

Chemical and medicinal evaluations of the *Valeriana* species in Turkey

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Abstract: The genus *Valeriana* (Valerianaceae) is represented by more than 350 species worldwide. In Turkey, it comprises about 17 species, of which 4 are endemic. The studies on these species are limited in consequence of a small number of the species in Turkey. It is aimed to evaluate them chemically and medicinally and determine the possibility of new studies.

Keywords: *Valeriana*, Turkey, medicinal evaluation

Introduction

The genus *Valeriana* (Valerianaceae) is represented by more than 350 species worldwide. In Turkey, it comprises about 17 species, of which 4 are endemic (Davis, 1972; 2008; Davis et al., 1988; Taherpouret al., 2010). *Valeriana officinalis* is used in hysteria, neurasthenia, nervous insomnia and palpitations traditionally in Turkey. Its infusions are preferred for the treatment of wounds (Baytop, 1999). The main compounds are sesquiterpenes, such as valerenic acid and its derivatives; iridoids, especially valepotriates; flavonoids; alkaloids; lignans; tri- and monoterpenes. It is a difficulty that the chemical constitutions of the *Valeriana* species are variable according to the seasons and its principle is unknown (Bos et al., 1998; Wang et al., 2010).

The studies on these species are limited in consequence of a small number of the species in Turkey. It is aimed to evaluate them chemically and medicinally and determine the possibility of new studies.

History

The Greek physician, Dioscorides, recommended valerian root to treat myriad disorders including heart palpitations, digestive problems, epilepsy

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and urinary tract infections. Valerian was recommended by Galen during the second century as a treatment for insomnia. By the 18 century, valerian was widely used as a sedative and to treat nervous disorders associated with a “restless” digestive tract as well as the “vapors” in women. Other common uses included the treatment of headaches, anxiety, palpitations, high blood pressure, irritable or spastic bowel, menstrual cramps, epilepsy and childhood behavior problems and learning disabilities. The plant was used to prevent and treat bomb shock in frontline troops during World War I. Because of valerian’s historical use as a sedative, anticonvulsant, migraine treatment and pain reliever, most basic scientific investigations have been directed at the interaction of valerian constituents with the GABA neurotransmitter receptor system. These studies remain inconclusive and all require independent replication. Valerian was listed as a sleep aid and anxiolytic on the US national formulary until the 1940’s. Valerian has been used as a medicinal herb since at least the time of ancient Greece and Rome. Hippocrates described its properties, and Galen later prescribed it as a remedy for insomnia. Valerian can be also consumed as a tea (Murti et al., 2011).

Studies in the World

85 sesquiterpenes, 66 iridoids, 14 flavonoids, 6 alkaloids were isolated from the *Valeriana* species. Several skeletons of sesquiterpenes can be discerned: bisabolane, eudesmane, guaiane, velerenane and some modified derivatives. The iridoids can be mainly classified into four groups: monoene, lytic monoene, diene and lytic diene. The most important iridoid compounds are the valepotriates, which are cytotoxic and inhibit DNA synthesis (Wang et al., 2010). The compounds isolated from *Valeriana* species are summarized in Table 1.

From *Valeriana officinalis* L., iridoid valepotriates (0.5-2%), such as valtrates, valtrates, isovaltrate, didrovaltrate and valerosidate; essential oil (0.2 – 2.8%), as like as bornyl isovalerenate and bornyl acetate; valerenic, valeric, isovaleric and acetoxyvalerenic acids; valeranal, valeranone, cryptofaurinol; alkaloids, (0.01 – 0.05%), valeranine, chatinine, alpha-methyl pyrrolketone, actinidine, skyanthine and naphthyridylmethylketone and lignans (hydroxypinoresinol) were isolated. The plant contains over 150 chemical constituents, many of them have physiological activity.

Its activity on the central nervous system has been variously attributed to valepotriates; valerenic acid, valeranal and valeranone, and other compounds in the essential oil. In addition, isovaleric acid is responsible for its unpleasant aroma. The essential oil is also thought to contribute to its sedative effects. Valerenic acid has spasmolytic and muscle relaxant activity (Murti et al., 2011).

The species are tested for their following activities: antispasmodic effect, sedative and anxiolytic effects, enhancers of NGF Action, antiviral activity, antituberculosis effect, cytotoxicity, effect on hepatic Mutation Induction.

