

## PHYTOECDYSTEROIDS OF PLANTS OF THE GENUS *Ajuga* AND THEIR BIOLOGICAL ACTIVITY.

### 1. DISTRIBUTION AND CHEMICAL STRUCTURES OF THE COMPOUNDS ISOLATED

Z. Saatov, V. N. Syrov, A. U. Mamatkhanov,  
and N. K. Abubakirov

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*In this review, literature information on the structures of phytoecdysteroids, their distribution in plants, and their biological activities is generalized.*

Ecdysteroids form a fairly large group of steroid compounds found in the animal and vegetable kingdoms [1-3]. The first molt hormone,  $\alpha$ -ecdysone (15) was isolated in 1954 by Butenandt and Karlson [4] from pupae of the silkworm *Bombyx mori*. Ecdysteroids have been found among representatives of the Protostomia, Arthropoda, Mollusca, worms, (Platyhelminthes, Nematoda, Annelida), and Echinodermata [5, 6]. Zooecdysteroids play an important role in the vital activity of invertebrates, exerting an influence on the basic processes of life. In arthropods, especially insects, these compounds fulfill the role of hormones and control at least three periods in ontogenesis: embryonic, post-embryonic, and the period of multiplication [6].

Publications of Japanese [7] and Australian [8, 9] authors at the end of the 1960's in which the presence of ecdysteroids in plants was reported proved to be completely unforeseen. The discovery of molting hormones in plants aroused enormous interest among entomologists and chemists. More than 120 ecdysteroids with different degrees of activity in relation to insect metamorphosis have now been found in plants. They have been detected in numerous species of plants belonging to almost 90 families [1]. Moreover, plant sources of ecdysteroids considerably exceed animal organisms with respect both to their qualitative composition and to their amounts. In plants, the level of ecdysteroids sometimes reaches 2.9% of the dry weight of the material [2, 3], while in animal organisms it does not exceed hundredths of a percentage part [1, 11]. Substances with structures close to those of molting hormones have been isolated from the red algae *Laurencia pinnata* and from the fungus *Polyporus versicolor* [12-14].

The biological function of the ecdysteroids in the life of plants is almost unknown. A number of researchers maintain the point of view that the phytoecdysteroids act as plant growth regulators [15, 16]. A hypothesis has been expressed of the appearance of ecdysone-like substances as the result of the coevolution of two large branches of the living world: the vegetable and animal kingdoms [11].

Ecdysteroids accumulate in various plant organs — in the flowers, leaves, stems, roots, and fruits. It has been reported that they stimulate the synthesis of proteins in the plant organisms and activate cell mitosis [11]. The amount of phytoecdysteroids in various plant organisms changes in the course of the whole vegetation period. A number of other workers have suggested the possibility of allelochemical properties of phytoecdysteroids as toxins for insects [1, 6, 17, 18].

In recent years, it has been established that phytoecdysteroids can also exert an influence on those organisms that are incapable of their endogenous production. Particular interest in this respect is presented by mammals, into whose organisms large amounts of phytoecdysteroids may pass with vegetable foodstuffs. Thus, it has been reported [19] that these compounds are analogous to the known steroid anabolic drug 4-chlorotestosterone, which is capable of enhancing the incorporation of labeled amino acids into the protein structures of mouse livers. The repeated introduction of phytoecdysteroids into the organism

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Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Fax (3712) 62 73 48. Translated from *Khimiya Prirodnnykh Soedinenii*, No. 2, pp. 152-160, March-April, 1994. Original article submitted January 25, 1993.

TABLE 1. Plants of the Genus *Ajuga* from Which Ecdysteroids Have Been Isolated

Plant	Ecdysteroid
1. <i>A. austral</i> R. Br.	5, 8, 13, 15
2. <i>A. chamaepity</i> (L.) Schreb.	1, 5, 13
3. <i>A. chia</i> Schreb.	8, 13
4. <i>A. decumbens</i> Thunb.	1, 3, 8, 13
5. <i>A. iva</i> Schreb.	3, 5, 8, 13
6. <i>A. incisa</i> Maxim	2, 6, 8, 13
7. <i>A. nipponensis</i> Makino	4, 6, 8, 13
8. <i>A. japonica</i> Mig.	3, 6, 8, 13
9. <i>A. multizora</i> Bgl.	13
10. <i>A. remota</i>	8, 13, 17
11. <i>A. reptans</i> L.	1, 6, 8, 9, 10, 11, 12, 13
12. <i>A. turkestanica</i> (Rgl.) Brdg.	1, 2, 7, 8, 13, 14, 15, 16
13. <i>A. ciliata</i>	6, 13

of animals has a favorable influence on the dynamics of their growth [20] and also exerts a certain tonic action [21]. No toxic effects of this have been reported [22].

