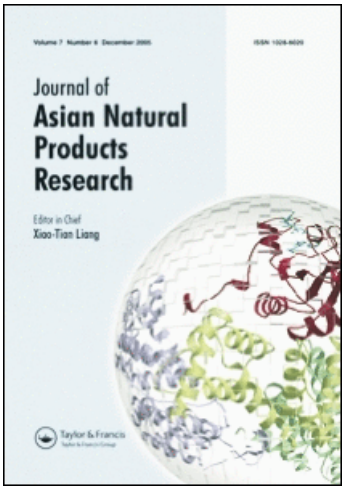

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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Online publication date: 04 February 2010

To cite this Article Yang, Jun-Li , Wang, Rui , Liu, Lei-Lei and Shi, Yan-Ping(2010) 'Phytochemicals and biological activities of *Saussurea* species', Journal of Asian Natural Products Research, 12: 2, 162 — 175
To link to this Article: DOI: 10.1080/10286020903496455
URL: http://dx.doi.org/10.1080/10286020903496455

Journal of Asian Natural Products Research
Vol. 12, No. 2, February 2010, 162–175

REVIEW

Phytochemicals and biological activities of *Saussurea* species

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(*Received 23 August 2009; final version received 17 November 2009*)

The genus *Saussurea* has been studied from phytochemical and pharmacological viewpoints for years, which resulted in the discovery of hundreds of secondary metabolites with various kinds of bioactivities. This review summarizes the research progress of the genus of *Saussurea* in the phytochemical and pharmacological viewpoints, which covered the period of 1990–June 2009.

Keywords: *Saussurea*; phytochemicals; bioactivities

1. Introduction

Saussurea, a cosmopolitan and important genus of the Composite family, contains more than 400 species, distributed mainly in Asia, as well as some species distributed in Europe and North America. There are approximately 300 species found all over China [1]. Selected *Saussurea* species are recorded in Chinese Pharmacopoeia (2005 edition) as Tibetan medicines. In China, the rare and important traditional Tibetan medicine 'Xue Lian' is well known all over the country, which just comprises several *Saussurea* species.

The history of phytochemical and pharmacological investigations on this genus goes back to the 1960s. From then on, more than 30 *Saussurea* species have been studied, from which hundreds of secondary metabolites have been isolated with a majority of terpenoids [1]. What is attractive is that some of the isolates show various kinds of significant bioactivities.

For years, the applications of the *Saussurea* species in traditional medicine and the significant pharmacological activities have attracted the views of scientists. In particular, due to the rich resources, Chinese scientists have been playing an important role in the area of study on *Saussurea*. Many valuable results were reported in Chinese. Selected *Saussurea* species, such as *S. involucrata*, *S. medusa*, *S. lappa*, *S. laniceps*, *S. gossypiphora*, *S. tridactyla*, *S. nivea*, *S. petrovii*, *S. polycolea*, and *S. stella*, have been investigated from the phytochemical and pharmacological viewpoints. Hundreds of secondary metabolites, including terpenoids, steroids, flavonoids, lignans, as well as other derivatives, have been isolated from the above-mentioned species and some of the isolates show good pharmacological activi-

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ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020903496455
http://www.informaworld.com

ties [2–44]. New analytical methods for the assay of main components of some species, such as *S. involucrata*, *S. medusa*, *S. lappa*, and *S. laniceps*, have been established, and this will be helpful for the quality control of these plants [45–59]. However, what is attractive is that the study on the biosynthesis of some secondary metabolites and the study on some species from the biological viewpoint, such as *S. involucrata*, *S. medusa*, and *S. laniceps*, have been undertaken [60–92]. Additionally, some focused or mini reviews provided a platform for further understanding of *Saussurea* [93–98].

Searching for bioactive compounds from nature has always been our interest. In the past few years, we have investigated several *Saussurea* species, such as *S. cauloptera*, *S. ussuriensis*, *S. oligantha*, *S. katochaete*, and *S. mongolica*, from the phytochemical and pharmacological viewpoints. Additionally, new capillary electrophoresis (CE) methods were established for simultaneous assay of main bioactive components from *S. mongolica* and *S. katochaete* [99–105]. The promising results stimulated our interests in *Saussurea* species for the discovery of more bioactive substances. In order to make a comprehensive and systematic understanding of this genus, we decided to review the state of the art in the study on bioactive chemical composition from *Saussurea* in the last 20 years.

