



## Review

# Traditional uses, phytochemistry, and pharmacology of *Ailanthus altissima* (Mill.) Swingle bark: A comprehensive review

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## ABSTRACT

**Ethnopharmacological relevance:** The dried bark of *Ailanthus altissima* (Mill.) Swingle (BAA), commonly designated as “Chunpi” in Chinese, is extensively used as a common traditional medicine in China, Korea, and India. It has been used to treat multiple ailments, including asthma, epilepsy, spermatorrhea, bleeding, and ophthalmic diseases, for thousands of years.

**Aim of the review:** To present a comprehensive and constructive review on the phytochemistry, pharmacology, pharmacokinetics, traditional uses, quality control, and toxicology of BAA; to aid the assessment of the therapeutic potential of BAA; to guide researchers working on the development of novel therapeutic agents.

**Materials and methods:** Information related to BAA (from 1960 to 2020) was retrieved from a wide variety of electronic databases, such as PubMed, Web of Science, China Knowledge Resource Integrated Database, ScienceDirect, SciFinder, and Google Scholar. Additional information and materials were acquired from Chinese Medicine Monographs, the 2020 edition of the Chinese Pharmacopoeia, and several web sources, such as the official website of The Plant List and Flora of China. Additionally, perspectives for future investigations and applications of BAA were extensively explored.

**Results:** Approximately 221 chemical compounds, including alkaloids, quassinoids, phenylpropanoids, triterpenoids, volatile oils, and other compounds, have been isolated and characterized from BAA; among these, the quassinoid ailanthone is the most typical. The crude extracts and active compounds of BAA have been reported to exert a wide range of pharmacological activities, such as antitumor, anti-inflammatory, antiviral, herbicidal, and insecticidal activities. Although BAA is safe when administered at a conventional dose, at higher doses, it exhibits toxicity due to the presence of quassinoids. Thus, more studies are required to evaluate the efficacy and safety of BAA.

**Conclusion:** Modern pharmacological studies have revealed that BAA, as a valuable medicinal resource, possesses the potential to treat a wide variety of ailments, especially, cancer and gastrointestinal inflammation. These studies present a wide range of perspectives for the development of new drugs related to BAA. However, only a few traditional uses are associated with the reported pharmacological activities of BAA and have been confirmed by preclinical and clinical studies. Moreover, the pharmacokinetics, toxicology, and quality control of BAA should be considered indispensable research topics.

## 1. Introduction

*Ailanthus altissima* (Mill.) Swingle (Simaroubaceae) is a deciduous tree indigenous to India and South East Asia that has been widely cultivated in Africa, Oceania, and Europe due to its ornamental value (Zhang et al., 2007; Fogliatto et al., 2020). In addition, it is frequently used in the production of paper to reduce environmental pollution

(Ferreira et al., 2013; Baptista et al., 2014; Zhang et al., 2016). The dried bark of *A. altissima* (BAA), first recorded in *Xin Xiu Ben Cao* (新修本草), has been commonly utilized as a traditional herbal medicine for more than 2000 years. BAA is known by different names, including Chunpi or Cortex Ailanthi (China), Shinju or Niwaurushi (Japan), and Ailanthi radice cortex (Korea) (Masami et al., 1985; Ministry of Food and Drug Safety, 2014; National Pharmacopoeia Commission, 2020) and has been used extensively to treat asthma, epilepsy, spermatorrhea, bleeding,

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**Abbreviations**

|                  |                                                                |
|------------------|----------------------------------------------------------------|
| t <sub>1/2</sub> | elimination half-life;                                         |
| UV               | ultraviolet                                                    |
| IR               | infrared                                                       |
| AR               | androgen receptor                                              |
| QC               | quality control                                                |
| IC <sub>50</sub> | half maximal inhibitory concentration                          |
| LD <sub>50</sub> | median lethal dose                                             |
| LT <sub>50</sub> | median lethal time                                             |
| P23              | co-chaperone p23 protein                                       |
| BAA              | dried bark of <i>Ailanthus altissima</i> (Mill.) Swingle       |
| TCM              | traditional Chinese medicine                                   |
| TLC              | thin layer chromatography                                      |
| NMR              | nuclear magnetic resonance                                     |
| TMV              | tobacco mosaic virus                                           |
| MTT              | (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) |
| SFC              | supercritical fluid chromatography                             |
| LPS              | lipopolysaccharide                                             |
| HPLC             | high-performance liquid chromatography                         |
| SGCC             | silica gel column chromatography                               |
| SIRT1            | silent information regulator two homologue 1                   |
| NADH             | nicotinamide adenine dinucleotide                              |
| COX-2            | cyclooxygenase-2                                               |

|                     |                                                                     |
|---------------------|---------------------------------------------------------------------|
| LC-MS               | liquid chromatography-mass spectrometry                             |
| HSCCC               | high-speed counter-current chromatography                           |
| GC-MS               | gas chromatography-mass spectrometry                                |
| GC-FID              | gas chromatography-flame ionization detector                        |
| AUC <sub>0-6h</sub> | area under the plasma concentration versus time curve from 0 to 6 h |
| VEGF-A              | vascular endothelial growth factor A                                |
| C <sub>0</sub>      | initial plasma concentration                                        |
| TNF                 | tumor necrosis factor                                               |
| PGE <sub>2</sub>    | prostaglandin E <sub>2</sub>                                        |
| ID <sub>50</sub>    | median infective dose                                               |
| MCP-1               | monocyte chemoattractant protein-1                                  |
| NF-κB               | nuclear factor-kappa B                                              |
| IL                  | interleukin                                                         |
| CCK-8               | cell counting kit-8                                                 |
| Nrf2                | NF-E2-related factor 2                                              |
| NO                  | nitric oxide                                                        |
| PI3K                | phosphoinositide 3-kinase                                           |
| AKT                 | protein kinase B                                                    |
| JAK                 | Janus kinase                                                        |
| STAT3               | signal transducer and activator of transcription 3                  |
| YAP                 | yes-associated protein                                              |
| UPC <sup>2</sup>    | ultrapformance convergence chromatography                           |
| SAR                 | structure-activity relationship.                                    |
| TRAIL               | TNF-related apoptosis-inducing ligand                               |

ascariasis, and ophthalmic diseases (Yang et al., 2014; Kim et al., 2016). In traditional Chinese medicine (TCM), BAA is specifically exploited for its abilities to control leukorrhea, eliminate dampness, stop bleeding and diarrhea, and clear heat (National Pharmacopoeia Commission, 2020). Meanwhile, traditional medicinal use for BAA has been documented in India to treat spasms and destroy human parasites (Kundu and Laskar, 2010). Moreover, according to the Korean traditional medicine system, BAA is primarily administered for the treatment of bleeding, fever, infection, and inflammation (Kang et al., 2010). To date, many prescriptions containing BAA have been reported to exert considerable therapeutic effects as Chinese patent medicines, including Qianjin Zhidai Wan, Fuke Zhidai Pian, and Baidai Wan (National Pharmacopoeia Commission, 2020).

Currently, 221 compounds have been isolated and identified from BAA, including alkaloids, quassinoids, phenylpropanoids, triterpenoids, and volatile oils (Kim et al., 2016; Wang et al., 2017; Jeong et al., 2018; Du et al., 2020; Yan et al., 2020). Modern pharmacological studies have revealed that isolated components and crude extracts of BAA exert antitumor, anti-inflammatory, insecticidal, and herbicidal effects (Li et al., 2010; Cho et al., 2018; Demasi et al., 2019a; Gao et al., 2019; Kong et al., 2019; Liu et al., 2019). However, sufficient links between these pharmacological effects and traditional uses of BAA have not yet been established, and the bioactivities of only a few of the components have been explored. Besides, based on the Chinese Pharmacopoeia (National Pharmacopoeia Commission, 2020), BAA is non-toxic when used at conventional doses; however, its potential toxicity, due to the presence of quassinoids, cannot be ignored. Hence, more *in vitro* and *in vivo* experiments are necessary to critically evaluate the clinical effectiveness and safety of BAA.

To the best of our knowledge, comprehensive and valuable insights concerning BAA are lacking. Therefore, in this review, we comprehensively summarize and analyze existing knowledge (from 1960 to 2020) on botany, chemical constituents, pharmacological properties, pharmacokinetics, traditional uses, quality control, and toxicology of BAA. It is anticipated that the information presented in this review will address the existing research gaps and prove beneficial for researchers to determine further research directions.

## 2. Botany

### 2.1. Botanical characteristics

*Ailanthus altissima*, commonly referred to as the “tree of heaven”, is frequently used worldwide for boosting environmental greenery and papermaking purposes (Ferreira et al., 2013; Hong et al., 2013; Baptista et al., 2014). However, the rapid growth of *A. altissima* and wind dispersion may result in damage to facilities and attraction of pests that can threaten local crops (Zhang et al., 2016; Brusa and Holzappel, 2018; Campagnaro et al., 2018; Knüsel et al., 2018; Moos et al., 2019; Planchuelo et al., 2019; Trotta et al., 2020).

The *A. altissima* tree is approximately 20 m high and has smooth bark with vertical stripes on the surface; it possesses odd-pinnate compound leaves, measuring 40–60 cm in length, and the petiole length is approximately 7–13 cm. The leaves are composed of 13–27 ovate-lanceolate leaflet pairs, with an approximate length and width of 7–13 cm and 2.5–4 cm, respectively. The terminal racemes and pedicels are 1–2.5 mm long. The calyx is arranged in an imbricate shape with five sepals, each measuring 0.5–1 mm in length. The filaments in male and female flowers are longer and shorter than the petals, respectively. The samaras are long and elliptical, with an approximate length and width of 3–4.5 cm and 1–1.2 cm, respectively. The seeds are located in the middle of the samara and are oblate in shape. The flowering period of *A. altissima* ranges from April to May, while its fruiting period is from August to October. Four stamens are present, and the anthers are oblong and approximately 1 mm in size (<http://www.iplant.cn/frps>).

### 2.2. Distribution

*A. altissima* is widely distributed globally, except in Antarctica (Fogliatto et al., 2020). The official website, Flora of China, states that the main producing areas of *A. altissima* plants in China are Henan, Hebei, Gansu, Shanxi, Beijing, and Hubei provinces (<http://www.iplant.cn/frps>) (Fig. 1).



Fig. 1. Worldwide distribution of *Ailanthus altissima* (Mill.) Swingle.

### 3. Traditional uses

BAA was initially recorded in *Xin Xiu Ben Cao*, a renowned TCM monograph in China. This book elucidated that BAA acts as an intestinal astringent, tourniquet, and insecticide and can maintain hemostasis (He, 2013). BAA has also been recorded in numerous TCM books, such as *Ben Cao Tong Xuan* (本草通玄), *Yao Xing Lun* (药性论), *Shi Liao Ben Cao* (食疗本草), and *Ben Cao Shi Yi* (本草拾遗). In the Tang dynasty, antidiarrheal and insecticidal effects of BAA were recorded in *Ben Cao Shi Yi* (Shang, 2004). In addition, BAA is commonly used for relieving diarrhea and reducing stool output, as recorded in *Ri Hua Zi Ben Cao Ji Zhu* (日华子本草辑注) (Chang, 2016). According to *Ben Cao Zai Xin* (本草再新) (Ye,

1933), BAA is also used to remove phlegm from the lungs and stomach. According to *Yi Lin Zhuan Yao* (医林纂要) (Jiang, 2015), the main function of BAA is to relieve spleen dampness. A decoction of BAA can be taken orally to cure uterine bleeding, postpartum hemorrhage, acute and chronic dysentery, metritis, and enteritis (陕西中草药) (Shaanxi Provincial Revolutionary Committee, 1971).

As a Chinese medicine, BAA has been widely used in Chinese medicinal clinics in complex prescriptions with other Chinese herbs, which are produced in five formulations, namely tablets, decoctions, powders, ointments, and pills. Select Chinese prescriptions that include BAA are presented in Table 1. Qianjin Zhidai Wan is used clinically to treat vaginal discharge, edema, and chronic inflammation of the female

**Table 1**  
Traditional and clinical uses of prescriptions containing BAA in China.

| Preparation name                         | Main composition                                                                                                                                                                                                                                                                                                                                                                                                           | Formulation | Traditional and clinical uses                                                                                                           | References                                              |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Qianjin Zhidai Wan (千金止带丸)               | BAA, <i>Codonopsis</i> Radix, <i>Angelicae sinensis</i> Radix, <i>Aucklandiae</i> Radix, <i>Foeniculi</i> Fructus, <i>Eucommiae</i> Cortex, <i>Psoraleae</i> Fructus, <i>Indigo Naturalis</i> , <i>Ostreae Concha</i> , <i>Atractylodis macrocephalae</i> Rhizoma, <i>Paeoniae radix Alba</i> , <i>Cyper</i> Rhizoma, <i>Amomi</i> Fructus, <i>Corydalis</i> Rhizoma, <i>Dipsaci</i> Radix, <i>Celosiae cristatae</i> Flos | Pills       | Treatment of irregular menstruation, morbid vaginal discharge, edema, and chronic inflammation                                          | ; (Chen, 2011; National Pharmacopoeia Commission, 2020) |
| Baidai Wan (白带丸)                         | BAA, <i>Phellodendri chinensis</i> Cortex, <i>Paeoniae radix Alba</i> , <i>Angelicae sinensis</i> Radix, <i>Cyper</i> Rhizoma                                                                                                                                                                                                                                                                                              | Pills       | Treatment of epilepsy, asthma, yellowish leukorrhea, trichomonas vaginitis, amoeba vaginitis, senile vaginitis, and cervix inflammation | ; (Chen, 2012; National Pharmacopoeia Commission, 2020) |
| Chunpi Tang (椿皮汤)                        | BAA                                                                                                                                                                                                                                                                                                                                                                                                                        | Decoction   | Treatment of uterine bleeding, postpartum hemorrhage, acute and chronic dysentery, metritis, and enteritis                              | Shaanxi Provincial Revolutionary Committee (1971)       |
| Fuke Zhidai Pian/ Jiaonang (妇科止带片/胶囊)    | BAA, <i>Phellodendri chinensis</i> Cortex, <i>Poria</i> , <i>Dioscoreae</i> Rhizoma, <i>Schisandrae chinensis</i> Fructus, <i>Testudinis carapax</i> et <i>Plastrum</i> , <i>Asini corii</i> Colla                                                                                                                                                                                                                         | Pills       | Treatment of chronic cervicitis, endometritis, and vaginal mucositis                                                                    | (National Pharmacopoeia Commission, 2020)               |
| Shaoqi Chunpi Tang (芍药椿皮汤)               | BAA, <i>Paeoniae radix Alba</i> , <i>Coptidis</i> Rhizoma, <i>Astragali</i> Radix, <i>Codonopsis</i> Radix, <i>Poria</i> , <i>Angelicae sinensis</i> Radix, <i>Arecae</i> Semen, <i>Aucklandiae</i> Radix, <i>Cinnamomi</i> Cortex, <i>Glycyrrhizae radix</i> et <i>Rhizoma</i>                                                                                                                                            | Decoction   | Treatment of large intestine damp-heat ulcerative colitis                                                                               | Li (2020)                                               |
| Qinjiao Chunpi Tang (秦艽椿皮汤)              | BAA, <i>Gentianae macrophyllae</i> Radix, <i>Atractylodis</i> Rhizoma, <i>Phellodendri chinensis</i> Cortex                                                                                                                                                                                                                                                                                                                | Decoction   | Treatment of ulcerative colitis                                                                                                         | Bu and Zhang (1997)                                     |
| Chunpi Shoutai Tang (椿皮寿胎汤)              | BAA, <i>Pulsatillae</i> Radix, <i>Lonicerae japonicae</i> Caulis, <i>Taxilli</i> Herba, <i>Asini corii</i> Colla, <i>Pseudostellariae</i> Radix, <i>Astragali</i> Radix, <i>Scutellariae</i> Radix, <i>Mori Folium</i>                                                                                                                                                                                                     | Decoction   | Treatment of late threatening abortion                                                                                                  | Wang and Chen (2019)                                    |
| Chunpi San (椿皮散)                         | BAA, <i>Zingiberis</i> Rhizoma, <i>Glycyrrhizae radix</i> et <i>Rhizoma</i> , <i>Aconiti lateralis radix Praeparata</i>                                                                                                                                                                                                                                                                                                    | Powder      | Treatment of anterior Wei relaxation, ruminant eating, and rumen gas in dairy cows                                                      | (Cao, 2012; Li, 2014, 2020)                             |
| Chunpi Gao (椿皮膏)                         | BAA                                                                                                                                                                                                                                                                                                                                                                                                                        | Ointment    | Treatment of stubborn flatulence                                                                                                        | Zhao and Niu (1993)                                     |
| Chunpi Yin (椿皮饮)                         | BAA, <i>Atractylodis macrocephalae</i> Rhizoma, <i>Platycladi</i> Cacumen, <i>Trachycarpi</i> Petiolus                                                                                                                                                                                                                                                                                                                     | Decoction   | Treatment of dysfunctional uterine bleeding induced by hepatic heat and spleen asthenia                                                 | Gao and Wang (1983)                                     |
| Jiuxiang Zhixie Changrong Pian (九香止泻肠溶片) | BAA, <i>Fraxini</i> Cortex, <i>Aucklandiae</i> Radix                                                                                                                                                                                                                                                                                                                                                                       | Tablets     | Treatment of damp-heat acute chronic diarrhea                                                                                           | Li et al. (2008)                                        |

reproductive system (Chen, 2011). Baidai Wan is used for the treatment of epilepsy, asthma, yellowish leukorrhea, trichomonas vaginitis, amoeba vaginitis, senile vaginitis, and cervix inflammation (Chen, 2012). Fuke Zhidai Pian is used to treat chronic cervicitis, endometritis, and vaginal mucositis (National Pharmacopoeia Commission, 2020). Shaoqi Chunpi Tang contains BAA, Paeoniae radix Alba, Coptidis Rhizoma, Astragali Radix, *Codonopsis* Radix, Poria, Angelicae Sinensis Radix, Areca Semen, Aucklandiae Radix, Cinnamomi Cortex, and Glycyrrhizae radix et Rhizoma, and it has been used to treat damp-heat ulcerative colitis of the large intestine (Qian, 2017). According to the latest version of the Chinese Pharmacopoeia (National Pharmacopoeia Commission, 2020), BAA has been described as cold in property and bitter in flavor. It is associated with the large intestine, stomach, and liver meridians. Based on its ability to clear heat and dampness; reduce astringency; and stop leukorrhea, diarrhea, and bleeding, BAA has been used to treat leukorrhea, cold, damp-heat and chronic diarrhea, bloody stool, and uterine bleeding. The recommended dosage is 6–9 g (National Pharmacopoeia Commission, 2020).

Apart from the above therapeutic effects, BAA has also demonstrated extensive medicinal value in folk medicine. Along with *Atractylodes macrocephala*, *Gardenia* spp., *Platycladus orientalis*, *Palm charcoal*, and *Sanguis Char*, it is effective in treating dysfunctional uterine bleeding induced by hepatic heat and spleen asthenia (Gao and Wang, 1983). Moreover, the application of Chunpi ointment to the belly button is recommended for the treatment of refractory flatulence and bacillary dysentery (Zhao and Niu, 1993). BAA has also been used in Chinese folk medicine in the form of Chunpi San, owing to its ability to ameliorate anterior gastric relaxation, ruminant eating, and rumen gas in dairy cows (Cao, 2012; Li, 2014, 2020).

