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Lagochilus species and diterpenes isolated from them. (Chiqarishga berilgan)

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Annotation. Lagohilus is a very common and promising medicinal plant. All over the world, extracting substances with high biological activity from the composition of plants and creating new medicines based on them is developing rapidly. Natural compounds isolated from the composition of plants have high biological activity, and their use in medical practice and folk economy occupies a special place. The main active ingredient of the Lagoxilus plant is the diterpenoid lagoxilin, which is a four-atom alcohol. Therefore, most plants belonging to the genus Lagochilus have hemostatic properties.

Key words: Lagochilus species, L.inebrians Bunge, Extraction, filtration, diterpenoids, lagochilin

Today, extracting substances with high biological activity from the composition of plants and creating new medicines based on them is developing rapidly all over the world. Natural compounds isolated from the composition of plants have high biological activity, and their use in medical practice and folk economy occupies a special place. Lagochilus is an intoxicating plant, preparations from which are used as a hemostatic and anti-allergic agent. The main active ingredient of the plant Lagoxilus is the diterpenoid lagochilin, which is a four-atom alcohol. Therefore, most plants belonging to the genus Lagochilus have hemostatic properties.

Based on the above, the study of the botany of lagochilus species, the method of obtaining new drugs based on its main active substance, the creation of simple, effective blood-stopping compounds is one of the urgent issues facing chemists.

Geographical distribution of the Lagochilus plant (Samarkand, Bukhara, Kashkadarya regions), Kazakhstan, Kyrgyzstan, Tajikistan and neighboring regions. Cultivated in Central Asia and Kuban [1,7].

Lagochilus grow in Central Asia. Of these, 34 species grow in the territory of the CIS (Independent Commonwealth). In the flora of Uzbekistan, this species is represented by 18 species (Table 1) [3].

The Lagochilus species is mainly distributed from the territory of Uzbekistan, from the deserts to the Tien-Shan and Pamir-Aloy mountain systems. Most of the species are found in the Pamir-Aloy mountains, in the southwestern part of the Tien-Shan and in the Turan lowland [4].

Four of the 18 species of Lagochilus in the flora of Uzbekistan are included in the Red Book of the Republic of Uzbekistan [5].

L. vvedensky, L. olgae, L. proskorjakovii and L. inebrians . These species grow mainly in Nurotau and Kyzylkum deserts. These are included in the Red Book in categories I (endangered) and II (rare species). In addition, species of this species with other natural distributions such as L. gypsaceus and L. acutilobus are also restricted worldwide [6]. Diversity and distribution of different Lagochilus species in Asia.

