Available online on www.ijppr.com
International Journal of Pharmacognosy and Phytochemical Research 2019; 11(3);116-121
doi: 10.25258/phyto.11.3.4
ISSN: 0975-4873

Review Article

A Review on Pharmacognocy of Bioactive Sesquiterpene Lactones

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Received: 19th May, 19; Revised and Accepted 30th May, 19; Available Online:25th Jun, 19

ABSTRACT
Sesquiterpene lactone is a prominent phytoconstituent.It shows anticancer, antiplasmodial, antibacterial, antifungal,antiinflammatory, insect antifeedant, mollucicidal, leishmanicidal, trypanocidal,wound healing and hepatoprotective activities etc.In this review we focus on identify new area of plant families,plants body parts to detect presence of sesquiterpene lactones and rest of biological activities,which is not studied or less observed by researcher.The objectives of this work to explore existing information to pin point key findings which would helpful to reveal medicinal importance of sesquiterpene lactones.

Keywords: Sesquiterpene lactones, Cytotoxic, Asteraceae, Germacranolide

INTRODUCTION

Sesquiterpene lactones (SLs)constitute a large group of the secondary metabolites, which are important constituents of essential oils. It is a class of terpanoid compounds. A large number of sesquiterpenes are found in members of Asteraceae[1].Where they are characteristic constituents of the family[2]. However, they have been reported from several plant families, such as Acanthaceae, Amaranthaceae, Apiaceae, Magnoliaceae and others. Sesquiterpene lactones posses a wide range of biological activities including plant growth regulating, insect antifeedant, antibacterial, cytotoxic, mollucicidal, antispasmodic, antiprotozoal, antiphlogistic and antitumougenic properties[3,4]. Therefore they play an important role on protection of plants against pathogens, herbivorus insects, mammals and function as allelopathic agents[5,6]. In this review we focused on pharmacological activities of various isolated and identified sesquiterpene lactones in many plant families. Sesquiterpene lactones can be divided into several main classes including Germacranolide, Guaianolides, Eudesmanolides, Heliangolides, Pseudoguaianolides, Hypocretenoli-des, Melampolides etc.

To provide information about biologicaly active sesquiterpene lactones in a single platform for reseachers. We collected and studied many research papers/articles, reference books and journals. There after we selected bioactive sesquiterpene lactones in a systematic way. In this present review, interest is focused on expermental studies performed on medicinal plants and their bioactive sesquiterpene lactones. We believe that the list of SLs presented in this review is useful to researcher, as well as pharmacologists. This list is best used only as preliminary screening of potential sesquiterpene lactones(Table-01).

The reported and observed details about potential sesquiterpene lactones is presented in the following paragraphs:

1.Germacranolide

Germacranolide type sesquiterpene lactone showed activity against the fungus *Candida albicans*.The ethyle acetate extract was the most active, showing inhibitory activity against five Gram positive (*Bacillus subtilis*, *Bacillus stearothermophilus*, *Bacillus polymyxa*, *Clostridium sporogenes*, *Streptococcus aureus*) and two Gram negative(*Escherichia coli*, *Klebsiella pneumoniae*) bacterial strains[4].[1]4,5-epoxy-6-hydroxy-1(10)E,11(13)-germacranolide-12,8-olide,[2]Tatridin A or Tavulin,[3] Tanachin showed invitro antiplasmodial activity against *P.falciparum* with IC_{50} 0.5mg/ml,0.4mg/ml and 0.5mg/ml respectivly. They are also showed cytotoxicity against a chinese hamister ovarian(CHO) cell line with IC_{50} 2.2mg/ml,6.0mg/ml and 6.4mg/ml respectively.[7]

Costunolide

It exhibited the highest mosquitocidal activity among the extracts and the isolated compounds with LC_{50} value of 58.48 mg/ml[8].Costunolide showed the strongest antifungal activity among the tested sesquiterpene compounds against three fungi, *Nigrospora* spp., *R.solani* and *Helminthosporium* spp.with EC_{50} values of 0.48,2.92 and 2.96 mg/ml,respectively[6].(+)-costunolide showed the antifungal activity against *Cunninghamella echinulata* with EC_{50} values (6mg/ml) close to that of ketoconazole (1.5mg/ml) used as reference antifungal drug[9].

