Chemical Constituents of Plants from the Genus *Valeriana*

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Abstract: The genus *Valeriana* (Valerianaceae) contains over 250 species distributed around the world and used in traditional medicines of many cultures. The main compounds isolated from *Valeriana* species are essential oils, valerenic acid and its derivatives and iridoids, accumulated mainly in the roots and rhizomes. This review lists 135 chemical constituents as well as their biosynthesis and bioactivity as reported by the end of 2008 (80 references).

Keywords: Valeriana, biosynthesis, chemical constituents, sesquiterpenoids, iridoids, flavonoids, biological activity.

1. INTRODUCTION

The genus *Valeriana* (Valerianaceae) contains over 250 species distributed around the world and used in traditional medicines of many cultures [1-3]. Roots of *Valeriana* species comprise the source of the drug Valerian used as a sedative since it was described by ancient Greeks and Romans [4]. The main compounds isolated from *Valeriana* species are essential oils, valerenic acid (**46**) and its derivatives and iridoids, accumulated mainly in the roots and rhizomes [5]. Reviewing valerian is very difficult, because, as described below, the active principle is unknown; chemical constitutions are variable among the Valeriana species and even seasonal variations can have a huge impact. Our hope is that this literature review will pave the way to further study of biologically active compounds of some plants in the genus *Valeriana*. In this article, we will summarize the progress on phytochemical studies followed by a discussion on the pharmacological activities and chemical varieties of several *Valeriana* species from the literature published to the end of 2008.

2. CHEMICAL CONSTITUENTS

All the reported chemical constituents of *Valeriana* (**1-135**) are shown in the Tables **1-3** below with their names, plant parts they were isolated from and their biological sources. As listed in the tables, sesquiterpenes and iridoids are the predominant constituents of this genus. Flavonoids and alkaloids were mainly obtained from the aerial parts of the *Valeriana* while the sesquiterpenes and iridoids in the roots and rhizomes [6,7].

2.1. Sesquiterpenes (Table 1)

There have been 49 sesquiterpenes isolated from *Valeriana* species (Figs. **1** and **2**). Though cyclized/oxidized information is complex, the characteristic methyl residues still could be easily detected. And we can discern several skeletons: bisabolane, eudesmane, guaiane, velerenane and some modified derivatives.

In 1994, two new bisabolane sesquiterpenoids, (1*R*,2*R*,7*R*)-2-hydroxy-β-bisabolol (**5**) and (1*R*,2*R*,7*R*)-2-acetoxy-β-bisabolol (**6**) were reported from *V. fauriei* cultivated in Korea [8]. Zhang recently reported the sole example of valerianin E (**12**) with a bicyclogermacrane skeleton [9]. Further study lead to the isolation of another unique guaiane lactone, valerianin C (**11**) from the root of *V. fauriei* Briq by the same group [10]. In 1995, valeracetate (**27**), where the methyl group in guaiane-type sesquiterpenoids is oxygenated along with three known sesquiterpenes were isolated from *V. officinalis* [11]. Though as in some compounds, the oxo bridge between C12 and C10 made the structure relatively complex, this class of sesquiterpenoids was not restricted to one or two species. Based on ^{13}C NMR data and decoupling experiments, the proposed structure for faurinone (**48**) was corrected in 1983 [12]. Tamariscene (**41**), pacifigorgiadienes (**42**, **43**) and valerenadiene (**44**) were all isolated and identified from *V. officinalis.* Tamariscenes may be a common precursor for both valerenanes and pacifigorfianes [13].

2.2. Iridoids (Table 2)

The iridoids of the genus *valeriana* can be mainly classified into four groups: monoene, lytic monoene, diene and lytic diene (Fig. **3**). The most important iridoid compounds found in Valerianaceae are the valepotriates [valtrate (**52**), isovaltrate (**56**), acevaltrate (**54**), didrovaltrate (**62**) and their homologues]. Few reports are available on the presence of normal iridoid glucosides with the glucose linked to C1. Most frequently found are the so-called 'valeriana compounds', characterized by isovaleric esters at C1 and C11 and occasionally acetyl groups or glycosyl moiety at C11. Besides Valerianaceae, these kinds of compounds have also been found in some genera such as *Viburnum* and *Sambucus* [14,15] and *Penstemon* (Scrophulariaceae) [16]. It is noteworthy that a few naturally occurring 5-hydroxy-substituted iridoids were found in this genus.

In 2007, four new diene valepotriates, sorbifolivaltrates A-D (**59**, **60**, **72**, **73**), were isolated by bioassay-guided fractionation of the cytotoxic hexanes and methyl ethyl ketone crude extracts of the aerial parts of *V. sorbifolia* [17]. 1-β-Aceacevaltrate (**55**) was previously reported from *Phyllactis pulvinata* Rauh et Willer and the genious *Phyllactis* was sometimes included in *Valeriana* or recognized as a section of *Valeriana* [18]. Dihydrocornin (**84**) differs from the iridoid glycosides usually found in *Valeriana* species and it was previously found in *Viburnum dentata* [19]. 1,5-Dihydroxy-3,8-epoxyvalechlorine A (**91**) is an unusual iridoid bearing a chlorine group at C10 and an oxo bridge connecting C3 and C8 and resulting in a rigid skeleton [20]. Over the past decades, standardized purified extracts of *Valeriana* species have largely replaced the traditional tincture in Western Europe where *Valeriana* is used both as a sedative and an antispasmodic. Since *Bounthan et al.* [21] reported that valepotriates (**90** etc.) were cytotoxic and inhibit DNA synthesis, the market is demanding products with a high content of valerenic acid (**46**) but low in valepotriates.

2.3. Flavonoids (Table 3, Fig. 4)

6-Methylapigenin (**102**) was the only example with a methyl group at C6 and as described below, there are some reports on its activity. Acacetin 7-*O*-β-sophoroside (**103**), acacetin 7-*O*-(6"-*O*-α-

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Table 1. Sesquiterpenoids (1-49)

