PHARMACEUTICAL BIOLOGY, 2017
VOL. 55, NO. 1, 2211–2233
https://doi.org/10.1080/13880209.2017.1397178

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REVIEW ARTICLE

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# The genus *Scrophularia:* a source of iridoids and terpenoids with a diverse biological activity

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**ABSTRACT**

**Context:** *Scrophularia* genus (Scrophulariaceae) includes about 350 species commonly known as figwort. Many species of this genus grow wild in nature and have not been cultivated yet. However, some species are in danger of extinction.

**Objective:** This paper reviews the chemical compounds, biological activities and the ethnopharmacology of some *Scrophularia* species.

**Materials and methods:** All information was obtained through reported data on bibliographic database such as *Scopus*, United States National Agricultural Library, Biological Abstracts, EMBASE, PubMed, MedlinePlus, PubChem and Springer Link (1934–2017). The information in different Pharmacopoeias on this genus was also gathered from 1957 to 2007.

**Results:** The structures of 204 compounds and their biological activity were presented in the manuscript: glycoside esters, iridoid glycosides and triterpenoids are the most common compounds in this genus. Among them, scropolioside like iridoids have shown potential for anti-inflammatory, hepatoprotective and wound healing activity. Among the less frequently isolated compounds, resin glycosides such as cryptophilic acids have shown potent antiprotozoal and antimicrobial activities.

**Conclusion:** The *Scrophularia* genus seems to be a rich source of iridoids and terpenoids, but isolation and identification of its alkaloids have been a neglected area of scientific study. The diverse chemical compounds and biological activities of this genus will motivate further investigation on *Scrophularia* genus as a source of new therapeutic medications.

**ARTICLE HISTORY**
Received 12 February 2017
Accepted 23 October 2017

**KEYWORDS**
Scrophulariaceae; phytochemistry; folk medicine; ethnopharmacology; biological activity; natural product; hepatoprotective; antimicrobial; phenylpropanoid; Phenylethanoid

## Introduction

The Scrophulariaceae family consists of 220 genera. *Scrophularia* genus is one of the large genera of the Scrophulariaceae. Distribution of these genera occurs mainly through mountainous regions (e.g., *Scrophularia farinosa* Boiss. and *Scrophularia amplexicaulis* Benth.) to rarely in deserts (e.g., *Scrophularia deserti* Delile). This genus is represented by 60 species in the flora of Iran and can be used as heart stimulant, circulatory stimulant and diuretic. Other traditional uses of this genus include antipyretic, febrifuge, antibacterial, anti-erythema, anti-constipation, antifurunculosis, ulcerous stomatitis and tonsillitis treatment.

Among these traditional uses of the *Scrophularia*, anti-inflammatory and anti-infections' treatment in different types of diseases is common (Viola 1966; Swiatek and Dombrowicz 1975). The therapeutic potential of the *Scrophularia* has led researchers to focus on the isolation and determination of their bio-active compounds. Some of these species are characterized mainly by glycoside esters or phenylpropanoid glycosides (Calis et al. 1988b; de Santos et al. 2000; Li et al. 2000, 2009), saponins, and iridoids (Çalis et al. 1993a; Yamamoto et al. 1993; Pachaly et al. 1994; Maksudov et al. 1996; Bhandari et al. 1997; Chen et al. 2007; Chebaki et al. 2011). According to some findings, phenylpropanoid glycosides and iridoids are the major part of *Scrophularia* genus secondary metabolites, which showed apparent therapeutic potential in numerous investigations (Figure 1). Several biological effects of phenylpropanoid such as antioxidants, hepatoprotective, antitumor, anti-inflammatory and other useful effects have been studied over the past few years (Garrido et al. 2004; Korkina et al. 2007). Another main class of secondary metabolites is iridoids compounds which constitute the most chemical and biological diversity in *Scrophularia* genus. The several reported biological activities of these compounds have led to increased inclination for the isolation of these classes of chemical compounds (Garg et al. 1994; Giner et al. 2000; Kim and Kim 2000; Kim et al. 2002a; Lee et al. 2002; Stevenson et al. 2002; Kim et al. 2003a; Tasdemir et al. 2005; Valiyari et al. 2012). Based on data extracted from different studies, most biological activities of iridoids include anti-inflammatory, anticancer and antiprotozoal (Dinda et al. 2009). This review presents a brief case for the medicinal uses and the phytochemical and pharmacological properties of the *Scrophularia* genus.

## Materials and methods

All information regarding the chemical and biological activity of the plants were obtained through reported data from 1934 to 2017 on bibliographic database such as Scopus, United States

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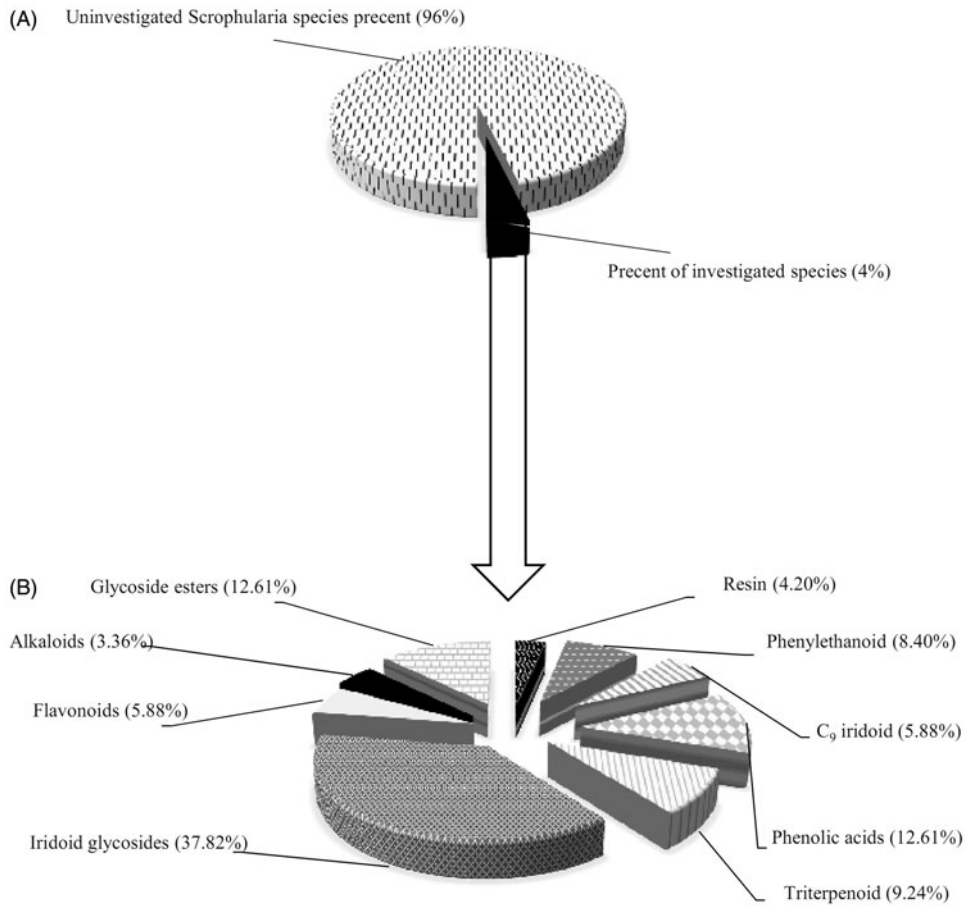


Figure 1. Comparison between chemical compounds isolated from investigated *Scrophularia* species. Part (A) shows investigated species percentage against the total species. Part (B) shows the relative percent of the various phytochemical class isolated from investigated *Scrophularia* species.

National Agricultural Library, Biological Abstracts, EMBASE, PubMed, MedlinePlus, PubChem and Springer Link. The search keywords without any language limitation were *Scrophularia*, biological activity, traditional uses, iridoids, phenylethanoids, alkaloids, resin glycosides, triterpenoid glycoside, essential oils and diterpenoids. The gathered information was then compared with data reported in recent publications (the last 17 years, 2000–2017), and the Pharmacopoeia of the People's Republic of China. Also, data collection on different Pharmacopeias including British Herbal Pharmacopoeia, the Japanese Pharmacopoeia, the French Pharmacopoeia and the Pharmacopoeia of the Royal College of Physicians at Edinburgh (1957–2007) was carried out in order to create a pharmaceutical overview about these species.

## Results

### Biology and ethnopharmacology

Most *Scrophularia* species are annual or perennial herbaceous plants, with woody base and rarely suffruticose, and can also be spinose in rare cases. However, a few of this genus are subshrubs. Flowers are urceolate or tubulose. The length of corolla ranges from 3 to 20 mm. Lips are equal or unequal, which is one of the important characteristics for distinguishing species. With thyrse inflorescence or in rare cases, racemose with one or two flower in each cyme, mostly have four-angled stems and opposite leaves. Some *Scrophularia* species are widely used as traditional medicine. Several countries, including China, Korea and Japan, have used these species as traditional therapeutics as anti-inflammatory and anticancer remedies. Roots of *S. ningpoensis* Hemsl. "Xuan Shen", *S. buergeriana* Miquel, Ann. Mus. Bot. Lugduno-Batavi. "Beixuan Shen" and *S. nodosa* L. (common figwort) have been used as therapeutic remedies in fever, swelling, constipation, pharyngitis, neuritis and laryngitis. In Europe, other species, such as *S. aquatica* L. (water figwort), are used as laxatives, heart stimulants, circulatory stimulants and diuretics. In ancient Iranian medicine, roots and aerial parts of *S. lucida* L. "Sinderitis" and *S. chryasanthemifolia* Bory & Chaub. "Heterasinderitis" are used as heart and circulatory stimulants. Table 1 shows *Scrophularia* species which are used traditionally as therapeutic remedy.

### Phytochemistry

From the genus *Scrophularia*, chemical compounds such as flavonoids, phenylethanoids and glycoside esters, phenolic acids, $C_9$ iridoid, glycosides, resin glycosides and fatty acids derivatives, triterpenes, triterpenoid glycosides, alkaloids, diterpenoids and essential oils can be isolated (Tables 2 and 3 and Figure 1). As mentioned above, some of these chemical substances produce bioactivities in various models (Table 4).

### Flavonoids and flavonoid glycosides

Although flavonoids are the major compounds in plants, and consist of the most dominant compounds in many of the plants family, *Scrophularia* genus is an exceptional case regarding the

Table 1. The traditional use of *Scrophularia* species mentioned in different pharmacopoeias.

| Name | Plant medicinal part | Traditional uses | Pharmacopeia | Other references |
|---|---|---|---|---|
| *S. ningopoensis* "Xuan Shen" (Chinese figwort) | Roots | Anti-inflammatory, treatment of cancer and antioxidant | Pharmacopoeia of the People's Republic of China (Commission 2005)<br>Society of Japanese Pharmacopoeia (Pharmacopoeia 2006) | Marty (1999), Wang et al. (2005) and Zhu (1998) |
| *S. aquatica* (water figwort)<br>*S. marilandica* (late figwort) | Roots and aerial parts | Laxative, heart stimulant, circulatory stimulant and diuretic | The Pharmacopoeia of the Royal College of the Physicians at Edinburgh, Materia Medica (Lewis et al. 1748)<br>French Pharmacopoeia (Ministry of Health 2012) | Marty (1999) |
| *S. buergeriana* "Bei xuan shen" | Roots | Treatment of fever, swelling, constipation, pharyngitis, neuritis and laryngitis | Pharmacopoeia of the People's Republic of China (Commission 2005) | Pinkas et al. (1994) and Wang et al. (2005) |
| *S. dentata* "Ye-Xin-Ba" (Tabatian figwort) | Aerial parts | Treatment of smallpox, measles, high-heat plague and poisoning | Pharmacopoeia of the People's Republic of China (Commission 2005) | Zhang et al. (2014) |
| *S. nodosa* (common figwort) | Roots and aerial parts | Treatment of Fever, swelling, constipation, pharyngitis, neuritis and laryngitis | French Pharmacopoeia (Ministry of Health, 2012)<br>British Herbal Pharmacopoeia (Willoughby et al. 1996) | Zhu (1998) |
| *S. lucida* L. "Sinderitis" | Roots and aerial parts | Heart stimulant, circulatory stimulant, diuretic | – | Goodyer and Gunther (1968) |
| *S. chryasanthemifolia* L. (Hetera sinderitis) | Roots and aerial parts | Heart stimulant, circulatory stimulant and diuretic | – | Goodyer and Gunther (1968) |
| *S. canina* "a ruta salvacce" (Ruta canina) | Roots | Treatment of dermatitis and rheumatoid arthritis | – | Berdini et al. (1991), Guarrera and Lucia (2007) and Pieroni et al. (2004) |

existence of flavonoids. Very negligible flavonoids compounds, such as quercetin (**1**), isorhamnetin-3-*O*-rutinoside (**2**), nepitrin (**3**) and haemoplantaginin (**4**) have been isolated from *S. striata* Boiss. *O*-methylated flavone and acacetin (**5**) have been isolated from endangered Korean species of *S. takesimensis* Nakai (Li et al. 2009; Monsef-Esfahani et al. 2010; Kim et al. 2012a). Other flavonoids such as scrophulein (**6**) and homoplantaginin (**9**) have been isolated from *S. grossheimii* Schischk. and *S. ningpoensis*, respectively (Akhmedov and Litvinenko 1969). An investigation on the bioactive compounds of *S. ilwensis* K.Koch. resulted in the isolation of quercetin-3-*O*-rutinoside (**7**) and kaempferol-3-*O*-rutinoside (**8**) from polar extract (Çalis et al. 1993a). Many bioactivities such as antioxidant, antibacterial, anti-inflammatory and antinociceptive activities have been reported of these compounds or flavonoid-rich extracts (Mahboubi et al. 2013; Nasri et al. 2013) (Table 2 and Figure 2).

