Chapter 1
Overview

Valeria P. Sülsen and Virginia S. Martino

Abstract Sesquiterpene lactones (STLs) are a group of naturally occurring compounds, most of them found in the Asteraceae family but also present in Apiaceae, Magnoliaceae, and Lauraceae. To date about 8000 compounds have been reported. They consist of a C15 backbone with numerous modifications resulting in a variety of structures but with the common feature of a γ-lactone ring. They are classified in four major groups: germacranolides, eudesmanolides, guaianolides, and pseudoguaianolides, though there are other subtypes. There has been an increasing interest in sesquiterpene lactones due to the wide range of biological activities they present. Among the activities found, antimicrobial, antitumor, anti-inflammatory, antioxidant, antiulcerogenic, molluscicidal, antihelminthic, hepatoprotective and hepatotherapeutic, antiprotozoal, antidepressant, and bitter properties have been described. Besides, they play an important role in the interaction of plants with insects acting as attractants, deterrents, and antifeedants. These compounds were considered at first highly cytotoxic, but chemical transformations have enhanced their biological activities and diminished their cytotoxicity, so considerable attention has been drawn again on them as lead molecules. Artemisinin derivatives, artesunate, and artemether are drugs currently being employed, and dimethylaminoparthenolide, a parthenolide synthetic analogue, and mipsagargin, a prodrug from thapsigargin, are under clinical trials.

A summary with the most important findings about the known sesquiterpene lactones, artemisinin, parthenolide, cynaropicrin, dehydroleucodine, mexicanin, helenalin, costunolide, santonin, arglabin, and thapsigargin, will be given.

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V. P. Sülsen, V. S. Martino (eds.), *Sesquiterpene Lactones*,
https://doi.org/10.1007/978-3-319-78274-4_1

Studies about the adverse health effects, toxicity, and ecological roles of some sesquiterpene lactones are also mentioned.

Keywords Sesquiterpene lactones · Chemical aspects · Biological activities · Adverse effects · Toxicity

1.1 Introduction

Since ancient times, natural products have played an important role in human health and have constituted one of the main sources of bioactive compounds and templates for synthetic modifications. According to Newman and Cragg (2016), the utilization of natural products and their derivatives in the development of new therapeutic drugs is still a promising approach. Recently, the 2015 Nobel Prize in Medicine has been awarded to Dr. Youyou Tu for the discovery of the natural product artemisinin, which is today an important component of the combined therapy for the treatment of malaria. This award highlighted the importance of the investigation of traditional medicine and drugs coming from natural sources (The Society for Medicinal Plant and Natural Product Research 2017). In the cancer research field, during the 1940–2014 period, 49% of all the small molecules approved for medical use were natural products or their derivatives. In other areas, such as the one corresponding to antimicrobial agents, the use of natural products is also frequent.

Sesquiterpene lactones (STLs) are a group of naturally occurring compounds, generally colorless and bitter in taste. Most of them are found in the Asteraceae family; however, they are also present in Apiaceae, Magnoliaceae, and Lauraceae families (Padilla González et al. 2016). They are mainly found in the leaves and in the flowering heads in a range from 0.001% to 8%/dry weight (Chaturvedi 2011). Some species store large amounts of STLs in leaf trichomes (Amorim et al. 2013).

Sesquiterpene lactones are present in food plants such as lettuce (*Lactuca sativa*) and chicory (*Cichorium intybus*), and star anise (*Illicium verum*) and in many medicinal plants such as feverfew (*Tanacetum parthenium*), qinghaosu (*Artemisia annua*), and yarrow (*Achillea* spp.) (Chaturvedi 2011).

There has been an increasing interest in STLs, mainly for their importance as chemical markers in biosystematic studies and for their wide range of biological activities. Among the activities explored for this group of compounds, antimicrobial, antitumor, anti-inflammatory, antioxidant, antiulcerogenic, molluscicidal, antihelminthic, hepatoprotective and hepatotherapeutic, antidepressant, and bitter properties have been described. Besides, they play an important role in the interaction of plants with insects acting as attractants, deterrents, and antifeedants (Chaturvedi 2011; Amorim et al. 2013).

Sesquiterpene lactones were considered at first highly cytotoxic. Chemical transformations have enhanced their biological activities and diminished their cytotoxicity, so considerable attention has been drawn again on them as lead molecules.

Artemisinin derivatives, artesunate, and artemether are drugs currently being employed, and dimethylaminoparthenolide, a parthenolide synthetic analogue, and mipsagargin, a prodrug from thapsigargin, are under clinical trials.

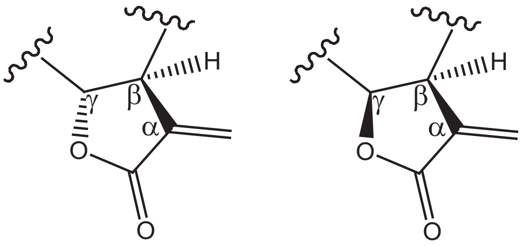
To date, about 8000 STLs have been reported (Macias et al. 2013). Some early reviews can be found in the literature about STLs which can be considered as a starting point for the present overview. In Yoshioka et al. (1973), the major skeleton types of STLs and the NMR spectra of 200 naturally occurring compounds are presented. Fischer et al. (1979) and Fischer (1990) summarize the biogenetic considerations concerning the different types of STLs as well as the regulation of their biosynthetic pathways. Rodriguez et al. (1976) and Picman (1986) disclose and discuss some of the more important biological activities of STLs. Other more recent reviews by Chaturvedi (2011) describe the structural characteristics and the biological activities of these compounds, while Chadwick et al. (2013) highlight the importance of STLs, not only for their potential as pharmaceutical agents but also for their importance as nutritional factors and for their physiological role in plants as antioxidants and growth factors, antifeedants, and allelochemicals and as the active constituents of many plants used in traditional medicine. Adekenov (2013) provides an overview of the available technology for the isolation of natural STLs and the chemical modifications to which STLs can be subjected and discusses their potential as source of new biologically active derivatives. In a subsequent publication, Adekenov and Atazhanova (2013) summarize the heteroatom-containing natural STLs, their natural occurrence, isolation methods, and biological activities, while Hohmann et al. (2016) disclose their anti-inflammatory effects. Padilla González et al. (2016) discuss the protective and physiological role of STLs in plants.