No.	Name	Part	Source	Ref.
1	epoxysesquithujene	roots/rhizomes	*V. hardwickii* var. *hardwickii*	[26]
2	sesquithujenol	root/rhizomes	*V. hardwickii* var. *hardwickii*	[26]
3	sesquithujene	root/rhizome	*V. hardwickii* var. *hardwickii*	[26]
4	α-santalene	root	*V. wallichii*	[7]
5	(1*R*,2*R*,7*R*)-2-hydroxyl-β-bisabolol	rhizome/root rhizome/root	*V. fauriei* *V. fauriei*	[59] [8]
6	(1*R*,2*R*,7*R*)-2-acetoxyl-β-bisabolol	rhizome root	*V. fauriei*	[8]
7	kissoone a	root	*V. fauriei*	[58]
8	kissoone b	root	*V. fauriei*	[58]
9	kissoone c	root	*V. fauriei*	[58]
10	2-demethyl-6-acetoxylkissoone a	rhizomes/root	*V. fauriei*	[59]
11	valerianin c	root	*V. fauriei* briq.	[10]
12	valerianin e	root	*V. fauriei*	[9]
13	maaliol	root root root	*V. wallichii* *V. himalayana* *V. hardvickii* var. *arnottiana*	[7] [7] [7]
14	β-gurjunene	root root root root	*V. wallichii* *V. himalayana* *V. hardvickii* var. *arnottiana* *V. pyrolaefolia*	[7] [7] [7] [7]
15	valeranone	root	*V. himalayana* *V. pyrolaefolia*	[7] [7]
16	*epi*-α-muurolol	root	*V. hardvickii* var. *arnottiana*	[7]
17	valerianol	rhizome/root essential oil	*V. hardvickii* *V. officinalis*	[7] [13]
18	kanokonol	root	*V. fauriei*	[37]
19	valerianannoid a	rhizome/root	*V. jatamansi*	[67]
20	patchouli alcohol	rhizome/root root root	*V. fauriei* *V. wallichii* *V. pyrolaefolia*	[68] [7] [7]
21	valerianannoid c 8-acetoxyl-patchouli alcohol 8-acetoxypatchouli alcohol	rhizome/root rhizome/ root root	*V. jatamansi* *V. fauriei* *V. wallichii*	[67] [68] [7]
22	valerianannoid b 8-hydroxylation-patchouli alcohol	rhizome/root rhizome/ root	*V. jatamansi* *V. fauriei*	[67] [68]
23	seychellene	root	*V. wallichii* *V. himalayana* *V. hardvickii* var. *arnottiana*	[7]
24	kessane	root root root root rhizome/ root	*V. wallichii* *V. himalayana* *V. hardvickii* *V. pyrolaefolia* *V. fauriei*	[7] [7] [7] [7] [69]
25	kessanyl acetate	root rhizome/ root	*V. hardvickii* var. *arnottiana* *V. fauriei*	[7] [69]
26	kessanol	root	*V. fauriei*	[37]
27	valeracetate	root root	*V. hardvickii* var. *arnottiana* *V. officinalis*	[7] [11]
28	kessyl glycol 8-acetate	rhizome/root root	*V. fauriei* *V. officinalis*	[69] [11]
29	kessyl glycol	rhizome/root	*V. fauriei*	[37, 69]
30	kessyl glycol 8-o-glucoside	rhizome/ root	*V. fauriei*	[69]
31	α-kessyl alcohol	root	*V. fauriei*	[37]
32	cyclokessyl acetate	rhizome/root root	*V. fauriei* *V. fauriei*	[69] [37, 70]

Table 1. contd…

No.	Name	Part	Source	Ref.
33	α-kessyl acetate	root root root rhizome/ root root	*V. himalayana* *V. hardvickii* var. *arnottiana* *V. hardwickii* var. *arnottiana* *V. fauriei* *V. officinalis*	[7] [7] [7] [69] [11]
34	8-epikessyl glycol diacetate	root	*V. hardvickii* var. *arnottiana*	[7]
35	kessyl glycol diacetate	root root rhizome/ root	*V. himalayana* *V. officinalis* *V. fauriei*	[7] [11] [37, 69]
36	kessyl glycol 2-acetate	rhizome/ root	*V. fauriei*	[69]
37	δ-guaiene	root	*V. wallichii*	[7]
38	α-gurjunene	root	*V. himalayana* *V. hardvickii* var. *arnottiana*	[7]
39	allo-aromadendrene	root	*V. pyrolaefolia*	[7]
40	viridiflorol	root root root	*V. wallichii* *V. himalayana* *V. hardvickii* var. *arnottiana*	[7] [7] [7]
41	(+)-tamariscene	essential oil	*V. officinalis*	[13]
42	(+)-pacifigorgia-1(9),10-diene	essential oil	*V. officinalis*	[13]
43	(+)-pacifigorgia-1(6),10-diene	essential oil	*V. officinalis*	[13]
44	(-)-valerena-4,7(11)-diene	essential oil	*V. officinalis*	[13]
45	(-)-3β,4β-epoxyvalerenic acid	root	*V. officinalis*	[71]
46	valerenic acid	root	*V. officinalis*	[71]
47	methyl valerenate	root	*V. officinalis*	[71]
48	faurinone	root	*V. officinalis*	[12]
49	(-)-pacifigorgiol	essential oil	*V. officinalis*	[13, 72]

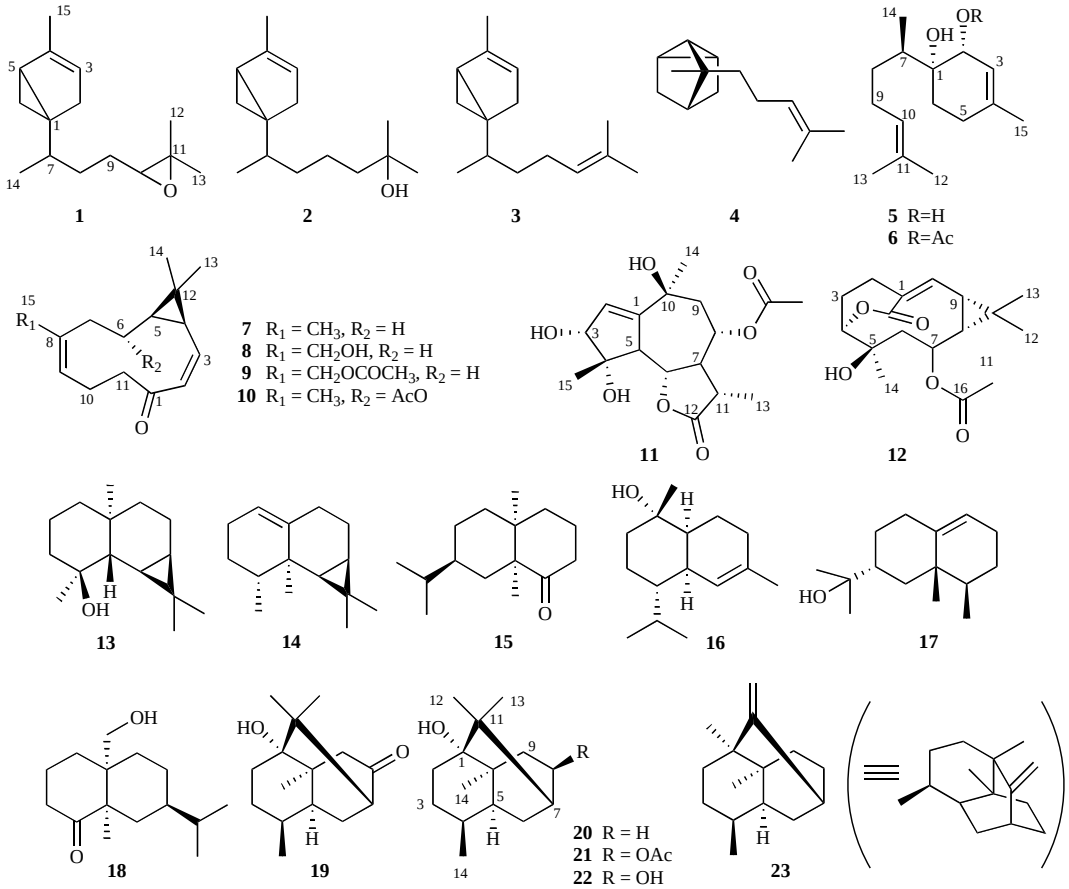


Fig. (1). Sesquiterpenes isolated from *Valeriana* species-1.

