hypericin and pseudohypericin (naphthodianthrones), hyperforin and adhyperforin (acylphloroglucinol derivatives), hyperoside, biapigenin, rutin, quercetin and quercitrin (flavonoids), garcinol and gambogic acid (benzophenones/xanthones), tanins and essential oils (Bombardelli and Morazzoni, 1995; Bruneton, 1995; Fu et al., 2006).

These species have been known in Turkish folk medicine with the names “kantaron, peygamber çiçegi, kılıçotu, kanotu, kuzukıran and binbirdelik otu” (Bingol et al., 2011). And used on the therapy of burns, bruises, swelling, inflammation, anxiety, and infections (Sezik et al., 2001; Tala et al., 2013).

The purpose of this study is to reveal the studies on endemic *Hypericum* species found in Turkey.

1.1. The Floristic Characters of *Hypericum* L.

Hypericum genus can be as (The Flora of Turkey -Vol 2) form of “shrubs or herbs. These plants are a glabrous perennial, vertical and usually arboreous. The leaves of the plants usually have translucent glands with sometimes red or black containing essential oils or hypericin. The leaves are ovate or linear, across, stemless, rarely whorled and have translucent black dots. The flowers bisexual and have five 5 sepals (little, subequal, entire, basally connate) and 5 petals (yellow). Stamens in 5 fascicles, anti- petalous, free or 4 of them combined in pairs to form 2 anti- sepalous compound fascicles. Flowers have 125 stamens, rarely alternating with sterile fascicules. The Ovary is upper with axile or parietal placentation. Styles of ovary (3-5), free and slender. The flowers bloom from June until September.

Fruit capsular, cracked septicidally, usually with resin-containing vittae or cyst in the wall, or rarely fleshy and indehiscent. The glands are described as marginal where they disconnect the circle of the organ, intramarginal where they happen near the margin without disconnect the contour and surface where they occur away from the margin. The glands in the ovary and capsule walls are called vittae, and low glands are described as vesicles (Davis, 1967; Hobbs, 1998).

2. Endemic *Hypericum* Species in Flora of Turkey

Turkey have a total of 96 *Hypericum* species in the flora of Turkey, and 45 of which are endemic so our country is an important gene centre for *Hypericum* species. (Guner et al., 2012) (Table 1).

It is reported that the Mediterranean Region ranks first with its endemic *Hypericum* species density and Aegean and Central Anatolia Region is richer in Eastern and Southeastern Anatolia in terms of endemic species (Akgöz, 2013).

2.1. Danger Situations of Endemic *Hypericum* species

The collection of species grown in natural environment for both treatment and trade is one of the factors that accelerate the extinction process of species. like the many plant species, 15 *Hypericum* types also which most of endemic, have been taken to the hazard catagory (Akgöz, 2013).

In a study was revealed that among these endemic species *H. capitatum* Choisy var. *capitatum* Choisy, *H. fissurale* Woron., *H. salsolifolium* Hand.-Mazz., *H. sorgerae* Robson were in critically endangered, *H. pseudolaeve* Robson, *H. spectabile* Jaub. & Spach were in vulnerable, *H. scabroides* Robson & Poulter, *H. thymbrifolium* Boiss. & Noe, *H. thymopsis* Boiss., *H. uniglandulosum* Hausskn. Ex Bornm. were in endangered risk categories in 2001 (Yüce, 2009).

3. Phenolic compound Contents of Endemic *Hypericum* Species

The genus *Hypericum* (Hypericaceae) has taken scientific interest due to it' s members have many medicinally bioactive compounds. So, a lot of researches have been performed on the phenolic components of endemic *Hypericum* species in Turkey (Table 2).

In a recent study, HPLC-DAD datas revealed that hypericin, pseudohypericin, hyperoside, chlorogenic acid, rutin, quercitrin, quercetin, isoquercitrin, kaempferol, hyperforin, and amentoflavone were the main compounds present in the methanol extracts of three endemic species which *H. thymbrifolium*, *H. spectabile* and *H. pseudolaeve* (Özkan et al., 2018b). Özen et al., 2005 studied the total phenol contents (26.84 µg) of *H. avicularifolium* Jaup.& Spach subsp. *depilatum* (Freyn & Bornm.) Robson var. *depilatum* (Table 2).

