

Saussurea involucrata

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5 ***Saussurea involucrata*: A review of the botany, phytochemistry and**
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8 **ethnopharmacology of a rare traditional herbal medicine**
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4 **ABSTRACT**
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6 **Ethnopharmacological relevance:** *Saussurea involucrata* Matsum. & Koidz. is an endangered
7 species of the Asteraceae family, growing in the high mountains of central Asia. It has been, and is,
8 widely used in traditional Uyghur, Mongolian and Kazakhstan medicine as well as in Traditional
9 Chinese Medicine as Tianshan Snow Lotus (Chinese: 天山雪蓮). In traditional medical theory, *S.*
10 *involucrata* can promote blood circulation, thereby alleviating all symptoms associated with poor
11 circulation. It also reputedly eliminates cold and dampness from the body, diminishes inflammation,
12 invigorates, and strengthens *Yin and Yang*. It has long been used to treat rheumatoid arthritis, cough
13 with cold, stomachache, dysmenorrhea, and altitude sickness in Uyghur and Chinese medicine.
14

15 **Aim of the review:** To comprehensively summarize the miscellaneous research that has been done
16 regarding the botany, ethnopharmacology, phytochemistry, biological activity, toxicology of *S.*
17 *involucrata*.
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19 **Method:** An extensive review of the literature was carried out. Apart from different electronic
20 databases including SciFinder, Chinese National Knowledge Infrastructure (CNKI), ScienceDirect
21 that were sourced for information, abstracts, full-text articles and books written in English and
22 Chinese, including those traditional records tracing back to the *Qing Dynasty*. Pharmacopoeia of
23 China and other local herbal records in Uighur, Mongolian and Kazakhstan ethnomedicines were
24 investigated and compared for pertinent information.
25

26 **Results:** The phytochemistry of *S. involucrata* has been comprehensively investigated. More than
27 70 compounds have been isolated and identified; they include phenylpropanoids, flavonoids,
28 coumarins, lignans, sesquiterpenes, steroids, ceramides, polysaccharides. Scientific studies on the
29 biological activity of *S. involucrata* are equally numerous. The herb has been shown to have
30 anti-neoplastic, anti-inflammatory, analgesic, anti-oxidative, anti-fatigue, anti-aging, anti-hypoxic,
31 neuroprotective and immunomodulating effects. Many have shown correlations to the traditional
32 clinical applications in Traditional Chinese Medicine and medicines. The possible mechanisms of *S.*
33 *involucrata* in treating various cancers are revealed in the article, these include inhibition of cancer
34 cells by affecting their growth, adhesion, migration, aggregation and invasion, inhibition of
35 epidermal growth factor receptor signaling in cancer cells, hindrance of cancer cell proliferation,
36 causing cytotoxicity to cancer cells and promoting expression of tumor suppressor genes. Dosage
37 efficacy is found to be generally concentration- and time-dependent. However, studies on the
38 correlation between particular chemical constituents and specific bioactivities are limited.
39

40 **Conclusion:** In this review, we have documented the existing traditional uses of *Saussurea*
41 *involucrata* and summarized recent research into the phytochemistry and pharmacology of
42 *Saussurea involucrata*. Many of the traditional uses have been validated by phytochemical and
43 modern pharmacological studies but there are still some areas where the current knowledge could
44 be improved. Although studies have confirmed that *Saussurea involucrata* has a broad range of
45 bioactivities, further in-depth studies on the exact bioactive molecules and the mechanism of action
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4 are expected. Whether we should use this herb independently or in combination deserves to be
5 clarified. The exact quality control as well as the toxicology studies is necessary to guarantee the
6 stability and safety of the clinic use. The sustainable use of this endangered resource was also
7 addressed. In conclusion, this review was anticipated to highlight the importance of *Saussurea*
8 *involucrata* and provides some directions for the future development of this plant.
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13 **Keywords:**

14 *Saussurea involucrata*; Traditional Chinese Medicine; Uyghur local medicine; Phytochemistry;
15 Ethnopharmacology; Rheumatoid arthritis
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19 **Abbreviations:**

20 DSE, dark-septate endophytic; SEM, scanning electron microscope; RA, rheumatoid arthritis; NO,
21 nitric oxide; PGE₂, prostaglandin E₂; ROS, reactive oxygen species; DPPH, 2,
22 2-diphenyl-1-picrylhydrazyl; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); HIF-1,
23 hypoxia-inducible factor-1; ATP, adenosine triphosphate; LAC, laccase; LD, lactate dehydrogenase;
24 SOD, superoxide dismutase; MDA, malondialdehyde; GPx, glutathione peroxidase; PBMC,
25 peripheral blood mononuclear cell.
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4 **Contents**

5 ABSTRACT

- 6
7 1. Introduction
8
9 2. Ethnopharmacology
10
11 3. Botany
12 3.1 Nomenclature
13 3.2 Plant occurrence
14 3.3 Botanical description
15 3.4 Conservation
16
17 4. Quality control
18 4.1 Species authentication
19 4.2 Limits of indicator compounds
20
21 5. Phytochemistry
22 5.1 Phenylpropanoids
23 5.2 Flavonoids
24 5.3 Coumarins
25 5.4 Lignans
26 5.5 Sesquiterpenes
27 5.6 Steroids
28 5.7 Ceramides
29 5.8 Polysaccharides
30
31 6. Bioactivity
32 6.1 Anti-neoplastic
33 6.2 Anti-arthritis
34 6.3 Anti-oxidative and anti-aging
35 6.4 Anti-fatigue
36 6.5 Neuro-protective and anti-hypoxic
37 6.6 Immunomodulation
38 6.7 Other pharmacological activities
39
40 7. Toxicological studies
41
42 8. Modern clinical application
43 8.1 Anti-arthritis
44 8.2 Counteracting infertility
45 8.3 Other application
46
47 9. Conclusions and prospects

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1. Introduction

In central Asia, *Saussurea involucrata* Matsum. & Koidz (**Fig. 1.**) has long been used under the herbal names "Tianshan Snow Lotus", "Xinjiang Xuelian", "Xuelian Hua" and "Xuehe Hua" (Flora of China Committee, 1999). *S. involucrata* has been an important medicinal herb in various ethnomedical systems which are namely Traditional Chinese Medicine, Uyghur medicine, Mongolian medicine and Kazakhstan medicine, among which similarities in pattern of usage has been manifested. These include treatment of rheumatoid arthritis and regulation of menstrual cycle. It is recorded in Pharmacopoeia of Peoples' Republic of China since 2005 and earlier in local herbal records of the above mentioned ethnomedicines (Chinese Pharmacopoeia Commission, 2010; The National Institute for Food and Drug Control of China, 1984).



Fig. 1. Photos of *Saussurea involucrata* plant and its medicinal material.

According to the Guangdong Provincial Traditional Chinese Medicine Hospital, which is the top Traditional Chinese Medicine hospital in China, *S. involucrata* has a broad-spectrum of clinical applications, including anti-inflammatory and analgesic, anti-oxidative, anti-hypoxia, anti-fatigue, anti-aging and hormonal-related gynecological disorders, infertility as well as immunomodulation.

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4 These are closely correlated with those traditional uses. In recent years, the effectiveness in
5 anti-cancer therapy has further put *S. involucrata* under the spotlight.
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9 Along with its growing reputation, chemical constituents of *Saussurea involucrata* have been
10 extensively studied. Phenylpropanoids, flavonoids, coumarins, lignans, sesquiterpenes, steroids,
11 ceramides and polysaccharides as main compositions were isolated and identified. Among them,
12 rutin and chlorogenic acid have been proven with pharmacological efficacy and active compounds
13 in abundance of *S. involucrata* (Yi et al., 2009b) and they are the chemical markers for its quality
14 control in the current version of Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission,
15 2010).
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19 In this review, advances in ethnopharmacology in different ethnomedical systems,
20 phytochemistry, biological and pharmacological activities, toxicology and clinical application of *S.*
21 *involucrata* are revealed.
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24 25 26 27 28 29 30 31 32 **2. Ethnopharmacology** 33 34

35 The dried aerial parts of *Saussurea involucrata* have long been used as an herbal medicine in
36 different parts of China and Kazakhstan. The use of *Saussurea involucrata* in local medicines in
37 Central Asia has a long history (**Table 1**). However, the earliest scientific record can only be traced
38 back to the Qing Dynasty (from 1636 A.D. to 1912 A.D.). The earliest literature on *Saussurea*
39 *involucrata* was in Bencao Gangmu Shiyi, in English ‘Supplement to Compendium of Materia
40 Medica’ (Zhao, 1963), in which *Saussurea involucrata* can be used to nourish *Yin and Yang*, which
41 is considered the origin of life and materials to maintain balance in body in Traditional Chinese
42 Medicine theory, treat diseases related to internal coldness (**Fig. 2**). It can also promote fertility in
43 aged people and enhance recovery from measles (Xie, 1968; Zhao, 1963). Impotence in men can
44 also be improved by using the decoction of 6 g of Herba Saussureae Involucratae together with 3 g
45 of Radix Angelicae Sinensis and Fructus Lycii each (Committee for National Revolution of
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Xinjiang Uyghur Autonomous Region Health Bureau, 1976).

