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- Review -

Sesquiterpene Lactones: A Review of Biological Activities

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Sesquiterpene lactones (STLs) are terpenoids found mostly in the Asteraceae family and are known for their strong cytotoxic properties, among other notable bioactivities. Some STLs, such as artemisinin and mipsagargin, are already commercially available and are used to fight malaria and tumor growth, respectively. Although the interest in STLs was low for a time after their discovery due to their toxic nature, past decades have witnessed a soar in STL-based studies focused on developing novel pharmaceuticals via chemical diversification. These studies have reported several promising physiological effects for STLs, including lower toxicity and diverse modes of action, and have demonstrated the antimicrobial, antioxidant, hepatoprotective, antiviral, antiprotozoal, phytotoxic, antitumor, and antiaging properties of STLs. STLs are mainly considered as valuable natural molecules for the fight against cancer since most STLs induce death of different types of cancer cells, as shown by in vitro and in vivo studies. Some STLs can also enhance the effects of drugs that are already in clinical use. Medicinal chemists use various STLs as starting molecules for the synthesis of new STLs or different bioactive compounds. All these developments warrant future research to provide more information on STLs, their bioactivities, and their mode of action. In this context, this review has summarized the bioactivities of some of the widely studied STLs, namely artemisinin, costunolide, thapsigargin, arglabin, parthenolide, alantolactone, cynaropicrin, helenalin, and santonin.

Key words : Anti-cancer, artemisinin, *Artemisia* spp., Asteraceae, sesquiterpene lactone

Background

Herbal remedies, traditional folk medicine, and, for a broader description, natural products have been part of human health maintenance since ancient times. Currently, natural origin substances are being the to-go lead molecules to develop pharmaceuticals and functional foods. Reports have shown that derivatization of natural products via synthetic or organic modifications is still a viable goal for the progression of preventive and therapeutic medicine [41]. Promising results have drawn increasing attention to natural-origin therapeutics with fewer side effects and notable bioavailability. The immense diversity of plants and their diverse secondary metabolites in both chemical structures and physiological activities, provide a promising collection of samples to be studied. The utilization of natural products as templates for medical use was a quite popular topic for pharmacology during the last decades. Numerous fields including but not limited to cancer research, anti-microbial agent development, metabolic disease prevention have employed natural products or their derivatives to develop novel and efficient therapeutic approaches [93].

Sesquiterpene lactones (STLs) are naturally occurring plant molecules under the group of terpenoids. STLs are very diverse and found in many plant species including food and medicinal plants. There are increasing amounts of studies reporting the biological activities of STLs and some notable reviews of their importance, chemical diversity, and therapeutic potential. However, due to the continuous expansion of the STL research and related reports and reviews, more often a necessity for a brief review and update arises. Therefore, this review aims to provide relevant information on the frequently studied STLs, their reported bioactivities, and recent developments in their diversification.

Sesquiterpene lactones

Up to date, the number of reported STLs is close to 10,000: hence, there is a wide range of structurally different STLs with different modifications on their C15 backbone. But all

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STLs contain γ-lactone ring as their common characteristic (Fig. 1). STLs are natural compounds that have been found in many plant species such as Solanaceae, Euphorbiaceae, Lauraceae, and Magnoliaceae families. However, STLs are known to be abundantly present in the Asteraceae family from where most of the known STLs with bioactivities were isolated [15]. A reasonable portion of these families are also mentioned in traditional medicine resources and studies pointed out that the STLs might be among their primary bioactive ingredients. Apart from their health beneficial effects in humans, STLs are important molecules for plants due to their crucial roles as mediators between insects and plants [20, 75]. Most of the reported STLs are used for attracting or deterring insects. Hence, STLs are gaining interest over time, mainly for their reported bioactivities and wide range of structural modifications. To date, studies have shown antitumor [62], anti-inflammatory [71], antimicrobial [73], antidepressant [37], antidiabetic [74], antioxidant [32], hypoglycemic [38], vasorelaxant [9], and hepatoprotective [12] activities, among others.

