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PHYTOECDYSTEROIDS AND OTHER BIOLOGICALLY ACTIVE COMPOUNDS FROM PLANTS OF THE GENUS *Ajuga*

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Literature data on the structures of phytoecdysteroids and other biologically active compounds and their biological activities were reviewed.

Key words: iridoids, ecdysteroids, vitasteroids, ajugareptansin, ajugachin and biosynthesis.

Ecdysteroids form a large group of natural polyhydroxysteroids that are isolated from the animal and plant kingdoms.

Plants usually contain small quantities of ecdysteroids of the order of 0.1-0.001 wt% of raw material although in some instances they can reach 2.5-2.9% and more [1, 2]. However, animals contain less than 0.01 wt% of ecdysteroids [3].

Ecdysteroids accumulate in various plant organs, e.g., flowers, leaves, stems, and fruit. It has been noted that they stimulate protein synthesis in plants and activate cell mitosis [4]. Many researchers think that phytoecdysteroids act as plant growth regulators [5, 6]. Others ascribe allelochemical properties to phytoecdysteroids that exhibit toxicity to insects [7-9].

Recent results indicate that this group of steroids is involved in plant metabolism. It has been found that qualitative and quantitative changes in ecdysteroids occur during plant development. The composition and content also depend on the habitat [10] and plant age [11]. Ecdysteroids are biosynthesized in various organs: in annual plants, in roots and leaves; in herbaceous perennials, in roots [12].

The present article describes ecdysteroids from plants of the genus *Ajuga* (Labiatae) and their biological activities.

Until now ecdysteroids have been observed in 17 *Ajuga* species, from which ecdysteroids **1**-**37** have been isolated (Table 1, Fig. 1).

Ten species of *Ajuga* grow in the CIS; two of them, in Central Asia.

Japanese chemists first reported ecdysteroids in plants of the genus *Ajuga* [13]. They isolated ecdysterone (**28**) and cyasterone (**8**) from the aerial organs of *A. decumbens*.

Besides ecdysterone and cyasterone, the most frequently encountered compounds in *Ajuga* are ajugalactone (**1**) and ajugasterone B (**2**). In all probability **8** and **28** should be considered the principal metabolic products. They are present in all studied species of *Ajuga*.

Usmanov and coworkers [14-19] studied in detail ecdysteroids of *A. turkestanica* (Rgl.) Brig. A series of known ecdysteroids, **28**, **8**, **1**, and **2**, was isolated from this plant (Table 1).

In addition to these compounds, roots of this plant afforded turkesterone (**7**). Its structure was proved using chemical transformations and spectral data [17]. Later **7** was found in the aerial organs of the plant. A study of the areial organs gave 22-acetylcyasterone (**12**) [18], the yield of which was several times greater than previously reported [19].

Conflicting data have been reported for the presence of ecdysteroids in certain species. Thus, some authors [20-23] observed them in *A. reptans* L. whereas we were unable to find ecdysteroids in this species. Saatov has studied *A. reptans* collected in Bashkortostan and shown that ecdysteroids are absent in this plant. He explained this by a dependence of the ability to synthesize them on the habitat [25]. Another explanation of this is the difficulty of identifying *Ajuga* species, the most complicated taxonomic group of the family (researchers pay attention to this). This leads to an incorrect determination of the species.

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Table 1. Ecdysteroids Isolated from Plants of the Genus *Ajuga*