Çırak et al., (2016b), showed that quantities of bioactive compounds have differented depending on the altitude of plant habitat in *H. polyphyllum*. The highest levels of hyperoside, 2,4-dihydroxybenzoic acid, adhyperforin, hyperforin, quercetin, (-) epicatechin and avicularin accumulated in the plants that growing at site of 1100 m altitude. Besides the highest levels of pseudohypericin, hypericin, rutin, chlorogenic acid, neochlorogenic acid, caffeic acid, 13, II8-biapigenin, quercitrin, isoquercitrin, and (+)-catechin were observed at the plants that growing site of 1600 m altitude. Cirak et al., (2013), revealed that the phenolic compound contents changed during plant development in *H. aviculariifolium* subp. *depilatum* var. *depilatum.* The highest amounts of pseudohypericin, hypericin, hyperoside, rutin, quercitrine, and isoquercetine contents reached at flowering stage and then the amounts of these phenolics decreased during fruit ontogenesis stage. But the amount of chlorogenic acid reached the highest level at the vegetative stage and then decreased with developing of plant phenology. The quercetine substances of complete plants rised with growth of plant and reached its the highest grade at mature fruiting stage (Cirak et al., 2006; 2013; Uzun, 2009). Additionally hyperforin was detected only at flowering in this species (Smelcerovic et al., 2008). The best accumulation of hypericin, pseudohypericin, hyperforin, adhyperforin, caffeic acid, amentoflavone, quercitrin, quercetin, rutin and (+)-catechin compound contents were determined in the flowers. Besides, the best accumulation of hyperoside, 2,4 dihydroxybenzoic acid, chlorogenic acid, neochlorogenic acid, isoquercitrin, (-)-epicatechin, and avicularin, contents were determined in the leaves of *H. confertum* Choisy (Camas et al., 2014b). HPLC analysis revealed that the flower, leaf and stems of *H. leptophyllum* accumulated hyperoside, chlorogenic acid, quercitrine and isoquercetine, but did not accumulate hypericin, hyperforin, pseudohypericin, kaempferol and rutin compounds (Camas et al., 2012). Ayan and Çırak (2008) not detected hypericin and pseudohypericin compounds in any stem, leaf and flower parts of *H. heterophyllum* in their study (Table 2) . Çırak et al., 2016b, the highest amount of hypericin, pseudohypericin, hyperoside, rutin, quercitrin, isoquercitrin, quercetin, II8-biapigenin, amentoflavone, (+)-catechin, (−)-epicatechin detected in the flower, besides the highest amount of neochlorogenic acid, avicularin, and 2,4-dihydroxybenzoic acid detected in leaf organs but caffeic acid not detected from *H.capitatum* Choisy var. *capitatum*, *H. capitatum* var. *luteum*, *H. spectabile*, *H. salsolifolium*.

4. Essential Oil Contents of Endemic *Hypericum* Species

The essential oil contens of several medicinally important species have clues on the chemotaxonomy of genus and whether used as a natural product resource. Yüce and Bagci (2017), determined the essential oil contents of aerial parts of *H. uniglandulosum* that growing naturally in the Eastern Anatolian region of Turkey, by GC, GC–MS. The α-pinene (35.1%), undecane (19.2%), benzoic acid (2.7%) and cyclohexasiloxane (2.3%) were determined as main constituents in the twenty-six essential oils of *H. uniglandulosum*. Besides in an earlier study, it was found that oleic acid (3.45 ± 0.17%), palmitic acid (12.16 ±0.69%), and α-linolenic acid (17.15 ± 0.84%) were the predominant fatty acids in the extracts for this species. Additionally, the extracts contained β sitosterol (289.33 ±4.96 μg/g), cholesterol (66.16 ±0.78 μg/g), stigmasterol (52.60 ± 0.57 μg/g), and as well as α-tocopherol (29.2 ±0.54 μg/g). The methanol extracts of this plant was determined the most effective on the free radicals (Turkoglu et. al., 2015).