8-hydroxypinoresinol and prinsepiol displayed powerful antioxidant activity in Trolox equivalent antioxidant activity (TEAC) and chemiluminescence (CL) tests. The ethanol and aqueous extracts of *V. officinalis* roots showed anti vasospastic effect on coronary artery, antihypertensive and anti-bronchospastic effects, significantly. These were similar to those exhibited by nifedipine and are due to the structural features of the active principles they contain, which explains the traditional use of this plant in the treatment of some respiratory and cardiovascular disorders (Wang et al., 2010).

The ethanol extracts, 70% ethanolic extracts, and aqueous alkaline extracts showed an anxiolytic effect. Additionally, acute administration of an aqueous extract reduced sleep latency. A sesquiterpene, valerenic acid was shown to possess anticonvulsant properties and decreased the locomotor activity of mice after administration. In addition, the pentobarbital induced sleeping time was prolonged. Hesperidin and 6-methylapigenin showed similar effect (Wang et al., 2010).

It was found that 1-hydroxypinoresinol, a lignan isolated from *V. officinalis*, is a ligand for the 5-HT_{1A} serotonin receptor with an IC₅₀ ~2.5 µM. Also, the methanol and aqueous extracts of *V. adscendens* Trel. were tested for affinity and selectivity towards different receptors, such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} serotonergic, D₁ and D₂ dopaminergic, α₁ and α₂ adrenergic receptors. Both extracts showed affinity to D₁ receptors, but only for the methanol extract the IC₅₀ value can be determined (30.14 µg/ml), while the aqueous extract showed weak affinity to 5-HT_{1A} (Wang et al., 2010).

Six compounds isolated from the roots of *V. jatamansi* Jones (Syn: *V. wallichii* DC.), were evaluated for their neuroprotective effects and 4 of them (valeriandoid A, valeriandoid C, chlorovaltrate and 1,5-dihydroxy-3,8-epoxyvalechlorine) showed moderate effects (Xu et al., 2011). After that, the extracts of roots and rhizomes of *V. amurensis* Smir. ex Komarov. were screened for the effectiveness against Alzheimer's disease (AD-EF), based on which neuroprotective active constituents from AD-EF were investigated. The protective effects of 17 isolated compounds on PC12 cells with neurotoxicity induced by amyloid-beta 1–42 (A β 1–42) were also evaluated, respectively. Consequently, an iridoid (xiecaoside E) and 7 lignans (lariciresinol-4,4'-di-O- β -D-glucopyranoside, olivil-4-O- β -D-glucopyranoside, 8-hydroxylariciresinol-4'-O- β -D-glucopyranoside, lariciresinol-4-O- β -D-glucopyranoside, neoarctin A, lariciresinol-4'-O- β -D-glucopyranoside, (-)-massoniresinol 3 α -O- β -D-glucopyranoside) were responsible for protecting against A β -induced toxicity in PC12 cells (Wang et al., 2014).

By antidepressant activity-guided fractionation of the MeOH extract, nine sesquiterpenes were isolated from the roots of *V. fauriei* Briq. The antidepressant activity of valerianin A, valerianin B, bicyclo [8, 1, 0] 5 β -hydroxyl-7 β -acetoxyl-5 α ,11, 11'-trimethyl-E-1(10)-ene-4 α , 15-olide and 8 α -acetoxyl-3 α ,4 α ,10-trihydroxyl-guaia-1(2)-ene-12, 6 α -olide was investigated by the FST on mice. Only bicyclo [8, 1, 0] 5 β -hydroxyl-7 β -acetoxyl-5 α ,11, 11'-trimethyl-E-1(10)-ene-4 α , 15-olide and 8 α -acetoxyl-3 α ,4 α ,10-trihydroxyl-guaia-1(2)-ene-12, 6 α -olide showed significant antidepressant activity (Liu et al., 2012). In an other study of dichloromethane extract of *V. wallichii* (Syn: *V. jatamansi* 10, 20 and 40 mg/kg, *p.o.*) in mice, the extract demonstrated antidepressant effect and significantly increased the norepinephrine and dopamine levels in mouse forebrain (Sah et al., 2011).

The acute and sub-chronic toxicity of iridoids rich fraction from *V. jatamansi* (IRFV) were determined and IRFV is extremely safe in the usual clinical dose, and may not have any single dose toxicity. The lethal dose with 50% mortality rate (LD50) on mice is over 2000 mg/kg bodyweight. The no-observed adverse effects level is 1200 mg/kg/day for rats. No direct correlation was found between the hematology, blood biochemical indexes, and organ coefficient of tested rats and the toxicity of IRFV (Xu et al., 2015).