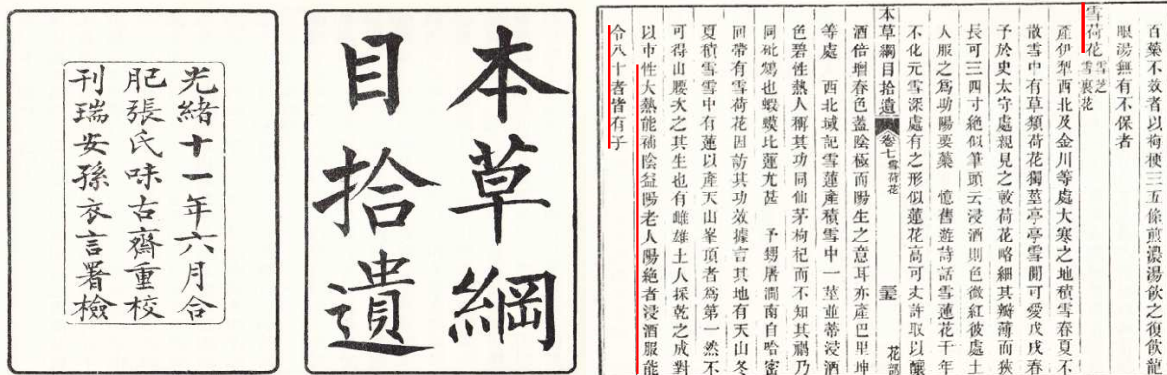


Fig. 2. The earliest literature on *Saussurea involucrata* (in Bencao Gangmu Shiyi book)

The extensive use of *Saussurea involucrata* has been demonstrated in different ethnomedical systems including Uyghur medicine, Mongolian medicine, Kazakhstan medicine and Traditional Chinese Medicine (Table 1). Amazingly, similarities in clinical applications among different local medicines were observed in treatment of gynecological disorders, reliving respiratory symptoms and pain-killing. It was worth to point out that unlike other herbs in Traditional Chinese Medicines, in traditional herbal records, *Saussurea involucrata* is usually used independently instead of in herbal formulas having prescription theories as “monarch, minister, assistant and guide” (Chinese Medicinal Materials Corporation, 1994).

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Table 1 The traditional uses of *Saussurea involucreata* in different ethnomedical systems.

	Traditional Chinese Medicine	Uyghur medicine	Mongolian medicine	Kazakhstan medicine	References	
Herbal name	"Tianshan Xuelian" (Chinese: 天山雪莲)	"Tage Leylishi" (Uyghur: 塔古来力斯)	"Banzhi Dawa" (Mongolian: 幫孜達娃)	"Huojia Quepu" (Kazakhstan: 霍加却僕)	(Chinese Pharmacopoeia Commission, 2010; Jia et al., 2005)	
Part(s) of herb used	Aerial parts	Whole part	Aerial parts	Not mentioned		
Dosage	3~6 g					
Indications on pregnancy	Prohibited	Prohibited	Not mentioned	Not mentioned		
Independent Use						
Drug Form	Clinical application	Traditional Chinese Medicine	Uyghur medicine	Mongolian medicine	Kazakhstan medicine	References
Decoction/ Tincture	Rheumatoid arthritis	√	√			(Chinese Pharmacopoeia Commission, 2010; Committee for National Revolution of Xinjiang Uyghur Autonomous Region Health Bureau, 1976; Jia et al., 2005; Liu and Shawuti, 1985; Commission of Chinese Materia Medica, 1999; Xie Z.W., 1975; National Institutes for Food and Drug Control, 1984)
	Menstrual pain	√	√	√		(Chinese Medicinal Materials Corporation, 1994; Chinese Pharmacopoeia Commission, 2010; Jia et al., 2005; Liu and Shawuti, 1985; Commission of Chinese Materia Medica, 1999; National Institutes for Food and Drug Control, 1984)
	Irregular menstruation cycle	√	√	√		(Chinese Medicinal Materials Corporation, 1994; Chinese Pharmacopoeia Commission, 2010; Jia et al., 2005; Liu and Shawuti, 1985; Commission of Chinese Materia Medica, 1999; Xie Z.W., 1975; National Institutes for Food and Drug Control, 1984)
	Infertility	√				(Chinese Pharmacopoeia Commission, 2010; Xie Z.W., 1975; Zhao, 1963)
	Labour-inducing agent			√		(Jia et al., 2005; Xie Z.W., 1975)
	Cough	√	√	√		(Jia et al., 2005; Commission of Chinese Materia Medica, 1999; Xie Z.W., 1975)

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	Other pain		✓	✓	✓	✓	(Jia et al., 2005; National Institutes for Food and Drug Control, 1984)
Decoction	Tuberculosis			✓			(Jia et al., 2005)
	Measles	✓	✓				(Chen, 1963; Commission of Chinese Materia Medica, 1999; Zhao, 1963)
	Strain			✓			(Jia et al., 2005)
Snow lotus injection (i.m.)	Rheumatoid arthritis; Inflammation	✓	✓				(Commission of Chinese Materia Medica, 2005)
Classic Formula							
Formula Name	Ingredients	Clinical application	Traditional Chinese Medicine	Uyghur medicine	Mongolian medicine	Kazakhstan medicine	References
Xuelian Tincture	Herba Saussureae Involucratae, Radix Angelicae Sinensis, Fructus Lycii	Menstrual pain, irregular menstruation cycle, infertility	✓	✓			(Committee for National Revolution of Xinjiang Uyghur Autonomous Region Health Bureau, 1976; Commission of Chinese Materia Medica, 1999)
Xuelian Honghua Tincture	Herba Saussureae Involucratae, Flos Carthami, Fructus Mori, Fructus Lycii	Immunodeficiency, poor blood circulation		✓			(Commission of Chinese Materia Medica, 2005)
Xuelian Lingzhi Tincture	Herba Saussureae Involucratae, Ganoderma	Infertility, immunodeficiency		✓		✓	(Commission of Chinese Materia Medica, 2005)

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Xuelian Patches (Protected formula)		Herba Saussureae Involucratae	Anti-neoplastic agent	✓	✓	✓	(Commission of Chinese Materia Medica, 2005)			
Other commonly used formula										
Formula Name	Ingredients	Clinical application	Traditional Chinese Medicine	Uyghur medicine	Mongolian medicine	Kazakhstan medicine	References			
Xuelian Tincture	Herba Saussureae Involucratae , Flos Carthami, Radix Gentianae Macrophyllae, Radix Angelicae Pubescentis, Fructus Lycii	Arthritis, pain	✓	✓			(Orally transmitted)			
Xuelian Fengshiling Mixture	Herba Saussureae Involucratae, Processed Radix Aconiti, Radix Angelicae Pubescentis	Rheumatoid arthritis, arthritis-related pain, inflammation	✓				(Orally transmitted)			
Xuelian Gutiqi Decoction	Herba Saussureae Involucratae, Radix Angelicae Sinensis, Radix Astragali	Forgetfulness, insomnia, dizziness, exhaustion	✓				(Orally transmitted)			
Xuelian Chongcao Mixture	Herba Saussureae Involucratae, Cordyceps	Polyuria, exhaustion	✓				(Orally transmitted)			

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5 **3. Botany**
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8 **3.1 Nomenclature**
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10 According to “The Plant List”, *Saussurea involucrata* Matsum. & Koidz is the
11 only accepted name for the herb, with a synonym “*Saussurea involucrata* (Kar. & Kir.)
12 Sch. Bip.” (The Plant List, 2013). However, being the more widely accepted name in
13 China, “*Saussurea involucrata* Kar. & Kir.” has been used as the official name instead
14 for the herb in Pharmacopoeia of Peoples’ Republic of China and Flora of China
15 (Chinese Pharmacopoeia Commission, 2010; Flora of China Editorial Committee,
16 1999).
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26 A recent review has indicated the importance of accurate scientific nomenclature
27 for plants so as to minimize ambiguity of species (Rivera et al., 2014) and therefore,
28 the confusion concerning *Saussurea involucrata* mentioned above is expected to be
29 resolved.
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35 **3.2 Plant occurrence**
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37 The habitats of *Saussurea involucrata* include mountain slopes, mountain valleys,
38 meadows and rock fissures at elevations of 2,400 - 4,100 m. Due to the incredibly
39 high altitudes at which it grows; *Saussurea involucrata* is named “Tianshan Snow
40 Lotus” which means the Snow Lotus that grows on sky-high mountains. The species
41 is mainly distributed in Xinjiang of China, but it also occurs in Kazakhstan,
42 Kyrgyzstan and Mongolia (Chen et al., 1999).
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50 Unfortunately, due to over-exploitation, the wild population of *Saussurea*
51 *involucrata* is dwindling rapidly (Kang et al., 2010). According to the People's Daily,
52 *Saussurea involucrata* has decreased from being found over 50,000,000 acres in the
53 1960’s and 1970’s to a few hundred acres at present. At this rate, in less than 10 years,
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4 this rare species could become extinct. It has thus been listed as a second grade
5 national protected wild plant in China (Fu and Jin, 1991).
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8 **3.3 Botanical description**

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10 *Saussurea involucrata* is a perennial herb 15-50 cm tall. It has an unbranched,
11 stout caudex which is densely covered with fibrous remains of petioles. Its stem is
12 solitary with its rosette and stem leaves petiolated. The leaf blades are narrowly ovate,
13 elliptic, or obovate, with both surfaces being green and glandular hairy. The
14 uppermost stem leaves are sessile, ovate to elliptic, being membranous with both
15 surfaces pale yellow; and stellately surround the synflorescence. The synflorescence is
16 hemispheric to broadly campanulate with 10-20 capitula. Its phyllaries are in 3 or 4
17 rows, dark or light brown with dark margins and sparsely pubescent. The achenes are
18 straw-colored with blackish spots, cylindrical, and each has a dirty-white pappus.
19 Plants flower from July to August and bear fruit from August to October (Flora of
20 China Editorial Committee, 1999).
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35 **3.4 Conservation**