#### 4. Phytochemistry

To date, more than 221 chemical compounds have been isolated from BAA and characterized by high-performance liquid chromatography (HPLC), thin-layer chromatography, silica gel column chromatography, Sephadex LH-20 column chromatography, nuclear magnetic resonance, ultraviolet-visible spectrophotometry, and infrared

spectroscopy (Kim et al., 2016; Jeong et al., 2018; Lv et al., 2020; Yan et al., 2020). The main isolated compounds are alkaloids, quassinoids, phenylpropanoids, triterpenoids, and volatile oils (Fig. 2). Among these, quassinoids are characteristic components and the most widely studied components in pharmacology. Ailanthone, a type of quassinoid, is the most characteristic and active ingredient of BAA. Owing to the presence of multiple compounds and significant pharmacological effects, BAA has great potential as a therapeutic drug in the future. Modern pharmacological studies have demonstrated that ailanthone is primarily associated with the treatment of cancer. In addition, canthin-6-one alkaloids are major active compounds and possess various biological properties, such as sedative, hypnotic, anti-inflammatory, and anticancer activities. Quassinoids and alkaloids have been considered promising chemical markers. However, the quantitative detection of these chemical compounds requires further detailed and comprehensive research. Furthermore, the compounds for quality evaluation in the Chinese Pharmacopoeia have not yet been determined. Therefore, the international harmonization of quality standards for some ingredients, such as canthin-6-one (14), 9-hydroxycanthin-6-one (19), 1-methoxy-canthin-6-one (22), ailanthone (34), and altissimacoumarin C (75) should be critically established. More notably, compounds including triterpenoids, phenylpropanoids, and volatile oils have not been found to possess remarkable bioactivities, and studies on these compounds should be conducted in the future. Detailed information concerning these compounds is listed in Table 2, and their corresponding chemical structures are outlined in Figs. 3–8.

##### 4.1. Alkaloids

Alkaloids are the main active components in BAA, of which indole alkaloids account for a large proportion. Indole alkaloids are primarily divided into three structural types: canthin-6-one,  $\beta$ -carboline, and canthin-6-one-3-N-oxide (Fig. 3). To date, 32 alkaloids have been isolated from BAA and have been found to possess multiple pharmacological activities. In particular, the activities of the canthin-6-one alkaloids have been comprehensively reported. Canthin-6-one (14) has a sedative and hypnotic effect on mice and displays anti-inflammatory

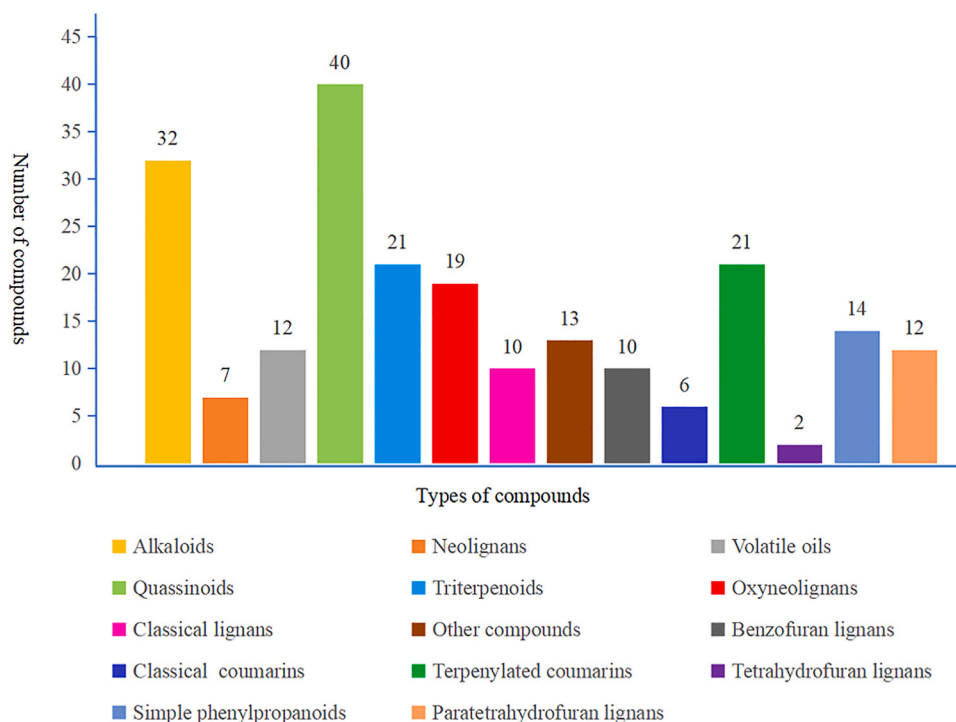


Fig. 2. Types and number of compounds isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

**Table 2**  
Compounds isolated from BAA.

| NO.                | Compound                                                                                                                       | Bioactivity                                                                          | Extraction solvent                              | Country                      | References                                                                     |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------|--------------------------------------------------------------------------------|
| <b>Alkaloids</b>   |                                                                                                                                |                                                                                      |                                                 |                              |                                                                                |
| 1                  | 1-methyl- $\beta$ -carboline                                                                                                   | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 2                  | 1-acetyl-4-methoxy- $\beta$ -carboline                                                                                         | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 3                  | 1-carbamoyl- $\beta$ -carboline                                                                                                | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto and Koike (1984)                                                        |
| 4                  | 1-ethyl-4-methoxy- $\beta$ -carboline                                                                                          | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 5                  | 1-ethyl- $\beta$ -carboline                                                                                                    | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 6                  | Methyl 4-methoxy- $\beta$ -carboline-1-carboxylate                                                                             | N/A                                                                                  | Benzene                                         | Hungary                      | Varga et al. (1980)                                                            |
| 7                  | 1-methoxycarbonyl-4,8-dimethoxy- $\beta$ -carboline                                                                            | N/A                                                                                  | Benzene                                         | Greece                       | Souleles and Kokkalou (1989)                                                   |
| 8                  | 1-methoxycarbonyl- $\beta$ -carboline                                                                                          | N/A                                                                                  | Benzene                                         | Greece                       | Souleles and Kokkalou (1989)                                                   |
| 9                  | 1-(2'-hydroxyethyl)-4-methoxy- $\beta$ -carboline                                                                              | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 10                 | $\beta$ -carboline-1-propionic acid                                                                                            | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto and Koike (1984)                                                        |
| 11                 | 1-(1', 2'-dihydroxyethyl)-4-methoxy- $\beta$ -carboline                                                                        | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 12                 | 1-(1', 2'-dihydroxyethyl)-3-hydroxymethyl- $\beta$ -carboline                                                                  | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 13                 | 1-(1-hydroxy, 2-methoxy)methyl-4-methoxy- $\beta$ -carboline                                                                   | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto and Koike (1984)                                                        |
| 14                 | Canthin-6-one                                                                                                                  | Anti-inflammatory activity, Antitumor Activity, Sedative activity, Hypnotic activity | Ethyl acetate, Chloroform, Benzene              | Japan, Korea, Hungary, China | (Ohmoto et al., 1981; Varga et al., 1980; Kim et al., 2016; Shao et al., 2020) |
| 15                 | 4-hydroxycanthin-6-one                                                                                                         | N/A                                                                                  | <i>N</i> -Butanol                               | Italy, Korea                 | (Crespi-Perellino et al., 2004; Kim et al., 2016)                              |
| 16                 | 1-hydroxycanthin-6-one                                                                                                         | N/A                                                                                  | <i>N</i> -buthanol                              | Italy                        | Crespi-Perellino et al. (2004)                                                 |
| 17                 | 5-hydroxycanthin-6-one                                                                                                         | N/A                                                                                  | <i>N</i> -buthanol                              | Italy                        | Crespi-Perellino et al. (2004)                                                 |
| 18                 | 2-hydroxycanthin-6-one                                                                                                         | N/A                                                                                  | <i>N</i> -buthanol                              | Italy                        | Crespi-Perellino et al. (2004)                                                 |
| 19                 | 9-hydroxycanthin-6-one                                                                                                         | Anti-inflammatory activity; Antitumor activity                                       | Ethyl acetate                                   | Korea                        | (Kim et al., 2016; Jeong et al., 2018)                                         |
| 20                 | 10-hydroxycanthin-6-one                                                                                                        | Antitumor activity                                                                   | Ethyl acetate                                   | Korea                        | (Kim et al., 2016; Jeong et al., 2018)                                         |
| 21                 | 11-hydroxycanthin-6-one                                                                                                        | N/A                                                                                  | Ethyl acetate                                   | Korea                        | Kim et al. (2016)                                                              |
| 22                 | 1-methoxy-canthin-6-one                                                                                                        | N/A                                                                                  | Chloroform, Benzene, Chloroform                 | Japan                        | (Ohmoto et al., 1981; Varga et al., 1980)                                      |
| 23                 | 5-hydroxymethylcanthin-6-one                                                                                                   | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto and Koike (1984)                                                        |
| 24                 | (R)-5-(1-hydroxyethyl)-canthin-6-one                                                                                           | Anti-inflammatory activity; Antitumor activity                                       | Ethyl acetate                                   | Korea                        | (Kim et al., 2016; Jeong et al., 2018)                                         |
| 25                 | Canthin-6-one-3 <i>N</i> -oxide                                                                                                | N/A                                                                                  | Chloroform                                      | Japan                        | Ohmoto et al. (1981)                                                           |
| 26                 | 1-methoxycanthin-6-one-3 <i>N</i> -oxide                                                                                       | N/A                                                                                  | Chloroform, <i>N</i> -Buthanol                  | Japan, Italy                 | (Ohmoto et al., 1981; Crespi-Perellino et al., 2004)                           |
| 27                 | 4, 5-dihydrocanthin-6-one                                                                                                      | N/A                                                                                  | <i>N</i> -buthanol                              | Italy                        | Crespi-Perellino et al. (2004)                                                 |
| 28                 | Ailantcanthin-6-one A                                                                                                          | N/A                                                                                  | <i>N</i> -buthanol                              | China                        | Zhang et al. (2007)                                                            |
| 29                 | Ailantcanthin-6-one B                                                                                                          | N/A                                                                                  | <i>N</i> -buthanol                              | China                        | Zhang et al. (2007)                                                            |
| 30                 | Canthin-6-one-1- <i>O</i> - $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 2)- $\beta$ -D-glucopyranoside                           | Anti-inflammatory activity                                                           | <i>N</i> -butanol                               | Korea                        | Kim et al. (2015)                                                              |
| 31                 | Canthin-6-one-1- <i>O</i> -[6- <i>O</i> -(3-hydroxy-3-methylglutaryl)]- $\beta$ -D-glucopyranoside                             | Anti-inflammatory activity                                                           | <i>N</i> -butanol                               | Korea                        | Kim et al. (2015)                                                              |
| 32                 | Canthin-6-one-1- <i>O</i> -[2- $\beta$ -D-apiofuranosyl-6- <i>O</i> -(3-hydroxy-3-methylglutaryl)]- $\beta$ -D-glucopyranoside | Anti-inflammatory                                                                    | <i>N</i> -butanol                               | Korea                        | Kim et al. (2015)                                                              |
| <b>Quassinoids</b> |                                                                                                                                |                                                                                      |                                                 |                              |                                                                                |
| 33                 | Amarolide                                                                                                                      | N/A                                                                                  | 95% Ethanol                                     | China                        | Wang et al. (2013)                                                             |
| 34                 | Ailanthone                                                                                                                     | Antitumor activity; Anti-inflammatory activity                                       | Water, 95% Ethanol, Dichloromethane             | Japan, China                 | (Niimi et al., 1986; Wang et al., 2013, 2017)                                  |
| 35                 | 2-dihydroailanthone                                                                                                            | Antitumor activity                                                                   | Dichloromethane                                 | China                        | Wang et al. (2017)                                                             |
| 36                 | Shinjudilactone                                                                                                                | Anti-inflammatory activity                                                           | Ethyl acetate, Dichloromethane                  | Japan, Korea                 | (Kim et al., 2015; Wang et al., 2017)                                          |
| 37                 | Shinjulactone A                                                                                                                | Antitumor activity, Anti-inflammatory activity                                       | <i>N</i> -Butanol, 50% Ethanol, 95% Ethanol     | Japan, China                 | (Naora et al., 1983; Wang et al., 2013; Yang et al., 2014)                     |
| 38                 | Shinjulactone B                                                                                                                | Anti-tumor activity                                                                  | <i>N</i> -Butanol, Dichloromethane, 95% Ethanol | Japan, China                 | (Furuno et al., 1984b; Wang et al., 2013, 2017)                                |
| 39                 | Shinjulactone C                                                                                                                | Antitumor activity                                                                   | 95% Ethanol, Dichloromethane, Water             | Japan; China                 | (Masami et al., 1982, 1983; Wang et al., 2013; Yang et al., 2014)              |
| 40                 | Shinjulactone D                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984b)                                                          |
| 41                 | Shinjulactone E                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984b)                                                          |
| 42                 | Shinjulactone F                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984a)                                                          |
| 43                 | Shinjulactone G                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Ishibashi et al. (1984)                                                        |
| 44                 | Shinjulactone H                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Ishibashi et al. (1984)                                                        |
| 45                 | Shinjulactone I                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984a)                                                          |
| 46                 | Shinjulactone J                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984a)                                                          |
| 47                 | Shinjulactone K                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Furuno et al. (1984a)                                                          |
| 48                 | Shinjulactone L                                                                                                                | N/A                                                                                  | Dichloromethane                                 | Japan                        | Masami et al. (1985)                                                           |

(continued on next page)

Table 2 (continued)

| NO.              | Compound                                                         | Bioactivity                                 | Extraction solvent       | Country         | References                                                |
|------------------|------------------------------------------------------------------|---------------------------------------------|--------------------------|-----------------|-----------------------------------------------------------|
| 49               | Shinjulactone M                                                  | Antitumor activity                          | Dichloromethane          | Japan;<br>China | (Niimi et al., 1986; Yang et al., 2014)                   |
| 50               | Shinjulactone N                                                  | N/A                                         | Dichloromethane          | Japan           | Niimi et al. (1986)                                       |
| 51               | Shinjulactone O                                                  | Antitumor activity                          | Water                    | China           | Yang et al. (2014)                                        |
| 52               | Ailantinal A                                                     | N/A                                         | Chloroform               | Japan           | Kubota et al. (1996a)                                     |
| 53               | Ailantinal B                                                     | N/A                                         | Chloroform               | Japan           | Kubota et al. (1996a)                                     |
| 54               | Ailantinal C                                                     | N/A                                         | Chloroform               | Japan           | Kubota et al. (1996b)                                     |
| 55               | Ailantinal D                                                     | N/A                                         | Chloroform               | Japan           | Kubota et al. (1996b)                                     |
| 56               | Ailantinal E                                                     | N/A                                         | Chloroform               | Japan           | Tamura et al. (2003)                                      |
| 57               | Ailantinal F                                                     | N/A                                         | Chloroform               | Japan           | Tamura et al. (2003)                                      |
| 58               | Ailantinal G                                                     | N/A                                         | Chloroform               | Japan           | Tamura et al. (2003)                                      |
| 59               | Altissinol A                                                     | Antitumor activity                          | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 60               | Altissinol B                                                     | Antitumor activity                          | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 61               | 13,18-dehydroglaucaurubinone                                     | Antitumor activity                          | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 62               | (-)-chaparrinone                                                 | Antitumor activity                          | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 63               | 6a-tigloyloxychaparrinone                                        | Antitumor activity                          | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 64               | 6a-tigloyloxychaparrin                                           | Antitumor activity                          | 50% Ethanol, 95% Ethanol | China           | (Wang et al., 2013; Yang et al., 2014)                    |
| 65               | Glaucaurubin                                                     | N/A                                         | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 66               | 11-acetylamarolide                                               | N/A                                         | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 67               | Chaparrilide                                                     | N/A                                         | 95% Ethanol              | China           | Wang et al. (2013)                                        |
| 68               | Shinjuglycoside B                                                | Anti-inflammatory activity                  | Dichloromethane          | Korea           | Kim et al. (2015)                                         |
| 69               | Isoailanthone                                                    | Antitumor activity                          | Dichloromethane          | China           | (Yang et al., 2014; Wang et al., 2017)                    |
| 70               | 12-dihydroisoailanthone                                          | Antitumor activity                          | Dichloromethane          | China           | Wang et al. (2017)                                        |
| 71               | Chuglycoside J                                                   | Antiviral activity                          | Chloroform               | China           | Tan et al. (2020)                                         |
| 72               | Chuglycoside K                                                   | Antiviral activity                          | Chloroform               | China           | Tan et al. (2020)                                         |
| Phenylpropanoids |                                                                  |                                             |                          |                 |                                                           |
| 73               | Altissimacoumarin A                                              | N/A                                         | Ethyl acetate            | Korea           | Hwang et al. (2005)                                       |
| 74               | Altissimacoumarin B                                              | N/A                                         | Ethyl acetate            | Korea;<br>China | (Hwang et al., 2005; Hong et al., 2013)                   |
| 75               | Altissimacoumarin C                                              | Deacetylation activity; Antitumor activity  | Ethyl acetate            | Korea           | (Dao et al., 2012; Yan et al., 2020; Duan et al., 2021)   |
| 76               | Altissimacoumarin D                                              | Deacetylation activity                      | Ethyl acetate            | Korea;<br>China | (Dao et al., 2012; Hong et al., 2013)                     |
| 77               | Altissimacoumarin E                                              | Deacetylation activity, Anti-tumor activity | Ethyl acetate            | Korea           | (Dao et al., 2012; Yan et al., 2020)                      |
| 78               | Altissimacoumarin F                                              | Deacetylation activity                      | Ethyl acetate            | Korea           | Dao et al. (2012)                                         |
| 79               | Altissimacoumarin G                                              | Anti-tumor activity                         | Methanol, Ethyl acetate  | China           | (Hong et al., 2013; Yan et al., 2020)                     |
| 80               | Altissimacoumarin H                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 81               | Altissimacoumarin I                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 82               | Altissimacoumarin J                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 83               | Altissimacoumarin K                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 84               | Altissimacoumarin L                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 85               | Altissimacoumarin M                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 86               | Altissimacoumarin N                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 87               | Altissimacoumarin O                                              | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 88               | Altissimacoumarin P                                              | N/A                                         | Ethyl acetate            | China           | Duan et al. (2021)                                        |
| 89               | Altissimacoumarin Q                                              | N/A                                         | Ethyl acetate            | China           | Duan et al. (2021)                                        |
| 90               | Zantholin A                                                      | N/A                                         | Ethyl acetate            | China           | Duan et al. (2021)                                        |
| 91               | Ailanthuscoumarin                                                | Anti-tumor activity                         | Ethyl acetate            | China           | Lv et al. (2020)                                          |
| 92               | Puberulin                                                        | Anti-tumor activity                         | Ethyl acetate            | China           | (Yan et al., 2020; Duan et al., 2021; Zhang et al., 2020) |
| 93               | 7-(3-methyl-2-butenyloxy)-6-methoxycoumarin                      | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 94               | Artelin                                                          | Anti-tumor activity                         | Ethyl acetate            | China           | Yan et al. (2020)                                         |
| 95               | (+)-7R,8R-cleomiscosin A                                         | N/A                                         | Ethyl acetate            | China           | Yan et al. (2018)                                         |
| 96               | (-)-7S,8S-cleomiscosin A                                         | N/A                                         | Ethyl acetate            | China           | Yan et al. (2018)                                         |
| 97               | Isofraxidin                                                      | N/A                                         | Ethyl acetate            | Korea           | Kim et al. (2015)                                         |
| 98               | Scopoletin                                                       | Antitumor activity                          | Ethyl acetate            | Korea           | (Kim et al., 2016; Jeong et al., 2018)                    |
| 99               | 5-hydroxy-6,7,8-trimethoxycoumarin                               | N/A                                         | Ethyl acetate            | China           | Zhang et al. (2020)                                       |
| 100              | (+)-7S,8R-4,9,9'-trihydroxy-3,7,3'-trimethoxy-8,4'-oxyneolignan  | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 101              | (-)-7R, 8S-4,9,9'-trihydroxy-3,7,3'-trimethoxy-8,4'-oxyneolignan | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 102              | (+)-7S,8S-4,9,9'-trihydroxy-3,7,3'-trimethoxy-8,4'-oxyneolignan  | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 103              | (-)-7R,8R-4,9,9'-trihydroxy-3,7,3'-trimethoxy-8,4'-oxyneolignan  | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 104              | (-)-7R,8R-4,9,9'-trihydroxy-7,3',5'-trimethoxy-8,4'-oxyneolignan | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 105              | (+)-7S,8S-4,9,9'-trihydroxy-7,3',5'-trimethoxy-8,4'-oxyneolignan | N/A                                         | N-buthanol               | China           | Du et al. (2019a)                                         |
| 106              |                                                                  | Neuroprotective activity                    | N-buthanol               | China           | Du et al. (2019a)                                         |