## Phenolic acids

Thirty-two (**10–42**) phenolic acid compounds with various substitutions were isolated from *S. frutescens* L. var *frutescens*, *S. canina* L., *S. takesimensis* and *S. grosheimii* (Akhmadov and Kharchenko 1969; Swiatek 1972; Swiatek and Dombrowicz 1975; Fernandez et al. 1996, 1998; Garcia et al. 1998).

*E*-*p*-Methoxycinnamic acid and *E*-isoferulic acid isolated from *S. buregeriana* significantly improved memory deficit, induced by scopolamine in mice (Kim et al. 2003a). *E*-*p*-Methoxycinnamic acid (Table 2 and Figure 3) also has a protective role against NMDA and glutamate-induced neurotoxicity (Kim et al. 2002b). In another experiment, *m*- and *p*-methoxycinnamic acid and ferulic acid showed hepatoprotective activities against carbon tetrachloride ($CCl_4$) in animal tests (Lee et al. 2002a; Kim et al. 2011).

## Phenylethanoid glycosides

Phenylethanoid as one of the main phytochemical compounds plays specific role in biological activity of these plants. Many biological activities such as antimicrobial, anti-inflammatory, antitumor, heart function improvement and neuroprotective activities are attributed to these compounds (Zhu 1998; Koo et al. 2005; Deyama et al. 2006; Georgiev et al. 2011). Previous studies revealed that one of the main constituents of *Scrophularia* plants is phenylethanoid glycosides, and many of the therapeutic potentials can be attributed to them (Zhang and Li 2011).

Sixteen phenylethanoid glycosides compounds (**43–59,** Figure 4) have been isolated from *Scrophularia* (Calis et al. 1988b; de Santos et al. 2000; Li et al. 2000; Lee et al. 2002a). Some of these compounds showed cytotoxicity upon investigations, for example, angoroside compounds which are isolated from *S. scopolii* Hoppe ex Pers. Among these isolated compounds, angoroside A (**39**) showed most cytotoxic activity compared with angoroside B (**40**) and angoroside C (**41**). The relationship between compound structures and their activities were elucidated.

The methoxy group on carbon (**3**) position in angoroside B and (**3′**) in angoroside C reduced cytotoxic activity compared with angoroside A (Saracoglu et al. 1997). In other research on anti-inflammatory activities of phenylpropanoids, acteoside (**43**), angoroside A (**39**) and angoroside C (**41**) have shown significant effects in $TXB_2$-release assay. In addition, angoroside A (**39**), angoroside D (**42**), acteoside (**43**) and isoacteoside (**44**) significantly inhibited LPS-induced $PGE_2$, NO and TNF-α (Díaz et al. 2004). An investigation on *S. dentata* showed that phenylethanoid glycosides such as acteoside (**43**), isoacteoside (**44**), lipedosidesA-I (**51**), osmanthuside B (**52**), martynoside (**53**) and diacetylmartynoside (**54**) were isolated from this species.

**Table 2.** Compounds isolated from the genus Scrophularia (the structure of the compounds illustrated in text).

| Plant name | Compound | No. | Ref. |
|---|---|---|---|
| *S. auriculata* | Scrovalentinoside | **130** | (Giner, et al. 2000, Giner et al. 1998) |
| | Verbascosaponin A | **188** | |
| | Scropolioside A | **134** | |
| | Ilwensisaponin A | **177** | |
| | Verbascoside | **48** | |
| *S.amplexicaulis* | Scropolioside D | **131** | (Pasdaran, et al. 2016) |
| | Scrophuloside $B_4$ | **117** | |
| | Salidroside | **75** | |
| | Verbascoside | **48** | |
| | Eugenol | **200** | |
| | Eugenol acetate | **203** | |
| | 1-Octen-3-ol | **204** | |
| *S. buergeriana* | Buergerinin F | **78** | (Kim and Kim 2000, Lin, et al. 2000, Kim, et al. 2002b, Kim, et al. 2003b, Jeong et al. 2008, Yan and Xie 2011) |
| | Buergerinin G | **79** | |
| | Buergerinin E | **80** | |
| | Ningpogenin | **86** | |
| | Buergerinin D | **82** | |
| | Buergerinin C | **84** | |
| | Buergerinin B | **85** | |
| | 8-*O*-E-p-methoxycinnamoyl harpagide | **102** | |
| | 8-*O*-Z-p-methoxycinnamoyl harpagide | **103** | |
| | 6′-*O*-E-p-methoxycinnamoyl harpagide | **104** | |
| | 6′-*O*-Z-p-methoxycinnamoyl harpagide | **105** | |
| | *Trans*-cinnamic acid | **11** | |
| | *(E)-p*-methoxycinnamic acid | **12** | |
| | *(E)-p*-methoxycinnamic acid methyl ester | **40** | |
| | *(E)*-o-methoxycinnamic acid | **10** | |
| | *(E)-p*-coumaric acid | **16** | |
| | *(E)*-caffeic acid | **41** | |
| | *(E)*-ferulic acid | **42** | |
| | Homovanilline alcohol | **36** | |
| | Buergeriside $A_1$ | **67** | |
| | Buergeriside $B_1$ | **66** | |
| | Buergeriside $B_2$ | **65** | |
| | Buergeriside $C_1$ | **64** | |
| | Harpagoside | **113** | |
| *S. canina* | 7,8-Didehydro-6b,10-dihydroxy-11-noriridomyrmecin | **83** | (Berdini, et al. 1991, Venditti et al. 2015) |
| | 8-*epi*-Loganic acid | **138** | |
| | Verbascoside | **48** | |
| | (*E*)-Phytol | **174** | |
| *S. cryptophila* | Crypthophilic acid A | **171** | (Tasdemir, et al. 2008) |
| | Crypthophilic acid B | **172** | |
| | Crypthophilic acid C | **173** | |
| | Buddlejasaponin III | **182** | |
| | 8-*O*-Acetyl harpagide | **100** | |
| | Harpagide | **114** | |
| *S. dentata* | Scrodentoside A | **139** | (Zhang, et al. 2015b, Zhang, et al. 2014) |
| | Scrodentoside B | **140** | |
| | Scrodentoside C | **141** | |
| | Scrodentoside D | **142** | |
| | Scrodentoside E | **143** | |
| | Scrodentoside F | **154** | |
| | Scrodentoside G | **155** | |
| | Scrodentoside H | **156** | |
| | Scropolioside G | **157** | |
| | Scropolioside H | **158** | |
| | Saccatoside | **159** | |
| | 6-*O*-Methyl catalpol | **94** | |
| | Catalpol | **93** | |
| | 6′-*O*-E-p-feruloyl harpagide | **107** | |
| | Scropolioside D | **131** | |
| | *Cis*-harpagoside | **144** | |
| | Harpagoside | **113** | |
| | Laterioside | **101** | |
| | Scorodioside | **145** | |
| | 6-*O*-α-*L*-(4″-*O*-trans-cinnamoyl)-rhamnopyranosylcatalpol | **146** | |
| | 6-*O*-α-*L*-(4″-*O*-trans-p-coumaroyl)-rhamnopyranosylcatalpol (Scropolioside F) | **147** | |
| | lagotisoside D | **148** | |
| | 8-*O*-Acetyl harpagide | **100** | |
| | 7-Deoxygardoside | **149** | |
| | Ajugoside | **89** | |
| | 8-*epi*-deoxyloganic acid | **150** | |
| | 6′-*O*-p-Coumaroyl harpagide | **151** | |

(*continued*)

**Table 2.** Continued

| Plant name | Compound | No. | Ref. |
|---|---|---|---|
| *S. dentata* (continued) | 10-Deoxygeniposidic acid | **152** | |
| | Geniposidic acid | **153** | |
| | Ajugol | **90** | |
| | Harpagide | **114** | |
| | Scrodentoid A | **195** | |
| | Scrodentoid B | **196** | |
| | Scrodentoid C | **197** | |
| | Scrodentoid D | **198** | |
| | Scrodentoid E | **199** | |
| | Lipedosides A-I | **51** | |
| | Osmanthuside B | **52** | |
| | Martynoside | **53** | |
| | Diacetylmartynoside | **54** | |
| | Verbascoside | **48** | |
| | Isoverbascoside | **49** | |
| | 3-*O*-*trans*-Feruloylrhamnopyranose | **76** | |
| | 2-*O*-*trans*-Feruloylrhamnopyranose | **77** | |
| *S. deserti* | 3-(*R*)-1-Octan-3-yl-3-*O*-β-D-glucopyranoside | **169** | (Ahmed, et al. 2003, Stavri, et al. 2006) |
| | 3(ζ)-Hydroxy-octadeca-4(*E*), 6(*Z*)-dienoic acid | **170** | |
| | 6-*O*-α-L-rhamnopyranosylcatalpol | **97** | |
| | Buddlejoside $A_8$ | **98** | |
| | Harpagoside B | **99** | |
| | 8-*O*-Acetyl harpagide | **100** | |
| | Koelzioside | **132** | |
| | Scropolioside D | **131** | |
| | Scropolioside $D_2$ | **133** | |
| | Scropolioside B | **135** | |
| | Scrospioside A | **136** | |
| | Laterioside | **101** | |
| *S. frutescens* | (Z)-*p*-Coumaric acid | **13** | (Fernandez, et al. 1998, Garcia, et al. 1998) |
| | (Z)-Caffeic acid | **14** | |
| | (Z)-Isoferulic acid | **15** | |
| | (Z)-p-Methoxycinnamic acid | **16** | |
| | (E)-p-coumaric acid | **17** | |
| | (E) 3, 4-Dimethoxy cinnamic acid | **18** | |
| | (Z) Ferulic acid | **19** | |
| | (Z)-Methoxycinnamic acid methyl ester | **20** | |
| | Syringic acid | **21** | |
| | Gentisic acid | **22** | |
| | Protocatechuic acid | **23** | |
| | Isovanillic acid | **24** | |
| | Catalpinic acid | **25** | |
| | Vanillic acid | **26** | |
| *S. ilwensis* | Ilwensisaponin A (Mimengoside A) | **177** | (Çalis, et al. 1993a, Çalis, et al. 1993b) |
| | Ilwensisaponin B | **178** | |
| | Ilwensisaponin C | **179** | |
| | Ilwensisaponin D | **180** | |
| | Karsoside | **116** | |
| | Scropolioside D | **131** | |
| | Aucubin | **109** | |
| | Harpagide | **114** | |
| | 8-*O*-Acetylharpagide | **100** | |
| | Ajugol | **90** | |
| | Angoroside C | **46** | |
| | Quercetin-3-*O*-rutinoside | **7** | |
| | Kaempferol-3-*O*-rutinoside | **8** | |
| *S. kakudensis* | Songarosaponin A | **189** | (Yamamoto A 1993) |
| | Saksisaponin A | **181** | |
| | Buddlejasaponin I | **182** | |
| | Buddlejasaponin II | **183** | |
| | Buddlejasaponin III | **184** | |
| | Scrophulasaponin II | **185** | |
| | Scrophulasaponin III | **186** | |
| | Scrophulasaponin IV | **187** | |
| *S. koelzii* | Koelzioside | **132** | (Bhandri et al. 1992, Garg, et al. 1994, Bhandari, et al. 1996, Bhandari, et al. 1997) |
| | Scropolioside A | **134** | |
| | Scropolioside B | **135** | |
| | 6-*O*-(3″-*O*-*p*-Methoxy-cinnamoyl)-α-L-rhmanopyranosylcatalpol | **161** | |
| | Scrokoelziside A | **175** | |
| | Scrokoelziside B | **176** | |
| *S. lepidota* | Ajugoside | **89** | (Tasdemir, et al. 2005) |
| | Ajugol | **90** | |
| | Sinuatol | **91** | |
| | 6-*O*-β-D-Xylopyranosylaucubin | **92** | |

(*continued*)

