Folia Biologica et Oecologica 11: 1–8 (2015)
Acta Universitatis Lodziensis

Loliolide - the most ubiquitous lactone

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ABSTRACT

The searching for biologically active compounds produced by living organisms led to the discovery of a number of compounds with more or less complicated structure. One of the simplest molecules are monoterpenoid lactones and loliolide is the most common among them.

Loliolide was found in animals (insects) and plants (flowers, shrubs, trees) both terrestrial and marine, such as algae and corals. Many years of research on plants used in traditional folk medicine of different countries have led to the conclusion that this compound has a variety of biological properties such as anti-cancer, antibacterial, antifungal and antioxidant ones. Moreover, plants containing loliolide are used in alternative medicine in treatment of diabetes and depression.

It is extremely interesting that this lactone also affects the behavior of ants as well as the development of certain plants (allelopathic activity). However, sometimes there are side effects as in the case of structural analogues of loliolide contributing to extinction of tropical coral.

KEY WORDS: monoterpenoid lactones, loliolide, biological activity fungi, HGT

Introduction

The world around us is full of a wide variety of organic compounds produced by both plants and animals. An important group among them are terpenoids (Grayson 1996, Grayson 1997, Grayson 2000, Molnár *et al.* 2010), derived from terpenes. Terpenes are composed of interconnected isoprene particles (consisting of 5 carbon atoms) which results in the fact that these particles of terpenes are composed of 5, 10, 15, etc. carbon atoms. Compounds structurally related to the terpenes, but constructed from a number of carbon atoms that is not a multiplication of 5 are called terpenoids. A common feature of their structure is oxygen, both in the form of hydroxyl groups and lactone rings. The simplest structural molecules containing both the lactone ring and the hydroxy group are called monoterpenoid lactones (Ragas *et al.* 2005, Ahmed *et al.* 2004, Garg & Agarwal 1994, Fukushima *et al.* 1998, Wong & Bron 2002, Chen *et al*. 2010).

The most common representative of monoterpenoid hydroxylactones, loliolide (**1**) (Fig. 1) consisting of 11

DOI: 10.1515/fobio-2015-0001

carbon atoms, is common in plants and animals, both terrestrial and marine. Despite simple structure loliolide shows a broad spectrum of biological activity which, combined with its ubiquity, makes it a very interesting compound.

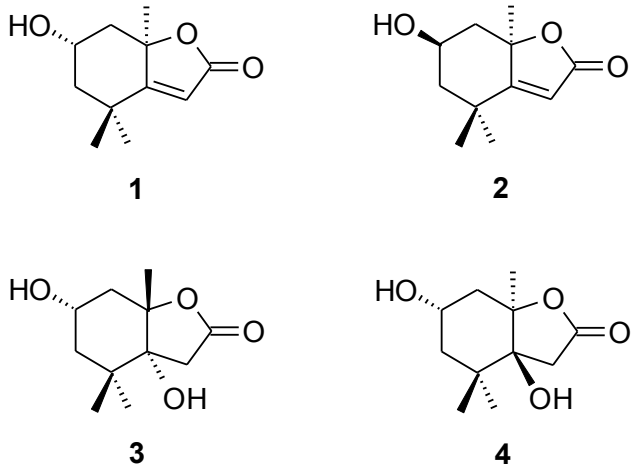

Figure 1. Loliolide and its derivatives.

Occurence of loliolide and its derivatives

Loliolide (**1**) was identified for the first time in English Ryegrass *Lolium perenne* in 1964 (Hodges & Porte 1964). Then it was discovered in bodies of queens of the red ant *Solenopsis invicta*, in which it is one of pheromones that enforce obedience to the queen's attendants (Rocca *et al*. 1983). In brown algae *Sargassum crassifolium* living in the seas stereoisomer epiloliolide (**2**) (Fig. 1) (Kuniyoshi 1985) was found beside loliolide. Over the years loliolide was found in many organisms. Sometimes, in addition to loliolide (**1**) and the aforementioned epiloliolide (**2**), dihydroxy derivatives of loliolide were also noted (**3, 4**) (Fig. 1).