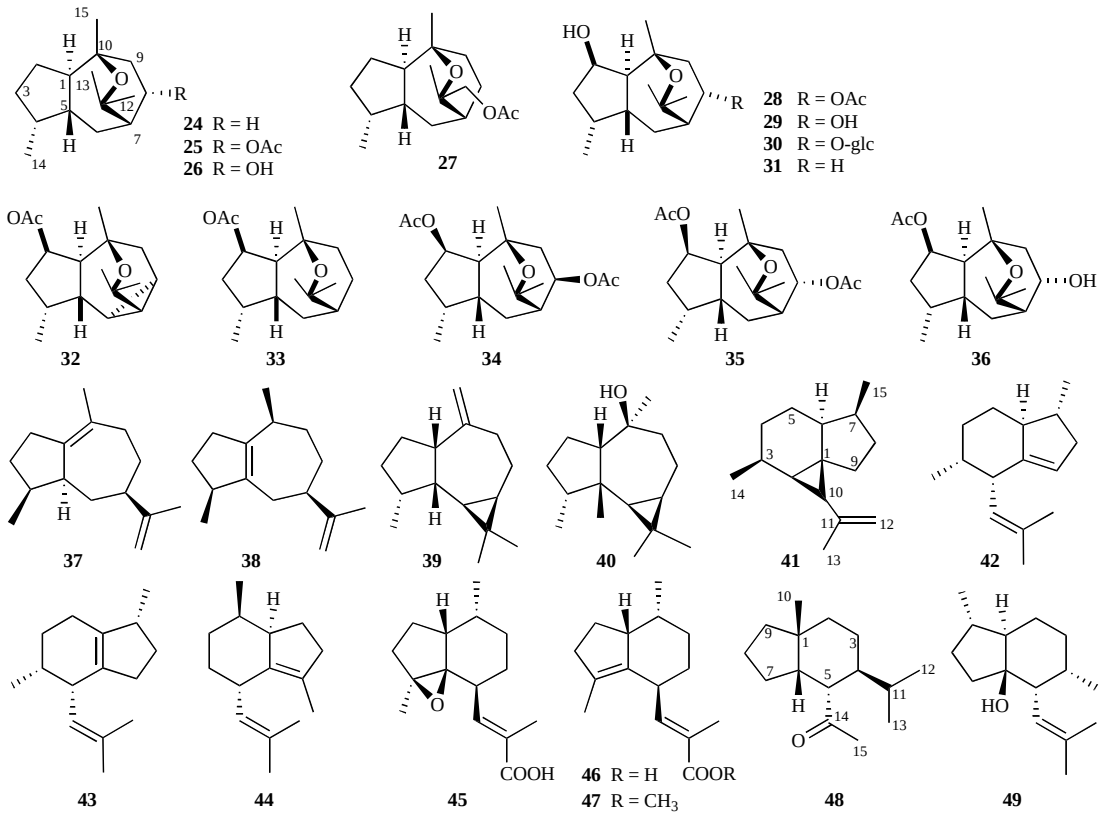


Fig. (2). Sesquiterpenes isolated from *Valeriana* species-2.

Table 2. Iridoids (50-91)

No.	Name	Part	Source	Ref.
50	1-homoacevaltrate	rhizome/root	*V. jatamansi*	[60]
51	1-homoisoacevaltrate	rhizome/root	*V. jatamansi*	[60]
52	valtrate	whole plant aerial parts rhizome aerial part -	*V. glechomifolia* *V. sorbifolia* *V. wallichii D.C* *V. microphylla* *V. jatamansi*	[73] [17] [74] [75] [63]
53	diavaltrate	whole plant aerial part	*V. glechomifolia* *V. microphylla*	[73] [75]
54	acevaltrate	whole plant rhizome aerial part -	*V. glechomifolia* *V.wallichii D.C* *V. microphylla* *V. jatamansi*	[73] [74] [75] [63]
55	1-β-aceacevaltrate	whole plant	*V. glechomifolia*	[73]
56	isovaltrate	aerial part aerial part	*V. sorbifolia* *V. microphylla*	[17] [75]
57	deacetylisovaltrate	root	*V. officinalis*	[76]
58	1-α-aceisovaltrate	root	*V. officinalis*	[77]
59	sorbifolivaltrate a	aerial part	*V. sorbifolia*	[17]
60	sorbifolivaltrate b	aerial part	*V. sorbifolia*	[17]
61	seneciovaltrate	aerial part	*V. sorbifolia*	[17]
62	didrovaltrate	whole plant rhizome aerial part	*V. glechomifolia* *V.wallichii D.C* *V. microphylla*	[73] [74] [75]
63	isodidrovaltrate	rhizome/root	*V. vaginata*	[78]
64	adh-valtrate	whole plant	*V. glechomifolia*	[73]
65	11-homohydroxyldihydrovaltrate	rhizome/root	*V. jatamansi*	[60]

Table 2. cond…

No.	Name	Part	Source	Ref.
66	10-isovaleryloxy kanokoside c	rhizome/ root	*V. fauriei*	[59]
67	kanokoside a	rhizome/root rhizome/root	*V. fauriei* *V. fauriei*	[69] [8]
68	kanokoside c	rhizome/root rhizome/root	*V. fauriei* *V. fauriei*	[69] [8]
69	1-de-3'-methylcrotonyl-1-iso-valerylvaltrate hydrine b7	rhizome/root	*V. fauriei*	[59]
70	10-acetoxy-1-homovaltrate hydrin	rhizome/root	*V. jatamansi*	[60]
71	10-acetoxy-1-acevaltrate hydrin	rhizome/root	*V. jatamansi*	[60]
72	sorbifolivaltrate c	aerial part	*V. sorbifolia*	[17]
73	sorbifolivaltrate d	aerial part	*V. sorbifolia*	[17]
74	valtrate hydrine b3	aerial part	*V. sorbifolia*	[17]
75	valtrate hydrine b7	aerial part	*V. sorbifolia*	[17]
76	valeriotriate a	root	*V. jatamansi*	[79]
77	valeriotriate b	root	*V. jatamansi*	[79]
78	patrinoside	rhizome/root rhizome/root	*V. fauriei* *V. fauriei*	[69] [8]
79	kanokoside d	rhizome/root rhizome/root	*V. fauriei* *V. fauriei*	[69] [8]
80	valechlorine	root	*V. officinalis*	[76]
81	isovaleroxyhydrm	root	*V. officinalis*	[76]
82	acetoxydeisovaleroxy-1-α-acetoxyisovaleroxy isovaltratehydrine	root	*V. officinalis*	[77]
83	(4*R*,5*R*,7*S*,8*S*,9*S*)-7-hydroxy-8-hydroxymethyl-4-methylperhydrocyclopenta	above-ground/root	*V. laxiflora*	[61]
84	dihydrocornin	whole plant	*V. glechomifolia*	[73]
85	valdiate (1*R*,2*S*,6*S*,9*S*)-5-acetyloxymethyl-9-methyl-3-oxabicyclo[4.3.0.]non-4-en-2-yl isovalerate	seed	*V. officinalis* var. *sambucifolia*	[80]
86	nardostachin	aerial part	*V. microphylla*	[75]
87	baldrinal	rhizome	*V. wallichii* D.C	[74]
88	valeriotetrate b	root	*V. wallichii*	[20]
89	valeriotetrate c	root	*V. wallichii*	[20]
90	8-methylvalepotriate	root	*V. wallichii*	[20]
91	1,5-dihydroxy-3,8-epoxyvalechlorine a	root	*V. wallichii*	[20]

