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Sesquiterpene Lactones: A Versatile Class of Structurally Diverse Biologically Potent Scaffolds in Drug Discovery Research

Devdutt Chaturvedi[1]* and Parmesh K Dwivedi[2]*

[1]Department of Applied Chemistry, Amity School of Applied Sciences, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226 028, Uttar Pradesh, India

[2]Laboratory of Medicinal Chemistry, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226 028, Uttar Pradesh, India

Editorial

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***For Correspondence**

Devdutt Chaturvedi, Department of Applied Chemistry, Amity School of Applied Sciences, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226 028, Uttar Pradesh, India, Tel: 91-5222994778-82

E-mail: devduttchaturvedi@gmail.com

Parmesh K Dwivedi, Laboratory of Medicinal Chemistry, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226 028, Uttar Pradesh, India, Tel: 91-5222994778-82

E-mail: parmeshdwivedi@gmail.com

Sesquiterpene lactones (SLs) are a group of secondary metabolites that represent a diverse and unique class of natural products and are important constituent of essential oils, formed from head-to-tail condensation of three isoprene units and subsequent cyclization and oxidative transformation to produce a *cis* or *trans*-fused lactone. In this editorial we are going to focus on anticancer, anti-inflammatory, antimalarial, antibacterial, antifungal, antileishmanial, antiviral, antidepressant and antidiarrheal activities of sesquiterpene lactones.

In recent years, many researchers over the world have reported that sesquiterpene lactones possess potential anticancer activity. Costunolide **(1)**, an important compound of this class, is an active component from the crude extract of the root of *Saussurea lappa clarks* plant. Besides costunolide, Isodihydrocostunolide (IC_{50}, 35.05 ± 9.37 µg/ml against MCF cell lines), 9 β-acetoxycostunolide (IC_{50}, 0.25 ± 0.02 µg/ml against KB Cells) also exhibited potent cytotoxic activity. Similarly, Parthenolide a traditional herb (IC_{50} value 8 µmol/l using MTT assay) and 9β-acetoxyparthenolide (IC_{50} values ranged from 0.29 to 1.08 µg/ml) were also found to possess potent cytotoxic properties. Helenalin, and 11α, 13-dihydrohelenalin acetate ($IC_{50,}$ 6.3 ± 0.31 to 6.5 ± 1 µM) has been reported to possess cytotoxicity and anti-cancer activity [1-3]. The antitumor effect of dihydroartemisinin derivatives, deoxoartemisinins and carboxypropyldeoxoartemisinins, dimeric and trimeric artemisinin derivatives have also been reported. Artemisinin-related endoperoxides, triazoyl substituted semisynthetic derivatives of artemisinin and dimer phosphate ester analogs of artemisinin exhibited good cytotoxicity [4]. In addition to this, arylidene substituted tourneforin derivatives, eupalinin A, inuviscolide, japonicone A, isoalantolactone, 6-*O*-angeloylenolin, aguerin B, cynaropicrin **(4)**, coronopilin, were also found to exhibited good cytotoxic effect against various cell lines.

The remarkable anti-inflammatory activity of sesquiterpene lactones such as costunolide **(1)**, parthenolide, helenalin (7) and other isolated guaianolides and germacranolides has been documented [5,6]. In addition to this, various experiments have supported the application of SLs like withanolide, budlein A, 7-hydroxyfrullanolide, cynaropicrin as potential anti-inflammatory compound.

Artemisinin **(8)**, a sesquiterpene lactone from *Artemesia annua* (Asteraceae) has been found to possess antimalarial activity. In addition to this, artemether, arteether and sodium artesunate (the analogs of artemisinin) were found to be effective against chloroquine-resistant strains of *P. falciparum* [7]. Beside these neurolenin B, tagitinin C **(3)** vernodalol, helenalin **(7)**, peruvin, Vernangulide A and vernangulide B, vernopicrin and vernomelitensin have also reflected the antiplasmodial activity.