Ecdysteroids, mp, °C, $[\alpha]_D$	Source, plant organ	Reference
Ajugalactone (**1**), $C_{29}H_{40}O_8$,	*Ajuga turkestanica* (Rgl.) Brig. (leaves, roots)	15
225-235 (255-260),	*A. decumbens* Thunb. (flowers)	3, 26-28
+86.5° (CH_3OH)	*A. chamaepitus*	24, 25, 28, 29
	A. reptans L. (aerial part)	27, 30-32
	A. bracteosa Benth.	29
	A. remota	25, 31, 33
	A. laxmanni Benth.	29
	A. linearifolia Pampan.	29
	A. genevensis L.	29
Ajugasterone B (**2**), $C_{29}H_{46}O_7$	*A. incisa* Max. (leaves)	3, 27, 34
	A. turkestanica (Rgl.) Brig. (leaves, roots)	16
	A. bracteosa Benth.	29
	A. reptans L.	22, 29
Ajugasterone C (**3**), $C_{27}H_{44}O_7$, amorph.,	*A. decumbens* Thunb. (flowers)	35
+37° (CH_3OH)	*A. remota*	33
	A. japonica Mig. (leaves)	3, 28
	A. bracteosa Benth.	29
	A. iva Schreb.	44
Ajugasterone D (**4**), $C_{27}H_{44}O_7$, 245-246	*A. nipponensis* Makino	2, 3
Ajugasterone A (Polipodine B) (**5**),	*A. incisa* Maxim (leaves)	34, 35
$C_{27}H_{44}O_8$, 252-254, +59.8°	*A. reptans* L. (aerial part)	29. 32
	A. ciliata	36
	A. nipponensis Makino	3
	A. bracteosa Benth.	29
Makisterone A (**6**), $C_{28}H_{46}O_7$,	*A. iva* (roots)	28
263-265	*A. australis* R. Br.	29
	A. chamaepitus	24
	A. laxmanni Benth.	29
Turkesterone (**7**), $C_{27}H_{44}O_8$,	*A. turkestanica* (Rgl.) Brig.	17
amorph., +81.7°	(roots, aerial part)	
Cyasterone (**8**), $C_{29}H_{44}O_8$,	*A. decumbens* Thumb. (whole plant)	13
164-165, +64.5°	*A. incisa* Maxim. (whole plant)	13
	A. japonica Miguel.	28
	A. australis	29
	A. miltiflora Bunge.	29
	A. reptans L. (aerial part)	29
	A. turkestanica (Rgl.)	14, 37
	A. chia Schreb. (leaves, flowers)	38
	A. remota	33, 39
	A. iva Schreb.	28, 40
	A. nipponensis Makino (whole plant)	13
	A. chamaepitus	24, 29
	A. linearifolia Pampan.	29
	A. bracteosa Benth.	29
29-Norcyasterone (**9**), $C_{28}H_{42}O_8$,	*A. reptans* L.	20, 28, 32, 41
152-155, +32.4°	*A. genevensis* L.	29
29-Norcyasteron-2-acetate (**10**), $C_{30}H_{44}O_9$, 214-218	*A. reptans* L.	23, 41
29-Norcyasteron-3-acetate (**11**), $C_{31}H_{46}O_9$, 235-248	*A. reptans* L.	23, 41

Table 1. (continued)