**Table 2.** Continued

| Plant name | Compound | No. | Ref. |
|---|---|---|---|
| *S. lepidota* (continued) | Catalpol | **93** | |
| | 6-*O*-Methyl catalpol | **94** | |
| | 3,4-Dihydro-methyl catalpol | **95** | |
| | 1-Dehydroxy-3,4-dihydro aucubigenin | **96** | |
| | Scrolepidoside | **137** | |
| | Aucubin | **109** | |
| | Angoroside C | **46** | |
| | Ningpogenin | **86** | |
| *S. ningpoensis* | Haemoplantaginin | **4** | |
| | 8-Hydroxycoumarin | **38** | |
| | 6-Hydroxyindan-1-one | **39** | |
| | 4-Methylcatechol | **35** | |
| | *trans*-Cinnamic acid | **10** | |
| | 3-Methylphenyl-*O*-β-xylopyranosyl-(1→6)-*O*-β-glucopyranoside | **70** | (Kajimoto, et al. 1989, Qian, et al. 1991, Qian et al. 1992, Li, et al. 2000, Nguyen, et al. 2005, Chen, et al. 2007, Chen et al. 2008, Li, et al. 2009, Niu, et al. 2009, Zhang et al. 2012, Zhu et al. 2013, Zhang, et al. 2015a) |
| | 4-Hydroxybenzaldehyde | **27** | |
| | 3′-Hydroxyacetophenone | **28** | |
| | Scrokoelziside A | **175** | |
| | Buergeriside A1 | **67** | |
| | Sibirioside A | **68** | |
| | Cistanoside F | **69** | |
| | Cistanoide D | **43** | |
| | 6′-*O*-Caffeoyl harpagide | **106** | |
| | 6′-*O*-*E*-*p*-Feruloyl harpagide | **107** | |
| | 6″-*O*-β-Glucopyranosylharpagoside | **108** | |
| | 8-*O*-Acetyl harpagide | **100** | |
| | β-Sitosterol | **192** | |
| | β-Sitosterol glucoside | **193** | |
| | Angoroside C | **46** | |
| | Nepitrin | **3** | |
| | Buergerinin A | **81** | |
| | Aucubin | **109** | |
| | Ningpogenin | **86** | |
| | Ningpogoside A | **87** | |
| | Ningpogoside B | **88** | |
| | 4′-hydroxyacetophenone | **30** | |
| | 3′,5′-Dimethoxy-4′-hydroxyacetophenone | **31** | |
| | 3′-Methoxy-4′-hydroxyacetophenone | **32** | |
| | (*Z*)-4-Hydroxycinnamic acid methyl ester | **34** | |
| | (*E*)-p-Methoxycinnamic acid | **11** | |
| | *trans*-Caffeic acid methyl ester | **33** | |
| | Scropolioside B | **135** | |
| | Scrophularianine A | **164** | |
| | Scrophularianine B | **165** | |
| | Scrophularianine C | **166** | |
| | 2,6-Dimethoxy-4-methoxymethylphenol | **37** | |
| | Homovanillic alcohol | **36** | |
| | Scrophuloside $B_4$ | **117** | |
| | Scrophuloside $A_4$ | **118** | |
| | 6-*O*-Feruloylb-fructofuranosyl-(2→1)-*O*-α-glucopyranosyl-(6→1)-*O*-α-glucopyranoside | **74** | |
| | Scrokoelziside B | **176** | |
| | 6-*O*-cinnamoyl b-fructofuranosyl-(2→1)-*O*-α-glucopyranosyl-(6→1)-*O*-α-glucopyranoside | **73** | |
| | Ningposide A | **61** | |
| | Ningposide B | **62** | |
| | Homoplantaginin | **9** | |
| | Eurostoside | **115** | |
| | 2-(3-Hydroxy-4-methoxyphenyl)ethyl-*O*-α-arabinopyranosyl-(1→6)-*O*-α-rhamnopyranosyl-(1→3)-*O*-β-Glucopyranoside | **72** | |
| | Phenyl*O*-β-xylopyranosyl-(1→6)-*O*-β-glucopyranoside | **71** | |
| | Ningpoensines B/C | **163** | |
| | Vanillin | **29** | |
| | 6-*O*-Methyl catalpol | **94** | |
| | 8- *O*-Feruloylharpagide | **110** | |
| | 8-*O*-(2-Hydroxycinnamoyl) harpagide | **111** | |
| | 6-*O*-α-D-Galactopyranosylharpagoside | **112** | |
| | Harpagoside | **113** | |
| | Harpagide | **114** | |
| | Ningposide C | **60** | |
| | Ningposide D | **63** | |
| | Buergeriside C1 | **64** | |
| | Buergeriside B2 | **65** | |
| | Buergeriside B1 | **66** | |
| | Ningpoensine A | **162** | |

(*continued*)

Table 2. Continued

| Plant name | Compound | No. | Ref. |
|---|---|---|---|
| *S. oxysepala* | Scrokoelziside A | 175 | (Orangi et al. 2013, Orangi et al. 2016, Valiyari et al. 2012) |
| | Scrokoelziside B | 176 | |
| | Verbascosaponin | 177 | |
| | Harpagoside B | 99 | |
| | Scropolioside D | 131 | |
| | 2-(4-chlorobenzyl amino) ethanol | 167 | |
| | Eugenol | 200 | |
| | Dehydroeugenol | 201 | |
| | Methyl benzyl alcohol | 202 | |
| | 1-Octen-3-ol | 204 | |
| *S. nodosa* | Jionoside D | 50 | (Miyase and Mimatsu 1999, Stevenson et al. 2002, Swiatek 1972) |
| | Scrovalentinoside | 130 | |
| | Angoroside C | 46 | |
| | Scrophuloside $A_2$ | 120 | |
| | Scrophuloside $A_4$ | 118 | |
| | Scrophuloside $A_5$ | 121 | |
| | Scrophuloside $A_6$ | 122 | |
| | Scrophuloside $A_7$ | 123 | |
| | Scrophuloside $A_8$ | 124 | |
| | Scrophuloside $A_1$ | 119 | |
| | Buddlejoside $A_5$ | 126 | |
| | Buddlejoside $A_3$ | 127 | |
| | Buddlejoside $A_4$ | 129 | |
| | Pulverulentoside II | 125 | |
| | Scrophuloside $A_3$ | 160 | |
| | Verbascoside A | 128 | |
| | Scrophuloside $B_1$ | 57 | |
| | Scrophuloside $B_2$ | 58 | |
| | Purpureaside C | 56 | |
| | Verbascoside | 48 | |
| | Angoroside A | 44 | |
| | *cis*-Verbascoside | 59 | |
| *S. scopolii* | Angoroside A | 44 | (Calis et al. 1988a, Calis, et al. 1988b) |
| | Angoroside B | 45 | |
| | Angoroside C | 46 | |
| | Angoroside D | 47 | |
| | Verbascoside | 48 | |
| | Isoverbascoside | 49 | |
| | ScropoliosideA | 134 | |
| | ScropoliosideB | 135 | |
| *S. striata* | Quercetin | 1 | (Monsef-Esfahani, et al. 2010) |
| | *trans*-cinnamic acid | 11 | |
| | Isorhamnetin-3-*O*-rutinoside | | |
| | Nepitrin | 3 | |
| | Verbascoside | 48 | |
| | 1-Octen-3-ol | 204 | |
| *S. scorodonia* | 8-*O*-Acetyl harpagide | 100 | (Emam et al. 1997, de Santos, et al. 2000, Bermejo, et al. 2002, Díaz, et al. 2004) |
| | Scrolepidoside | 137 | |
| | Saikosapoinin I (Buddlejasaponin IV) | 190 | |
| | Saikosapoinin II (Sandrosaponin I) | 191 | |
| | Isoangoroside C | 55 | |
| | Buddlejasaponin I | 182 | |
| *S. takesimensis* | Isorhamnetin-3-*O*-rutinoside | 2 | (Kim, et al. 2012a) |
| | Nepitrin | 3 | |
| | β-Sitosterol | 192 | |
| | α-Spinasterol 3-*O*-β-D-glucopyranoside | 194 | |
| | 5-Hydroxypyrrolidin-2-one | 168 | |
| | *trans*-Cinnamic acid | 11 | |
| | *(E)*-*p*-Methoxycinnamic acid | 12 | |
| | *(E)*-*o*-Methoxycinnamic acid | 10 | |
| | Acacetin | 5 | |
| *S. trifoliata* | Catalpol | 93 | (Ramunno et al. 2006) |
| | Aucubin | 109 | |

Phenylethanoid glycosides isolated from *Scrophularia* genus are listed in Table 2.

## Glycoside esters

Several glycoside esters (**60**–**77**, Figure 5) with various substitutions have been isolated from *S. ningpoensis* and *S. buregeriana* (Chen et al. 2007) phenylpropanoid esters of rhamnose, buergerisides $A_1$, $B_1$, $B_2$ and $C_1$ isolated from *S. buregeriana*, exhibited significant neuroprotective effects against glutamate-induced neurotoxicity (Kim and Kim 2000). Another isolated glycoside ester, ningposide D (**63**) isolated from *S. ningpoensis*, demonstrated a mild cytotoxic effect on human cancer cell line K662 on investigation (Nguyen et al. 2005). Isolated glycoside esters from various *Scrophularia* plants are listed in Table 2.

### $C_9$ iridoid

Several $C_9$ iridoids (**78**–**88**) have been isolated from *S. buregeriana* and *S. ningpoensis*. These compounds are in glycosides and non-glycosides forms (Lin et al. 2000, 2006; Niu et al. 2009). $C_9$ iridoids isolated from these plants are listed in Table 2 and Figure 6.

**Table 3.** Some of the *Scrophularia* species essential oil major compounds.

| Species | Major compounds |
|---|---|
| *S. oxysepala* | Methyl benzaldehyde, methyl benzyl alcohol, 1-octen-3-ol, eugenol and phytol |
| *S. amplexcaulis* | Eugenol, 1-cten-3-ol, anethole, caryophyllene oxide and eugenol acetate |
| *S. striata* | 1-octen-3-ol, banzyl banzoat, benzaldehyde, linalool and phytol |
| *S. frigida* | Oxygenated monoterpenes, L-linalool, geraniol, α-terpineol, and 1-octen-3-ol |

### Iridoid glycosides

Using different chromatography methods such as reverse phase column chromatography (RP-HPLC), size exclusion chromatography and thin layer chromatography yielded 72 iridoid glycosides from various species of *Scrophularia* (Table 2 and Figure 7) (Sticher et al. 1980; Calis et al. 1988b; Kajimoto et al. 1989; Berdini et al. 1991; Qian et al. 1991; Pachaly et al. 1994; Maksudov et al. 1996; Bermejo et al. 2002; Niu et al. 2009; Chebaki et al. 2011). Many of these compounds demonstrated various pharmacological activities such as hepatoprotective and

**Table 4.** Pharmacological activities of some *Scrophularia* species.

| Species | Biological activity | Responsible compound or extract | References |
|---|---|---|---|
| *S. amplexicaulis* | Antibacterial (aginest *S. aureus*) | Essential oil | Pasdaran et al. (2012, 2016) |
| | Antimalarial | Methanolic extract & fractions | |
| | Free radical scavengering activities and general toxicity | Methanolic extract & fractions | |
| *S. dentata* | Anti-inflammatory activity significantly inhibited CoA-induced splenocyte proliferation | Iridoids & Scrodentoids A–E, scropoliosides | Zhang et al. (2014, 2015b) |
| *S. auriculata* | Antibacterial | Phenolic acids | Cuéllar et al. (1998) and Giner et al. (2000) |
| | Anti-inflammatory | Iridoids and saponins, Hydroalcoholic extract | |
| *S. buergeriana* | Neuroprotective & Anti-amnestic | Chloroformic & methanolic extracts from roots, harpagoside and 8-*O*-E-p-methoxycinnamoylharpagide | Kim and Kim (2000), Lee et al. (2002), Kim et al. (2003b), Jeong et al. (2008), and Kim et al. (2011, 2012b) |
| | | Phenylpropanoids & Phenolic acids | |
| | Hepatoprotective | | |
| | Anti-inflammatory | | |
| *S. canina* | Insecticidal activity | Plant, phenolic acids | Germinara et al. (2011) |
| *S. cryptophila* | Antiprotozoal and antimycobacterial activities | Crypthophilic acid A, C & buddlejasaponin III, acetylharpagide | Tasdemir et al. (2008) |
| *S. deserti* | inhibiting an enzyme or enzymes of Type II fatty acid synthesis (FAS) | Unsaturated fatty acids, ethanolic extract | Ahmed et al. (2003), Stavri et al. (2006) and Bahmani et al. (2013) |
| | Anti-inflammatory | Scropolioside-$D_2$ & harpagoside B | |
| | Antidiabetic | Scropolioside-$D_2$ & harpagoside B | |
| *S. frutescens* | Antibacterial | Aerial part aqueous extract, phenolic acids | Fernandez et al. (1996, 1998) and Garcia et al. (1998) |
| | Anti-inflammatory | Phenolic acids, Iridoids | |
| | Cytostatic activity | Phenolic acids | |
| *S. grossheimi* | Hepatoprotective | 1,6-di-*O*-caffeoyl-β-D-glucopyranose & flavonoids | Akhmadov et al. (1969), Akhmedov and Litvinenko (1969) and Galindez et al. (2001) |
| *S. koelzii* | Hepatoprotective & immunostimulant | Scropolioside-A, koelzioside, harpagoside, 6-*O*-(3″-*O*-p-Methoxy-cinnamoyl)-α-L-rhmanopyranosyl catalpol, chloroform fraction of the aerial parts | Garg et al. (1994) |
| *S. lepidota* | Anti-protozoal & Antiplasmodial | Ningpogenin, sinuatol | Tasdemir et al. (2005) |
| *S. ningpoensis* | Cardioprotective | Trans-caffeic acid methyl ester & 4-methylcatechol, 6″-*O*-caffeoylharpagide, 6″-*O*-(p-coumaroyl) harpagide, harpagoside and Phenylethanoide glycosides | Chen et al. (2008) and Zhu et al. (2013) |
| | Anti-inflammatory | Ningpogenin, ningpogoside A and ningpogoside B and hydrophilic extract | Qian et al. (1991) |
| | Antibacterial | Scrokoelziside A and ethanolic leave extract | Li et al. (2009) |
| *S. nodosa* | Wound healing activity | Scopolioside A, scrophuloside A4 and scrovalentinoside | Stevenson et al. (2002) |
| *S. oxysepala* | Insecticidal activity | Essential oil, methanolic fractions | Pasdaran et al. (2013, 2017) and |
| | Apoptosis | Dichloromethane and methanol extracts | Valiyari et al. (2012) and Orangi et al. (2013) |
| | Cytotoxic | Methanolic fractions, scropolioside D, harpagoside B &2-(4-chlorobenzyl amino) ethanol | Pasdaran et al. (2017) |
| | Free radical scavenging | | |
| *S. striata* | Wound healing and Anti-inflammatory | Ethanolic extract, ethyl acetate extract | Hajiaghaee et al. (2007) and Azadmehr et al. (2009) |
| | Antibacterial | Ethanolic extract | Benito et al. (1998) and Bahrami and Ali (2010) |
| | Antioxidant | Ethanolic extract | Díaz et al. (2004) |
| *S. scorodonia* | Anti-inflammatory | Angoroside A, angoroside C, angoroside D, acteoside, isoacteoside, Buddlejasaponin I& Saikosapoinin I, II | |
| | Antiviral | Scorodioside, Buddlejasaponin IV | Bermejo et al. (2002) |
| *S. takesimensis* | Strong aldose reductase (AR) inhibitory activity | Acacetin | Kim et al. (2012a) |