36 *Saussurea involucrata* is a valuable medicinal herb and it has also been an
37 important source of a wide range of bioactive compounds; syringin, chlorogenic acid,
38 and 1, 5-dicaffeoylquinic acid are the chemicals most commonly extracted from it
39 (Chen et al., 2014b). Wild populations of *Saussurea involucrata* are dwindling rapidly.
40 To reduce the demand for the wild *Saussurea involucrata*, researches have been done
41 to increase yield of chemicals by modified cultivation method, developing tissue
42 culture systems for its rapid propagation and finding substitutes.
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53 According to a study, the increasing duration of growth in the cultivation of
54 *Saussurea involucrata* can increase the amount of some of its bioactive compounds (Y.
55 R. Chen et al., 2013). Besides, a dark-septate endophytic (DSE) fungus EF-37 isolated
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4 from the roots of *Saussurea involucrata* has also demonstrated a significant positive
5 effect on plant growth and its rutin content (Wu and Guo, 2008; Wu et al., 2010),
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7 though with withheld mechanism. Optimization in conditions of micropropagation
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9 systems for maximization of chemicals having desirable biocativities have been
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11 investigated, such as the reduction of atmospheric pressure which has resulted in
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13 variation of morphogenic potential and anti-oxidative enzymatic activities (Guo et al.,
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15 2011, 2007). According to one study, hairy root culture system of *Saussurea*
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17 *involucrata* through agrobacterium-mediated transformation was established and the
18
19 amount of syringin and hispidulin, two of the active components, was found to be
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21 even higher than in the wild species (Fu et al., 2006; Qiu et al., 2010). These suggest
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23 the feasibility of using tissue culture of *Saussurea involucrata* to replace its wild plant
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25 source.
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31 Closely-related plant species often share similar secondary metabolites and
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33 bioactivities (Cock et al., 2010). With reference to a recent review on the genus, the
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35 *Saussurea* shows resemblance in phytochemical constituents as well as bioactivities.
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37 Dehydrocostus lactone (Li and Jia, 1989; Madhavi et al., 2012), 3a,8a-dihydroxy-
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39 11bH-11,13-dihydrodehydrocostus lactone (Li and Jia, 1989), 35,36, 3a,8a-
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41 dihydroxy-11bH-11,13-dihydrodehydrocostus lactone 8-*O*- β -D-glucopyranoside (Fan
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43 et al., 2006; Li and Jia, 1989), 8a-hydroxy-11bH-11,13-dihydrodehydrocostus lactone
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45 (Fan et al., 2006; Li and Jia, 1989) are phytochemicals present in *Saussurea*
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47 *involucrata*, but are also found in other close species including *S. lappa*, or other
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49 easily confused species of *Saussurea involucrata* like *S. medusa* or *S. laniceps* (Wang
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51 et al., 2010). Besides, *S. ussuriensis*, *S. petrovii*, *S. costus* and *S. medusa* have similar
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53 pharmacological function in anti-rheumatic arthritis (Wang et al., 2010). These can
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55 serve as evidence for the possible substitution of herbal resources by their
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4 closely-related species. Cock has pointed out, which would provide insight into new
5 direction of research as in principal active compound identification, common
6 phytochemicals are good targets for bioactivity testing when one or more species
7 within a genus are known to possess similar therapeutic properties (Cock et al., 2010).
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10 11 12 13 14 **4. Quality control**

15 16 17 **4.1 Species authentication**

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19 Snow Lotus prepared by herbs of different species or different places of origin
20 contains different amount of chemical constituents and thus give rise to different
21 medical value. Therefore, quality control is crucial, for both drug efficacy and safety.
22 There are confusions in the species of herbs contributing to the Chinese Materia
23 Medica “Snow Lotus”. Three representative easily-confused species include
24 *Saussurea involucrata*, *Saussurea laniceps*. and *Saussurea medusa* (Chen et al.,
25 2014a). According to the Pharmacopoeia of China, *Saussurea involucrata* is the only
26 species being accepted (Chinese Pharmacopoeia Commission, 2010). Therefore,
27 traditional and contemporary authentication methods are required to ensure the use of
28 the official species. As demonstrated by a study, the confused species can be
29 differentiated using macroscopic identification of the crude drug, microscopic
30 identification of the powdered crude drug and a combination of microscopic
31 identification methods of its pollen grains including ordinary light microscopy,
32 polarized light microscopy and SEM (Chen et al., 2014a).
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50 51 **4.2 Limits of indicator compounds**

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53 In the view of its chemical content, chlorogenic acid (not less than 0.15% of
54 dried sample) and rutin (not less than 0.15% of dried sample), being the major
55 chemical constituents of *Saussurea involucrata*, are used as the indicator compound to
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4 characterize the quality of this herb (Chinese Pharmacopoeia Commission, 2010). The
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6 abundance of chemical constituents differs in herbs obtained from different origins. It
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8 is believed that the quality of Snow Lotus sourced from Tianshan of Xinjiang in China
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10 (Yi et al., 2009b) is the best of all.
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13 14 **5. Phytochemistry**

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17 More than 70 compounds have so far been isolated and identified from
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19 *Saussurea involucrata*. As aerial parts of *Saussurea involucrata* have been used as in
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21 Traditional Chinese Medicine, other folk medicine systems and remain the only
22
23 medicinal part till now, chemical constituent analysis mainly focused on its
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25 above-ground portion. HPLC-MS has been the most common analytical means for
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27 qualitative analysis of chemicals present in *Saussurea involucrata*; a diversity of
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29 compounds were identified including phenylpropanoids, flavonoids, coumarins,
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31 lignans, sesquiterpenes, steroids, ceramides and polysaccharides. In quantitative
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33 analysis of the chemicals, which is not as comprehensive as qualitative analysis,
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35 HPLC was mainly used. The contents of chlorogenic acid and rutin, which have been
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37 set for quality control for *Saussurea involucrata* in the Chinese Pharmacopoeia 2010
38
39 edition, ranged from 1.19 to 14.43 mg/g and 0.14 to 16.02 mg/g respectively. Total
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41 phenolic content was found to be ranging from 23.58 to 41.56 mg/g while the content
42
43 for total flavonoid is 9.08 and 15.84 mg/g. Other bioactive compounds were
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45 qualitatively determined as well, including syringin (0.20-0.58 mg/g), arctiin
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47 (0.05-1.62 mg/g), apigenin (0.005-0.015 mg/g) and hispidulin (0.05-0.16 mg/g) (R.
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49 Chen et al., 2013; Li and Zhong, 2013; Qiu et al., 2010; Xu et al., 2009; Yi et al.,
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51 2009b).
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5.1 Phenylpropanoids

Syringin (**1**), 3-caffeoylquinic acid (**2**), 5-caffeoylquinic acid (**3**), 4-caffeoylquinic acid (**4**), 1,3-dicaffeoylquinic acid (**5**), 1,4-dicaffeoylquinic acid (**6**), 1,5-dicaffeoylquinic acid (**7**), 4,5-dicaffeoylquinic acid (**8**), 1,5-dicaffeoyl-3-succinoylquinic acid (**9**), 1,5-dicaffeoyl-4-succinoylquinic acid (**10**), 1,5-dicaffeoyl-3,4-disuccinoylquinic acid (**11**) have been found in *Saussurea involucreta* (R. Chen et al., 2013; X. Chen et al., 2013; Qiu et al., 2010). One study also found tangshenoside III (**12**) (Chen et al., 2010).

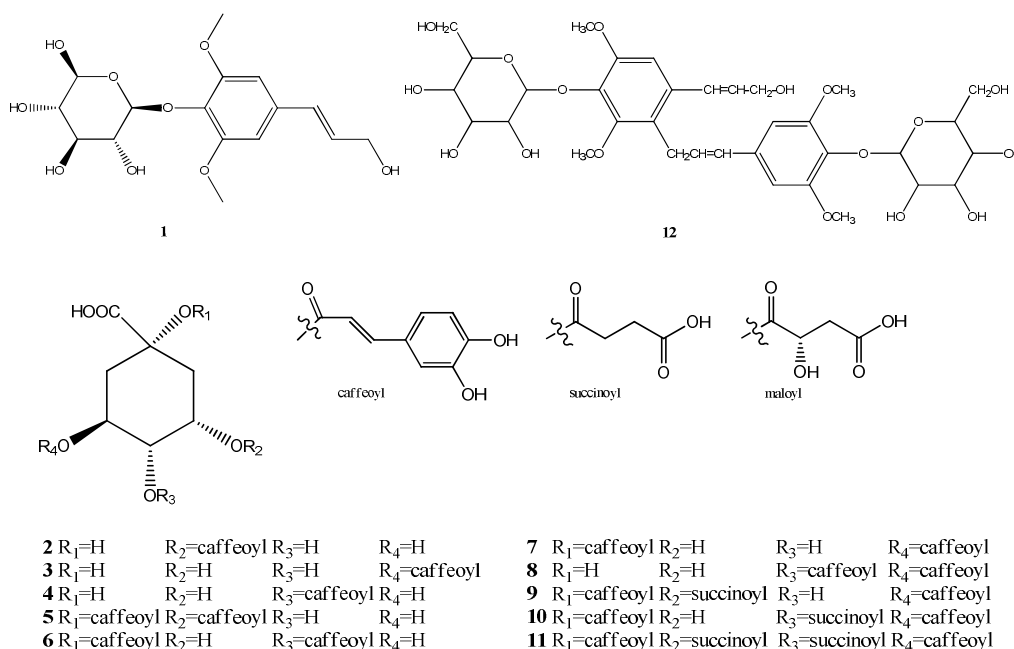


Fig. 3. Structures of phenylpropanoids in *Saussurea involucreta*.

5.2 Flavonoids

Many studies have reported finding a variety of flavonoids in *Saussurea involucreta*. These different flavonoids can be categorized into four sub-groups, namely flavone aglycones, flavone glycosides, flavonol aglycones and flavonol glycosides.

The flavone aglycones include hispidulin (**13**), jaceosidin (**14**), luteolin (**15**), nepetin (**16**), apigenin (**17**) and 5,6-dihydroxy-7,8-dimethoxyflavone (**18**). The flavone glycosides include apigenin 7-*O*-glycoside (**19**), hispidulin 7-*O*-glucoside (**20**), luteolin 7-*O*-glucoside (**21**), nepetin 7-*O*-glucoside (**22**), apigenin 7-*O*-glucuronide (**23**), chrysoeriol 7-*O*-glucuronide (**24**), chrysoeriol 7-*O*-glycoside (**25**) and chrysoeriol 7-*O*-rhamnoside (**26**) (Iwashina et al., 2010; Jing et al., 2013; Qiu et al., 2010).