Table 1. The isolated compounds from *Valeriana* species (Wang et al., 2010; 2014; Xu et al., 2011; Liu et al., 2012; Wu et al., 2014; Dong et al., 2015a; 2015b)

Group	Compound	Used Part	Source
Sesquiterpenes	Epoxysesquithujene, sesquithujenol, sesquithujene, α -santalene, (1R,2R,7R)-2-hydroxyl- β -bisabolol, (1R,2R,7R)-2-acetoxy- β -bisabolol, kissoone a, kissoone b, kissoone c, 2-demethyl-6-acetoxykissoone a, valerianin c, valerianin e, maaliol, β -gurjunene, valeranone, epi- α -muurolof, valerianol, kanokonol, valeriananoid a, patchouli alcohol, valeriananoid c, 8-acetoxy-patchouli alcohol, 8-acetoxy-patchouli alcohol, valeriananoid b, 8-hydroxylation-patchouli alcohol, seychellene, kessane, kessanyl acetate, kessanol, valeracetate, kessyl glycol 8-acetate, kessyl glycol, kessyl glycol 8-o-glucoside, α -kessyl alcohol, cyclo-kessyl acetate, α -kessyl acetate, 8-epikessyl glycol diacetate, kessyl glycol diacetate, kessyl glycol 2-acetate, δ -guaiene, α -gurjunene, allo-aromadendrene, viridiflorol, (-)-3 β ,4 β -epoxyvalerenic acid, valerenic acid, methyl valerenate, faurinone, caryophyllenol A, isovolvalerenal D, madolin B, madolin A, volvalerenic acid A, kissoone A, kissoone A acetate, kissoone B, kissoone C, 1-hydroxyl,11,11-trimethyldecahydrocyclopropane azulene-10-one, 15-hydroxypathulenol, (-)- α -bisabolol, volvalerenal D, valeriananoids D, valeriananoids E, clovane-2 β -isovalerony-9 α -ol, 1 β ,10 α -dihydroxyl-8 α -acetoxy-10 β ,11,11-trimethyl-4-formyl-bicyclogermacren-E-4(5)-ene, 1 β -hydroxyl-8 α -acetoxy-11,11-dimethyl-4-formyl-bicyclogermacren-E-4(5),10(14)-diene	Rhizome/root	<i>V. hardwickii</i> Wall. <i>V. fauriei</i> Briq. <i>V. himalayana</i> Grub. <i>V. pyrolaefolia</i> Decne. <i>V. officinalis</i> L. <i>V. jatamansi</i> Jones <i>V. amurensis</i> Smir. ex Kom
	(+)-tamariscene, (+)-pacifigorgia-1(9),10-diene, (+)-pacifigorgia-1(6),10-diene, (-)-valerena-4,7(11)-diene, (-)-pacifigorgiol	Essential oil	<i>V. officinalis</i> L.
	13-hydroxypatchoulol A, 11-epi-13-hydroxypatchoulol A, bisabola-7(14), 10-dien-4b, 5b, 15-triol, eremophila-1(10)-en-4a-ol, 3b-hydroxyl-b-(cis)-epoxide-a-guaiene, patchouli alcohol, 8-acetoxy-patchoulol, 9-hydroxypatchoulol, 9-acetoxy-patchoulol, valeranone, cyperusol, pogostol	Whole plant	<i>V. stenoptera</i> Diels
Iridoids	1-homoacevaltrate, 1-homoi-soacevaltrate, valtrate, acevaltrate, deacetylisovaltrate, 1- α -aceisovaltrate, didrovaltrate, isodidrovaltrate, 11-homohydroxyldihydrovaltrate, 10-isovaleryloxy kanokoside c, kanokoside a, kanokoside c, 1-de-3'-methylcrotonyl-1-iso-valerylvaltrate hydrine b7, 10-acetoxy-1-homovaltrate hydrin, 10-acetoxy-1-acevaltrate hydrin, valeriotriate a, valeriotriate b, patrinoside, kanokoside d, valechlorine, isovaleronyhydrin, acetoxydeisovalerony-1- α -acetoxyisovalerony isovaltratehydrine, (4R,5R,7S,8S,9S)-7-hydroxy-8-hydroxymethyl-4-methylperhydrocyclopenta, nardostachin, baldrinal, valeriotetrate b, valeriotetrate c, 8-methylvalepotriate, 1,5-dihydroxy-3,8-epoxyvalechlorine a, xiecaoside A, xiecaoside B, xiecaoside C, xiecaoline A, jatamanvaltrates R, jatamanvaltrates S, jatamanin Q, valerianoid A, valerianoid B, valerianoid C	Root Rhizome/root	<i>V. jatamansi</i> Jones <i>V. officinalis</i> L. <i>V. vaginata</i> Kunth. <i>V. fauriei</i> Briq. <i>V. laxiflora</i> DC. <i>V. amurensis</i> Smir. ex Komarov
	Valtrate, diavaltrate, acevaltrate, 1- β -aceacevaltrate, isovaltrate, sorbifolivaltrate a, sorbifolivaltrate b, seneciovaltrate, didrovaltrate, sorbifolivaltrate c, sorbifolivaltrate d, valtrate hydrine b3, valtrate hydrine b7, nardostachin	Aerial part	<i>V. sorbifolia</i> Kunth. <i>V. microphylla</i> Kunth. <i>V. jatamansi</i> Jones
	Valtrate, diavaltrate, acevaltrate, 1- β -aceacevaltrate, didrovaltrate, adh-valtrate, dihydrocornin, stenopterlin A-E, patrinoside-aglucone, (4b, 8b)-8-ethoxy-3-methyl-10-methylen-2, 9-dioxatricyclo[4.3.1.03,7]decan-4-ol, 6-hydroxy-7-(hydroxymethyl)-4-methylenehexahydrocyclopenta[c]pyran-1(3H)-one, (4R,5R,7S,8S,9S)-7-hydroxy-7-hydroxymethyl-methyl-perhydrocyclopenta[c]pyran-1-one	Whole plant	<i>V. glechomifolia</i> Meyer <i>V. stenoptera</i> Diels
	Valdiate, (1R,2S,6S,9S)-5-acetyloxymethyl-9-methyl-3-oxabicyclo[4.3.0.1]non-4-en-2-yl isovalerate	Seed	<i>V. officinalis</i> L. var. <i>sambucifolia</i> Mikano

