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Sesquiterpene lactones – occurrence and biological properties. A review

Laktony seskwiterpenowe – występowanie i właściwości biologiczne
Praca przeglądowa

Summary. Sesquiterpene lactones are secondary metabolites commonly found in higher plants as well as mosses, lichens, and fungi. Currently, over 5000 of such compounds have been identified with a majority isolated from Asteraceae plants. They are characterised by different chemical structures associated with the presence of various carbon pathways and functional groups, which exert an impact on their pharmacological activity. These colourless substances are soluble in fats, alcohols, or water. They are often bitter ingredients regarded as bitter compounds. They are accumulated mainly in leaves, flower parts and seeds; less frequently, they are present in roots. Sesquiterpene lactones exhibit multidirectional biological activity: some of them have anticancer, anti-inflammatory, antidiabetic, analgesic, antiparasitic, antifungal, and bacteriostatic effects. Therefore, high hopes are placed on the medical and pharmaceutical use of these substances. Lactone compounds are also regarded as a potential source of new active substances used in agriculture to combat plant pathogens.

Key words: bioactive compounds, sesquiterpene lactones, biological activity

INTRODUCTION

It is estimated that the Earth is occupied by 298,000 plant species [Mora et al. 2011]. These organisms, as a result of metabolism, produce differentiated secondary substances, the number of which, depending on the study, is estimated at 100–200,000. Furthermore, due to the progressive development of phytochemistry, and as a result of detailed research, about 1600 new compounds are detected every year [Wysokińska and Chmiel

2006]. Plant secondary metabolites include alkaloids, quinones, phenols, flavonoids, tannins, glycosides, coumarins, saponins, steroids, terpenes, and essential oils. Sesquiterpene lactones, that due to their diversified chemical structure and resulting properties, are used in many areas of life, are an interesting group. These substances have become the object of interest not only in the pharmaceutical and medical industries, but also works are being undertaken towards non-industrial use, mainly in agriculture.

CHEMICAL STRUCTURE OF LACTONES

Lactones are cyclic hydroxy acid esters produced during intramolecular condensation. Depending on the location of the hydroxyl and carboxyl groups in the hydroxy acid, molecules differ in the size of the cyclic ring (Fig. 1) [Gawdzik et al. 2015].

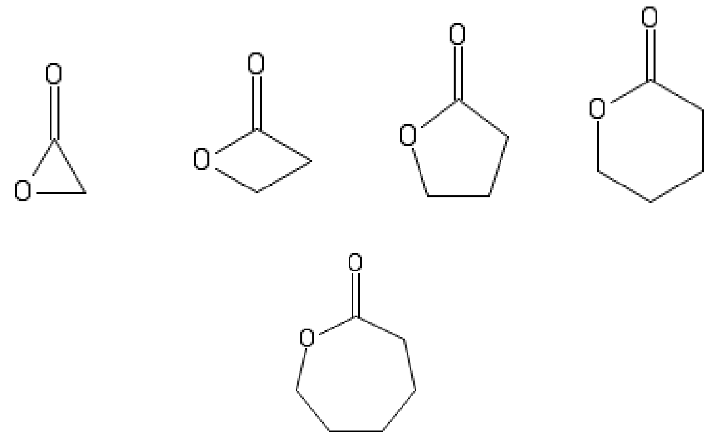

Fig. 1. Skeletal formulas of lactones. Left to right: α-lactone, β-lactone, γ-lactone, δ-lactone, ε-lactone [Gawdzik et al. 2015].

The esterification reaction of γ and δ carboxylic acids occurs as a result of spontaneous water loss (Fig. 2). Formed five- and six-atomic cyclic structures are characterized by greater durability and stability. The α-lactones, due to torsion and angular tensions between the atoms forming the ring, are very unstable compounds, similarly to lactone moieties containing more than six atoms in the cyclic ring [Morrison and Boyd 2010, Gawdzik et al. 2015].

