The *Angelica dahurica*: A Review of Traditional Uses, Phytochemistry and Pharmacology

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Angelica dahurica (*A. dahurica*) root is a famous edible medicinal herb that has been used in China for thousands of years. To date, more than 300 chemical constituents have been discovered from *A. dahurica*. Among these ingredients, coumarins and volatile oils are the major active compounds. Moreover, a few other compounds have also been isolated from the root of *A. dahurica*, such as alkaloids, phenols, sterols, benzofurans, polyacetylenes and polysaccharides. Modern pharmacological studies demonstrated that the root of *A. dahurica* and its active components displayed various bioactivities such as anti-inflammation, anti-tumor, anti-oxidation, analgesic activity, antiviral and anti-microbial effects, effects on the cardiovascular system, neuroprotective function, hepatoprotective activity, effects on skin diseases and so on. Based on these studies, this review focused on the research publications of *A. dahurica* and aimed to summarize the advances in the traditional uses, phytochemistry and pharmacology which will provide reference for the further studies and applications of *A. dahurica*.

Keywords: *Angelica dahurica*, coumarins, imperatorin, anti-inflammation, anti-tumor, review

1 INTRODUCTION

*Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., belonging to Apiaceae family, exerts dual functions as medicine and food, which is pervasively distributed in eastern, northern and southeastern Asia. As a well-known traditional Chinese medicine (TCM), the root of *A. dahurica* (Chinese name: 白芷) has been commonly used either alone or in combination with other herbal medicines to treat cold fever, headache, toothache, cold-damp pain and some skin diseases in China for centuries (Lee B.W. et al., 2020). Many classic formulas containing *A. dahurica* root have been widely used in clinic and have made important contributions to the health of people in China and
other traditional medicinal systems in Asia. For example, the combination of A. dahurica root with Atractylodes lancea (Chinese name: 苍术) could significantly enhance the effect of eliminating dampness, thus be used in treating arthrodynia. The combination of A. dahurica root with Xanthium sibiricum (Chinese name: 苍耳子) has been commonly used for the treatment of rhinitis and nasosinusitis. In folk, A. dahurica root is often used as to make tea and health-care product, which is benefi- cient to treat cold-damp pain and rhinitis, and nourish blood. However, it is noteworthy that the vast and irrational use of A. dahurica root could lead to spasm and paralysis, and pregnant women and those with yin deficiency and blood heat should not use it.

In the past few decades, A. dahurica root has attracted widespread attention as an important herbal medicine. Significant progress on isolation and identification of active constituent in A. dahurica has been made in relevant researches. Numerous studies have demonstrated that A. dahurica contains a broad spectrum of phytochemical constituents. The main chemical components of A. dahurica include coumarins and volatile oils, which are regarded as the representative constituents with putative bioactivities (Lee B.W. et al., 2020; Wu et al., 2016). There are more than 150 coumarins have been identified from A. dahurica, including simple coumarins, furanocoumarins, coumarins glycosides, other coumarins and coumarin derivatives. Among them, furanocoumarin imperatorin (22, IMP, Figure 1) is the most representative coumarin in A. dahurica root (Deng et al., 2020). The volatile oils isolated from A. dahurica mainly include terpenes, aromatics, alcohols, aldehydes, ketones, acids, esters and alkanes. Extensive studies indicated that A. dahurica exhibits a broad range of bioactivities, which can be attributed to the presence of multiple active components. Some of these bioactivities are consistent with the traditional uses of A. dahurica root, such as analgesic activity and effects on skin diseases. In addition, A. dahurica also exerts specific effects, related to anti-diabetic (Han et al., 2018), lowering blood lipids (Lu et al., 2016), improving immunity (Wang et al., 2021), anti-ulcer (Hu et al., 2021) and cosmetic effects (Cho et al., 2006).

Although A. dahurica has been widely studied on its chemical constituents and bioactivities, there is no comprehensive review about this edible medicinal herb. Therefore, the present article provides a systematic overview of A. dahurica covering its botany, traditional uses, phytochemistry, pharmacology, pharmacokinetics, quality control and safety. It is anticipated

FIGURE 1 | A. dahurica: (A) aerial parts (B) flowers (C) roots (D) chemical structure of imperatorin.
that this review will provide a new insight for the further study on the chemical constituents and bioactivities of *A. dahurica*.

## 2 BOTANY

*A. dahurica* is a member of Apiaceae family and is commonly distributed in eastern, northern and southeastern Asia (https://www.gbif.org). Wild *A. dahurica* often grows in forests, forest margins, streams, shrubs and valleys. Nowadays, *A. dahurica* is cultivated in many areas, and its roots are collected for medicinal purposes. As a perennial herb, *A. dahurica* grows to the height of 1–2.5 m (Figure 1). The root of *A. dahurica* is cylindrical with branches and its epidermis is tawny to brown with a strong smell. The stem of *A. dahurica* is hollow and 2–5 cm in diameter with the color of purple. The leaves are often ovate or triangular, with petioles up to 15 cm long. The flowers are compound umbels that are 10–30 cm in diameter with rough hairs in peduncles, rays and flower stalks. There are approximately 18–40 rays in *A. dahurica* and even as many as 70 in the center. *A. dahurica* fruits are round to ovoid with the color of yellowish-brown. The flowering phase ranges from July to August, and the mature fruit stage is typically from August to September (Flora of China Editorial Committee, 2006).