The characteristic γ-lactone ring of STLs is mostly bound to the main backbone in a trans configuration although cis-bound STLs are present. Even though there are several subtypes, STLs are mainly divided into four major groups depending on the carbocyclic skeleton: eudesmanolides, germacronolides, guaianolides, and pseudoguaianolides. Reports suggested that their bioactivities mostly stemmed from the unsaturated group of methylene-γ-lactone forming a bond with the therapeutic targets such as enzymes, membrane-bound receptors, and ligand-activated transcriptional factors [82]. Besides, the biological activity of STLs was suggested to arise from the other functional groups such as hydroxyls, angelate, and benzoates in their chemical structure.

At first, most of these compounds were regarded as highly cytotoxic which hindered their utilization as bioactive ingredients [75]. However, developments in modification and/

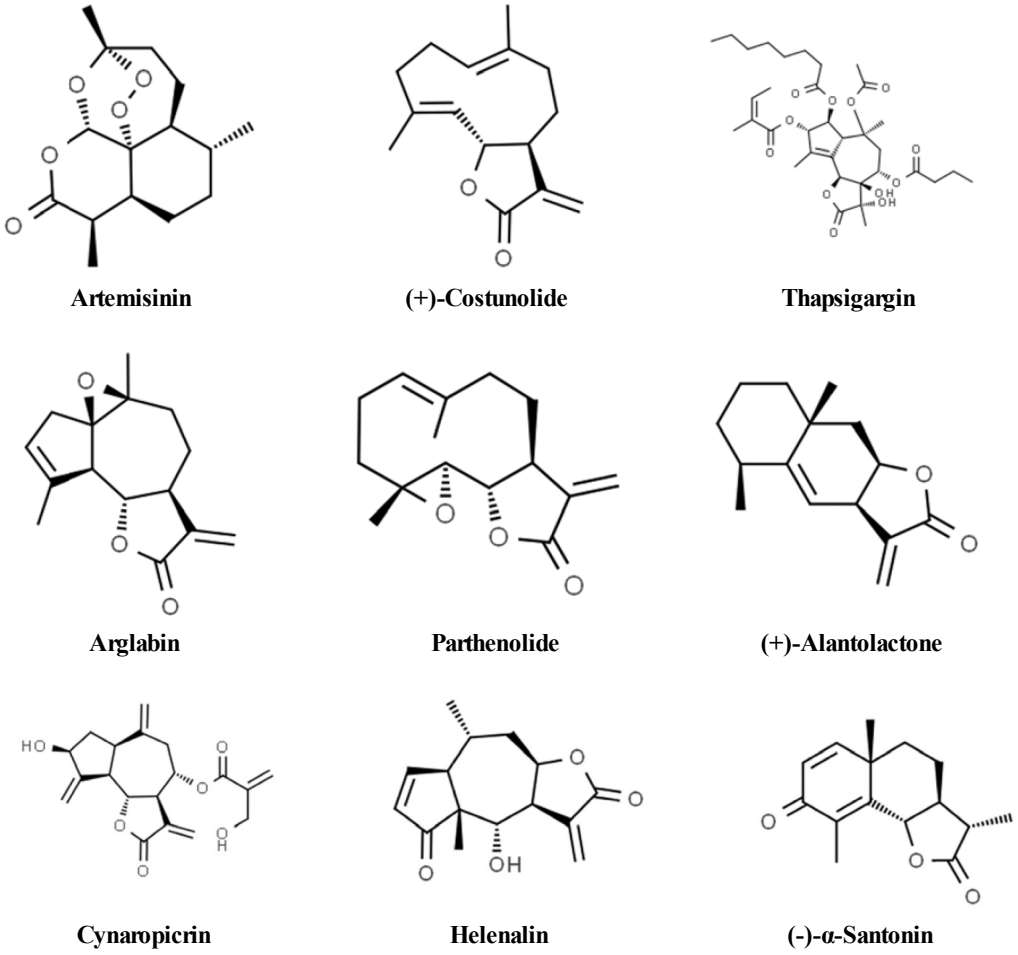

Fig. 1. Chemical structures of some known bioactive sesquiterpene lactones.