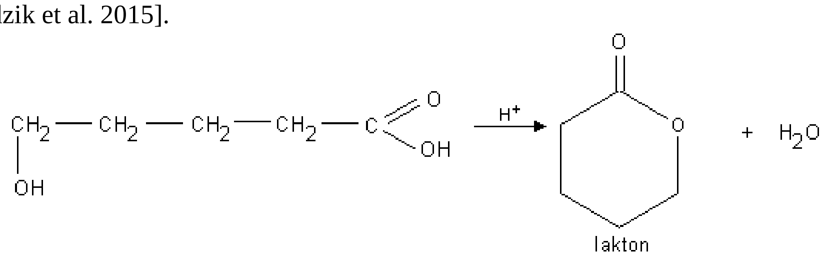

Fig. 2. Intramolecular esterification of hydroxy acid

Due to the low durability of α-lactones, it is difficult to clearly indicate their natural sources. Also, β-lactones are not commonly found in nature [Gawdzik et al. 2015]. This group includes, e.g. lipostatin isolated from the raw material of *Streptomyces toxytricini*, which is a strong and selective inhibitor of human pancreatic lipase [Bai et al. 2014]. An example of β-lactone of industrial importance is propiolactone, used as an intermediate agent in organic syntheses (mainly acrylic acid and its esters) and disinfectant in medicine (e.g. for sterilization of blood plasma, tissue transplants and during production of vaccines) [Rydzyński 2000].

Lactones that are cyclic esters determine the taste and smell of fruits and vegetables. The fragrances of lactones depend on the presence and dimensions of substituents within the lactone ring. The γ-lactones include γ-decalactone and dec-3-en-4-olid responsible for the peach aroma, while 5-ethyl-γ-lactone gives the scent of caramel and licorice. Also, the mint lactone and its isomers belong to the 4-carbon lactones [Gawdzik et al. 2015]. One of the best-known is the gulonic acid lactone, also known as ascorbic acid, which is part of vitamin C [Czerwiecki 2009].

The δ-lactones give a fragrance to dairy and fermented products. For example, the sweet coconut-peach aroma of δ-nanolactone can be found in mango, coconut and raspberry, while that of δ-decalactonlactone is present in tropical fruits. The perfumery industry uses jasmine lactone present in the flowers of tuberose (*Polianthes tuberosa* L.) and jasmine (*Jasminum officinale* L.) [Libiszewska 2011, Gawdzik et al. 2015].

Besides mono-ring lactones, bicyclic and macrocyclic ones are distinguished (Fig. 3), commonly used by the perfumery industry. The coumarin ring widely used in nature is present, e.g. sweet vernal grass (*Anthoxanthum odoratum* L.), manna grass (*Hierochloë odorata* L.) and true lavender (*Lavandula angustifolia* L.). This compound is also responsible for the smell of fresh hay. Another group is made up by polycyclic (macrocyclic) lactones. These include, e.g. exaltolide found in the essential oil from angelica, which gives a musky sweet fragrance to the whole plant [Libiszewska 2011, McGint et al. 2011, Adaszyńska-Skwirzyńska and Swarcewicz 2014, Gawdzik et al. 2015].

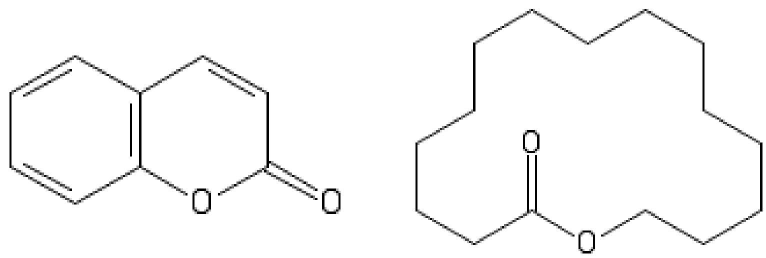

Fig. 3. Skeletal formula of coumarin (left) and exaltolide [Gawdzik et al. 2015]

SESQUITERPENE LACTONES – OCCURRENCE AND PROPERTIES

Sesquiterpenes are a particular group of terpene lactones. Due to the presence of 15 carbon atoms, they are also called *one-and-a-half-terpenes*. They are formed from trans-trans-farnesyl diphosphate by means of enzymatic cyclisation and oxidation that modifies their conformation.