## 3 TRADITIONAL USES

The root of *A. dahurica* has a long history of use and is characterized by pungent in taste and warm in nature. It has been widely used in TCM with excellent therapeutic effects for the treatment of cold, headache, forehead pain, epistaxis, nasosinusitis, toothache, abnormal leucorrhoea in women and sore. An oral dosage of 3–10 g of *A. dahurica* has been recommended in the 2020 edition of Chinese pharmacopoeia. Moreover, the external use of *A. dahurica* root can treat boils, carbuncles, sores and painful swellings (Chinese Pharmacopoeia Commission, 2020). Dating back more than 1700 years of history, *A. dahurica* root was first documented in “Shen Nong Ben Cao Jing” (神农本草经) (Dong Han Dynasty, 25–220 A.D.), which is the earliest classic on TCM. Later, it was listed in many other well-known works on Chinese herb, including "Ming Yi Bie Lu" (名医别录) (Wei and Jin Dynasty, 220–420 A.D.), “Yao Xing Lun” (药性论) (Tang Dynasty, 618–907 A.D.) “Ri Hua Zi Ben Cao” (日华子本草) (Song Dynasty, 960–1279 A.D.) “Dian Nan Ben Cao” (滇南本草) (Ming Dynasty, 1368–1644 A.D.) and “Ben Cao Gang Mu” (本草纲目) (Ming Dynasty, 1368–1644 A.D.).

### Table 1 | The traditional uses of *A. dahurica* root in ancient books.

| No. | Traditional uses | References |
|-----|------------------|------------|
| 1   | Treating abnormal leucorrhoea in women, pudendal swelling, cold fever and wind evil invading the head and eyes, nourishing the skin | Shen Nong Ben Cao Jing (神农本草经) (Dong Han Dynasty, 25–220 A.D.) |
| 2   | Curing vomiting, headache with vertigo and itchy eyes | Ming Yi Bie Lu (名医别录) (Wei and Jin Dynasty, 220–420 A.D.) |
| 3   | Treating heart tingling, flooding, hiccup, wind evil, lumbago and apocynosis, brightening eyes and stopping tears | Yao Xing Lun (药性论) (Tang Dynasty, 618–907 A.D.) |
| 4   | Treating red eyes, pterygium, abortion, mastitis, ulcer in back, scrofula, hematotachezia, apocynosis, scabies and lento, breaking blood stasis and producing new blood | Ri Hua Zi Ben Cao (日华子本草) (Song Dynasty, 960–1279 A.D.) |
| 5   | Removing wind of the skin, curing stomach cold, belliache and cold-damp pain | Dian Nan Ben Cao (滇南本草) (Ming Dynasty, 1368–1644 A.D.) and Ben Cao Gang Mu (本草纲目) (Ming Dynasty, 1368–1644 A.D.) |
| 6   | Curing nasosinusitis, epistaxis, toothache, pain in supraorbital bone, constipation, hematochezia, dizziness, vomiting and sores, antiasenic poison and snake venom |  |

Of note, the root of *A. dahurica* has been used in China for centuries as both a food and traditional medicine. For example, many soups with *A. dahurica* root as ingredient have significant
## TABLE 2 | The Prescriptions and traditional uses of A. dahurica root in China.

| Prescriptions          | Main compositions                                      | Traditional Uses                                                                 | References                                |
|------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------|
| Jiu Wei Qiang Huo      | Root: Notopterygium incisum Ting ex H. T. Chang,      | Curing cold, rheumatic arthritis, migraine and lumbar muscle strain             | Ci Shi Nan Zhi (此事难知) (Yuan Dynasty, 1,279–1368 A.D.) |
| Decoction (九味羌活汤) | Saposhnikovia divaricate (Turcz.) Schischk, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Rehmannia glutinosa Libosch, Scutellaria baicalensis Georgi, Rhizome; Atractylodes Lancea (Thunb.) DC., Ligusticum chuanxiong Hort. Root and Rhizome: Asarum sieboldii Miq, Glycyrrhiza uralensis Fisch | | |
|                         | Root: Pulsatilla chinensis DC, Pueraria lobata (Wild.) Ohwi, Scutellaria baicalensis Georgi, Notopterygium incisum Ting ex H. T. Chang, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. Root and Rhizome: Glycyrrhiza uralensis Fisch | | |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Saposhnikovia divaricate (Turcz.) Schischk, Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. Root and Rhizome: Asarum sieboldii Miq, Glycyrrhiza uralensis Fisch | | |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Notopterygium incisum Ting ex H. T. Chang, Saposhnikovia divaricate (Turcz.) Schischk, Aerial part: Nupeta cataria L, Mentha haplocalyx Briq. Rhizome: Ligusticum chuanxiong Hort. Root and Rhizome: Glycyrrhiza uralensis Fisch, Asarum sieboldii Miq | | |
|                         | Root: Gentiana macrophylla Pall, Angelica sinensis (Oliv.) Diels, Paeonia lactiflora Pall, Notopterygium incisum Ting ex H. T. Chang, Saposhnikovia divaricate (Turcz.) Schischk, Scutellaria baicalensis Georgi, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Rehmannia glutinosa Libosch, Heracleum hemsleyanum Diels. Rhizome: Ligusticum chuanxiong Hort. Atractylodes macrocephalae Koidz. Root and Rhizome: Glycyrrhiza uralensis Fisch, Asarum sieboldii Miq | | |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Notopterygium incisum Ting ex H. T. Chang, Saposhnikovia divaricate (Turcz.) Schischk, Aerial part: Nupeta cataria L, Mentha haplocalyx Briq. Rhizome: Ligusticum chuanxiong Hort. Root and Rhizome: Glycyrrhiza uralensis Fisch, Asarum sieboldii Miq | | |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. | Curing facial distortion, tongue stiffness and inability to move hands and feet | Su Wen Bing Ji QI Yi Bao Ming Ji (素问病机气宜保命集) (Jin Dynasty, 1,155–1234 A.D.) |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. | Dispelling wind, relieving pain and stopping spasm | Wai Ke Zheng Zong (外科正宗) (Ming Dynasty, 1,368–1644 A.D.) |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. | Curing typhoid headache, asthma, cough and spleen–stomach dampness | Tai Ping Hui Min He Ji Ju Fang (太平惠民和剂局方) (Song Dynasty, 960–1279 A.D.) |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC. | Treating menstrual cramps | Ny Ke Zhi Zhang (女科指掌) (Qing Dynasty, 1,636–1912 A.D.) |
|                         | Root: Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Paeonia lactiflora Pall, Platycodon grandiflorus (Jacq.) A. DC., Angelica sinensis (Oliv.) Diels, Aucklandia lappa Decne. Rhizome: Atractylodes Lancea (Thunb.) DC., Cyperus rotundus L, Ligusticum chuanxiong Hort. Root and Rhizome: Glycyrrhiza uralensis Fisch, Panax ginseng C. A. Meyer, Pericarp: Citrus reticulata Blanco. Bark: Magnolia officinalis Rehd. et | | |