In the present paper we describe the isolation and biological activities of ecdysteroids from plants of the genus *Ajuga* (family Labiatae).

In the CIS, ten species of plants of the genus *Ajuga* have been found, two of them in Central Asia. The presence of ecdysteroids in plants of the species *A. decumbens* (Table 1) was first shown by Japanese chemists in 1969 [23]. Ecdysterone (13) and cyasterone (8) were isolated from the epigeal organs of this plant. Ecdysterone — the universal molt hormone of insects — predominates in the quantitative respect over all other ecdysteroids in all the species examined, as, in fact, it does in all flowering plants studied for the presence of ecdysterone-like substances. This indicates that, in the physiological respect, ecdysterone is the main active principle, and the other compounds, in spite of certain, sometimes fundamental, differences in chemical structure must be considered as metabolites. In addition to ecdysterone, such compounds as cyasterone (8) are most frequently found in *Ajuga*.

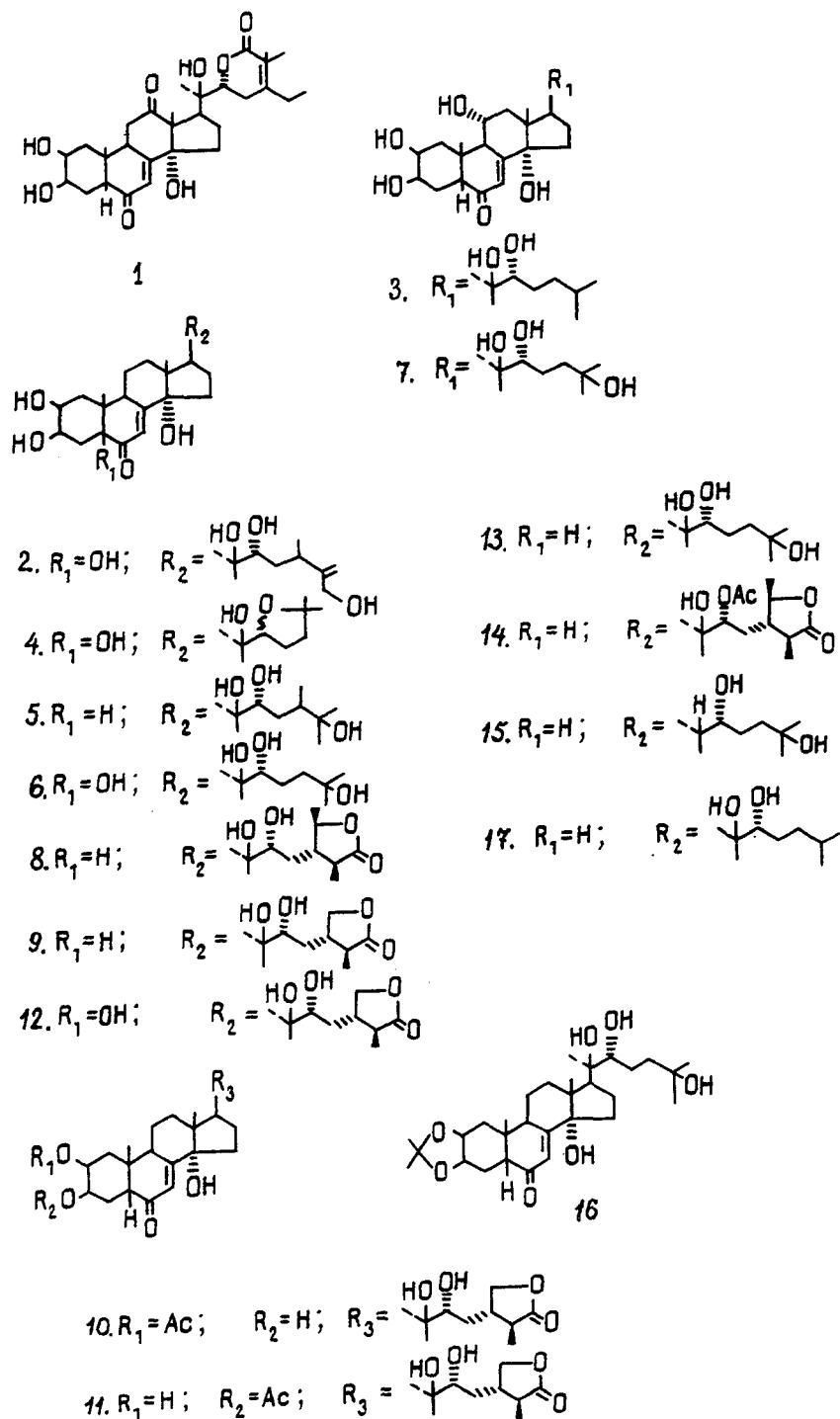
Characteristic for plants of this genus is the presence of compounds with a 5- or 6-membered lactone ring in the side chain. In all probability, cyasterone (8) and ajugalactone (1) must be assigned to the main metabolic products. They are present in all the species of *Ajuga* investigated.