1.2 Chemical Aspects

Sesquiterpene lactones consist of a fifteen-carbon (C15) backbone, being the majority cyclic, with numerous modifications and resulting in a variety of structures. A distinctive feature of STLs is the presence of a γ-lactone ring closed toward either C-6 or C-8. This γ-lactone contains, in many cases, an *exo*-methylene group conjugated to the carbonyl group (Padilla González et al. 2016; Picman 1986). The stereochemistry of the lactonization can be either α or β, since the lactone ring can be fused to the remaining skeleton in either a *trans* or *cis* configuration (*trans*- or *cis*-fused STLs) (Padilla González et al. 2016; Ahern and Whitney 2014). The *trans*-configuration is the most common, and as a rule, the H-7 of STLs is α-oriented (Fischer 1990) (Fig. 1.1).

In some STLs, the exocyclic methylene is reduced, as is the case of artemisinin, matricin, achillin, and santonin, or the double bond can be endocyclic (Padilla González et al. 2016).

Sesquiterpene lactones are classified in four major groups: germacranolides (10-membered ring), eudesmanolides (6–6 bicyclic compounds), guaianolides, and pseudoguaianolides (5–7 bicyclic compounds) (Yoshioka et al. 1973) (Fig. 1.2). Nevertheless, according to their skeletal arrangement, there are other subtypes of



a **b**

Fig. 1.1 α,β-unsaturated γ-lactone moiety present in the sesquiterpene lactones. (**a**) *trans*-fused lactone ring, (**b**) *cis*-fused lactone ring

STLs (Fischer et al. 1979; Rodriguez et al. 1976; Picman 1986; Padilla Gonzalez et al. 2016). The suffix "olide" indicates the presence of a lactone group in the structure. The presence of epoxy groups, hydroxyls, and hydroxyls esterified with acetate, which is the most frequent, propionate, isobutyrate, methacrylate, isovalerate, epoxymethacrylate, 2-methylbutanoate, tiglate, angelate, senecioate, epoxyangelate, sarracinate, acetylsarracinate, and other similar residues is frequently found in STLs. Only a few glycosylated lactones or lactones bearing halogen or sulfur atoms in their structures have been described. A cyclopentenone moiety (dehydroleucodin, achillin) and a second α,β-unsaturated lactone ring (mikanolide, deoxyelephantopin) can also be found in STLs (Rodriguez et al. 1976; Picman 1986; Schmidt et al. 2002).

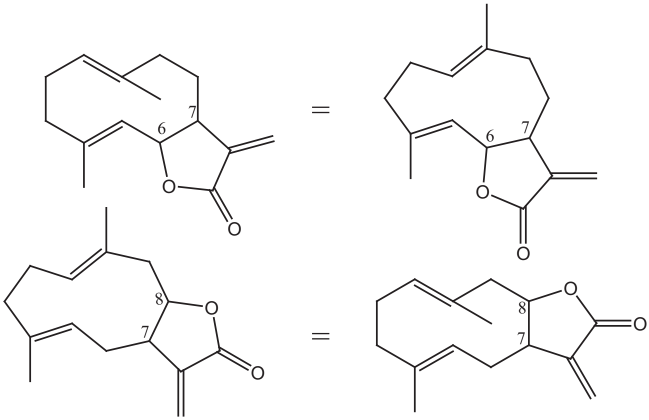
1.3 Some Representative Sesquiterpene Lactones

The STLs included in this chapter have been selected based upon the number of studies found in the literature, their biological activities, and/or the fact they are actually being used as medicines or are in clinical trials (Fig. 1.3).

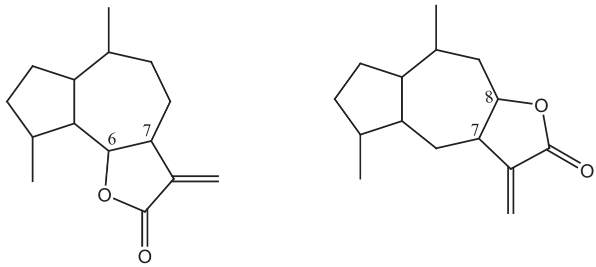
1.3.1 Santonin

Santonin **(1)** is an eudesmanolide present in *Artemisia santonica* and is one of the earliest STLs discovered (1830). This STL has been used as ascaricide and to remove all kind of worms and for the retention of urine and enuresis caused by atony or of other origins. Its pharmaceutical use was abandoned due to its toxic effects. Its anti-inflammatory, antipyretic, and analgesic effects have been reported (al-Harbi et al. 1994). Numerous chemical modifications have been introduced on the santonin structure in order to enhance its antiproliferative activity and cell differentiation on leukemia cells (Khazir et al. 2013; Kweon et al. 2011; Arantes et al. 2010) and its antimalarial activity (Tani et al. 1985). This molecule has been selected as the starting point for the synthesis of other guaianolides and eudesmanolides. Its structure was one of the first to be elucidated among STLs (Birladeanu 2003).