Parthenolide

Parthenolide is a sesquiterpene lactone of the germacranolide class. It is occurs in highest concentration in the flowers and fruits. Parthenolide revealed the strongest molluscicidal activity among the tested extracts and compounds against the fresh water snail with LC_{50} value of 14.65 mg/ml. This compound also showed the

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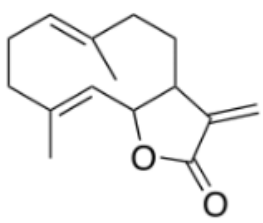
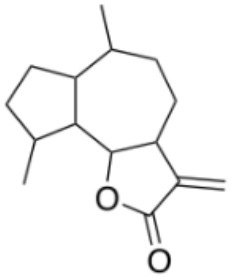
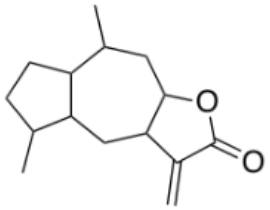


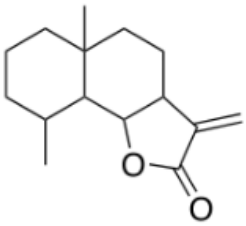
I Germacranolides



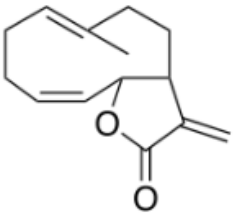
II(a) Guaianolides



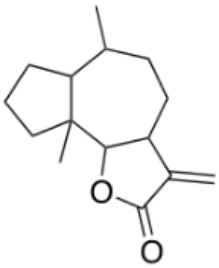
II(b) Guaianolides



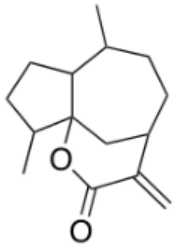
III Eudesmanolides



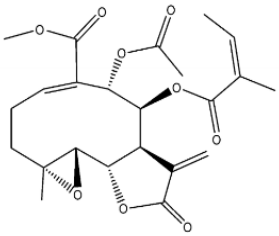
IV Heliangolides



V Pseudoguaianolides



VI Hypocretenolides



VII Melampolides

Figure 1: Structures of some sesquiterpene lactones

most potent molluscicidal activity against terrestrial snails. It exhibited the highest antifungal activity against *A.alternata* and *F.culmorium*(EC_{50}=4.07 and 50.27 mg/ml, respectively)[6].Parthenolide showed the highest inhibitory effect with an EC_{50} against Hs605T,MCF-7 and SiHa (Human cervical cancer cell line) of 2.6mg/ml,2.8mg/ml,2.7mg/ml respectively. The results revealed that apigenin and luteolin might have moderate to weak synergistc effects with parthenolide on the inhibition of cancer cell growth of Hs605T,MCF-7 and SiHa[10].

2.Guaianolides

Chlorojanerin, Cynaropicrin and janerin showed invitro cytotoxic activity against human cancer cell lines of malignant melanoma(SK-MEL),epidermoid(KB),ductal(BT-549) and ovarian (SK-OV-3) carcinomas with IC_{50} value of 2.6mg/ml[11]. 3β,8β-dihydroxy-4α-methoxy-10(14),11(13)-guaiadien-12,6-olide these sesquiterpene lactones were tested for their activities agianst *Plasmodium falciparum*(strain K 1) invitro. It showed lower antiplasmodial activity with an IC_{50} values of 11.4±2.4mm[12].

Eight sesquiterpene lactones(1to8) were isolated from *Ixeris dentata* forma albifora. Compound zaluzanin(1),9α-hydroxyguaian4(15),10(14),11(13)-triene-6-,12-olide(2) and Crepiside (7) revealed relatively high cytotoxicity on human colon carcinoma cell (HT-29) and lung adeno-carcinoma cell (A549),while compounds ixerin M(5) and crepiside I(7) showed acyl-CoA:cholesterol acyltransferase(ACAT) inhibitory activity. Compound 1,2&7 exhibited relatively mild cytotoxicity(1.A549,IC_{50}:0.26mm;HT-29,IC_{50}:0.19mM;2:A549,IC_{50}:1.63mM;HT 29,IC_{50}:0.25mM;7:HT-29,IC_{50}:6.75mM), with IC_{50} values many orders of magnitude higher then the positive control,mithramycin(A549,IC_{50}:0.06mm;HT-29,IC_{50}:0.07mm).Compound 5 and 7 showed ACAT inhibitory activity with values of 46.4 ±1.1% and 66.5 ±0.9% respectively,at 100mg/ml[13].