(Continued on following page)
TABLE 2 | (Continued) The Prescriptions and traditional uses of A. dahurica root in China.

| Prescriptions       | Main compositions                                                                 | Traditional Uses                                                                 | References                  |
|---------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------|
| Bai Zhu Shi Hu Decoction (白术石解汤) | Wills, Cinnamonum cassia Presl. Tub. Pinellia ternata (Thunb.) Brit. Fruitt. Citrus aurantium L. Herbaceous stem: Ephedra sinica Stapf. | Curing qi and blood deficiency, limb burnout and pain of hands and feet | Sheng Ji Zong Lu (圣济总录) (Song Dynasty, 980–1279 A.D.) |
| Jia Wei Xin Yi San (加味辛夷散) | Root: Atragranurus membranaceus (Fisch.) Bunge., Angelica sinensis (Oliv.) Diels. Paeonia lactiflora Pall, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. | Treating pus shed from nose | Xian nian Ji (仙年集) (Qing Dynasty, 1,636–1912 A.D.) |
| Bai Hu Ge Gen Decoction (白虎甘根汤) | Root: Pueraria lobate (Willd.) Ohwi, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Rhizome: Anemarrhena asphodeloides Bunge. Gypsum | Curing headache and fever | Shang Han Da Bai (伤寒大白) (Qing Dynasty, 1,636–1912 A.D.) |
| Jia Wei Qing Liang Yin (加味清凉饮) | Root: Paeonia lactiflora Pall, Notopterygium incisum Ting ex H. T. Chang, Angelica sinensis (Oliv.) Diels, Saposhnikovia divaricate (Turcz.) Schischk, Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., Scutellaria baicalensis Georgii Rhizome: Panax ginseng C. A. Meyer, Asarum sieboldi Miq., Glycyrrhiza uralensis Fisch., Fruitt. Magnolia denudata Desr. Root and Rhizome: Rheum palmatum L., Glycyrrhiza uralensis Fisch., Aerial part: Nepeta cataria L. Herbaceous stem: Ephedra sinica Stapf. | Treating facial sores | Song Ya Zi Sun Sheng (嵩崖圣生) (Qing Dynasty, 1,636–1912 A.D.) |

health benefits, such as nourishing blood, warming liver and strengthening kidney. Bai zhi bo he liquor (白芷薄荷酒), which is a popular medicinal diet in China, is often used to dispel wind, unblocking stuffy orifice and relieving pain. Interestingly, the root of A. dahurica can also be used in cosmetic to improve a person’s skin (Cho et al., 2006). In a word, A. dahurica root is a kind of well-known TCM with both food and medicine. Due to its low price and easy availability, many studies indicated that the root of A. dahurica should be deeply exploited to treat various diseases and health care.

Additionally, the root of A. dahurica is often used in formulas in TCM to cure cold, fever, headache, rheumatic arthritis and other conditions. The well-known prescriptions containing A. dahurica root, which have been handed down from many ancient works or ethnic medicine experience are still widely used in modern times (Table 2). Among them, chuan xiong cha tiao san (川芎茶调散) is one of the most typical prescriptions to explain the traditional uses of A. dahurica root (Chang et al., 2014). The main compositions of the formula include Ligusticum chuanxiong Hort, Nepeta cataria L., A. dahurica, Notopterygium incisum, etc. In TCM, chuan xiong cha tiao san is used to treat headache, fever and nasal obstruction. In detail, the root of A. dahurica is used in chuan xiong cha tiao san formula plays an important role in dispelling wind, curing headache and unblocking stuffy nasal cavity. However, few documents provide the chemical composition about the formulas. Consequently, the clinical effects and functions of A. dahurica root still need further exploration. The Chinese names of all the medical books and prescriptions are listed in Table 3.