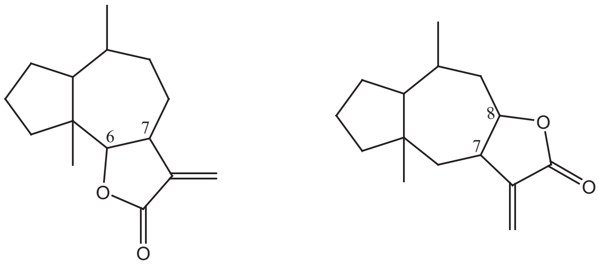
Germacranolides



Guaianolides



Pseudoguaianolides



Eudesmanolides

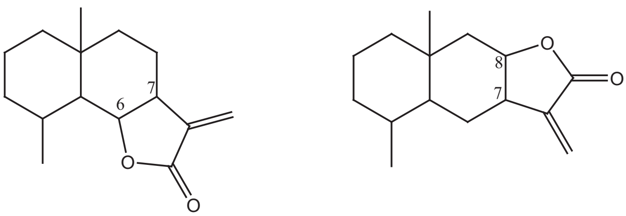


Fig. 1.2 Major skeletal types of sesquiterpene lactones

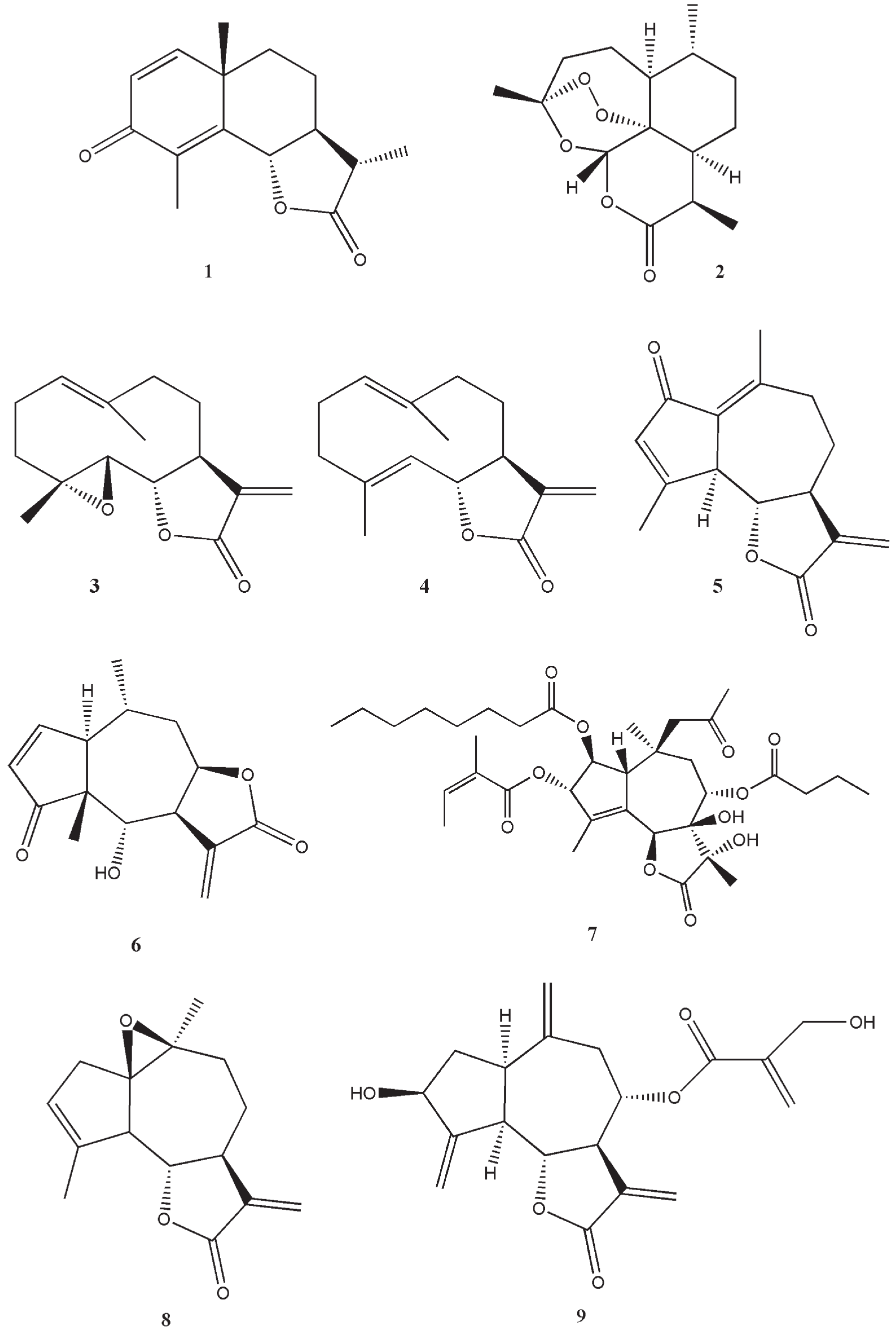


Fig. 1.3 Some representative sesquiterpene lactones

1.3.2 Artemisinin

Artemisinin **(2)** is a very a particular compound, for it presents an endoperoxide ring in its molecular structure. This STL has been isolated from *Artemisia annua* (Asteraceae). The aerial parts of this plant have been used as febrifuge in Chinese traditional medicine. Nowadays artemisinin and its derivatives are used as antimalarial against chloroquine-resistant *Plasmodium falciparum.* Other activities reported for this STL include leishmanicidal (Lezama Dávila et al. 2007; Ghaffarifar et al. 2015) and anticancer. The latter property is due to its capacity to inhibit cell growth and to induce apoptosis in human hepatocellular carcinoma cells (SMMC-7721) (Deng et al. 2013) and other cell lines (Crespo Ortiz and Wei 2012; Das 2015). Artemisinin also shows antischistosomal activity (Saeed et al. 2016). Activity against *Helicobacter pylori* has also been reported (Sisto et al. 2016).

Artemisinin derivatives are currently being assessed in phase I and II trials against lupus nephritis and breast, colorectal, and lung cancers (Lone et al. 2015).

1.3.3 Parthenolide

Parthenolide **(3)** is the active principle of feverfew (*Tanacetum parthenium*, Asteraceae). It is a traditional herbal medicine that has been used for centuries for the treatment of migraine, fever, and arthritis (Chaturvedi 2011). This STL has antiproliferative activity on multiple cancer cells such as melanoma; breast, colon, and lung cancer; and leukemia, among others (Wu et al. 2006; Parada Turska et al. 2007; Czyz et al. 2010: Gunn et al. 2011, Mathema et al. 2012). The compound selectivity to exert apoptosis in cancer cells provides an important and novel therapeutic strategy for the treatment of cancer and inflammation-related disorders (Liu 2013).