H. aviculariifolium Jaub. et Spach subsp. *depilatum var. depilatum* also is one of *Hypericum* species that analyzed for essential oil composition. The GC and GC- MS analyses of ariel parts showed that this plant have a total of 41 components, β-pinene (3.6%), germacrene D (8.5%), and α-pinene (52.1%) were the dominant components. Additionally, monoterpene concentrations were higher than that of the sesquiterpenes in oils (Yuce and Bagci, 2012). The GC-FID and GC-MS analyses of the volatile constituents of this plant showed that a total of 56, 49 and 50 EO ingredients. Likewise significant compositional variations were between these two populations of the same species show the significance of genetic agents affecting secondary metabolite constituents (Cirak and Bertoli, 2013).

The studies also have performed on the essential oil composition of some other endemic *hypericum* species. For instance, the essential oils from the aerial parts of *H.capitatum* Choisy analyzed by GC and GC-MS. The undecane (3.8 %), β-caryophyllene (6.5 %), hexadecanoic acid (8.9 %), caryophyllene oxide (11.8 %), α-pinene (20.3 %), and were identified as main constituents among the forty-eight compounds in the essential oils of var. *capitatum* with (Bagci and Yuce, 2011). The variations of the essential oils from the vegetative, flowering and fruiting stages of *H. scabroides* Robson & Poulter were also analyzed by GC and GC-MS. As result of analyses, the delta 3-carene and sabinene were found as the main components in *H. scabroides* oil (Bagci and Bekci, 2010). Bagci and Yuce (2010) determined the essential oils of two *Hypericum* L. (*H. thymbrifolium* Boiss. & Noë and *Hypericum pseudolaeve* Robson) species with GC and GC-MS system. Forty-five compounds were found in the essential oils the aerial parts of *H. pseudolaeve*; β-selinene (3.02 %), spathulenol (5.21 %), α-pinene (5.76 %), caryophyllene oxide (7.96 %), α-cadinol (10.67 %), δ-limonene (11.19 %), and *trans*caryophyllene (23.92 %). Among the fifty-four components were identified in *H. thymbrifolium* oil it was determined as the main constituents, naphthalane (1.88 %), spathuleneol (2.92 %), β-myrcene (3.30 %), β-pinene (3.68 %), germacrene D (4.70 %), undecane (4.94 %), and α-pinene (51.31 %). The results obtained from essential oil studies have supports the usability of oils as renewable resources and give the knowledge on the chemotaxonomy of these plants. The aerial parts of *Hypericum* were also analysed by GC and GC/MS for composition the essential oil and obtained 72 compounds (82.4% of the oil). The main components found were g-cadinene (4.4%), 2,3,6-trimethylbenzaldehyde (5%), g-muurolene (5.9%), germacrene D (6.1%), d-cadinene (7.1%), and spathulenol (10.8%). The oil was rich in sesquiterpene hydrocarbons (Ozkan et al., 2009). *H. heterophyllum* Vent. were determined by GC and GC– MS and it was found that β -caryophyllene (4.5%), γ -cadinene (5.5%), *n*-decane (5.8%), γ -muurolene (8.2%), δ -cadinene (9.5%), α-pinene (11.6%), and isocaryophyllene (17.1%), to be major constituents. The oil of *H. heterophyllum* was consisting mainly of sesquiterpenes with 72.9% of the total oil (Cakir et al., 2004). It was reported that steam volatiles of the endemic *H. adenotrichum* contained germacrene D (38%) as the major constituent, and forty five compounds were identified representing 93% of the total compounds (Erken et al., 2001).

5. Biological Activities of Endemic *Hypericum* Species

Studies on some endemic *Hypericum* species have helped to identify some of the biological activities that these species have(Table 3).

It is revealed that *H. spectabile* extracts have quite good antioxidant, anti-inflammatory, and AChE inhibition potential (Ozkan et al., 2018b). It shown that the inhibition of lipid peroxidation, scavenging DPPH, and superoxide anion radicals activity of *H. neurocalycinum* higher than *H.*

malatyanum. So it demonstrated stronger antioxidant properties and more effective AChE inhibitör (Ozkan et al., 2018a). Additionally, it was found that the *H. adenotrichum* Spach. showed cytotoxic and genotoxic activity depending on the cell type (Sarimahmut et. al., 2016), and ıt was exhibited potent p53- independent anti-neoplastic features (Özmen et. al., 2009). *H. heterophyllum* Vent to be the cytotoxic effects as well as proliferative effects (Öcal and Eroğlu, 2012).