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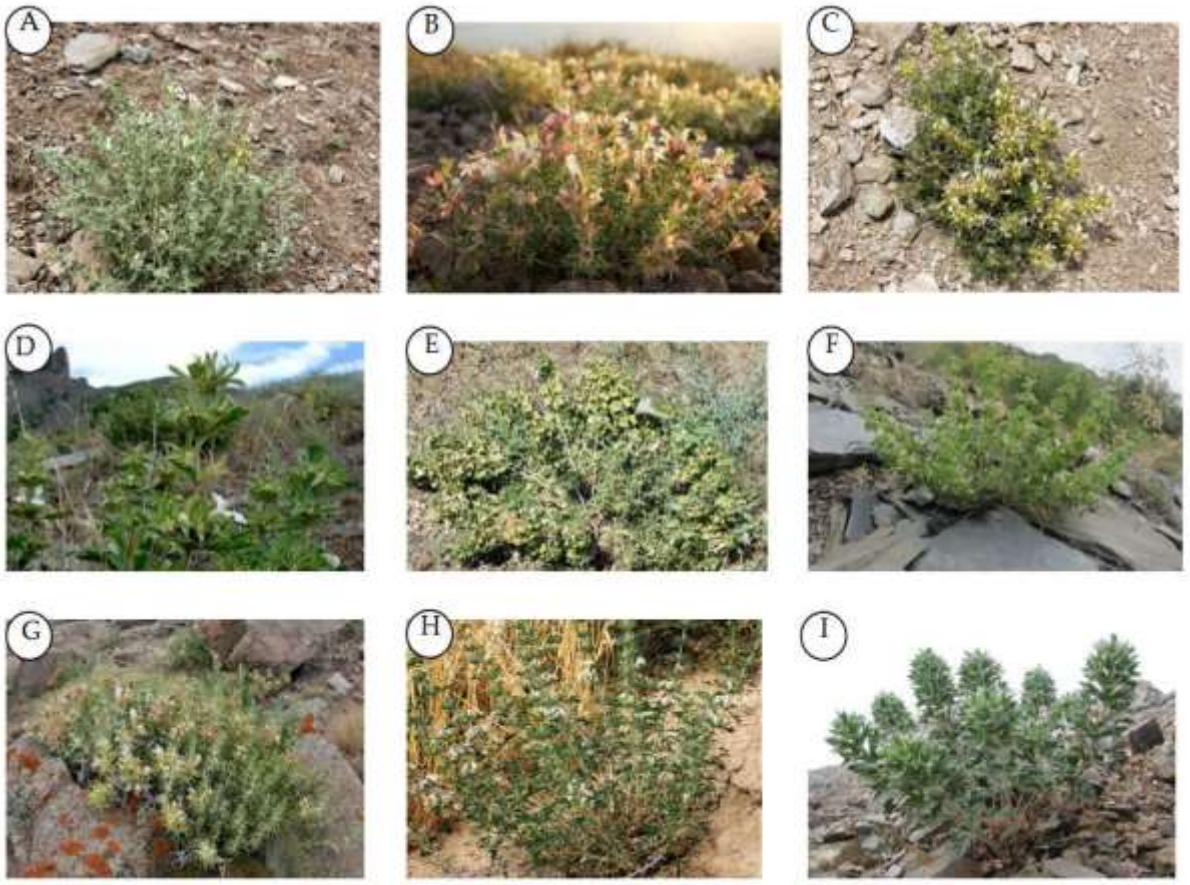

Figure 1. Lagochilus species in the flora of Uzbekistan:
(**A**): L. inebrians , (B): L. nevskii , (**C**): L. occultiflorus ., (**D**): L. olgae , (**E**): L. platycalyx , (**F**) : L. proskorjakovii (**G**): L. seravschanicus (**H**): L. setulosus (**I**): L. vvedenskyi .

Table 1

State name	Name of the area	Common species
Kazakhstan	Qoratau, Karjantau, Aksu-Jabagli	L. acutilobus (Ledeb.) Fisch. and CA May ., L. bungei Benth. , L. longidentatus Knorr., L. inebrians Bunge,
Uzbekistan	Nurota and Kyzylkum deserts, Tien-Shan and Pamir-Aloy mountains	L. acutilobus (Ledeb.) Fisch. et CA Mey., L. botschantzevii Camelinet Zukerv., L. diacanthophyllus (Pall.) Benth., L. gypsaceus Vved . , L. hirsutissimus Vved., L. inebrians Bunge, L. knorringianus Pavlov, L. kschtutensis Knorr., L. nevskii Knorr., L. olgae R. Kamelin , L. paulsenii Briq., L. pubescens Vved. L. platycalyx Schrenk, L. seravschanicus Knorr.,
Tadjikistan	Pamir-Aloy mountains	L. botschantzevii Kamelin and Tzukerv., L. gypsaceus Vved., L. hirsutissimus Vved, L. inebrians Bunge

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L agochilus inebrianse Bunge species. - Calyx tubular-campanular, 5-veined, oblique, five-toothed, teeth oblong, ovate-lanceolate, triangular, prickly, sharp, the top sometimes cut deeper than the bottom. At the base of the half-lobes and in the leaf axils there are sharp prickly or subulate branches-thorns. Inside with hairy ring, upper seed oblong, straight, flat, densely hairy outside, toothed top, 2-lobed; lower cotyledon oblong, three-lobed, with lateral short, flat lobes and a larger middle one, in turn, more or less deeply cut into 2 lobes. Stamens (4) shorter than or equal to the corolla, their basal filaments hairy or close to each other, with hairy cilia. The stem has almost equal lobes at the end. [3]