Other activities have been described for parthenolide such as antiprotozoal (against *Trypanosoma cruzi* and *Leishmania* spp.) (Izumi et al. 2008; Tiuman et al. 2005), anti-inflammatory (Wang and Li 2015), antiherpetic (Onozato et al. 2009), and antiosteoclastogenic (Kim et al. 2014).

1.3.4 Costunolide

Costunolide **(4)** is a germacranolide-type STL present in *Saussurea lappa* roots, a traditional Chinese medicinal herb that has anticancer and anti-inflammatory properties. This compound has also been isolated from other plant species such as *Magnolia* sp., *Laurus nobilis*, and *Costus speciosus*, among others. It exhibits a broad spectrum of bioactivities: antidiabetic and antioxidant (Eliza et al. 2009, 2010), anti-inflammatory (Butturini et al. 2014), antiulcerogenic (Zheng et al. 2016), anticlastogenic

(Cheon et al. 2014), and potential anticancer activity. Costunolide exerts its antiproliferative effect by inducing apoptosis through ROS generation (Wang et al. 2016) and cell cycle arrest (Liu et al. 2011; Lin et al. 2016), among other mechanisms. This STL is active on lung carcinoma (Wang et al. 2016; Hua et al. 2016); breast (Roy and Manikkam 2015), colon (Dong et al. 2015), bladder (Rasul et al. 2013), and platinum-resistant ovarian cancer (Yang et al. 2011); hepatoma (Liu et al. 2011); and leukemic (Choi and Lee 2009) cells.

1.3.5 Dehydroleucodine

Dehydroleucodine **(5)** is a STL isolated from *Artemisia douglasiana* which shows cytotoxic activity against human leukemia cells (Ordoñez et al. 2016) and inhibits the growth of melanoma cells in an animal model (Costantino et al. 2016). It reduces inflammation and gastrointestinal ethanol-induced damage, protecting the gastric mucosa, as demonstrated in in vivo models (Guardia et al. 2003; Wendel et al. 2008; Repetto and Boveris 2010). This compound has inhibitory effect on *T. cruzi* infective forms and *Leishmania mexicana* promastigotes (Jimenez Ortiz et al. 2005; Barrera et al. 2008). Antimicrobial activity against *Pseudomonas aeruginosa* multiresistant strains has also been reported for this compound (Mustafi et al. 2015).

1.3.6 Helenalin

Helenalin **(6)** is a guaianolide STL isolated from *Arnica montana* and other species of the Asteraceae family. It has been reported to possess cytotoxic (Grippo et al. 1992), hepatoprotective, anti-inflammatory, antioxidant (Lin et al. 2014), and antimicrobial properties against *Staphylococcus aureus* (Boulanger et al. 2007). It affects steroidogenesis in rat adrenocortical cells (Supornsilchai et al. 2006) and has cardiotonic activity (Itoigawa et al. 1987). Trypanocidal effects have also been reported (Schmidt et al. 2002; Jimenez-Ortiz et al. 2005).

1.3.7 Thapsigargin

Thapsigargin **(7)** is a guaianolide STL isolated from *Thapsia garganica* (Apiaceae). This Mediterranean medicinal plant was mentioned by Hippocrates, Theophrastus, Dioscorides, and Plinius as skin irritant, useful for pulmonary disease, catarrh, and fever and for the relief of rheumatic pains. In search for the skin-irritant principle, thapsigargin was isolated from the fruits and roots, and its structure and absolute configuration were determined between 1980 and 1985. This compound proved to be a potent histamine liberator and a cocarcinogen promoting skin cancer in mice

(Anderson et al. 2016). Nevertheless, the increasing interest in thapsigargin arose with the discovery of its ability to inhibit the sarco-endoplasmic reticulum calcium ATPase (SERCA) pump. The inhibition of this pump produces a high concentration of calcium in the cytosol, which leads to apoptosis. Several analogues have been obtained from thapsigargin, and a prodrug, termed mipsagargin, has been designed. Mipsagargin has shown an acceptable tolerability and a favorable pharmacokinetic profile in patients with solid tumors. Phase I clinical trials have been completed (Mahalingam et al. 2016). This compound has been authorized by the FDA to enter phase II clinical trials on patients suffering from hepatocellular carcinoma who had failed the first-line treatment with sorafenib and also on patients suffering from glioblastoma (Nhu and Christensen 2015). Inspyr Therapeutics Inc. (Texas, USA) has announced the initiation of a phase II clinical trial of mipsagargin for newly diagnosed prostate cancer patients (Inspyr 2016).

1.3.8 Arglabin

Arglabin **(8)** is a STL of the guaianolide type isolated for the first time by Adekenov et al. (1982) from *Artemisia glabella*, which is a plant species growing in Kazakhstan. It is present in the above ground parts (leaves, bud flowers, and stems). Later on, arglabin has been reported to be present in *A. myriantha* (Wong and Brown 2002), which is a well-known plant used in Chinese traditional medicine.

Arglabin shows promising antitumor activity against different tumor cell lines. Many derivatives have been obtained, and those bearing bromine and chlorine atoms and an epoxy group on the C(3)=C(4) double bond seem to have an increased antitumor activity. Dimethylamino arglabin, one of these derivatives, has been used to treat lung, liver, and ovarian cancers and is under study in phase I and II clinical trials (Lone et al. 2015). This STL has been patented in the USA and has been registered as an antitumor medicine in the Russian Federation, Kazakhstan, Uzbekistan, Tajikistan, the Kirghiz Republic, and Georgia (Adekenov 2016).

Arglabin acts as antitumor by a different mechanism from artemisinin, thapsigargin derivative, and parthenolide. It inhibits the farnesyl transferase, which is an enzyme that has been demonstrated to be involved in the formation of malignant tumors. Besides, this compound shows other biological activities: it has an inhibitory effect on influenza A virus, it can restore the synthesis of cytokines and other anti-inflammatory mediators acting as anti-inflammatory in in vivo models of inflammation (carrageenan, histame, and formalin models), and it has immunomodulatory activity (Lone et al. 2015). Abderrazak et al. (2016) have demonstrated that arglabin reduces inflammation in pancreatic β-cells in vivo and in the INS-1 cell line in vitro, thus concluding that it may represent a new promising compound to treat inflammation and type 2 diabetes mellitus.