Ecdysteroids, mp, °C, $[\alpha]_D$	Source, plant organ	Reference
Cyasteron-22-acetate (**12**), $C_{31}H_{46}O_9$,	*A. turkestanica* (aerial part)	18, 19, 37
212-215, +96°	*A. australis* R. Br.	29
	A. bracteosa Benth.	29
3-Epicyasterone (**13**), $C_{29}H_{44}O_8$	*A. bracteosa* Benth.	29
3-Epi-22-acetylcyasterone (**14**), $C_{31}H_{46}O_9$	*A. bracteosa* Benth.	29
28-Episengosterone (**15**), $C_{29}H_{44}O_9$	*A. reptans* L.	21 (a), 29
29-Norsengosterone (**16**), $C_{28}H_{42}O_9$,	*A. reptans* L. (aerial part)	20, 32
amorph., +51°	*A. genevensis* L.	29
2-Dehydroajugalactone (**17**), $C_{29}H_{38}O_8$	*A. reptans* L.	21 (a)
3-Dehydroajugalactone (**18**), $C_{29}H_{38}O_8$	*A. reptans* L.	21 (a)
5,29-Dihydroxycapitasterone (**19**), $C_{29}H_{44}O_9$	*A. reptans* L.	21 (a)
22-Dehydro-12-hydroxycyasterone (**20**), $C_{29}H_{42}O_9$	*A. reptans* L.	21 (b)
22-Dehydro-12-hydroxy-29-norcyasterone (**21**), $C_{28}H_{40}O_9$	*A. reptans* L.	21 (b)
22-Dehydro-12-hydroxy-29-norsengosterone (**22**), $C_{29}H_{42}O_{10}$	*A. reptans* L.	21 (b)
Reptansterone (**23**), $C_{29}H_{44}O_8$	*A. reptans* L.	21 (b)
Sengosterone (**24**), $C_{29}H_{44}O_9$,	*A. reptans* L.	29, 32, 42
159-161, +39.6°	*A. bracteosa* Benth.	29
22-Oxocyasterone (**25**), $C_{29}H_{42}O_8$	*A. iva* Schreb.	43
23-Hydroxycyasterone (**26**), $C_{29}H_{44}O_9$,	*A. iva* Schreb.	44
235-236		
22-Dehydro-12-hydroxysengosterone (**27**), $C_{29}H_{42}O_{10}$	*A. reptans* L.	21 (b)
Ecdysterone (**28**), $C_{27}H_{44}O_7$,	*A. decumbens* Thunb. (whole plant)	13
241-242, +60.7°	*A. incisa* Maxima (whole plant)	13
	A. iva Schreb.	28, 40
	A. japonica Miguel.	28
	A. multiflora	29
	A. reptans L. (aerial part)	22, 29
	A. nipponensis Makino (whole plant)	13
	A. remota	28
	A. turkestanica (Rgl.) Brig.	14, 37
	A. chamaepitus	29
	A. australis R. Br.	29
	A. chia Schreb.	45
	A. ciliata	36
	A. laxmanni Benth.	29
	A. linearifolia Pampan.	29
	A. bracteosa	29
Ponasterone (**29**), $C_{27}H_{44}O_6$	*A. remota*	33
Ecdysterone 2,3-monoacetonide (**30**), $C_{30}H_{48}O_7$,	*A. turkestanica* (Rgl.) Brig.(aerial part)	37
242-244, +59.2°		
α-Ecdysone (**31**), $C_{27}H_{44}O_6$,	*A. turkestanica* (Rgl.) Brig. (aerial part)	37
239-241, +63.8°	*A. australis* R. Br.	28
24,25-Dehydroprecyasterone (**32**), $C_{29}H_{42}O_6$	*A. iva* Schreb.	43
2-Acetyl-20-hydroxyecdysone (**33**), $C_{29}H_{48}O_8$	*A. australis* R. Br.	29
	A. reptans L.	41
3-Acetyl-20-hydroxyecdysone (**34**), $C_{29}H_{48}O_8$	*A. multiflora* Bunge.	29
	A. reptans L.	41
Amarasterone A (**35**), $C_{29}H_{48}O_7$	*A. australis* R. Br.	29