Two flavonol aglycones have been found, quercetin (**27**) and kaempferol (**28**). The flavonol glycosides found include quercetin 3-*O*-rhamnoside (**29**), quercetin 3-*O*-rutinoside (rutin) (**30**), quercetin 3-*O*-glucoside (**31**), isorhamnetin 3-*O*-rutinoside (**32**) and kaempferol 7-*O*-glucopyranoside (**33**) (Iwashina et al., 2010).

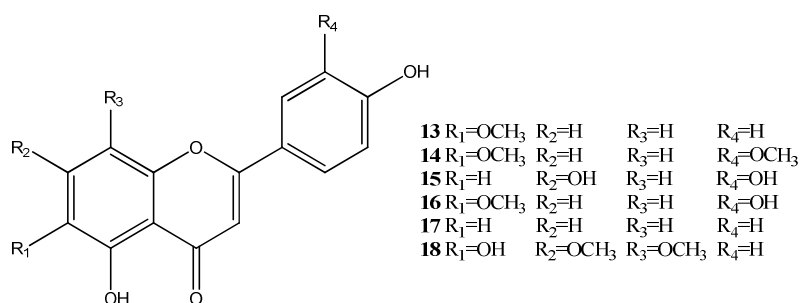


Fig. 4. Structures of flavone aglycones in *Saussurea involucrata*.

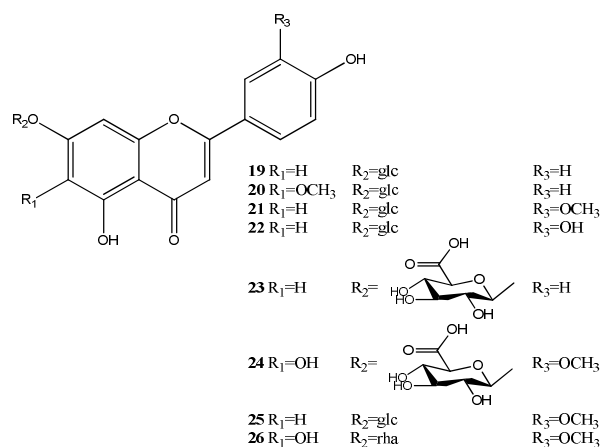
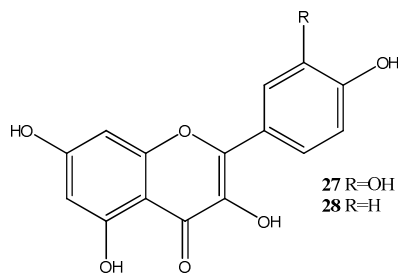
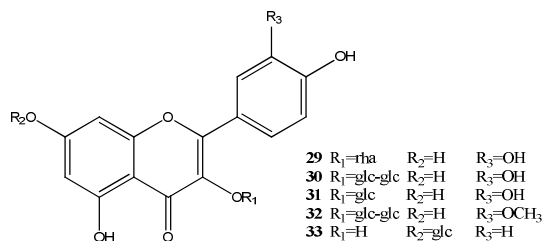


Fig. 5. Structures of flavone glycosides in *Saussurea involucrata*.



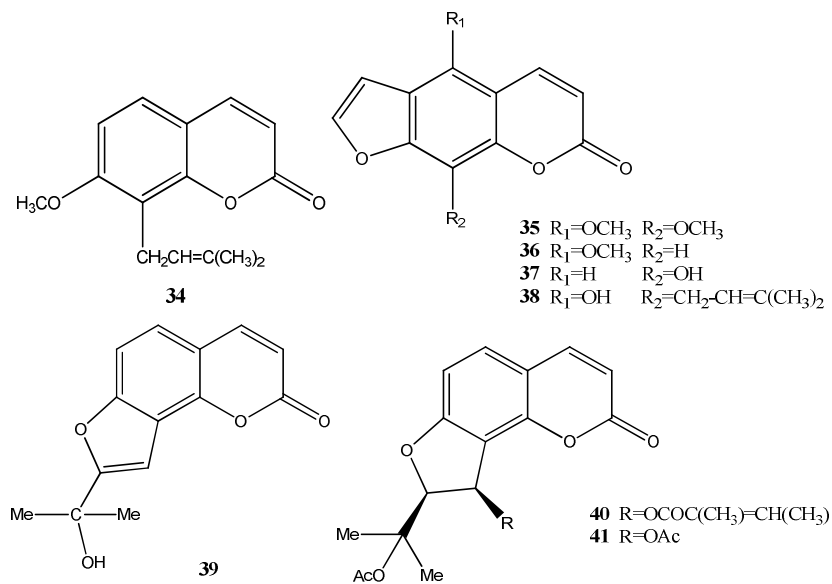
14 **Fig. 6.** Structures of flavonol aglycones in *Saussurea involucreata*.



25 **Fig. 7.** Structures of flavonol glycosides in *Saussurea involucreata*.

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30 **5.3 Coumarins**

31 Eight coumarins have been isolated from *Saussurea involucreata*. These include one
32 simple coumarin, osthol (**34**), and seven pyranocoumarins. The latter are
33 isopimpinellin (**35**), bergapten (**36**), xanthotoxol (**37**), alloisimperatorin (**38**),
34 oroselol (**39**), edultin (**40**) and vaginidiol diacetate (**41**) (Yang et al., 2006).
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Figure 8 Structures of coumarins in *Saussurea involucrata*.

5.4 Lignans

Several lignans including arctigenin-4-*O*-(6''-*O*-acetyl- β -d-glucoside) (**42**), arctigenin-4-*O*-(2''-*O*-acetyl- β -d-glucoside) (**43**), arctigenin-4-*O*-(3''-*O*-acetyl- β -D-glucoside) (**44**), arctiin (**45**) and arctigenin (**46**) have been identified (Li et al., 2012; Liu and Aisa, 2010).

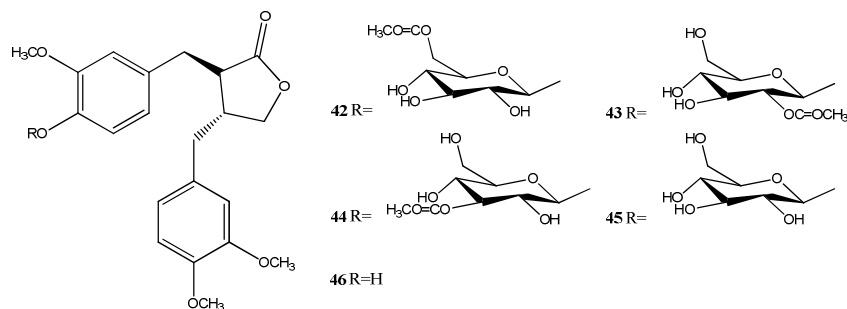
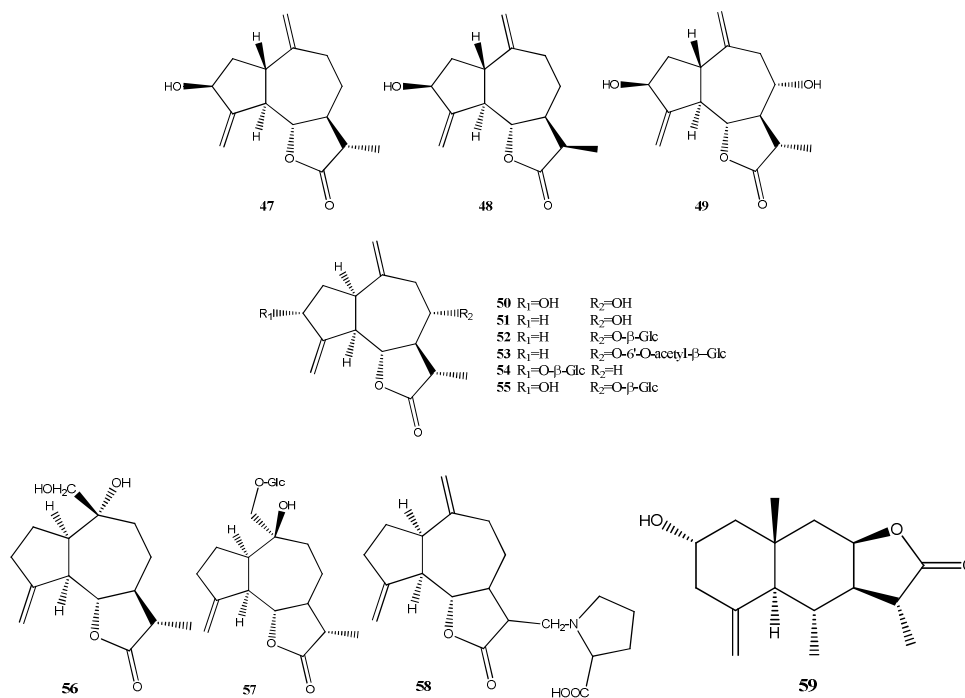


Fig. 9. Structures of lignans in *Saussurea involucrata*.