1.3.9 Cynaropicrin

Cynaropicrin **(9)** is the bitter principle of *Cynara scolymus.* It is a guaianolide-type STL that has also been isolated from *Saussurea lappa.* This compound inhibits the growth of both *Trypanosoma brucei* (Zimmermann et al. 2013) and *T. cruzi* (Da Silva et al. 2013). It acts as an antiphotoaging agent (Tanaka et al. 2013) and shows cytotoxic activity on leukemic cell lines (Cho et al. 2004), and it has antispasmodic activity (Emerdorfer et al. 2005).

1.4 Adverse Health Effects and Toxicity of Sesquiterpene Lactones

The biological properties of STLs are attributed to the α-methylene-γ-lactone group, though other groups such as α,ß cyclopentenones, unsaturated side chains, and epoxides may influence their activity. The α,ß moiety may react with sulfhydryl groups present in enzymes and other proteins, leading to important toxic effects. The same features that make STLs useful medicines can also be responsible for severe toxicity.

Plants containing these compounds have long been known by farmers due to the observation of contact dermatitis and toxic symptoms in animals. Grazing animals, such as sheep, goats, horses, and cattle, show nasal, ocular, and gastrointestinal irritation upon consumption of certain species (*Centaurea solstitialis*, *C. maculosa*, *C. repens*, *Helenium* spp. and *Hymenoxis* spp., *Eupatorium urticifolium*, *Lactuca virosa*, and *Tanacetum vulgare*).

After feeding on *C. solstitialis* for a long period of time, horses may develop an illness named equine nigrostriatal encephalomalacia (ENE). This is a neurological disorder producing Parkinson-like symptoms and eventually death. Cynaropicrin and other amines present in the species are considered responsible for the symptoms.

Sesquiterpene lactones of the picrotoxane and seco-prezizaane type act as neurotoxins. Epileptoid convulsions have been reported in children consuming fruits of *Coriaria myrtifolia* and *C. ruscifolia*, which contain picrotoxane STLs. *Illicium verum* (Chinese star anise) used as spice can be confused or adulterated with *Illicium anisatum* which presents anisatin, a seco-prezizaane STL that causes tonic and clonic seizures.

There are literature data indicating the toxic effects of STLs on mammalian herbivores, the insecticidal activity, the livestock poisoning, the deleterious effects on animal reproduction, and the capacity to cause contact allergic dermatitis (Heywood et al. 1977).

Studies assessing the genotoxicity of STLs are scarce. Artemisinin, which is currently being used against malaria, has shown embryotoxic effects on rats and rabbits, though no side effects in pregnant women have been reported. Nevertheless, the WHO advises that this antimalarial drug should not be used during the first trimester of pregnancy.

Other genotoxicity studies on helenalin have demonstrated that this STL induces mutations on *Bacillus subtilis*, while hymenoxin alkylates and causes DNA cross-linkage. Other STLs display genotoxic activity through different mechanisms: centratherin induces sister chromatid exchange, and glaucolide B induces structural chromosomal aberrations.

Artemisinin has been demonstrated to alkylate different proteins but not DNA, while artesunate and artemether break DNA through oxidative damage. Aneugenesis has been observed with parthenin (Amorim et al. 2013).

Members of the Asteraceae family have demonstrated to cause dermatitis not only by direct contact but also by the inhalation of airborne allergens. Another example is *Thapsia garganica*, which is known for its skin-irritant properties and from which thapsigargin has been isolated and found to inhibit the SERCA pump. The elevated Ca^{+2} levels in the cytoplasm produced by the inhibition of this pump leads to mast cell degranulation and histamine release with the consequent skin irritation.

Moreover, there are reports indicating the presence of STLs in milk and meat as well as the contamination of soils in cultivated areas. This contamination with STLs is due to either leaching or to the incorporation of these compounds from dead plant material that is left behind in the field. *Artemisia annua* is cultivated in Asia and in Africa for the extraction of artemisinin to be used as antimalarial. The cultivated area is increasing to meet the necessities of the infected people. Besides, *A. annua* is also experimentally cultivated in the Netherlands, Switzerland, Finland, and Denmark. A possible contamination of underground water with STLs should be taken into account due to their toxic chronic effects on human health (Knudsmark Jessing and Duke 2014). In the latter report, authors inform about other effects of this compound on insects and other invertebrates and its phytotoxic and other antimicrobial properties and discuss the possible ecological role of this compound under biotic and abiotic stress. Authors conclude that artemisinin is produced as a defense mechanism against biotic factors. Antifungal and antibacterial effects of artemisinin in vitro as well as the insecticidal activity in field experiments are not conclusive. Its accumulation in the trichomes of young leaves and its subsequent decrease in fully developed plants may account for a protective effect against herbivores or pathogens for the young vulnerable plants. Artemisinin is washed off from the leaf surface after the breaking of trichomes and leaches from debris of fallen leaves into the soil, thus exerting an herbicide effect, suggesting its role as an allelochemical. It also reduces and changes the soil microbiota under field conditions.