Another aim of this review is to draw the attention of natural product chemists for the evaluation of biological and pharmacological activities of the isolated components from *Saussurea* in order to justify the use of medicinal plants belonging to this genus in folk medicines. The highlight of biological activities may make some isolates from this genus as the lead compounds for design of new drug molecules.

2. Chemical constituents

During the period of 1990–June 2009, there have been hundreds of secondary metabolites isolated from the genus *Saussurea* for the first time, including sesquiterpenoids, diterpenoids, triterpenoids, steroids, flavonoids, lignans, and phenolic derivatives, as well as others, and some new pharmacological activities deduced from the isolates of *Saussurea* were reported during the period (see Table 1 and Figure 1) [2–44,100–153]. There are approximately 121 new natural products discovered from this genus during 1990–June 2009, and these new compounds are discussed in view of the structural feature as follows.

2.1 Sesquiterpenoids

There are approximately 64 new sesquiterpenoids isolated, including 3 megastigmane derivatives, 34 guaiane derivatives, 20 eudesmane derivatives, 4 germacrane derivatives, as well as others.

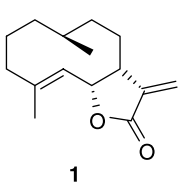
There are three new megastigmane derivatives isolated from this genus during the period. One was found from *S. medusa* by Duan *et al.* in 2002 and named 3β-hydroxy-5α, 6α-epoxy-7-megastigmen-9-one. The other two megastigmane derivatives were also discovered from this plant and named saussureosides A and B.

Guaiane derivatives compose the majority of new sesquiterpenoids. In view of the structural feature, all of them possess a five-membered lactone ring formed between 6-OH and 12-COOH. Most of them possess a double bond between C-4 and C-15 or between C-10 and C-14. The substitution of OH often occurs at C-3 and C-8. However, 3-OH is always oxygenated to carbonyl, while 8-OH is always esterified.

There are approximately 20 new eudesmane sesquiterpenoids, which compose the second popular kind of sesquiterpenoids within this genus. Compared to the guaiane derivatives, most of them are not isolated in the form of lactones. A double bond is often formed between C-4 and C-15. The positions C-1 and C-3

Table 1. New chemical constituents with significant bioactivities from the genus *Saussurea*.

No.	Compound class and name	Plant source	References
1	Isodihydrocostunolide	*S. lappa*	[125]
2	Saussureamine A	*S. lappa*	[108]
3	7α-Hydroxygerin	*S. cauloptera*	[104]
4	8-*O*-Deacetylgerin	*S. cauloptera*	[104]
5	3α,7α,12-Trihydroxyeudesm-4(15),-11(13)-diene	*S. laniceps*	[117]
6	Saussureamine B	*S. lappa*	[108]
7	Saussureamine C	*S. lappa*	[108]
8	3α,8α-Dihydroxy-1αH,5αH,6βH,7αH,11βH-guai-4(15),10(14)-dien-6,12-olide 8-*O*-2-hydroxymethylacrylate	*S. laniceps*	[117]
9	3α,8α-Dihydroxy-1αH,5αH,6βH,7αH,11βH-guai-4(15),10(14)-dien-6,12-olide 8-*O*-(2-methyl)acrylate	*S. laniceps*	[117]
10	4β-Methoxydehydrocostus lactone	*S. lappa*	[113]
11	Saussureal	*S. lappa*	[127]
12	Lappadilactone	*S. lappa*	[109]
13	Taraxast-20-ene-3β,30-diol	*S. petrovii*	[130]
14	20α,21α-Epoxy-taraxastane-3β,22α-diol	*S. petrovii*	[130]
15	Oliganthas B	*S. oligantha*	[102]
16	3-*O*-β-D-Quinovopyranosylperiplogenin	*S. stella*	[134]
17	3-*O*-β-D-Glucopyranosyl-(1 → 4)-α-L-rhamnopyranosylcannogenin	*S. stella*	[134]
18	3′-(3*R*-Acetoxy-5,5-dimethylcyclopent-1-ene)-4′-*O*-methylscutellarein 7-*O*-(6‴′-*O*-acetyl)-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside	*S. lappa*	[136]
19	Kaempferol-3-*O*-β-D-glucopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 6)-β-D-galactopyranoside 7-*O*-(6‴′-*O*-acetyl)-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside	*S. lappa*	[136]
20	Kaempferol-3-*O*-β-D-glucopyranosyl(1 → 2)-β-D-(6a′-*O*-caffeoyl)-glucopyranoside 7-*O*-(6‴′-*O*-acetyl)-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside	*S. lappa*	[136]
21	Kaempferol-3-*O*-α-L-(2a′,3a′-*E*-di-*p*-coumaroyl)-rhamnoside 7-*O*-(6‴′-*O*-acetyl)-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside	*S. lappa*	[136]
22	2α-Guaicyl-4-oxo-6α-catechyl-3,7-dioxabicyclo[3.3.0]octane	*S. medusa*	[106]
23	1α-Hydroxy-2α,4α-guaicyl-3,7-dioxabicyclo[3.3.0]octane	*S. medusa*	[106]