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Table 2 (continued)

| NO. | Compound                                                                              | Bioactivity                                     | Extraction solvent        | Country      | References                             |
|-----|---------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------|--------------|----------------------------------------|
| 107 | (-)-7R,8R-4,9,9'-trihydroxy-3,7,3',5'-tetramethoxy-8,4'-oxyneolignan                  | Neuroprotective activity                        | N-buthanol                | China        | Du et al. (2019a)                      |
| 108 | (+)-7S,8S-4,9,9'-trihydroxy-3,7,3',5'-tetramethoxy-8,4'-oxyneolignan                  | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 109 | (-)-7R,8S-4,7,9-trihydroxy-3,3',9'-trimethoxy-1'-allyl-8,4'-oxyneolignan              | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 110 | (+)-7S,8S-4,7,9-trihydroxy-3,3',9'-trimethoxy-1'-allyl-8,4'-oxyneolignan              | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 111 | (-)-7R,8R-4,7,9-trihydroxy-3,3',9'-trimethoxy-1'-allyl-8,4'-oxyneolignan              | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 112 | (+)-7S,8R-4,7,9,9'-trihydroxy-3'-methoxy-8,4'-oxyneolignan                            | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 113 | (-)-7R,8S-4,7,9,9'-trihydroxy-3'-methoxy-8,4'-oxyneolignan                            | N/A                                             | N-buthanol                | China        | Du et al. (2019a)                      |
| 114 | (-)-7R,8S-guaiacylglycerol 8-(4-hydroxymethyl-2-ethoxyphenyl) ether                   | Neuroprotective activity                        | N-buthanol                | China        | Du et al. (2019a)                      |
| 115 | (+)-7R,8S-guaiacylglycerol 8-(4-hydroxymethyl-2-ethoxyphenyl) ether                   | Anti-inflammatory activity; Anti-tumor activity | Ethyl acetate             | Korea        | (Kim et al., 2016; Jeong et al., 2018) |
| 117 | Evofofin B                                                                            | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 118 | 7R,8R-threo-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-O-4'-neolignan                     | N/A                                             | Chloroform                | China        | Tan et al. (2020)                      |
| 119 | Seco-dehydrodiconiferyl alcohol-4-O- $\beta$ -D-glucopyranoside                       | N/A                                             | Water                     | China        | Tan et al. (2012)                      |
| 120 | Dehydrodiconiferyl alcohol-4-O- $\beta$ -D-glucopyranoside                            | N/A                                             | Water                     | China        | Tan et al. (2012)                      |
| 121 | Dihydrodehydrodiconiferyl alcohol                                                     | N/A                                             | Water                     | China        | Tan et al. (2012)                      |
| 122 | Dihydrodehydrodiconiferyl alcohol-4-O- $\beta$ -D-glucopyranoside                     | N/A                                             | Water                     | China        | Tan et al. (2012)                      |
| 123 | 7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan-4-O- $\beta$ -D-glucopyranoside | Antiviral activity                              | Water                     | China        | Tan et al. (2012)                      |
| 124 | Sonchifolignan B                                                                      | Antiviral activity                              | Water                     | China        | Tan et al. (2012)                      |
| 125 | Citrusin B                                                                            | Antiviral activity                              | Water                     | China        | Tan et al. (2012)                      |
| 126 | (+)-7S,8R-ailanthussin A                                                              | Anti-tumor activity                             | Ethyl acetate             | China        | Yan et al. (2018)                      |
| 127 | (-)-7R,8S-ailanthussin A                                                              | Anti-tumor activity                             | Ethyl acetate             | China        | Yan et al. (2018)                      |
| 128 | (+)-7S,8R-curlignan                                                                   | N/A                                             | Ethyl acetate             | China        | Yan et al. (2018)                      |
| 129 | (-)-7R,8S-curlignan                                                                   | N/A                                             | Ethyl acetate             | China        | Yan et al. (2018)                      |
| 130 | Toonin C                                                                              | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 131 | Balanophonin                                                                          | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 132 | 4,9-dihydroxy-3,5'-dimethoxy-4',7-epoxy-8,5'-neolignane-9'-ylacetate                  | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 133 | Jatrointelignan D                                                                     | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 134 | Dehydroconiferyl alcohol                                                              | Antitumor activity                              | Ethyl acetate, Chloroform | China; Korea | (Jeong et al., 2018; Tan et al., 2020) |
| 135 | Curcasinlignan B                                                                      | N/A                                             | Chloroform                | China        | Tan et al. (2020)                      |
| 136 | Threo-2,3-bis-(4-hydroxy-3-methoxyphenyl)-3-methoxypropanol                           | N/A                                             | N-butanol                 | China        | Tan et al. (2020)                      |
| 137 | Alangilignoside D                                                                     | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 138 | 3',4-dimethoxy-7,9'-epoxylignane-3,4'-diol                                            | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 139 | Buddlenol C                                                                           | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 140 | Buddlenol D                                                                           | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 141 | Buddlenol E                                                                           | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 142 | Kandelisesquillignan A                                                                | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 143 | Conidendrin                                                                           | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 144 | Hedyotisol A                                                                          | N/A                                             | Ethyl acetate             | China        | Zhang et al. (2020)                    |
| 145 | Ficusesquillignan B                                                                   | Antitumor activity                              | Ethyl acetate             | Korea        | (Kim et al., 2016; Jeong et al., 2018) |
| 146 | Syringaresinol                                                                        | Anti-inflammatory activity                      | Ethyl acetate             | Korea        | Kim et al. (2015)                      |
| 147 | Tetrahydro-2-(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxyphenyl) methyl]-3-furanmethanol | N/A                                             | Trichloromethane          | China        | Tan et al. (2020)                      |
| 148 | (+)-lariciresinol                                                                     | N/A                                             | N-butanol                 | China        | Tan et al. (2020)                      |
| 149 | (+)-(1R,2S,5R,6S)-2,6-di(4'-hydroxyphenyl)-3,7-dioxabicyclo [3.3.0]octane             | N/A                                             | Chloroform                | China        | Tan et al. (2020)                      |
| 150 | (+)-pinoresinol                                                                       | N/A                                             | N-butanol                 | China        | Tan et al. (2020)                      |
| 151 | 7'S*-methoxy-7-epi-lariciresinol                                                      | Anti-tumor activity                             | N-butanol                 | China        | Du et al. (2019b)                      |
| 152 | (-)-secoisolariciresinol                                                              | Anti-tumor activity                             | N-butanol                 | China        | Du et al. (2019b)                      |
| 153 | (+)-isolariciresinol                                                                  | Anti-tumor activity                             | N-butanol                 | China        | Du et al. (2019b)                      |
| 154 | (+)-isolariciresinol 3 $\alpha$ -O- $\beta$ -glucopyranoside                          | Anti-tumor activity                             | Chloroform                | China        | Tan et al. (2020)                      |
| 155 | Burselignan                                                                           | N/A                                             | N-butanol                 | China        | Tan et al. (2020)                      |
| 156 | Densipicoside                                                                         | N/A                                             | Chloroform                | China        | Tan et al. (2020)                      |
| 157 | Secoisolariciresinol                                                                  | N/A                                             | Chloroform                | China        | Tan et al. (2020)                      |
| 158 | (-)-lyoniresinol                                                                      | Antitumor activity                              | N-butanol                 | China        | Du et al. (2019b)                      |

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Table 2 (continued)

| NO.             | Compound                                                                                                  | Bioactivity                | Extraction solvent | Country      | References                             |
|-----------------|-----------------------------------------------------------------------------------------------------------|----------------------------|--------------------|--------------|----------------------------------------|
| 159             | Polystachyol                                                                                              | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 160             | (+)-7S,8S-alatusol A                                                                                      | N/A                        | Ethyl acetate      | China        | Yan et al. (2018)                      |
| 161             | (-)-7R,8R-alatusol A                                                                                      | N/A                        | Ethyl acetate      | China        | Yan et al. (2018)                      |
| 162             | 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one                                                      | Anti-inflammatory activity | Ethyl acetate      | Korea        | Kim et al. (2015)                      |
| 163             | <i>p</i> -coumaric acid                                                                                   | Anti-inflammatory activity | Ethyl acetate      | Korea        | Kim et al. (2015)                      |
| 164             | Ferulic acid                                                                                              | N/A                        | Ethyl acetate      | Korea        | Kim et al. (2015)                      |
| 165             | <i>Trans</i> -4- <i>O</i> - $\beta$ -D-glucopyranosyl ferulic acid                                        | N/A                        | <i>N</i> -Butanol  | Korea        | Kim et al. (2015)                      |
| 166             | Dihydroconiferyl alcohol                                                                                  | N/A                        | Ethyl acetate      | Korea        | Jeong et al. (2018)                    |
| 167             | Epoxyconiferyl alcohol                                                                                    | Antitumor activity         | Ethyl acetate      | Korea        | Jeong et al. (2018)                    |
| 168             | Sinapaldehyde                                                                                             | Anti-inflammatory activity | Ethyl acetate      | Korea        | Jeong et al. (2018)                    |
| 169             | Coniferyl alcohol                                                                                         | N/A                        | Petroleum ether    | Korea        | Zhou et al. (2011)                     |
| 170             | Methyl 3-(2- <i>O</i> - $\beta$ -D-glucopyranosyl-3,4,5,6-tetramethoxyphenyl)-propanoate                  | Anti-tumor activity        | <i>N</i> -butanol  | China        | Du et al. (2019b)                      |
| 171             | Altissmaphenylpropanoid A                                                                                 | N/A                        | Ethyl acetate      | China        | Duan et al. (2021)                     |
| 172             | Altissmaphenylpropanoid B                                                                                 | N/A                        | Ethyl acetate      | China        | Duan et al. (2021)                     |
| 173             | 2-[4-(3-methoxy-1-propenyl)-2-methoxyphenoxy]-propane-1,3-diol                                            | Anti-tumor activity        | <i>N</i> -butanol  | China        | Du et al. (2019b)                      |
| 174             | 2-[4-(3-hydroxy-1-propenyl)-2-methoxyphenoxy]-1,3-propanediol                                             | Anti-tumor activity        | <i>N</i> -butanol  | China        | Du et al. (2019b)                      |
| 175             | 2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]propane-1,3-diol                                                  | Anti-tumor activity        | <i>N</i> -butanol  | China        | Du et al. (2019b)                      |
| Triterpenoids   |                                                                                                           |                            |                    |              |                                        |
| 176             | Altissimanin A                                                                                            | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 177             | Altissimanin B                                                                                            | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 178             | (24S)-24,25-dihydroxytirucall-7-en-3-one                                                                  | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 179             | Niloticin                                                                                                 | Anti-tumor activity        | Methanol           | China        | Hong et al. (2013)                     |
| 180             | Piscidinol A                                                                                              | Anti-tumor activity        | Methanol           | China        | Hong et al. (2013)                     |
| 181             | Bourjotinolone B                                                                                          | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 182             | (23E)-3 $\beta$ ,25-dihydroxytirucalla-7,23-diene                                                         | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 183             | Hispidol B                                                                                                | Antitumor activity         | Ethyl acetate      | Korea        | (Kim et al., 2016; Jeong et al., 2018) |
| 184             | Alianthusaltinin A                                                                                        | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 185             | 4,4,14-trimethyl-3-oxo-24-nor-5 $\alpha$ ,13 $\alpha$ ,14 $\beta$ ,17 $\alpha$ ,20S-chol-7-en-23-oic acid | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 186             | Altissimanin C                                                                                            | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 187             | Isofouquierone                                                                                            | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 188             | (20S)-hydroxy-25-methoxy-dammar-23-en-3-one                                                               | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 189             | 24,25-dihydroxydammar-20-en-3-one                                                                         | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 190             | Cabralealactone                                                                                           | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 191             | Betulafolienediolone                                                                                      | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 192             | (20S,24R)-12 $\beta$ ,25-dihydroxy-20,24-epoxydammaran-3-one                                              | N/A                        | Methanol           | China        | Hong et al. (2013)                     |
| 193             | 20(R)-24, 25-trihydroxy-dammaran-3-one                                                                    | Antitumor activity         | Ethyl acetate      | Korea        | (Kim et al., 2016; Jeong et al., 2018) |
| 194             | Hydroxydammarone I                                                                                        | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 195             | Ocotillone                                                                                                | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 196             | 11 $\beta$ -hydroxy-23/24-epi-brumollisol A                                                               | N/A                        | Dichloromethane    | China        | Zhu et al. (2020a)                     |
| Volatile oils   |                                                                                                           |                            |                    |              |                                        |
| 197             | Monoethylhexylphthalate                                                                                   | N/A                        | Petroleum ether    | China        | Li et al. (2010)                       |
| 198             | Hexadecanoic acid                                                                                         | N/A                        | Petroleum ether    | China        | Li et al. (2010)                       |
| 199             | Hexadecanal                                                                                               | N/A                        | Petroleum ether    | China        | Li et al. (2010)                       |
| 200             | <i>Cis</i> - $\alpha$ -copaene-8-ol                                                                       | N/A                        | <i>N</i> -hexane   | China        | Lou et al. (2011)                      |
| 201             | $\alpha$ -copaene                                                                                         | N/A                        | <i>N</i> -hexane   | China        | Lou et al. (2011)                      |
| 202             | Germacrene D                                                                                              | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 203             | Pentadecanal                                                                                              | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 204             | Hexahydrofarnesyl acetone                                                                                 | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 205             | Caryophyllene oxide                                                                                       | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 206             | $\alpha$ -cadinol                                                                                         | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 207             | $\tau$ -cadinol                                                                                           | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| 208             | Humulene epoxide                                                                                          | N/A                        | <i>N</i> -hexane   | Tunisia      | El Ayeb-Zakhama et al. (2014)          |
| Other compounds |                                                                                                           |                            |                    |              |                                        |
| 209             | (S)-2-hydroxy-4-methoxy-4-oxobutyl 4-hydroxy-3-methoxybenzoate                                            | Neuroprotective activity   | <i>N</i> -butanol  | China        | Du et al. (2020)                       |
| 210             | 4-hydroxy- <i>N</i> -(4-hydroxybutyl)-3-methoxybenzamide                                                  | Neuroprotective activity   | <i>N</i> -butanol  | China        | Du et al. (2020)                       |
| 211             | Ailanthaltone A                                                                                           | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 212             | Stigmasta-4-ene-3-one                                                                                     | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 213             | Stigmasta-4,6,8(14),22-tetraen-3-one                                                                      | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 214             | 2,6-dimethoxyhydroquinone                                                                                 | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 215             | Antiarol                                                                                                  | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 216             | 4-hydroxybenzaldehyde                                                                                     | N/A                        | Petroleum ether    | China        | Zhou et al. (2011)                     |
| 217             | Gallic acid                                                                                               | Water, 70% Ethanol         | Methanol           | China, Korea | (Tan et al., 2012; Kim et al., 2015)   |
| 218             |                                                                                                           | N/A                        | Methanol           | China        | Tan et al. (2012)                      |

(continued on next page)

Table 2 (continued)

| NO. | Compound                                                         | Bioactivity                                    | Extraction solvent | Country | References          |
|-----|------------------------------------------------------------------|------------------------------------------------|--------------------|---------|---------------------|
|     | 4- <i>O</i> - $\beta$ -D-glucopyranosyl-3,5-dimethoxygallic acid |                                                |                    |         |                     |
| 219 | 4-hydroxybenzoic acid                                            | Anti-inflammatory activity                     | Ethyl acetate      | Korea   | Kim et al. (2015)   |
| 220 | Vanillic acid                                                    | Anti-inflammatory activity                     | Ethyl acetate      | Korea   | Kim et al. (2015)   |
| 221 | <i>Trans</i> -4(R)-hydroxyl-2-nonenic acid                       | Antitumor activity, Anti-inflammatory activity | Ethyl acetate      | Korea   | Jeong et al. (2018) |

activity (Kim et al., 2016; Shao et al., 2020). 9-hydroxycanthin-6-one (19) and 1-methoxy-canthin-6-one (22) were reported to possess anti-cancer activity and the ability to block the activation of macrophages (Ammirante et al., 2006; Jeong et al., 2018). In addition, the content of canthin-6-one (14) obtained from BAA was quantified by HPLC; its contents were notably different between test batches, ranging from 14.11  $\mu\text{g/g}$  to 33.24  $\mu\text{g/g}$  (Li et al., 2020).

Structural changes occur frequently at the C-1, C-3, C-4, and C-8 positions of the  $\beta$ -carboline skeleton. Specifically, the C-4 position is frequently substituted with a methoxy group, whereas the C-1 position is primarily occupied by oxygen-containing functional groups. The substituents on canthin-6-one alkaloids are mostly hydroxyl groups, while the primary difference between the canthin-6-one-3-*N*-oxide and canthin-6-one skeletons is the oxidization of a nitrogen atom at the C-3 position in canthin-6-one-3-*N*-oxide. Currently, only two such alkaloids have been discovered (Ohmoto et al., 1981; Crespi-Perellino et al., 2004).

#### 4.2. Quassinoids

Quassinoids are considered characteristic components of BAA and largely comprise tetracyclic triterpene lactones and pentacyclic triterpene lactones (Fig. 4). The chemical structure of quassinoids is characteristic, and a specific classification has not been determined yet. However, at least one six-membered lactone ring exists in the structure. To date, 40 quassinoids have been reported in BAA. Recent research has focused on ailanthone (34) due to its extensive bioactivity and representative structure. Numerous antitumor activities of ailanthone (34) have been reported, including anti-liver cancer, anti-gastric cancer, anti-lung cancer, and anti-breast cancer activities (Zhuo et al., 2015; Chen et al., 2017; Ni et al., 2017; Gao et al., 2019). It has also been reported to possess several pharmacological activities, including anti-tuberculosis, antiplasmodial, and herbicidal activities (Lehmann et al., 2020). Multiple protein targets were also found to be associated with ailanthone (34), such as co-chaperone p23 protein (P23), cyclooxygenase-2 (COX-2), vimentin, and androgen receptor (AR). These multiple targets indicate the potential value of developing ailanthone (34) for further applications. Moreover, the content of ailanthone (34) in BAA has been reported to differ within the various regions of China. Among them, the BAA from Henan province had the highest ailanthone content (0.1788%), followed by Anhui (0.0755%), Jiangsu (0.0722%), and Shanxi (0.064%) provinces (He et al., 2018). In 2013, Wang et al. (2013) elucidated the structures of two new quassinoids, altissinol A (59) and altissinol B (60), from BAA ethanol extracts and found that these compounds exhibited potent cytotoxic activities, with altissinol B demonstrating greater cytotoxic activity than altissinol A (Wang et al., 2013). Moreover, a new quassinoid named shinjulactone O (51), isolated from BAA ethanol extracts, was reported to display cytotoxic activities against four human tumor cell lines (MCF-7, MDA-MB-231, HepG2, and A549) (Yang et al., 2014).