or diversification of STLs proved fruitful to considerably increase their biological activities while lowering cytotoxicity to safe levels [81]. Therefore, interest in developing natural therapeutic agents increased proportionally. To name a few, artesunate and artemether are two drugs being used for the treatment of malaria and both are derivatives of common STL artemisinin [88]. Mipsagargin, a prodrug derived from thapsigargin isolated from *Thapsia garganica*, is currently in clinical trials for the treatment of prostate cancer and hepatocellular carcinoma [68, 69]. Much more STLs have been studied and many biological activities were reported with different action mechanisms both *in vitro* and *in vivo* models.

Biological activities of common STLs

Artemisinin

Artemisinin is an STL with an endoperoxide ring and commonly isolated from *Artemisia* spp., *A. annua* Linn being the first source. Some traditional folk medicine recipes credit *A. annua* as an antipyretic [31]. Artemisinin and its derivatives are famous for their antimalarial properties, especially against the chloroquine-resistant *Plasmodium falciparum* [33]. Other studies reported apoptosis-inducing and growth suspending abilities in cancer cells including human hepatocellular carcinoma [34, 51, 102]. Also, there are artemisinin derivatives currently going under clinical trials for their anti-cancer properties against some breast, lung, and colon cancer types [10, 64].

Kim et al. [54] documented preliminary anti-inflammatory, antioxidant and antimicrobial effects for artemisinin extracts obtained from *A. annua* L. In addition, in a study by Cao et al. [19], artemisinin exerted an anti-atherosclerosis effect in n high-fat diet-fed ApoE-/- mice via attenuating the pro-inflammatory IFN-γ and TNF-α signaling when administrated orally. The possibility of artemisinin and its derivatives to be effective against metabolic disorders was realized by the report of Li et al. [14]. The presence of artemisinin in the daily diet resulted in the conversion of pancreatic α-cells to β-cells with insulin-secreting capacity by targeting GABA a receptor. This promoted artemisinin as a potential lead molecule with beneficial effects in the treatment of type I diabetes. Recent developments also showed that although being studied for a long period, artemisinin still holds the potential to exhibit novel bioactivities as studies reported new potential mechanisms for anti-fibrotic [98], antiviral [96], and ferroptosis-inducing [111] properties.

Costunolide

Costunolide is an STL isolated from several species but it is mainly present in *Costus speciosus*, *Saussurea lappa, Laurus nobilis, and Magnolia* sp. among others. It is a germacranolide and the species that contain costunolide may be found in medicinal herb repositories with anti-inflammatory and hypoglycemic properties [16, 35]. Expectedly, costunolide showed anti-inflammatory activities via suppressing LPS-induced inflammatory response through downregulation of NO production mechanism via iNOS and its upstream activator NF-κB signaling [56, 52]. Costunolide also did not show any oral toxicity in terms of mortality and/or behavioral changes on Wistar rats according to acute toxicity tests that lasted for 10 days [28]. An anti-diabetic activity was also proposed for costunolide after it decreased the blood glucose levels while increasing blood insulin and tissue glycogen levels in STZ-induced diabetic rats when administrated orally [29]. Besides, cholesterol levels (total cholesterol and LDL-C) were notably decreased after costunolide treatment. Promising antioxidant capabilities were reported for costunolide by Eliza et al. [28]. The presence of costunolide strongly inhibited lipid peroxidation and TBARS and at the same time levels of antioxidant enzymes and reduced glutathione levels were observed to be increased. Several reports indicated that this STL also had promising anti-tumor properties with different action mechanisms. Wang et al. [99] showed that costunolide induced apoptosis in A549 lung adenocarcinoma cells via elevation of ROS. Different reports proposed similar action mechanisms on different cancer cells such as the bladder [78] and ovarian [105] cancer cells. In another report, costunolide treatment resulted in breast cancer cell lines entering apoptosis via cell cycle arrest [77]. This mechanism was further suggested in gastric adenocarcinoma [79] and melanoma [60] cells following the costunolide or costunolide-including extract treatment.