Table 3. Others (92-135)

No.	Name	Part	Source	Ref.
92	acacetin	above-ground/root	*V. officinalis*	[22, 23]
93	luteolin	above-ground/root	*V. officinalis*	[22, 23]
94	diosmetin	above-ground/root	*V. officinalis*	[22, 23]
95	apigenin	above-ground/root	*V. officinalis*	[22, 23]
96	linarin	above-ground/root	*V. officinalis*	[22, 23]
97	tricin	above-ground/root	*V. officinalis*	[61]
98	5,7,3'-trihydroxy-4'-methoxyflavone	above-ground/root	*V. officinalis*	[61]
99	quercetin	above-ground/root	*V. officinalis*	[22, 23]
100	kaempferol	above-ground/root	*V. officinalis*	[22, 23]
101	5,7-dihydroxy-3,6,4'-trimethoxyflavone	above-ground/root	*V. officinalis*	[61]
102	6-methylapigenin	roots/rhizome	*V. wallichii*	[45, 50]
103	acacetin 7-o-β-sophoroside	roots/rhizome	*V. jatamansi*	[81]
104	acacetin7-o-(6"-o-α-l-rhamnopy- ranosyl)-β-sophoroside	roots/rhizome	*V. jatamansi*	[81]
105	2*S*(-)-hesperidin	roots/rhizome	*V. wallichii*	[45]
106	valerine a	above-ground/root	*V. officinalis*	[22, 23]
107	valerine b	above-ground/root	*V. officinalis*	[22, 23]
108	6,7-dihydro-2-(p-hydroxyphenethyl)-4,7-dimethyl-5h-2-pyrindinium salt	root	*V. officinalis*	[82]

Table 3. contd….

No.	Name	Part	Source	Ref.
109	actinidine	above-ground/root	*V. officinalis*	[22, 23]
110	valerianine	above-ground/root	*V. officinalis*	[22, 23]
111	valerine	above-ground/root	*V. officinalis*	[22, 23]
112	(+)-1-hydroxy-2,6-bis-epi-pinoresinol	above-ground/root	*V. laxiflora*	[61]
113	pinoresinol	aerial part	*V. microphylla*	[75]
114	prinsepiol	above-ground/root	*V. laxiflora* *V. prionophylla*	[61] [1]
115	prinsepiol-4-o-β-d-glucopyranoside	root	*V. prionophylla*	[1]
116	fraxiresinol-4'-o-β-d-glucopyranside	root	*V. prionophylla*	[1]
117	8-hydroxypinoresinol-4'-o-β-d-glucopyranoside	root	*V. prionophylla*	[1]
118	8-hydroxypinoresinol (+)-1-hydroxypinoresinol	root above-ground/root aerial part	*V. prionophylla* *V. laxiflora* *V. microphylla*	[1] [61] [75]
119	betulin	above-ground/root	*V. laxiflora*	[61]
120	betulinic acid	above-ground/root	*V. laxiflora*	[61]
121	23-hydroxyursolic acid	above-ground/root	*V. laxiflora*	[61]
122	ursolic acid	above-ground/root	*V. laxiflora*	[61]
123	oleanolic acid	above-ground/root	*V. laxiflora*	[61]
124	ferulic acid	above-ground/root	*V. laxiflora*	[61]
125	α-pinene	above-ground/root	*V. officinalis*	[23, 30]
126	β-pinene	above-ground/root	*V. officinalis*	[23, 30]
127	sabinene	above-ground/root	*V. officinalis*	[23, 30]
128	camphor	above-ground/root	*V. officinalis*	[23]
129	borneol	above-ground/root	*V. officinalis*	[23]
130	camphene	above-ground/root	*V. officinalis*	[23, 30]
131	bornyl acetate	above-ground/root root root root root	*V. officinalis* *V. wallichii* *V. himalayana* *V. hardwickii* var. *arnottiana* *V. pyrolaefolia*	[23, 30] [7] [7] [7] [7]
132	α-fenchene	above-ground/root	*V. officinalis*	[23, 30]
133	δ-elemene	above-ground/root	*V. officinalis*	[13, 23, 30]
134	α-terpined	above-ground/root	*V. officinalis*	[23]
135	limonene	above-ground/root	*V. officinalis*	[23, 30]

L-rhamnopyranosyl)-β-sophoroside (**104**) and hesperidin (**105**) were glycosides.

2.4. Alkaloids (Table 3, Fig. 5)

The alkaloids are the minor constituents of the genus *valeriana* mainly isolated from *V. officinalis* [22,23].

2.5. Others (Table 3, Fig. 6)

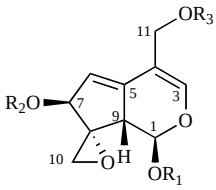
The others constituents contain lignans, triterpenes and some monoterpenes of the essential oil.

3. CHEMICAL VARIETY

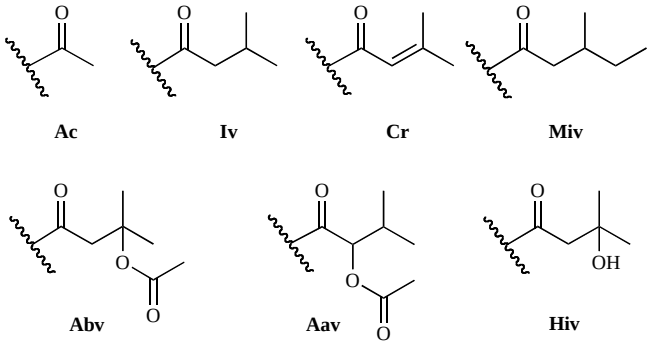
Four Valeriana species were investigated for their terpenoid compositions by means of GC and GC/MS analyses [7]. The results showed that valeranone (**15**), maaliol (**13**), α-kessyl acetate (**33**), and kessane (**24**) are the major constituents of the essential oil from roots of *V. himalayana*. Patchouli alcohol (**20**), and valeranone (**15**) are present in the root oil of *V. pyrolaefolia* Decne. *V. hardwickii* var. *arnottiana* exhibited two chemotypes growing in separate habitats. Chemotype I contains, as major constituents, valeracetate (**27**), 8-epikessyl glycol diacetate (**34**), and α-kessyl acetate (**33**), whereas, in the case of chemotype II, maaliol (**13**) and kessanyl acetate (**25**) are the most abundant ingredients. More than 200 samples collected during 1998 and 2003 from different natural habitats of *V. wallichii* have two distinct chemical compositions. The marker compound [maaliol (**13**)] in chemotype I was not present even in trace amounts in chemotype II. In turn, the major constituent, patchouli alcohol (**20**) from chemotype II, has not been detected in chemotype I either. Also, an earlier report on *V. wallichii* had assumed that this species existed only as a single chemotype [24].