#### 4.3. Phenylpropanoids

Plant-derived phenylpropanoids are known to be synthesized from the amino acids phenylalanine and tyrosine. Phenylpropanoids are important active components found in natural medicines and can be

classified into, for example, terpenylated coumarins, classical coumarins, oxyneolignans, neolignans, benzofuran lignans, tetrahydrofuran lignans, paratetrahydrofuran lignans, classical lignans, and simple phenylpropanoids (Du et al., 2019a; Zhang et al., 2020; Yang et al., 2021). To date, a total of 103 phenylpropanoids have been isolated and identified from BAA, including 21 terpenylated coumarins (73–93), 6 classical coumarins (94–99), 19 oxyneolignans (100–118), 7 neolignans (119–125), 10 benzofuran lignans (126–135), 2 tetrahydrofuran lignans (137–138), 12 paratetrahydrofuran lignans (139–150), 10 classical lignans (136, 151–159), and 14 simple phenylpropanoids (160–175). As shown in Fig. 9, terpenylated coumarins and oxyneolignans are the main structure types, contributing approximately 24.14% and 21.84% of the total phenylpropanoids, respectively. Terpenylated coumarins represent a series of representative compounds originating from the dehydration reaction between terpenoids and chromene analogs, with many studies having sought to elucidate their pharmacological activities. For instance, Lv et al. (2020) isolated a new terpenylated coumarin, named ailanthuscoumarin, from the ethanol extract of BAA, and this compound possessed the potential to block liver cancer development. Additionally, Yan et al. used the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) viability assay and reported that altissimacoumarin C (75) inhibited the growth of liver cancer cells (Yan et al., 2020). Moreover, six terpenylated coumarins, namely altissimacoumarin C (75), altissimacoumarin D (76), altissimacoumarin P (88), altissimacoumarin Q (89), zantholin A (90), and puberulin (92), were isolated from the ethanol extract of BAA. Among these, altissimacoumarin C (75) exhibited moderate inhibitory effects against the HepG2 hepatocarcinoma cell line, with an  $\text{IC}_{50}$  value of 27.86  $\mu\text{M}$  (Duan et al., 2021). Neolignan glycosides are mostly ester glycosides formed between the glucose carboxyl group and the hydroxyl group at the C-2, C-3, or C-4 positions. Tan et al. (2012) obtained eight neolignan glycosides from the methanol extract of BAA, among which 7, 9,9'-trihydroxy-3,3',5'-trimethoxy-8-*O*-4'-neolignan-4-*O*- $\beta$ -D-glucopyranoside (123), sonchifolignan B (124), and citrulin B (125) possessed varying degrees of inhibitory effects on tobacco mosaic virus (TMV). Oxyneolignans are formed by the oxidative coupling of two phenylpropane units via an ether bond between the C-8 and C-4 positions. As the major subclass of oxyneolignans, 8,4'-oxyneolignans possess a wide variety of pharmacological effects, such as neuroprotective, anti-tumor, and anti-inflammatory activities (Du et al., 2019a). In 2019, 16 kinds of 8,4'-oxyneolignans (100–115) were discovered in BAA and their neuroprotective effects against  $\text{H}_2\text{O}_2$ -induced oxidative stress in human neuroblastoma SH-SY5Y cells were investigated. The results revealed that (–)-7R,8R-4,9,9'-trihydroxy-3,7,3',5'-tetramethoxy-8,4'-oxyneolignan (106), (+)-7S, 8S-4,9, 9'-trihydroxy-3,7,3',5'-tetramethoxy-8,4'-oxyneolignan (107), and (+)-7R, 8S-guaiacylglycerol 8-(4-hydroxymethyl-2-ethoxyphenyl) ether (115) displayed moderate neuroprotective activity (Du et al., 2019a). Nevertheless, the pharmacological activities of phenylpropanoids in BAA have not attracted enough attention and have been simply tested *in vitro*. Detailed information regarding the phenylpropanoids in BAA is presented in Table 2 and their chemical structures are presented in Fig. 5.

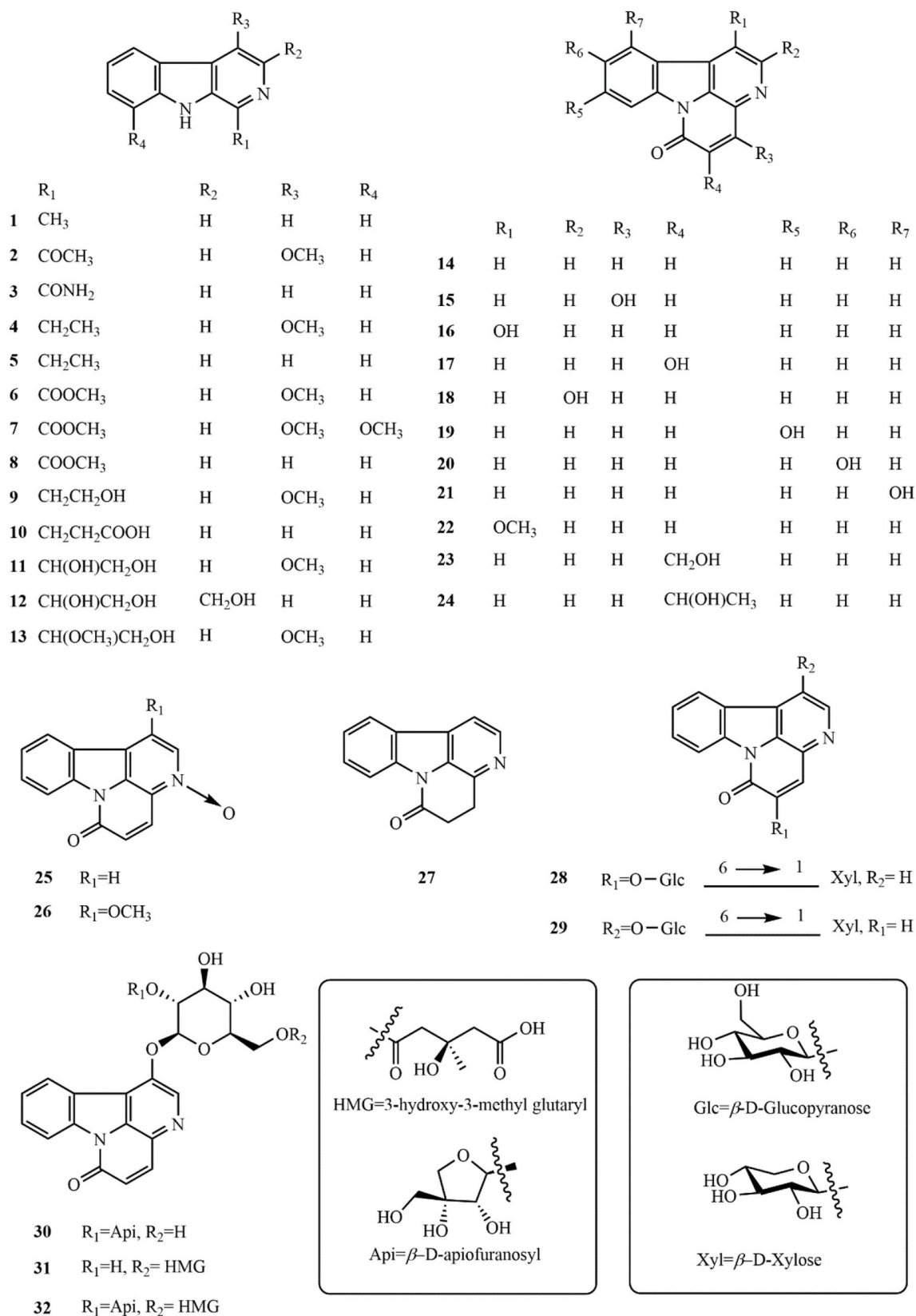


Fig. 3. Structures of alkaloids isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

#### 4.4. Triterpenoids

Triterpenoids are a large class of terpenoids containing a 30-carbon chain structure, which consists of six consecutive isoprene units

concatenated in head-tail or non-head-tail order (Fig. 6). Currently, 23 triterpenes have been isolated from BAA, most of which are tetracyclic and pentacyclic triterpenes. These compounds can be categorized into two skeleton types, tirucallane-type (174–180, 189–194) and

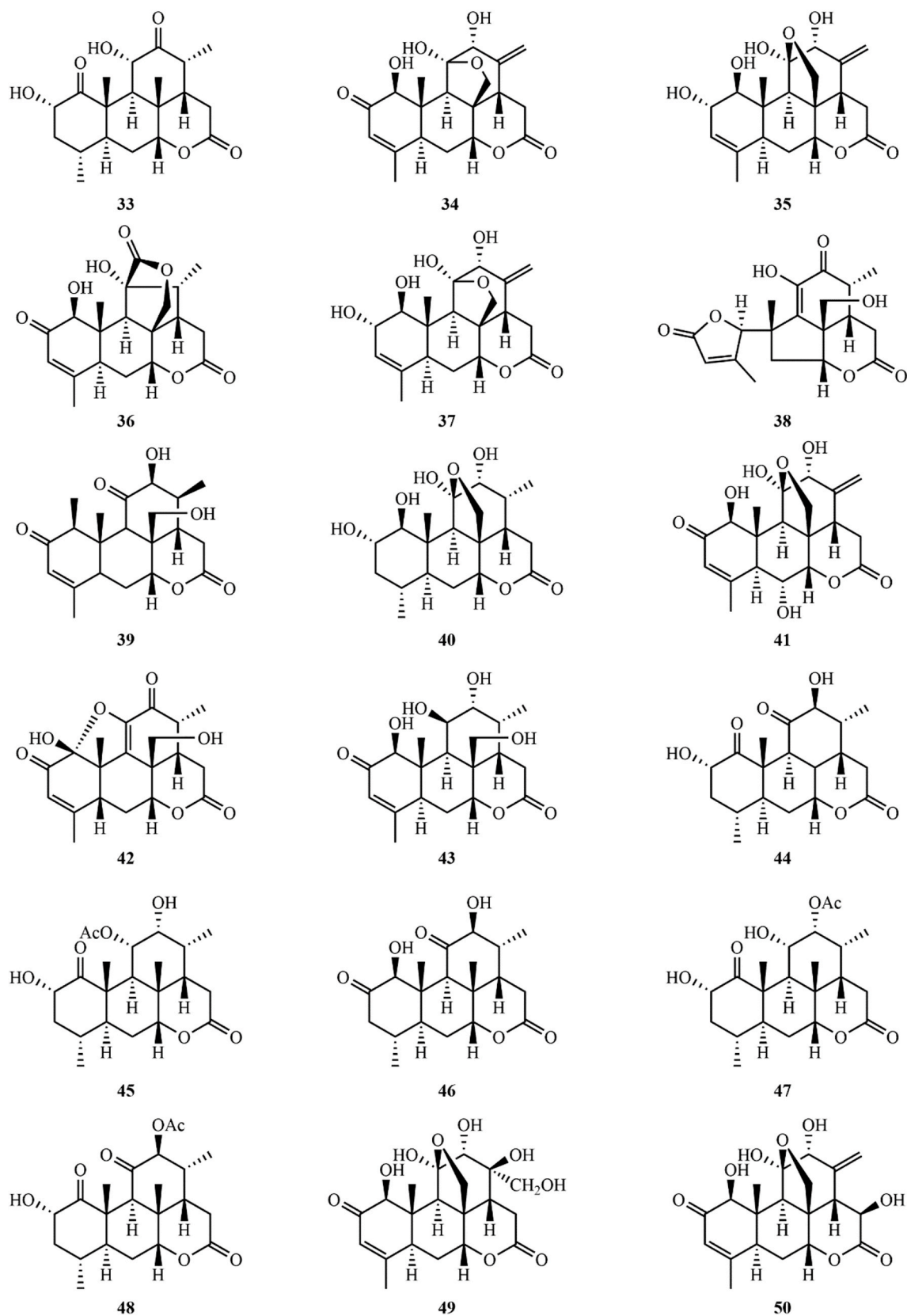


Fig. 4. Structures of quassinoids isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

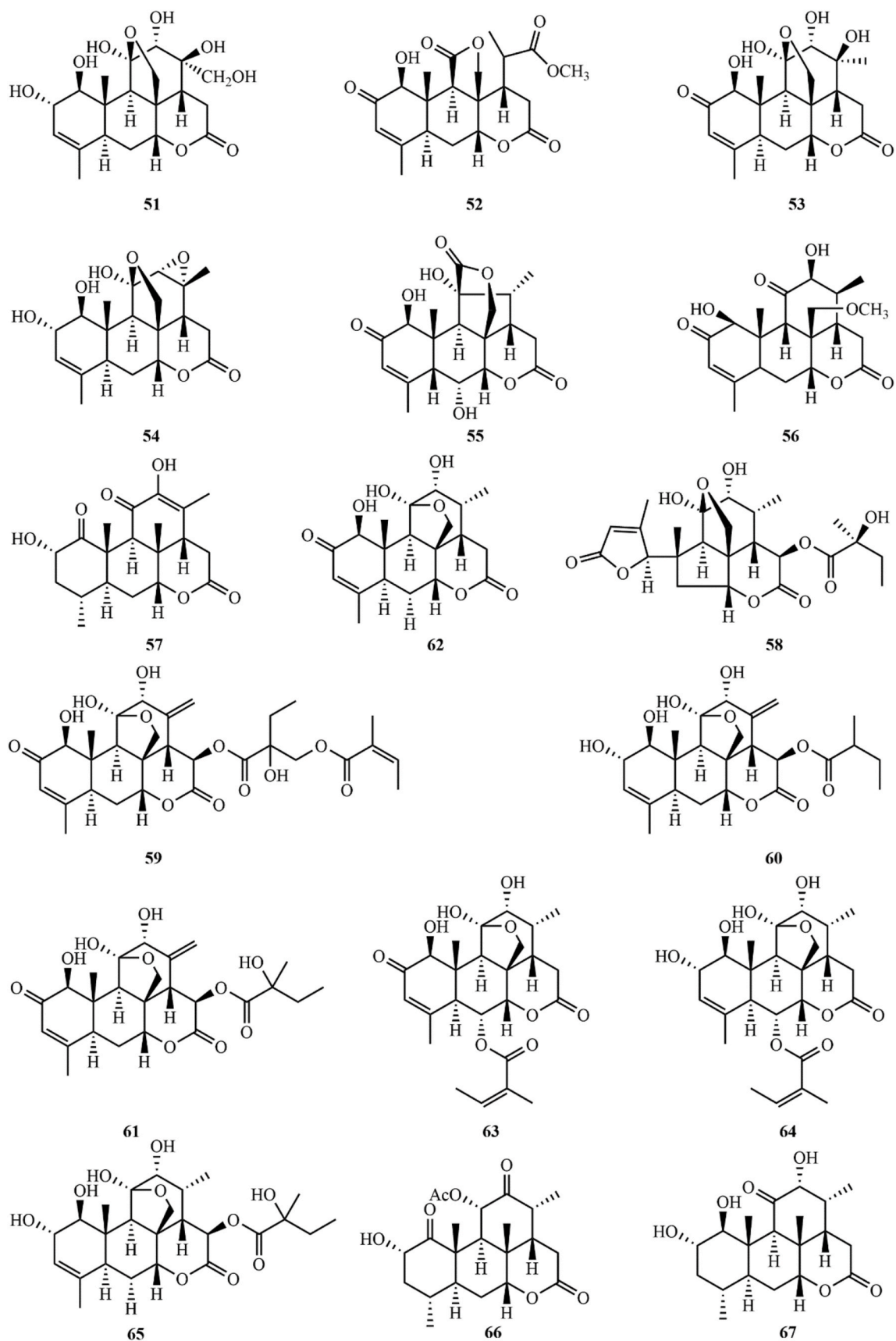


Fig. 4. (continued).

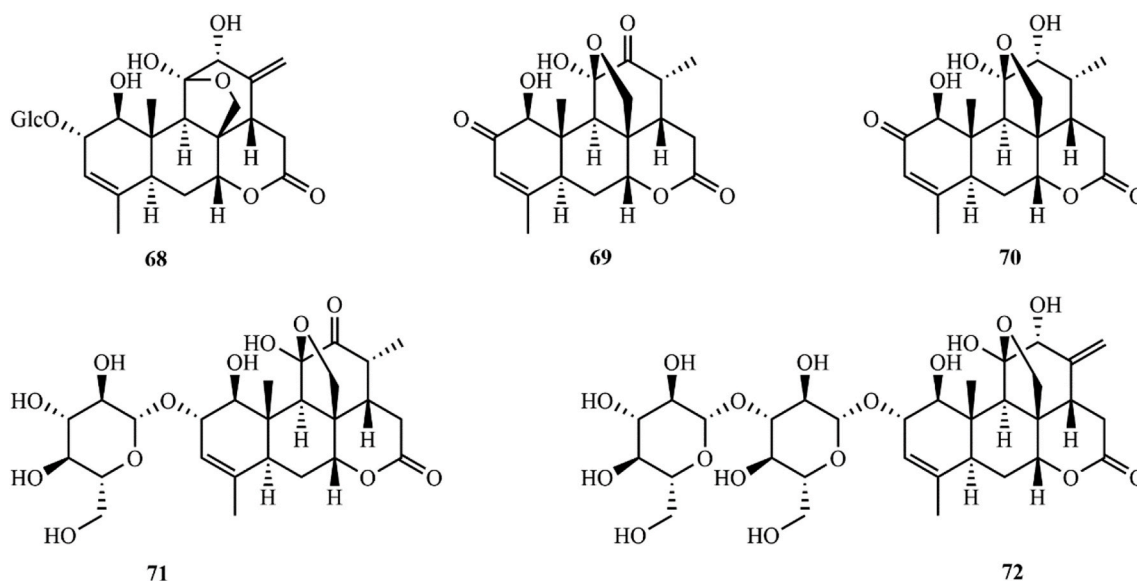


Fig. 4. (continued).

dammarane-type (181–187, 195, 196) triterpenoids. Carbonyl groups are mostly attached to the C-3 position and a double bond is frequently attached to the C-7(8) position. Based on the literature, triterpenoids identified from BAA have no remarkable bioactivity. Although current evidence concerning the activity of these triterpenoids is limited, they may represent promising chemical markers for BAA.

#### 4.5. Volatile oils

Studies have also reported the presence of volatile oils in BAA. These include mainly esters, fatty acids, and olefins, but terpenoids and epoxy compounds have also been detected (Fig. 7). To extract volatile oils from BAA, steam distillation is frequently used (Li et al., 2010; Lou et al., 2011; El Ayeb-Zakhama et al., 2014). The chemical components of the volatile oils have been analyzed primarily via gas chromatography–mass spectrometry (GC-MS). Of note, it was verified that the main compounds are mono-ethylhexyl phthalate, hexadecanoic acid, and hexadecanal, with mono-ethylhexyl phthalate accounting for 87% of the total (Li et al., 2010). Lou et al. (2011) reported that the major compounds in the volatile oil of BAA synthesized by hydrodistillation were (+)-spathulenol (11.59%), *cis*- $\alpha$ -copaene-8-ol (8.37%),  $\alpha$ -copaene (5.87%), cadinene (5.76%), and  $\alpha$ -cubebene (4.40%). In another study, GC-MS and gas chromatography–flame ionization detector (GC-FID) were used to analyze and determine the volatile oil content isolated from BAA via water distillation (El Ayeb-Zakhama et al., 2014). Thirty chemical compounds, comprising 17.8% of the volatile oil, were identified with the major components reported as hexadecanal (4.5%), germacrene D (10.3%), and pentadecanal (3%) (El Ayeb-Zakhama et al., 2014).

#### 4.6. Other compounds

Apart from the aforementioned compounds, benzoic acid derivatives (207, 208), sterols (209–211), phenols (212–220), and *trans*-4(R)-hydroxyl-2-nonenic acid (221) have also been isolated from BAA (Fig. 8).

### 5. Pharmacology

Previous *in vitro* and *in vivo* pharmacological studies have revealed that BAA possesses diverse biological effects such as antitumor, anti-inflammatory, antifertility, antiviral, herbicidal, and insecticidal properties due to the presence of various bioactive constituents (Table 3). However, except for anti-inflammatory and anti-fertility activities, most

of the pharmacological activities reported have not established a corresponding relationship with the traditional use of BAA. Hence, we suggest that future research should be focused on confirming its traditional applications by modern pharmacological methods. Therefore, a comprehensive exploration of the pharmacodynamic basis of the components of BAA extract and their mechanisms of action is urgently required.