5.5 Sesquiterpenes

Sesquiterpenes are bitter substances. They often contain as a major structural feature an α,β -unsaturated- γ -lactone which, in recent studies, has been shown to be associated with anti-tumor, cytotoxic, anti-microbial and phytotoxic activities (Picman., 1983). Bioassay-directed separation of the ethyl acetate extract of the aerial parts of *Saussurea involucrata* has led to the isolation of sausinlactone A-(1S, 3S, 5S, 6S, 7S, 11S)-3-hydroxyl-11, 13-dihydrodehydrocostuslactone (**47**), sausinlactone B-(1S, 3S, 5S, 6S, 7S, 11R)-3-hydroxyl-11, 13-dihydrodehydrocostuslactone (**48**), sausinlactone C-(1S, 3S, 5S, 6S, 7S, 8S, 11S)-3-hydroxyl-11,13-dihydrodehydrocostuslactone (**49**), 3 α , 8 α -dihydroxyl-11 β H-11, 13- dihydrodehydrocostuslactone (**50**) 8 α -hydroxyl-

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4 11 β H-11,13-dihydrodehydrocostuslactone (**51**), 11 β ,13-dihydrodehydrocostuslactone-
5 8-*O*- β -D-glucoside (**52**), 11 β ,13-dihydrodehydrocostuslactone-8-*O*-[6'-*O*-acetyl- β -D-
6 glucoside] (**53**), 11 α ,13 -dihydroglucozaluzanin C (**54**) 3 α -hydroxyl-11 β ,13-
7 dihydrodehydrocostuslactone-8-*O*- β -D-glucoside (**55**) and japonicolactone (**56**) (Li et
8 al., 2007; Wang et al., 2007). 10 β ,14-Dihydroxy-11 β H-guai-4-(15)-ene-12,6 α -olide
9 14-*O*- β -D-glucoside (**57**) and involucratin (**58**), and 11 β H-2 α -hydroxy-eudesman-
10 4(15)-en-12,8 β -olide, which is a eudesmanolide (**59**), were also isolated (Chen et al.,
11 2010).



46 **Fig. 10.** Structures of sesquiterpenes in *Saussurea involucrata*.

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51 **5.6 Steroids**

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53 Seven steroids have been isolated from *Saussurea involucrata*. These are: bufotalin
54 (**60**), telocinobufagin (**61**), gamabufotalin (**62**), daucosterol (**63**), β -sitosterol (**64**),
55 3-*O*-(6'-*O*-palmitoyl- β -D-glucosyl)- β -sitosterol (**65**) and 3-*O*-(6'-*O*-linoleoyl- β -D-
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4 glucosyl)- β -sitosterol (**66**) (Chen et al., 2010; Wu et al., 2009).
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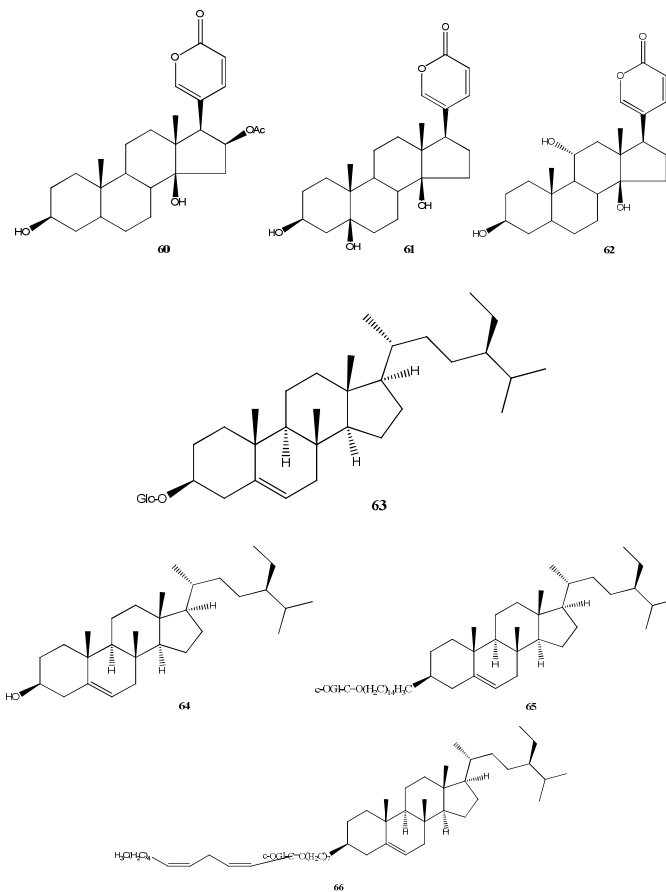
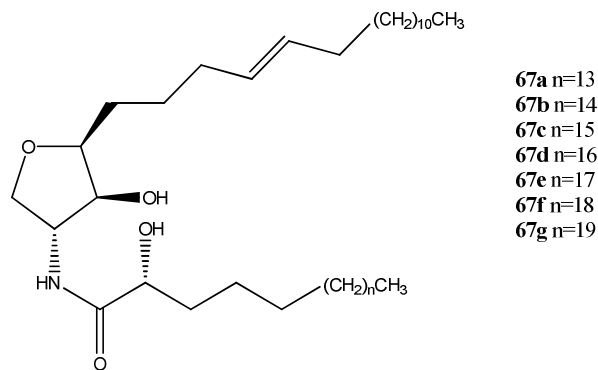


Fig. 11. Structures of steroids in *Saussurea involucrata*.

5.7 Ceramides

Rel-(3R,4S,5S)-3-[(2R)-2-hydroxynonadecanoyl~pentacosanoylamino]-4-hydroxy-5-[(4E)-heptadecane-4-ene]-2, 3, 4, 5-tetrahydrofuran (**67a-67g**) were the identified ceramides from *Saussurea involucrata* (Wu et al., 2009).



18 **Fig. 12.** Structures of ceramides in *Saussurea involucrata*.

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22 **5.8 Polysaccharides**

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Total polysaccharides with high purities have been separated from *Saussurea involucrata* through adsorption using macroporous resin and precipitation using ethanol (Wang et al., 2012). Polysaccharides from cultivated *Saussurea involucrata* (CSIP) were purified; two major fractions (CSIP1-2 and CSIP2-3) were investigated for their molecular weights, monosaccharide compositions and *in vitro* antioxidant activities. According to the results, the molecular weights of CSIP1-2 and CSIP2-3 were approximately 163.5 kDa and 88.6 kDa, respectively. CSIP1-2 was composed of glucose, galactose, xylose, rhamnose, arabinose and galacturonic acid with a molar ratio of 1.65: 0.39: 0.06: 8.33: 1.76: 40.43. CSIP2-3 was composed of glucose, galactose, xylose, rhamnose, arabinose and galacturonic acid with a molar ratio of 0.76: 0.66: 0.11: 5.59: 0.32: 44.66 (Yao et al., 2012).

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6. Bioactivity

Saussurea involucrata is traditionally used to treat a wide spectrum of disorders; its efficacy is grounded by long history of usage and promising experimental results. Traditional clinical applications were considered guide for bioactivity evaluations, and

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4 many correlations were found between the pharmacological action in traditional
5 records of the herb and bioactivities confirmed in modern studies (**Table 2**).
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8 Researches have revealed more bioactivities and its therapeutic spectrum of *Saussurea*
9 *involucrata* is still broadening, with scientific evidence.
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11 12 13 **6.1 Anti-neoplastic**

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15 It has been an emerging clinical application for *Saussurea involucrata* to be used
16 as an anti-neoplastic agent in the recent decade. *Saussurea involucrata* has gained
17 widespread global praise owing to its effectiveness in anti-cancer therapy.
18 Experiments have verified the anti-cancer bioactivity of *Saussurea involucrata*
19 through different mechanism of action, including its interference on the cell growth
20 process (Byambaragchaa et al., 2013), mainly by causing cell apoptosis (Chen et al.,
21 2012; Way et al., 2010) and cytotoxicity (Wu et al., 2009; Xiao et al., 2011b; X.
22 Zhang et al., 2011); affecting cell adhesion, migration and aggregation; while in gene
23 level, it also has certain impact on transcription activity (Byambaragchaa et al., 2013).
24 Human cancer cell lines were mainly targets in the anti-cancer bioactivities
25 assessments and different assays were used to monitor the level of certain protein
26 expression in the tumor cells (Byambaragchaa et al., 2013; Chen et al., 2012; Way et
27 al., 2010; Wu et al., 2009; X. Zhang et al., 2011) while *in vivo* experiments involved
28 the xenograft model (Chen et al., 2012; Way et al., 2010). The principal active
29 compound has not yet been confirmed so far but experiments have suggested high
30 possibility for it to be lying within the ethanol extract (75-95%) or the ethyl acetate
31 fraction. The effective dose ranged from microgram level *in vitro* to milligram level
32 *in vivo*; dose- and time-dependent manner has been demonstrated in some studies
33 (Byambaragchaa et al., 2013; Chen et al., 2012; Way et al., 2010; Wu et al., 2009; X.
34 Zhang et al., 2011).
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6.2 Anti-arthritic

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disorder of withheld etiology for which there is no cure. (Doan and Massarotti, 2005) It is characterized by synovial inflammation and destruction of cartilage and bone (Klareskog et al., 2014). Currently, the aim of treatment is to mitigate the symptoms and prevent disability (Doan and Massarotti, 2005). *Saussurea involucrata*, which is used for the treatment of rheumatoid arthritis in folk medicines, has demonstrable anti-inflammatory and analgesic effects (Zhai et al., 2010).

The anti-inflammatory activity of *Saussurea involucrata* extract has been observed in mice and rats, with xylene or carrageenan-induced paw edema and ear edema (Jia et al., 2011; Wang et al., 2011; Yi et al., 2010; Zhai et al., 2010). Acetic acid-induced excessive abdominal capillary permeability (Jia et al., 2011; Zhai et al., 2010), primary and secondary adjuvant arthritis were the other models used in anti-inflammatory evaluation (Tao et al., 2007; Wang et al., 2011). RAW 264.7 macrophage were monitored for examination of the inhibitory effect of *Saussurea involucrata* in nitric oxide (NO) and prostaglandin E₂ (PGE₂) production in LPS-activated macrophage (Xiao et al., 2011a). NO is considered as a pro-inflammatory mediator that induces inflammation due to over production in abnormal situations (Sharma et al., 2007). PGE₂ is one of the most abundant PGs produced in the body. During inflammation, PGE₂ is of particular interest because it is involved in all processes leading to the classic signs of inflammation: redness, swelling and pain (Ricciotti and FitzGerald, 2011; Funk, 2001). Therefore, their relative abundance in the animal models can act as indicators for the degree of inflammation.