Lagochilus diacantiophyllus (Pall.) logohilus biacicularis. This type of plant was studied by T.R Abdurahmanov. The stem is 10-30 cm high, with small vertical roots, densely hairy leaves; lower leaves branched 5-10 mm, the upper growth with prickly hairs. Flowers 6 semi-lobed; covered with sparse hairs along branches, 3-15 mm long; The calyx is narrow-tube-bell-shaped, the teeth are oblong, 9-12 mm long and 3-5 mm wide, with edges equal to or 1.5 times higher than the calyx. [3]

In a pharmacological study conducted by T.R Abdurakhmonov, a 10% infusion of flowers and leaves of Lagohilus dvongolchaty was found to be toxic to frogs from a dose of 30 ml/kg, unlike all species. However, this species also has some anticonvulsant action in strychnia-induced convulsions; At a concentration of 2-0.1%, it has a negative chronotropic and positive inotropic effect; Finally, unlike other species, the infusion of Lagohilus biacicularis does not accelerate, but slows down blood clotting time by 70%, according to Fonno. plasma recalcification time by 44%. reduces plasma tolerance to heparin by 35%. [3,8,9]

Lagochilus ferganensis lkramdan - Lagohilus Fergana - This type of plant was studied by N. A Ibragimov. new species of this species was described by M. Ikromov. Perennial plant. The root is vertical, multi-headed. The stem is woody at the bottom, straight, multi-branched, densely hairy. The leaves have a rhomboid shape, the bases are pointed, ovate, three-five-lobed, ovate-pointed. The flowers are semilobular in the axils of the upper leaves. The flower is bell-shaped, the tips are sharp and flat. The calyx tube is single-hairy, densely covered with hairs. Gultij is white, protrudes from the tube, the lower lip is three-lobed. Blooms in June-July, bears fruit in July-August. [3]

In the first pharmacological study conducted by N.Ibragimov, the effect of accelerating the process of blood coagulation and hemostasis was determined, and the pharmacological properties of intoxicating L. inebrians were determined both in terms of the effect on hemocoagulation and sedative-hypotensive properties . It is characteristic that the infusion at a dose of 0.5 g/kg has a greater effect than at doses of 1 and 2 g/kg. [3,8]

Lagochilus gypsaceusVved.- lagochilus gipsavoi. This type of plant was also studied by TR Abdurahmanov. It is very close to L. inebrians . It differs from it by a long and hard, but not protruding, fluffy tuft, which is horizontally separated from it. [3]

TRAbdurakhmanov, in a pharmacological study of this species of Lagochilus, found that it is almost non-toxic: intravenous administration of Lagochilus tincture to dogs at a dose of 10 mg/kg accelerates blood clotting time by 30% after 30 minutes and by 33% after 60 minutes, recalcification time, respectively, by 38 and reduces by 40% and increases the resistance of plasma to heparin. 35% and 33% and reduces blood pressure by 7%. [3,8]

Lagochilus hirtus Fisch . This type of plant was studied by I.E Akopov, V.A Konovalova, M.M Mansurov. The stem is 15-20 cm high, hairless or hairy at the bottom; leaves wedge-shaped, glabrous, cut 3-5 times; Branches 8-10 mm long, spine-shaped, covered with dense hairs; 6-8-flowered half whorls; calyx tubular bell-shaped, densely hairy, hairs one to four lobed, thick, teeth triangular, 3-4 mm long, 2 times shorter than the tube. [3]

I.E Akopov, V.A Konovalova, M.M Mansurov were the first to pharmacologically study this species of Lagohilus and stahydrin alkaloid obtained from it (NF Proskurina, LM Utkin). They found that both 10% herb tincture and stachydrine hydrochloride solution at a dose of 5 ml/kg slightly accelerates the blood clotting process and slightly lowers blood pressure in dogs. [3,8,9]

Lagochilus hirsutissimus Vved .- hard-haired lagohilus- This type of plant is also IIIbragimov. Perennial plant. The stem is woody, straight, simple or slightly branched, densely short, protruding, hairy, with many interspersed stems. The leaves are rhomboid with an oblong contour, tufted, the stem is toothed,

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deeply lobed or ends with a separate, very short, thick pointed tip. The flowers are standing in the axils of the upper leaves. The inflorescence is thin, needle-like. Gulkossa leaf joints are ovate. [3]