(-)-dehydrocostuslactone showed the antifungal activity against *C.echinulata* with EC_{50} values (6mg/ml) close to that of ketoconazole (1.5mg/ml) used as refrence drug[9].

3.Eudesmanolides

Seven eudesmanolide type sesquiterpene lactones were isolated from *E.semialatum*. All the compounds were found to have some activity against *P.falciparum*.IC_{50} values ±SE of 1to7 against *P.falciparum*(strain K1) invitro (n=6) are 31.7 ±4.0mm, 28.5±3.2mm, 27.0

Table 1: Some potant Sesquiterpene lactones of plants showing biological activities.

S.NO.	Family	Plant's name	Plant's part used	Sesquiterpene lactones	Biological activities	Reference No.
1	Asteraceae	*Tithonia diversifolia*	Leaves	Germacranolide type	Antibacterial,Antifungal	1
2	Asteraceae	*Oncosiphon piluliferum*	Aerial parts	Germacranolide type, Eudesmanolide type	Antiplasmodial	7
3	Magnoliaceae	*Magnolia grandiflora*	Leaves	Crepiside,Costunolide, Parthenolide	Molluscicidal,Insecticidal,Antifungal	8
4	Asteraceae	*Saussurea lappa*	Roots	(+)-costunolide, (-)-dehydrocostuslactone	Antifungal(against *Cunninghamella echinulata*)	9
5	Asteraceae	*Tanacetum parthennium*	Whole plant	Parthenolide	Anticancer	10
	Asteraceae	*Centaurothamnus maximus,*	Aerial parts	Chlorojanerin, Cynopicrin, Janerin	Cytotoxic	11
6		*Vicoa pentanema*	Aerial parts	2α-Acetoxy-3β-hydroxyalantolactone	Cytotoxic	
7	Asteraceae	*Eupatorium semialatum*	Leaves	Guaianolide type,Eudesmanolide type	Antiplasmodial	12
8	Asteraceae	*Ixeris forma dentata* albiflora	Roots	Zaluzanin,Ixerin M,	Cytotoxic,ACAT inhibitory	13
9	Asteraceae	*Inula helanium*	Roots	Alantolactone,Isoalantolactone, 5-epoxyalantolactone	Anticancer,Induction of detoxyfying enzyme (Quinine reductase)	14
10	Asteraceae	*Pulicaria laciniata*	Flower & Aerial parts	Alantolactone	Antibacterial	15
11	Asteraceae	*Ambrosia tenufolia* sprengel	Aerial parts	Psilostachyin,Peruvin	Trypanocidal, Leishmanicidal, Antiplasmodial	16,29
12	Asteraceae	*Elephantopus scaber*	Aerial parts	Deoxyelephantopin	Wound healing	17
13	Asteraceae	*Smallanthus sonchifolius*	Leaves	Malampolide type (Fluctuanin)	Antibacterial	18
14	Asteraceae	*Arnica montana*	Flowers	Helenalin	Antiinflammatory, Cardiotonic	19,30,32
15	Asteraceae	*Artemisia annuna*	Leaves	Artemisinin	Antimalarial,Anticancer	20,26,31
16	Apiaceae	*Smyrnium olusatrum*	Fruits	Germacranolide type, Eudesmanolide type	Cytotoxic	21
17	Asteraceae	*Cichorium itybus*	Roots	Guaianolide type	Antiinflammatory,Hepatoprotective	22
18	Asteraceae	*Chrysanthemum coronarium* L.	Flowers	Pyrethrosin, 1,10-epi-pyrethrosin	Cytotoxic	23
19	Asteraceae	*Moquinia kingii*	Aerial parts	Cynaropicrin	Trypanocidal	24
20	Asteraceae	*Moquinia kingii*	Aerial parts	Cynaropicrin	Antibacterial,Antifungal	25
21	Euphorbiaceae	*Croton cajucara*	Bark & leaves	Dehydrocrotonin	Cytotoxic(on human lymphocytes)	27
22	Asteraceae	*Inula helanium, Centaurea* species	Roots	Isoalantolactone,dehydrocostuslactone	Plant growth regulating	28
23	Asteraceae	*Ambrosia ambrosioides*	Leaves	Tulirinol,Damsin,Damsinic acids	Cytotoxic,protection of plants from beetles	33,34

±3.7mm, 26.2 ±1.5mm, 16.3 ±1.9mm, 8.9 ±1.8mm,13.3±4.1mm, respectively[12].