B. Z. Usmanov et al. [24] have studied the ecdysteroids of *Ajuga turkestanica* (Rgl.) Brdg. in detail. A number of known ecdysteroids — ecdysterone (13), cyasterone (8), ajugalactone (1), ajugasterone B (2), and  $\alpha$ -ecdysone (15) have been isolated from this plant (Tables 1 and 2). In addition to known compounds, a new compound was isolated from the roots of this plant — turkesterone (7). Its structure was established with the aid of IR, mass, and PMR spectroscopies [25, 26]. Later, turkesterone was also found in the epigeal organs of the plant.

In a study of the epigeal organs, 22-acetylcyasterone (14) was also isolated [41]. The yield of this compound was somewhat higher than was reported previously [27]. Z. Saatov — one of the authors of this paper — explained this by the assumption that the amount of ecdysteroid (14) depends on the vegetation period. He also detected the isopropylidene derivative (16) (Table 2).

Ecdysteroids have been detected in 13 species of the genus *Ajuga* (Tables 1 and 2), including *A. reptans* [28, 29]. However, in a study of *A. reptans* gathered in Bashkortostan, Z. Saatov showed that there were no ecdysteroids in this plant, explaining this by the assumption that the capacity for their synthesis depends essentially on the growth site.

## Structural formulas of ecdysteroids isolated from plants of the genus *Ajuga*



## Biological Activity

The phytoecdysteroids isolated from plants of the genus *Ajuga*, like the majority of compounds of this class studied up to the present time [43, 44], exert an appreciable influence on metabolic process in the organisms of higher animals. On their use, above all, a clear protein-anabolic action was revealed which was most clearly expressed in young animals with a normal hormonal status. In this case, the increase in body weight (Table 3) and also the increase in the weight of the internal organs and the skeletal muscles (because of the increase in the total amount of protein in them) [45, 46] was expressed