This plant was first studied pharmacologically by II Ibragimov. He found that lagohilue stubby has low toxicity, at a concentration of up to 0.5% it reduces the heart rate of the frog's heart according to Shgraub (8-18%) and increases their amplitude (35-50%). this same concentration increases the amount of liquid flowing from the veins of the isolated frog liver by 27%. Infusion at a dose of 2 ml reduces the frequency of in situ contraction of the frog heart (by 8-32%). [3,8]

Lagochilus Kporringianus Pavl . Lagohilus knorrigovsky - This type of plant is P.K Alimbaeva. studied by Stem 15-35 cm high, vertical root, dense leaves; the stems in the lower part are sparsely hairy: the leaves are five-lobed, oblong-lobed, round or blunt. Flowers are collected in half folds: calyx covered with very short adpressive hairs, branches 8-20 mm thick; corolla pink, equal to or longer than the calyx [3].

This species of Lagohilus was studied pharmacologically for the first time by P.K Alimboyeva. It was determined that the dry weight of the plant contains: tannins (3%), calcium salts (2.02%), essential oils (0.21%). resins (4.48%). consists of ascorbic acid (112.64 mg%), coumarins, flavonoids and cardiac glycosides. Intravenous administration of Lagohilus knorrigovsky tincture was found to accelerate blood clotting time by an average of 25%. [3,8,9]

Lagochilus Paulseni Brig.- I.Ibragimov , T.R Abdurahmonov, Yu. Scientists such as M. Mamadov conducted scientific research **.** The stem is 30-50 cm high, straight and crooked, growing under the crown, short hairy. The outline of the leaves is broad rhombic, twice or three times divided into lanceolate and linear pieces; Two-flowered half-folds; branches are thin, sharp, under half lobes, 15-17 mm long; calyx narrowly four-toothed; teeth oblong, 17-27 mm long and 3 mm wide, 2-3 times as long as calyx tube; corolla equal to the cup, pink, with dark veins. [3]

In a pharmacological study, I.I Ibragimov, T.R Abdurakhmanov and Yu.M.Mamadov discovered a stimulating effect of its infusion on the blood coagulation process. II Ibragimov presented previous data in his experiments and found that the infusion of this type of Lagohilus at doses of 0.1, 0.5, 1 and 2 g/kg accelerates the blood clotting process. In addition, when administered intravenously, smaller doses (0.1 and 0.5 g / kg) were more effective than larger doses: they inhibited blood clotting by an average of 20% after 30 minutes, and after 60 minutes Speeds up by 27%. [3,8]

Lagochilus seraschanicus Knorr is a thorny logochilus This type of plant was also studied by TR Abdurahmanov. The stem is 14-45 cm high, the root is thick; leaves sparse above and below, lower leaves 5-8 mm long. The flowers are 4-6 semi-lobed, the branches are thick, 10-20 mm long; calyx narrowly bell-shaped, slightly curved tooth, wide oblong, rounded at the top, 12-18 mm long and 5-6 mm wide, 1/5 longer than the tube.[3]

This species of Lagohilus was studied for the first time by T.R Abdurahmanov. He found that the infusion of this plant was not toxic; A 10% infusion at a dose of 10 ml/kg slows the onset of strychnine-induced convulsions by 31% and has a known antitoxic effect. After intravenous administration of such an infusion dose to dogs, the clotting time was slowed by 33% after 30 minutes, and no changes were noted after 60 minutes; plasma recalcification time was accelerated by 33% and 38%, respectively. plasma heparin resistance increased by 50 and 53%. the amount of free heparin in plasma was reduced by 7 and 13%, and by 28%, and the prothrombin time was slowed down by 5 and 30%. [3,8,9]

Plants of the genus Lagochilus are known as valuable astringents and are among the most popular medicinal plants of the East. Preparations based on Lagochilus are successfully used to stop various bleeding. The main active substance is four-atom alcohol, diterpenoid lagoxilin, on the basis of which a number of acetyl and isopropylidene derivatives were obtained, and it was shown that the hemostatic activity depends to some extent on the number of free hydroxyl groups of lagoxilin and its derivatives. [9-13]. Therefore, the synthesis of water-soluble derivatives of lagoxilin is a promising direction, as it is possible to increase their water solubility and hemostatic activity.[14]