Thapsigargin

Thapsigargin was first isolated from *Thapsia garganica*, a medicinal plant from the Mediterranean region. *T. garganica* is a well-known herbal medicine ingredient for the relief of pain and fever and is also mentioned as a skin irritant [46]. However, studies showed that thapsigargin is a very potent histamine release stimulator and a carcinogen evidenced by its ability to promote squamous cell carcinoma in mice [39]. Despite its harmful presence, future studies revealed that thapsigargin exerts apoptosis-inducing ability through in-

hibiting calcium pump mechanisms in the sarco-endoplasmic reticulum [85, 101]. This discovery led to studies that showed thapsigargin might possess antitumor properties by inducing apoptosis in different types of cancer types such as prostate cancer [42], adrenocortical carcinoma [101], and breast cancer cells. To eliminate its side-effects and utilize its potential as an antitumor agent led to the discovery of a thapsigargin analog, a prodrug called mipsagargin (Fig. 2). Mipsagargin is a very promising pharmaceutical agent which showed notable effects against solid tumors [8]. It has already completed Phase I trials and Phase II clinical trials provided favorable results in patients with progressive advanced hepatocellular carcinoma as well as in prostate cancer [68, 69].

Arglabin

Like many other bioactive STLs, arglabin was isolated from an Asteraceae family member, *Artemisia glabella*, a plant endemic to Kazakhstan, and was further found in *A. myriantha*, a plant mentioned in several Chinese traditional medicine recipes.

Initial studies reported that arglabin showed anti-proliferative effects in different cancer cell lines [66]. Similar to other STLs with potential anti-cancer properties, arglabin has been derivatized to enhance its antitumor activities. Among these derivatives, dimethylamino arglabin reached the Phase II clinical trial stage where it was used to treat patients with lung, ovarian, and liver cancers [80]. Upon these developments, it has been approved to be used against cancer as a pharmaceutical agent in Kazakhstan, Tajikistan, and Georgia [3]. Unlike artemisinin and mipsagargin which induce ROS elevation to kill cancer cells, arglabin derivatives target the farnesyl transferase enzyme, to suppress the tumorigenesis [4]. In another study, arglabin also exerted anti-cancer effects on oral squamous cancer cells via mitochondrial apoptosis [95].

Besides, arglabin also ameliorated the cytokine release mechanisms in *in vivo* inflammation models, restoring the balance in histamine and formalin-induced inflammatory mediator synthesis [2]. This anti-inflammatory activity of arglabin was also reported in pancreatic β-cells *in vivo* [1], suggesting that it may hold potential in preventive medicinal approaches against type 1 and 2 diabetes mellitus.

Parthenolide

Parthenolide isolated from another Asteraceae family member, *Tanacetum parthenium* commonly known as feverfew. Feverfew is a very common herbal medicine used throughout Asia Minor and middle Europe to treat headaches and fever [76]. Parthenolide was suggested to be the