TABLE 2. Ecdysteroids Isolated from Plants of the Genus *Ajuga*

Ecdysteroid	mp °C	$[\alpha]_D$ deg	Source, plant organ*, yield, % on the air-dry raw material	Liter- ature
1. Ajugalactone $C_{29}H_{40}O_8$	225—235	—	A. decumbens Thunb. (f—0.01) A. turkestanica (Rgl.) Brig. (l—0.001; r—0.001) A. chamaepity A. reptans L. (e.p.—0.0068) A. remuta	30 31 32 28 32
2. Ajugasterone B $C_{29}H_{46}O_7$	240	—	A. incisa Maxim (l—0.0008) A. turkestanica (Rgl.) Brig. (l—0.002; r—0.003) A. decumbens (f—0.0015)	33 34 35
3. Ajugasterone C $C_{27}H_{44}O_7$	Amorph.	—	A. decumbens Thunb. (f—0.0015) A. japonica (l—0.01) A. iva Schreb. A. remota	36 35 28; 32
4. Ajugasterone D $C_{27}H_{44}O_7$	245—246	—	A. nippensis Makino	10
5. Makisterone A $C_{28}H_{46}O_7$	263—265	—	A. austral R. Br. A. iva Schreb. A. chamaepity A. nippensis Makino	18 37 32 10
6. Ajugasterone A (polypodine B) $C_{27}H_{44}O_8$	252—254	+59.8	A. incisa Maxim (l) A. japonica Mig. (l) A. reptans (e.p.—0.0039) A. ciliata	33, 37 28 37
7. Turkesterone $C_{27}H_{44}O_8$	Amorph.	+81.7	A. turkestanica (Rgl.) Brig. (r—0.052; e.p.—0.17)	25, 26
8. Cyasterone $C_{29}H_{44}O_8$	164—165	+64.5 (pyridine)	A. decumbens Thunb. (p— 0.008) A. incisa Maxim (l—0.008) A. japonica Miguel A. chia Schreb. (l, s, f— 0.002) A. iva Schreb. A. remota	23 37 38 37 39, 28, 32 24, 25
9. 29-Norcyasterone $C_{28}H_{42}O_8$	152—155	+32.4	A. reptans	28
10. 29-Norcyasterone 2-acetate $C_{30}H_{44}O_9$	214—28	—	A. reptans	29
11. 29-Norcyasterone 3-acetate $C_{30}H_{44}O_9$	235—248	—	A. reptans L.	29

TABLE 2 (continued)

Ecdysteroid	mp °C	$[\alpha]_D$ deg	Source, plant organ*, yield, % on the air-dry raw material	Liter- ature
12. 29-Norsengosterone $C_{28}H_{42}O_9$	Amorph.	+51	A. reptans L. (e.p. —0.0066)	28
13. Ecdysterone $C_{27}H_{44}O_7$	241—242	+60.7	A. decumbens Thunb. (p—0.012) A. incisa Maxim (p—0.012) A. iva Schreb. A. japonica Miguel A. multiflora A. reptans (e.p. —0.0066) A. nipponensis Makino (p—0.012) A. remota A. turkestanica (Rgl.) Brig. A. chamaepity A. austral R. Br. A. chia Schreb. A. ciliata	23 37, 40 36 18 28, 29 23 39, 28, 32 25 28 18 24, 35 37
14. 22-Acetylcy- asterone $C_{31}H_{46}O_9$	212—215	+96.0	A. turkestanica (e.p. —0.05) (e.p. —0.12)	27 41
15. $\alpha$ -Ecdysone. $C_{27}H_{44}O_6$	239—241	+63.8	A. turkestanica (Bgl.) Brig. (e.p. —0.04) A. austral R. Br.	42 18
16. Ecdysterone 2,3- monoacetonide $C_{30}H_{48}O_7$	242—244	+59.2	A. turkestanica (Rgl.) Brig. (e.p. —0.08)	42
17. Ponasterone A. $C_{27}H_{44}O_6$			A. remota	32

\*e.p. — epigeal part; r — roots; l — leaves; p — plant as a whole; f — flowers; s — stems.

considerably more strongly than in young gonadectomized and adult sexually mature animals. The total amount of proteins and albumins in the blood serum increased most powerfully in young intact animals [45]. In all the experiments, turkesterone was distinguished by the greatest anabolic activity, which, in a number of experiments, reached the level of such a highly active anabolic agent as nerobol (methandrostenolone) [47, 48]. The castration and hypophysectomy of male rats greatly weakened the capacity of phytoecdysteroids for stimulating the protein-synthesizing processes in the organism [45, 46, 49]. In addition, in contrast to nerobol, the phytoecdysteroids studied exhibited none of the specific hormonal effects characteristic for this drug. They exhibited no androgenic, antigenadotropic, thymolytic, or uterotrophic action [48, 50]. Experiments with turkesterone showed that the stimulation of protein biosynthesis by phytoecdysteroids in the mammalian organism is not connected with their influence on the synthesis of RNA, as well, but is only a reflection of an acceleration in translation processes [51].

