PROMISING BIOLOGICAL ACTIVITIES OF SESQUITERPENE LACTONES

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PROMISING BIOLOGICAL ACTIVITIES OF SESQUITERPENE LACTONES (Abstract): Sesquiterpene lactones (SQLs) are an important group of bioactive compounds that are usually found in the *Asteraceae* family, where they seem to be some of the most important constituents for defense against microorganisms. These secondary metabolites have a skeleton of 15 carbon atoms and are derived from farnesyl diphosphate. It is generally believed that they might present certain biological actions in humans. Some of these actions are worth extended research: anti-inflammatory, antitumor, antibacterial, antifungal, antinociceptive, antiulcer and hepatoprotective. It seems that the presence of the α-methylene-γ-lactone group is correlated with the existence of many pharmacological actions. Due to promising results on human cancer cell lines, the research was expanded to clinical trials investigating the antitumor potential. Sesquiterpene lactones inhibit the expression of the nuclear factor kappa-light-chain-enhancer of activated B cells, which could explain the anti-inflammatory effect. They also have good activity against Gram positive bacteria. As a result, some of these compounds show promise for practical use in the treatment of cancer, different inflammatory diseases and even as antibacterial or antifungal agents, while some have already been introduced in therapy as antimalarial agents (artemisinin and its semisynthetic derivatives). However, more studies regarding their biological activities and toxicity mechanisms are still to be done. **Keywords:** SESQUITERPENE LACTONES, BIOLOGICAL ACTIONS, ANTITUMOR, ANTI-INFLAMMATORY.

INTRODUCTION

Medicinal plants have always been an important source of therapeutic agents, having a large variety of pharmacological activities (1). Nowadays, it is estimated that secondary metabolites extracted from plants still play an important role in the production of medicines and dietary supplements, covering around half of their total number (2, 3). Taking into consideration the need for discovering new agents for existent diseases, more and more researchers are focusing on the plant kingdom in the hope of discovering new efficient treatments or confirming new actions described by traditional medicine (4).

Around 30,000 compounds have been classified as terpenoids, which show a remarkable role in the defense mechanism of the plant. Many of these exert various biological actions and are currently used in the pharmaceutical industry, which explains the constant search for new similar structures and the tests carried out for dif-

ferent types of activities (3). Some terpenoid compounds represent constituents of volatile oils that produce the specific aroma of plants (4).

Sesquiterpenes are an important and complex group of natural terpenoids, in which have been included around 11,000 structures, with almost half of them representing the subclass of sesquiterpene lactones (5).

They are biosynthetically derived from farnesyl diphosphate and their name is related to the chemical structure, which contains a 15-carbon atoms skeleton formed by three isoprene units. Sesquiterpenes may or may not contain cycles in their structure, which leads to the following classification: acyclic, monocyclic, bicyclic, tricyclic and tetracyclic sesquiterpenes (3).

Sesquiterpene lactones (SQLs) represent a highly diversified group of bioactive compounds that can be found almost exclusively in the *Asteraceae* family, but have also been identified in species belonging to the other families such as *Cactaceae* and *Solanaceae* (2, 6). These compounds are stable secondary metabolites with bitter taste and a relatively high lipophilicity, lacking color (7). They are components of the plant latex, showing good antibacterial activity, but can also be synthetized in other types of cells, especially in case of plant injury (6). Sesquiterpene lactones can be extracted with different solvents, such as methanol, acetonitrile, n-hexane, chloroform and dichloromethane or by using supercritical carbon dioxide (8). The analysis of this type of compounds can be made using chromatographic methods, such as High-Performance Liquid Chromatography (HPLC) and Thin-Layer Chromatography (TLC) or hyphenated methods, such as HPLC-UV and Gas Chromatography-Mass Spectrometry (GC-MS) (9, 10).

Sesquiterpene lactones can be classified according to their carbocyclic skeleton in germacranolides, which represent the largest group and are precursors for other types of SQLs, guaianolides, pseudoguaianolides, eudesmanolides, eremophilanoides and hypocretenolides (6, 7).

Supposedly, SQLs present certain therapeutic actions in humans and some of these, including the anti-inflammatory, antitumor, antibacterial, antiprotozoal, antinociceptive, antiulcer and hepatoprotective properties, are currently being investigated (2, 6, 11). Some compounds derived from artemisinin, thapsigargin and parthenolide have already been included in cancer clinical trials, given their significant cytotoxic activity (7). However, new studies have revealed other potential activities of this type of compounds (e.g. histamine H1 receptor antagonism in the gut), proving the importance of research on sesquiterpene lactones (12). However, SQLs might be responsible for a series of conditions in humans, such as contact dermatitis, and could also present genotoxic activity, reproductive toxicity and teratogenesis (13, 14).