Table 1. List of selected of plant species and sesquiterpene lactones isolated therefrom. The species are grouped alphabetically within botanical families

No.	Botanical family	Latin and English names of the species	Raw material	Lactone	Source of information
1	*2*	*3*	*4*	*5*	*6*
1.	*Apiaceae*	*Thapsia garganica* (L.) (deadly carrots)	root, fruits	tapsigargin	Thastrup et al. [1987], Makunga et al. [2005], Samiec [2010]
2.	*Asteraceae*	*Achillea millefolium* (L.) (common yarrow)	stem, flower	achillicin, dihydropartenolide	Nowak [2009]
3.		*Anthemis nobilis* (L.) (chamomile)	flower	nobilin	Capasso et al. [2000]
4.		*Anvillea garcinii* (Burm. DC.) (Arabian oxeye)	stem	9α-hydroxy-partenolide	Nawrot et al. [2015]
5.		*Arnica chamissonis* (Less.) (chamisso arnica)	flower	helenalin	Sugier [2013], Kowalski et al. [2015]
6.		*Arnica montana* (L.) (mountain arnica)	flower stem, roots	helenalin, 11 α, 13 dihydrohelenalin	Sugier [2013]
7.		*Artemisia absinthium* (L.) (absinthe)	stem	hydroxypelenolide	Grabarczyk et al. [2014]
8.		*Artemisia annua* (L.) (sweet sagewort)	stem	artemizin	Libiszewska [2011]
9.		*Artemisia baldschuanica (Krasch.)* (-)	stem	ambrosin	Egamberdieva et al. [2016]
10.		*Artemisia glabella* (Kar. et Kir.) (-)	leaf, flower	arglabin	Grech-Baran and Pietrosiuk [2010]
11.		*Artemisia indica* (Willd.) (mugwort)	stem	artemizin	Hadaś and Derda [2014]
12.		*Artemisia myriantha* (Wall ex Bess.) (-)	stem	arglabin	Grech-Baran and Pietrosiuk [2010]
13.		*Artemisia pallens* (Wall.) (dhavanam)	stem	5b-epoxy-10β-hydroxy-1-en-3-one-trans-germacran-6a,12-olide and its 10α-epimer	Pujar et al. [2000], Grabarczyk et al. [2014]
14.		*Calea ternifolia* (Kunth.) (bitter-grass)	leaf	caleicins, caleocromens	Piekoszewski and Florek [2009], Siemonienko et al. [2013]