Desacetyle-β-cyclo-pyrethrosin and sivasinolide showed *in vitro* antiplasmodial activity against *Plasmodium*

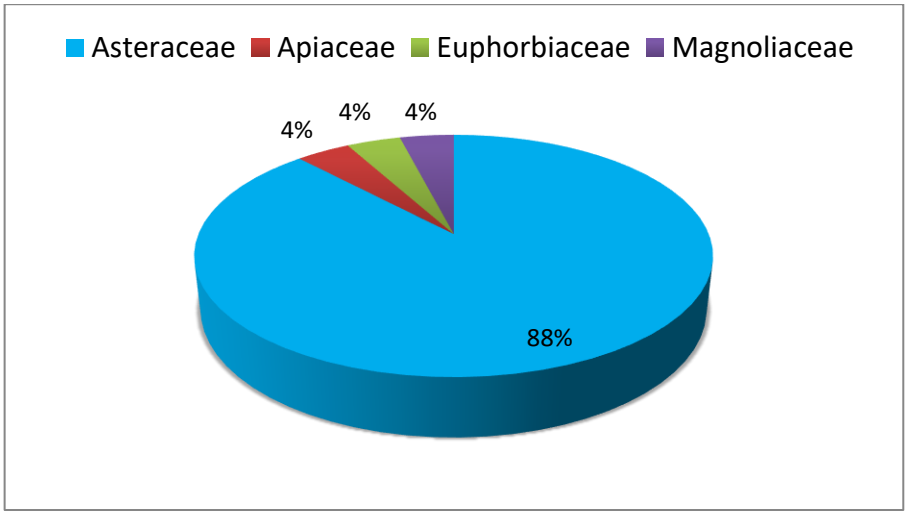


Figure 2: percentage showing presence of SLs in plant families.

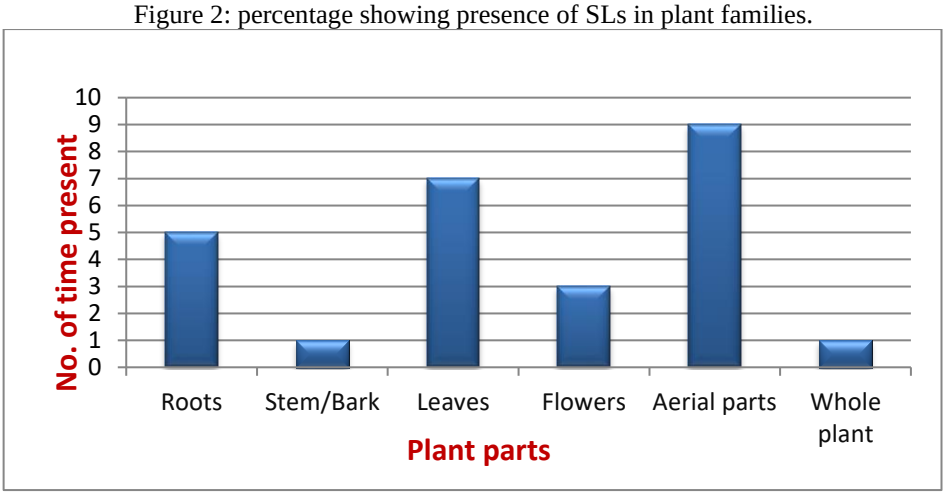


Figure 3: Showing occurance of SLs in Plant parts.

Table 2: Percentage of studied plants showing biological activities of SLs.

S.No.	Biological activities	No. of Plants showed the activity	Percentage (%)
1	Antibacterial	04	16%
2	Antiplasmodial	04	16%
3	Antiinflammatory	02	8%
4	Antifungal	04	16%
5	ACAT inhibitory	01	4%
6	Cytotoxic	08	32%
7	Detoxyfying	01	4%
8	Insecticidal	02	8%
9	Leishmanicidal	01	4%
10	Molluscicidal	01	4%
11	Plant growth regulating	01	4%
12	Hepatoprotective	01	4%
13	Trypanocidal	02	8%
14	Wound healing	01	4%
15	Cardiotonic	01	4%

falciparum with IC_{50} 4.4mg/ml and 2.6mg/ml respectively[7].