Loliolide (**1**) and its derivatives are usually present in small quantities. Their amount ranges from $5.8 \cdot 10^{-5}$ % to $8.0 \cdot 10^{-4}$ % of dry weight of lactone in the case of plants while in marine organisms it averages between $2.0 \cdot 10^{-4}$ % and $3.0 \cdot 10^{-3}$ % of lactone in dry matter. Therefore extraction and purification of lioliolide is very complicated, labor-intensive and expensive. First step parts of plants are subjected to extraction with EtOH, EtOAc, MeOH or CH_2Cl_2. The obtained extract after evaporation of a solvent is suspended in H_2O or organic solvent and extracted again. The second extract is fractionated by silica gel column chromatography. Succeeding fractions are subjected to several chromatographic runs on silica gel column or preparative HPLC. After all these steps pure loliolide is obtained in mg yield (for example 20 mg from 1.3 kg of raw material).

Loliolide (**1**) and its isomer - epiloliolide (**2**) have been identified in many plant extracts. Their sources listed in order of amount of lactone are given in Table 1.

Many years of research on plants used in folk medicine of different countries have brought a lot of evidence about very common occurrence

of loliolide, and information about its various biological properties.

The researchers in Japan found that loliolide (**1**) was one of the compounds present in common purple loosestrife (*Lythrum salicaria* L.), which was known and used for many years in medicine. It exhibits astringent, antipyretic, anti-inflammatory and vasodilatory effects (Fujita *et al.* 1972).

Table 1. Loliolide (**1**) and epiloliolide (**2**) occurring in land plants.

Compound	The source of origin	The isolated amount of loliolide in% of dry matter
(1)	The roots of *Rauvolfia yunnanensis Tsiang* which is a traditional medicinal plant in China (Geng & Liu 2008)	$8.3 \cdot 10^{-4}$
(1)	Persian speedwell (*Veronica persica* Poir.) from the *Plantaginaceae* family, growing in south-east Asia (Sarker *et al.* 2000)	$6.2 \cdot 10^{-4}$
(1)	Hydrilla (*Hydrilla verticillata* (L. f) Royle) belonging to the family *Hydrocharitaceae* from China (Xiao *et al.* 2007)	$5.6 \cdot 10^{-4}$
(2)	Flower plant *Eirmocephala megaphylla* of northern Argentina (Borkosky *et al.* 1996)	$5.0 \cdot 10^{-}$
(1)	*Salvia divinorum* from the family *Lamiaceae* occurs endemically in the Sierra Mazatec in Mexico at altitudes 300–1800 m above sea level (Valde`s 1986)	$4.4 \cdot 10^{-4}$
(1)	Cornflower *Centaurea Conifera* belonging to the family *Asteraceae* from Spain (Fernandez *et al.* 1995.)	$2.9 \cdot 10^{-4}$
(1)	Leaves of *Schefflera taiwaniana*, plant from the *Araliaceae* family, growing in Taiwan (Kuo *et al.* 2002)	$6.0 \cdot 10^{-5}$
(1)	*Athyrium yokoscense* which is a species of fern in the family *Athyriaceae*, growing in Japan, especially in areas contaminated with heavy metals, around the mines and smelters (Kurokawa *et al.* 1998)	$1.0\ 10^{-5}$
(1)	Shrub *Yerba mate* from South America (Da Costa *et al.* 2008)	no data

Loliolide (1) was found in the extract from heliotrope leaves. Heliotrope *Heliotropium angiospermum* is a shrub from the south-eastern Mexico, belonging to the B*oraginaceae* family. It is used as an anti-inflammatory agent, it accelerates wound healing and is also applied to treat dysentery and diarrhea (Erosa-Rejón *et al*. 2009).

Researchers from Brazil found that lactone loliolide (1) isolated from dried leaves of burdock exhibited anti-proliferative activity with respect to the colon adenocarcinoma cell Caco-2. The study was inspired by the fact that the greater burdock (*Arctium lappa* L.) belonging to the *Asteraceae* family, found throughout the world, exhibits antitumor activity against a number of cell lines (Machado *et al*. 2012).

Powdered roots of common sowthistle (*Sonchus oleraceus* L.) growing in Egypt proved to be another source of loliolide (1). Sowthistle comes from the *Asteraceae* family, commonly occurring in Europe, Asia and North Africa, where it is widely regarded as a weed. It turned out, however, that even the weed may be useful. *In vitro* tests showed that loliolide (1) highly cytotoxic to the mouse lymphoma cell line L5187Y (ED50 = 4.7 mg/ml)

and exhibited antibacterial activity against strains of *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Neisseria gonorrhoeae* (Elkhayat 2009).