References

Abderrazak A, El Hadri K, Bosc E et al (2016) Inhibition of the inflammasome NLRP3 by arglabin attenuates inflammation, protects pancreatic β-cells from apoptosis, and prevents type 2 diabetes mellitus development in ApoE2Ki mice on a chronic high-fat diet. J Pharmacol Exp Ther 357(3):487–494. https://doi.org/10.1124/jpet.116.232934

Adekenov SM (2013) Natural sesquiterpene lactones as renewable chemical materials for new medicinal products. Eurasian Chem Technol J 15:163–174

Adekenov SM (2016) Chemical modifications of arglabin and biological activity of its new derivatives. Fitoterapia 110:196–205

Adekenov SM, Atazhanova GA (2013) Heteroatom-containing natural sesquiterpene lactones and methods for their obtaining. Eurasian Chem Technol J 15:195–208

Adekenov S, Mukhammetzhanov MN, Kagarlittski AN et al (1982) Arglabin a new sesquiterpene lactone from *Artemisia glabella*. Chem Nat Compd 18:623–624

Ahern JR, Whitney KD (2014) Sesquiterpene lactone stereochemistry influences herbivore resistance and plant fitness in the field. Ann Bot 113(4):731–740. https://doi.org/10.1093/aob/mct297

al-Harbi MM, Qureshi S, Ahmed MM et al (1994) Studies on the antiinflammatory, antipyretic and analgesic activities of santonin. Jpn J Pharmacol 64(3):135–139

Amorim HR, Gil da Costa RM, Lopes C et al (2013) Sesquiterpene lactones: adverse health effects and toxicity mechanisms. Crit Rev Toxicol 43:559–579

Andersen TG, Quiñonero López C, Manczak T et al (2016) Thapsigargin from *Thapsia* L. to mipsagargin. Molecules 20:6113–6127

Arantes FF, Barbosa LC, Maltha CR et al (2010) Synthesis of novel α-santonin derivatives as potential cytotoxic agents. Eur J Med Chem 45(12):6045–6051. https://doi.org/10.1016/j.ejmech.2010.10.003

Barrera PA, Jimenez-Ortiz V, Tonn C et al (2008) Natural sesquiterpene lactones are active against *Leishmania mexicana*. J Parasitol 94(5):1143–1149. https://doi.org/10.1645/GE-1501.1

Birladeanu L (2003) The stories of santonin and santonic acid. Angew Chem Int Ed Engl 42(11):1202–1208

Boulanger D, Brouillette E, Jaspar F et al (2007) Helenalin reduces *Staphylococcus aureus* infection *in vitro* and *in vivo*. Vet Microbiol 119:330–338

Butturini E, Di Paola R, Suzuki H et al (2014) Costunolide and dehydrocostuslactone, two natural sesquiterpene lactones, ameliorate the inflammatory process associated to experimental pleurisy in mice. Eur J Pharmacol 730(1):107–115

Chadwick M, Trewin H, Gawthrop F et al (2013) Sesquiterpenoid lactones: benefits to plants and people. Int J Mol Sci 14:12780–12805. https://doi.org/10.3390/ijms140612780

Chaturvedi D (2011) Sesquiterpene lactones: structural diversity and their biological activities. In: Tiwari VK, Mishra BB (eds) Opportunity, challenge and scope of natural products in medicinal chemistry. Research Signpost, Kerala, pp 313–334. ISBN: 978-81-308-0448-4

Cheon YH, Song MJ, Kim JY et al (2014) Costunolide inhibits osteoclast differentiation by suppressing c-Fos transcriptional activity. Phytother Res 28(4):586–592

Cho JY, Kim AR, Jung JH et al (2004) Cytotoxic and proapoptotic activities of cynaropicrin, a sesquiterpene lactone, on the viability of leukocyte cancer cell lines. Eur J Pharmacol 492(2–3):85–94

Choi JH, Lee KT (2009) Costunolide-induced apoptosis in human leukemia cells: involvement of c-Jun N-terminal kinase activation. Biol Pharm Bull 32(10):1803–1808

Costantino V, Lobos Gonzalez L, Ibáñez J et al (2016) Dehydroleucodine inhibits tumor growth in a preclinical melanoma model by inducing cell cycle arrest, senescence and apoptosis. Cancer Lett 372:10–23

Crespo Ortiz MP, Wei MQ (2012) Antitumour activity of artemisinin and its derivatives: from a well-known antimalarial agent to a potential anticancer drug. J Biomed Biotechnol 2012:247597. https://doi.org/10.1155/2012/247597

Czyz M, Lesiak Mieczkowska K, Koprowska K et al (2010) Cell context-dependent activities of parthenolide in primary and metastatic melanoma cells. Br J Pharmacol 160(5):1144–1157

Da Silva CF, Da Gama JB, De Araujo JS et al (2013) Activities of psilostachyin a and cynaropicrin against *Trypanosoma cruzi in vitro* and *in vivo*. Antimicrob Agents Chemother 57(11):5307–5305

Das AK (2015) Anticancer effect of antimalarial artemisinin compounds. Ann Med Health Sci Res 5(2):93–102. https://doi.org/10.4103/2141-9248.153609

Deng XR, Liu ZX, Liu F et al (2013) Holotransferrin enhances selective anticancer activity of artemisinin against human hepatocellular carcinoma cells. J Huazhong Univ Sci Technolog Med Sci 33(6):862–865

Dong GZ, Shim AR, Hyeon JS et al (2015) Inhibition of Wnt/β-catenin pathway by dehydrocostus lactone and costunolide in colon cancer cells. Phytother Res 29(5):680–686

Eliza J, Daisy P, Ignacimuthu S et al (2009) Normo-glycemic and hypolipidemic effect of costunolide isolated from *Costus speciosus* (Koen ex. Retz.) Sm. in streptozotocin-induced diabetic rats. Chem Biol Interact 179(2–3):329–334

Eliza J, Daisy P, Ignacimuthu S (2010) Antioxidant activity of costunolide and eremanthin isolated from *Costus speciosus* (Koen ex. Retz) Sm. Chem Biol Interact 188(3):467–472. https://doi.org/10.1016/j.cbi.2010.08.002

Emerdorfer F, Bellato F, Noldin VF et al (2005) Antispasmodic effect of fractions and cynaropicrin from *Cynara scolymus* on Guinea pig ileum. Biol Pharm Bull 28(5):902–904

Fischer NH (1990) Sesquiterpene lactones: biogenesis and biomimetic transformations. In: Towers G, Towers H (eds) Biochemistry of the mevalonic acid pathway to terpenoids. Plenum Press, New York, pp 161–201

Fischer NH, Oliver EJ, Fischer HD (1979) The biogenesis and chemistry of sesquiterpene lactones. In: Herz W, Grisebach H, Kirby GW (eds) Progress in chemistry of organic natural products, vol 38. Springer, New York, pp 47–390