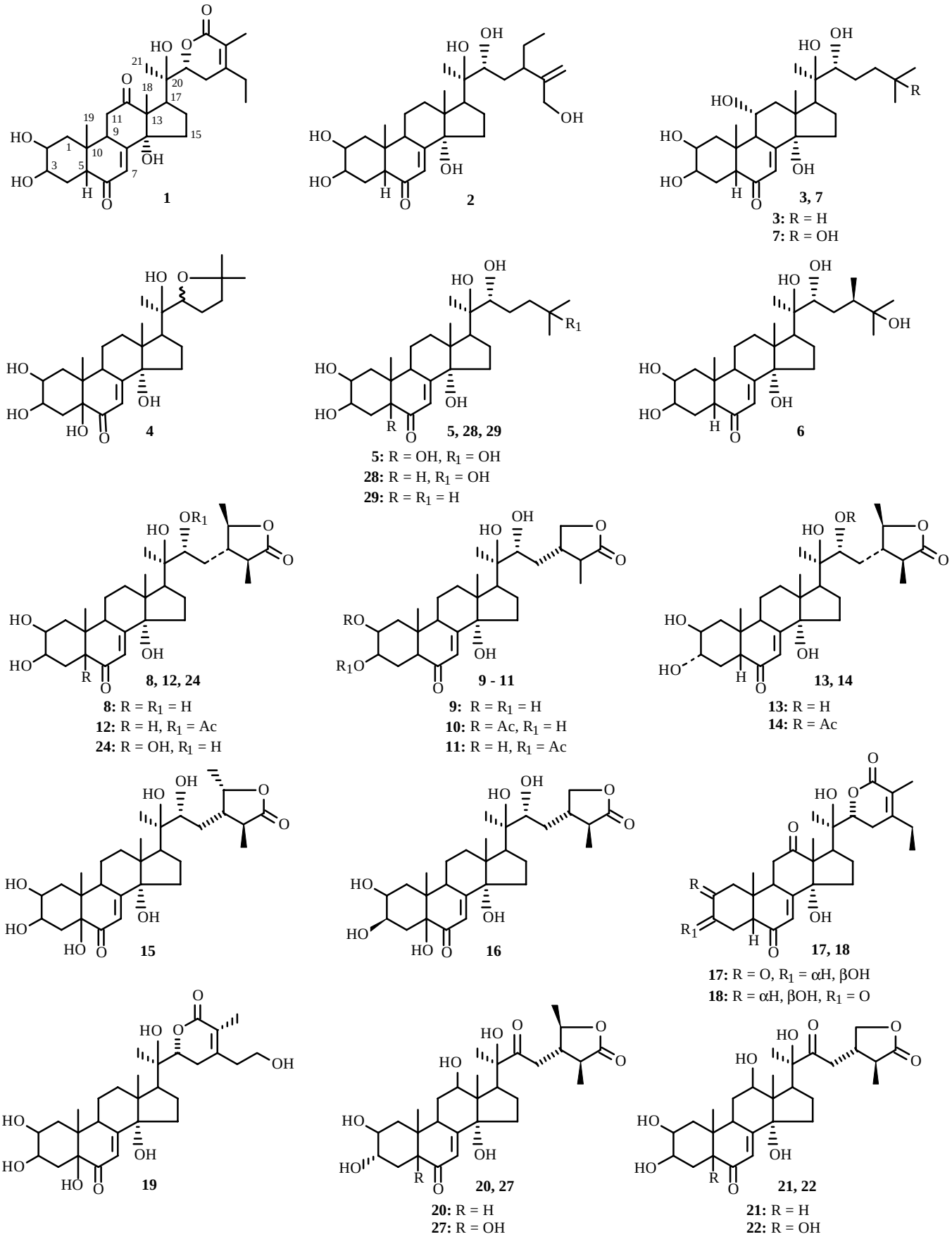


Fig. 1. Structures of ecdystedoids isolated from plants of the genus *Ajuga*.