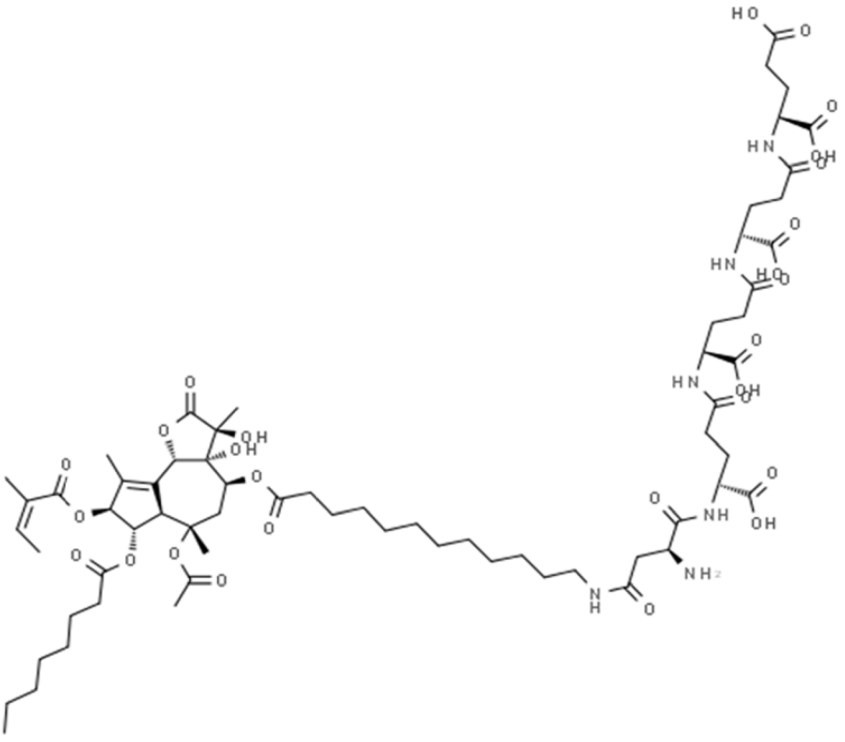

Fig. 2. Chemical structure of the thapsigargin derivative mipsagargin, a prodrug under trial for the treatment of prostate cancer and prostatic neoplasms.

active ingredient of feverfew among some other common polyphenols [40]. Expectedly, parthenolide was shown to induce apoptosis in multiple types of tumor cells such as breast, lung, skin, bone, and colon [6, 27, 36, 65, 89]. Its antitumor mechanism was similar to the aforementioned STLs which is stimulating ROS production in cancer cells. It also exerts anti-inflammatory properties via the same mechanism as costunolide [56]. Although slightly less effective than costunolide, parthenolide suppressed LPS-induced nitrogen oxide production.

Izumi et al. [45] proposed antiprotozoal activity for parthenolide against epimastigote and amastigote forms of *Trypanosoma cruzi*. It was also reported that parthenolide inhibited the viral activities of the herpes simplex virus [13]. According to another report, parthenolide has the potential to be used against bone disorders due to its ability to hinder osteoclast differentiation and bone resorption suggestively through suppression of NFATc1 signaling [84].

Apart from its physiological effects, parthenolide is also used to synthesize arglabin, another bioactive STL, through a biomimetic semi-synthesis pathway along with micheliolide [106]. The latter is a derivative of parthenolide and found to be less toxic and more effective as an antitumor and anti-inflammatory agent [92].

Alantolactone

Alantolactone is the active ingredient of most *Inula* spp. although can be found in other species. It was first isolated from *Inula helenium*. Inula spp. are very common herbal medicine ingredients across most of Asia, Europe, and Africa traditional medicine. Similar to other STLs, alantolactone has been intensively studied for its antitumor [11], anti-inflammatory [97], and antioxidant activities, and its beneficial effects against obesity and diabetic conditions [53, 112].

This STL showed promising potential as a tumor cell apoptotic agent against leukemia [104]. Treatment with alantolactone significantly increased the lifespan of leukemia NOC/SCID mice compared to non-treated groups. Similar effects were observed *in vivo*, using breast and gastric cancer models where alantolactone treatment shrinks the tumor size and weight while inhibiting the tumor growth [24, 107]. Another positive point from these studies was alantolactone did not show any notable toxicity in organs as well as not affecting the body weight. A study by Khan et al. [49] exhibited that mice treated with 100 mg/kg oral alantolactone did not present any liver or kidney toxicity. Also, coupled with its antitumor activity, alantolactone was shown to enhance the effects of some chemotherapy drugs by sensitizing cancer cells such as A549 lung adenocarcinoma and human pancreatic cancer cells via STAT3 inhibition [70, 109]. Considering its antitumor activity, drug sensitizing properties, and low to no toxicity, alantolactone was also a target for diversification with promising results to develop novel anticancer and anti-inflammatory drugs.