ANTITUMOR ACTIVITY

It is believed that three major characteristics are responsible for the antitumor and anti-inflammatory activities of SQLs: alkylating properties, high lipophilicity which facilitates the passage through membranes and conformational flexibility (7). Research has shown that the α-methylene-γ-lactone moiety is of major importance regarding most biological actions exerted by these compounds (15). This structure reacts with nucleophilic groups, such as sulfhydryl groups that can be found in enzymes and proteins, leading to the disruption of different functions (2, 13). Therefore, certain SQLs have the capacity

of modifying the redox state, inducing oxidative stress and apoptosis in cancer cells in a relatively selective manner (5).

There are several ongoing cancer clinical trials in which SQLs are investigated as potential antitumor agents. Artesunate, a well-known antimalarial drug, is being investigated regarding its safety and efficiency in stage II/III Colorectal Cancer (ClinicalTrials.gov Identifier: NCT02633098), as treatment in patients with cervical dysplasia (ClinicalTrials.gov Identifier: NCT02354534) and as treatment of HPV-associated anal intraepithelial neoplasia (ClinicalTrials.gov Identifier: NCT03100045). A phase one study was also conducted to evaluate its safety and pharmacokinetic properties when administered orally in patients with advanced hepatocellular carcinoma (ClinicalTrials.gov Identifier: NCT02304289). Artemether, which is currently used to treat malaria, has also been included in a phase 1/2a study that will assess its potential use in treating cancer (ClinicalTrials.gov Identifier: NCT02263950). Another phase II trial studies how well a thapsigargin prodrug works in treating patients with recurrent or progressive glioblastoma (NLM Identifier NCT02067156) (16). The activity of some SQLs has been examined on cancer cells, revealing potential benefits in different types of cancer (tab. I).

TABLE I.
Examples of Sesquiterpene Lactones and Their Anticancer Activity Based on Research on Human Cell Lines

SQL	Type of human cancer cell line	Reference
Parthenolide	Multiple myeloma cell lines	17
	Colorectal cancer cells	18
	Non-small cell lung cancer cells	19
	Pancreatic cancer cells	20
	Cervical cancer cells	21
	Osteosarcoma cancer cell	22
	Bladder cancer cells	23
	Breast cancer cell line	24
	Prostate cancer cell lines	25
	Melanoma cells	26
	Leukemic monoblastic U937 cell line	27
Costunolide	Osteosarcoma cells	28
	Esophageal cancer cells	29
	Colon cancer cell	30
	Lung squamous carcinoma cells	31
	Breast cancer cells	32,33
	Prostate cancer cells	34
	Ovarian cancer cells	35
	Promonocytic leukemia U937 cells	36
Alantolactone	Lung Squamous Cancer Cells	37
	Breast cancer MDA-MB-231 cells	38
	Colorectal cancer cells	39
	Hepatoma cells	40
	Leukemia HL-60 cells	41
	Human glioblastoma cell lines	42

ANTI-INFLAMMATORY ACTIVITY

It is believed that SQLs can prevent the production of mediators involved in the inflammatory response, therefore modulating functions present in both acute and chronic inflammation (43).

The Nuclear Factor kappa-light-chain enhancer of activated B cells (NF-κB) represents a protein complex that plays an important part in a series of processes such as inflammation, immune regulation, cell death and proliferation (44). However, it is involved in pathological processes as well, given the fact that it controls some mechanisms through which apoptosis and metastasis develop (6). Normally, NF-κB can be found in the cytoplasm tied to its inhibitory subunit (IκBα). The existence of proinflammatory stimuli leads to the activation of IκB kinase, which causes the release of NF-κB from IκBα and its displacement into the nucleus, where it initiates the transcription of genes associated with inflammation (43). Therefore, the inhibition of this transcription factor by SQLs could reduce the inflammatory response and block the multiplication of tumor cells (6).

Nevertheless, the inhibition of 5-lipoxygenase and cyclooxygenase has also been considered as another possible mechanism of action. For example, rudbeckolide from *Rudbeckia hirta* and ziniolide from *Xanthium spinosum* show good inhibitory activity on these enzymes (45, 46).

ANTIBACTERIAL AND ANTIPROTOZOAL ACTIVITIES

To resist the attacks of fungi, bacteria and viruses, plants can produce several chemical substances, such as phenolic compounds, tannins, alkaloids and terpenoids (4). In the *Asteraceae* family, sesquiterpene lactones seem to be some of the most important constituents for defense against microorganisms (6).