Hypericum has been used for centuries in the treatment of bacterial and viral infections. Research has shown that many species of *hypericum* have antibacterial activity. The methanol extracts of *H. capitatum* Choisy var. *capitatum* showed highest activity against *Escherichia coli* with an MIC value of 10 µg/mL (Boga et al., 2016). It was reported that the *H. rupestre* Jaub & Spach., *H. vacciniifolium* Hayek & Siehe, *H. imbricatum* Poulter, *H. kazdaghensis* Gemici et Leblebici and *H. havvae* A. Guner species showed good antibacterial effect on the methicillin-resistant *Staphylococcus aureus* (Dulger and Hacioglu, 2009; Dulger et al., 2010).

The extracts (chloroform, acetone and methanol) that obtained leaves of *H. kazdaghensis* exhibited strong antimicrobial effect on all tested bacteria. (Dulger and Gonuz, 2005). Dulger et al., (2005) revealed that the *H. vacciniifolium*, *H. rupestre* and *H. imbricatum* exhibited great antimicrobial activity against especially Gram-positive bacteria and the Gram-negative bacterium *Bordetella bronchiseptica.* These results support the use of these species in traditional medicine to treat skin and eye infections**.** The mentioned activities of *Hypericum* species may be showed the exist of the plant compounds or metabolic toxins on these plants. These properties revealed to the effect of *Hypericums* for treating wounds and abscesses in traditional medicine. There are a lot of studies that showed *Hypericum* species have antifungal activity. Dulger and Dulger, (2014) reported that the extracts of *H. havvae* A. Guner exhibited strong antifungal effect against the yeast cultures especially *Candidiasis*, additionally the combination of the plant extracts (leaf + root) possessed stronger antifungal potency against *Candida albicans* and *Cryptococcus laurentii*. The essential oils of *H. heterophyllum* showed activity against several fungal species, viz F. acuminatum, AG-5 and especially AG-11. Among the compounds of these oils, both β-caryophyllene oxide and α-terpineol were inhibitory to the growth of all fungi (Çakır et al., 2004).

6. Anatomical Studies of Endemic *Hypericum* Species

Turkey is one of the important gene centers for the *Hypericum* species with 41% endemism ratio (Meseguer & Sanmartin, 2012). The total number of *Hypericum* in Turkey is represented by 96 taxa in 21 sections. Those which, 40 taxa are endemic to Turkey (Özhatay et al., 2011).

Different *Hypericaceae* (Guttiferae) taxa has been studied according to their morphological, anatomical, palynological, secretional and pharmalogical features by different researchers until today. In addition to these, some Hypericaceae taxa, has not been studied previously and also such investigations on *Hypericum* species are rather limited.

Tekin, (2017) revealed the morphologic, anatomic and histologic properties of the aerial vegetative and reproductive organs of the *H. thymopsis* a recent study. Dogan et al., (2017), analyzed the phylogenetic relationships of *Drosanthe* section of *Hypericum* genus by using non-coding chloroplast DNA region (*trn*L 3'-*trn*F) for 58 individuals. In the results, two clades were formed to show phylogenetic relationships within the *Drosanthe* section of the genus *Hypericum*. According to this classification, the first clade was composed of 16 taxa and include endemic species *H. thymbrifolium, H. thymopsis, H. pseudolaeve, H. salsolifolium, H. uniglandulosum, H. capitatum* var. *capitatum, H. scabroides* and *H. microcalycinum* in *Drosanthe*, on the other hand, the second clade have the 4 taxa, including *H. spectabile* and *H. sorgerae*. Ocak et al., (2013) examined the detailed pollen morphological structures of some endemic Hypericum taxa showing the natural distribution in Turkey: H. sect. Heterophyllum (*H. heterophyllum* Vent.), H. Sect. Taeniocarpium (*Hypericum confertum* Choisy subsp. *confertum*), H. sect. Crossophyllum (*H. adenotrichum* Spach), H. sect. Origanifolia (*H. avicularifolium* Jaub and Spach subsp. *depilatum* (Freyn and Bornm.) Robson var. *depilatum*, *H. avicularifolium* Jaub. and Spach subsp. *byzantinum*). These taxa were studied under light microscope and scanning electron microscope for the first time.

