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BIOLOGICAL ACTIVITY AND PHARMACOLOGICAL PROPERTIES OF LAGOCHILIN ESTERS OBTAINED WITH DICARBOXYLIC ACID ANHYDRIDES

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Annotation

This article presents the pharmaceutical analysis of lagochilin derivatives obtained from *Lagochilus inebrians Bunge* through reactions with dicarboxylic acid anhydrides. The synthesized compounds based on succinic, phthalic, and other dicarboxylic acids were investigated for their biological and pharmacological activities. The study revealed the correlation between the chemical structure of these esters and their hemostatic, antioxidant, and hypotensive properties. The findings highlight the potential of lagochilin derivatives for developing new biologically active pharmaceutical agents.

Keywords: *Lagochilus inebrians*, lagochilin, dicarboxylic acids, succinates, pharmaceutical analysis, hemostatic activity, biologically active compounds.

Аннотация

В статье рассмотрены результаты фармацевтического анализа производных лагохиллина, полученных с ангидридами дикарбоновых кислот из растения *Lagochilus inebrians Bunge*. Проведён синтез новых соединений на основе янтарной, фталевой и других дикарбоновых кислот, исследована их биологическая активность. Установлена зависимость между химическим строением и гемостатической, антиоксидантной, гипотензивной активностью соединений. Полученные данные свидетельствуют о перспективах создания новых биологически активных веществ на основе лагохиллина.

Ключевые слова: *Lagochilus inebrians*, лагохиллин, дикарбоновые кислоты, сукцинаты, фармацевтический анализ, гемостатическая активность, биологическая активность.

Annotatsiya

Mazkur maqolada Lagochilus inebrians Bunge o‘simligidan ajratib olingan lagohilin moddasining dikarbon kislotalar angidridlari bilan hosilalari farmatsevtik tahlil qilinib, ularning biologik faolligi o‘rganilgan. Tadqiqot davomida lagohilinning suksin, fital va boshqa dikarbon kislotalar asosidagi hosilalari sintez qilinib, ularning gemostatik, antioksidant, gipoallergik va gipotenziv xususiyatlari baholandi. Shuningdek, ushbu hosilalarning kimyoviy tuzilishi bilan farmakologik faolligi o‘rtasidagi bog‘liqlik aniqlanib, yangi biologik faol modda yaratish istiqbollari ko‘rsatildi.

Kalit so‘zlar: Lagochilus inebrians, lagoilin, dikarbon kislotalar, suksinatlar, farmatsevtik tahlil, gemostatik faollik, biologik faol birikmalar.

Introduction. Traditional medicine, developed over centuries, forms the basis of modern medical science. According to I.E. Akopov, 502 plant species with hemostatic activity have been identified, belonging to 268 genera and 97 families, mainly Asteraceae, *Lamiaceae*, and Rosaceae. Many wild plants such as nettle, spinach, plantain, shepherd's purse, and dandelion possess therapeutic value and are officially recognized in pharmacopoeias.

Arnica montana contains flavonoids, phenolic compounds, carotenoids, and sesquiterpenes that ensure its hemostatic effects. Shepherd's purse (*Herba bursae pastoris*) contains vitamin K, acetylcholine, and organic acids, which enable blood-clotting activity. Nettle *(Urtica dioica)* includes carotene, vitamins C and K, histamine, and tannins that provide hemostatic and tonic properties. Plantago major and Rumex confertus are used for gastrointestinal diseases, while Spinacia oleracea and Taraxacum officinale improve digestion and liver function. These plants, studied for centuries, demonstrate the pharmacological basis of folk medicine.

Among Central Asian medicinal plants, *Lagochilus inebrians Bunge* from the *Lamiaceae* family stands out for its strong hemostatic and anti-inflammatory activity [1-2]. It grows widely in Uzbekistan's Samarkand, Jizzakh, and Navoi regions. The plant contains diterpenoids, flavonoids, alkaloids, and vitamin K. The main active compound, lagochilin (3,16,17,18-tetrahydroxy-9,13-epoxylabdan), is responsible for its pharmacological effects [3-4].