The antimicrobial activity of these secondary metabolites is correlated with the presence of the α-methylene-γ-lactone functional group and of a double α, β-unsaturated carbonyl group. It is assumed that SQLs induce alteration of the phospholipidic wall of membranes and modifications of protein synthesis (47).

Sesquiterpene lactones seem to have a better activity against Gram positive bacteria than against Gram negative bacteria (48). Examples of sesquiterpene lactones with good antibacterial activity include alantolactone and isoalantolactone, which are active against *Staphylococcus aureus*, but also on *Mycobacterium tuberculosis* (48, 49). A study focusing on germacranolide shows that parthenolide was the most active of the tested substances against both *Mycobacterium tuberculosis* and *Mycobacterium avium*. The same study highlights that the α-methylene-γ-lactone moiety, the presence of another alkylating site and a good lipophilicity seem to be responsible for the antimycobacterial activity (50).

Some of these secondary metabolites possess antiprotozoal activity, artemisinin being currently used as an antimalarial agent. Its discovery in the 1970s followed by clinical observations of its potent activity against *Plasmodium falciparum* led to its introduction in therapy along with other semisynthetic derivatives (4). It is believed that the compound acts in two phases. The intra-parasitic iron is thought to be responsible for the breakage of the endoperoxide moiety, followed by production of free radicals, which will eventually form stable bonds with the parasitic proteins (1).

SQLs are also active on other parasites such as *Trichomonas vaginalis* and *Entamoeba hystolitica* (51, 52).

ANTIFUNGAL ACTIVITY

Sesquiterpene lactones from *Centaurea thessala* and *Centaurea attica* have been investigated for their antifungal action, showing good activity against fungi from the *Aspergillus* and *Penicillium* genera (53). A study that included 36 SQLs emphasized the good antifungal activity of some SQLs such as dehydrozaluzanin C, dehydrocostus lactone, costunolide and zaluzanin C against *Colletotrichum acutatum* and *C. fragariae* (54).

In a research conducted by Picman, almost half of the 45 sesquiterpene lactones considered showed activity against *Microsporum cookei, Trichophyton mentagrophytes*, while only a few demonstrated activities against *Fusarium* spp., highlighting that eudesmanolides seem to be the most active (55). It was also proved that some guaianolides can inhibit the growth of *Candida albicans* (56). However, the research done to study the antifungal properties of this class of secondary metabolites is still insufficient.

CONCLUSIONS

Sesquiterpene lactones are a large class of constituents of the *Asteraceae* family with many potential therapeutic actions due to the α-methylene-γ-lactone group and other characteristic functional groups.

Some of these compounds show promise for practical use in the treatment of cancer, different inflammatory diseases or even as antibacterial agents, but extensive research on pharmacological actions and toxicity is still to be done.

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NEWS

BLOCK COPOLYMER-BORON CLUSTER CONJUGATE FOR EFFECTIVE BORON NEUTRON CAPTURE THERAPY OF SOLID TUMORS

The cancer is considered a major health problem worldwide and a big socio-economic burden which increases day by day. The mainstream treatment modalities in treating this disease are surgery, chemotherapy and radiotherapy. Boron neutron capture therapy (BNCT) is a selective tumor radio-therapeutic technique which is emerging as a hopeful tool in treating of cancer. This method is based on the administration of 10B-compounds in selectively tumor tissues and further thermal neutron irradiation of these to kill the cancer cells. Until now, the boron derivatives of sodium borocaptate and borophenylalanine presented an important potential for cancer therapy, especially in the cases where the traditional methods are difficult to be applied. In this study, the authors developed new block copolymer boron cluster conjugates, using sodium borocaptate (BSH) and poly(ethylene glycol)-b-poly(glutamic acid) copolymer in order to obtain a safe and efficient boron neutron capture therapy (an homogenous delivering of the boron clusters into the tumor cells and an effectively penetration in cancer tissues). The both synthetized conjugates showed a high cellular uptake by cancer cells and a high tumor accumulation, the most important elements for an efficient BNCT. The PEGylated BSH-polymer conjugate demonstrated a better profile in comparison with the non-PEGylated one. The obtained results are promising in the cancer therapy using PEG-modified clusters to develop new drug delivery systems (Mi P, Yanagie H, Dewi N, Yen H-C, Liu X, Suzuki M, Sakurai Y, Ono K, Takahashi H, Cabral H, Kataoka K. Block copolymer-boron cluster conjugate for effective boron neutron capture therapy of solid tumors. *Journal of Controlled Release* 2017; 254: 1-9).

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