Investigations on the analgesic effects included acetic acid-induced writhing (Jia et

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4 al., 2011; Wang et al., 2011; Zhai et al., 2010), hot-plate test (Zhai et al., 2010) in
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6 mice. Central analgesic effect was also demonstrated by (Almeida and Navarro,
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8 2001).
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11 Ethanol extracts of *Saussurea involucrata* were given to mice and rats via
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13 intragastric route (*i.g.*) with dose ranging from 15-400 mg/kg and not more than 42
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15 mg/kg in rats depending on the area of edema for no longer than 7 days (Jia et al.,
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17 2011; Wang et al., 2011; Yi et al., 2010); while a much lower dose of 0.36 mg/kg was
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19 given to mice by injection form (Tao et al., 2007). According to the report in the rat
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21 paw edema model (Yi et al., 2010), the peak inhibitory effects of *Saussurea*
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23 *involucrata* (42.2%) were recorded with a dose of 400 mg/kg at 3h post-carrageenan
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25 injection; while oral administration of *Saussurea involucrata* extract (400 mg/kg)
26
27 resulted in a significant 33.3% inhibition of ear edema in mice. Flavonoids, found to
28
29 be present in plasma after administration of the extracts, are believed to be the basis of
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31 the observed pharmacological effects (Yi et al., 2010).
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36 In addition, the tissue culture of *Saussurea involucrata* was found to exhibit
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38 anti-inflammatory and analgesic activities, suggesting that cultured tissue of
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40 *Saussurea involucrata* could substitute for wild-grown plant material in the
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42 pharmaceutical industry (Jia et al., 2011).
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45 However, the resemblance of animal models of arthritis to the patients developing
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47 symptoms and therefore the predictive power of these researches is in doubt. Animal
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49 models of arthritis are widely used to de-convolute disease pathways and to identify
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51 novel drug targets and therapeutic approaches. However, the high attrition rates of
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53 drugs in phase II/III rates means that a relatively small number of drugs reach the
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55 market, despite showing efficacy in pre-clinical models (McNamee et al., 2015).
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57 Other assays for better prediction of efficacy of herbs in treating arthritis are
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4 anticipated (McNamee et al., 2015).
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6 **6.3 Anti-oxidative and anti-aging**

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9 According to the free radical theory of aging, aging results from the accumulation
10 of deleterious effects caused by free radicals, and the ability of an organism to cope
11 with cellular damage induced by reactive oxygen species (ROS) plays an important
12 role in determining organismal lifespan (Harman, 1956). Experimentally, increased
13 ROS production is frequently detected in aged tissues (Maynard et al., 2009; Sawada
14 et al., 1992; Sohal and Sohal, 1991) and many studies have found that increased
15 oxidative damage in cells is associated with aging (Chakravarti and Chakravarti, 2007;
16 Fraga et al., 1990; Hamilton et al., 2001; Oliver et al., 1987).
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27 With reference to traditional records (Zhao, 1963), *Saussurea involucrata* has been
28 used to postpone aging by invigorating *Yin* and *Yang* in body, which in some sense
29 means promoting the activity of different organs in body. Multiple phytochemicals
30 from *S. involucrata* were found to possess anti-oxidative pharmacological function.
31 Polysaccharides of *Saussurea involucrata* have demonstrated anti-oxidative effect by
32 scavenging superoxide anions in nitroblue tetraazolium colorimetric method, DPPH,
33 hydroxyl and ABTS radical scavenging assay and by inhibiting the formation of
34 thiobarbituric acid reactant in mouse liver homogenate (Yao et al., 2012; Zheng et al.,
35 1993). Research has also revealed a positive correlation between antioxidant activity
36 and the amount of phenolic and flavonoid compounds in *Saussurea involucrata*
37 extracts, suggesting they could be the active constituents accounting for the
38 antioxidant activity (Qiu et al., 2010; Wang et al., 2012). Further *in vitro* bioactive
39 investigations have demonstrated that 3,
40 5-dicaffeoyl-1-*O*-(2-*O*-caffeoyl-4-maloyl)-quinic acid has significant anti-oxidative
41 effect in DPPH and ABTS radical scavenging assays (Zou et al., 2014).
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4 The oxidation-inhibitory effects were found to be in a concentration-dependent
5 manner by comparison with the effects of the same doses of vitamin C that the
6 scavenging effect of *Saussurea involucrata* on free radicals increased with quantity
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11 (Lee et al., 2011).
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13 **6.4 Anti-fatigue**

15 Physiological fatigue, an incapacitating or disabling illness, means a reduction in
16 the force output and energy generating capacity of a body after chronic exposure to
17 work or usual activities at the same intensity (Shevchuk, 2007). Studies focused on
18 the character of reactive oxygen species in confirmation of anti-fatigue bioactivity.
19 Extensive evidence has accumulated demonstrating the beneficial effects of
20 antioxidants in chronic fatigue. *Saussurea involucrata*'s effectiveness in coping with
21 the ROS has been discussed in section 6.3. Besides, the ability of *Saussurea*
22 *involucrata* to reduce fatigue has also been tested in experiments with mice.
23 Decreased oxygen consumption and prolonged swimming time were observed after
24 administration of polysaccharides of *Saussurea involucrata*. This provides clear
25 evidence of its anti-fatigue effect and supports the traditional belief that the Snow
26 Lotus herb can strengthen and invigorate the body (Zheng et al., 1993).
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43 **6.5 Neuro-protective and anti-hypoxic**

44 Petroleum ether extract, ethyl acetate extract and ethanol extract of *Saussurea*
45 *involucrata* were found to possess neuro-protective effect and can reverse damage of
46 brain cells under hypoxia state (Ma et al., 2014a, 2014b; Yang et al., 2011).
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51 In hypoxic state, hypoxia-inducible factor-1 (HIF-1), which is a transcription
52 factor and also a heterodimer composed of HIF-1 α and HIF-1 β protein subunits. It is
53 essential for the activation of hypoxia-inducible genes like erythropoietin, some
54 glucose transporters, the glycolytic enzymes, and vascular endothelial growth factor.
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4 As HIF-1 activation may promote cell survival in hypoxic tissues, studies focused on
5 the effect of hypoxic preconditioning on HIF-1 expression in hypoxia models of mice
6 or rats (Bergeron et al., 2000; Ma et al., 2014b; Yang et al., 2011) by Western Blot
7 assay (Ma et al., 2014b). Metabolism parameters, including ATP, ATPase, LAC, LDH,
8 LD (Ma et al., 2011; Yang et al., 2011) and levels of oxidative stress indicators like
9 SOD and MDA levels (Ma et al., 2014a; Yang et al., 2011) in pretreated hypoxic mice
10 models were also determined in some studies. Besides, in other experiments,
11 prolonged survival time of mice in conditions of acute anoxia and drop in mortality
12 under acute decompression conditions were shown (Ma et al., 2011; Yang et al., 2011).
13 Extracts had to be administered via intraperitoneal injection route (Ma et al., 2014a,
14 2014b) in order to be blood-brain-barrier crossing.

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29 The neuroprotective activity of *Saussurea involucrata* has been demonstrated by
30 the ability of its ethyl acetate fraction to inhibit MDA expression level, increase GPx
31 activity, and decrease the expressions of COX-2, PARP and caspase-3, via
32 downregulation of NF-kappaB. This biochemical cascade ultimately protects neural
33 tissue (Y. L. Chen et al., 2013).

34 35 36 37 38 39 40 **6.6 Immunomodulation**

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42 Both whole extracts (Jia and Wu, 2007) and specific components of *Saussurea*
43 *involutrata* including flavones (Fan et al., 1996; Ma et al., 1998), XL-12 fraction of
44 extraction (Wang et al., 2011) have been shown to have modulatory effects on
45 immunity. Non-specific defense mechanisms and delayed hypersensitivity in mice has
46 been inhibited by *Saussurea involucrata*, but humoral immunity activity has been
47 stimulated upon administration of higher doses of *Saussurea involucrata* (Jia and Wu,
48 2007). Another experiment also reveals that *Saussurea involucrata* extract has an
49 anti-allergic effect (Wang et al., 2011).

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Enhanced activity of mononuclear phagocytic system was reflected by increased colloidal carbon clearance index rate demonstrated in an *in vivo* mice study (150 mg/kg; once a day; intragastrically administered for a consecutive 7 days) (Fuller, 1992; Jia and Wu, 2007). *Saussurea involucrata* has also induced cytotoxicity of PBMC against K562 myelocytic leukemia cells and Raji Burkitt lymphoma cells and enhanced suboptimal concentration of rhIL-2-induced cytotoxicity but exhibited no effect on the large dose rhIL-2-induced cytotoxicity (Ma et al., 1998). Besides, significant enhancement of murine immunological function was observed, as reflected in increased percentage of lymphocyte transformation induced by PHA, the titer of serum hemagglutinin antibody against SRBC and hemolysin antibody (Fan et al., 1996). Apart from that, proliferation of T lymphocytes was promoted while B lymphocyte proliferation was hindered by *Saussurea involucrata* injection of the same concentration (Tao et al., 2007) and this serves as a ultimate proof of *Saussurea involucrata*'s performance in two way adjustment function.

These research finding is consistent with Traditional Chinese Medicine usage as *Saussurea involucrata* has been described possessing invigorating power of both *Yin and Yang*, which include a meaning of maintaining balance in body.