In relation to its anti-inflammatory effect, alantolactone exerted beneficial effects against obesity-related inflammatory responses. Alantolactone decreased the pro-inflammatory IL-6 levels and macrophage infiltration in adipocytes under normal and obese conditions [53]. Similar effects were also observed in muscle and liver cells where alantolactone presence hindered IL-6-induced glucose intolerance and insulin resistance. A neuroprotective effect was also proposed by the study of Seo et al. [86] during which alantolactone provided cortical neuron viability in mouse models with conditions similar to Alzheimer's disease. Despite its potential, studies also showed that alantolactone has a low water solubility which results in low bioavailability with oral administration [103]. Intravenous application of alantolactone has also resulted in rapid metabolization [110].

Cynaropicrin

This STL takes its name from artichoke, scientifically named as *Cynara scolymus* from where it was isolated for the first time. Other *Cynara* species were also found to contain cynaropicrin along with many species of the Asteraceae family which is famous for their STL content.

Cynaropicrin possesses the expected bioactivities similar to other well-known STLs: Antitumor, and anti-inflammatory activities [23, 61]. However, this STL is known for being the first natural product to exhibit antitrypanosomal activity against the *Trypanosoma brucei in vivo* models [113]. A suggestive mechanism was through the trypanothione redox system of the protozoa [114]. A study by Tanaka et al. [90], on the other hand, presented a different activity for cynaropicrin, unlike other common STLs. It was shown that the presence of this STL was able to relieve the photoaging-related detrimental effects in keratinocytes and melanocytes suggestively via providing the proliferation ability to skin cells which were diminished through photoaging-induced NF-κB activation.

Helenalin

Helenalin is the main active principle of the plant *Arnica montana* with antitumor and anti-inflammatory activities. *A. montana* has been used as a common constituent of many traditional herbal medicines for the treatment of small wounds owing to its strong effect to suppress inflammation [44]. Related to this, other herbal remedies for arthritis, hematoma, muscle injuries, and soreness uses *A. montana* as one of its ingredients. Helenalin as its active component inhibits NF-κB expression to exert its anti-inflammatory properties [21]. It also shows strong antitumor potential by decreasing the proliferation of cancer cells via expected ROS elevation-induced apoptosis and unlike other STLs, telomerase inhibition [108].

It was also credited to be a promising platelet aggregation inhibitor reducing clot formation via inhibited phospholipase A2 [83]. Wound-care gels prepared with helenalin-rich *A. montana* extract along with ibuprofen provided enhanced pain relief for osteoarthritis patients compared to the ibuprofen-only treatment group [100]. Its effect on the NF-κB mechanism was suggested to underly this effect. In another study by Boulanger et al. [18], helenalin was promoted as a strong antimicrobial agent *in vivo* against *Staphylococcus aureus* in mouse models with infected mammary glands. Also, several studies concluded that helenalin should be further investigated for its hepatoprotective effects, as it both protected liver injuries in mice caused by LPS/D-GaIN and promoted hepatic stellate cell death providing relief from liver fibrosis [63].

On a side note, some notable trypanocidal effects were reported for helenalin along with antioxidant activity in alcohol-induced hepatic fibrosis models [30].

Santonin

Santonin is one of the first naturally obtained STLs with pharmaceutical value. It was used for the removal of human and animal roundworms [94]. For the past two decades, its use was discontinued due to its toxic presence in the liver and kidneys and causing mental side effects. Nevertheless, reports indicated that santonin possessed antioxidant [57], antibacterial [48], antiviral [43], anti-inflammatory [5], and anti-tumor [80] activities. Therefore, studies focused on using santonin as a lead molecule to develop derivatives with these bioactivities without the side effects of santonin. Studies showed that semisynthetic derivatives of α-santonin exerted better anti-cancer properties with significantly less toxicity [50]. Other derivatives showed herbicidal [17], anti-malarial [72], PPAR pathway agonizing [91], and phytotoxic activities [67] with less to no toxicity.