Alantolactone, isoalantolactone and 5 epoxyalantolactone induced significantly Quinine reductase (QR) activity in Hepa 1c1c7 and BPRc 1 cells. Thus, sesquiterpenes with high QR induction potential may generate high levels of free radicals, which was acompained and induction of apoptosis[14].

The antibacterial activities of alantolactone were determined against seven bacterial strain.It showed best activity against *Staphylococcus aureus* and *E.faecalis*. Neverthless alantolactone presented minor activity against negative gram rods *E.coli* and *Se.marcescens*[15].

4.Psilostachyin & Peruvin

IC_{50} values of Psilostachyin and Peruvin were similar on the non-infective form of *Trypanosoma cruzi* (Psilostachyin:1.22mg/ml; Peruvin:1.65mg/ml,72h), Psilostachyin was more active on the trypomastigote forms (0.76mg/ml vs 52.8mg/ml). The inhibitory activity of Psilostachyin and Peruvin on *Leishmania* spp. promastigotes is noticeable. After 120h the values of IC_{50} were 0.12 and 0.39 mg/ml for both compounds respectively[16].

5.Deoxyelephantopin

The ethanolic extract and the isolated constituent deoxyelephantopin of *Elephantopus scaber* promoted wound healing activity in three wound models.

Table 3: Showing occurance percentage of SLs in plant parts.

S.No.	Parts of Plant Body	No. of time present (SLs)	Percentage of occurance
1	Roots	05	20%
2	Stem/Bark	01	4%
3	Leaves	07	28%
4	Flowers	03	12%
5	Aerial parts	09	36%
6	Whole Plant	01	4%

Significant($P<0.01$) increase in the rate of wound contraction on day 16 (98.8%,$P<0.01$),skin-breaking strength (412g,$P<0.01$) and weight of the granulation tissue on day 10 (74mg/100g,$P<0.01$) were observed with deoxyelephantopin treated animals. In ethanolic extract treated animals, the rate of wound contraction on day 16, skin breaking strength and weight of granulation on day 10 ($P<0.01$) were 92.4%,380g and 61.67mg/100g respectively[17].

6.Melampolide type

The newly identified compound,8β-methacryloyloxy-melampolid-14-oic acid methyl ester, exhibited potent antimicrobial activity against *Bacillus subtilis* and *Pyricularia oryzae*, while 8β-tigloyloxy melampolid-14-oic acid methyl ester showed lower activity. Fluctuanin exhibited the strongest antibacterial activity against *B.subtilis* among all the tested six sesquiterpene lactones[18].

CONCLUSION

In this review, we found that SLs showed various potant biological activities. In most of the cases, they show anticancer or cytotoxic activities.Eight plants(32%)in out of 25 studied plants have cytotoxic SLs. Some other SLs also reveal antibacterial(16%), antifungal(16%) and antiplasmodial(16%) activities(Table-02).Thus, it is clear that there is a great requirement of study to know the anticancerous property of SLs and mechanism of action at the molecular level for further use. This manuscript also indicates new area of biological activities for sesquiterpene lactones, which is not observed or less studied by researcher. Twenty two studied plants(88%) in out of 25 studied plants belongs to family Asteraceae or daisy family. For this reason, sesquiterpenes known as the characteristic compounds of family Asteraceae. 4% plants from each family Apiaceae, Magnoliaceae and Euphorbiaceae were observed for detection of sesquiterpene lactones(Fig.02).We should focus on new plant families for extraction and purification of SLs and their activities. The presence of SLs in various parts of plant body also studied. We notices that in 25 studied plant samples, mostly nine plants(36%)revealed the presence of SLs from aerial parts, seven plants(28%) in leaves and five plants(20%) in roots.(Table and Fig.03).It is a big need of time that researcher or scientists should focus on this area for further studies like SLs and it's new biological activities, their mechanism of action, isolation from new plant species other than family Asteraceae. So that it can be utilized as an effective therepeutic agent specially for anticancerous treatment in future.

ACKNOWLEDGEMENT

We gratefully acknowledge Department of Chemistry, J.H.Govt.P.G.College Betul(MP)India for providing valuable literature and guidance. We also thank our colleagues and students for improving an earlier draft of this manuscript.

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