#### 5.1. Antitumor activity

Numerous *in vitro* studies have demonstrated that the active compounds obtained from BAA, primarily ailanthone (34), exert antitumor effects in several cancer cell lines (e.g., A549, MDA-MB-231, LAPC4, A375, B16, SGC-7901, Hun7, 253J B-V, and 253J). Ailanthone (34) exerts antitumor effects by inducing apoptosis, arresting the cell cycle, inhibiting invasion and metastasis, and regulating microRNA levels.

##### 5.1.1. Inducing apoptosis and cell cycle arrest

Ailanthone (34) has been shown to inhibit the growth of B16 and A375 melanoma cell lines in a concentration-dependent manner via different mechanisms, including mitochondria-mediated apoptosis and cell cycle arrest induced by the PI3K-AKT pathway (Liu et al., 2019). However, the study reporting these results failed to include a control group to compare the antitumor activity. Furthermore, the minimum effective concentration of ailanthone (34) was not reported. In another study, Chen et al. (2017) investigated the proapoptotic effect of ailanthone (34) in the SGC-7901 gastric cancer cell line using cell counting kit-8 (CCK-8), APC/7-ADD, and Western blot assays. The results showed that ailanthone (34) (0.5, 1, 2, 4, and 8  $\mu$ M) exerted potent concentration- and time-dependent antiproliferative effects on the cells by inducing cell cycle arrest and apoptosis in the G<sub>2</sub>/M phase, with IC<sub>50</sub> values of 5.473, 2.906, and 2.470  $\mu$ M at 24, 48, and 72 h, respectively. Zhuo et al. (2015) reported that ailanthone (34) strongly inhibited the growth of Hun7 cells in a concentration- and time-dependent manner (IC<sub>50</sub>: 24 h, 0.677  $\pm$  0.050  $\mu$ M; 48 h, 0.399  $\pm$  0.015  $\mu$ M; 72 h, 0.351  $\pm$  0.017  $\mu$ M). The antitumor mechanism was attributed to the caspase-dependent mitochondrial pathway and G<sub>0</sub>/G<sub>1</sub> phase arrest. In an *in vivo* experiment in mice, it was observed that after treatment with ailanthone (5 mg/kg/day, 10 mg/kg/day, and 15 mg/kg/day, intraperitoneal injection), the tumor volumes and weights in the mice were significantly suppressed compared with those in the positive control (5-fluorouridine-treated) mice ( $P$  < 0.05) (Zhuo et al., 2015).

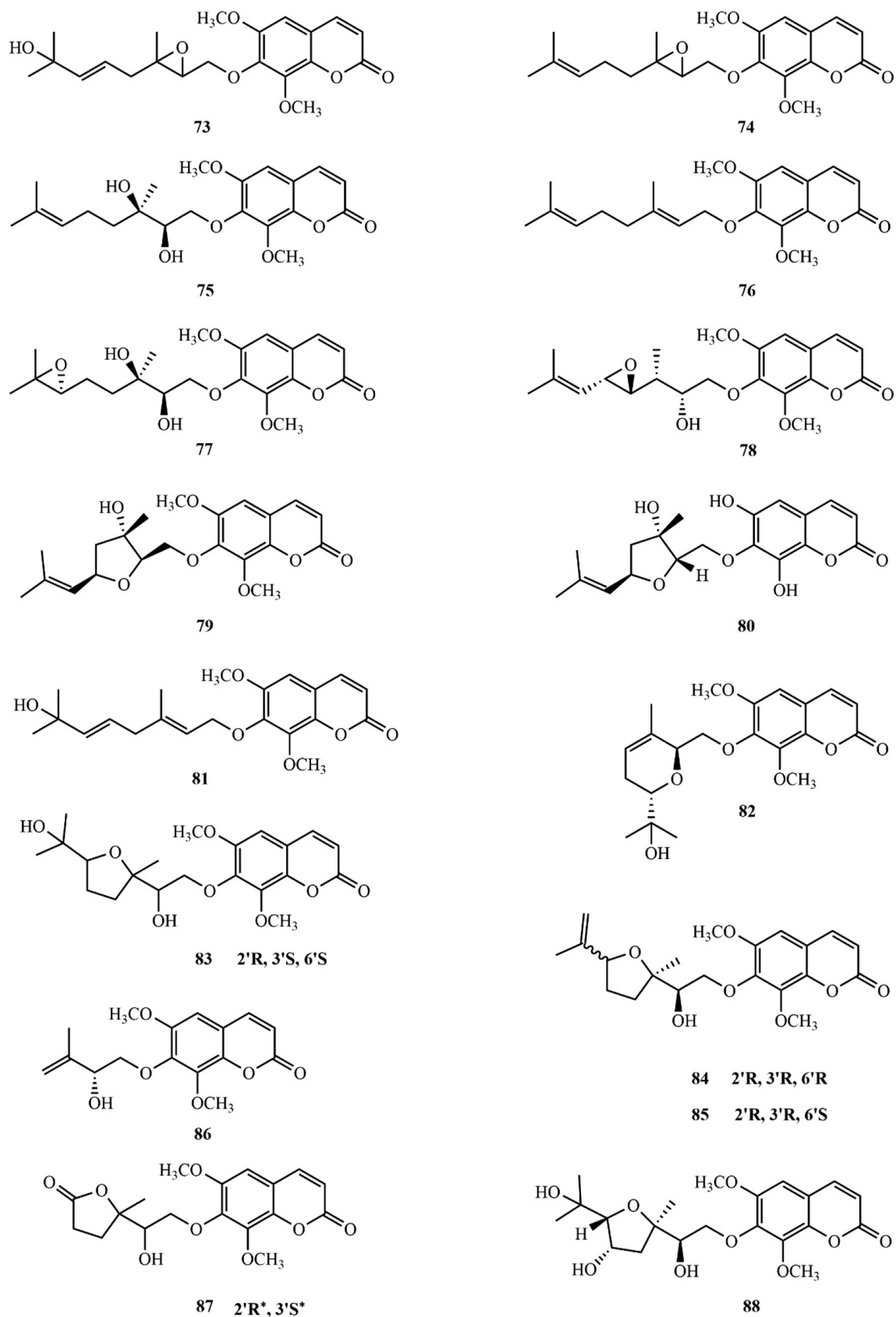


Fig. 5. Structures of phenylpropanoids isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

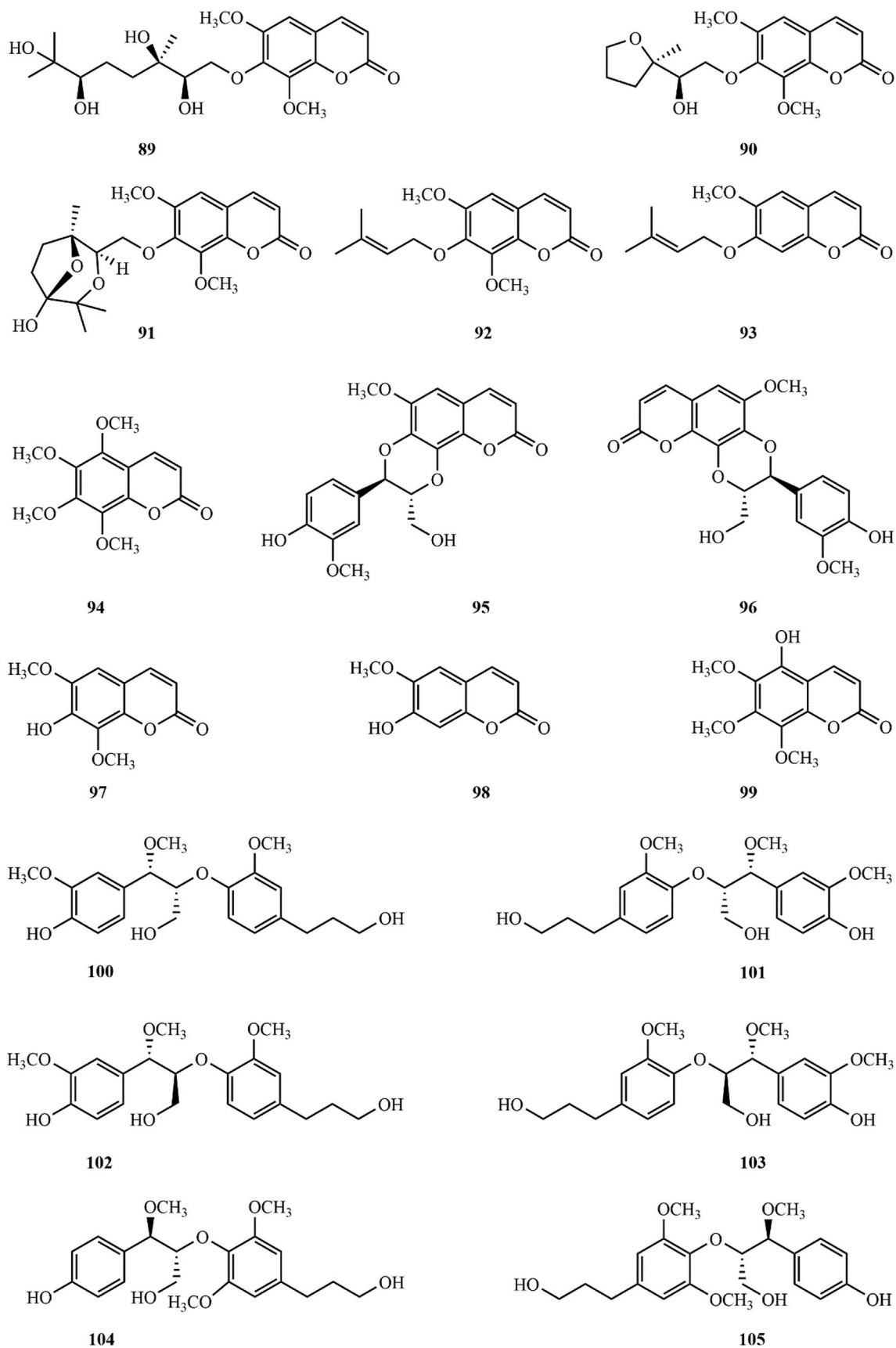


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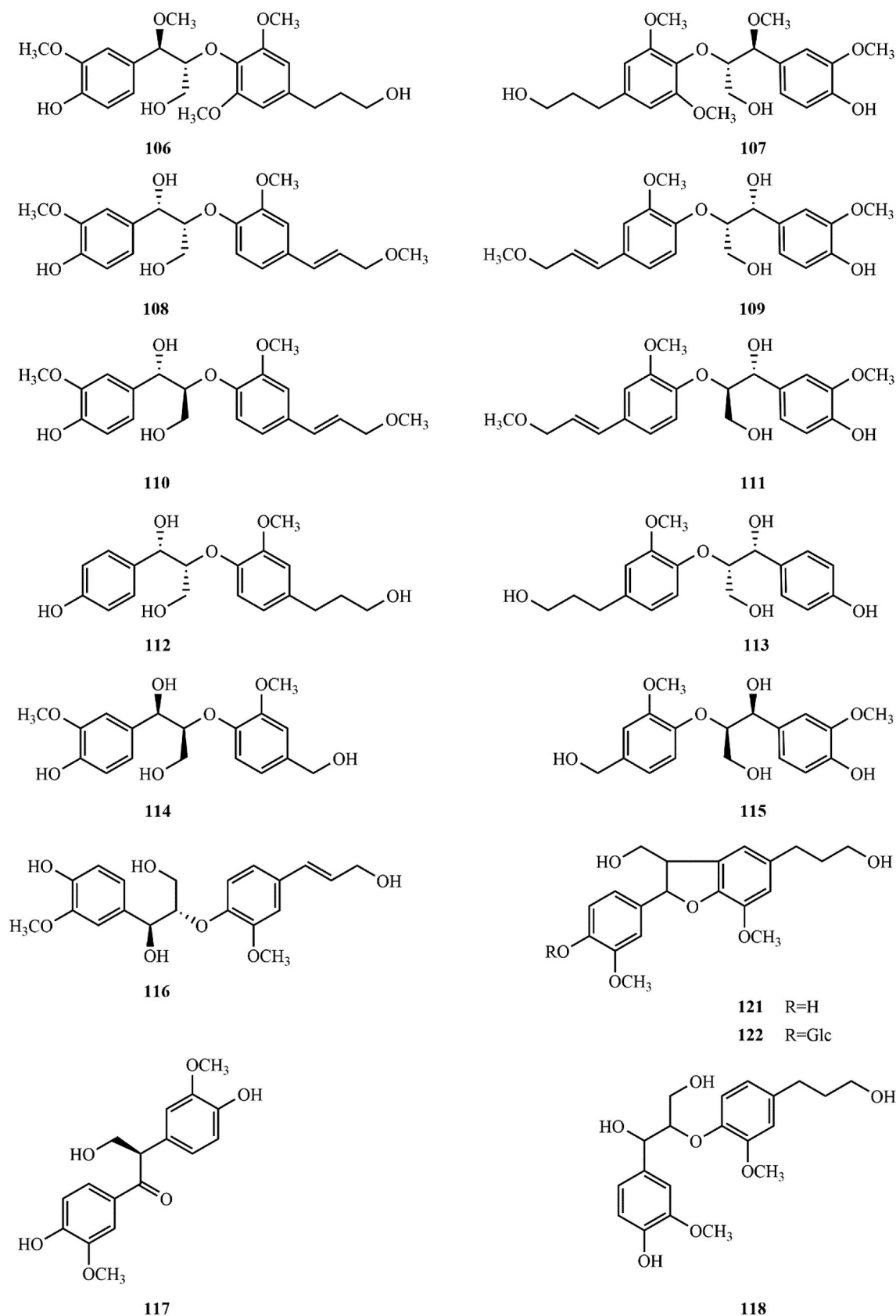


Fig. 5. (continued).

### 5.1.2. Inhibiting invasion and metastasis

Ailanthone (34) has been shown to prevent cancer progression of the 253J B-V and 253J bladder cancer cell lines via suppression of their

proliferation and invasion. Further in-depth investigations indicated that the precise mechanism of this activity might be attributed to downregulation of the expression of NF-E2-related factor 2 (Nrf2), yes-

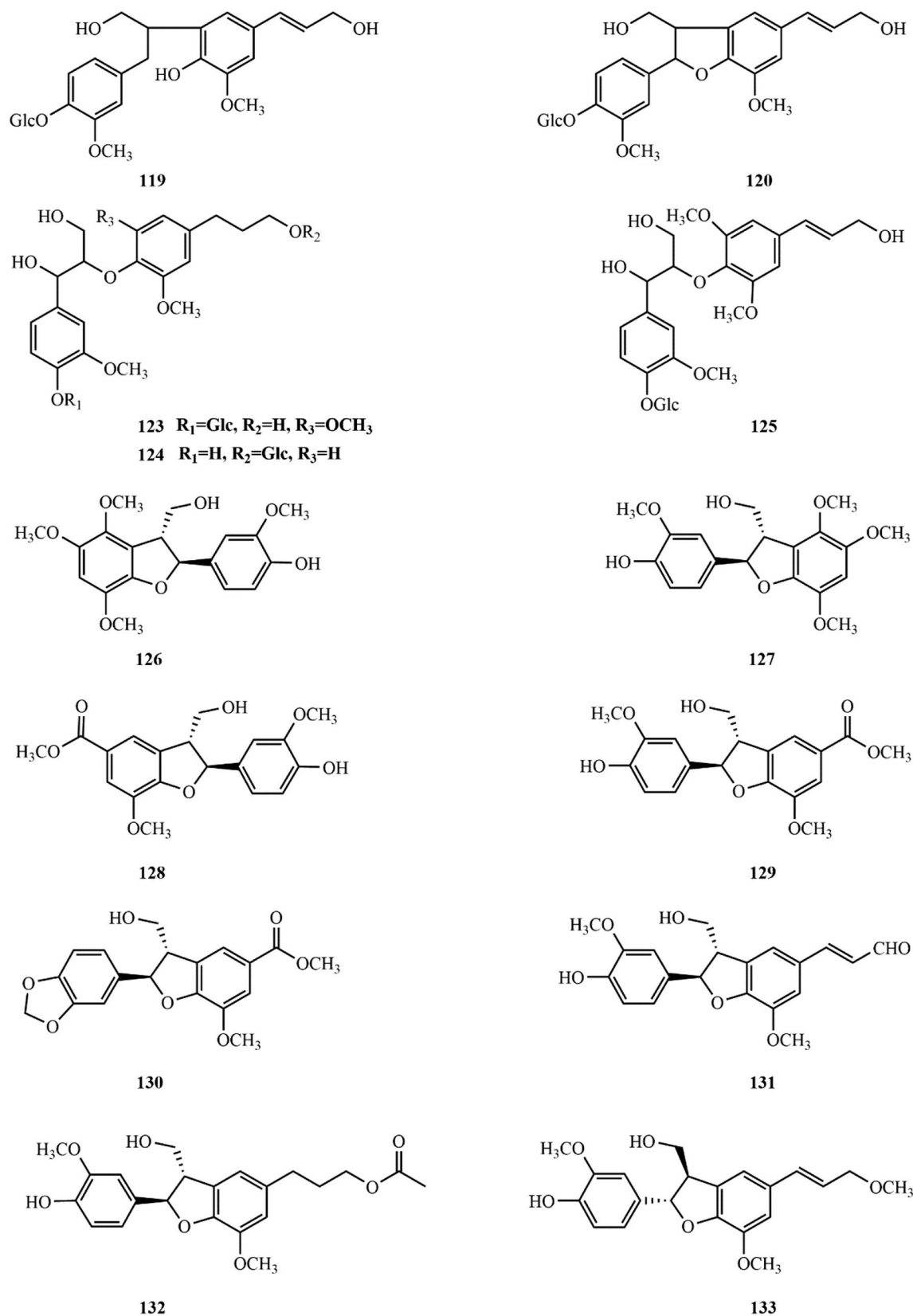


Fig. 5. (continued).

associated protein (YAP), and c-Myc (Daga et al., 2019). However, this study lacked proper positive and negative controls. Furthermore, it did not investigate whether the activity was concentration- or time-dependent. Another study demonstrated that aianthone (34)

inhibits the migration and invasion of non-small cell lung cancer H460 cells via suppression of protein kinase B (AKT) and Src phosphorylation. The main shortcoming of this study was that no positive control group was included. He et al. (2016) reported that aianthone (34) inhibited