Lactone loliolide (1) was also found in the Philippine bush *Malachra fasciata*. This shrub, belonging to the *Malvaceae* family, is also known for its anti-cancer properties. Therefore, the tests were conducted to investigate antimutagenic properties of this plant, the properties that were closely associated with the former ones. It was found that loliolide (1) occurring in this plant, given to mice at a dose of 14.8 mg/kg reduced the number of micronucleated polychromatic erythrocytes induced by mitomycin C by 64.4%. This indicates that it is in fact antimutagen (Ragasa *et al*. 1997).

Loliolide (1) was also found in the Mexican plant called *Penstemon campanulatus* (Cav.) Willd. belonging to the *Plantaginaceae* family. Its antibacterial activity (1) against: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* strains was found (Zajdel *et al*. 2012).

Loliolide (1) was also detected in the extract of dried leaves of the Philippine tree *Pterocarpus indicus*. Extracts from leaves, wood, bark and roots of this tree have been used among the local population as a medicine for various ailments such as ulcers, diarrhea and dysentery. Testing the effects of loliolide (1) it was found that this compound had a low antibacterial activity against strains of *Pseudomonas aeruginosa* and *Escherichia coli*. It also has moderate antifungal activity against *Candida albicans* and *Aspergillus niger* (Ragasa *et al*. 2005).

Loliolide (1) was found in the leaves of white mulberry (*Morus alba* L.), a species of small deciduous trees of the *Moraceae* family. White mulberry leaves stabilize blood sugar level, reducing its absorption by a human organism and therefore can be used to help type 2 diabetes. *In vitro* studies conducted by researchers from Hungary showed that the dose of 100μg/ml extract of mulberry leaves, the dominant component of which (40.3%) was loliolide (1) had the same effect as a dose of 50 mg/ml of rosiglitazone, a drug used to treat diabetes (Hunyadi *et al*. 2012).

Lactone loliolide (1) was also found in the extract of dried leaves of *Mondia whitei*, a South African plant, known as Ginger White, used in folk medicine to treat diseases of a nervous system. In addition, its dried roots are believed to be an aphrodisiac by the local tribes. In the *in vitro* studies it was found that loliolide (1) had high affinity for a serotonin transporter, thus demonstrating an anti-depressant characteristic. Since it is not a nitrogenous compound typical for antidepressants, it means that its mechanism of action may be different from those known so far (Neergaard *et al*. 2010).

Loliolide and its plant-plant and plant-animal interactions

The tests of plants in the acquisition of these new valuable substances are not limited to the search for medicaments for humans. Equally important are the findings on interactions between plants or between plants and animals.

Loliolide (1) was isolated from fresh leaf extract of horsetail *Equisetum arvense* occurring in Japan. It was found that 250 ppm of the compound

completely inhibited germination of lettuce seeds (Hiraga *et al*. 1997).

Loliolide (1) is also present in Jerusalem artichoke *Helianthus tuberosus* L., which is widespread throughout the world as an edible, forage and decorative plant. It was isolated from this plant growing in the U.S. state of Ohio and the Mississippi River valley. It was found that this compound slightly (15–20%) stimulated accumulation of metabolites involved in plant defense against pathogens (Pan *et al*. 2009).

Loliolide (1) was isolated from an extract of crabgrass *Digitaria sanguinalis* roots. This plant belongs to the *Poaceae* family that occurs in north-eastern China. It exhibited allelochemic activity, on the one hand on the inhibition of soybean root growth, on the other, it stimulated growth of maize shoots (Zhou *et al*. 2013).

Lactone loliolide (1) was isolated from an extract of dried leaves of *Xanthoxyllum setulosum* P. Wilson, a plant occurring in Costa Rica. This plant has been considered in the search for plant protection against pests. It is so because the plant is known to deter ants *Atta cephalotes* (Attini). Loliolide (1) was used for the test with choice for a captive colony of hundreds of ants. The ants were supposed to choose from rye flakes saturated with a solution of loliolide at the concentration of 6.8 mg/g and wheat flakes soaked only with clean solvent. The results showed that the ants definitely chose the cereal without the compound. The authors concluded that this might indicate that loliolide is the sought ant-repellent for these ants (Okunade & Wiemer 1985).