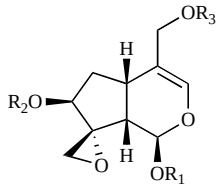
Based on the morphological similarity [25] between *V. wallichii* and *V. pyrolaefolia*, the latter is often collected together with the former for commercial purposes; nevertheless, there is no similarity with respect to the major constituents of their oils. Valeranone (**15**), the major constituent of *V. pyrolaefolia*, has not been found in *V. wallichii*.

Mathela reported the chemical differences of *V. hardwickii* var. *hardwickii* and *V. javanica* [26]. Organic solvent extraction of the steam distillate of the root and rhizomes of *V. hardwickii* var. *hardwickii* afforded epoxysesquithujene (**1**) along with 20 other compounds. Thymol methyl ether (1.81%), bornyl acetate (20.45%),

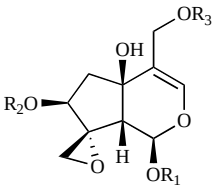


No.	R_1	R_2	R_3
50	Miv	Abv	Ac
51	Miv	Ac	Aav
52	Iv	Iv	Ac
53	Iv	Ac	Ac
54	Iv	Abv	Ac
55	Abv	Abv	Ac
56	Iv	Ac	Iv
57	Iv	H	Iv
58	Aav	Ac	Aav
59	Cr	Iv	Iv
60	Cr	Miv	Ac
61	Cr	Iv	Ac

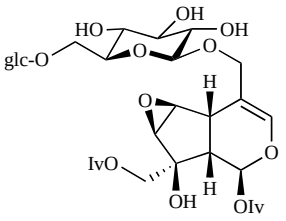




62 R_1 = Iv, R_2 = Ac, R_3 = Iv
63 R_1 = Iv, R_2 = Iv, R_3 = Ac



64 R_1 = Iv, R_2 = Ac, R_3 = Aav
65 R_1 = Iv, R_2 = Ac, R_3 = Miv



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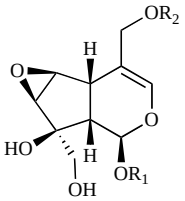
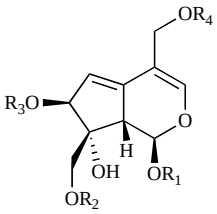
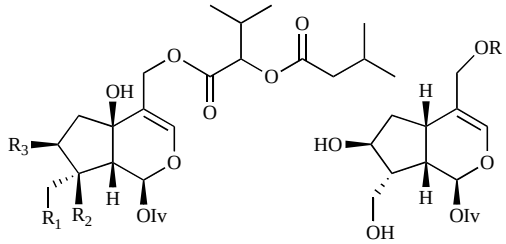


67 R_1 = Iv, R_2 = glucose
68 R_1 = Iv, R_2 = gentiobiose

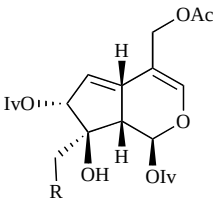


No.	R_1	R_2	R_3	R_4
69	Iv	Iv	Iv	Ac
70	Miv	Ac	Iv	Ac
71	Abv	Ac	Iv	Ac
72	Hiv	Iv	Iv	Iv
73	Cr	Iv	Miv	Ac
74	Hiv	Iv	Iv	Ac
75	Cr	Iv	Iv	Ac

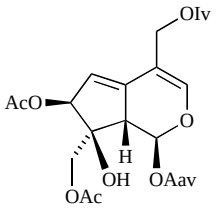


76 R_1 = OH, R_2 = OEt, R_3 = OAc
77 R_1 = AcO, R_2 = OH, R_3 = OH

78 R = glucose
79 R = gentiobiose



80 R = Cl
81 R = OIv



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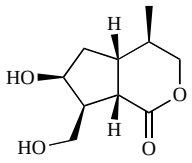

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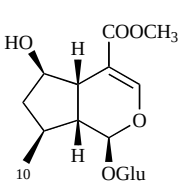

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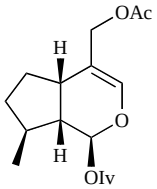

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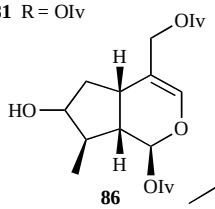

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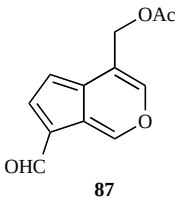

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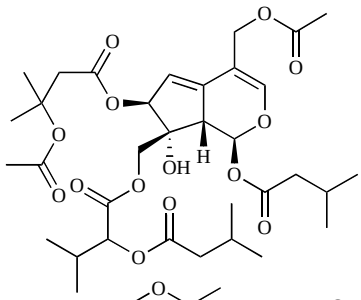

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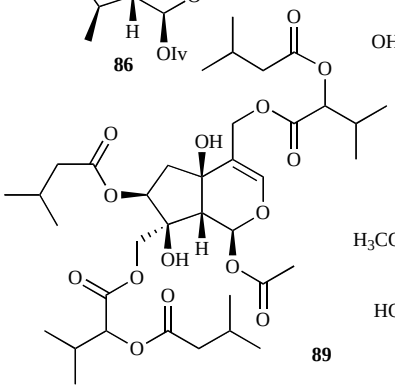

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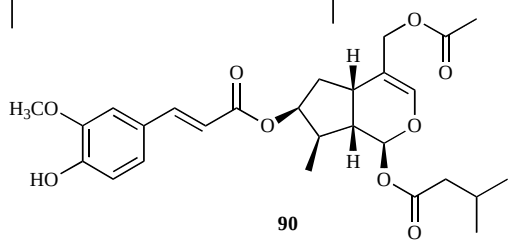