Flavonoids	Acacetin, luteolin, diosmetin, apigenin, linarin, tricrin, 5,7,3'-trihydroxy-4'-methoxyflavone, quercetin, kaempferol, 5,7-dihydroxy-3,6,4'-trimethoxyflavone, 6-methylapigenin, acacetin-7-o- β -sophoroside, acacetin-7-o-(6''-o- α -L-rhamnopyranosyl)- β -sophoroside, 2S(-)-hesperidin	Above ground/ root Rhizome /root Root	<i>V. officinalis</i> L. <i>V. jatamansi</i> Jones
Alkaloids	Valerine a, valerine b, 6,7-dihydro-2-(p-hydroxyphenethyl)-4,7-dimethyl-5h-2-pyrindinium salt, actinidine, valerianine, valerine	Above ground/ root Root	<i>V. officinalis</i> L.
Others	(+)-1-hydroxy-2,6-bis-epi-pinoresinol, pinoresinol, prinsepiol, prinsepiol-4-o- β -d-glucopyranoside, fraxiresinol-4'-o- β -d-glucopyranoside, 8-hydroxypinoresinol-4'-o- β -d-glucopyranoside, 8-hydroxypinoresinol, (+)-1-hydroxypinoresinol, betulin, betulinic acid, 23-hydroxyursolic acid, ursolic acid, oleanolic acid, ferulic acid, α -pinene, β -pinene, sabinene, camphor, borneol, camphene, bornyl acetate, α -fenchene, β -elemene, α -terpinene, limonene, xiecaoside D, xiecaoside E	Above ground/ root Root Aerial part	<i>V. laxiflora</i> DC. <i>V. microphylla</i> Kunth. <i>V. prionophylla</i> Standl. <i>V. officinalis</i> L. <i>V. jatamansi</i> Jones <i>V. himalayana</i> Grub. <i>V. hardwickii</i> Wall. <i>V. pyrolaefolia</i> Decne.

Studies in Turkey

Ethnobotanical Studies:

In an ethnobotanical study in East Anatolia, it was determined that *V. alliarifolia* Adams is used traditionally in Van (Özalp), Erzurum (Horasan), Erzincan (Kemah) and Bitlis (Hizan). The infusion (tea) prepared from its roots preferred as sedative, antispasmodic (Özgökçe & Özçelik, 2004).