15.		*Centaurea pullata* (L.) (-)	stem	11b, 13 dihydrosalo--nitenolide, 8a-hydroxy-11b, 13-dihydro--4-epi-sonchucarpolide, melitensin	Djeddi et al. [2008]
16.		*Centaurea solstitialis* (L.) (golden starthistle)	stem	solstitialin A acetate and solstitialin A	Grabarczyk et al. [2014]
17.		*Chamomilla recutita* (L.) (wild chamomile)	flower	matricin	Grys et al. [2014]
18.		*Chrysanthemum cinerariaefolium* (Trev.) (Dalmatian chrysan-themum)	flower	pyretrozin	Struciński [2009]
19.		*Cichorium endivia* (L.) (endive)	leaf	intybin	Cieślik and Gajda [2010]
20.		*Cichorium intybus* (L.) (common chicory)	root	lactucin, lactucopycrin	Jędrzejko et al. [2009]
21.	*Asteraceae*	*Cnicus benedictus* (L.) (spotted thistle)	stem	knicin	Najda [2015]
22.		*Cynara scolymus* (L.) (globe artichoke)	leaf, flower	cynaropycrin, dehydrocynaropycrin, cynaratriol, grosheimin	Kulza et al. [2012]
23.		*Helenium amarum* (Raf.) (bitter sneezeweed)	stem	tenulin	Ivie et al. [1975]
24.		*Helianthus annuus* (L.) (common sunflower)	stem	annuolide F	Gniazdowska [2007]
25.		*Inula helenium* (L.) (elfdock)	root	alaktolaktone, isoalactolactone, dihydroalactolactone	Kędzia [2008], Bilińska and Buchwald [2015]
26.		*Ligularia platyglossa* (Franch.) (Hand.-Mazz.) (leopard plant)	root	eremophilinolide dimer, eremophyll and furanoemeremillyl derivatives	Liu et al. [2008], Grabarczyk et al. [2014]
27.		*Onopordum acanthium* (L.) (cotton thistle)	root	4β, 15-dihydro-3--dehydrozaluzanin C, zaluzanin C, 4β, 15,11 p, 13-tetrahydrozaluzanin C	Csupor-Löffler et al. [2014]

Table 1 – cont.

1	*2*	*3*	*4*	*5*	*6*
28.	*Asteraceae*	*Tanacetum parthenium* (L.) (Sch. Bip.) (feverfew)	stem	partenolide 11, 13-dehydro--compressanolide, costunolide, sanatamarin, artekanin, kanin	Grynkiewicz and Gadzikowska [2002], Studzińska-Sroka [2013], Hadaś and Derda [2014], Najda [2015]
29.		*Tanacetum vulgare* (L.) (common tansy)	stem, flower	tanacetin, arbuskulin-A, germacrene D, crispolide	Derda et al. [2012]
30.		*Traxacum officinale* (Web. ex Wigg.) (common dandelion)	root, leaves	tetrahydroridentin B, ixerin D, ainsliozide, taraxacolide glucopiranoside, taraxacoside, acetylated γ-butyrolactone glicoside	Najda [2015], Lis and Grabek-Lejko [2016]
31.		*Vernonia amygdalina* (Del.) (bitter leaf)	leaf	vernolide, vernodalol	Erasto et al. [2006]
32.		*Xanthium strumarium* (L.) (large cocklebur)	root, stem	xanthin, xanthumin and 8-epi-xanthatin	Wolski et al. [2009]
33.		*Zoegea baldschuanica* (C. Winkl.) (-)	stem	9α-hydroxypartenolide	Nawrot et al. [2015]
34.		*Zoegea mesopotamica* (Czerep.) (-)	stem	9α-hydroxypartenolide	Nawrot et al. [2015]
35.	*Chloranthaceae*	*Chloranthus japonicus* (Siebold.) (-)	whole plant, root	chlojaponilactone, atractilenolide III, neolithacoumone B, szizucanolide B, C and E-H	Kawabata et al. [1995], Fang et al. [2012], Grabarczyk et al. [2014]
36.	*Ginkgoaceae*	*Ginkgo biloba* (L.) (gingko)	leaf	bilobalide	Kobus-Cisowska et al. [2017]
37.	*Lauraceae*	*Lindera strychnifolia* (Sieb. et. Zucc.) (evergreen lindera)	root	linderolides, strychnilactone	Liu et al. [2013], Grabarczyk et al. [2014]
38.		*Lindera aggregata* (Sims.) (Kosterm.) (evergreen lindera)	root, tuber	linderagalactone E, hydroksylindestenolide	Grabarczyk et al. [2014]
39.	*Magnoliaceae*	*Magnolia grandiflora* (L.) (southern magnolia)	leaves	costunolide, partenolide	Abdelgaleil and Fumio [2007]
40.	*Zingiberaceae*	*Curcuma wenyujin* (Chen et. Ling) (-)	rhizome	curcunolide, 8,9-seco-4β-hydroxy--1α,5βH-7(11)-guaen--8,10-olide	Grabarczyk et al. [2014]