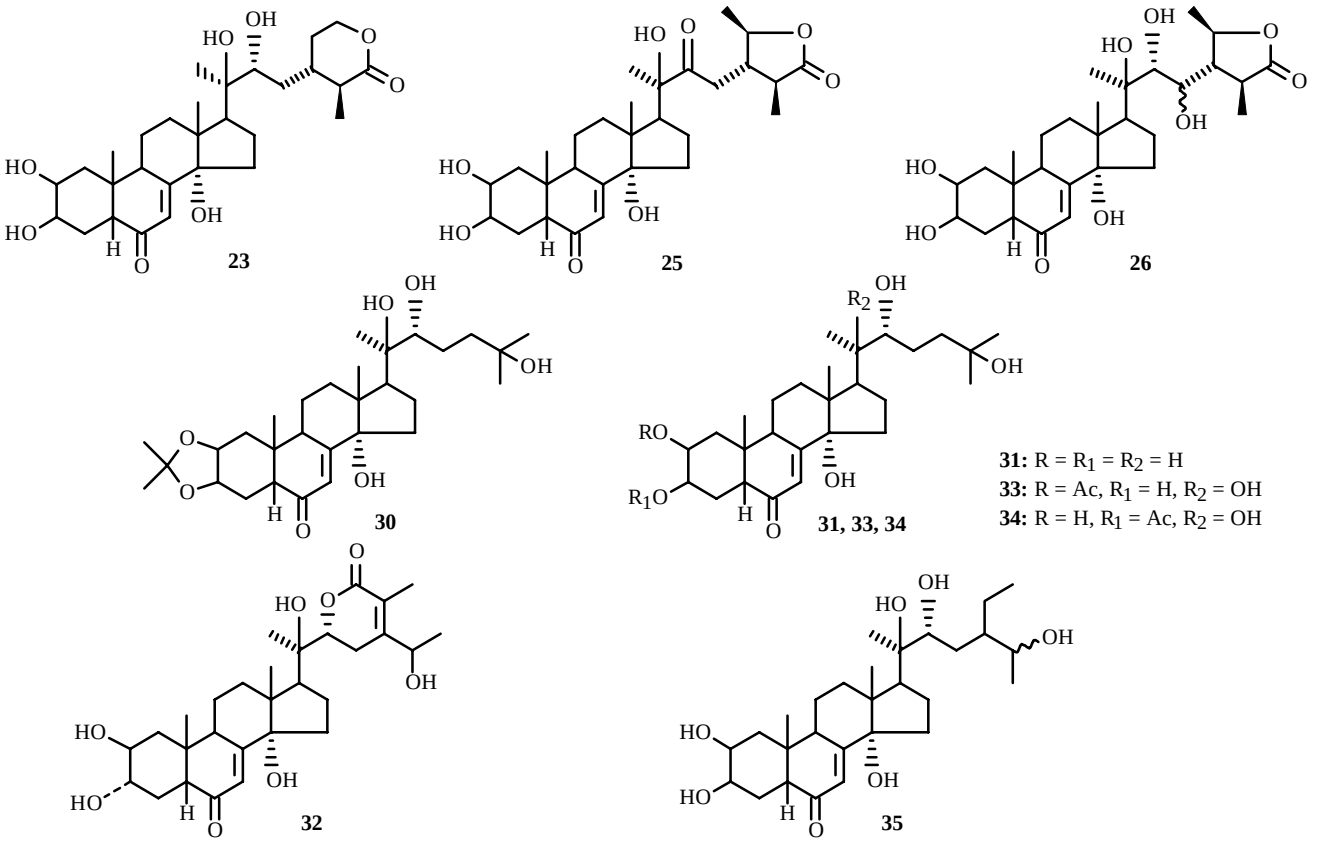
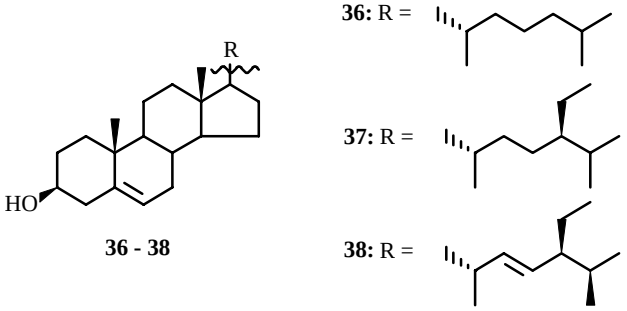


Fig. 1 (continued). Structures of ecdystedoids isolated from plants of the genus *Ajuga*.