Lagochilin was isolated from cultured Lagochilus plants using the method reported in the literature according to the following scheme.[14-16]

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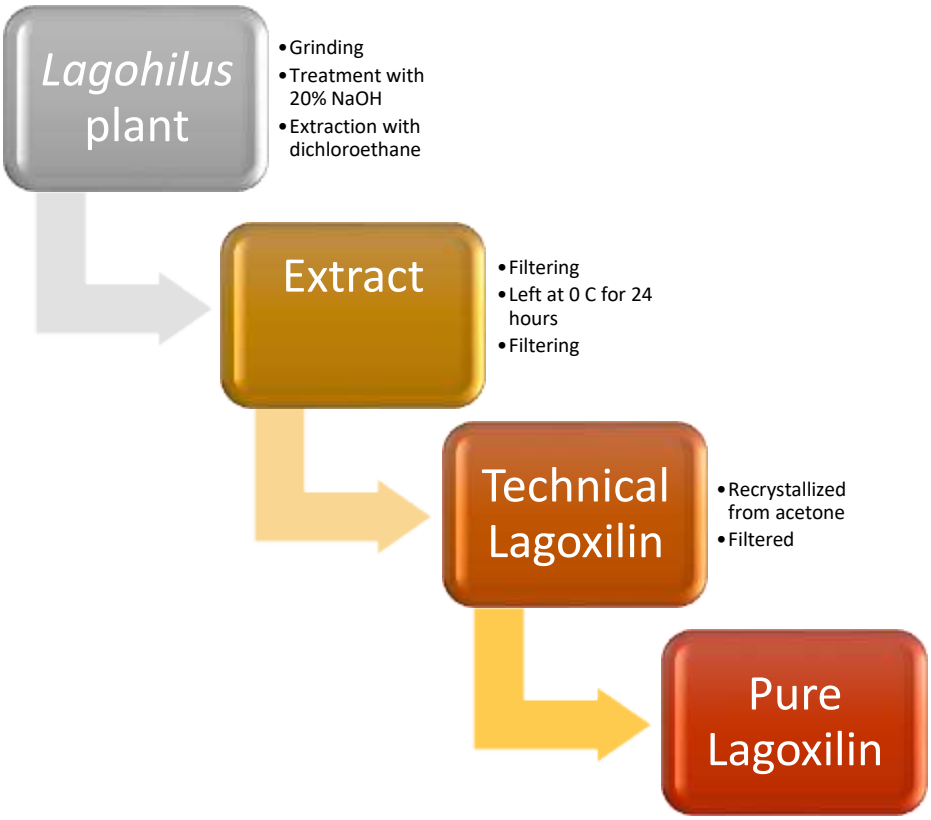

General scheme for the isolation of lagochilin from the plant " Lagochilus".

The dried plant was crushed, treated with 10% NaOH solution and dried. Dichloroethane was taken in a ratio of 1:5 and extracted at 80-85 ° C for 2 hours . The dichloroethane (DXE) extract was filtered and left in the refrigerator for 24 h. Precipitated technical lagoxiline crystals were isolated. Technical lagoxiline was recrystallized from acetone. The average yield of Lagoxilin was 1.7-1.8% .[16-18]

The genus Lagochilus contains diterpenoids, flavonoids, phenolic compounds, triterpenoids, It is reported that there are glycosides, lignans, steroids, alkaloids, polysaccharides, simple and complex esters , lipids, carbohydrates, minerals, vitamins and about 150 other secondary metabolites. Among these compounds, diterpenoids show high biological activity. Types of chemical compounds isolated from each species of Lagochilus . [19-25] Diterpenes isolated from Lagochilus species and their sources are listed in Table 2.

Table 2.