Öz Aydın et al. published the traditional usage of *V. officinalis* in their study on the plants used as analgesic. This species has an usage for analgesic and sedative effects in Uşak (Eşme). (Öz Aydın et al., 2006).

An infusion is prepared from the roots of *V. officinalis* at the western Mediterranean Region in Turkey, This infusion is used for the treatment of neural diseases and as tranquilizer (Fakir et al., 2009).

Studies on Chemical Constituents:

A PhD thesis was published, which carried out to determine the effects of different row spaces and harvest times on yield and quality of the essential oil from *V. officinalis* growing in Çukurova region (Turkey). It was found that the yield of essential oil optimum harvest time was June and row spaces was 25 cm. Seventy nine compounds were characterized in dry roots. The main compounds were bornyl acetate (14.8-30.8 %), valeranal

(8.4-19.7 %), camphene (1.6-12.4 %), cedrandiol (1.3-9.8 %), spathulenol (2.2-9.0 %), α -pinene (2.7-6.5 %) and fenchene (3.2-6.1 %) (Kaya, 2006).

Özbay et al. investigated the volatile constituents from roots and rhizomes of *V. alpestris* Stev., collected in Van (Turkey) by GC and GC/MS analysis. The oil yield of the plant material was 0.2% (v/w) on a dry weight basis. 82 components were identified, mainly hexadecanoic acid (12%), decadienal (3.3%), thymol (1.9%), γ -terpinene (1.7%), and dimethoxybenzene (1.7%) (Özbay et al., 2009).

In an other study by the same research group, the yield and composition of the essential oil from the roots and rhizomes of *V. phu* L. were established by GC and GC/MS (EI) analysis. The yield of essential oil was 0.64% (v/w) on a dry weight basis. 70 compounds were founded: with a valeranal isomer (11.3%), valerianol (3.1%), patchouli alcohol (2.9%) and valeranone (2.2%). One new component was isolated and identified as 1-hydroxy-1,11,11-trimethyldecahydrocyclopropane azulene-10-one for the first time (Aslan et al., 2009).

Additionally, *V. alliariifolia*, used as sedative, antispasmodic traditionally, was studied. The subterranean parts of *V. alliariifolia* Adams were hydrodistilled. The chemical composition of the oil was identified by using capillary Gas Chromatography (GC) and GC/MS simultaneously. In total 68 constituents were identified, representing 87.6% of the total oil. The major compounds of the essential oil were isovaleric acid (28.6%), by following δ -guaiane (7.2%), α -humulene (4.7%), hexadecanoic acid (4.3%), valeric acid (3.7%) and humulene epoxide-II (3.6%) (Özgökçe & Özçelik, 2004; Bardakçı et al., 2012).

Studies on Biological Activities:

The acetylcholinesterase enzyme (AChE) inhibitor activity was tested *in vitro* from several plants in human erythrocytes and serum. In this study, the effect of soluble extracts of five plants on AChE activity was investigated and all plants founded active at different concentrations. This was the first study to show the relationships of erythrocyte and human serum AChE activity, in Lamiaceae family, *V. officinalis* L., *Chrysophthalmum montanum* (DC.) Boiss., *Ziziphora tenuior* L. and *Melissa officinalis* (Özdemir et al., 2013).

Furthermore, the antioxidant activity of *V. dioscoridis* SM. was evaluated comparing with 6 other plants (*Asplenium ceterach* L., *Doronicum orientale* Hoffm., *Cota pestalozzae* (Boiss.) Boiss., *Eremurus spectabilis* M. Bieb., *Asphodeline lutea* (L.) Rchb. and *Smyrniium connatum* Boiss. and Kotschy) (Karadeniz et al., 2015).

Beside of all studies, a review about herbal drugs and drug interactions was published by a Turkish researcher. The importance of ‘herbal drugs and drugs interactions’ knowledge was emphasized in parallel with the widely usage in Turkey in light of the published studies (Dülger, 2012).

Conclusion

The *Valeriana* species are used traditionally worldwide, also in different regions of Turkey. The chemical contents and activities of all species, grown in Turkey, have to be proved by identification and tests (*in vitro* and *in vivo*) for the safely usage; but existing studies are limited in Turkey. The increase of the numbers of studies will enhance the introduction of these species in treatment.

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