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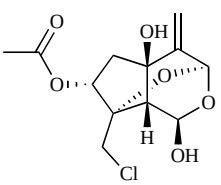
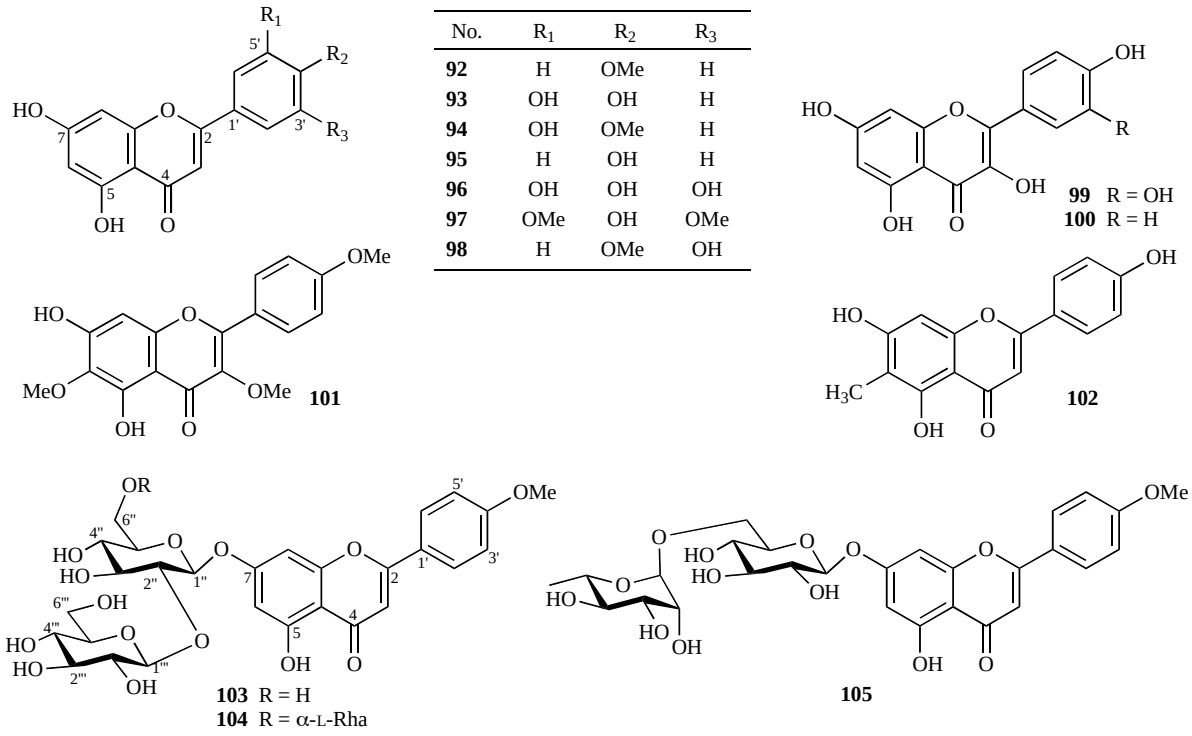


91

Fig. (3). Iridoids isolated from *Valeriana* species.



No.	R_1	R_2	R_3
92	H	OMe	H
93	OH	OH	H
94	OH	OMe	H
95	H	OH	H
96	OH	OH	OH
97	OMe	OH	OMe
98	H	OMe	OH

Fig. (4). Flavonoids isolated from *Valeriana* species.

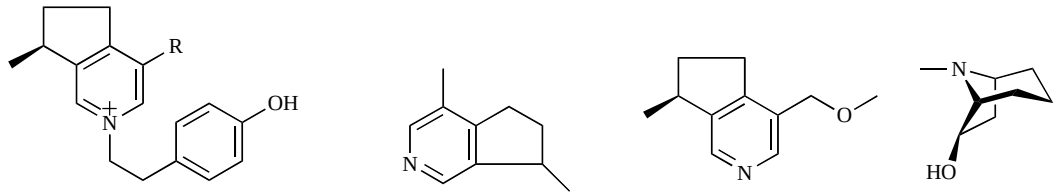


Fig. (5). Alkaloids isolated from *Valeriana* species.

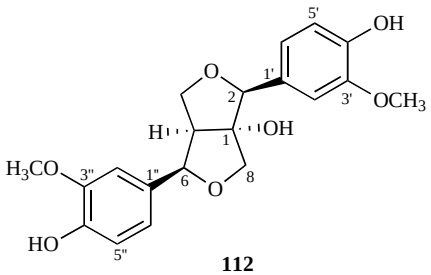
and *cis*-caryophyllene (3.22%), were among the major compounds identified. On the contrary, *V. javanica*, a morphologically indistinguishable species, has been reported to possess kessyl acetate (**33**, 36.2%), patchouli alcohol (**20**, 10.3%), kessane (6.8%) and valeranone (**15**, 3.2%) [27].

Significantly epoxysesquithujene was the major component of *V. hardwickii* var. *hardwickii* with ca. 50% of the total essential oil and has not been found in any other *Valeriana* sp. Thus the distinction in their flavor compositions may consequently affect their use as medicine and flavour materials.

Indian Valerian, *V. wallichii* DC., has been used as an ingredient in Indian herbal medicines and as a substitute of the European *V. officinalis*. Charak Samhita, an ancient Indian medical text, described two forms of *V. wallichii* distinguishable in the field alone [28]. Ved Prakash also described it as variable in general size of plants, but with no specific difference in other plant characters [29]. Thus, though used extensively for centuries, *V. wallichii* has not been reported earlier to have subspecies or chemotypes.

V. officinallis is a perennial plant distributed in most parts of Europe and Northern Asia. As the most important plant of the genus *Valeriana*, it was used mainly used as a sedative and an anxiolytic. *Valeriana officinalis* displays a considerable diversity in its morphology. Polyploidy occurs and there are diploid, tetraploid and octoploid types. While it is obvious that the composition of the essential oils of the normal and the transformed roots of *V. oflicinalis* var. *sambucifolia* (which is an octopioid form) is complex. Numerous differences have been noticed, in particular the high content of kessyl alcohol (**31**) (10.5%) and kessyl acetate (**33**, 10.4%) in the hairy roots, whereas these compounds presented in low amounts in the normal oil. Up to now, no satisfactory explanation has accepted for the differences between the normal and the transformed essential oils and it remains unanswered largely [30].

Valtrate (**52**), DIA-valtrate (**53**), acevaltrate(**54**), 1-β-acevaltrate (**55**) and didrovaltrate (**62**) have been quantitatively estimated by reverse-phase HPLC in species of *V. glechomifolia*, *V. catharinensis*, *V. chamaedryfolia*, *V. eichleriana*, *V. polysthachya*, *V. scanden*, *V. eupatoria*, *V. salicariifolia* and *V. tajuvensis*. All plants contained valepotriates with *V. glechomifolia* as the richest (2.04%). In *V. glechomifolia*, the main compound was acevaltrate (**54**), present in all the studied organs, completing 0.73% and the second most abundant was valtrate (**52**, 0.56%) followed by didrovaltrate (**62**, 0.49%). It is interesting to observe that contrarily to the other studied plants, the aerial parts of *V. glechomifolia* are richer in valpotriates than that of underground organs [31].