4 PHYTOCHEMISTRY

To date, more than 309 chemical components were isolated and identified from A. dahurica. Phytochemical studies have revealed the presence of coumarins, volatile oils, alkaloids, phenols, sterols, benzoferans, polyacetylenes, polysaccharides and others. Currently, studies on the chemical components of A. dahurica mostly focus on the root of A. dahurica. Coumarins and volatile oils are the predominant constituents of A. dahurica root.

4.1 Coumarins

Coumarins are the most abundant and main bioactive constituents present in of A. dahurica. They have a broad spectrum of pharmacological activities, such as anti-viral (Liu et al., 2021), anti-tumor (Banikzami et al., 2021), anti-osteoporosis (Jia et al., 2016) and effects on the cardiovascular system (Najmanova et al., 2015). To date, a total of 153 coumarins have been isolated from the root and stem of A. dahurica, include 18 simple coumarins (1–18), 93 furanocoumarins (19–111), 41 coumarins glycosides (112–147), 3 other coumarins (148–150) and 3 coumarin derivatives (151–153). Among them, furanocoumarins are the most abundant coumarins, which are mainly divided into linear and angular types based on the location.
of the furan group. The furan ring in linear furocoumarins is connected to the 6 and 7 carbon atoms, while the substituent often occurs in the positions of C8 or C9 in angelic furocoumarins (Sumorek-Wiadro et al., 2020). Furanocoumarin IMP (22) is the most principal and representative active component of *A. dahurica* root, which has anti-inflammatory, analgesic, anti-allergic and neuroprotective activities (Deng et al., 2020). Moreover, other furanocoumarins such as isomomperatorin (19), oxypeucedanin (20), phellopterin (26) and byakangelicin (41) are also characteristic constituents of *A. dahurica* root with a wide range of bioactivities (Cho et al., 2006; Kang et al., 2008; Lee, B.W. et al., 2020; Li and Wu, 2017). These furanocoumarins are characterized by the attachment of different substituents to C8 or C9 in the parent nucleus of linear furocoumarins. In addition to furanocoumarins, some simple coumarins, such scopletin (3) in the root and stem of *A. dahurica* also exhibited anti-microbial and neuroprotective effects (Kwon et al., 1997; Luo et al., 2020), which contribute to the bioactivities of *A. dahurica*. The information and chemical structures of all these coumarins are listed in Supplementary Table S1 and Supplementary Figure S1.

### 4.2 Volatile Oils

Volatile oils are other major physiologically active compounds in *A. dahurica*. The components of volatile oil can be roughly divided into four categories, including terpenoids, aromatic compounds, aliphatic compounds and other compounds. Among them, terpenoids are the most common type. Numerous studies declared that the cluster of the compounds possess extensive bioactivities and act as antibacterials, antivirals and insecticides in plants (Cascaes et al., 2021). So far, approximately 121 volatile components have been identified from the root of *A. dahurica*. These volatile oils include terpenes (154–200), aromatics (201–212), alcohols (213–234), aldehydes (235–246), ketones (247–252), acids (253–260), esters (261–270) and alkanes (271–274). The major components of the volatile oils in *A. dahurica* root include α-pinene (154), myrcene (199), terpinen-4-ol (219), 1-dodecanol (221) and sabinden (160). However, the extraction yields of volatile oil are different as the plant materials came from different regions. It was reported that the extraction yield of volatile oil from *A. dahurica* root cultivated in yizhou, China is 1.4% (ml/g), including α-pinene (44.91%), myrcene (8.72%), terpinen-4-ol (8.01%), 1-dodecanol (6.43%) and sabinden (3.42%). These

| No | Medical books or prescriptions | Chinese names | Traditional names |
|----|--------------------------------|--------------|-------------------|
| 1  | Shen Nong Ben Cao Jing         | 神农本草经   | 神農本草经 |
| 2  | Ming Yi Bi Lu                  | 名医别录     | 名醫別錄  |
| 3  | Yao Xing Lun                   | 药性论       | 藥性論 |
| 4  | Ri Hua Zi Ben Cao              | 日华子本草   | 日華子本草 |
| 5  | Dian Nan Ben Cao               | 淇南本草     | 淇南本草 |
| 6  | Ben Cao Gang Mu                | 本草纲目     | 本草綱目 |
| 7  | Lei Gong Pao Zhi Lun           | 雷公炮炙论   | 雷公炮炙論 |
| 8  | Bo Ji Fang                     | 博济方       | 博濟方 |
| 9  | Chuang Yang Jing Yan Quan Shu  | 疡疮经验全书 | 疡瘍經驗全書 |
| 10 | Shi Yi De Xiao Fang            | 世医得效方   | 世醫得效方 |
| 11 | Ben Cao Meng Quan              | 本草蒙筌     | 本草蒙筌 |
| 12 | Ci Shi Nian Zhi                | 此事難知     | 此事難知 |
| 13 | Shang Han Liu Shu              | 伤寒六书     | 傷寒六書 |
| 14 | Jiao Zhu Fu Ren Liang Fang     | 校注妇人良方 | 校注婦人良方 |
| 15 | Tai Ping Hui Min He Ji Ju Fang | 太平惠民和剂局方 | 太平惠民和劑局方 |
| 16 | Su Wen Bing Ji Qi Yi Bao Ming Ji | 素问病机气宜保命集 | 素問病機氣宜保命集 |
| 17 | Wai Ke Zhong Zong              | 外科正宗     | 外科正宗 |
| 18 | Nv Ke Zhi Zhang                | 女科指掌     | 女科指掌 |
| 19 | Sheng Ji Zong Lu              | 圣济总录     | 聖濟總錄 |
| 20 | Xian nian Ji                  | 仙拈集       | 仙拈集 |
| 21 | Shang Han Da Bai               | 伤寒大白     | 傷寒大白 |
| 22 | Song Ya Zun Sheng              | 高丽尊生     | 高麗尊生 |
| 23 | Jiu Wei Qiang Huo Decoction    | 九味羌活汤   | 九味羌活湯 |
| 24 | Chai Ge Jie Ji Decoction       | 川芎解肌汤   | 川芎解肌湯 |
| 25 | Xian Fang Huo Ming Yin         | 仙方活命飲 | 仙方活命飲 |
| 26 | chuan xiong cha tiao san       | 川芎茶调散   | 川芎茶調散 |
| 27 | Da Qin Jiao Decoction          | 大秦艽汤     | 大秦艽湯 |
| 28 | Yu Zhen San                   | 玉真散       | 玉真散 |
| 29 | Huo Xiang Zheng Qi San         | 霍香正气散 | 霍香正氣散 |
| 30 | Jia Wei Wu Ji Yin              | 加味五积饮 | 加味五積飲 |
| 31 | Bai Zhu Shi Hu Decoction       | 白术附汤     | 白術附湯 |
| 32 | Jia Wei Xin Yi San            | 加味辛夷汤 | 加味辛夷湯 |
| 33 | Bai Hu Ge Gen Decoction        | 白虎加藤汤  | 白虎加藤湯 |
| 34 | Jia Wei Qing Liang Yin         | 加味清凉饮 | 加味清凉飲 |
| 35 | Bai zhi bo he liuqor           | 白芷薄荷酒 | 白芷薄荷酒 |
### TABLE 4 | Volatile oils isolated from A. dahurica.