Ecdysterone, 2-deoxyecdysterone, 2-deoxy- $\alpha$ -ecdysone, polypodine B, cyasterone, and turkesterone also appreciably improve the immunological status of the organism and activate protein biosynthesis in human skin fibroblasts in *in vitro* experiments [22]. Under the action of phytoecdysteroids isolated from *Ajuga* there are appreciable positive shifts in other types of metabolic processes closely connected with protein processes. Thus, their hypoglycemic action [47, 53] and their capacity for updating the synthesis of glycogen in the heart, liver, and muscles [47] has been shown. The hypocholesteremic and hypotriglyceridemic action of these compounds has been reported [54].

Ecdysterone and turkesterone exert a pronounced favorable action on the energetic reactions of the organism by enhancing the synthesis of enzymes playing an important role in them (glutamate, succinate, and NADH dehydrogenases, and succinate and NADH oxidases) and raising their activity. As a result, the intensity of oxidative phosphorylation rises and the elaboration of macroenergetic phosphorus compounds increases [55, 56]. It must be mentioned that ecdysterone and turkesterone also possess the capacity for blocking processes of free-radical oxidation [57]. A distinct potassium fixing action has been reported for turkesterone [58].

By bringing about positive shifts in metabolic processes, ecdysterone, turkesterone, and cyasterone exert a considerable therapeutic action on various experimental pathological states: in myocardial infarct [59], myocarditis [60], atherosclerosis [54],

TABLE 3. Influence of the Ten-day Administration of Ecdysteroids Isolated from Plants of the Genus *Ajuga* and Their Derivative on the Increase in Body Weight of Male Rats ( $M \pm m$ ,  $m = 10$ )

Compound	Adult sexually mature animals (210-250 g)		Young sexually immature (70-80 g)			
	mg/g/day	% on control	intact		castrated	
			mg/g/day	% on control	mg/g/day	% on control
Control	5.2 ± 0.66	—	15.3 ± 1.5	—	12.5 ± 1.1	—
Ecdysterone	7.9 ± 0.81*	51.9	27.8 ± 2.7*	81.7	18.1 ± 1.4*	44.8
Ecdysterone triacetate	7.1 ± 0.49*	36.5	25.2 ± 1.7*	64.7	15.9 ± 1.1*	27.2
Ecdysterone tetraacetate	6.8 ± 0.44	30.8	23.9 ± 2.3*	56.2	15.2 ± 1.4	21.6
Ecdysterone monoacetonide	—	—	20.1 ± 1.2*	31.4	14.3 ± 1.9	14.4
Ecdysterone diacetonide	—	—	17.3 ± 0.67	13.1	13.5 ± 1.6	8.0
α-Ecdysterone	6.3 ± 0.51	21.1	19.5 ± 1.2*	27.4	14.1 ± 1.3	12.8
Cyasterone	7.9 ± 0.58*	51.9	30.2 ± 2.4*	97.4	18.9 ± 2.7*	51.2
Cyasterone triacetatae	7.6 ± 0.58*	46.1	27.5 ± 2.2*	79.7	17.9 ± 1.8*	42.4
22-Acetyl-cyasterone	7.7 ± 0.67*	48.1	28.4 ± 1.8*	85.6	18.3 ± 2.1*	46.4
Turkesterone	8.5 ± 0.58*	63.5	33.9 ± 3.0*	121.6	20.8 ± 2.8*	66.4
Turkesterone tetraacetate	8.3 ± 0.60*	59.6	31.5 ± 2.4*	105.8	19.2 ± 2.2*	53.6
Polypodine B	8.0 ± 0.51*	53.8	28.4 ± 2.8*	85.6	18.5 ± 2.3*	48.0
Nerobol	8.1 ± 0.45*	55.7	32.7 ± 3.7*	113.7	27.8 ± 3.4*	122.4

\*Significant at  $p < 0.05$ .

diabetes [56], and hepatitis [61]. Under the action of ecdysterone and turkesterone the physical efficiency of animals rises [62]. It is interesting to note that ajugasterone C, isolated from *Ajuga remota* [63], possesses antifeedant activity. Ajugasterone C is also known as a metabolite of animal origin [64]. Ajugalactone acts as an antiecdysone in the *Chilo* test [30].

Thus, the facts given in the present paper characterize plants of the genus *Ajuga* as a source of phytoecdysteroids highly effective in the biological respect.

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