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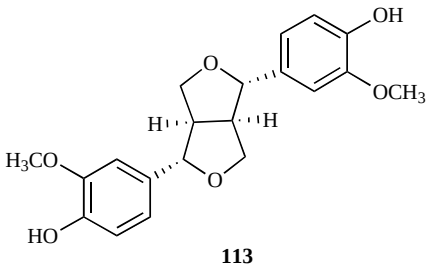

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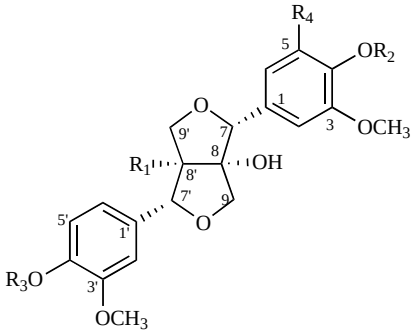
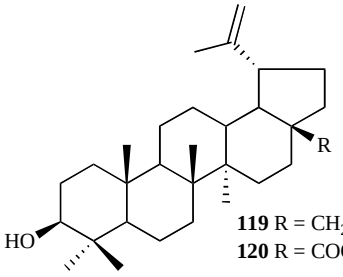
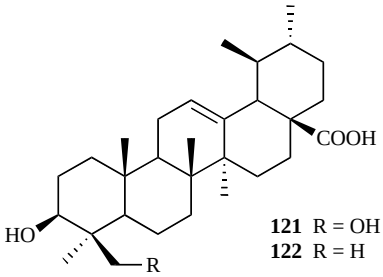


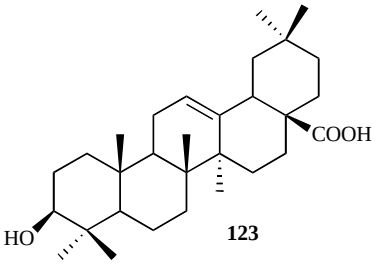
No.	R_1	R_2	R_3	R_4
114	OH	H	H	H
115	OH	β-D-glc	H	H
116	H	H	β-D-glc	OMe
117	H	H	β-D-glc	H
118	H	H	H	H



119 R = CH_2OH
120 R = COOH



121 R = OH
122 R = H



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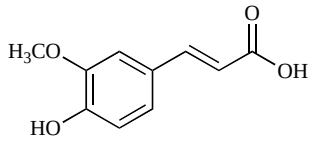

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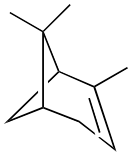

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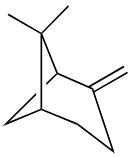

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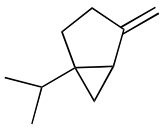

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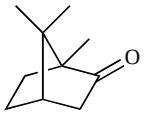

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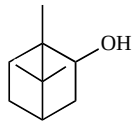

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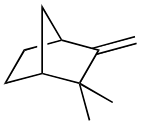

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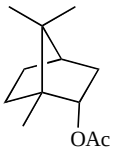

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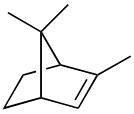

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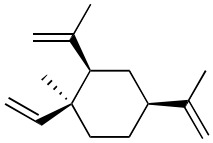

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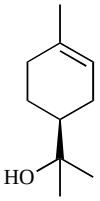

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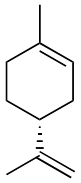

135

Fig. (6). Others from *Valeriana* species.

The valpotriates (**90**) concentrations are variable among the *Valeriana* species and seasonal variations can occur as well [5].

4. BIOACTIVITY

4.1. Antispasmodic

Valeriana prionophylla, a plant species distributed in Guatemala, Mexico, and Costa Rica, is widely used in traditional medicines in the form of aqueous infusions as a sedative and antispasmodic [1].

The aglycones 8-hydroxypinoresinol (**118**) and prinsepiol (**114**) displayed powerful antioxidant activity in Trolox equivalent antioxidant activity (TEAC) and chemiluminescence (CL) assays. In addition, compound **118** showed a stronger vasorelaxant activity than compounds prinsepiol-4-*O*-*β*-D-glucopyranoside (**115**), 8-hydroxypinoresinol-4'-*O*-*β*-D-glucopyranoside (**117**), and **114**. Compound **117**, which is structurally related to **118**, was inactive, suggesting that the presence of a glycoside causes the loss of the observed effect [1].

Two valeriana extracts (ethanol and aqueous extracts of *V. officinalis* L. roots) possessed significant anticoronaryspastic, antihypertensive and antibronchospastic properties. 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 [32].

Girani reported the antispasmodic and hypotensive effects of *Valeriana wallichii*. The mechanism of these effects is possibly mediated through KATP channel activation, which supports its use in gastrointestinal and cardiovascular disorders [33].

4.2. Sedative and Anxiolytic Effects

Genus *Valeriana* species intensively have been used as a sedative and anxiolytic since ancient time, and still has a role to play. It is commonly assumed that efficacy of valerian preparations in sleep disorders could be due to putative sedative properties of these extracts. However, results of studies which tested valerian for the proposed sedative effects and its influence on vigilance are contradictory to this hypothesis.

It has been reported that all ethanolic extracts [34], 70% ethanolic extracts, and aqueous alkaline extracts [35] of *Valeriana* show pronounced anxiolytic effects. Following oral administration, three preparations were tested for their sedative and anxiolytic activity. Results obtained in the elevated plus maze test revealed a pronounced anxiolytic effect of the 45% methanolic and 35% ethanolic extracts as well as of phytofin Valerian 368 in a dose range of 100–500 mg/kg bw. Additionally phytofin Valerian 368 showed antidepressant activity in the forced swimming test after subacute treatment. Myorelaxant effects were not observed in dosages up to 1000 mg/kg bw. Against the background that enhanced GABAA-ergig transmission, the known mechanism for benzodiazepines, is associated with a loss of muscle strength, these findings affirm that valerian-induced CNS-related effects might not be caused by interference with the GABAA receptor [36]. In the forced swimming test, α-kessyl alcohol (**31**) together with kessanol (**26**), cyclokessyl acetate (**32**) exhibited remarkable antidepressant activity [37].

Acute administration of an aqueous extract reduced sleep latency [38]. Using subacute treatment regimes, an extract made with 70% v/v ethanol affected different sleep parameters in a positive manner as well [39]. Furthermore an improvement of sleep quality comparable to treatment with 10 mg oxazepam was observed for the same ethanolic extract in two comparative studies [40,41]. Another *in vivo* experiment revealed a significant shortening of sleep latency in sleep-disturbed rats after treatment with a 70% ethanolic preparation [42].

However *in vivo* studies also provided inconsistent results. For instance, extracts made with 70% ethanol varied in their capability to affect motor activity in mice. A reduction in spontaneous activity has been observed as well by testing an aqueous alkaline extract [43].

Valerenic acid (**46**) was shown to possess anticonvulsant properties [35]. A decrease of locomotor activity of mice was also noticed after administration of **46**. In addition, it was found to prolong the pentobarbital induced sleeping time [44]. *Marder* reported similar effects on hesperidin (**105**) [45]. Additionally, 6-methylapigenin (**102**) was shown to be active in the elevated plus maze procedure.