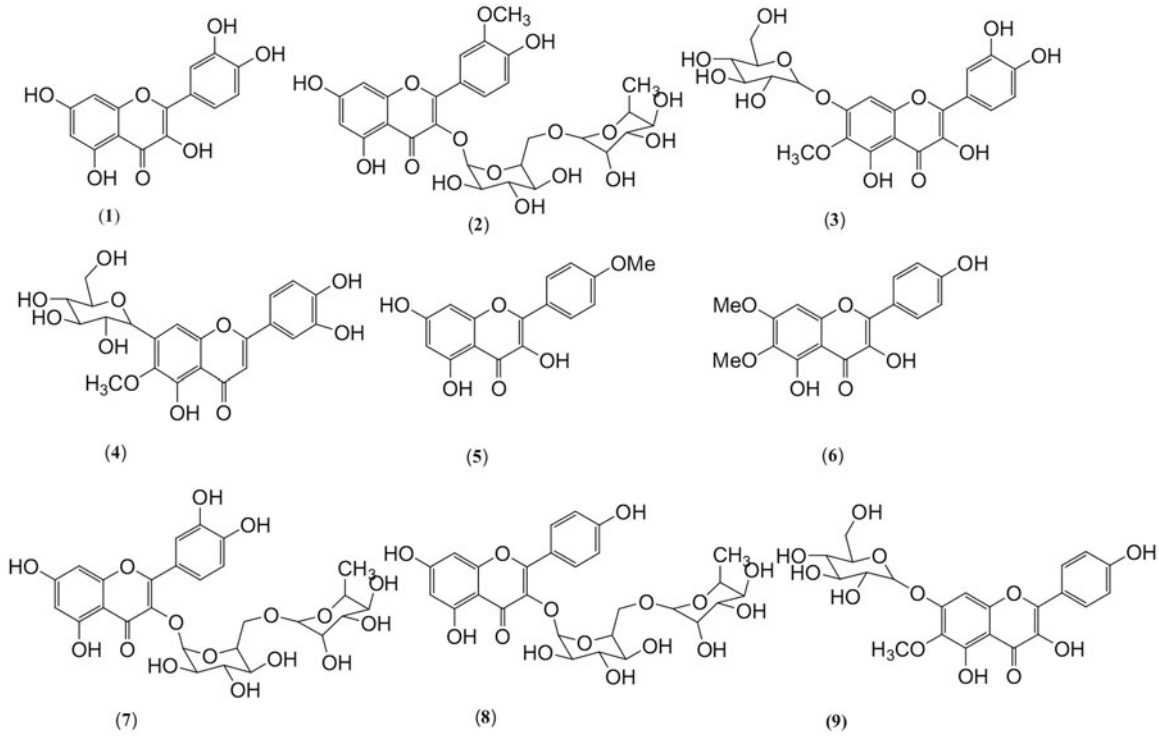


Figure 2. Isolated flavonoids and flavonoid glycosides from *Scrophularia* genus.

anti-inflammatory activities (Table 4). Among the chemical compounds isolated from *S. koelzii* Pennell. such as harpagoside (**113**), koelzioside (**132**) and scropolioside A (**134**), scropolioside A demonstrated maximum hepatoprotective activity against thioacetamide-induced hepatotoxicity in animal model (Garg et al. 1994). Research on *S. deserti* led to the isolation of scropolioside $D_2$ (**133**) and harpagoside B (**99**), which have significant antidiabetic and anti-inflammatory activities (Ahmed et al. 2003).

Among the various bioactivities observed of these compounds, anti-inflammatory effect is the most investigated. Zhu et al. (2015), in working on anti-inflammatory activity of isolated iridoid glycosides from *S. dentata* Royle ex Benth. and comparison between their potentials, reported their anti-inflammatory activities against LPS-induced NF-κB activity, cytokines mRNA expression, IL-1β secretion and cyclooxygenase-2 activity depending on whether the 6-*O*-substituted cinnamyl moiety was linked to C″ 2-OH, C″ 3-OH or C″ 4-OH, and on the number of moieties linked, which is closely related to the enhancement of anti-inflammatory activity (Pieroni et al. 2004). Structural diversity of iridoid glycosides in this genus can be categorized into three classes including (**a**) moieties which exist on cyclopentane ring, (**b**) moieties which exist on different position of glucose attached in [*c*] pyran ring and (**c**) moieties which exist on different position of rhamnose that are attached in C6 cyclopentane ring. Among these structural classes, diversity of iridoid glycosides with moieties in rhamnose attached in C6 cyclopentane ring position is more than other classes. Subsequently, structures with moieties are placed in different positions of cyclopentane ring, and finally structures with moieties in different positions of glucose are attached in [*c*] pyran ring. Table 2 shows various isolated *Scrophularia* iridoid glycosides.

## Alkaloids

Several pyridine alkaloids are isolated from *Scrophularia* (Table 2 and Figure 8), three novel zwitterionic alkaloids-ningpoensine A **(162)** and ningpoensines B/C **(163)** (pair of epimers) were isolated from the root of *S. ningpoensis* (Zhang et al. 2015a). Ningpoensines B/C can promote wound closure in human embryonic keratinocytes in researches (Maksudov et al. 1996). In another research, three new monoterpene pyridine alkaloids, scrophularianines A–C **(164–166)** with cyclopenta [c] pyridine skeleton, were reported from *S. ningpoensis*. Other unusual new halogenated alkaloids, [2-(4-chlorobenzyl amino) ethanol] **(167)** with cytotoxic effects, were also isolated from *S. oxysepala* Boiss. (Orangi et al. 2016). Another cyclic alkaloid is 5-hydroxypyrrolidin-2-one **(168)** isolated from Korean species, *S. takesimensis* (Kim et al. 2012a).

## Resin glycosides and fatty acids derivatives

Six resin glycosides and fatty acids derivatives were isolated from *Scrophularia* (Figure 8) (Stavri et al. 2006; Çalis et al. 2007). Among these compounds, crypthophilic acids A–C **(171–173)** isolated from *S. cryptophila* Boiss. were examined for antiprotozoal and antimycobacterial activities. Crypthophilic acids A and C showed activity against *Trypanosoma brucei rhodesiense* and *Leishmania donovani* (Kajimoto et al. 1989). In another research on traditional remedy, where *S. deserti* was used as an antipyretic in Middle East countries, two unsaturated fatty acid compounds including 3(ζ)-hydroxy-octadeca-4(*E*), 6(*Z*)-dienoic acid (**170**) and 3R-1-octan-3-yl-3-*O*-β-D-glucopyranoside (**169**) were isolated. Among these compounds, 6(*Z*)-dienoic acid showed antibacterial activity against both *Staphylococcus aureus* and mycobacteria (Table 2; Ahmed et al. 2003).

## Triterpenoid glycosides and sterols

Oleanane-type triterpenoid glycoside is a major triterpenoid in *Scrophularia* species (Çalis et al. 1993b; Bhandari et al. 1996,

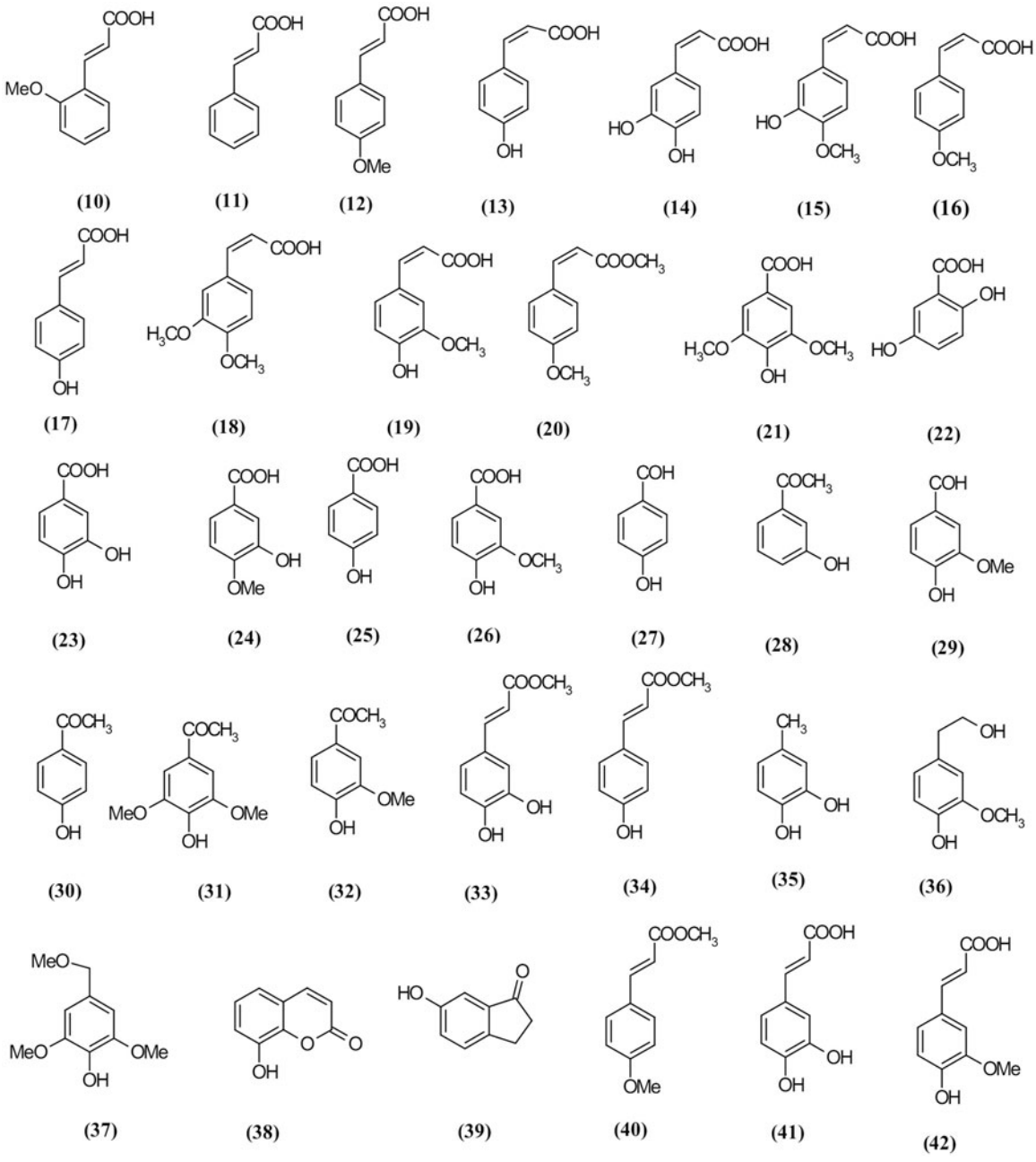


Figure 3. Phenolic acids compounds reported from *Scrophularia* plants.

1997). Verbascosaponin A (**188**) as an oleanane-type triterpenoid was isolated from *S. auriculata* ssp. *pseudoauriculata* (Sennen) O. de Bolòs & J. Vigo which showed an excellent anti-inflammatory activity in the acute 12-*O*-tetradecanoylphorbol 13-acetate (TPA) model (Giner et al. 2000). In addition, three saikosaponin homologs, scrophulasaponins II–IV were isolated from *S. kakudensis* Franch. (Figure 9) (Yamamoto et al. 1993). Other isolated triterpenoid glycoside and their origin species are listed in Table 2.

## Diterpenoids

Five new 19(4→3)-abeo-abietane diterpenoids, scrodentoids A–E (**195–199**) were isolated from *S. dentata,* which is a famous traditional remedy for the treatment of smallpox, measles, high-heat plague and poisoning (Zhang et al. 2015a). These compounds are isolated from low-polar extract of *S. dentata* by column chromatography and reversed-phase HPLC techniques. The anti-inflammatory, immunosuppressive, antifertility, anticystogenesis and anticancer activities of 19(4→3)-abeo-abietane diterpenoids have been previously reported (Zhang et al. 2015b). Scrodentoids A–E were investigated for immunosuppressive effect and cytotoxic effects, especially against B16 and MCF-7 cells line. According to this investigation, scrodentoids A (**195**) and D (**198**) showed the most potential in this biological test (Table 2 and Figure 10).