Explanation: (-) – lack of English name

Herz et al. [1977], referring to the origin of lactones, divided them based on the straucture of a carbon skeleton into groups corresponding to particular biogenesis stages. In the first phase, germacranolides are formed, giving rise to eudesmanolides and guaianolides, which in turn are intermediates in the biosynthesis of other types of carbon skeletons [Grech-Baran and Pietrosiuk 2010]. The main types of basic sesquiterpene lactones systems include germacranolides, elemanolides, eudesmanolides, cadinanolides and guaianolides Herz et al. [1977] [Kączkowski 1993].

The sesquiterpene lactones have been described as colorless, bitter, fat- alcohol-, and water-soluble substances. Due to their sensory and taste properties, they protect plants against herbivores in natural environment. They fulfill their role due to the bitter taste, which can be sensed, among others, in lettuce (*Lectuca* sp.) and plants that form a part of the meadow sward [Ivie et al. 1975, Gawdzik et al. 2015].

Sesquiterpene lactones are commonly found in higher plants, mosses, lichens, bacteria and fungi. These metabolites are primarily characteristic of the *Asteraceae* family. Over 3,000 of more than 5,000 identified structures have been detected in plants from this family. For this reason, their presence is utilized in modern taxonomic methods. Sesquiterpene lactones are also sporadic in families such as *Apiaceae*, *Magnoliaceae*, *Lauraceae*, *Winteraceae*, *Illiaceae*, *Aristolochiaceae*, *Menispermaceae*, *Cortiariaceae* and *Acanthaceae*. Table 1 presents selected plant species, from which the sesquiterpene-type lactones have been isolated.

Compounds belonging to sesquiterpene lactones are located in glandular hairs found on the leaves, flowers and seeds of plants. Although their content usually does not exceed 1% of dry matter, a 3% share of tenulin in dry matter of *Helenium amarum* (Raf.) has been reported [Grech-Baran and Pietrosiuk 2010, Bosco and Golsteyn 2017].

POSSIBILITIES OF SESQUITERPENE LACTONES USE

Due to different biological and chemical properties, sesquiterpene lactones are used in many areas of life. They are used in the prevention and treatment of cancer, diabetes and in the alleviation of pain and inflammation. The biocidal properties of lactones, that were used in the fight against human parasites and plant pathogens, have also been widely studied [Ashour et al. 2012, Kozioł et al. 2017] .

The antitumor potential of this group of biologically active compounds is based on cytostatic properties and the induction of cancer cell apoptosis. Grabarczyk et al. [2014] indicate inhibition of the division of HL-60 cell lines (promyeloblastic leukemia) by sesquiterpene lactones isolated from *Ligularia platyglossa* (Franch.). In turn, Grynkiewicz and Gadzikowska [2002] refer to the cytostatic properties of parthenolide against tumor cells. The authors emphasize the possibility of using the lactone present in feverfew (*Tanacetum parthenium* (L.) Sch. Bip.) as an auxiliary substance in anticancer therapy. These properties have also been described for arglabin identified in two species from the *Artemisia* family (*Artemisia glabella* Kar. et Kir. and *Artemisia myriantha* Wall. ex Bess). Its derivative, DMA-arglabin (dimethylaminoarglabin) has been registered in Kazakhstan, Russia and the USA as an anti-cancer substance [Grech-Baran and Pietrosiuk 2010]. Effective substances in cancer phytotherapy are found among guaianolides (*Cynara scolymus* L., *Eupatorium laeve* DC), pseudoguaianolides (*Arnica montana* L.), eudesmanolides (*Spilanthes acmella* Murr., *Taraxacum officinale* Web. ex Wigg), vernolepin (*Vernonia amygdalina* Del.), melampodynin A (*Melampodium americanum*

L.), and eupatoriopicrin (*Eupatorium cannabinum* L.) [Klasik-Ciszewska et al. 2016]. However, due to large variation of sesquiterpene lactones, compounds of neoplastic transformation of cells promoter features were also identified among them, e.g. tapsigargin isolated from *Thapsia garganica* (L.) [Samiec 2010].