Identified compounds	Sources
Lagochilin (**1**)	L. gypsaceus, L. inebrians, L. setulos us, L. pubescens, L. proskorjacovii, L. hirsutissimus
3-Mono-O-acetyllagochiline (**2**)	L. inebrians
15-Mono-O-acetyllagochilin (**3**)	L. inebrians, L. pubescens
16-Mono-O-acetyllagochilin (**4**)	L. inebrians, L. pubescens
3,18-di-O-Acetyllagochiline (**5**)	L. inebrians, L. pubescens
15,16-di-O-Acetyllagochiline (**6**)	L. inebrians, L. pubescens
3,15,18-tri-O-Acetyllagochiline (**7**)	L. inebrians, L. pubescens
3,16,18-tri-O-Acetyllagochiline (**8**)	L. inebrians, L. pubescens
15,16,18-tri-O-Acetyllagochiline (**9**)	L. inebrians, L. pubescens
tetra-Acetyllagochilin (**10**)	L. inebrians, L. pubescens

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3,18-O-Isopropylidene-lagochiline (**11**)	L. inebrians, L. pubescens, L. proscorjacovii
3,18-O-Isopropylidene-lagochiline-15-acetate (**12**)	L. inebrians, L. pubescens
16-O-Acetyl-3,18-O-isopropylidene-lagochiline (**13**)	L. inebrians, L. pubescens
3,18-O-Isopropylidene-lagochiline-15,16-diacetate (**14**)	L. inebrians, L. pubescens
di-O-Acetyl-3,18-O-isopropylidene-lagochiline (**15**)	L. inebrians, L. pubescens
Vulgarol (**37**)	L. inebrians
Vulgarol acetate (**38**)	L. inebrians

in table 2 listed diterpenes are the most characteristic and important phytochemicals in the Lagochilus plant, and the largest number of them was recorded in L. inebrians, L. pubescens and L. platyacanthus (Table 1, Figure 1) [9-15] . It is the main component of the general extractives of many species of Lagochilus. Lagochilin (1) has been identified in L. inebrians, L. setulosus, L. gypsaceus , L. hirsutissimus, L. proskorjacovii and L. pubescens . In L. inebrians found in Samarkand region, 2.3% lagochilin, L. setulosus found in Shymkent region 1.1%, L. gypsaceus found in Kashkadarya region 2.1%. Lagochirsin (16) occurs freely in three plant species , L. hirsutissimus, L. setulosus, and L. gypsaceus. However, its amount in these plants was 0.2-0.3%.[8,9]