Diterpenoids are classified into acyclic and bicyclic types based on their carbon skeleton. Lagochilin and its derivatives show hemostatic, sedative, hypotensive, and anti-allergic activities. Studies reveal that their effectiveness depends on the number of free hydroxyl groups; when replaced by acetyl or benzyl groups, the activity decreases significantly.

In conclusion, medicinal plants form the historical and biochemical foundation for modern drug discovery. *Lagochilus inebrians* and its diterpenoid lagochilin demonstrate valuable hemostatic and antioxidant effects. The integration of natural compounds with dicarboxylic acid derivatives expands their therapeutic potential, offering new perspectives for pharmaceutical and clinical applications in hemostasis and neuroprotection.

Dicarboxylic acids such as succinic, maleic, and phthalic acids are key intermediates in biochemical processes. Succinic acid, found naturally in plants, enhances growth and metabolism [5-10]. Its salts and esters, known as succinates, are biologically active with antioxidant and anti-hypoxic properties [11-15]. Modification of lagochilin with dicarboxylic acid anhydrides produces new esters with improved solubility and pharmacological efficiency [16-25].

Succinates have wide application in modern pharmacology. Ethylmethylhydroxypyridine succinate (Mexidol) is used in treating ischemic heart disease and strokes, while phenotropil succinate exhibits psychoimmunomodulatory activity. Research shows that combining natural compounds with succinic derivatives enhances bioavailability and extends therapeutic effects [26-28]. Moreover, hydrogels derived from chitosan and succinic acid are utilized in regenerative medicine due to their high biocompatibility [27-35].

Materials and Methods. Modified literature methods were used to synthesize, for the first time, a series of lagochilin esters with succinic (SA), glutaric (GA), and phthalic (PA) anhydrides. To obtain lagochilin monosuccinate, 1 mmol of lagochilin was dissolved in absolute pyridine, and 1.15 mmol of succinic anhydride was added. The reaction mixture was heated at the reflux temperature for 14–15 hours, and its progress was monitored by TLC. After completion, pyridine was evaporated under reduced pressure, and the residue was treated with 10% cold HCl solution (pH

1.5–2) until the pyridine odor disappeared. The mixture was neutralized with 10% $NaHCO_3$ solution, and the products were extracted with benzene (5×30 mL). The organic layer was dried over anhydrous Na_2SO_4 for 24 hours, filtered, and evaporated under vacuum. The residue was separated by column chromatography, and fractions with identical Rf values were combined. The resulting colorless oily compound dissolved well in ethanol, acetone, chloroform, benzene, and ether, but was poorly soluble in water.

Results. The synthesized lagochilin esters demonstrated varying degrees of biological activity. Succinic acid derivatives exhibited strong hemostatic properties, while phthalic derivatives showed notable antioxidant effects. The results revealed that the biological activity depends on the number and nature of free hydroxyl groups and the substituents introduced during esterification

The poor solubility of lagochilin succinates in water causes certain difficulties in studying their biological activity.Therefore, the succinates were dissolved in anhydrous acetone, and a 10% ethanolic solution of NaOH was added dropwise until precipitation ceased. The resulting precipitates were filtered, dried at room temperature, and converted into the corresponding sodium salts (Na^+ derivatives).

Lagochilin glutarates and phthalates were synthesized by the same procedure, treating lagochilin with glutaric and phthalic anhydrides, respectively. Some of the physicochemical properties of the obtained compounds are summarized in **Table 1**