The use of lactone raw materials with anti-inflammatory, analgesic and especially anti-migraine properties is widely studied. Nowak [2009] reported that chamomile (*Chamomilla recutita* L.) and yarrow (*Achillea millefolium* L.), the anti-inflammatory properties of which result from the presence of lactones, are also used in the treatment of cardiovascular diseases. A well-known raw material used in the treatment of hematomas, contusions, post-traumatic edemas and skin inflammations, are flower heads of mountain arnica (*Arnicae anthodium*) containing helenaline and its derivatives [Libiszewska 2011, Sugier 2013]. In turn, parthenolide obtained from the leaves of feverfew (*Parthenii folium*) shows, apart from the anti-inflammatory effect, also analgesic properties. Preparations based on parthenolide are particularly recommended in the supplementation of patients struggling with migraine. It should be emphasized that the anti-migraine activity of feverfew described by traditional medicine has been confirmed in clinical trials [Grynkiewicz and Gadzikowska 2002, Studzińska-Sroka 2013]. The issue of hepatoprotective and antioxidant activity of ethanolic extracts from *Vernonia amygdalin* (Del.) was also raised. Based on the results obtained by Iwo et al. [2017], it can be concluded that these extracts can be applied to protect the liver during anti-tuberculosis treatment with a combination of isoniazid and rifampicin.

Also, antidiabetic, spasmolytic, and supportive activity of lactones in peripheral circulation disorders [Nowak 2009] as well as narcotic properties, were also analyzed, which mainly refers to the extension of the REM sleep period after the use of *Calea ternifolia* (Kunth.) infusion [Piekoszewsk and Florek 2009, Kowalczuk et al. 2012, Simonienko et al. 2013]. In a study upon rats, it was proved that 3-hydroxypterolactone isolated from the bark of *Cyclocarya paliurus* (Batal.) Iljinsk. reduces the blood glucose [Grabarczyk et al. 2014]. In contrast, cinaropicrin contained in artichoke (*Cynara scolymus* L.) is a compound responsible for the smooth muscle relaxing effect and can be successfully used in gastrointestinal disorders [Kulza et al. 2012]. In addition to documented positive effects on health, sesquiterpene lactones may also cause allergic reactions of a cutaneous nature [Struciński 2009].

Scientific research confirms beneficial biocidal and static properties against microorganisms and indicates the possibility of using sesquiterpene lactones in the treatment of parasitic infections. Positive effects were recorded, among others, after the use of lactones derived from common cocklebur (*Xanthium strumarium* L.) and feverfew (*Tanacetum parthenium* (L.) Sch. Bip.) in the therapy of leishmaniasis, as well as artemisinin in relation to malaria and helenaline in the treatment of trypanosomiasis [Wolski et al. 2009, Libiszewska 2011, Hadaś and Derda 2014]. Based on microbiological tests, stronger effect of sesquiterpene lactones isolated from *Centaurea pullata* (L.) compared to streptomycin has been demonstrated. The antiviral properties of ε-lactones present in the curcuma rhizome (*Curcuma wenyujin* Chen et. Ling) were also confirmed [Mazur 2011, Grabarczyk et al. 2014]. Erasto et al. [2006], when analyzing the biocidal properties of vernolide and vernodalol isolated from *Vernonia amygdalin* (Del.), showed considerable bactericidal activity against five strains of Gram-positive bacteria (*Bacillus cereus*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Micrococcus kristinae*, *Streptococcus pyrogens*). In antifungal tests, vernolide showed high activity against *Penicillium notatum*, *Aspergillus flavus*, *Aspergillus niger* and *Mucor hiemalis*, while vernodalol was characterized by moderate inhibition of *Aspergillus flavus*, *Penicillium notatum* and *Aspergillus niger*. Sesquiterpene lactones, due to their biostatic action, can be a potential source of new biological substances used in agriculture. Their allelopathic activity has been demonstrated (annuolid F from sunflower) [Gniazdowska 2007, Chadwick et al. 2013] as well as insect growth inhibitory (including xanthumine and 8-epi-xanthatin from burdock limit the development of *Drospohila melanogaster*); furthermore, they were found in pheromones (dodecalactone) [Wawrzeńczyk and Olejniczak 1998]. In turn, Smith et al. [1983] and Wolski et al. [2009] indicate that melampodin A and melampodinin A obtained from *Melampodium americanum* (L.) inhibit the growth and feeding of *Spodoptera frugiperda*. Rochalska et al. [2010], who analyzed the effectiveness of treating the seeds obtained from plants containing lactones (common yarrow, chamomile and tansy), showed that in field conditions, the dressings used, especially for tansy, were characterized by similar or better protective properties than synthetic agents (Funaben T).