In addition, santonin was one of the first STLs of which the chemical structure was elucidated and since its chemical orientation presents strong reactivity, currently santonin is being used as an origin molecule in medicinal chemistry to synthesize novel compounds [22]. Also, some other guaianolides and eudesmanolides are being synthesized from santonin with higher yields than natural isolation.

Negative health effects and potential side-effects of STLs

A review of the literature for STLs reveals that almost all of the bioactive STLs show cytotoxicity where this property is what makes them usable against most of the cancer types. Studies showed that mainly γ-lactone rings with the help of unsaturated side-chains and/or α,ß cyclopentenone groups are responsible for the physiological activities of STLs. However, the same active chains may react readily with most of the enzymes and proteins *in vivo* resulting in unwanted effects, mostly toxicity. Farm animals who consume some species known for their STL content developed gastrointestinal irritation [26, 87]. Picrotoxane STLs were suggested to cause convulsions in children who consume fruits of *Coriaria myrtifolia* [25]. STL-rich plants, especially *Artemisia* spp., are known to be allergens and cause contact dermatitis in both humans and animals [7]. Besides, some studies reported the danger of *Artemisia* spp. which are rich in STLs such as *A. vulgaris*, *A. herba-alba* and *A. annua* during pregnancy as they have fertility decreasing effects [59]. There is not enough report to provide information regarding the genotoxicity of STLs except one report by Jones et al. [47] indicating the DNA damaging effect of hymenoxon, helenalin, and tenulin using repair-deficient *Bacillus subtilis* mutants. Apart from human health, researchers argue that the STL contamination of soil via the cultivation of STL-rich plants may negatively affect the environment due to the strong toxicity of STLs towards other plants, insects, and microorganisms [55].

Conclusions

Sesquiterpene lactones have been studied intensively since their first elucidation and shown to possess promising

health beneficial effects, anticancer and anti-inflammatory being the most notable and prevalent. Almost all STLs show cytotoxicity and chronic accumulation of STLs was shown to lead to some negative effects. However, diverse, and strong bioactivities of STLs motivate the studies to utilize their potential. Also, STLs are open to diversification, and studies in medicinal chemistry proved that diversification of STLs leads to new molecules with substantially lower toxicity and enhanced bioactivities. Structure-activity relationship studies revealed that the STL pharmacophore justifies further studies to develop novel pharmaceuticals from naturally occurring STLs through diversification which essentially enable the discovery of new efficient drugs, against tumor growth and inflammation in particular.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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세스퀴테르펜 락톤(Sesquiterpene lactones; STL) 화합물은 테르페노이드의 일종으로 주로 국화과에서 발견이 되고 강한 세포 독성을 나타내는 생리학적 특성을 지니고 있다. 이러한 세스퀴테르펜 락톤은 강한 세포 독성으로 인해 연구가 미미하였으나, 최근 화학적 변형을 통해 독성이 적은 형태로 합성하여 새로운 의약품 개발로서의 연구가 활발히 진행되고 있다. 세스퀴테르펜 락톤 화합물인 artemisinin 및 mipsagargin 화합물은 현재 말라리아 및 종양성장에 대한 약물로 사용되고 있다. 또한 항산화, 간보호, 항바이러스, 항균, 항종양 및 항노화 등의 생리활성 효능이 보고되어 있으며, 종양세포에서 자멸사를 유도하여 항암제로서의 연구가 진행되고 있다. 본 연구에서는 세스퀴테르펜 락톤 화합물인 artemisinin, costunolide, thapsigargin, arglabin, parthenolide, alantolactone, cynaropicrin, helenalin, 및 santonin의 생리활성 효능에 대한 연구 동향을 검토하고자 한다.