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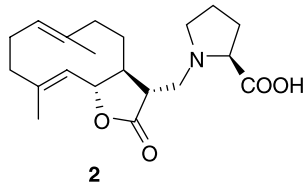

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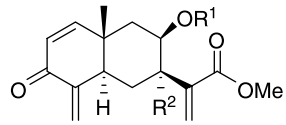
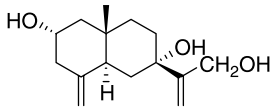


	R^1	R^2
3	Ac	OH
4	H	H



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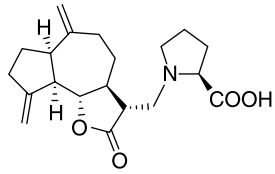

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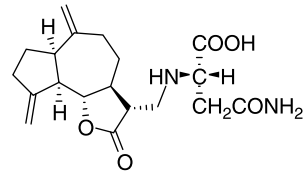

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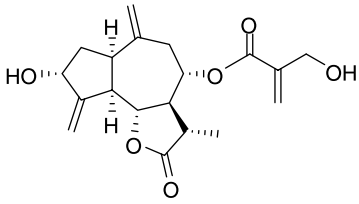

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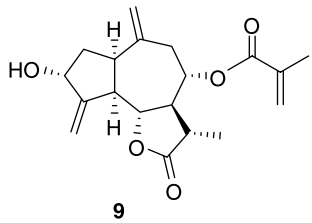

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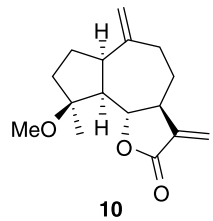

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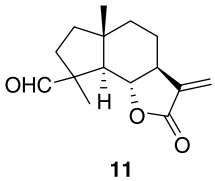

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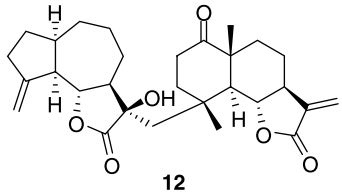

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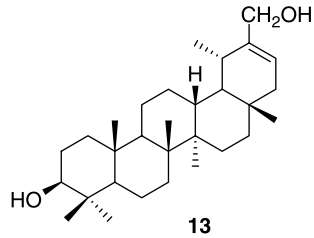

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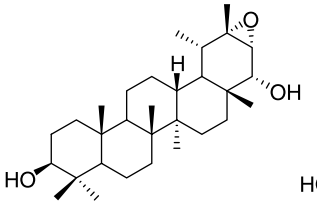

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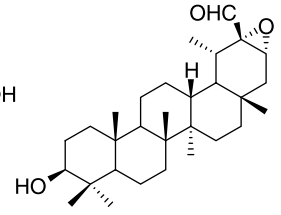

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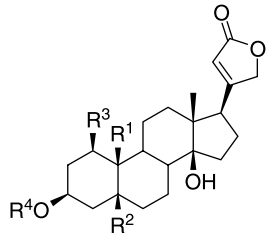
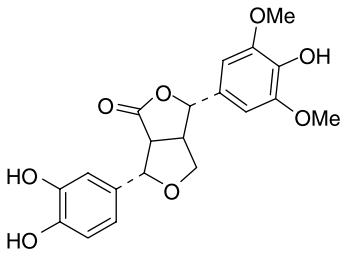


	R^1	R^2	R^3	R^4
16	Me	OH	H	Qui
17	CHO	H	H	Rha(4→1)Glc



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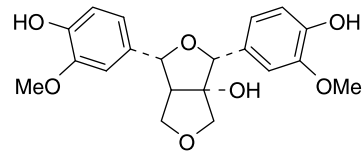