6.7 Other pharmacological activities

It has been listed in Supplement to Compendium of Materia Medica (Zhao, 1963) since *Qing Dynasty*, which is a few hundred years ago, that *Saussurea involucrata* can be used to treat infertility due to aging (Zhao, 1963). Besides, *Saussurea involucrata* has been listed in modern Pharmacopoeia of China and local Pharmacopoeia regarding its menstrual cycle regulation effect (Chinese Pharmacopoeia Commission, 2010; Liu and Shawuti, 1985). Researches have consistently demonstrated its effect in prevention of premature ovarian failure of mice, which has correlations to estrogen

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regulation, caused by continuous light upon intra-gastric administration of 0.5 mL extract of *Saussurea involucrata* together with 0.9% of NaCl (Zhang et al., 2013).

Other bioactivities of *Saussurea involucrata* include anti-microbial and anti-fungal (Lv et al., 2010), anti-hypertensive (Yu and Chen, 2009), and anti-radiation (Gao et al., 2003; Jia et al., 2005). It appears that its water-soluble constituents, flavonoids and polysaccharides are responsible for these effects. (Chinese Pharmacopoeia Commission, 2010) Furthermore, *Saussurea involucrata* also has the ability to increase replication of bone mesenchymal stem cells (A. G. Zhang et al., 2011)

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Table 2 Bioactivities of *Saussurea involucrata* as demonstrated in experiments.

Activity	Experimental protocol	Target animal(s)/ cell(s)	Result (+/-)	Dose	Chemical(s) /extract(s)	Reference(s)
Anti-neoplastic						
Cell growth	CCK-8 cell proliferation assay kit	SK-Hp1 human HCC cell line	+	200-400 µg/mL	95% ethanol extract	(Byambaragchaa et al., 2013)
> Cell cycle arrest	P21 and p27, cyclin D1, CDK4 biomarker	Human PC-3 cells	+	12.5-200 µg/mL	Ethyl acetate fraction of SI (incl. hispidulin, rutin)	(Chen et al., 2012; Way et al., 2010)
> Apoptosis	Bax expression, cytochrome C release, caspase-3 and caspase -9 activation, Bel-2 expression	Human PC-3 cells	+	12.5-200 µg/mL	Ethyl acetate fraction of SI (incl. hispidulin, rutin)	(Chen et al., 2012; Way et al., 2010)
-	EGFR overexpression, Akt, STAT3	PC-3 xenograft model	+	dose-dependent; 10 and 30 mg/kg; i.g.; 3 times/week	Ethyl acetate fraction of SI (incl. hispidulin, rutin)	(Chen et al., 2012; Way et al., 2010)
> Cytotoxicity	Cytotoxicity MTT assay	GepG2, MCF-7 cell lines	+	IC ₅₀ 0.05-0.5 µM	Bufotalin, telocinobufagin, gamabufotalin	(X. Zhang et al., 2011)
		HL-60, A375-S2, HeLa cell lines	+	-	Ceramides (75% ethanol extract)	(Wu et al., 2009)
		A549 cells	+	IC ₅₀ 0.01 µM (A) IC ₅₀ 2.89 µM (B)	Susquiterpene lactones sausinlactones A, B	(Xiao et al., 2011b)
Cell adhesion	Cell adhesion assay	SK-Hp1 human HCC cell line	+	200-400 µg/mL	95% Ethanol extract	(Byambaragchaa et al., 2013)
Cell migration	Wound closure assay	SK-Hp1 human HCC cell line	+	200 µg/mL	95% Ethanol extract	(Byambaragchaa et al., 2013)
Cell aggregation	Cell aggregation assay	SK-Hp1 human HCC cell line	+	400 µg/mL	95% Ethanol extract	(Byambaragchaa et al., 2013)

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							2013)	
Gene transcriptional level and activity	mRNA analysis, reverse transcription-PCR, quantitative real time assays	SK-Hp1 human HCC cell line	+	dose-dependent	95% Ethanol extract		(Byambaraghaa et al., 2013)	
Anti-arthritis related disorders								
Anti-inflammatory	Xylene induced-ear edema	Mice	+	-	30-50% Ethanol extract		(Zhai et al., 2010)	
		Mice	+	15-60 mg/kg	XL-12		(Wang et al., 2011)	
		Mice	+	-	95% Ethanol extract		(Jia et al., 2011)	
	Xylene-induced paw edema	Mice	+	400 mg/kg; i.g.	50% Ethanol extract		(Yi et al., 2010)	
		Rats	+	400 mg/kg; i.g.	50% Ethanol extract		(Yi et al., 2010)	
	Carrageenan-induced paw edema	Rats	+	75-300 mg/kg; i.g.; 7 d	95% Ethanol extract		(Jia et al., 2011)	
		Mice	+	-	30-50% Ethanol extract		(Zhai et al., 2010)	
	Acetic acid-induced excessive abdominal capillary permeability	Mice	+	75-300 mg/kg; i.g.; 7 d	95% Ethanol extract		(Jia et al., 2011)	
		Mice	+	0.36 mg/kg; inj.	-		(Tao et al., 2007)	
	Adjuvant arthritis induced by injection of Freund's complete adjuvant (primary)	Rats	+	10.5-42 mg/kg	XL-12		(Wang et al., 2011)	
		Rats	+	10.5-42 mg/kg	XL-12		(Wang et al., 2011)	
	Adjuvant arthritis induced by injection of Freund's complete adjuvant (secondary)	RAW 264.7 macrophage proliferation, NO production		+	25-200 µmol/L	95% Ethanol extract		(Xiao et al., 2011a)
		Acetic acid induced-writhing test	Mice	+	-	30-50% Ethanol extract		(Zhai et al., 2010)
	Analgesic		Mice	+	75-300 mg/kg; i.g.;	95% Ethanol extract		(Jia et al., 2011)

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	Mice				7 d				(Wang et al., 2011)
Hot plate test	Mice	+			15-60 mg/kg		XL-12		(Zhai et al., 2010)
Central analgesic	Mice	+			20 mg/kg		NA		(Almeida and Navarro, 2001)

Immunomodulation [+ Stimulatory; - Inhibitory]

Carbon clearance rate(Non-specific immunity)	Mice	-			150 mg/kg; i.g.; 7 d		Ethanol extract		(Jia and Wu, 2007)
Serum hemolysis formation	Mice	+			300 mg/kg; i.g.; 7 d		Ethanol extract		(Jia and Wu, 2007)
Peripheral blood mononuclear cells (PBMC) specific cytotoxicity to Human K562, Raji cell lines	PBMC	+			0.6 µg/mL		Total flavone		(Ma et al., 1998)
PHA induced-lymphocyte transformation percentage	Mice	+			40-80 µg/kg		Total flavone		(Fan et al., 1996)
Serum hemagglutination antibody against SRBC	Mice	+			40-80 µg/kg		Total flavone		(Fan et al., 1996)
Hemolytic antibody	Mice	+			40-80 µg/kg		Total flavone		(Fan et al., 1996)
DNCB induced-delated hypersensitivity (non-specific immunity)	Mice	-			300 mg/kg; i.g.; 7d		Ethanol extract		(Jia and Wu, 2007)
T cell and B lymphocyte proliferation	Rats	-			0.13-0.14 mg/mL		XL-12		(Wang et al., 2011)

Neuro-protective and anti-hypoxic

Metabolism parameters (ATP, ATPase, LAC, LDH)	Mice	+			51 mg/kg		Petroleum ether extract		(Ma et al., 2011)
Metabolism parameters (LD, LDH, ATP, ATPase)	Normobaric, decompression, and chemistry poisoning	+			250-500 mg/kg		Ethanol extract		(Yang et al., 2011)

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	hypoxia in mice						
	Brain tissues of hypoxia in rats	+		125-500 mg/kg; i.p.	Petroleum ether extract	(H. P. Ma et al., 2014a)	
	Normobaric, decompression, and chemistry poisoning hypoxia in mice	+		250-500 mg/kg	Ethanol extract	(Yang et al., 2011)	
	Brain tissues of hypoxia rats (hypoxia)	+		125-500 mg/kg; i.p.	Petroleum ether extract	(H. P. Ma et al., 2014a)	
	D-galactose induced-brain injury in mice	+		30 mg/kg/d; 6 weeks	Ethyl acetate extract; rutin	(Y. L. Chen et al., 2013; Yang et al., 2012)	
	Mice	+		52 mg/kg	Petroleum ether extract	(Ma et al., 2011)	
	Normobaric, decompression, and chemistry poisoning hypoxia in mice	+		250-500 mg/kg	Ethanol extract	(Yang et al., 2011)	
	Mice	+		50 mg/kg	Petroleum ether extract	(Ma et al., 2011)	
	Brain tissues of hypoxia in rats	+		125-500 mg/kg; i.p.	Petroleum ether extract	(H. P. Ma et al., 2014b)	
	Brain tissues of hypoxia in rats	+		125-500 mg/kg; i.p.	Petroleum ether extract	(H. P. Ma et al., 2014b)	

Anti-oxidative and anti-aging

	Superoxide radical assay	+		-	Polysaccharides	(Yao et al., 2012)	
		+		-	Apigenin	(Fan and Yue, 2003; Li	