Numerous sesquiterpene lactones have found their application in industry, especially compounds with a pleasant aroma isolated from essential oils. These substances are used as ingredients in aromatic compositions of cosmetic products and food essences [Wawrzeńczyk and Olejniczak 1998, Libiszewska 2011, Gawdzik et al. 2015].

SUMMARY

Sesquiterpene lactones are a widespread group of ring compounds, particularly characteristic of the *Asteraceae* family, in which nearly 75% of known substances were isolated. These compounds are collected in secretory structures located mainly on leaves, flowers and seeds. The sesquiterpene lactones have a multidirectional biological activity, in which the inhibition of cell division is the most important, which allowed for the isolation of a group of anticancer compounds. Some lactones have anti-inflammatory, analgesic, antidiabetic, antiparasitic, antifungal and bacteriostatic effects. For this reason, particularly high hopes are put in the medical and pharmaceutical use of lactones. Lactone compounds are also perceived as a potential source of new substances used in agriculture to combat plant pathogens. Due to the continuous development of botany and phytochemistry as well as sciences using the potential of sesquiterpene lactones, identification of further compounds, learning new properties and indication of other directions of their use should be expected.

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Streszczenie. Laktony seskwiterpenowe są metabolitami wtórnymi występującymi powszechnie w roślinach wyższych, a także w mchach, porostach i grzybach. Obecnie znanych jest ponad 5000 tego typu związków, z czego większość wyizolowano z roślin należących do rodziny Asteraceae. Cechą charakterystyczną omawianej grupy jest zróżnicowanie struktury chemicznej, wynikające z obecności różnych typów szlaków węglowych oraz grup funkcyjnych, które modyfikują działanie farmakologiczne. Ze względu na właściwości fizyczne laktony półtoraterpenowe są substancjami bezbarwnymi, rozpuszczalnymi w tłuszczach, alkoholach lub wodzie, opisywanymi jako substancje gorzkie lub związki goryczowe. Gromadzone są głównie w liściach, częściach flowerów i nasionach, rzadziej zaś w korzeniach. Laktony seskwiterpenowe wykazują wielokierunkową aktywność biologiczną, wśród nich są związki o działaniu przeciwnowotworowym, przeciwzapalnym, przeciwcukrzycowym, przeciwbólowym, przeciwpasożytniczym, przeciwgrzybiczym i bakteriostatycznym. Z tego względu szczególnie duże nadzieje podkładane są w medycznym i farmaceutycznym zastosowaniu tych substancji. Związki laktonowe postrzegane są także jako potencjalne źródło nowych substancji czynnych wykorzystywanych w rolnictwie, stosowanych do zwalczania patogenów roślin.

Słowa kluczowe: związki biologicznie czynne, laktony seskwiterpenowe, aktywność biologiczna

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