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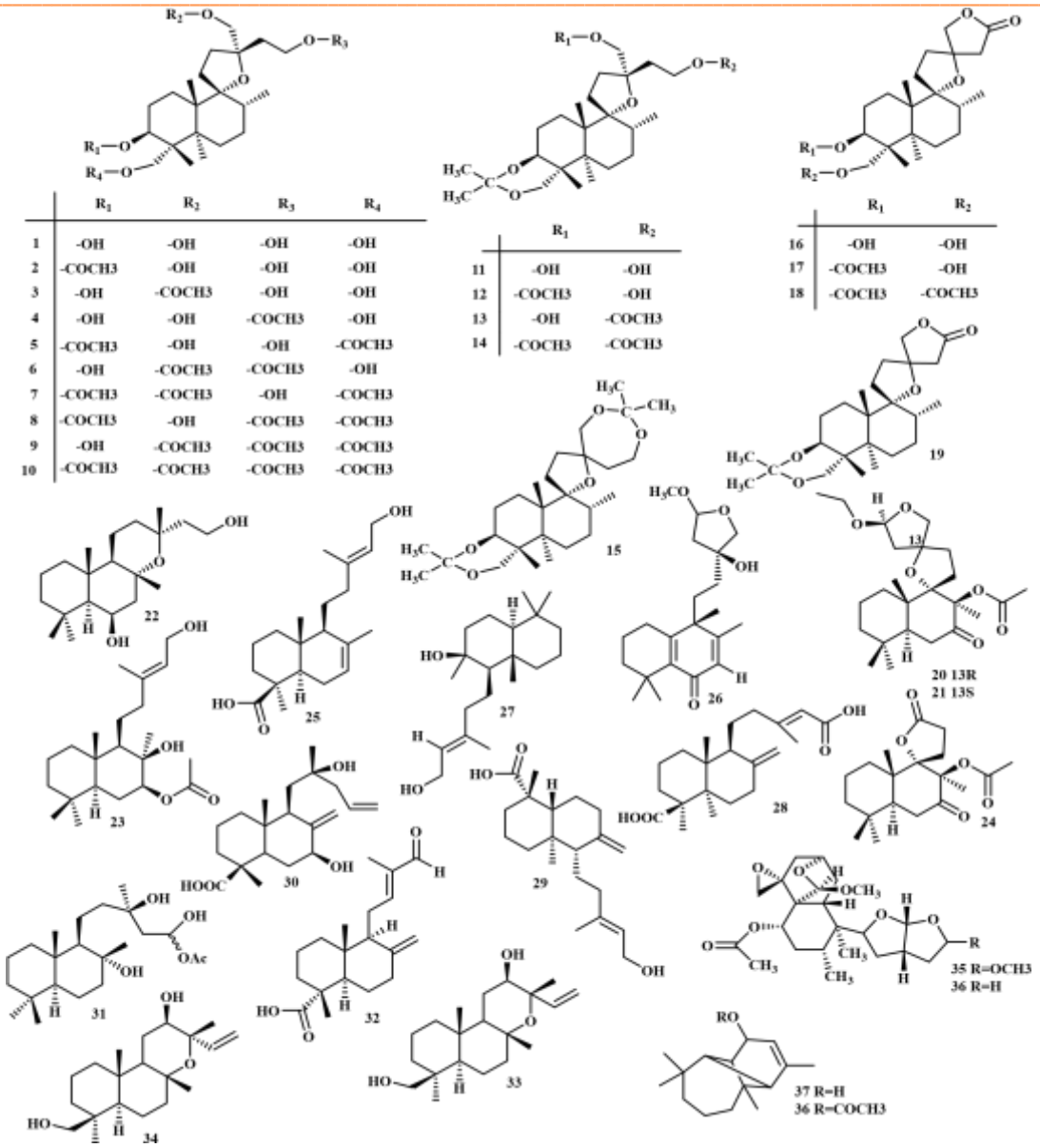

Figure 2 . Chemical structure of diterpenes isolated from the genus Lagochilus

Summary

Thus, a number of scientists studied the chemical composition of plants of the Lagochilus family in depth, and a number of diterpenes with high biological activity were isolated from them. Their chemical structure was confirmed on the basis of physical and chemical research methods.

References

1. Т.И.Цукерваник. Система рода Lagochilus (Lamiaceae). Ботанический журнал. 1985г. Т. 70.с.1183-1190.
2. Tskervanik, T.I. System of the genus Lagochilus (Lamiaceae). Bot. Zhurnal. 1985, 70, 1183–1190
3. Акопов И.Е. «Важнейшие лекарственные растения и их применение», «Медицина» УзССР 1986. 422-425.
4. Mamedov, N.A.; Egamberdieva, D. Phytochemical components and pharmacological effects of licorice: a review. Plant and human health; Springer International Publishing: Cham, Switzerland, 2019; Volume 3, pages 1–21. ISBN 9783030044084.
5. Шомуродов, Х.Ф.; Ахмедов, А .; Сарибаева, С.Ю. Распространение и современное состояние Lagochilus acutilobus (Lamiaceae) в связи с развитием нефтегазовой отрасли Узбекистана. Экол. Квест. 2014, 19, 45–49, doi: 10.12775 / EQ.2014.004.