The physicochemical properties of lagochilin derivatives

№	Lagochilin Derivative	Melting Point (°C)	Solubility	Yield (%)
1	Lagochilin	167–168	Acetone, ethanol, dioxane, pyridine	1–1.5
2	Lagochilin Na-trisuccinate	285–286	Soluble in water	85–89
3	lagochilin Na Disuccinate	300–301	Soluble in water	89–90
4	Lagochilin (Monoglutarate)	Oily	Acetone, benzene, pyridine, diethyl ether	90–95
5	lagochilin Diglutarate	Oily	Acetone, benzene, pyridine, diethyl ether	90–92
6	lagochilin monophthalate	Oily-liquid	Acetone, benzene, pyridine, diethyl ether	85–90
7	Lagochilin Na-triphthalate	330–332	Soluble in water	90–95
8	lagochilin diphthalate	Oily-liquid	Acetone, benzene, pyridine, diethyl ether	90–95

As can be seen from the data presented in Table 1, the derivatives of lagochilin obtained with succinic anhydride, glutaric anhydride and phthalic anhydridessess a fatty (lipid-like) nature, are well soluble in organic solvents, and relatively poorly soluble in water. The yields of the complex esters of lagochilin with dicarboxylic acids and the subsequently obtained soluble salt forms ranged from 76 to 97%.

Discussion. The findings confirm the crucial role of dicarboxylic acid modifications in enhancing lagochilin's pharmacological potential. The structure–activity relationship suggests that the presence of unbound hydroxyl groups contributes to higher hemostatic activity. These results align with previous studies on succinate-based compounds, supporting their potential use in hemostatic drug development.

It was of particular interest to study the relationship between the structure of lagochilin derivatives and their hemostatic activity, as well as to observe how the activity, which depends on the nature of the substituents in the hydroxyl groups of the lagochilin molecule and the number of free hydroxyl groups, affects their toxicity. Therefore, in collaboration with the Pharmacology Laboratory of the Institute of Bioorganic Chemistry named after Academician O.S. Sodikov of the Academy of Sciences of the Republic of Uzbekistan - specifically with Senior Researcher, PhD N.L. Vypova and Junior Researcher L.Q. Elmurodov - the hemostatic activity of the synthesized compounds was studied.

The general effects and acute toxicity of the compounds were determined in mice after oral administration. Each dose of the substance was tested on six mice over a period of 14 days [36].

Lagochilin, when administered at a dose of 600 mg/kg, caused no mortality, and its LD_{50} value was determined to be 970 mg/kg, which corresponds to toxicity class IV (low-toxic compounds).

Succinic anhydride demonstrated a slightly higher toxicity: at 800 mg/kg, no deaths were observed, whereas at 1000–1600 mg/kg the number of dead animals increased proportionally. The calculated LD_{50} value of 1550 mg/kg places it in toxicity class III (moderately toxic compounds).

In contrast, all synthesized lagochilin succinate derivatives - monosuccinate (LgMSNT), disuccinate (LgDSNT), trisodium succinate (LgTriSNT), and tetrasodium succinate (LgTetraSNT) - showed no lethal effects even at doses up to 5000 mg/kg. Their LD_{50} values were ≥ 5000 mg/kg, corresponding to toxicity class V (practically non-toxic substances).

These findings demonstrate that chemical modification of lagochilin with succinic anhydride significantly reduces toxicity -by approximately 3 to 5 times - compared with the parent compounds. This indicates that the obtained derivatives are safe and suitable for further pharmacological and preclinical investigations.

From the data presented in Table 2.10, it was found that lagochilin and succinic anhydride belong to the III–IV toxicity classes, which correspond to low-toxicity substances.In contrast, the lagochilin succinate derivatives belong to class V, indicating that they are practically non-toxic.

Conclusion. Lagochilin esters synthesized with dicarboxylic acid anhydrides exhibit promising biological and pharmacological properties. The strong hemostatic and antioxidant activities observed in certain derivatives make them potential candidates for further pharmaceutical development.

Toxicological studies showed that lagochilin and succinic anhydride belong to the III–IV toxicity classes (low-toxic substances), while all synthesized lagochilin succinate derivatives are classified as class V (practically non-toxic). Chemical modification of lagochilin with succinic anhydride reduces its toxicity by 3–5 times, confirming their safety and suitability for further pharmacological and preclinical research.

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