## Essential oils

The essential oils of a few *Scrophularia* species have been investigated until now. The essential oil of *S. oxysepala*, an endemic plant of western and central regions of Iran, was characterized by

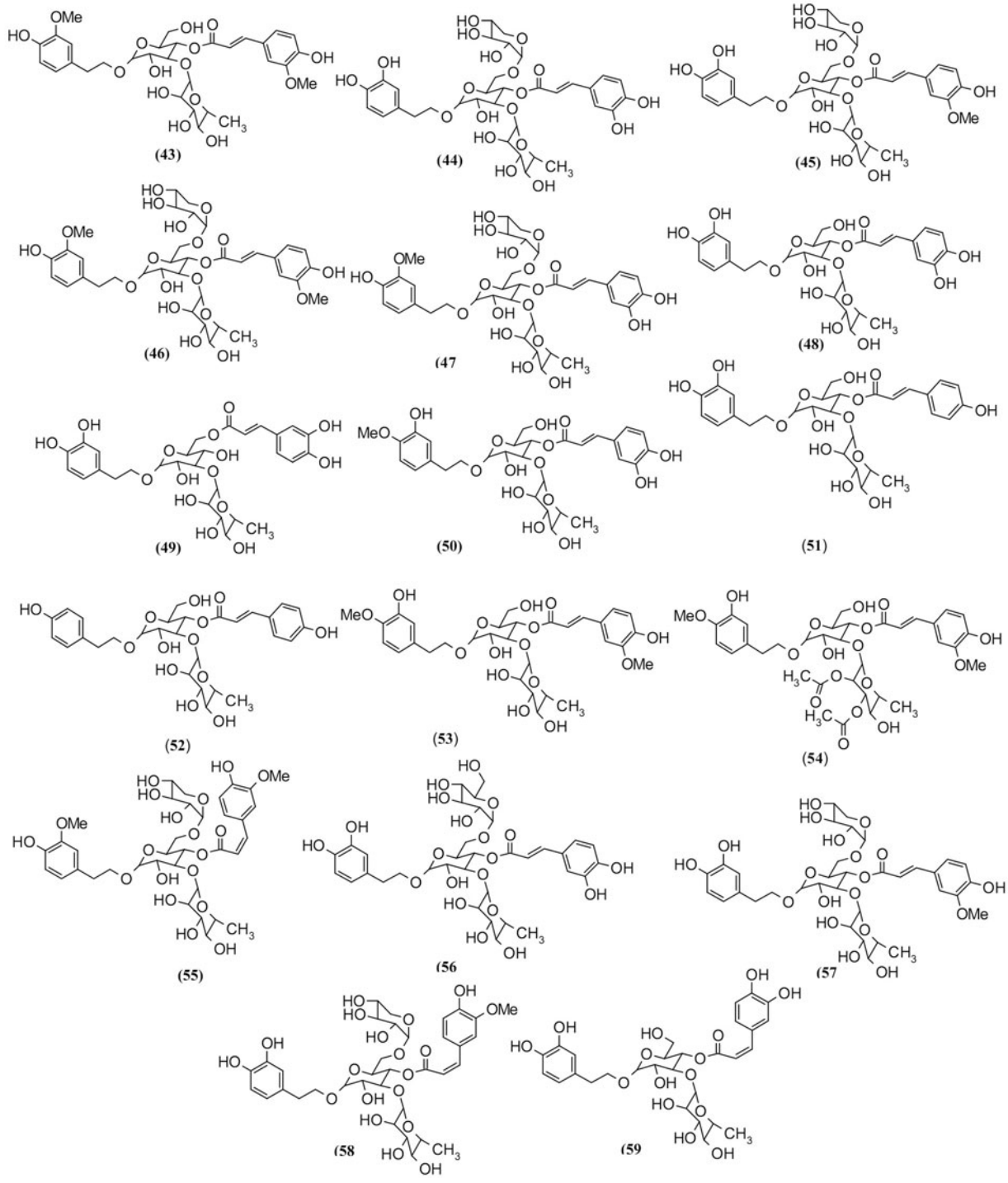

Figure 4. Phenylethanoid glycosides isolated from *Scrophularia* plants.

the presence of high percent of eugenol (**200**), dehydroeugenol (**201**) and methyl benzyl alcohol (**202**) as phenolic compounds. In addition, a high amount of eugenol (**200**) and eugenol acetate (**203**) have been reported from the essential oil of *S. amplexicaulis* Benth, another endemic plant of Iran, which showed antimicrobial activity against *S. aureus* (Pasdaran et al. 2012, 2013). According to research on *S. oxysepala*, *S. amplexicaulis*, *S. striata* and *S. frigida* Boiss, it was indicated that probably, 1-octen-3-ol (**204**) is a chemical compound marker in *Scrophularia* species (Table 3 and Figure 10) (Miyazawa and Okuno 2003; Amiri et al. 2011).

## Biological activity

### Anti-inflammatory

*Scrophularia denata* "Ye-Xin-Ba" a traditional Chinese herbal medicine is native to Tabatian region. The iridoids isolated from this plant showed anti-inflammatory effects in NF-κB-mediated reporter gene luciferase assay. Scropolioside B (**135**) and scropolioside D (**131**) had significant inhibitory effect against nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation with an $IC_{50}$ value of 43.7 and 1.02 μM, respectively (Zhang et al. 2014). Zhu et al. (2015) investigated the anti-

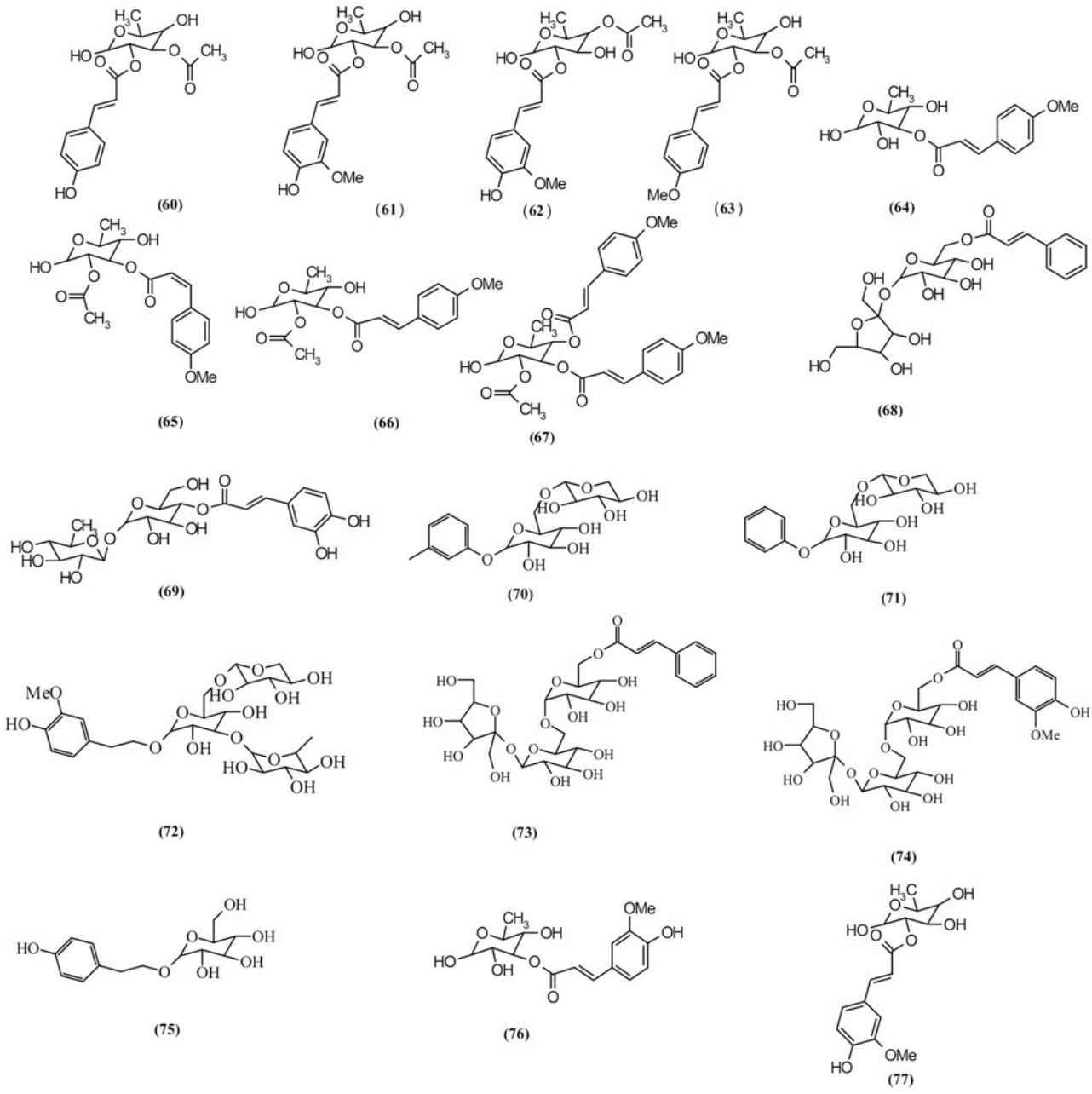


Figure 5. Chemical structures of *Scrophularia* glycoside esters.

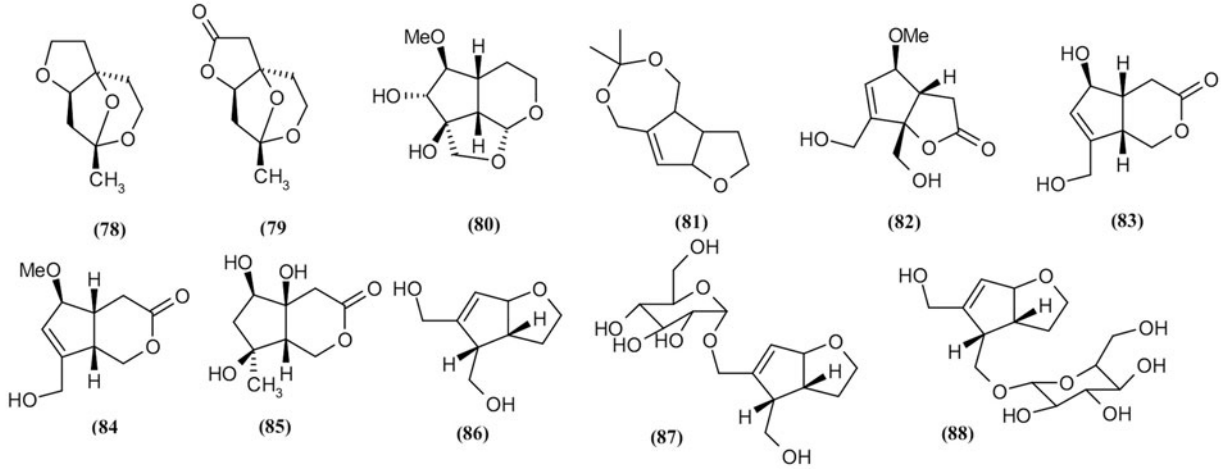


Figure 6. Chemical structures of *Scrophularia* $C_9$ iridioides.

inflammatory potential of various scropoliosides isolated from *S. denata* against LPS-induced NF-κB activity, cytokines mRNA expression, interleukin 1β (IL-1β) secretion and cyclooxygenase-2 activity. Scropoliosides B (**135**), F (**147**) and G (**157**) and 6-*O*-methylcatapol (**94**) significantly reduced IL-1β maturation, and secretion in the cultured medium of the THP-1 cells. Other scropoliosides A (**134**), B (**135**) and D (**131**) also inhibited IL-1β mRNA expression. Scrodentosides A and B inhibited cyclooxygenase 2 (COX-2) activity (Zhu et al. 2015). In working on *S. auriculata* ssp. *pseudoauriculata*, compounds such as verbascosaponin A (**188**) and verbascosaponin (**177**) were isolated, verbascosaponin inhibited the carrageenan paw oedema and ear

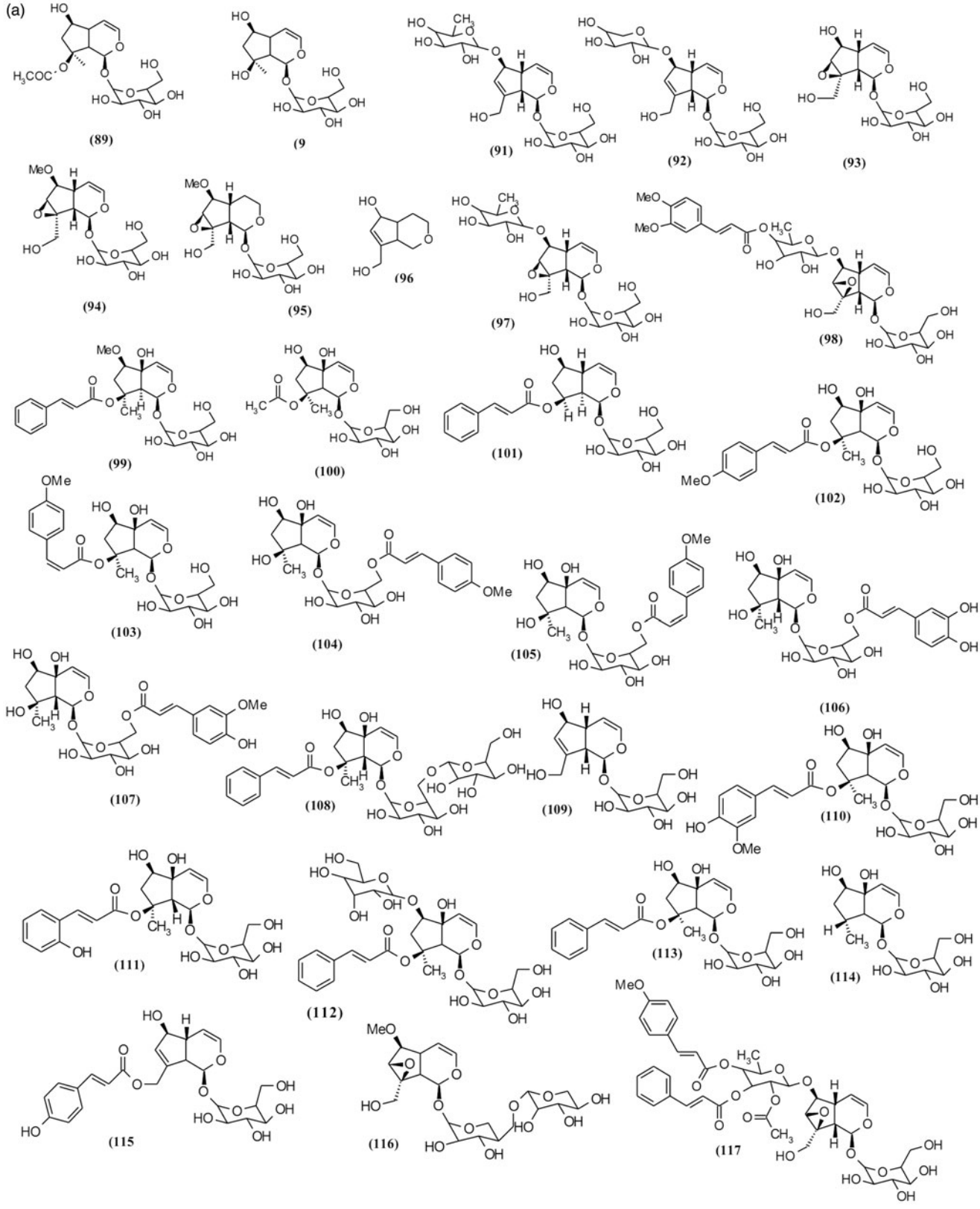


Figure 7. Chemical structures of isolated *Scrophularia* iridoid glycosides.