ISSN NO: 2771-8840
Date of Publication: 28-07-2022

6. Красная книга Республики Узбекистан. Заводы (Ташкент: Чинор ЭНК) 2009, 1, 256.
7. Chjan, M.L.; Zeng, X.Q .; Sanderson, S.C .; Byalt, V.V .; Suxorukov, A.P. The concept of Central Asian flora from the Cenozoic The origin and irradiation of the Tianshan Mountains of Lagochilus (Lamiaceae). PLoS ONE 2017, 12, e0178389, doi: 10.1371 / journal.pone.0178389.
8. Jiang, M .; Chjao, S .; Yang, S .; Lin, X .; U, X .; Vey, X .; Song, Q .; Li, R .; Fu, C .; Chjan, J .; and others. “The main herbal medicine” is licorice: a review of phytochemicals and their effects in combination preparations. J. Ethnopharmacol. 2020, 249, 112439. [CrossRef]
9. Sokolov, S .; Zamotaev, I. Handbook of Medicinal Plants; Medicine: Moscow, Russia, 1985. (in Russian
10. The acute toxicity of the new derivatives of lagochilin was 3-5 times less than their initial components (succinic anhydride and lagochilin).
11. The most effective dose for succinates of lagochilin was a dose of 1 mg / kg, which reduced the bleeding time in rats by 3.0-4.5 times as compared to intact animals.
12. Flora of the USSR. M., L.: AN SSSR. 1954.
13. M.M. Abramov., S.A. Yaparova. // Obtaining the main active principle from the intoxicating Lagohilus // Jurn. app.
14. chemistry. 1963. T36. No. 11. p. 2554-2556.
15. N. Zainutdinov, R. Islamov, D. N. Dalimov, T. R. Abdurakhmanov,A.D.Matchanov., N. L. Vypova // Structure-activity relationship for hemostatic lagochilin diterpenoids // 38 pp. 161-163. 2002, vol.
16. N.S. Gulyamova, G.Yu Akmalova, A.Kh. Islomov, U.N. Zainutdinov, G. Rakhmanberdiev. // Technology of production of Lagochirzin and its sodium salt (lagoden) // Chemistry and Chemical Technology. Tashkent. 2010. No. 2, P. 35-38.
17. U.N. Zaynutdinov., R. Islomov, D.N. Dalimov., T.R
18. Abdurakhmonov., A.D Matchanov., N.L. Vypova //Structure-activity relationship for hemostatic lagochilin diterpenoids// 38 pp. 161-163. 2002, vol.
19. Zaynutdinov U.N, Mavlyanqulova Z.I, Aslanov, K.A. Chemical study of Lagochilus pubescens. Chemistry. Nat. Compd. 1975, 11, 287–288, doi: 10.1007 / BF00570708.
20. Mavlankulova Z.I, Zaynutdinov U.N, Aslanov, K.A. Lagochilus pubescens diterpenlari. Chemistry. Nat. Compd. 1977, 13, 39–41, doi: 10.1007 / BF00566167.
21. Islomov R, Zaynutdinov U.N, Aslanov, K.A. Lagochilin 3-monoacetate Lagochilus inebrians. Chemistry. Nat. Compd. 1978, 14, 342–343, doi: 10.1007 / BF00713342.
22. Nurmatova M.P, Zaynutdinov U.N, Kamaev F.G, Aslanov K.A. Structure and configuration of new diterpenoid lactone from Lagochilus hirsutissimus. Chemistry. Nat. Compd. 1979, 15, 695–699, doi: 10.1007 / BF00565564.
23. Рахимов Д.А, Маликова М.Х, Вахобов А.А, Рузиев И.О, Абдурахмонов Т.Р. Растительные полисахариды. Полисахариды Lagochilus и их биологическая активность. Химия. Нац. комп. 1995, 31, 260–261, doi: 10.1007 / BF01170221.
24. Рахимов, Д.А, Маликова, М.Х, Вахобов, А.А, Абдурахмонов, Т.Р, Розиев, О.И. Растительные полисахариды. IX. Выделение и антикоагулянтная активность полисахаридов Lagochilus usunachmaticus. Химия. Нац. комп. 1997, 33, 534–535. дои: 10.1007 / BF02254796.
25. Зайнутдинов, У.Н, Исламов Р. Активные вещества Lagochilus inebrians. Журнал «Хим-Фарми». 1986, 20, 583–584.
26. Абрамов, М.М, Япарова, С.А. Получение основного активного начала из Lagochilus inebrians. журнал Приклад. Сим. 1963, 11, 2554–2556.
27. Sobirova Fotima, Esanov Rakhmat, Elmurodov Laziz, Nataliya Vypova, Alimjon Matchanov Synthesis and Biological Activity of Succinates 3,15,16,18 Tetrahydroxy 9-13-Epoxylabdane International Journal of Materials and Chemistry 2020, 10(1): 8-15 DOI: 10.5923/j.ijmc.20201001.03

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