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						et al., 2006; Matkowski, 2008)
	-			+	10 ⁻⁶ M	Quercetin, rutin, morin (Chen et al., 1990)
DPPH radical scavenging assay	-			+	-	Polysaccharides (Yao et al., 2012)
	-			+	16 mg/mL	Methanol extract (Wang et al., 2012)
	-			+	0.74- 1.05 mmol/L	Phenolic acids (Zou et al., 2014)
Hydroxyl radical scavenging assay	-			+	-	Polysaccharides (Yao et al., 2012)
ABTS radical scavenging assay	-			+	0.94 mg/mL	Methanol extract (Wang et al., 2012)
	-			+	54.75 μ mol/g	PCA, CGA, rutin, cynarine, hispidulin (Qiu et al., 2010); (Qiu et al., 2013)
	-			+	0.55 - 0.99 mmol/L	Phenolic acids (Zou et al., 2014)
Ferric reducing/antioxidant power (FRAP) assay	-			+	82.62 μ mol/g	PCA, CGA, rutin, cynarine, hispidulin (Qiu et al., 2010) (Qiu et al., 2013)
Anti-aging Lipid peroxidation	D-galactose induced-brain injury in mice			+	30 mg/kg/d; 6 weeks	Ethyl acetate extract; rutin (Yang et al., 2012)
Anti-fatigue						
Reduction in serum urea nitrogen	Mice			+	1 g/kg; p.o.; 15 d	95% Ethanol extract (Jia and Wu, 2008)
Oxygen consumption and swimming time	Mice			+	-	Polysaccharides (Zheng et al., 1993)
	Mice			+	1 g/kg; p.o.; 15 d	95% Ethanol extract (Jia and Wu, 2008)

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5 **7. Toxicological studies**
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8 The use of *Saussurea involucrata* in pregnant women is prohibited in the
9 Pharmacopoeia of China (Chinese Pharmacopoeia Commission, 2010). Similarly, it is
10 proven to be abortion inducing in rats in early, mid-trimester and late pregnancy with
11 different abortion rate. The highest rate has found to be as high as 100% in
12 mid-trimester and late pregnancy for 0.3 mL administered intravenously once per day
13 for consecutive two days. Early pregnancy is also sensitive to *Saussurea involucrata*
14 injection. Apart from having toxicity to fetus, it is also accused for causing arrhythmia,
15 hypotension, paralysis, nausea and other nervous and cardiovascular disorders as its
16 adverse effects in overdose condition (Commission of Chinese Materia Medica,
17 1999).
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21 However, contradictorily, *Saussurea involucrata* injection has been proven to be
22 safe, with no evidence of any distinct toxicity or side effects in some researches. In
23 one long-term toxicology test, rats were injected with *Saussurea involucrata* for 45
24 days; blood routine examination and pathologic histology examination showed no
25 damaging effects (Sun et al., 2005). Another experimental study of the toxicity of
26 long-term *Saussurea involucrata* injection was carried out. In this study, rats were
27 given intraperitoneal injection for 90 days and were observed for 14 days
28 subsequently. No abnormal changes of appearance or organ function, as indicated by
29 blood and liver and kidney function evaluation, and pathological examination of 13
30 kinds of visceral tissue, were discovered. These studies, as well as the centuries of
31 traditional use, confirm the safety of *Saussurea involucrata* in clinical use (Lian et al.,
32 1996). Therefore, more qualified toxicological studies are expected for prediction of
33 the therapeutic index so as to ensure safe use *Saussurea involucrata*.
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8. Modern clinical application

8.1 Anti-arthritic

The uses of *Saussurea involucrata* are extensive (Xiao et al., 2011a); however, in modern actual practice, it is seldom used independently, but typically in association with other herbs nowadays.

Xuelian injection, which is the only pharmaceutical product that involved only extract of *Saussurea involucrata*, is officially used in hospitals in China for treatment of rheumatoid arthritis. Clinical trials were performed in order to evaluate its efficacy since 2006. One study involved 48 individuals who had developed rheumatoid arthritis with similar stage and 12 of them were randomly the positive control group which was injected with an efficacy-proven drug called ‘Compound arthritis injection’. Xuelian injection of 4 mL was intramuscularly injected into the 36 individuals in experimental group once per day consecutively for 20 days. Total effective rate was found to be increased by 22.2% compared to the positive control group (Bao et al., 2006). Besides, another study has investigated the deviation in efficacy if the Xuelian injection was injected in more specific sites, i.e. acupuncture points according to the theory of Traditional Chinese Medicine. The rate of effectiveness was found to be increased to 100% in 60 tested individuals, with 4 mL of Xuelian injection dissolved in 2 to 3 mL of 0.9% NaCl injection once a day for 15 days. Reoccurrence was developed in only 25% of the individuals after one year of treatment (Gu et al., 2009).

8.2 Counteracting infertility

Recently, the efficacy of Xuelian injection has been tested on treating erectile dysfunction. Seventy individuals were involved and among them, thirty were randomly selected to be the positive control group with injection of Vitamin B with same dose as the experimental group while the remaining 40 individuals were injected,

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4 in specific acupuncture points, 0.5 mL of Xuelian injection. The result was promising,
5 compared to the positive control group, an increase of 20.83% of effective rate,
6 defined by successful vaginal penetration for not less than 1 min before ejaculation
7 has been shown (Liu and Zhang, 2013).
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10 **8.3 Others application of *Saussurea involucrata*-containing compound** 11 **prescription** 12

13 As mentioned, compound prescription of herbs is one of the key characteristics
14 of Traditional Chinese Medicine. The underlying principal is herbal interaction effects
15 including synergistic and antagonistic effect. The chemical profile of an herb can be
16 very sophisticated and interactions of herbs, to be more specific, of different chemical
17 constituents in herbs, can further complicate the case. Hundreds of years of clinical
18 practices in China have demonstrated that best efficacy is reached only when herbs
19 are used together. Therefore, there are vast amount of pharmaceutical products
20 containing, but not merely, *Saussurea involucrata* as the active components and they
21 are used to treat a wide variety of disorders; these include neoplasm (Liang, 2013),
22 cardiovascular diseases (Baima, 1997), allergies and asthma (Hu, 1996),
23 dermatological disorders and injury (Xing et al., 2012).
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41 This indicated the potential of *Saussurea involucrata* in treating a wide spectrum
42 of diseases. Identification of principal active compound, however, would be of utmost
43 importance for further studies on maximizing of efficacy while minimizing of toxicity.
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48 **9. Conclusion and prospects** 49

50 *Saussurea involucrata* is a rare alpine herb that is frequently prescribed in various
51 ethnomedical systems especially central Asia. This review summarized the existing
52 botany, phytochemistry, pharmacological properties and application researches on
53 *Saussurea involucrata*. The amount of modern experimental data manifested the
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4 multiple disease ameliorating properties of *Saussurea involucrata* and evidenced the
5 traditional medical uses. Among them, the most widespread traditional use of this
6 alpine herb has been for the treatment of inflammation. As inflammation has long
7 been considered to be associated with the development of cancer, in recent decade, the
8 emerging efficacy in treating cancer has further put *Saussurea involucrata* under the
9 spotlight.
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18 However, although increasing interest has prompted more studies on *Saussurea*
19 *involucrata*, it is still noteworthy that several gaps in our understanding of its
20 application exist. The first gap is that the intrinsically active compositions and the
21 mechanism of action of *Saussurea involucrata* were ambiguous. For example,
22 although *Saussurea involucrata* has gained widespread global praise owing to its
23 effectiveness in anti-cancer therapy, the possible mechanism is still not conclusive
24 and the responsible active components has not yet been confirmed only attributed to
25 the ethanol extract or the ethyl acetate fraction. Therefore, further more studies should
26 undoubtedly have the priority to identify the individual bioactive component and to
27 more clearly dissect the molecular mechanism of the pharmacological effects of
28 *Saussurea involucrata*.
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43 Secondly, interestingly we have observed that the traditional use of *Saussurea*
44 *involucrata* is seldom coupled with other herbs, while in modern clinical practice,
45 *Saussurea involucrata* is usually used in associations with other herbs. Since
46 compound prescription is one of the key characteristics of Traditional Chinese
47 Medicine, therefore it is important to verify this contradictory phenomenon whether
48 we should use this herb independently or in combination with other herbs by both
49 traditional theory and modern pharmacological evidences.
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59 Thirdly, the contents of chlorogenic acid and rutin, which have been set for the
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4 quality control of *Saussurea involucrata* in the Chinese Pharmacopoeia 2010 edition,
5 varied from 1.19 to 14.43 mg/g and 0.14 to 16.02 mg/g respectively in the herbs
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7 obtained from different habitat and/or harvest's time. This may contribute to
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9 differences in the quality of various batches of *Saussurea involucrata*. Thus, how to
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11 exclusively and accurately monitor and evaluate quality of samples, to ensure and
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13 maintain their clinical and pharmaceutical stability, should be further studied. In
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15 addition, since it is proven to be abortion inducing in rats in early, mid-trimester and
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17 late pregnancy and also accused for causing arrhythmia, hypotension, paralysis,
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19 nausea and other nervous and cardiovascular disorders in overdose condition, further
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21 research into its toxic effects is necessary for prediction of the therapeutic index so as
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23 to ensure the safe use of *Saussurea involucrata*.
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29 Lastly, *Saussurea involucrata*, under stress habitats in rocky and alpine
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31 environments, has limited distributions and grows very slowly. In recent years, the
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33 wild sources of *Saussurea involucrata* are dwindling dramatically due to the
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35 exhaustive exploitation. In order to cope with the problem of over-exploitation and its
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37 endangered species status, the use of *Saussurea involucrata* must be restricted to
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39 sustainable levels, and alternatives to the wild material must be developed. The use of
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41 the cultivated and/or tissue-cultured species as an alternative to the wild *Saussurea*
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43 *involucrata* should be encouraged, as studies have provided proof of their equivalent
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45 effectiveness. Another possibility is to explore other species of the genus *Saussurea* as
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47 potential substitutes for *Saussurea involucrata*. Other species are in fact currently
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49 being used, together with *Saussurea involucrata*, and recent research has
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51 demonstrated common biological activities and similarities in chemotaxonomy (Yi et
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53 al., 2009a; 2009b; 2010, 2012, 2014).
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58 In a word, *Saussurea involucrata* is a valuable herb that is worth additional
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4 attention because of its wide uses, extensive biological activities, and reliable clinical
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6 efficacy. Deep phytochemical and pharmacological investigation of *Saussurea*
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8 *involucrata*, especially its mechanism of action, to illustrate its ethno-medicinal use
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10 will undoubtedly be the focus of future research.
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