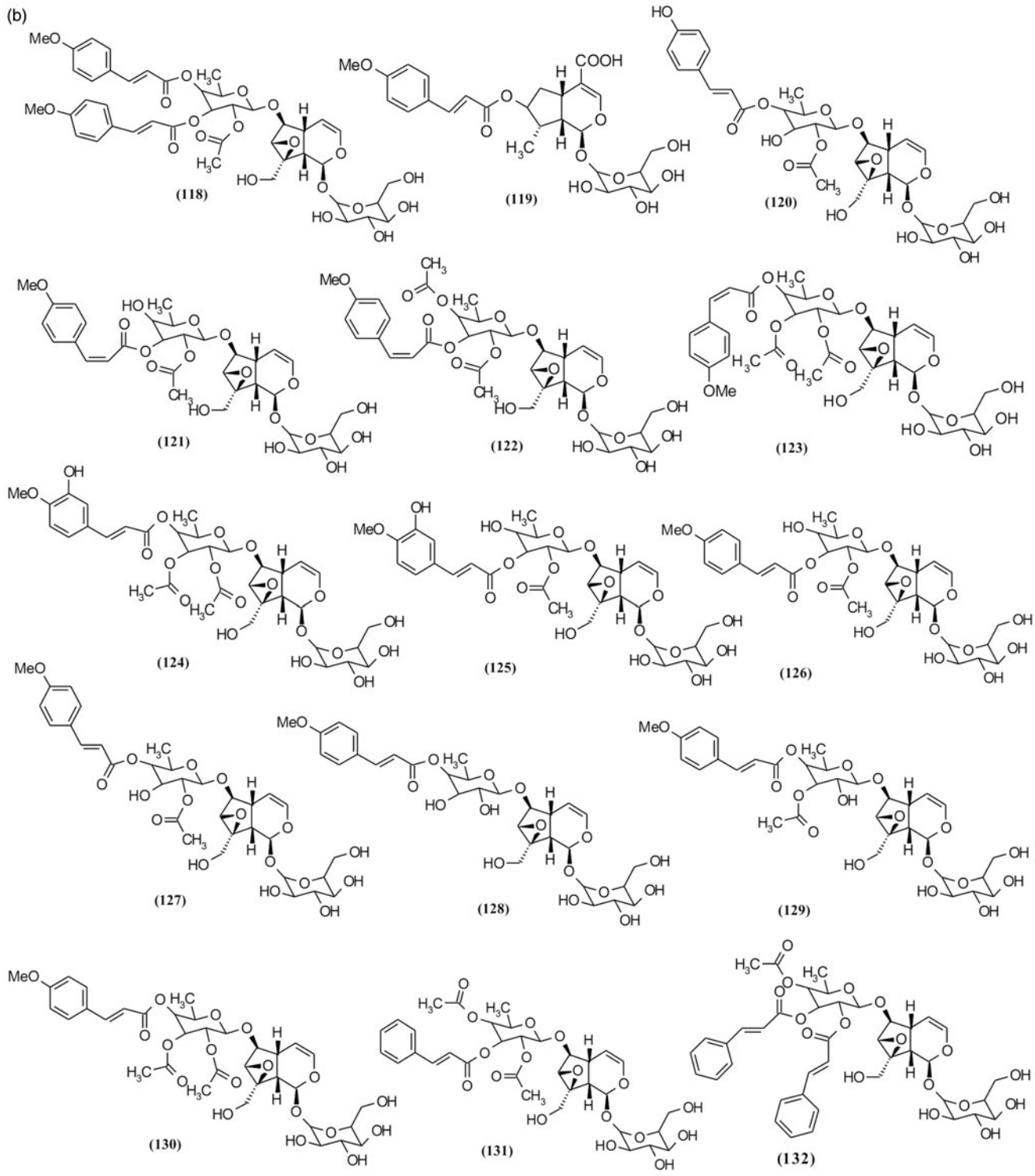


Figure 7. Continued.

oedema induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA test). Results showed that verbascosaponin A (**188**) and verbascosaponin (**177**) with an $ID_{50}$ value of 0.32 and 0.18 µmol/ear, respectively, in comparison with indomethacin 0.35 µmol/ear have an excellent anti-inflammatory effects (Giner et al. 2000). The ethanol–water extracts of aerial parts of *S. auriculata* L. and roots of *S. buergeriana* display significant inhibition against oxazolone-induced contact-delayed hypersensitivity mouse ear oedema (DTH) and release of histamine, tumour necrosis factor-α (TNF-α), IL-4 in inflammation model, respectively (Giner et al. 2000; Kim et al. 2012b). During the investigation of *S. deserti* anti-inflammatory potential, five iridoid glycosides, including scropolioside $D_2$ (**133**), harpagoside B (**99**), scropolioside D (**131**), koelzioside (**132**) and 8-*O*-acetylharpagide (**100**) were isolated and characterized (Zhu et al. 2015). Scropolioside D (**131**) and harpagoside B (**99**) isolated from *S. deserti* possess significant anti-inflammatory activity in carrageenan paw oedema (Ahmed et al. 2003). Fernandez et al. (1996, 1998) reported the

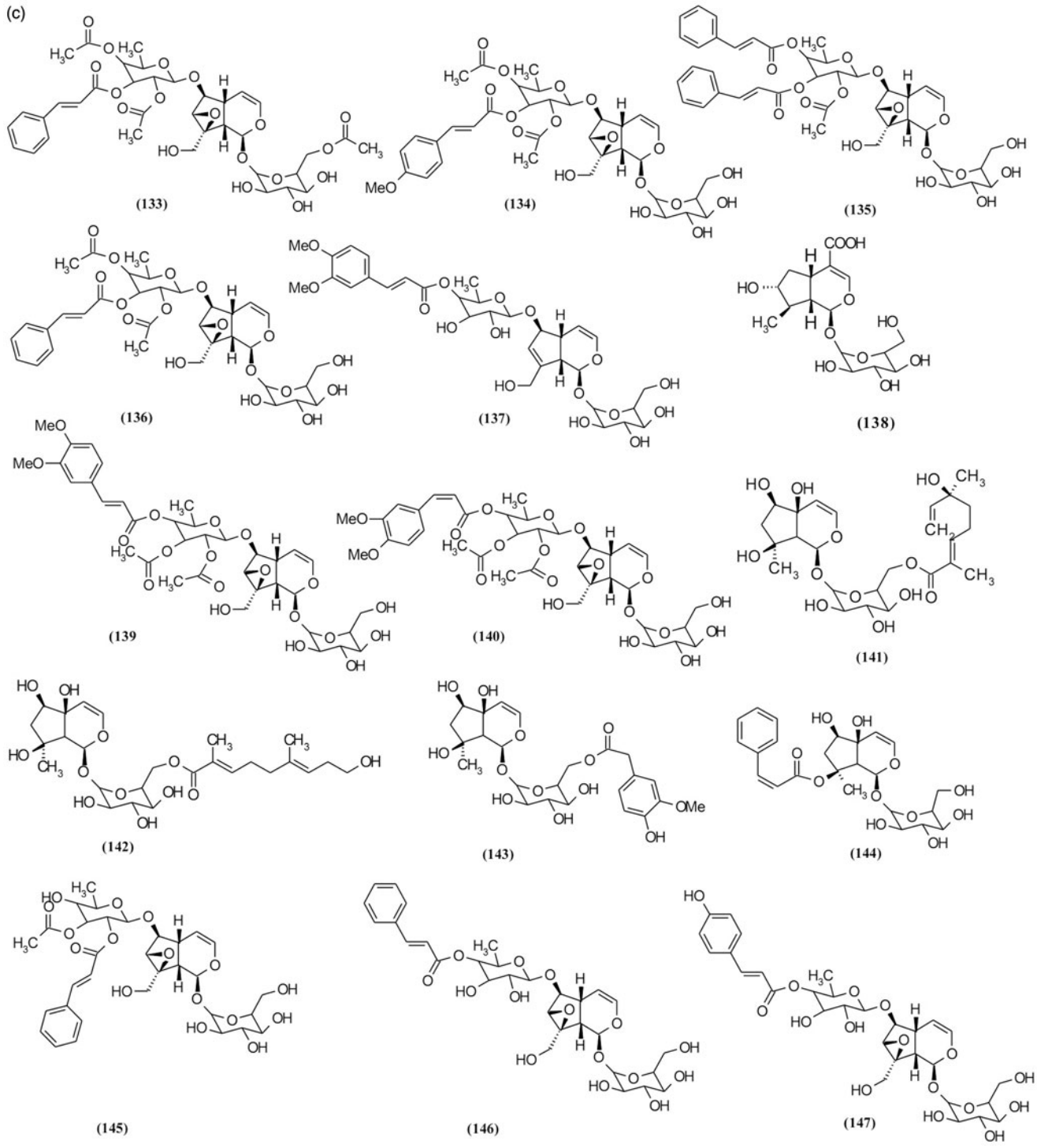


Figure 7. Continued.

anti-inflammatory activity of different extracts from *S. frutescens* L. In further screening for finding active compounds, several phenolic acids were remarkably active in the TPA test, among these isolated phenolic acid compounds, ferulic (**19**), gentisic (**22**), protocatechuic (**23**) and syringic (**21**) acids significantly inhibited oedema (protocatechuic with 71.59% inhibition; syringic with 74.43% inhibition and ferulic with 71.02% inhibition) (Fernandez et al. 1998). The roots of *S. ningpoensis* "Xuan Shen" as Chinese traditional medicine which is used against swelling, laryngitis and neuritis, consist of several iridoids and phenylethanoids, hydrophilic extract of this plant showed significant inhibitory effect ($ED_{50}$ 20 mg/kg) on this animal model (Qian et al. 1991). *Scrophularia striata,* an Irano-Turanian region endemic plant, showed that in several anti-inflammatory models, ethyl acetate extract of *S. striata* inhibits IL-1β, TNF-α and prostaglandin E2 (PGE2) secretion in mouse peritoneal macrophages induced by lipopolysaccharide (LPS) (Figures 11 and 12; Azadmehr et al. 2013).

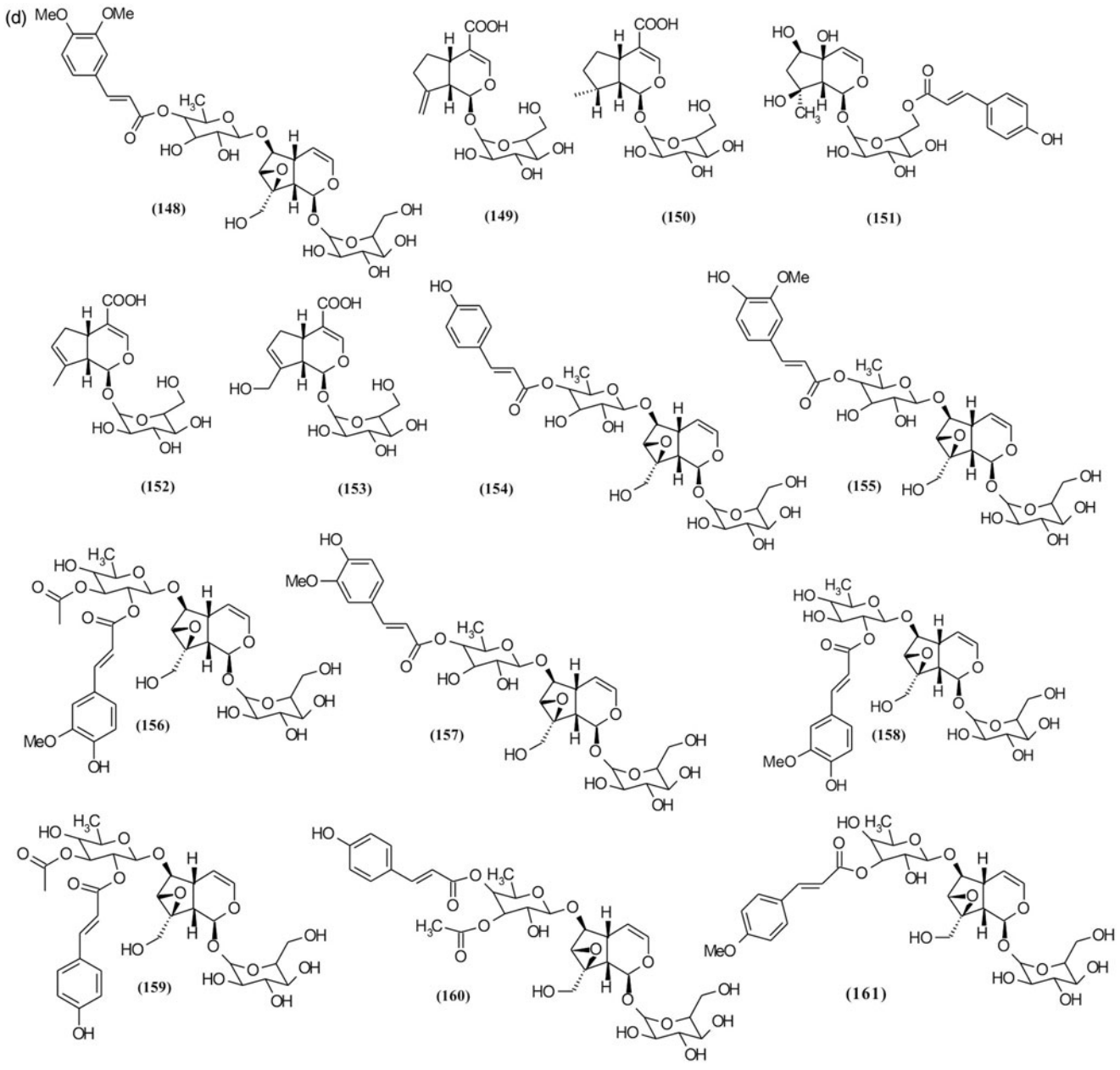


Figure 7. Continued.