| No  | Names        | Plant parts | Formulas | References                  |
|-----|--------------|-------------|----------|-----------------------------|
| 154 | α-Pinene     | Roots       | C₁₀H₁₆   | Sun et al. (2017)           |
| 155 | 1-Caryophyllene | Roots       | C₁₅H₂₄   | Sun et al. (2017)           |
| 156 | E-1,3-tetradecadiene | Roots      | C₁₄H₂₆   | Sun et al. (2017)           |
| 157 | 1-Methylcyclooctene | Roots     | C₁₀H₁₆   | Hu et al. (2019)            |
| 158 | Camphene     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 159 | β-Pinene     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 160 | Sabinene     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 161 | β-Myrcene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 162 | α-Phellandrene | Roots      | C₁₀H₁₆   | Hu et al. (2019)            |
| 163 | α-Terpinene  | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 164 | D-Limonene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 165 | β-Phellandrene | Roots      | C₁₀H₁₆   | Hu et al. (2019)            |
| 166 | Eucalyptol   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 167 | γ-Terpinene  | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 168 | Trans-β-Ocimene | Roots     | C₁₀H₁₆   | Hu et al. (2019)            |
| 169 | α-Copaene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 170 | β-Cubebene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 171 | Selina-5,11-diene | Roots   | C₁₀H₁₆   | Hu et al. (2019)            |
| 172 | Longifolene-(V4) | Roots  | C₁₀H₁₆   | Hu et al. (2019)            |
| 173 | (−)-β-Elemene | Roots      | C₁₀H₁₆   | Hu et al. (2019)            |
| 174 | Caryophyllene | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 175 | Aromandendrene | Roots      | C₁₀H₁₆   | Hu et al. (2019)            |
| 176 | γ-Elemene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 177 | cis-β-Farnesene | Roots  | C₁₀H₁₆   | Hu et al. (2019)            |
| 178 | Humulene     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 179 | γ-Murolene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 180 | δ-Elemene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 181 | β-selinene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 182 | δ-Cadinene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 183 | α-Gurjunene  | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 184 | α-Guaiene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 185 | γ-Selinene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 186 | β-Guaiene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 187 | Germacrone B | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 188 | Caryophyllene oxide | Roots    | C₁₀H₁₆   | Hu et al. (2019)            |
| 189 | α-thujene    | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 190 | Limonene     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 191 | Perilien     | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 192 | Trans-β-bergamotene | Roots  | C₁₀H₁₆   | Hu et al. (2019)            |
| 193 | Selina-4,11-diene | Roots  | C₁₀H₁₆   | Hu et al. (2019)            |
| 194 | β-Bisabolene | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 195 | α-Selinene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 196 | Selina-4(15)(7(11)-diene | Roots | C₁₀H₁₆   | Hu et al. (2019)            |
| 197 | Humulene epoxide II | Roots | C₁₀H₁₆   | Hu et al. (2019)            |
| 198 | δ-3-Carene   | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 199 | Myrcene      | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 200 | Sesquisabinene | Roots      | C₁₀H₁₆   | Hu et al. (2019)            |

Aromatics

| No  | Names                              | Plant parts | Formulas | References                  |
|-----|------------------------------------|-------------|----------|-----------------------------|
| 201 | 1-Methoxy-4-[[2-prop-1-enyl]benzene | Roots       | C₁₀H₁₆   | Sun et al. (2017)           |
| 202 | p-Cymene                           | Roots       | C₁₀H₁₆   | Hu et al. (2019)            |
| 203 | Toluene                            | Roots       | C₈H₁₀    | Hu et al. (2019)            |
| 204 | 1,3-dimethylbenzene                | Roots       | C₈H₁₀    | Hu et al. (2019)            |
| 205 | α-Xylene                           | Roots       | C₈H₁₀    | Hu et al. (2019)            |
| 206 | α,p-Dimethylstyrrene               | Roots       | C₈H₁₂    | Hu et al. (2019)            |
| 207 | α,3-Dimethylstyrrene               | Roots       | C₈H₁₂    | Hu et al. (2019)            |
| 208 | Estragole                          | Roots       | C₈H₁₂    | Hu et al. (2019)            |