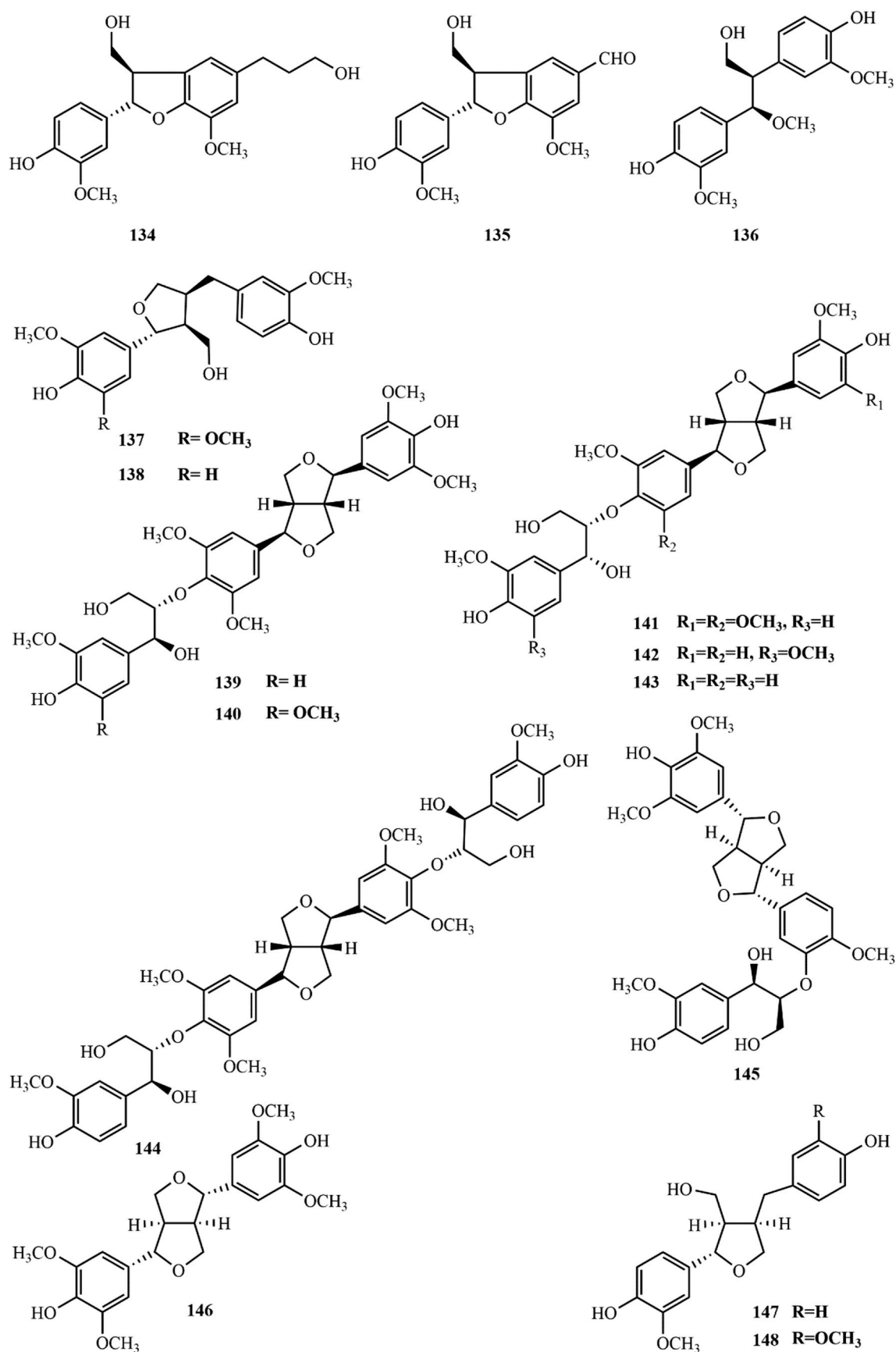


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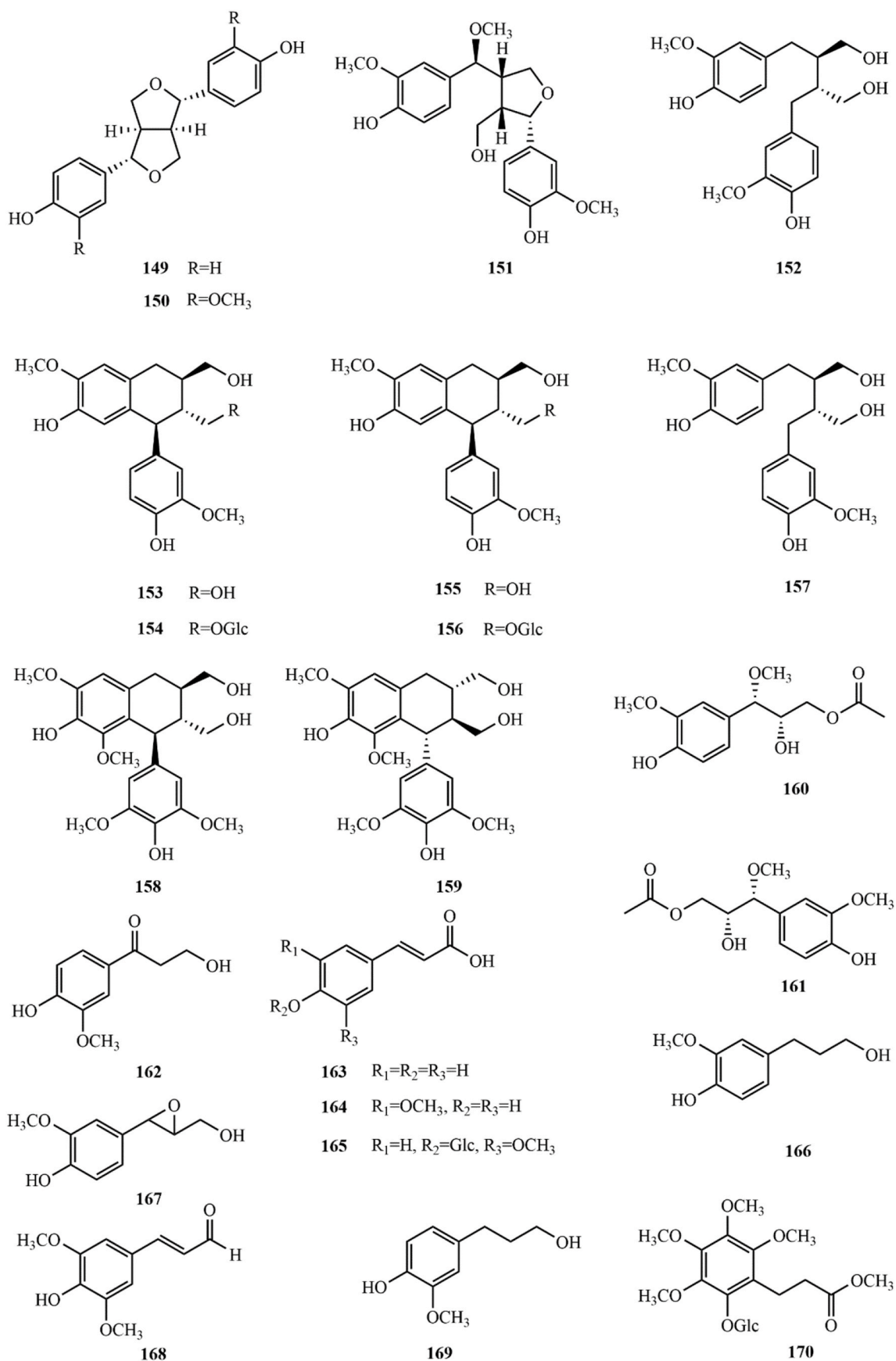


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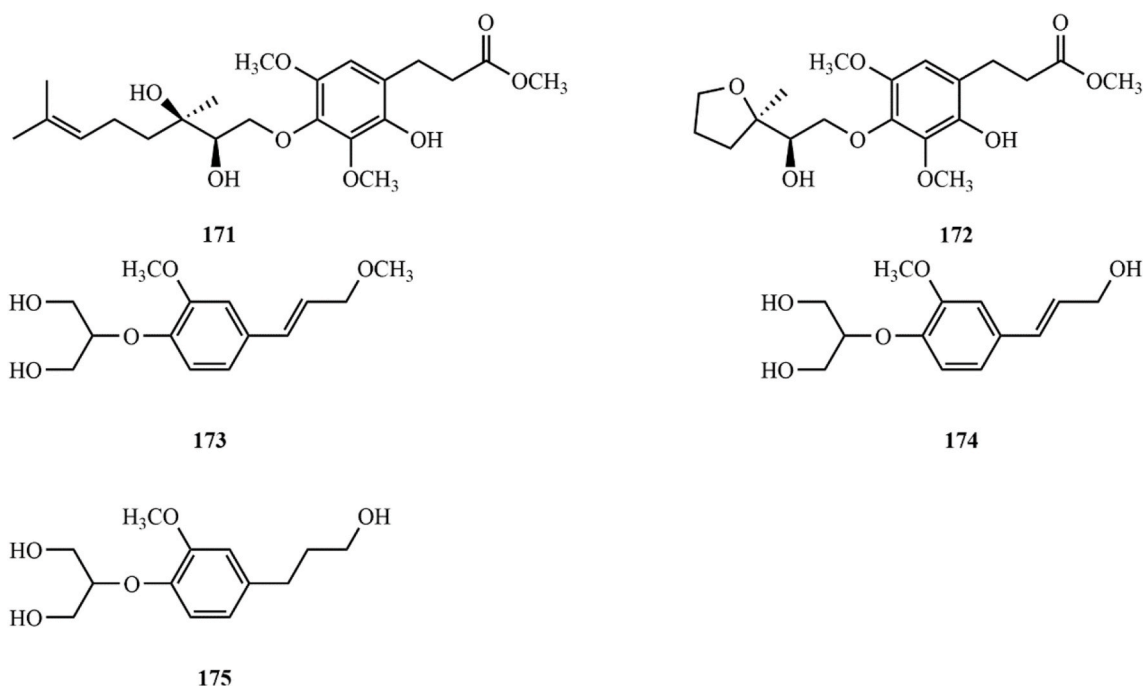


Fig. 5. (continued).

the growth and metastasis of both c4-2b and LAPC4 prostate cancer cell lines by targeting p23 and activating DNA damage responses, thus, providing novel perspectives to develop natural anticancer drugs.

#### 5.1.3. Regulating microRNA levels

Ailanthone (34) exerted proapoptotic effects in MDA-MB-231 breast cancer cells, with an IC<sub>50</sub> of 9.8  $\mu$ M, via upregulation of miR-148a expression (Gao et al., 2019). However, a positive control group was not included. Therefore, additional scientific evidence is needed to evaluate the antitumor activity of ailanthone (34). Another study demonstrated that ailanthone (34) prevents tumor progression in A549 cells via upregulation of microRNA-195 expression, thereby suppressing the phosphorylation of phosphoinositide 3-kinase (PI3K), AKT, Janus kinase (JAK), and signal transducer and activator of transcription 3 (STAT3) (Ni et al., 2017). Yang et al. further reported that ailanthone (34) exhibits significant cytotoxicity against human vestibular schwannoma cells. The authors suggested that the mechanism of action may be closely related to the downregulation of miR-21, as well as blockage of the Ras/Raf/MEK/EPK and mTOR pathways (Yan et al., 2018). However, the results of this study remain controversial due to the lack of comparison with standard drugs. Ailanthone (34) reportedly inhibits the viability of MG63 osteosarcoma cells by upregulating miR-126 expression and subsequently degrading vascular endothelial growth factor A (VEGF-A) (Kong et al., 2019).

Taken together, numerous pharmacological studies have indicated that ailanthone (34) is the most significant antitumor component in BAA. Nevertheless, gastrointestinal damage triggered by ailanthone (34) has limited its development as a natural anticancer drug (Bailey, 2020; Ding et al., 2020). Therefore, further investigations are required to continue the search for effective and less toxic ailanthone derivatives obtained from BAA. In addition, it is important to ascertain if it is feasible to modify the structure of ailanthone (34) to reduce its toxicity and enhance its antitumor activity. Diverse tumor cell lines have been frequently utilized to evaluate the *in vitro* cytotoxicity of ailanthone (34); however, *in vitro* studies focused on elucidating the mechanism of action are not sufficient to establish BAA as an anticancer drug and the significance of clinical trials and *in vivo* research remains unknown. Therefore, future investigations focusing on animal models and

human-based clinical studies are warranted to obtain more robust data. Moreover, several methodological challenges have been noted regarding experimental design, such as improper doses and the absence of positive or negative controls. Notably, although the antitumor activity of ailanthone (34) obtained from BAA has been extensively studied, it seems to be unrelated to the traditional use of BAA.

#### 5.2. Anti-inflammatory activity

BAA is prominently used in folk medicine owing to its anti-inflammatory effects. Traditionally, BAA has been used for the treatment of chronic cervicitis, endometritis, ulcerative colitis, and vaginal mucositis. Inflammation refers to the defense response of living tissues to injury, with the help of the circulatory system, but excessive inflammation can have major detrimental effects on human health. The inflammation model using lipopolysaccharide (LPS) activation is currently the most frequently used (Calixto et al., 2003). Compounds isolated from BAA have been reported to possess anti-inflammatory properties; the mechanism underlying their action is closely related to the suppression of nitric oxide (NO) and nuclear factor-kappa B (NF- $\kappa$ B) production. The *in vitro* anti-inflammatory potential of BAA may support its traditional use in the treatment of the aforementioned diseases. Kim et al. (2016) reported that six canthin-6-one alkaloids demonstrated remarkable anti-inflammatory activities via suppression of NO production, with IC<sub>50</sub> values ranging from 5.92  $\pm$  0.9 to 15.09  $\pm$  1.8  $\mu$ M. However, further in-depth studies are required to clarify the specific mechanism responsible for the anti-inflammatory effects of BAA. In a study by Cho et al., canthin-6-one (14) inhibited the generation of prostaglandin E<sub>2</sub> and expression of COX-2 in LPS-activated RAW 264.7 macrophages and decreased the levels of monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) when used at 1  $\mu$ M and 5  $\mu$ M. The authors revealed that the underlying anti-inflammatory mechanism may be associated with the downregulation of both the NF- $\kappa$ B and AKT pathways (Cho et al., 2018). However, considering that the above studies were *in vitro* studies, further in-depth investigations should be encouraged to validate the effectiveness of BAA in animal models.

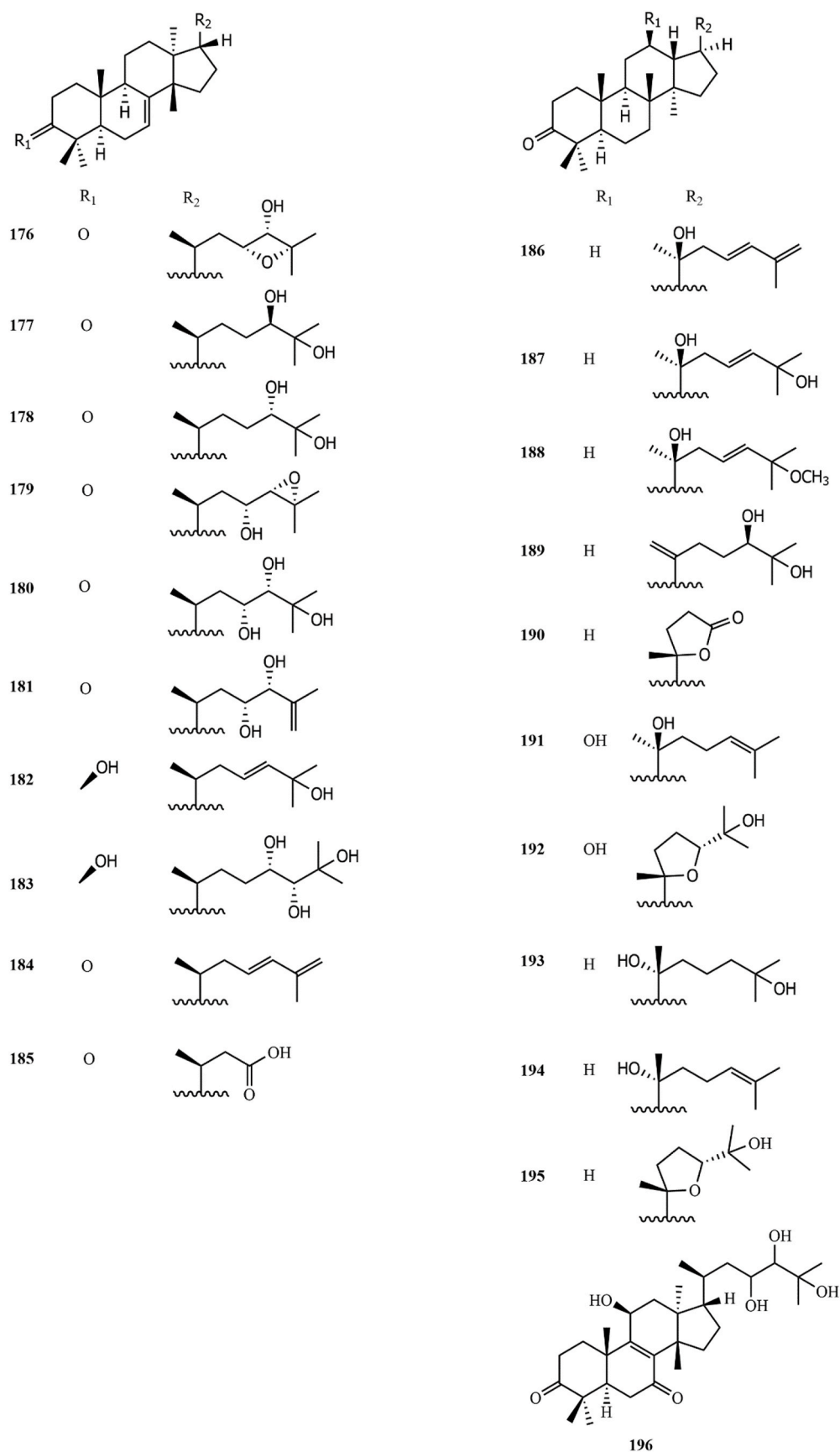


Fig. 6. Structures of triterpenoids isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

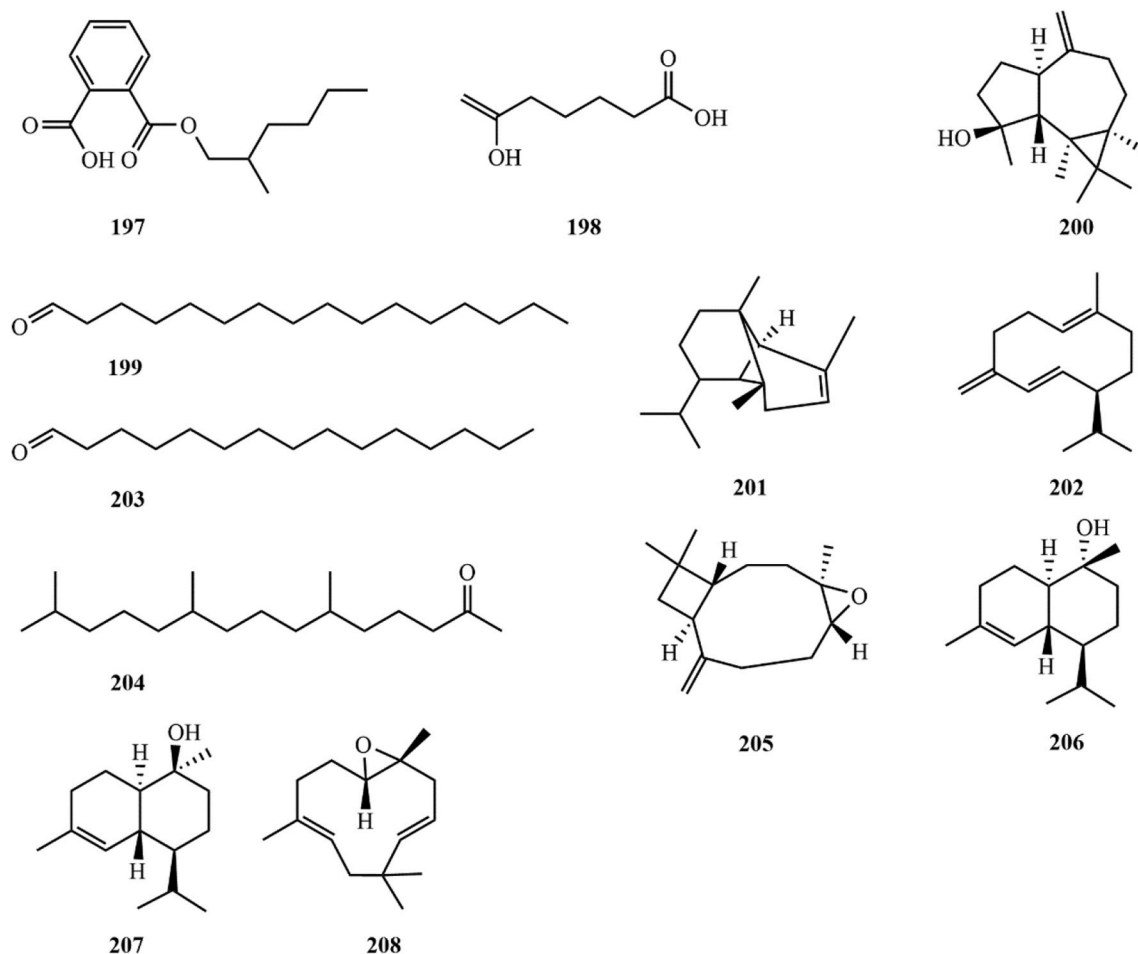


Fig. 7. Structures of volatile oils isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

### 5.3. Antiviral activity

Compounds obtained from BAA were reported to possess antiviral activities. TMV is an RNA virus that specifically infects plants, especially, tobacco and plants from the family Solanaceae. Tan et al. (2012) found that aianthone (34) and 6 $\alpha$ -tigloyloxyparrinone (63) displayed moderate inhibitory effects against TMV *in vitro*, with IC<sub>50</sub> values of 0.30 and 0.26 mmol/L, respectively. Furthermore, the inhibitory effects of eighteen quassinoids from BAA on TMV were evaluated, among which aianthone (34) exerted the strongest antiviral activity in a concentration-dependent manner, with an IC<sub>50</sub> value of 0.19  $\mu$ M (Tan et al., 2018). Two new quassinoid glycosides, chuglycosides J (71) and K (72), identified from BAA, exerted potent TMV growth-inhibitory effects with IC<sub>50</sub> values of 56.21  $\pm$  1.86 and 137.74  $\pm$  3.57  $\mu$ M, respectively (Tan et al., 2020). These *in vitro* results may present a novel approach for the development of antiviral agents. However, it is worth mentioning that the mechanism responsible for this antiviral activity should be further elucidated. Moreover, several studies only reported the effects of ingredients derived from BAA on TMV, but determining the effective duration of the activity of the crude extract and the specific mechanism underlying the action of the extract are still needed.