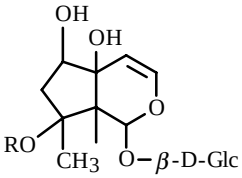
Ajugasterone C (**3**), ajugasterone D (**4**), **8**, and **12** were found in *A. nipponensis* growing in Spain [13, 24]. Ecdysterone was not observed. Phytoecdysteroids **3**, **7**, **8**, and **12** were observed for the first time in these species.

It was demonstrated [25] that a single *Ajuga* species collected at different sites contained different quantities and types of ecdysteroids.

Compounds isolated from plants of the genus *Ajuga* typically have 5- or 6-membered saturated and unsaturated (**1**, **8**, **23**) lactone rings in a side chain. They form a group of phytoecdysteroids that includes 29 C atoms and are unique to the plant kingdom. If a precursor of ecdysterone (**28**) in plants is cholesterol (**36**), then *Ajuga* ecdysteroids may be biosynthesized through sitosterol (**37**) or stigmasterol (**38**), which are also constructed of 29 C atoms.



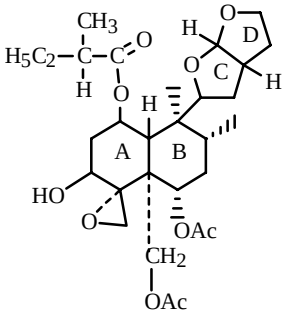
Investigations of plants of the genus *Ajuga* showed that they also contain other classes of compounds in addition to ecdysteroids. Thus, iridoid glycosides 8-O-acetylharpagide (**39**) and harpagide (**40**) were isolated from them [45].



39, 40

39: R = Ac; **40:** R = H

Diterpenoids ajugareptansin (**41**) and neocleradone (**42**) were isolated from *A. reptans* and *A. chameapitus* [46].



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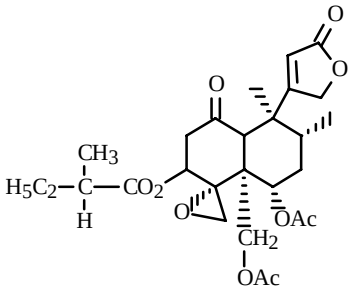

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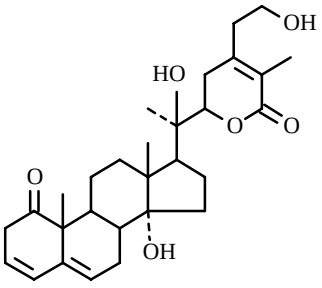
Vitanolides ajugin A (14α,20,28-trihydroxy-1-oxo-(20*R*,22*R*)-vita-3,5,24-trienolide) (**43**) and B (14α,20,27-trihydroxy-1-oxo-(20*R*,22*R*)-vita-5,24-dienolide) (**44**) were observed in *A. parviflora* growing in Pakistan [47].



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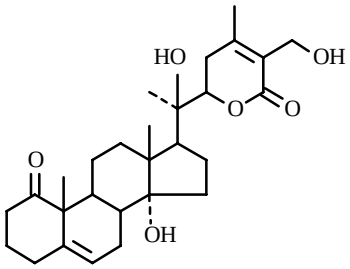

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BIOLOGICAL ACTIVITY

Ecdysteroids possess a wide spectrum of biological activities and have a distinct tonic effect on mammals. Ecdysterone is a component of certain preparations with tonic, anabolic, and adaptogenic properties that are used to increase the mental and physical capabilities and improve compound exchange.

Ecdysterone is an active compound that has a specific action and can intensify peroxide oxidation of lipids (POL) by affecting the physicochemical parameters of the cell metabolism regulation system. A study of the antioxidant properties of ecdysterone as a function of the extent of the oxidative processes in a model system over a wide concentration range showed that the antioxidant and peroxidant properties of ecdysterone are determined by the concentration of the preparation and the rate of initiation of the oxidative reactions in the system.

Taken as a whole, the literature data lead to the conclusion that the principal biological effect of ecdysterone is its participation in the regulation of POL processes in complicated biological systems.