(Continued on following page)
### TABLE 4 | (Continued) Volatile oils isolated from *A. dahurica*.

| No | Names                  | Plant parts | Formulas         | References               |
|----|------------------------|-------------|------------------|--------------------------|
| 209| Anethole               | Roots       | C₁₀H₁₂O          | Hu et al. (2019)         |
| 210| Isoelemicin            | Roots       | C₁₂H₁₆O₃         | Hu et al. (2019)         |
| 211| Cuparene               | Roots       | C₁₁H₂₂          | Tabanca et al. (2014)    |
| 212| Carvacrol methyl ether| Roots       | C₁₁H₁₆O         | Dongying Wang et al. (2020) |
| 213| Dodecyl alcohol        | Roots       | C₁₂H₃₄O         | Sun et al. (2017)        |
| 214| 1-Pentadecanol         | Roots       | C₁₅H₃₀          | Sun et al. (2017)        |
| 215| Linalool               | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 216| 3-Buten-2-ol, 2-methyl-| Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 217| Prenol                 | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 218| 1-Hexanol              | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 219| Terpinen-4-ol          | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 220| Benzyl alcohol         | Roots       | C₁₅H₂₀          | Hu et al. (2019)         |
| 221| 1-Dodecanol            | Roots       | C₁₅H₂₀          | Hu et al. (2019)         |
| 222| 1-Hexadecanol          | Roots       | C₁₆H₃₂O         | Hu et al. (2019)         |
| 223| Spathulenol            | Roots       | C₁₅H₂₀          | Hu et al. (2019)         |
| 224| 2-Methyl-3-buten-2-ol  | Roots       | C₁₅H₃₀O         | Tabanca et al. (2014)    |
| 225| cis-p-Menth-2-en-1-ol  | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 226| trans-Pinocarveol      | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 227| cis-Piperitol          | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 228| Myrtenol               | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 229| p-Menth-1,5-dien-7-ol  | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 230| p-Cymen-8-ol           | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 231| 1-Tridecanol           | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 232| Cumin alcohol          | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 233| Guasia-6,6,10 (14)-dien-4β-ol | Roots | C₁₄H₂₀O | Tabanca et al. (2014) |
| 234| 2-Nonanol              | Roots       | C₁₀H₁₆O         | Dongying Wang et al. (2020) |
| 235| Butanal, 3-methyl-     | Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 236| Hexanal                | Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 237| 2-Methyl-2-butenal     | Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 238| Heptanal               | Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 239| Octanal                | Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 240| (E)-2-Octenal          | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 241| Nonanal                | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 242| Decanal                | Roots       | C₁₂H₂₄O         | Hu et al. (2019)         |
| 243| Benzaldehyde           | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 244| (E)-2-Nonenal          | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 245| 2,6-Octadienal, 3,7-dimethyl- (2)- | Roots | C₁₀H₁₆O | Hu et al. (2019) |
| 246| Cumin aldehyde         | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 247| 6-Methyl-5-hepten-2-one| Roots       | C₁₂H₂₂O         | Hu et al. (2019)         |
| 248| 2-Nonanone             | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 249| Camphor                | Roots       | C₁₀H₁₆O         | Hu et al. (2019)         |
| 250| Phinocarvone           | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 251| Cryptone               | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 252| Verbenone              | Roots       | C₁₀H₁₆O         | Tabanca et al. (2014)    |
| 253| Tridecanoic acid       | Roots       | C₁₀H₂₆O₂        | Sun et al. (2017)        |
| 254| Linoleic acid          | Roots       | C₁₀H₂₆O₂        | Sun et al. (2017)        |
| 255| Palmitic acid          | Roots       | C₁₂H₂₆O₂        | Zhang et al. (2018)      |
| 256| Stearic acid           | Roots       | C₁₄H₂₆O₂        | Zhang et al. (2018)      |
| 257| Acetic acid            | Roots       | C₂H₄O₂          | Hu et al. (2019)         |
| 258| Hexanoic acid          | Roots       | C₂H₄O₂          | Hu et al. (2019)         |
| 259| Oleic Acid             | Roots       | C₁₈H₃₄O₂        | Hu et al. (2019)         |
| 260| Dodecanoic acid        | Roots       | C₁₂H₂₆O₂        | Hu et al. (2019)         |

(Continued on following page)
Volatile oils were confirmed to show obvious antioxidant activity (Wang D. et al., 2020). All the identified volatile oils are listed in Table 4 and their structural formulas are displayed in Supplementary Figure S2.

### 4.3 Alkaloids

Biologically important alkaloids have been less distributed in *A. dahurica*. Approximately 13 types of alkaloids have been isolated from this plant (Table 5 and Supplementary Figure S3), including dahurines A–F (275–280), (8R,11S,12R)-Funebral (281), (8R,11S,12R)-3,4-dihydro-3-amino-4,5-dimethylfuran-2[5H]-one-2-formyl pyrrole (282), 4″-butyl-2-formyl-5-(hydroxymethyl)-1H-pyrrole-1-butanoic acid (283), butyl 2-formyl-5-butoxymethyl-1H-pyrrole-1-butanoate (284), hemerocallisamine II (285), butyl 2-pyrrolidinone-5-carboxylate (286) and corydalidine (287) (Sun et al., 2017; Qi et al., 2019).