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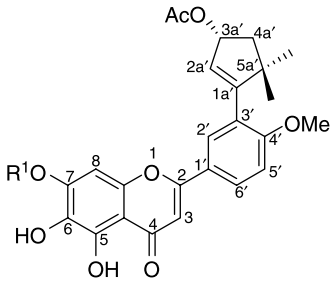
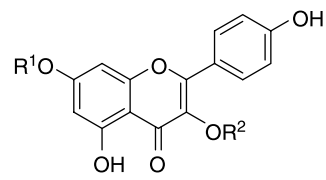
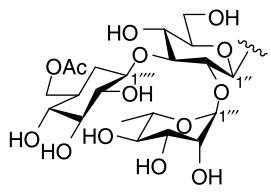


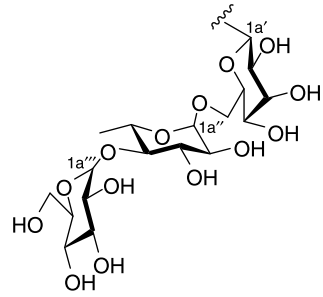
	R1
20	FG1



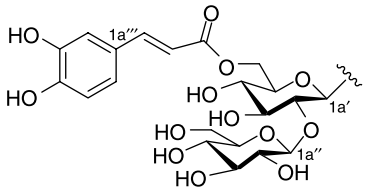
	R1	R2
21	FG1	FG2
22	FG1	FG3
23	FG1	FG4



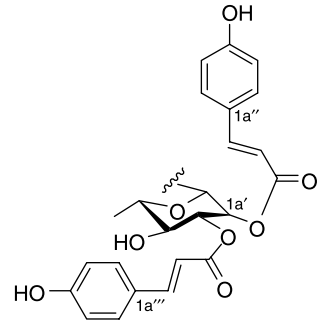
FG1



FG2



FG3



FG4

Figure 1. The structures of new chemical constituents with significant bioactivities from *Saussurea*.

are often substituted by OH, while a carbonyl is sometimes attached to C-10. In addition, several glycosides are formed at C-1 or C-3.

Except for the above skeletons, four germacrane sesquiterpenoids as well as three compounds with other skeletons are also found from this genus. Saussureal features a rearranged eudesmane skeleton. Lappadilactone is a dimer formed by a guaiane moiety and an eudesmane moiety with a C—C linkage pattern. The third compound belongs to a linear sesquiterpenoid.

Of all the new sesquiterpenoids isolated, 12 compounds feature novel frameworks of amino acid–sesquiterpene lactone dimers, which indicate that the genus *Saussurea* may be a rich source of natural products with skeleton diversity.

2.2 Diterpenoids

During the period, there is only one diterpenoid isolated. Fortunately, it was found in our laboratory from *S. cauloptera* in 2008 and named 3α-hydroxy-*ent*-labda-8(20),13-dien-16,15-olide.

2.3 Triterpenoids

There have been approximately 18 new triterpenoids isolated from *Saussurea* during the period. They comprise oleanane, taraxastane, and ursane types, as well as dammarane and lanosterol types. Of them, oleanane types hold up the majority of these structures, followed by taraxastane types.

2.4 Steroids

Approximately seven new steroids are discovered from this genus during this period. *S. lappa* and *S. stella* are the main plant sources of this kind of compounds. There are two steroids isolated from *S. lappa* and three are found from *S. stella*. Additionally, from *S. ussuriensis* and *S. gossypiphora*, there is one steroid discovered, respectively.

2.5 Flavonoids

During the past 20 years, there have been only seven new flavonoids isolated from this genus. All of them are isolated in the form of *O*-glycosides and the sugar moieties are often esterified by aromatic or other groups.

2.6 Lignans

There are about 15 new lignans discovered. Some of them are isolated in the form of *O*-glycosides. The most important feature of this kind of compounds is that the benzene moieties are often substituted by OH or OMe. In addition, there is a dimer of lignans with a C—O—C linkage pattern and named conicaol A.

2.7 Phenol derivatives

There are three new phenol derivatives isolated from this genus during 1990–June 2009. Two of them are isolated from *S. involucrata* and the other is found from *S. japonica*. All of them are discovered in the form of *O*-glycosides.

2.8 Others

Two chlorophyll derivatives are isolated from *S. medusa*. One is isolated in the form of the corresponding methyl ester of the other.