### 5.4. Herbicidal activity

Although modern agriculture is gradually transforming because of standardization and industrialization, weed control has always been a primary challenge facing farmers. Recent studies have shown that BAA extracts exhibit potent herbicidal activities, demonstrating the tremendous potential of BAA to be developed as a novel plant-based herbicide.

The herbicidal effects of different BAA solvent extracts (diethyl ether, dichloromethane, ethyl acetate, and the remaining crude extract) were evaluated against *Amaranthus*, *Chenopodium*, and *Festuca* spp. The dichloromethane extract exhibited the strongest herbicidal activity, which was directly related to aianthone concentration, with the lowest extract concentration required to halve root growth (ID<sub>50</sub>) values of 2, 2, and 1 mg/L, respectively (Pedersini et al., 2011). Another study showed that aianthone (34), at concentrations of 1, 1.5, 2, 2.5, 5, 7.5, and 10 mg/L, displayed potential herbicidal effects on two model plant species (*Lepidium sativum* and *Raphanus sativus*), in a concentration-dependent manner (Demasi et al., 2019a,b). In addition, that study reported that aianthone (34) in filter paper and soil exhibited a strong inhibitory effect on the growth of these two plants at a concentration of 7.5 mg/L, with an inhibition rate ranging from 80% to 90% (Demasi et al., 2019a, b). Meng et al. (2015) investigated the herbicidal effects of the ethanolic extracts (25, 50, 100, and 200 mg/L/day for 5 days) of BAA against *Microcystis aeruginosa* and found that these extracts markedly suppressed the growth of *M. aeruginosa* in a concentration-dependent manner within five days, compared with the control group ( $P < 0.05$ ).

### 5.5. Insecticidal activity

Food crop safety and human health are also frequently affected by insects. Hence, an urgent need exists for the development of natural insecticides. According to the report by (Lü and He, 2010), BAA extracts (160  $\mu$ L/L air) exhibit potent fumigant toxicity against three major stored-grain pests, *Oryzaephilus surinamensis*, *Sitophilus oryzae*, and *Liposcelis paeta*, with death rates of 100.0%, 77.2%, and 40.3%, respectively. These results indicate the potential of BAA to be developed as a

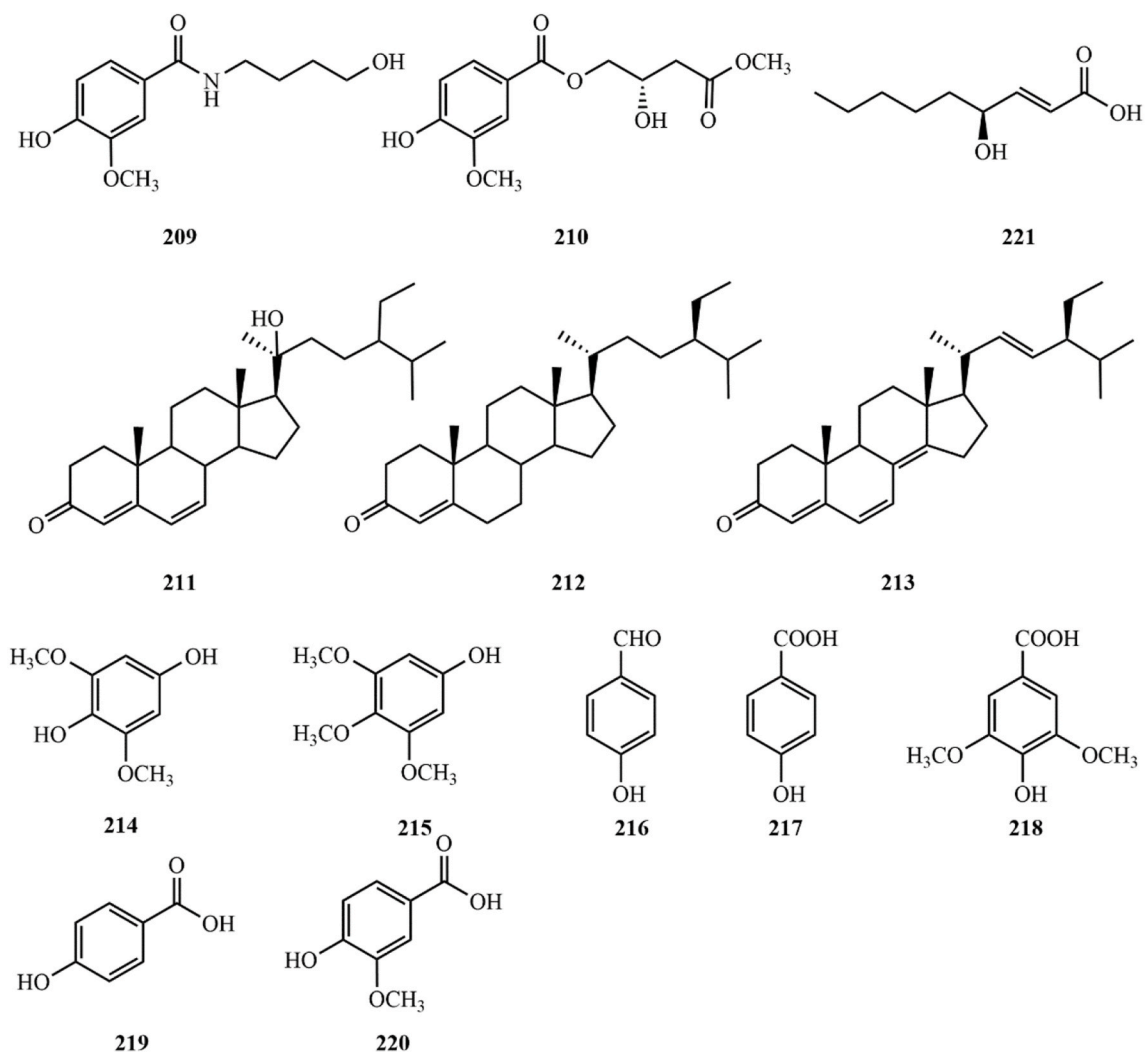


Fig. 8. Structures of other compounds isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

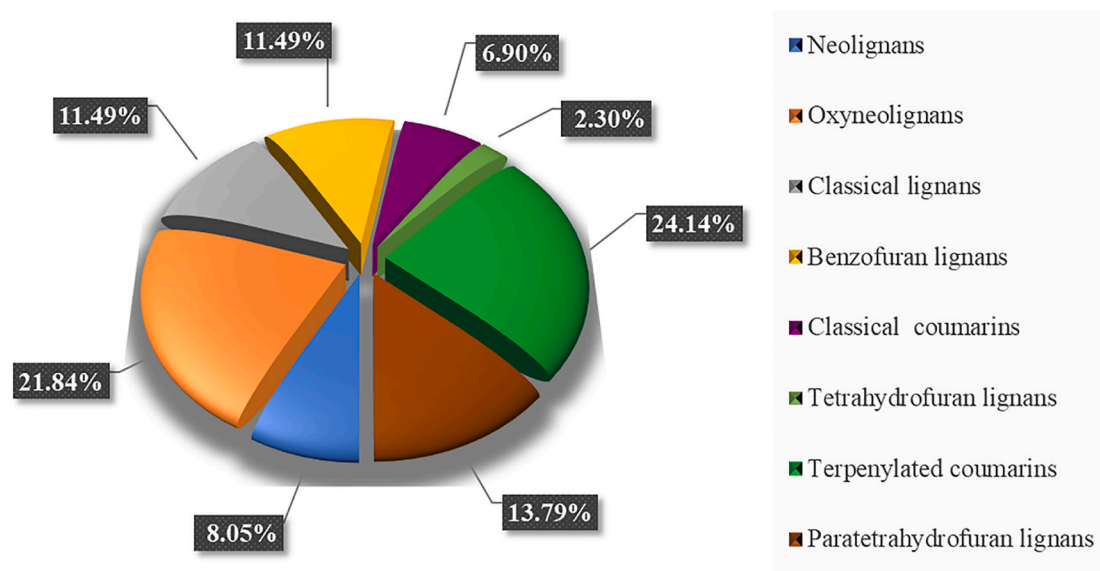


Fig. 9. Classes of phenylpropanoids isolated from the bark of *Ailanthus altissima* (Mill.) Swingle.

**Table 3**  
Main pharmacological effects of BAA.

| Pharmacological effects                             | Extracts or compounds                        | Animals/Cells/Plants                                                    | Dosage/Concentration                                                                             | Time                                    | Effects/Mechanisms                                                                                                                                                                                                                                                                                               | References                             |
|-----------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Antitumor activity                                  |                                              |                                                                         |                                                                                                  |                                         |                                                                                                                                                                                                                                                                                                                  |                                        |
| Treating melanoma                                   | Ailanthone (34)                              | B16 and A375 Cells                                                      | 0.25, 0.5, 1, 2, 4, 8, and 16 $\mu\text{M}$                                                      | 24 h                                    | Inducing mitochondria-mediated apoptosis; arresting cell cycle at the G0/G1 phase in B16 cells and the G2/M phase in A375 cells; activating PI3K-AKT signaling pathway; suppressing the expression of Bcl-2; increasing the expression of Apaf-1 and Bax                                                         | Liu et al. (2019)                      |
| Treating stomach cancer                             | Ailanthone (34)                              | SGC-7901 cells                                                          | 0.5, 1, 2, 4, and 8 $\mu\text{M}$                                                                | 24, 48, and 72 h                        | Suppressing the expression of Bcl-2; increasing the level of Bax; inducing G2/M phase cell cycle arrest                                                                                                                                                                                                          | Chen et al. (2017)                     |
| Treating liver cancer                               | Ailanthone (34)                              | Hun7 cells<br>Male nu/nu BALB/c mice                                    | 0.2, 0.4, and 0.8 $\mu\text{M}$<br>5, 10, and 15 mg/kg                                           | 48 h<br>18 days                         | Inducing G0/G1 phase cell cycle arrest; activating PI3K-AKT signaling pathway; suppressing the growth and angiogenesis of tumor xenografts; inducing mitochondrion-mediated apoptosis                                                                                                                            | Zhuo et al. (2015)                     |
| Treating bladder cancer                             | Ailanthone (34)                              | 253J B-V and 253J cells                                                 | 0.01, 0.05, and 0.1 $\mu\text{g/mL}$                                                             | 24 h                                    | arresting cell cycle at G <sub>2</sub> /M phase; suppressing the expression of Nrf2, YAP, and c-Myc; inhibiting cell proliferation and invasiveness                                                                                                                                                              | Daga et al. (2019)                     |
| Treating non-small lung cancer                      | Ailanthone (34)<br>Ailanthone (34)           | A549, H1299, and H1975 cells<br>Male BALB/c mice<br>H460 cells          | 0, 0.625, 1.25, 2.5, and 5.0 $\mu\text{M}$<br>2 mg/kg<br>0.2, 0.4, 0.6, 0.8, and 1 $\mu\text{M}$ | 24, 48, and 72 h<br>and 58 days<br>48 h | Inducing G <sub>1</sub> or G <sub>2</sub> /M phase cell cycle arrest; inhibiting DNA replication; downregulating the expression of RPA1; inhibiting cell viability; extending the survival time of tumor-bearing mice<br>Suppressing the phosphorylation of AKT and Src; inhibiting Cyclin D1 protein expression | Ni et al. (2017)<br>(Fan et al., 2020) |
| Treating nerve cancer                               | Ailanthone (34)                              | Vestibular schwannoma cells                                             | 0.2, 0.4, 0.6, 0.8, and 1 $\mu\text{M}$                                                          | 48 h                                    | Decreasing cell viability; triggering apoptosis and autophagy; downregulating the level of miR-21; blocking the Ras/Raf/MEK/EPK and mTOR pathways; downregulating the expression of miR-21                                                                                                                       | Yang et al. (2018)                     |
| Treating breast cancer                              | Ailanthone (34)                              | MDA-MB-231 cells                                                        | 0, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5, and 25 $\mu\text{M}$                               | 48 h                                    | Inhibiting cell migration and invasion; inducing cleavage of caspase-3 and -9; decreasing cell viability; upregulating the expression of miR-148a                                                                                                                                                                | Gao et al. (2019)                      |
| Treating lung cancer                                | Ailanthone (34)                              | A549 cells                                                              | 0.2, 0.4, 0.6, 0.8, and 1.0 $\mu\text{M}$                                                        | 48 h                                    | Promoting cell apoptosis and autophagy; upregulating the expression of microRNA-195; inhibiting the phosphorylation of PI3K, AKT, JAK, and STAT3; inhibiting cell viability and proliferation                                                                                                                    | Hou et al. (2019); Ni et al. (2017)    |
| Treating ovarian and bladder cancer                 | Ailanthone (34)                              | 253J B-V, 253J B-V CDDP-resistant as well as A2780 and A2780/CP70 cells | 0.1, 0.5, 1, and 2 $\mu\text{g/mL}$                                                              | 24 h and 48 h                           | Inhibiting the expression of Nrf2 and YAP; increasing oxidative stress; inhibiting cell proliferation and migration                                                                                                                                                                                              | Cucci et al. (2020)                    |
| Treating osteosarcoma                               | Ailanthone (34)                              | MG63, u2os, hos, saos-2, and hfob1.19 cells                             | 0.5, 1, 1.5, and 2 $\mu\text{M}$                                                                 | 24 h                                    | Inhibiting PI3K/AKT signaling pathway; upregulating the expression of miR-126                                                                                                                                                                                                                                    | Kong et al. (2019)                     |
| Treating glioma                                     | 2-dihydroailanthone (35)                     | U251 cells                                                              | 1.00, 4.00, and 8.00 $\mu\text{g/mL}$                                                            | 48 h                                    | Inducing apoptosis and G <sub>0</sub> /G <sub>1</sub> phase cycle arrest; upregulating expression pro-apoptotic Bax protein and downregulating expression of anti-apoptotic Bcl-2 protein and their mRNA                                                                                                         | Wang et al. (2016)                     |
| Treating liver cancer                               | Altissimacoumarin C (75)                     | HepG2 Cells                                                             | 10, 20, 40, and 80 $\mu\text{M}$                                                                 | 48 h                                    | Moderate inhibitory effects against HepG2 hepatocarcinoma cells with an IC <sub>50</sub> of 27.86 $\mu\text{M}$                                                                                                                                                                                                  | Duan et al. (2021)                     |
| Treating leukemia, thyroid cancer, and liver cancer | 1-methoxy-canthin-6-one (22)                 | Jurkat, ARO, NPA, and HuH7 cells                                        | 4, 10, 20, 40, and 80 $\mu\text{M}$                                                              | 30 min, 1, 2, 4, and 6 h                | Upregulating expression of JNK; regulating other factor(s) that participated in TRAIL-induced apoptosis.                                                                                                                                                                                                         | Ammirante et al. (2006)                |
| Anti-inflammatory activity                          | Ailanthone (34)                              | RAW 264.7 cells                                                         | 1.875, 3.75, and 7.5 $\mu\text{M}$                                                               | 1 h                                     | Reducing expression of TNF- $\alpha$ with IC <sub>50</sub> values in the range of 5.92 $\pm$ 0.9 to 15.09 $\pm$ 1.8 $\mu\text{M}$                                                                                                                                                                                | Kim et al. (2016)                      |
|                                                     | Canthin-6-one (14)                           | RAW 264.7 cells                                                         | 0.5, 1, and 5 $\mu\text{M}$                                                                      | 24 h                                    | Inhibiting generation of PGE <sub>2</sub> and expression of COX-2; decreasing the levels of MCP-1 and TNF- $\alpha$ ; downregulating NF- $\kappa$ B and AKT pathways                                                                                                                                             | Cho et al. (2018)                      |
| Antiviral activity                                  | Ailanthone (34)<br>(-)-Chaparrinone (62)     | TMV U1 strain                                                           | 0.078, 0.156, 0.313, 0.625, and 1.25 $\mu\text{M}$                                               | 48 h                                    | Moderate inhibitory effect against TMV <i>in vitro</i> , with IC <sub>50</sub> values of 0.30 and 0.26 mmol/L for compounds 34 and 62, respectively                                                                                                                                                              | Tan et al. (2012)                      |
|                                                     | Chuglycosides J (71)<br>Chuglycosides K (72) | TMV U1 strain                                                           |                                                                                                  |                                         | Potent antiviral activities against TMV <i>in vitro</i> , with IC <sub>50</sub> values of 56.21 $\pm$ 1.86 and                                                                                                                                                                                                   | Tan et al. (2020)                      |

(continued on next page)