### 4.4 Phenols

There have been four phenolic compounds identified from the ethanol extract of *A. dahurica* root, including angelicols A (288), angelicols B (289), (1S)-2-OZ-Feruloyl-1-(4-hydroxyphenyl)ethane-1,2-diol (290) and (1S)-2-O-E-Feruloyl-1-(4-hydroxyphenyl)ethane-1,2-diol (291) (Shu et al., 2020a). Another phenolic compound, ferulic acid (292) was isolated from the EtOAc-soluble fraction of *A. dahurica* root (Kwon et al., 1997). In addition, five flavonoids, including cyanidin (293), rutin (294), catechin (295), epicatechin (296) and kaempferol (297) have been found in the water extract or ethanol extract (Pervin et al., 2014). Zhao X. Z. et al. (2007) reported a kind of new neolignan glycoside, namely 4-O-β-D-glucopyranosyl-9-O-β-D-glucopyranosyl-(7R,8S)-dehydropseudotroponol alcohol (298) from the fresh root of *A. dahurica*. The information of them is shown in Table 5 and Supplementary Figure S3.

### 4.5 Sterols

Sterols such as β-sitosterol (299) and daucosterol (300) were identified from the root of *A. dahurica* (Table 5 and Supplementary Figure S3) (Li and Wu, 2017). Plant sterols have been reported to reduce the circulating total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) to prevent cardiovascular disease (Chen et al., 2019). Although these compounds have been shown to be potential and safe drugs by many in vitro and in vivo studies, clinical studies are needed to prove the implications of these compounds on some specific diseases so as to develop them into notable drugs (Babu and Jayaraman, 2020).

### 4.6 Benzofurans

Benzofurans are an important class of heterocyclic compounds, which are diffusely presented in natural products and synthetic materials (Khodarahmi et al., 2015). In a recent study, six benzofuran derivatives have been acquired from the root of *A. dahurica* (Table 5 and Supplementary Figure S3), including 3-[6,7-furano-9-hydroxy-4(2″,3″-dihydroxy-3″-methylbutyloxy)]-phenyl propionic acid (301), 3-[6,7-furano-9-β-D-glucopyranosyl-4(2″,3″-dihydroxy-3″-methylbutyloxy)]-phenyl propionic acid (302), 3-[6,7-furano-9-β-D-glucopyranosyl-4(2″,3″-dihydroxy-3″-methylbutyloxy)]-phenyl propionic acid methyl ester (303), cinnoside A (304), methylcinnamidose A (305) and methylpicraquassioside (306) (Matsuo et al., 2020).
### TABLE 5 | Alkaloids, phenols, sterols, benzofurans and polyacetylenes isolated from *A. dahurica*.