7. In Vitro Studies of Endemic *Hypericum* Species

The plant culture systems are also significant applications for manipulation of the biosynthesis of secondary metabolities that have important usage in medicine and industry. Besides, these tissue and cell culture systems have yield a higher productivity compared to naturally grown plants (Kirakosyan et al., 2001). Plant regeneration studies of the a lot of *Hypericum* species has been carried out by using as explants the several plant parts such, hypocotyl sections, leaves, leaf discs, stem segments, and adventitious roots (Ćellárová et al., 1992; Zobayed et al., 2004; Pretto and Santarém, 2000; Ayan et al., 2005; Goel et al., 2009).

It is found that the in vitro studies on the endemic *Hypericum* species to be limited. In our recent study we reported that the increasing concentrations of BAP stimulated shoot multiplication but did not affect on the seed germination rates or total hypericin content in in vitro cultures of *H. scabroides* (Asan et al., 2015). It was found that the under osmotic stress conditions, the concentrations of hypericins changed in in vitro seedling culture of *H. adenotrichum* (Yamaner and Erdag, 2013). In additionally the elicitors mannan and pectin can be evaluated for production of secondary metabolites for this plant (Yamaner et al., 2013). Cırak et al., (2007d) performed a study to improve the germination rate of *H. aviculariifolium* subsp. *depilatum* var. *depilatum* seeds, which have a low germination rate under normal laboratory situations. They revealed that the seeds of this plant have exogenous dormancy and need a light for germination. They also reported that the washing in tap water of the capsule and seed coat removed the exogenous dormancy caused by a chemical inhibitor.

Our study showed that the studies on the these species were limited compared of the number of endemic *Hypericum* species in Turkey. The future studies are needed to introduce particularly medically important compounds contained in these species.

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Table 1. Endemic *Hypericum* species in Flora of Turkey

Hypericum species	**Phytogeographical Region**
H. adenotrichum Spach	
H. aviculariifolium Jaub. and Spach subsp. *aviculariifolium* var. *albiflorum* Hub.-Mor.	EM
H. aviculariifolium Jaub. and Spach subsp. *aviculariifolium* var. *aviculariifolium*	EM
H. aviculariifolium Jaub. and Spach subsp. *byzantinum* (Azn.) Robson	
H. aviculariifolium Jaub. and Spach subsp. *depilatum* (Freyn and Bornm.) Robson var.*bourgaei* (Boiss.) Robson	
H. aviculariifolium Jaub. and Spach subsp. *depilatum* (Freyn and Bornm.) Robson var. *depilatum*	IT
H. aviculariifolium Jaub. and Spach subsp. *depilatum* (Freyn and Bornm.) Robson var. *leprosum* (Boiss.)Robson	EM
H. aviculariifolium Jaub. and Spach subsp. *uniflorum* (Boiss. and Heldr.) Robson	
H. capitatum Choisy var. *capitatum*	IT
H. confertum Choisy subsp. *confertum*	
H. crenulatum Boiss.	
H. elongatum var. *antasiaticum* Grossh. N. Robson	IT
H. elongatum var. *lythrifolium* N. Robson	IT
H. fissurale Woron	
H. havvae Guner	EM
H. hedgei N. Robson	IT
H. heterophyllum Vent.	A
H. huber-morathii Robson	EM
H. ichelense N.Robson	EM
H. imbricatum Poulter	
H. kazdagensis Gemici and Leblebici	EM-MT
H. kotschyanum Boiss.	
H. lanuginosum Lam. var. *pestalozzae* (Boiss.) Robson	EM
H. lanuginosum Lam. var. *scabrellum* (Boiss.) Robson	EM
H. laxiflorum N.Robson	EM
H. malatyanum Peşmen	IT
H. marginatum Woron	
H. minutum Davis and Poulter	EM
H. monadenum Robson apud Poulter	EM
H. musadoganii Yıld.	*IT*
H. neurocalycinum Boiss. and Heldr.	
H. olympicum L. subsp. *macrocalyx* (Freyn) Robson	EM-MT
H. pamphylicum Robson and Davis	EM
H. peshmenii Yıldırımlı	IT
H. polyphyllum Boiss. and Bal. subsp. *lycium* Robson and Hub.-Mor.	EM
H. polyphyllum Boiss. and Bal. subsp. *polyphyllum*	EM
H. polyphyllum Boiss. and Bal. subsp. *subcordatum* Robson and Hub.-Mor.	EM
H. pseudolaeve Robson	IT
H. pseudorepens N.Robson	IT
H. pumilio Bornm.	IT
H. rupestre Jaub. and Spach	EM
H. salsolifolium Hand.-Mazz	IT
H. salsugineum Robson and Hub.-Mor.	
H. saxifragum Robson and Hub.-Mor.	EM-MT
H. saxifragum subsp. *eglandulosum* Parolly & Eren	EM
H. scabroides Robson and Poulter	IT
H. sechmenii Ocak & Koyuncu	IT
H. sorgerae Robson	IT
H. spectabile Jaub. and Spach	IT
H. ternatum Poulter	EM
H. thymbrifolium Boiss. and Noë	IT
H. thymopsis Boiss.	IT
H. uniglandulosum Hausskn. ex Bornm	IT
H. vacciniifolium Hayek and Siehe	EM
H. vaccinioides N.Robson	IT