Two epimers were found in our laboratory from *S. katochaete* in 2005. The absolute configuration of C-4 is deduced as *R* by the CD spectrum. However, the stereochemistry of C-7 is still uncertain.

Additionally, a novel ceramide is isolated from *S. involucrata*, which also affords another compound, *n*-butyl-β-D-fructopyranoside.

3. Bioactivities

3.1 Cytotoxicity

3.1.1 Sesquiterpenoid-induced cytotoxicity

Sesquiterpenoids, especially sesquiterpenoid lactones, have been reported to show significant activity toward tumor cells [1], which was supported by the research of cytotoxicity of isolates from the genus *Saussurea*.

In 2001, petrovins A and B, isolated from *S. petrovii*, were reported to exhibit significant *in vitro* cytotoxic activity against human hepatoma cells (SMMC-7721), human uterine cervix carcinoma cells (HeLa), and mouse melanotic carcinoma cells (B16). The results showed that the antitumor activity of petrovin A is comparable to that of antitumor drug vincristine in the case of B16 and HeLa cell lines [123].

In 2003, Jia *et al.* reported that encelin, isolated from *S. parviflora* as a known natural product, revealed competitive antitumor activity on three tumor cell lines, human hepatocytes L02, human hepatoma cell SMMC-7721, and human ovarian neoplasm cell HO-8910. The survival rates of cells were determined by applying the MTT method with vincristine as a positive control. The result showed effective antitumor activity of encelin with IC_{50} values of $1.47 \pm 0.01\,\mu M$ for L02 cell, $0.57 \pm 0.26\,\mu M$ for SMMC-7721 cell, and $0.85 \pm 0.06\,\mu M$ for HO-8910 cell [121].

It has been a long history that *S. lappa* is used as a traditional medicine for the treatment of cancer. In 2003, Lee *et al.* reported that lappadilactone (**12**) as well as dehydrocostuslactone and costunolide, isolated from *S. lappa*, exhibited potent cytotoxicity with CD_{50} values in the range of 1.6–3.5 μg/ml in dose- and time-dependent manners. The cytotoxicities were not specific and showed similar activities against HepG2, OVCAR-3, and HeLa cell lines. The structure–activity relationship showed that the α-methylene-γ-lactone moiety is necessary for cytotoxicity, and activity is reduced with the presence of a hydroxyl group [109]. In 2008, Rao *et al.* reported that isodihydrocostunolide (**1**), with a good cytotoxicity, was isolated from *S. lappa*. In the test for *in vitro* cytotoxicity, isodihydrocostunolide revealed a significant activity on colon, skin, and breast cancer lines with IC_{50} values of 27.03 ± 0.67, 107 ± 7.46, and $35.05 \pm 9.37\,\mu M$, respectively, and moderate activity on lung cancer lines with an IC_{50} value of $125 \pm 0.95\,\mu M$ [125].

In 2008, our laboratory carried out an investigation on *S. cauloptera* from the phytochemical and pharmacological viewpoints, which led to the isolation of two compounds (**3** and **4**) with good cytotoxicity. In the test for their ability to inhibit human gastric carcinoma (SGC-7901) cells using the MTT[3] colorimetric assay with 5-fluorouracil (5-FU) as a positive control, **3** showed significant activity ($IC_{50} = 42.3 \pm 2.3\,\mu M$) similar to that of 5-FU ($IC_{50} = 39.3 \pm 0.2\,\mu M$), while **4** demonstrated a better activity ($IC_{50} = 22.5 \pm 0.7\,\mu M$) compared to that of 5-FU [104].

3.1.2 Triterpenoid-induced cytotoxicity

The cytotoxicity of two triterpenoids (**13** and **14**) was reported by Yang *et al.* in 2001. The antitumor activity of the two isolates was determined using the MTT assay with three tumor cell lines, i.e. human hepatoma cells (SMMC-7721), human uterine cervix carcinoma cells (HeLa), and mouse melanotic carcinoma cells (B16), with vincristine as a positive control. The IC_{50} values of compounds **13** and **14** are comparable to vincristine in the case of HeLa cells and much smaller than vincristine in the case of B16 cells. What is attractive is that the IC_{50} value of 20 μg/ml demonstrates **13** as being an effective inhibitor of B16 cells compared

to vincristine with an IC_{50} value of 70 μg/ml [130].