Table 3 (continued)

| Pharmacological effects | Extracts or compounds  | Animals/Cells/Plants                                                                      | Dosage/Concentration                          | Time             | Effects/Mechanisms                                                                                                                                                                                                                                                                                                | References               |
|-------------------------|------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Insecticidal activity   | BAA methanol extracts  | <i>Oryzaephilus surinamensis</i> , <i>Sitophilus oryzae</i> , and <i>Liposcelis paeta</i> | 10, 20, 40, 80, and 160 $\mu\text{L/L}$ air   | 24 h             | 137.74 $\pm$ 3.57 $\mu\text{M}$ for compounds <b>71</b> and <b>72</b> , respectively<br>BAA extracts (160 $\mu\text{L/L}$ of air) exhibited remarkable fumigant toxicity against <i>O. surinamensis</i> , <i>S. oryzae</i> , and <i>L. paeta</i> , with mortality rates of 100.0%, 77.2%, and 40.3%, respectively | Li et al. (2010)         |
|                         | BAA methanol extracts  | Model organism <i>Caenorhabditis elegans</i>                                              | 0.1, 0.5, 2.5, and 5 mg/mL                    | 72 h             | Complete or partial inhibition of the development of oocytes leading to the activation of the transcription factor DAF-16;                                                                                                                                                                                        | Lehmann et al. (2020)    |
| Herbicidal activity     | BAA methanol extracts  | <i>Microcystis aeruginosa</i>                                                             | 25, 50, 100, and 200 mg/L                     | 0, 2, and 5 days | Remarkable inhibition of <i>M. aeruginosa</i> in a concentration-dependent manner within five days                                                                                                                                                                                                                | Meng et al. (2015)       |
|                         | BAA methanol extracts  | <i>Lolium</i>                                                                             | 1, 2, 3, 5, 10, 15, and 20 mg/L               | 10 days          | BAA extracts displayed a significant pre-emergence herbicide activity                                                                                                                                                                                                                                             | Pedersini et al. (2011)  |
|                         | Ailanthone (34)        | <i>Lepidium sativum</i> and <i>Raphanus sativus</i>                                       | 1, 1.5, 2, 2.5, 5, 7.5, and 10 mg/L           | 4 days           | Suppressing plant growth with inhibition rates between 80% and 90%                                                                                                                                                                                                                                                | Demasi et al. (2019a,b)  |
| Other activities        |                        |                                                                                           |                                               |                  |                                                                                                                                                                                                                                                                                                                   |                          |
| Anti-anaphylact-ic      | BAA methanol extracts  | Male Sprague–Dawley rats HMC-1 cells                                                      | 2, 4, 6, and 8 g/kg<br>0.01, 0.1, and 1 mg/mL | 24 h<br>24 h     | Decreasing expression of NF- $\kappa$ B/Rel A; suppressing I $\kappa$ B $\alpha$ degradation                                                                                                                                                                                                                      | Kang et al. (2010)       |
| Anti-fertility          | BAA methanol extracts  | Female albino Wistar rats                                                                 | 100, 150, and 200 mg/kg                       | 10 days          | Inhibiting implantation and abortifacient action                                                                                                                                                                                                                                                                  | (Mani and Rathore, 2016) |
| Deacetylation           | Compounds <b>75–78</b> | HEK293 cells                                                                              | 1, 2, 3, and 4 $\mu\text{M}$                  | 12 h             | Direct stimulatory effect on SIRT1 deacetylation activity                                                                                                                                                                                                                                                         | Dao et al. (2012)        |
| Antidiarrheal           | BAA methanol extracts  | Locally bred rabbits                                                                      | 50, 100, 300, and 500 mg/kg                   | 24 h             | Extenuating castor oil-induced diarrhea in a concentration-dependent manner                                                                                                                                                                                                                                       | Rahman et al. (2019)     |
| Smooth muscle relaxant  |                        | BAA dichloromethane fraction                                                              | 0.003, 0.03, 0.3, and 3 mg/mL                 | 24 h             | Suppressing spontaneous and spasmogenic contractions in jejunum separated from rabbit in a concentration-dependent manner, blocking calcium channels                                                                                                                                                              | Rahman et al. (2019)     |

novel agent with high insecticidal activity. However, scientific evidence was limited in this study as no positive control drugs were used. In another study, the acaricidal effect of BAA extracts (1.0, 0.5, 0.25, and 0.125 g/mL) on *Psoroptes cuniculi* and *Sarcoptes scabiei* var. *cuniculi* was determined *in vitro* by probit analysis. The findings showed that BAA extracts (1.0, 0.5, and 0.25 g/ml for 1, 2, 3, 4, 5, 6, and 7 h) exhibited strong acaricidal effects (time- and concentration-dependent), with median lethal times of 0.60, 0.78, and 1.48 h, respectively, for *P. cuniculi*, and 0.74, 1.29, and 3.33 h, respectively, for *S. scabiei* var. *cuniculi* (Gu et al., 2014). Unfortunately, the aforementioned studies have not received sufficient attention. In addition, as only the insecticidal activity of the crude extract of BAA has been studied, future research should investigate the insecticidal active ingredients using bioassay-guided isolation. Therefore, further experiments are required to isolate and characterize compounds with insecticidal activity from BAA crude extracts to discover novel insecticide candidates with unique properties. Moreover, although it has been established that BAA extracts possess insecticidal activity, the potential mechanisms of action remain unclear. Hence, the insecticidal activities of BAA should be explored in depth in various animal and cell models.

### 5.6. Other activities

Apart from the pharmacological effects described above, the isolated compounds or crude extracts of BAA also display other pharmacological activities, including antiallergic, antifertility, antidiarrheal, and smooth muscle relaxant effects. The *in vivo* and *in vitro* antiallergic effects of the decoction of BAA were evaluated by histamine, MTT, and enzyme-linked immunosorbent assays. Results from *in vivo* experiments showed that when the decoction of BAA was administered orally to male Sprague–Dawley rats at doses of 2 g/kg and 4 g/kg, mast-cell-activated edema and systemic anaphylaxis were significantly suppressed. Additionally, in HMC-1 cells, BAA decoction decreased the expression level of NF- $\kappa$ B/Rel A and the generation of TNF, interleukin (IL)-6, and IL-8 in

the nucleus, thus revealing that BAA may be used to treat allergic diseases, such as asthma, rhinitis, and atopic dermatitis (Kang et al., 2010). In 2016, Main et al. investigated for the first time, the antifertility activity of the methanolic extract of BAA in Wistar albino rats at oral doses of 100, 150, and 200 mg/kg. Reproductive variables containing both the number of litters and percentage resorption were investigated. Among the tested doses, 100 mg/kg was considered optimal for inhibition of male reproduction. These findings demonstrate the traditional use of BAA to inhibit fertility (Mani and Rathore, 2016). However, it should be noted that high doses of BAA were used during the experiments, raising questions concerning the antifertility effects *in vivo* or *in vitro* fertility models. Besides, the detailed mechanisms responsible for the antifertility effects of BAA require investigation. It has been reported that four terpenylated coumarins (compounds **75–78**) isolated from BAA possess direct stimulatory effects on sirtuin 1 (SIRT1) deacetylation activity in HEK293 cells. Furthermore, the NAD-to-NADH ratio in HEK293 cells was reported to increase, indicating that BAA may treat certain age-related diseases (Dao et al., 2012). Furthermore, BAA and its fractions suppressed spontaneous and spasmogenic contractions in the jejunum isolated from rabbits in a concentration-dependent manner. BAA also markedly extenuates castor oil-induced diarrhea in a concentration-dependent manner. The underlying mechanism may be attributed to the blockage of calcium channels (Rahman et al., 2019).

## 6. Quality control

For the quality control of BAA, the Chinese Pharmacopoeia adopts several conventional identification methods, including morphological, microscopic, and thin-layer methods of identification (National Pharmacopoeia Commission, 2020). However, relying solely on these methods to evaluate the quality of BAA is controversial. Therefore, it is of great significance to establish a complete quality evaluation system for BAA. In particular, several ingredients should be recommended as chemical markers to evaluate the quality and to serve as a basis for

further determination of the clinical dosage. Moreover, considering that TCM involves multiple components and multiple targets, it is insufficient to evaluate the quality of BAA in terms of the content of a single compound. Hence, the simultaneous analysis of multiple components has attracted the attention of some scholars. With continuous improvements in modern separation and identification methods, some investigators have used various methods to evaluate the chemical compounds and to control the quality of BAA. For example, Li et al. (2020) investigated the content of canthin-6-one (14) in three different batches of BAA by HPLC. The results showed that the content of canthin-6-one (14) ranged from 14.11  $\mu\text{g/g}$  to 33.24  $\mu\text{g/g}$ . In another study, HPLC and similarity evaluations were used to establish the chromatographic fingerprints of ten BAA samples obtained from different provinces (He et al., 2018), revealing 19 common peaks in the fingerprints of BAA obtained from ten habitats. In fact, the similarity of fingerprints from all regions was less than 1.5% (He et al., 2018). Li et al. (2010) used GC-MS to separate and determine the volatile oil content in BAA obtained by steam distillation. Twenty-two compounds were characterized, accounting for 99% of the total volatile oil. The most common compounds in the volatile oil were mono-ethylhexyl phthalate (87%), *n*-hexadecanoic acid (2.48%), and hexadecanal (1.03%). Lou et al. (2011) also employed GC-MS to analyze and identify 53 compounds from the volatile oil of BAA, accounting for 88.02% of the total volatile oil. Among these compounds, relatively high percentages of (+)-spathulenol (11.59%), *cis*- $\alpha$ -copaene-8-ol (8.37%),  $\alpha$ -copaene (5.87%), cadinene (5.76%), and  $\alpha$ -cubebene (4.40%) were reported. However, these results were inconsistent with those reported in a study by Li et al. (2010), which may be attributed to the differences in the production areas, harvest season, and growth environment of BAA.

In summary, BAA quality control has not attracted adequate attention from scholars. Therefore, further studies focusing on multicomponent quantification and improvements in analytical techniques are warranted. Future investigations should also explore and solve multiple problems in the quality control system for BAA and conduct quality standard research based on clinical trials.

## 7. Pharmacokinetics and toxicity

Few studies have demonstrated the pharmacokinetics and toxicity of BAA and its bioactive compounds via *in vitro* and *in vivo* experiments. To date, studies have only focused on aianthone (34); Tan et al. (2018) used liquid chromatography-tandem mass spectrometry (LC-MS/MS) to investigate the toxicity associated with this compound. Results from the analysis showed that BAA caused severe hepatic and gastrointestinal tract injuries when high doses were used, with a median lethal dose of 27.3 mg/kg. In the subacute toxicity study, aianthone (2.5, 5, and 10 mg/kg for 28 days) caused steatohepatitis, splenomegaly, gastrointestinal mucosal damage, and reproductive system abnormalities; reduced the weight of male mice; and increased the weight of female mice when compared with the corresponding parameters in the mice from the control group (Tan et al., 2018). However, the mechanism underlying the toxicity of aianthone (34) requires further examination. In another study, the pharmacokinetic profiles of aianthone (34) were determined using a validated LC-MS/MS method (Chen et al., 2015). For a single intravenous administration of aianthone (34) at different doses (0.5, 1.0, 1.5 mg/kg), the elimination half-lives were  $105.5 \pm 13.6$ ,  $113.3 \pm 39.6$ , and  $95.8 \pm 23.9$  min, respectively. In addition, the area under the plasma concentration versus time curve from 0 to 6 h ( $\text{AUC}_{0-6\text{h}}$ ) and initial plasma concentration ( $C_0$ ) showed a linear relationship (Chen et al., 2015). Although the above-mentioned studies are extremely relevant, only two studies on pharmacokinetics and safety evaluation have been reported. Consequently, there is a need to investigate the pharmacokinetics and toxicity parameters of aianthone (34), thereby providing beneficial guidance and reference for determining its optimal dosage in clinical applications.

## 8. Conclusions and future perspectives

This review article provides detailed information on BAA from the perspectives of its traditional uses, phytochemistry, toxicology, pharmacokinetics, quality control, and pharmacology. Based on the renowned TCM monograph and the Chinese Pharmacopoeia (2020 edition), BAA has been traditionally used for treating asthma, epilepsy, spermatorrhea, bleeding, ascariasis, and ophthalmic diseases. With thousands of years of clinical applications, BAA has been confirmed to be reliable. To this day, more than 221 compounds have been isolated and identified from BAA. These chemical constituents have been reported to possess several pharmacological activities, especially, anticancer and anti-inflammatory activities, thus revealing the potential of BAA as an anticancer and anti-inflammatory drug. Although alkaloids and quassinoids are the main active compounds in BAA, numerous scholars have mainly focused on canthin-6-one (14) and aianthone (34). Therefore, further studies are required to identify other active ingredients in BAA. With regard to its pharmacological activity, many *in vivo* and *in vitro* studies have verified the traditional uses of BAA via bioassay techniques. However, several gaps exist in the scientific research on BAA. In this review, we have highlighted a few interesting topics, as summarized below, which should be investigated further.

First, there are only a few studies regarding the pharmacokinetics and toxicity profiles of BAA and its active compounds. Although BAA is considered safe according to TCM, only a few clinical studies have demonstrated the safety of BAA in patients with underlying ailments. Furthermore, potential hepatic and gastrointestinal tract injury should not be ignored, especially, the acute toxicity induced by quassinoids. Therefore, it is important to determine the therapeutic and safe doses of the active components in BAA through scientific pharmacokinetic and pharmacological studies. In addition, the potential mechanisms of toxicity triggered by BAA and its active compounds must be investigated.

Second, although a wide range of pharmacological activities of various alkaloids and quassinoids isolated from BAA has been reported, investigation on other chemical compounds in BAA, such as triterpenoids and phenylpropanoids, has been ignored. Most of the pharmacological activities of triterpenoids and phenylpropanoids have been tested *in vitro* only through cytotoxicity assays. This severely limits the diversity of BAA-associated research and the development of related drugs. Therefore, future research directions for BAA should place more emphasis on exploring active compounds with specific pharmacological activities and revealing their mechanisms of action.

Third, researchers currently afford little attention to the scientific quality control standards of BAA. Based on the premise of strengthening the material basis and efficacy, future research should focus on canthin-6-one (14), 9-hydroxycanthin-6-one (19), 1-methoxycanthin-6-one (22), aianthone (34), 2-dihydroaianthone (35), and altissimacoumarin C (75) as the main indicators for quality evaluation and establish content detection methods and BAA extract fingerprints to evaluate the quality of BAA.

Fourth, studies have revealed that BAA possesses significant pharmacological effects, such as antitumor, antiviral, and anti-inflammatory effects. Therefore, BAA extracts or active compounds may be used to develop novel anti-inflammatory agents, antitumor candidates, and antiviral agents. Furthermore, it is worth noting that while aianthone (34) possesses a wide range of antitumor activities, its potential toxicity seriously hinders its development as an anticancer drug. Therefore, future studies should focus on the preparation of the derivatives of aianthone (34) through structural modifications and chemical synthesis to enhance its antitumor activity and reduce its toxicity. Moreover, BAA and its active ingredients are expected to be developed as a new type of herbicide and insecticide.

Fifth, although BAA has been traditionally utilized for treating several diseases, few investigations have been conducted to verify the traditional uses of BAA, except for anti-inflammatory and antifertility

studies. Moreover, most investigators have focused their research only on antitumor issues that are currently popular. Therefore, future studies need to be performed to demonstrate folk medicinal uses via well-designed pharmacological and toxicological tests as well as randomized clinical trials.

Sixth, based on currently available information, investigations on the structure-activity relationships (SARs) of compounds in BAA are very limited. Since quassinoids are considered the characteristic components of BAA, emphasis can be placed on investigating the SARs for quassinoids and revealing the mechanisms of action of potential clinical agents in the future. Modern pharmacological studies have shown that quassinoids isolated from BAA exhibit extensive pharmacological effects such as antitumor, antiviral, anti-inflammatory, antimicrobial, and antiparasitic effects. Among them, antitumor and anti-inflammatory activities have attracted much research attention. Quassinoids have been shown to exert antitumor activity against diverse cancer cell lines mainly through their antiproliferative effects. Wang et al. (2013) discovered that 6a-tigloyloxychaparrinone (**63**) and 6a-tigloyloxychaparrin (**64**) isolated from BAA inhibited the proliferation of three hepatocellular carcinoma cell lines, namely HepG2 (IC<sub>50</sub> values:  $0.55 \pm 0.01 \mu\text{M}$  and  $10.54 \pm 1.13 \mu\text{M}$  for **63** and **64**, respectively), Hep3B (IC<sub>50</sub> values:  $0.05 \pm 0.01 \mu\text{M}$  and  $2.43 \pm 0.12 \mu\text{M}$  for **63** and **64**, respectively), and R-HepG2 (IC<sub>50</sub> values:  $16.90 \pm 2.14 \mu\text{M}$  and  $>50 \mu\text{M}$  for **63** and **64**, respectively). This suggests that the active strength of derivatives with glycosyl ketone carbonyl groups in the C-2 position is much higher than those with methyl groups. Moreover, ailanthone (**34**), shinjulactone A (**37**), and shinjuglycoside B (**68**) isolated from BAA were revealed to suppress the LPS-induced production of NO in RAW 264.7 cells (Kim et al., 2015). Comparing the activities of these compounds, it was found that their anti-inflammatory potency could be increased by substitution of ketone carbonyl groups at the C-2 position (IC<sub>50</sub> values: 5.18, 56.4, and  $>100 \mu\text{M}$  for **34**, **37**, and **68**, respectively). These studies revealed that substitution at the C-2 position of derivatives is crucial to the potency of their antitumor and anti-inflammatory activities. However, there is a lack of scientific SAR-based studies to confirm this hypothesis. Therefore, more SAR studies should be conducted to determine the relationships between the relationship between the structural characteristics of various quassinoids and their pharmacological effects to provide new perspectives for the development of drugs with clinical potential. The structures of ailanthone (**34**), shinjulactone A (**37**), 6a-tigloyloxychaparrinone (**63**), 6a-tigloyloxychaparrin (**64**), and shinjuglycoside B (**68**) are summarized in Fig. 10.

Seventh, it is common knowledge that the therapeutic effects of medicinal plants are closely related to their pharmacological effects, while the main effect of plant-based drugs is influenced by the active compounds contained in the plant material. Therefore, it is critical to emphasize the isolation and identification of additional bioactive chemical constituents from BAA to select natural drug candidates with therapeutic potential and promote its development and application. We believe that the isolation and identification of 221 compounds from BAA represent only the “tip of the iceberg”. Moreover, most phytochemistry investigations, particularly those related to the isolation of quassinoids and alkaloids, were carried out decades ago. Therefore, future studies should focus on the separation of additional chemical components through advanced scientific, technological, and separation techniques, including ultra-performance convergence chromatography (UPC<sup>2</sup>), high-speed counter-current chromatography (HSCCC), supercritical fluid chromatography (SFC), and ultrasonic extraction.

Finally, although BAA has demonstrated diverse therapeutic potential owing to its antitumor, anti-inflammatory, and antiviral activities, *in vivo* studies and clinical trials testing BAA have rarely been reported. Moreover, the designs of some pharmacological experiments were controversial, such as the lack of positive or negative control settings and inappropriate doses.

Taken together, according to previous investigations on BAA, we believe BAA is a valuable medicinal resource that possesses promising

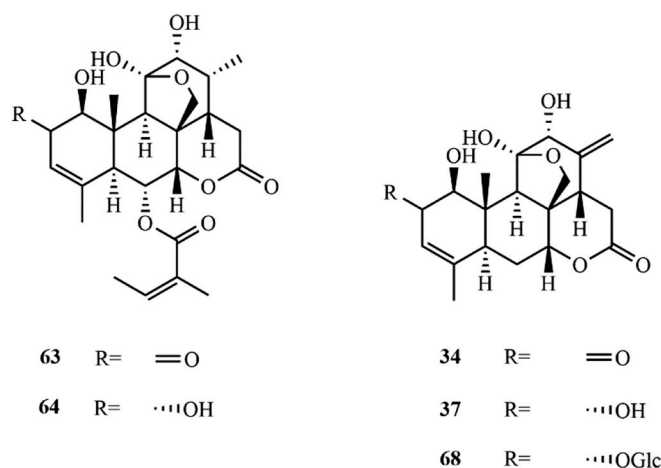


Fig. 10. Structures of ailanthone (**34**), shinjulactone A (**37**), 6a-tigloyloxychaparrinone (**63**), 6a-tigloyloxychaparrin (**64**), and shinjuglycoside B (**68**).

therapeutic properties. Moving forward, more comprehensive studies regarding metabolism, pharmacokinetics, quality control, and toxicity as well as clinical trials in humans are of extreme importance to demonstrate the clinical efficacy and safety of BAA extracts and their isolated bioactive constituents.

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#### Author contributions

Xiang Li wrote the following sections of this review article: Introduction, Phytochemistry, Pharmacology, Quality control, Pharmacokinetics, and Toxicity. Yao Li wrote the Conclusion section; Jianping Ren drew the structures of the chemical constituents; Qianqian Zhao, Linrui Duan, Shanbo Ma, Junsheng Wu, and Yanhua Xie sorted the references and edited the paper's language; and Siwang Wang conceived and designed the structure of the review. All authors have read and agreed to submit this manuscript.

#### Declaration of competing interest

The authors have no conflict of interest to declare.

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