A. reptans L., which is of interest as a medicinal plant used to produce adaptogens and cardiotropic and wound-healing preparations, contains significant quantities of ecdysteroids. The use of this plant as an antihemorrhagic [48, 49] and

antimalarial agent has been reported. *A. genevensis* growing in Central Asia is mentioned as a medicinal agent for treating liver and spleen disease and for hepatitis [50].

Japanese researchers showed that administration of phytoecdysteroids to mice increases markedly protein-synthesizing processes in them [51, 52]. Administration of phytoecdysteroids to various animals at doses of 5-10 mg/kg increased the body mass and the masses of their internal organs and skeletal muscle [53]. These changes were due to increased protein biosynthesis under the influence of the ecdysteroids and to an increase of its total content in the liver, heart, kidneys, and anterior tibial and other muscles [54].

The protein-anabolic action of ecdysteroids in animals was evident as an increase under their influence of the total blood protein content, primarily due to albumin, an increase in the number of erythrocytes in peripheral blood, and an increased of hemoglobin content in them [53a]. Ecdysteroids increased in various organs and tissues the activities of glutamatedecarboxylase [55, 56], acetylcholinesterase [57], alkaline phosphotase [58], succinatedehydrogenase, and lactatedehydrogenase [59]. The data indicate that ecdysteroids have significant anabolic activity whereas they lack androgenic activity [54, 60].

Grimova et al. showed [61] that ecdysteroids exhibit membrane-stabilizing action. This was confirmed by results showing that incubation of rabbit erythrocytes with ecdysterone, viticosterone E, polypodine B, α-ecdysone, and cyasterone increased their stability index calculated using acid erythrograms [58]. It could be that the stabilizing effect of ecdysteroids on membranes is based on their anti-inflammatory action for certain forms of experimental inflammation [62]. Ecdysterone prevents development of pathological changes in the liver, positively affects its reparative regeneration processes, and assists restoration of the normal liver structure during toxic hepatitis caused by heliotrine [63].

The ability of phytoecdysteroids to lower the urea and residual nitrogen blood levels and to improve kidney functioning in various pathological states has been studied experimentally. Experimental clinical studies established the ability to broaden the indications for use of ecdysten preparation for eye complications in chronic glumerulonephritis patients [37].

In addition to the anabolic effect, phytoecdysteroids exhibit hypoglycemic action [64-66]. The effect of the total ecdysteroid preparation from *A. turkestanica* was investigated first in rats with alloxan diabetes. In addition, the effects of turkesterone and ecdysterone in combination with insulin and sugar-lowering preparations were studied.

Turkesterone gave good results when used to treat insulin-dependent diabetes [67].

Thus, total phytoecdysteroids and pure compounds can be considered promising as potential hypoglycemia agents.

Ecdysterone use has also produced improvement of metabolic processes in myocardium and positive changes in the clinical condition of patients with cardiac ischemia. The central and cerebral hemodynamics were normalized [68]. Ecdysterone was rather promising also for treating nephrologic patients [69] and those with ulcers of the stomach and duodenum [70].

Iridoid glycosides, which are present in *A. turkestanica* in addition to phytoecdysteroids, are also presently considered promising natural compounds for development as new medicinal agents.

They have been reported to have antimicrobial, fungicidal, antitumor, sedative, cholegogic, antifidant, and other types of activity.

A preparation of total iridoids from *A. turkestanica* consisting of harpagide (**40**) and 8-O-acetylharpagide (**39**) was studied as an agent for influencing specific liver functions such as bile secretion, bile-acid synthesis, and bilirubin and cholesterol exchange. It was found that it not only strengthened bile-formation processes in normal animals but also restored it in animals with various toxic liver conditions. Iridoids improved basic exchange processes in hepatocytes and increased their antitoxic function [72].

Thus, phytoecdysteroids and iridoids are very interesting biologically active natural compounds not only in theory but also in practice as medicinal preparations for correcting disrupted metabolic processes in man during treatment of various diseases.

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