3.1.3 Steroid-induced cytotoxicity

In 2007, compounds **16** and **17**, as well as seven related compounds, were isolated from the cytotoxic EtOH extract of *S. stella* by Cai *et al.* All of them were tested for potent inhibitory effects on the growth of two cell lines: BGC-823 human gastric cancer cells and Bel-7402 human hepatoma cells. The IC_{50} values of all compounds were all < 1 μM. Of the nine compounds tested, compound **17**, which has a two-sugar side chain, showed the least potent inhibitory effects toward the cancer cell lines tested. Additionally, the results indicated that compounds with an aldehyde group at C-10 were more potent than those with a methyl group at C-10 in inhibiting the growth of these cancer cell lines [134].

3.2 Cell-protective activities

3.2.1 Sesquiterpenoid-induced cell-protective activities

In 2000, the methanolic extract of Chinese *S. lappa* was reported to show a potent inhibitory effect on acidified ethanol-induced gastric lesions in rats, from which saussureamines A (**2**), B (**6**), and C (**7**) were isolated.

Acidified ethanol-induced gastric mucosal lesions are often used as the experimental model for the analysis of cellular protective action. Stress-induced gastric ulceration in rats or mice is also used for the evaluation of anti-ulcer drugs. An experiment has been carried out to determine the cell-protective activity of the three compounds. The results indicated that the oral administration of the methanolic extract of *S. lappa* showed a potent inhibitory effect on gastric mucosal lesions induced by 60% ethanol containing 150 mM hydrochloride (HCl–EtOH) in rats, and its potency was stronger than that of reference drugs, cetraxate, cimetidine, and omeprazole. Saussureamines A–C showed significant protective effects at doses of 50 and/or 100 mg/kg. Saussureamines A and B especially showed more potent effect than a reference drug, cetraxate. The structure–activity research (SAR) study showed that the 13-amino acid moiety was the principal center responsible for this activity. The experiment also revealed that saussureamines A–C were the principal active constituents of the polar fraction for HCl–EtOH-induced gastric lesions.

In addition, the effects of saussureamines A–C on water-immersion stress-induced gastric mucosal lesions were also studied. Oral administration of saussureamine A showed significant protective effects at doses of 100 and 200 mg/kg. But, saussureamines B and C lacked the significant effect on this lesion at a dose of 200 mg/kg.

The above results suggested that saussureamines A–C could be potential agents for the treatment of stomachic disorders [108].

3.2.2 Phenolic compound-induced cell-protective activities

A phenolic compound, apigenin 7-*O*-[α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside], was isolated from *S. medusa* by Yue *et al.* as a known natural compound in 2003. The pharmacological study showed the remarkable activity induced from this compound to attenuate the scopolamine-induced memory deficit in an animal model. After oral administration of this compound at the dosages of 10, 15, and 20 mg/kg and then injection of scopolamine at the dose of 4.5 mg/kg for each group of mice 30 min later, the mice taking the compound in the tested groups obviously reduced the errors to enter non-exit and shortened the time to reach the platform than those injected only 4.5 mg/kg scopolamine.

Additionally, another pharmacological evaluation indicated that this compound showed moderate protective activity against H_2O_2-induced damage in rat pheochromocytoma line PC12 cells [138].

3.3 Immunosuppressive activity

3.3.1 Sesquiterpenoid-induced immunosuppressive activity

In 2005, compounds **5**, **8**, and **9** were isolated from *S. laniceps* by Qin *et al.* They were tested for the immunosuppressive activity in an *in vitro* murine lymphocyte proliferation assay induced by concanavalin A (ConA) and lipopolysaccharide (LPS). The result showed that compounds **8** and **9** revealed weak activity, while compound **5** had strong inhibition on proliferation of murine T and/or B cells. The practice of using *S. laniceps* in Tibetan medicine for the treatment of rheumatic arthritis has been for a long time, which is supported by the promising immunosuppressive activity of **5** [117].

3.3.2 Lignan-induced immunosuppressive activity

Lignans **22** and **23** were isolated from *S. medusa* in 2002 by Duan *et al.* The pharmacological investigation showed good immunosuppressive activity induced from the two compounds, which was examined through the inhibitory effect on cytokine production. The results showed a significant inhibitory effect on cytokine production from LPS (or phytohemagglutinin)-stimulated human peripheral mononuclear cells compared with the reference compound, prednisolone [106].

3.4 Antifungal and antibacterial activities

3.4.1 Sesquiterpenoid-induced antibacterial activity

We have mentioned that petrovins A and B, isolated from *S. petrovii*, exhibited significant *in vitro* cytotoxicity. In addition, the two compounds also exhibited promising antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*. The test showed that the antibacterial activity of both petrovins A and B is comparable to chloramphenicol [123].