In vitro studies of test extracts or isolated constituents provided specific evidence for an involvement of the GABAA-system in the psychotropic effects of valerian. In addition, the adenosine system may also account for central actions since in some studies an interaction of valerian extracts as well as of an olivil derivate with the adenosine A1-receptor was observed. Due to the ambiguous pharmacological profile, intensive research was done to elucidate the proved efficacy.

Holzl and *Godau*, using a dichloromethane extract of *V. officinalis* and some of its fractions detected inhibition on the binding of ^{3}H-FNZ to the BDZ-bs [46]. *Mennini et al.* made a valuable effort to characterize the interactions with brain receptors of crude extracts of *V. officinalis* and of two purified components in them. Neither hydroxyvalerenic acid nor dihydrovaltrate exerted inhibition on the receptors tested [47]. *In vitro* studies testing the binding of valerian extract to GABA receptors showed that the agonist muscimol was displaced, suggesting valerian binding to these receptors [48]. Valerinic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain, resulting in sedation [49]. Compound 6-methylapigenin, isolated from *V. wallichii*, was proved as a benzodiazepine binding site (BDZ-bs) ligand and, as described, was able to cause anxiolytic effects in mice [50]. Also, a novel compound (-)-(2*S*)-hesperidin (**105**) in valerian has sedative and sleep enhancing properties [45]. Note that CNS active isomer is the (-)-(2*S*)-form and the racemic were generally known in the citrus industry [51].

Receptors are not the only mechanism through which GABA transmission is controlled. It is hypothesized that GABA levels in the brain may be increased by either stimulating glutamic acid decarboxylase (GAD) or inhibiting GABA transaminase (GABA-T). Extracts from *Centella asiatica* (gotu kola) and *V. officinalis* (valerian) stimulated GAD activity by over 40% at a dose of 1 mg/mL [52].

Another contribution in this field was made by *Bodesheim* and *Holzl* who were able to demonstrate that the lignan 1-hydroxypinoresinol (**118**), isolated from *V. officinalis*, is a ligand for the 5-HT_{1A} serotonin receptor with an IC_{50} ~2.5 μM [53]. After that, methanolic and aqueous extracts of *V. adscendens* were examined for affinity and selectivity towards 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} serotononergic, D_1 and D_2 dopaminergic, a_1 and a_2 noradrenergic receptors by a preliminary binding screen. The results showed weak affinity to 5-HT_{1A} for the aqueous extract. Both extracts showed affinity to D1 receptors, but only for the methanolic extract the IC_{50} value was determinable (30.14 μg/ml). No affinity for the other receptors was recorded [54].

In addition, the adenosine system may also account for central actions. While polar extracts of valerian roots (*Valeriana officinalis* L.) activated adenosine A1 receptors (partial agonistic activity), nonpolar extracts showed antagonistic or inverse agonistic activity at A1 receptors, as demonstrated by GTPgS binding assays to human recombinant A1 receptors stably expressed in Chinese hamster ovary (CHO) cells. Guided by radioligand binding assays, lipophilic extraction led to the isolation of isovaltrate (**56**), which was characterized as a potent, highly efficacious inverse agonist at adenosine A1 receptors (Ki rat A1: 2.05 μM) [55]. Besides, in some studies the interaction of valerian extracts as well as of an olivil derivate at the adenosine A1-receptor was observed [56,57].

4.3. Enhancers of NGF Action

The pharmacology of nerve growth factor (NGF) has been subjected to extensive studies. Kissoones A, B, and C (**7**, **8**, **9**) did not affect neurite outgrowth from PC12D cells in the absence of NGF. The NGF (2ng/mL)-induced increase in the proportion of neurite-bearing cells was enhanced by 42% and 38% by **8** and **9**, respectively, but not by **7** [58]. (1*R*,2*R*,7*R*)-2-Hydroxyl-β-bisabolol (**5**) and 2-demethyl-6-acetoxylkissoone A (**10**), isolated from the rhizomes and roots of *V. fauriei*, showed enhancing activity of NGF-induced neurite outgrowth in PC 12D cells [59].

4.4. Other Activities

4.4.1. Antiviral Activity

V. jatamansi, an annual herb distributed in the southwestern area of China, was known in Chinese folk medicine to have tranquilizing hypnotic and antiviral activities and its juice was used to treat eye infections and pimples [60]. Valerianannoid B (**22**) exhibited moderate *in vitro* antirotavirus activities.

4.4.2. Antitubercular

Ethnobotanical uses of *V. laxiflora* in Chile vary from killing stomach worms to sedative effects. The hexane- and CH_2Cl_2-

soluble extracts of the above-ground biomass and roots of *V. laxiflora* were found to exhibit inhibitory effects on the growth of *Mycobacterium tuberculosis* H37Rv with minimum IC 50 of 100 μg/mL, respectively [61].

4.4.3. Cytotoxicity

A number of valepotriates have been reported to be cytotoxic to cancer cells [19]. It has been noted that the presence of double bond(s) at C3(4),C5(6) in these compounds is essential for cytotoxic activity, whereas the oxirane ring, a potential alkylating moiety, is not required for the activity [62]. When tested in cancer cell proliferation inhibition (cytotoxicity) assay, sorbifolivaltrate A (**59**), isovaltrate (**56**) and valtrate (**52**), showed strong activity (IC_{50} 2.6, 3.1, 1.7 mM, respectively) against the PC-3M human metastatic prostate cancer cell line, suggesting the importance of the oxirane ring for cytotoxicity in these compounds. Although an obvious structure–activity relationship was not discernible, these data suggested that cytotoxic activity of valepotriates (**90**) is partly dependent on the location and relative size of the acyl groups and on the overall conformation of these compounds as well as the functional groups present [17]. Valtrate (**52**) showed antineoplastic activities against cervical cancer cells, stomach cancer cells, and lung cancer cells [63].

4.4.4. Effect on the Hepatic

Recently *in vitro* data showed the inductive effect of valerian on cytochrome P450 (CYP), 3A4 and 2D6 enzymes [64]. Adverse effects were detected in the interactions between haloperidol and valerian causing hepatic damage related to oxidative stress [65].

4.4.5. Mutation Induction

The Ames test revealed that *Gnaphalium* sp. and *V. procera* extracts induced mutations of *S. typhimurium* TA98 with or without the S9 microsomal fraction, and TA100 in the presence of the enzymatic fraction, respectively. The tincture of *V. procera*, however, was non-mutagenic. In the case of *V. procera* it should strongly recommended the use of tinctures or extracts free of valepotriates [66].

5. CONCLUSION

In summary, as a principle medicinal herb of commerce, genus Valeriana is a rare case, with a long history for medicinal usage, while active principles are generally unknown. *In vivo* and *in vitro* experiments are in progress and several hypotheses as mentioned above were put forward to elucidate the interactions. More importantly, some active compounds can be used as new lead structures for the development of targeting preparation, and as probes to explore the mechanism of action.

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