Ghaffarifar F, Esavand Heydani F, Dalimi A et al (2015) Evaluation of apoptotic and antileishmanial activities of artemisinin on promastigotes and BALB/C mice infected with *Leishmania major*. Iran J Parasitol 10(2):258–267

Grippo AA, Hall IH, Kiyokawa H et al (1992) The cytotoxicity of helenalin, its mono and difunctional esters, and related sesquiterpene lactones in murine and human tumour cells. Drug Des Discov 8(3):191–206

Guardia T, Juarez AO, Guerreiro E et al (2003) Antiinflammatory activity and effect on gastric acid secretion of dehydroleucodine isolated from *Artemisia douglasiana*. J Ethnopharmacol 88(2–3):195–198

Gunn EJ, Williams JT, Huynh DT et al (2011) The natural products parthenolide and andrographolide exhibit anticancer stem cell activity in multiple myeloma. Leuk Lymphoma 52(6):1085–1097

Heywood VH, Harbone JB, Turner BL (1977) An overture to the Compositae. In: Heywood JB, Harbone JB, Turner BL (eds) The biology and chemistry of the Compositae, vol 1. Academic Press, New York/London, pp 1–20

Hohmann M, Longhi-Balbinot D, Guazelli C et al (2016) Sesquiterpene lactones: structural diversity and perspectives as anti-inflammatory molecules. In: Atta-ur-Rahman FRS (ed) Studies in natural products chemistry: bioactive natural products, vol 49. Elsevier, Amsterdam, pp 313–334

Hua P, Zhang G, Zhang Y et al (2016) Costunolide induces G1/S phase arrest and activates mitochondrial-mediated apoptotic pathways in SK-MES 1 human lung squamous carcinoma cells. Oncol Lett 11(4):2780–2786

Inspyr Therapeutics Inc. (Texas, USA) (2016) Inspyr Therapeutics announces mipsagargin Ph 2 trial for patients with clear cell renal cell carcinoma expressing PSMA. http://www.inspyrtx.com/news/press-releases/detail/625/inspyr-therapeutics-announces-mipsagargin-ph-2-trial-for. Accessed 18 Aug 2016

Itoigawa M, Takeya K, Furukawa H et al (1987) Mode of cardiotonic action of helenalin, a sesquiterpene lactone, on Guinea pig ventricular myocardium. J Cardiovasc Pharmacol 9(2):193–201

Izumi E, Morello LG, Ueda-Nakamura T et al (2008) *Trypanosoma cruzi*: antiprotozoal activity of parthenolide obtained from *Tanacetum parthenium* (L.) Schultz Bip. (Asteraceae, Compositae) against epimastigote and amastigote forms. Exp Parasitol 118(3):324–330

Jimenez-Ortiz V, Brengio SD, Giordano O et al (2005) The trypanocidal effect of sesquiterpene lactones helenalin and mexicanin on cultured epimastigotes. J Parasitol 91(1):170–174

Khazir J, Singh PP, Reddy DM et al (2013) Synthesis and anticancer activity of novel spiro-isoxazoline and spiro-isoxazolidine derivatives of α-santonin. Eur J Med Chem 63:279–289. https://doi.org/10.1016/j.ejmech.2013.01.003

Kim J, Cheon Y, Yoon KH et al (2014) Parthenolide inhibits osteoclast differentiation and bone resorbing activity by down-regulation of NFATc1 induction and c-Fos stability, during RANKL-mediated osteoclastogenesis. BMB Rep 47(8):451–456

Knudsmark Jessing K, Duke S (2014) Potential ecological roles of artemisinin produced by *Artemisia annua* L. J Chem Ecol. https://doi.org/10.1007/s10886-014-0384-6

Kweon SH, Kim KT, Hee Hong J et al (2011) Synthesis of C (6)-epimer derivatives of diacetoxy acetal derivative of santonin and their inducing effects on HL-60 leukemia cell differentiation. Arch Pharm Res 34(2):191–198. https://doi.org/10.1007/s12272-011-0202-4

Lezama Dávila CM, Satoskar AR, Úc Encalada M et al (2007) Leishmanicidal activity of artemisinin, deoxoartemisinin, artemether and arteether. Nat Prod Comm 2(1):1–4

Lin X, Shijun Z, Renbin H et al (2014) Helenalin attenuates alcohol-induced hepatic fibrosis by enhancing ethanol metabolism, inhibiting oxidative stress and suppressing HSC activation. Fitoterapia 95:203–213

Lin X, Peng Z, Su C (2016) Potential anti-cancer activities and mechanisms of costunolide and dehydrocostuslactone. Int J Mol Sci 16(5):10888–10906

Liu YH (2013) Progress in the research of structure and pharmacological activity of parthenolide (review). Chin J Pharm Biotechnol 20(6):586–589

Liu CY, Chang HS, Chen IS et al (2011) Costunolide causes mitotic arrest and enhances radiosensitivity in human hepatocellular carcinoma cells. Radiat Oncol 6:56. https://doi.org/10.1186/1748-717X-6-56

Lone SH, Bhat KA, Khuroo MA (2015) Arglabin: from isolation to antitumor evaluation. Chem Biol Interact 240:180–198

Macías FA, Santana A, Durán AG et al (2013) Guaianolides for multipurpose molecular design. In: Beck J, Coats J, Duke S, Koivunen M (eds) Pest management with natural products, vol 1141. ACS, New York, pp 167–188. https://doi.org/10.1021/bk-2013-1141.ch012

Mahalingam D, Wilding G, Denmeade S et al (2016) Mipsagargin, a novel thapsigargin-based PSMA-activated prodrug: results of a first-in-man phase I clinical trial in patients with refractory, advanced or metastatic solid tumours. Br J Cancer 114(9):986–994

Mathema VB, Koh Y, Thakuri BC et al (2012) Parthenolide, a sesquiterpene lactone, expresses multiple anti-cancer and antiinflammatory activities. Inflammation 35(2):560–565. https://doi.org/10.1007/s10753-011-9346