Loliolide found in marine organisms

Looking for new sources of potential medicines people also turned to organisms living in coastal waters, because wide variety of plants and animals, often unknown to science live in seas and oceans.

Dried and powdered brown algae *Sargassum ringgoldianum* subsp. *Coreanum* proved to be a good source of loliolide (1), exhibited antioxidant properties protecting the cell against the harmful effects of free radicals produced by the action of H2O2 (Yang *et al*. 2011).

Loliolide (1) was also extracted from molluscs of the genus *Opisthobranch* living in the Indian Ocean. Tests showed that this compound inhibited the growth of tumor cells of human nasopharyngeal carcinoma KB (ED50 = 10 μg/ml) and murine lymphocytic leukemia P-388 (ED50 = 3.5–22 μg/ml) (Pettit *et al*. 1980).

Epiloliolide (2) with its dihydroderivative (3) were isolated from red algae *Galaxaura filamentosa* occurring on the reefs of Votua (Fiji). These compounds were found during tests on the effects of algal growth combined with a simultaneous extinction of corals on tropical reefs. These lactones were found to inhibit of photosynthesis in coral, causing their deaths, even up to 79% of the population within 24 hours of the contact of alga-coral (Rasher *et al*. 2011).

Loliolide (1) and its dihydroderivative (3, 4) were also found in other marine plants and animals, such as algae or corals which are presented in Table 2.

Summary

Currently, there is growing interest in what our ancestors knew well, that nature is the source of various products valuable for us. Instead of synthesizing often very expensive and complicated compounds, it is better to use the compounds that nature has already created. Lactone loliolide (**1**) is a very simple molecule with a wide variety of properties commonly found in living organisms on Earth, both on land and in water. It should be emphasized that lactone loliolide (**1**) found in many different organisms is always the same compound. This makes its anti-inflammatory, anti-tumor or anti-bacterial activity even more important. However, its beneficial effects in diabetes or depression treatment are also significant. Undoubtedly, further studies of plants used in traditional folk medicine will lead to finding new sources of loliolide and the subsequent discovery of its properties and applications.

Table 2. Loliolide and its derivatives in marine organisms.

Compound	The source of origin	The isolated amount of loliolide in% of dry matter
(1)	Brown algae Cladostephus spongiosus f verticillatus occurring in the Mediterranean Sea and the coastal waters of the Atlantic from Morocco to Ireland (El Hattab *et al*. 2008)	no data
(1)	Brown algae Dictyota dichotomia occurring in the coastal waters of Pakistan (Ali *et al*. 2003, Ali 2012)	no data
(1)	Brown algae Padina tetrastromatica occurring in the coastal waters of India (Parmeswaran *et al*. 1996)	no data
(1)	Green algae Codium Divaricatum Holmes occurring in the coastal waters of China (He *et al*. 2010)	2.0·10-4
(1)	Soft corals Sinularia capillosa from Dongsha atoll (Taiwan) (Cheng *et al*. 2010)	2.0·10-4
(3,4)	Brown algae Undaria pinnatifida from Japanese sea (Kimura & Maki 2002)	1.4·10-3

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Streszczenie

Poszukiwania związków biologicznie aktywnych wytwarzanych przez organizmy żywe doprowadziły do odkrycia wielu związków o mniej lub bardziej skomplikowanej strukturze. Jednymi z najprostszych cząsteczek są laktony monoterpenoidowe, zaś najczęściej spotykanym spośród nich jest loliolid.

Loliolid spotykany jest w organizmach zwierzęcych (owady) i roślinnych (rośliny kwiatowe, krzewy, drzewa) zarówno lądowych jak i morskich takich jak glony lub koralowce. Wieloletnie badania prowadzone nad roślinami używanymi w tradycyjnej medycynie ludowej różnych krajów doprowadziły do stwierdzenia, że związek ten ma różnorodne właściwości biologiczne np. antynowotworowe, antybakteryjne, antygrzybiczne, antyoksydacyjne. Ponadto rośliny zawierające lioliolid są stosowane w medycynie alternatywnej przy leczeniu cukrzycy oraz depresji.

Niezmiernie interesujący jest fakt, że lakton ten wywiera również wpływ na zachowanie mrówek jak i na rozwój niektórych roślin (aktywność alleplopatyczna). Czasami jednak można zaobserwować również działania niepożądane jak w przypadku analogów strukturalnych loliolidu mających swój udział w wymieraniu raf tropikalnych.