The antibacterial activity of various SLs are has also been recorded [8]. In this context, SLs such as vernodalin **(9)**, vernolide **(12)** were screened against *S. aureus* and *B. subtilis.* The results showed the higher sensitivity towards these bacterial species. Helenalin **(7)**, a SL was found to have the inhibitory activity against *Mycobacterium tuberculosis* as well as *Corynebacterium diptheriae.*

The antifungal activities of certain SLs have also been documented. The SLs as antifungal agents includes isoalantolactone, elema-1,3,11-trien-8,12-olide, 40-acetoxymalacitanolide, 8α-hydroxy-4-epi-sonchucarpolide etc. [9]. Two isolated SLs, isoalantolactone and elema-1,3,11-trien-8,12-olide inhibited the radial growth of helminthosporium with the MIC being 650 µg/ml for both SLs. The *Cladosporium cladosporioides* species showed good sensitivity towards 40-acetoxymalacitanolide, with a MIC value of 0.06 µg/ml. 8α-hydroxy-4-epi-sonchucarpolide and 40-acetoxymalacitanolide had indentical MICs against *Penicillium funiculosum,* showing no disparity between these two SLs in their inhibitory action against this particular species.

The anti-HBV activity of artemisinin **(8)** and artesunate has been published in a report [10]. In addition, it was discovered that, in comparison to lamivudine as positive control, the TI value of artesunate is quite low. Artesunate was also tried in combination treatment with lamivudine. In the experiment, when both compounds with concentration of 20 nM were administered together, it was found that there were no sign of toxicity but a synergic inhibitory effect in HBsAg release had been observed. Hsieh and their coworkers reported the anti-viral potential of various SLs against hepatitis C virus. They have tested a series of 10 compounds where they found that the best anti-HCV activity was shown by helenalin.

The antidepressant potential of podoandin, an isolated sesquiterpenoid from *Hedyosmum brasiliense* has been demonstrated [11]. Z-ligustilide, atractylenolide I and atractylenolide II, the major components of low polar fraction of Xiaoyaosan (XYS) were evaluated for antidepressant action and it was concluded from the results that low polar fraction exerts antidepressant effects in experimental animal model.

The *in vitro* activity of parthenolide against *Leishmania amazonensis* was also investigated. Significant leishmanicidal activities have been shown by SLs psilostachyin and peruvin [12]. Three SLs helenalin **(7)**, mexicanin and dehydroleucodine were evaluated using cultured *Leishmania mexicana* promastigotes. It was proved that the compounds strongly attenuated the invasion of vero cells by the parasites, the percentage of infected cells dropped from 83% to 52–55% and the number of parasites per cell decreased dramatically. In addition to this, 4-hydroxyanthecotulide also showed the potent leishmanicidal activity.

The chloroform fraction of *Centaurea solstitialis ssp. solstitialis* (CSS) containing chlorojanerin and 13-acetyl solstitialin A displayed 99.5% ulcer inhibition [13]. The dichloromethane extract of *T. diversifolia* containing tagitinin C **(3)** reflected the potent gastroprotective activity (approx. 90% when using doses between 10 to 100 mg/kg). The gastroprotective mechanism of the onopordopicrin fraction (termed as ONP fraction), obtained from *A. lappa* leaves suggested that an antisecretory mechanism involved with the antiulcerogenic effect of the ONP fraction.

Tirotundin and tagitinin A **(2)**, isolated from *T. diversifolia* were examined for their activity against peroxisome proliferator-activated receptors (PPARs). The results suggested their potential for the treatment of diabetes [14].

Dehydroleucodine (DhL), a sesquiterpene lactone obtained from *Artemisia douglasiana* (Compositae) was screened for antidiarrheal effects. It was concluded that DhL produces an inhibitory action on gastrointestinal functions, motility and secretion hence represent an important tool in relieving gastrointestinal colic, diarrhea [15].

The structural diversity and diverse potential biological activities such as anticancer, anti-inflammatory, anti-tumor, anti-malarial, antiviral, antibacterial, antifungal *etc.* of SLs have made further interest among the chemists to the drug discovery research. The present overview on the various kinds of biological activity of structurally diverse sesquiterpene lactones may be useful for the chemists/pharmacologists working in the area of drug discovery.

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