A: Anatolian Element, **EM**: East Mediterranean Element, **EM-MT**: East Mediterranean Mountainous Element, **IT**: Irano-Turanian Element (Davis et al., 1967, Ekim et al., 2000, Güner et al., 2000).

Table 2. Phenolic Compound Studies on The Endemic Hypericum Species from Turkey

H.adenotrichum	Hypericin, pseudohypericin, hyperoside, chlorogenic acid, rutin, quercitrin, quercetin, amentoflavone, kaempferol, apigenin-7-O-glucoside	HPLC	Çırak et al., 2009
H. aviculariifolium subsp. *aviculariifolium* var. *albiflorum*	Hypericin, pseudohypericin, hyperforin, adhyperforin, hyperoside, chlorogenic acid, neochlorogenic acid, caffeic acid, rutin, 2,4 dihydroxybenzoic acid, quercitrin, isoquercitrin, quercetin, avicularin, 13,118-biapigenin , (+)-catechin	HPLC	Çırak et al., 2016a
Hypericum aviculariifolium subsp. *depilatum* var. *depilatum* Robson var. *depilatum*	Hypericin, pseudohypericin, hyperforin, chlorogenic acid, rutin, hyperoside, isoquercetine, quercitrine and quercetine, apigenin-7-o-glucoside	HPLC	Çırak et al., 2006, 2007d, 2013; Uzun, 2009
H. capitatum var. *capitatum*	Hypericin, pseudohypericin, hyperforin, adhyperforin, hypericin, chlorogenic acid, neochlorogenic acid, rutin, caffeic acid, 2,4 dihydroxybenzoic acid, isoquercitrin, quercitrin, quercetin, avicularin, (+)-catechin, 13,118-biapigenin, amentoflavone, mangiferin, kaempferol	HPLC	Çırak et. al., 2016b; Boga et al., 2016;
H. confertum Choisy	Hypericin, pseudohypericin, hyperforin, adhyperforin, hyperoside, chlorogenic acid, neochlorogenic acid, rutin, caffeic acid, 2,4 dihydroxybenzoic acid, isoquercitrin, quercitrin, quercetin, avicularin, (+)-catechin, amentoflavone	HPLC	Camas et al., 2014b,
H. heterophyllum Vent.	Hypericin, pseudohypericin, hyperforin, hyperoside, rutin, quercitrin, quercetin,	LC/MS/MS, HPLC	Smelcerovic et al., 2008; Ayan and Çırak 2008
H. leptophyllum	Chlorogenic acid, hyperoside, isoquercetine, quercitrin, quercetin	HPLC	Camas et al., 2012
H. malatyanum	Hypericin, pseudohypericin, chlorogenic acid, rutin, hyperoside, isoquercitrin, kaempferol, quercitrin, quercetin, amentoflavone, hyperforin	HPLC	Ozkan et. al., 2018a
H. neurocalycinum	Hypericin, pseudohypericin, chlorogenic acid, rutin, hyperoside, isoquercitrin, kaempferol, quercitrin, quercetin, amentoflavone, hyperforin	HPLC	Ozkan et. al., 2018a
Hypericum pamphylicum	Hypericin, hyperforin, chlorogenic acid, hyperoside, isoquercitrin, quercetin.	HPLC	Ozkan et. al., 2013b
H. polyphyllum Boiss. & Bal.	Hypericin, pseudohypericin, hyperforin, adhyperforin, chlorogenic acid, neochlorogenic acid, caffeic acid, 2,4-dihydroxybenzoic acid, 13,II8-biapigenin, hyperoside, isoquercitrin, quercitrin, quercetin, avicularin, rutin, (+)-catechin, (-)-epicatechin	HPLC	Çırak et al., 2016b
H. pseudolaeve	Hypericin, pseudohypericin, chlorogenic acid, rutin, hyperoside, isoquercitrin, kaempferol, quercitrin, quercetin, amentoflavone, hyperforin	HPLC-DAD	Ozkan et. al., 2018b
H. spectabile	Hypericin, pseudohypericin, hyperforin, adhyperforin, hyperoside, chlorogenic acid, neochlorogenic acid, rutin, caffeic acid, 2,4 dihydroxybenzoic acid, isoquercitrin, quercitrin, quercetin, avicularin, (+)-catechin, 13,118-biapigenin, amentoflavone, mangiferin, kaempferol	HPLC HPLC-DAD	Ozkan et. al., 2018b; Çırak et. al., 2016b
H. thymbrifolium	Hypericin, pseudohypericin, chlorogenic acid, rutin, hyperoside, isoquercitrin, kaempferol, quercitrin, quercetin, amentoflavone, hyperforin	HPLC-DAD	Ozkan et. al., 2018b