Mustafi S, Veisaga ML, López LA et al (2015) A novel insight into dehydroleucodine mediated attenuation of *Pseudomonas aeruginosa* virulence mechanism. Biomed Res Int 2015:216097. doi.org/10.1155/2015/216097

Newman DJ, Cragg G (2016) Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 79(3):629–661. https://doi.org/10.1021/acs.jnatprod.5b01055

Nhu TQ, Christensen SB (2015) Thapsigargin, origin, chemistry, structure activity relationship and prodrug development. Curr Pharm Des 21:5501–5517

Onozato T, Nakamura CV, Garcia Cortez DA et al (2009) *Tanacetum vulgare*: Antiherpes virus activity of crude extract and the purified compound parthenolide. Phytother Res 23(6):791–796

Ordóñez PE, Sharma KK, Bystrom LM et al (2016) Dehydroleucodine, a sesquiterpene lactone from *Gynoxys verrucosa*, demonstrates cytotoxic activity against human leukemia cells. J Nat Prod 79(4):691–696. https://doi.org/10.1021/acs.jnatprod.5b00383

Padilla Gonzalez GF, Antunes dos Santos F, Batista Da Costa F (2016) Sesquiterpene lactones: more than protective plant compounds with high toxicity. CRC Crit RevPlant Sci 35(1):18–37

Parada Turska J, Paduch R, Majdan M et al (2007) Antiproliferative activity of parthenolide against three human cancer cell lines and human umbilical vein endothelial cells. Pharmacol Rep 59(2):233–237

Picman A (1986) Biological activities of sesquiterpene lactones. Biochem Syst Ecol 14(3):255–281

Rasul A, Bao R, Malhi M et al (2013) Induction of apoptosis by costunolide in bladder cancer cells is mediated through ROS generation and mitochondrial dysfunction. Molecules 18(2):1418–1433

Repetto MG, Boveris A (2010) Bioactivity of sesquiterpenes: compounds that protect from alcohol-induced gastric mucosal lesions and oxidative damage. Mini Rev Med Chem 10(7):615–623
Rodriguez E, Towers GHN, Mitchell JC (1976) Biological activities of sesquiterpene lactones. Phytochemistry 15:1573–1580
Roy A, Manikkam R (2015) Cytotoxic impact of costunolide isolated from *Costus speciosus* on breast cancer via differential regulation of cell cycle - an *in-vitro* and *in-silico* approach. Phytother Res 29(10):1532–1539
Saeed MEM, Krishna S, Greten HJ et al (2016) Antischistosomal activity of artemisinin derivatives *in vivo* and in patients. Pharmacol Res 110:216–226
Schmidt TJ, Brun R, Willuhm G et al (2002) Antitrypanosomal activity of helenalin and some structurally related sesquiterpene lactones. Planta Med 68(8):750–751
Sisto F, Scaltrito MM, Masia C et al (2016) *In vitro* activity of artemisone and artemisinin derivatives against extracellular and intracellular *Helicobacter pylori*. Int J Antimicrob Agents 48(1):101–105
Supornsilchai V, Söder O, Svechnikov K (2006) Sesquiterpene lactone helenalin suppresses Leydig and adrenocortical cell steroidogenesis by inhibiting expression of the steroidogenic acute regulatory protein. Reprod Toxicol 22(4):631–635
Tanaka YT, Tanaka K, Kojima H et al (2013) Cynaropicrin from *Cynara scolymus* L. suppresses photoaging of skin inhibiting the transcription activity of nuclear factor kappa B. Bioorg Med Chem Lett 23(2):518–523
Tani S, Fukamiya N, Kiyokawa H et al (1985) Antimalarial agents. 1. Alpha-santonin-derived cyclic peroxide as potential antimalarial agent. J Med Chem 28(11):1743–1744
The Society for Medicinal Plant and Natural Product Research (2017) Nobel Prize for the discovery of natural product-derived drugs. https://www.ga-online.org/events-2/ifpvgksc21/Nobel-Prize-for-the-discovery-of-natural-productderived-drugs-. Accessed 8 Aug 2016
Tiuman TS, Ueda-Nakamura T, Garcia Cortez DA et al (2005) Antileishmanial activity of parthenolide, a sesquiterpene lactone isolated from *Tanacetum parthenium*. Antimicrob Agents Chemother 49(1):176–182
Wang M, Li Q (2015) Parthenolide could become a promising and stable drug with anti-inflammatory effects. Nat Prod Res 29(12):1092–1101
Wang Z, Zhao X, Gong X (2016) Costunolide induces lung adenocarcinoma cell line A549 cells apoptosis through ROS (reactive oxygen species)-mediated endoplasmic reticulum stress. Cell Biol Int 40(3):289–297
Wendel GH, María AOM, Guzmán JA et al (2008) Antidiarrheal activity of dehydroleucodine isolated from *Artemisia douglasiana*. Fitoterapia 79(1):1–5
Wong HF, Brown GD (2002) Dimeric guaianolides and a fulvenoguaianolide from *Artemisia myriantha*. J Nat Prod 65:481–486
Wu C, Chen F, Rushing JW et al (2006) Antiproliferative activities of parthenolide and golden feverfew extract against three human cancer cell lines. J Med Food 9(1):55–61
Yang YI, Kim JH, Lee KT et al (2011) Costunolide induces apoptosis in platinum-resistant human ovarian cancer cells by generating reactive oxygen species. Gynecol Oncol 123(3):588–596
Yoshioka H, Mabry TJ, Timmerman B (1973) Sesquiterpene lactones. University of Tokio Press, Tokio
Zheng H, Chen Y, Zhang J et al (2016) Evaluation of protective effects of costunolide and dehydrocostuslactone on ethanol-induced gastric ulcer in mice based on multi-pathway regulation. Chem Biol Interact 250:68–77
Zimmermann S, Oufir M, Leroux A et al (2013) Cynaropicrin targets the trypanothione redox system in *Trypanosoma brucei*. Bioorg Med Chem 21(22):7202–7209