### Antimicrobial and antiprotozoal

Essential oil of Iranian endemic plant, *S. amplexicaulis,* showed antibacterial activity against *S. aureus* in the well diffusion method. The essential oil of this plant is characterized by a high content of eugenol (53.8%) and eugenol acetate (24.5%), and the antibacterial activity of these compounds has been identified previously (Didry et al. 1994; Pasdaran, et al. 2012). In another research on methanolic extract and fractions of *S. amplexicaulis*, 80% and 60% ($IC_{50}$ 0.827, 0.431 mg/mL) methanol in water of solid-phase extraction (SFE) showed significant activity in haeme biocrystallization assay for potential antimalarial property (Pasdaran et al. 2016). Tasdemir et al. (2005, 2008) investigated the antiprotozoal and antimycobacterial activities of the chemical compounds of *S. cryptophila*, tryptophan and buddlejasaponin III (**184**) which showed growth-inhibitory effect against *Trypanosoma brucei* ($IC_{50}$ 4.1 and 9.7 mg/mL). Harpagide (**114**) and crypthophilic acid C (**173**) showed the best leishmanicidal activity ($IC_{50}$ 2.0 and 5.8 mg/mL) in comparison with other isolated compounds. In antimalarial activity against *Plasmodium falciparum,* crypthophilic acid C (**173**), tryptophan and buddlejasaponin III (**184**) showed antimalarial activity with $IC_{50}$ values of 4.2, 16.6 and 22.4 mg/mL, respectively (Tasdemir et al. 2008). Investigation on the ethanol extract of *S. deserti* showed that plant have antibacterial potential against *Brucellla melitensis*, in other studies related to this plant, three isolated compounds including 3(ζ)-hydroxy-octadeca-4(*E*), 6(*Z*)-dienoic acid (**170**), ajugoside (**89**) and scropolioside B (**135**) exhibited moderate antibacterial activity against multidrug and methicillin-resistant *S. aureus* (MRSA) as well as mycobacteria with minimum inhibitory concentration (MIC) values, ranging from 32 to 128 µg/mL (Stavri et al. 2006; Bahmani et al. 2013). Fernandez et al. investigated the antibacterial and active fraction of *S. frutescens* and *S. sambucifolia* L. on several micro-organisms such as *Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *S. aureus*,

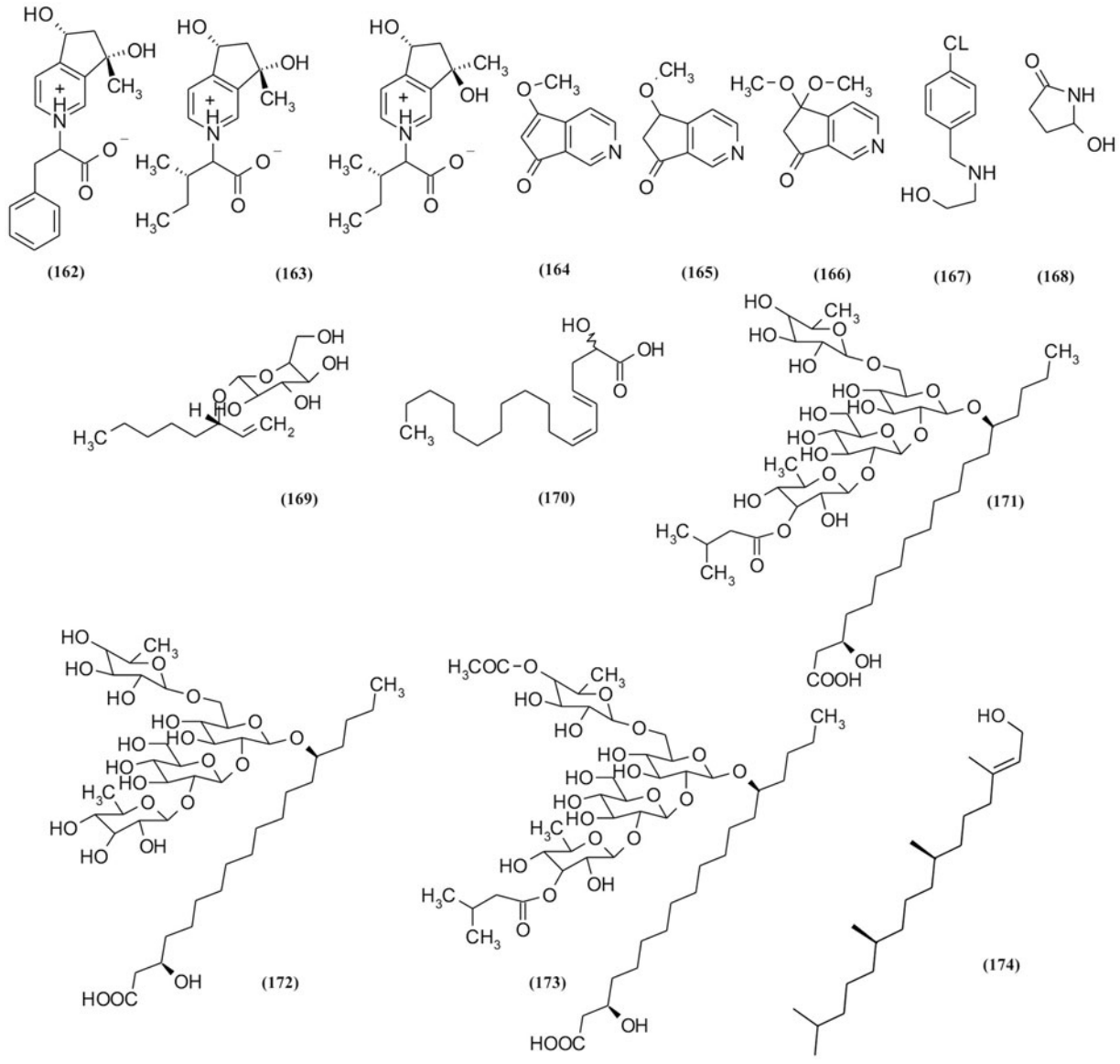


Figure 8. Alkaloids, resin glycosides and fatty acids derivatives of *Scrophularia* plants.

*Escherichia coli*, *Serratia marcescens*, *Salmonella typhimurium* and *Moraxella lacunata*. Results of this investigation indicated that the phenolic fractions of both species showed more activity against Gram-positive bacteria, specifically against *Bacillus* sp. (Fernandez et al. 1996). The 70% ethanol extracts of leaves and scrokoelziside A (**175**) which were isolated from *S. ningpoensis* "Xuan Shen" showed anti-bacterial activity against *beta-haemolytic streptococci* (Figures 11 and 12; Li et al. 2009).

### Hepatoprotective and neuroprotective

*E-p*-Methoxycinnamic acid (**12**) isolated from *S. buergeriana* showed anti-amnesic activity and protective effect on cultured neuronal cells against neurotoxicity induced by glutamate (Kim et al. 2003a). Future investigations for finding other active compounds of *S. buergeriana* in neuroprotection led to the isolation of 10 phenylpropanoid esters from roots of this plant, although all isolated phenylpropanoid esters exerted significant protective effects against glutamate-induced neurodegeneration, but buergeriside A1 (**67**), buergeriside B1(**66**) and (*E*)-*p*-methoxycinnamic acid (**12**) exhibited better protection (Kim and Kim 2000). In the continuous isolation of other neuroprotective compounds, 8-*O*-*E*-*p*-methoxycinnamoyl harpagide (**102**) and harpagide (**114**), 8-*O*-*Z*-*p*-methoxycinnamoyl harpagide (**103**), 6′-*O*-E-*p*-methoxycinnamoy lharpagide (**104**), 6′-*O*-Z-p-methoxycinnamoyl harpagide (**105**) *E*-harpagoside and *Z*-harpagoside were isolated from these plants and tested for the reduction of glutamate-induced neurotoxicity in rat. According to the result, these compounds demonstrated protective effect on cultured neurons against glutamate-induced oxidative stress (Kim and Kim 2000; Kim et al. 2002a, 2003b). Isolated phenylpropanoids from roots of *S. buergeriana* exhibit hepatoprotective effect in $CCl_4$-induced toxicity (Kim et al. 2002a). Chloroformic fraction of the alcoholic extract of the aerial parts of *S. koelzii* showed hepatoprotective activity. Further investigation led to the isolation of several iridoid glycosides, and among these compounds, scropolioside A showed maximum hepatoprotective activity in thioacetamide hepatotoxicity model (Figures 11 and 12; Garg et al. 1994).

## Conclusion

Recently, the amount of research on metabolites, pharmacological activities and traditional uses of the various *Scrophularia* species has increased significantly. According to reviewed literatures, several reasons could contribute to the screening of this genus which include (1) some of the species have been used as a traditional or local therapeutic remedy especially in Asia and Europe for long time, and the effectiveness and safety of these species have been established. Therefore, such sources have generated much interest and new field for easier search of potential compounds. (2) Iridoid glycosides, phenolic acids and triterpenoid

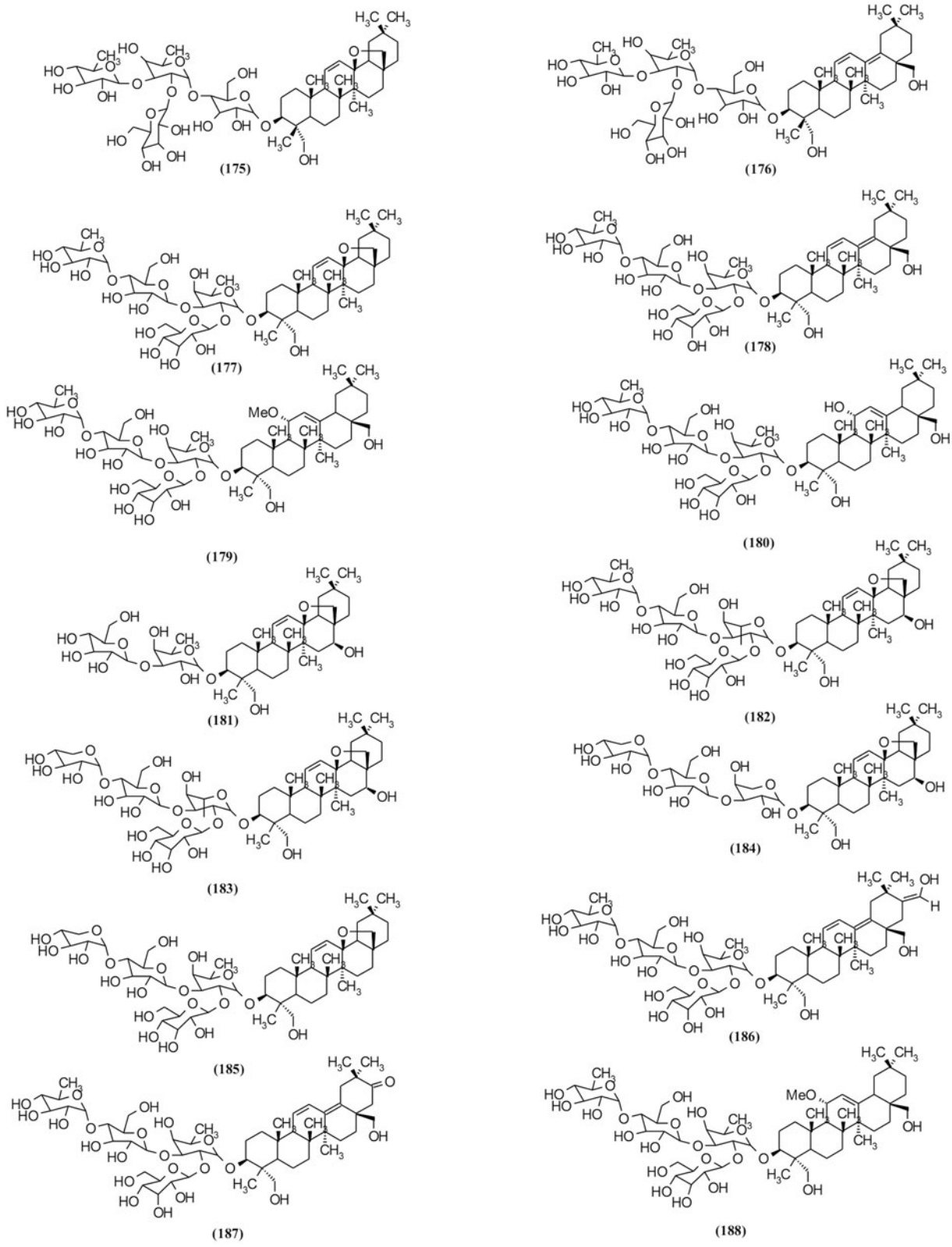


Figure 9. Chemical structures of triterpenoid glycosides and sterols of *Scrophularia* species.