*The species are listed in alphabetically.

Table 3. Studies on The Biological Activity of Endemic *Hypericum* Species in Turkey

Species	**Biologycal activities**	**References**
H. adenotrichum Spach.	cytotoxic and genotoxic activities	Aztopal et. al., 2016, Sarimahmut et. al., 2016, Özmen et. al., 2009
H. aviculariifolium Jaub. and Spach subsp. *depilatum*	Antioxidant, Antibacterial	Maltas et al., 2013
H. capitatum var. *capitatum*	Antioxidant, antimicrobial, anticholinesterase, DNA damage inhibitor	Boğa et al., 2016
H. confertum subsp. *confertum*	Antimicrobial	Kunduhoglu et al., 2011
H. havvae	Antifungal Activity	Dulger and Dulger, 2014
H. heterophyllum Vent.	Antifungal, cytotoxic, proliferative, mitotic effects properties.	Çakır et al., 2004; Öcal and Eroğlu**,** 2012;
H. malatyanum	Antioxidant, AChE inhibitory activities	Ozkan et al., 2018a
H. neurocalycinum	Antioxidant, Antimicrobial, AChE inhibitory activities,	Ozkan et al., 2018a; Ozkan et al., 2013a
H. origanifolium Willd.	anti-aging,	Boran 2018.
H. pamphylicum	Antioxidant, antimicrobial	Ozkan et al., 2013b
H. pseudolaeve	Antioxidant activities (EC50 values), AChE inhibitory, anti-inflammatory	Ozkan et al., 2018b
H. salsugineum Robson and Hub.-Mor.,	Anti-cancer, Antioxidant, Antibacterial	Bender et al., 2018; Maltas et al., 2013
H. spectabile	Antioxidant activities (EC50 values), AChE inhibitory, anti-inflammatory,	Ozkan et al., 2018b
H. thymbrifolium	Antioxidant activities (EC50 values), AChE inhibitory, anti-inflammatory	Ozkan et al., 2018b
H. uniglandulosum	Antioxidant activities,	Turkoglu et al., 2015