3.4.2 Triterpenoid-induced antibacterial activity

Except for the cytotoxicity, compounds **13** and **14** were tested for their antibacterial activity against *B. subtilis*, *E. coli*, and *S. aureus* with a positive control of chloramphenicol. It was found that the two triterpenoids, especially **13**, possess antibacterial activity close to that of the positive control, chloramphenicol [130].

Compound **15**, as well as 22-oxo-20-taraxasten-3β-ol and taraxast-20-ene-3β, 30-diol, was isolated from *S. oligantha* in our laboratory in 2008. All of the three isolates were tested for their antibacterial activity based on the minimum inhibitory concentration method. The results showed that all of them revealed strong activity against *Actinomyces viscosus* ATCC27044, when compared with the positive control, triclosan [102].

3.4.3 Flavonoid-induced antifungal and antibacterial activities

Four novel acylated flavonoid glycosides **18**–**21** were isolated from *S. lappa* in 2007. The *in vitro* antifungal and antibacterial activities of the isolated compounds and their mixture were tested on nine fungal and four bacterial strains, using the microdilution method. In the antifungal activity, compound **21** possessed the highest potential, while **18**–**20** shows medium activity. All the compounds show greater antifungal activity than miconazole, a commercial fungicide, which was used as a control. As for the antibacterial potential, only compound

21 is active against all bacterial strains tested [136].

3.5 Plant growth regulatory activity

3.5.1 Sesquiterpenoid-induced plant growth regulatory activity

In 1992, Kalsi *et al.* reported that compounds **10** and **11**, isolated from *S. lappa*, showed significant bioactivity as plant growth regulators. A series of SAR indicated that the guaianolides possessed potent plant growth regulatory activity more than other carbon skeletons, and the presence of a five-membered ring A enhanced the plant growth regulatory activity associated with the α-methylene-γ-lactone moiety [113,127].

3.6 Protein tyrosine phosphatase 1B inhibition activity

3.6.1 Triterpenoid-induced protein tyrosine phosphatase 1B inhibition activity

In 2009, betulinic acid and betulinic acid methyl ester, isolated from *S. lappa*, were reported to have significant protein tyrosine phosphatase 1B (PTP1B) activity by Ahn *et al.* The two compounds were tested for the PTP1B activity and the results revealed that the two compounds strongly inhibited PTP1B activity with 0.70 ± 0.03 and 0.93 ± 0.07 μg/ml, respectively, which was comparable to those of ursolic acid (0.7 ± 0.05 μg/ml) and RK-682 (1.2 ± 0.09 μg/ml) used as positive controls. The results suggested that betulinic acid and betulinic acid methyl ester could be developed as drugs of metabolic disease [141].

3.7 Anti-inflammatory activity

3.7.1 Lignan-induced anti-inflammatory activity

Three lignans, arctigenin, matairesinol, and diarctigenin, were reported from *S. conica* as known natural compounds in 2006 by Yue *et al.* They were subjected to the bioassay of NO production by LPS-activated Sprague Dawley rat macrophages *in vitro* with hydrocortisone acetate as the positive control. Arctigenin and matairesinol showed dose-relevant suppressing effects on NO production with IC_{50} values of 3.8 and 7.6 μg/ml, respectively. Diarctigenin revealed weak activity with an IC_{50} value of 16.1 μg/ml. The positive control, hydrocortisone acetate, an anti-inflammatory drug, showed strong activity with an IC_{50} value of 0.0016 μg/ml. The described activity could contribute to understanding of the traditional application of this plant in the treatment of rheumatic arthritis, dysmenorrheal, and other disorders of gynopathy in both Chinese and Tibetan traditional medicine [139].

4. Conclusions

In this review, we summarize the secondary metabolites reported from *Saussurea* species as well as their biological activities during the period of 1990–June 2009. All the information showed that *Saussurea* is a promising and rich source for natural products with chemical and pharmacological diversity. The competitive results stimulate us to get a better understanding of *Saussurea* species from the phytochemical and pharmacological viewpoints and to elucidate the chemical composition of substances responsible for the pharmacological activities.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC 20621091), the National Key Technology Research and Development Program of China (No. 2007BAI37B05), and the National 863 Program of China (No. 2007AA09Z403).

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