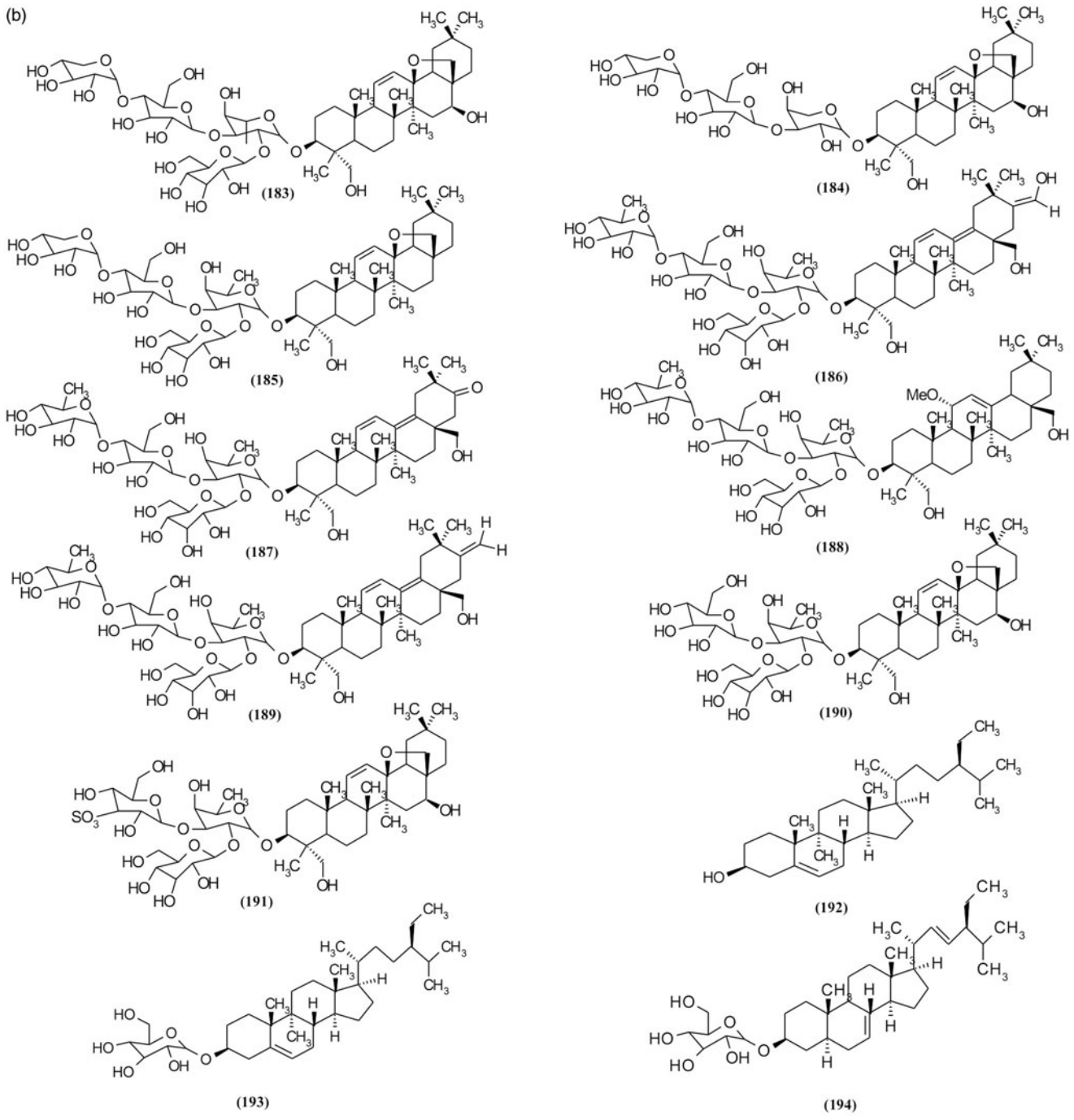


Figure 9. Continued.

glycosides have been identified as the three main chemical compositions of *Scrophularia*. Among them, scropoliosides like iridoid structures have shown potential for anti-inflammatory, hepatoprotective and wound healing activity effects. Among the less frequently isolated compounds, resin glycosides such as cryptophilic acids have shown good properties in antiprotozoal and antibacterial assays. Therefore, chemical compounds of this genus will motivate further investigation on *Scrophularia,* and have great potential as sources of finding new therapeutic medications. (3) Only 17 of the approx. 350 species have been studied in some detail. Among the isolated metabolites from *Scrophularia* spp., only a few of them has been investigated for their biological activities. Many of the conducted researches on isolation or biological screening have been conducted on iridoids and phenylethanoids while other classes of phytochemicals such as alkaloids, diterpenoids and flavonoids have been less considered by researchers.

On one hand, most of the studies on the isolated compounds have been carried and *in vitro/in vivo* and we could not find any clinical trials on biological activities of *Scrophularia*. Thus, pharmacokinetic and metabolism of these metabolites are unclear in human body. On the other hand, the exact mechanism of the active isolated molecules is still unknown. Considering these issues, there is huge gap between the current situation and the final goal which is developing approved drug from the isolated molecules or even developing supplements from the *Scrophularia*

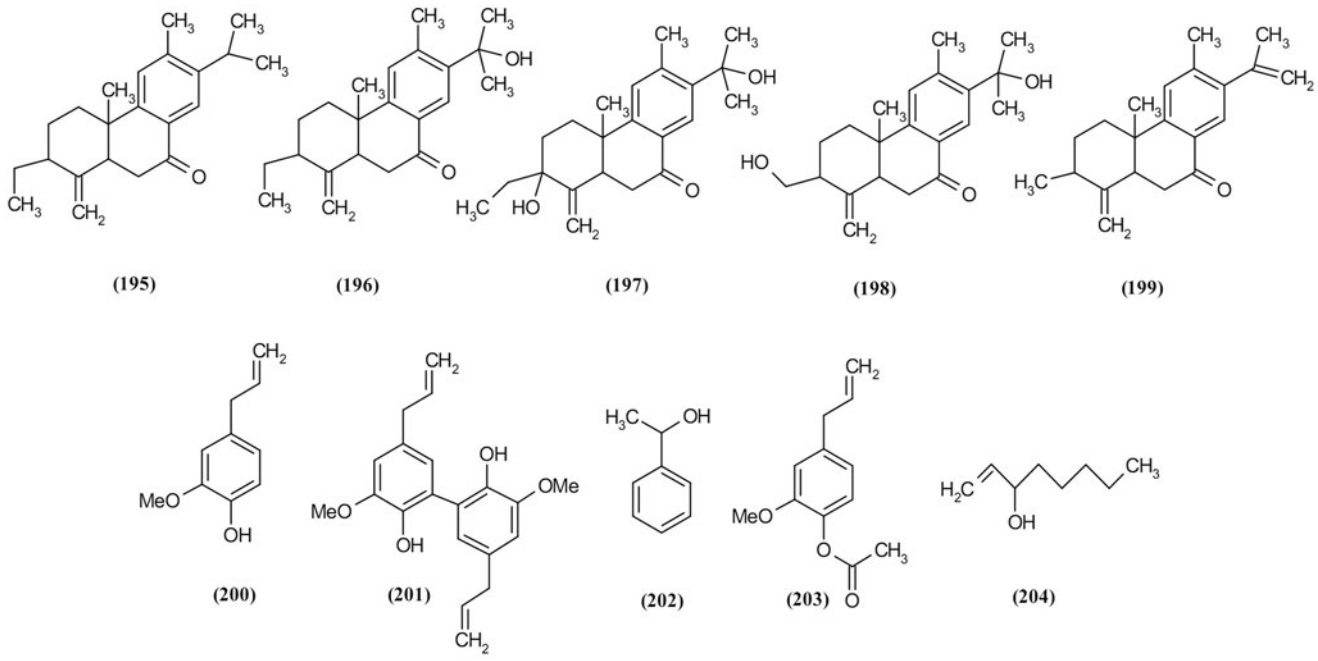


Figure 10. Diterpenoids and some of the essential oil major compositions of *Scrophularia* species.

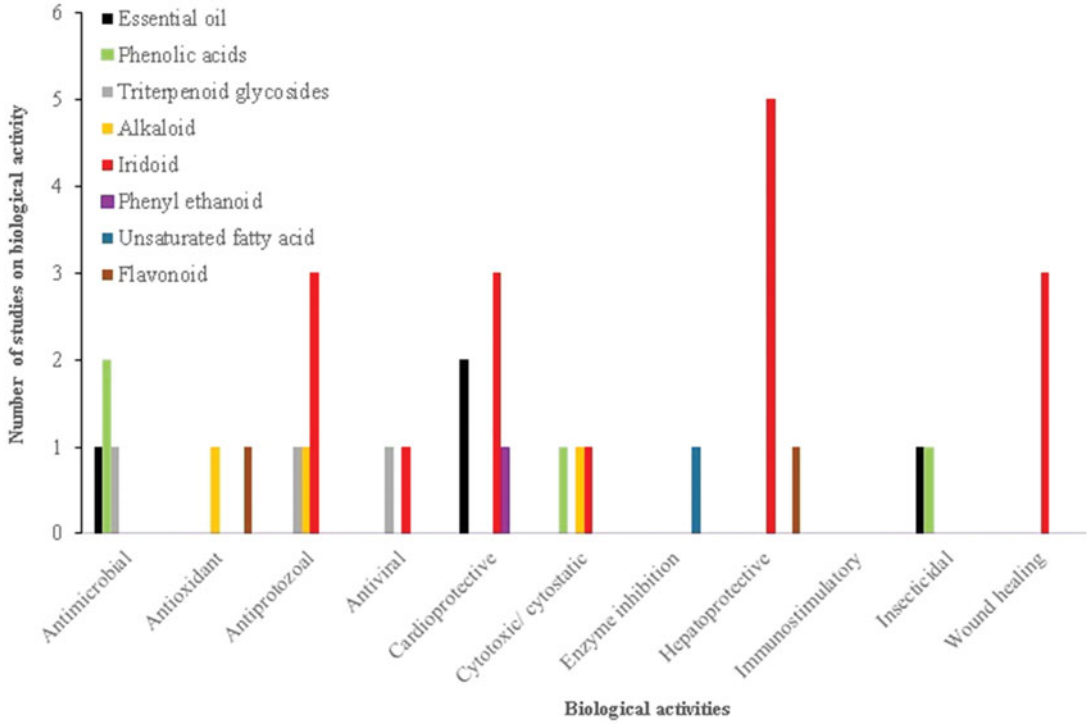


Figure 11. Studies on biological actives of *Scrophularia* spp. phytochemicals.

spp. extracts. Conducting ADME (absorption, distribution, metabolism and excretion) studies on the isolated bioactive compound of the genus seems to be essential.

In most cases, quantitative analysis of bioactive compounds has not been considered which might guide researchers to find other species of *Scrophularia* with more content of bioactive compounds. Despite the presence of some *Scrophularia* species in different pharmacopeias and their application in tradition or folk medicine of different societies, lack of analytical investigations on the bioactive compounds of these species resulted in difficulties in quality control and standardizations of these herbs.

Some metabolites, such as iridoids which also demonstrated some biological activities, are common between these plants and it is possible to consider them as biomarkers for *Scrophularia* spp.

Conducting complementary studies on isolated bioactive compound from this genus, such as Quantitative structure–activity relationship (QSAR) studies on the isolated bioactive compounds

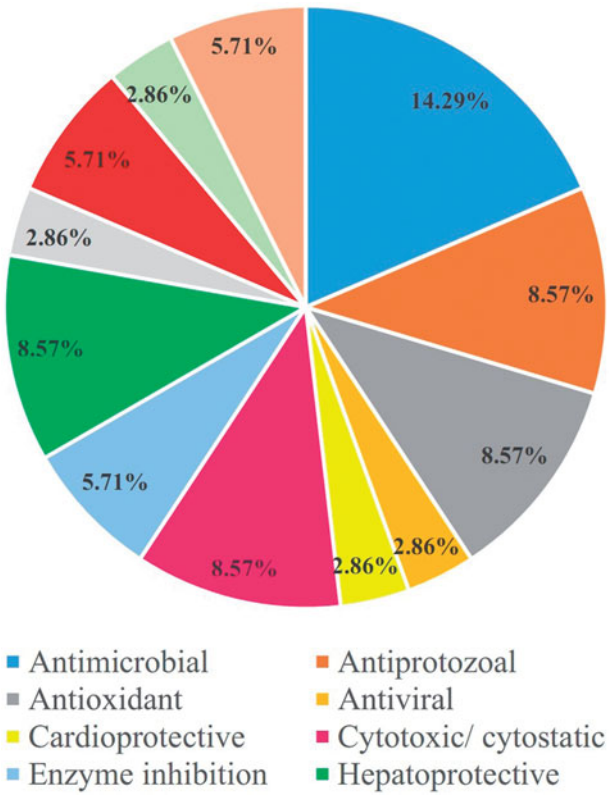


Figure 12. The ratio of biological activities reported for *Scrophularia* spp.

as well as preparing semi-synthetic derivatives, may result in more active metabolites.

## Disclosure statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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