| No   | Names                  | Plant parts | Formulas          | References                |
|------|------------------------|-------------|-------------------|---------------------------|
| 275  | Dahurine A             | Roots       | C_{17}H_{20}N_{2}O_{6} | Qi et al. (2019)           |
| 276  | Dahurine B             | Roots       | C_{16}H_{23}NO_{4}   | Qi et al. (2019)           |
| 277  | Dahurine C             | Roots       | C_{16}H_{23}NO_{4}   | Qi et al. (2019)           |
| 278  | Dahurine D             | Roots       | C_{12}H_{15}NO_{3}   | Qi et al. (2019)           |
| 279  | Dahurine E             | Roots       | C_{23}H_{31}NO_{4}   | Qi et al. (2019)           |
| 280  | Dahurine F             | Roots       | C_{17}H_{27}NO_{4}   | Qi et al. (2019)           |
| 281  | (8R,11S,12R)-Funebral  | Roots       | C_{12}H_{17}NO_{4}   | Qi et al. (2019)           |
| 282  | (8R,11S,12R)-3,4-dihydro-3-amino-4,5-dimethylfuran-2 [5H]-one-2-formyl pyrrole | Roots | C_{12}H_{17}NO_{4} | Qi et al. (2019) |
| 283  | 4″-Butyl-2-formyl-5-(hydroxymethyl)-1H-pyrole | Roots | C_{12}H_{17}NO_{4} | Qi et al. (2019) |
| 284  | Butyl 2-formyl-5-butoxymethyl-1H-pyrole-1-butanolate | Roots | C_{12}H_{17}NO_{4} | Qi et al. (2019) |
| 285  | Hemerocalisamine II    | Roots       | C_{16}H_{20}N_{2}O_{4} | Qi et al. (2019) |
| 286  | Butyl 2-pyrrolidone-5-carboxylate | Roots | C_{18}H_{31}NO_{4} | Qi et al. (2019) |
| 287  | Corydalidine           | Roots       | C_{18}H_{28}N_{2}O_{6} | Sun et al. (2017) |
| 288  | Angelicols A           | Roots       | C_{10}H_{14}O_{3}   | Shu et al. (2020a)         |
| 289  | Angelicols B           | Roots       | C_{18}H_{20}O_{6}   | Shu et al. (2020a)         |
| 290  | (1S)-2-O-Z-Feruloyl-1-(4-hydroxyphenyl)ethane-1,2-diol | Roots | C_{18}H_{20}O_{6} | Shu et al. (2020a) |
| 291  | (1S)-2-O-E-Feruloyl-1-(4-hydroxyphenyl)ethane-1,2-diol | Roots | C_{18}H_{20}O_{6} | Shu et al. (2020a) |
| 292  | Ferulic acid           | Roots       | C_{18}H_{20}O_{4}   | Kwon et al. (1997)         |
| 293  | Cyanidin               | Roots       | C_{18}H_{16}O_{6}   | Pervin et al. (2014)      |
| 294  | Rutin                  | Roots       | C_{18}H_{16}O_{12}  | Pervin et al. (2014)      |
| 295  | Catechin               | Roots       | C_{18}H_{16}O_{6}   | Pervin et al. (2014)      |
| 296  | Epicatechin            | Roots       | C_{18}H_{16}O_{6}   | Pervin et al. (2014)      |
| 297  | Kaempferol             | Roots       | C_{18}H_{16}O_{6}   | Pervin et al. (2014)      |
| 298  | 4-O-β-D-Glucopyranosyl-9-O-β-D-glucopyranosyl-(7R,8S)-dehydrodiconiferyl alcohol | Roots | C_{20}H_{24}O_{6} | Zhao et al. (2007a)       |
| 299  | β-Sitosterol           | Roots       | C_{20}H_{24}O_{6}   | Li and Wu, (2017)         |
| 300  | Daucoesterol           | Roots       | C_{20}H_{24}O_{6}   | Li and Wu, (2017)         |
| 301  | 3-[6,7-Furano-9-hydroxy-4-([2″,3″-dihydroxy-3″-methylbutyloxy])phenyl propionic acid | Roots | C_{18}H_{20}O_{7} | Matsuo et al. (2020) |
| 302  | 3-[6,7-Furano-9-([β-D-glucopyranosyloxy]-4-([2″,3″-dihydroxy-3″-methylbutyloxy])phenyl propionic acid | Roots | C_{20}H_{24}O_{12} | Matsuo et al. (2020) |
| 303  | 3-[6,7-Furano-9-([β-D-glucopyranosyloxy]-4-([2″,3″-dihydroxy-3″-methylbutyloxy])phenyl propionic acid methyl ester | Roots | C_{20}H_{24}O_{12} | Matsuo et al. (2020) |
| 304  | Cnidioside A           | Roots       | C_{19}H_{22}O_{9}   | Matsuo et al. (2020)      |
| 305  | Methylcnidioside A     | Roots       | C_{19}H_{22}O_{9}   | Matsuo et al. (2020)      |
| 306  | Methylpicraquassioside | Roots       | C_{19}H_{22}O_{12}  | Matsuo et al. (2020)      |
| 307  | Falcarindiol           | Roots       | C_{19}H_{22}O_{12}  | Matsuo et al. (2020)      |
| 308  | Octadeca-1,9-dien-4,6-diyne-3,8,18-triols | Roots | C_{19}H_{22}O_{12} | Matsuo et al. (2020) |
| 309  | Adenosine              | Roots       | C_{12}H_{17}NO_{4}  | Shu et al. (2020b)        |
4.8 Polysaccharides

A. dahurica polysaccharides have also been reported in some research publications. A latest study reported a new acidic A. dahurica polysaccharide (ADP) composed of rhamnose, mannose, glucose, galactose, arabinose, galacturonic acid and glucuronic acid with a Mw of 6.09 × 10^3 Da (Dong et al., 2021). Xu et al. (2011) isolated four ADPs from the water extract of A. dahurica root and found that they have different degrees of anti-oxidant activity. Moreover, Wang et al. (2021) isolated a gluco-arabian consisting of a trace of glucose and arabinose with a Mw of 9,950 Da by water extraction and ethanol precipitation from the root of A. dahurica.

4.9 Other Compounds

In addition to the compounds mentioned above, adenosine (309) was also isolated from the root of A. dahurica (Table 5 and Supplementary Figure S3) (Shu et al., 2020b). Moreover, A. dahurica also contains sucrose and amino acids (Zhao and Yang, 2018).

5 PHARMACOLOGY

As of the present, a strong body of evidence for the bioactivities of A. dahurica has been discovered. The crude extract and active components of A. dahurica contain various bioactivities, such as anti-inflammation, anti-tumor, anti-oxidation, analgesic activity, antiviral and anti-microbial effects, effects on the cardiovascular system, neuroprotective function, hepatoprotective activity, effects on skin diseases and so on. These biological activities have proved most implications of A. dahurica root in treating cold, headache, toothache, cold-damp pain, rhinitis and skin diseases. Next, these bioactivities were discussed and the recapitulative summary was listed in Supplementary Table S2.

5.1 Anti-Inflammatory Activity

5.1.1 Crude Extracts

Nowadays, there have been growing evidence showing that A. dahurica has been widely used for inflammation-associated diseases. For example, the 50% ethanol extract of A. dahurica root showed a significant inhibitory effect on lipopolysaccharide (LPS)-induced inflammation in Raw 264.7 cells (10 and 100 μg/ml for 2 h) and rat models of periodontitis (1 and 100 mg/ml for 14 days). The expression of inflammatory genes, including interleukin-1β (IL-1β), IL-6, IL-8 and interferon-γ (IFN-γ) were decreased in gingival tissues of ligature-induced periodontitis rats and LPS-induced Raw 264.7 cells upon treatments with ethanol extract of A. dahurica. Moreover, the extract of A. dahurica root inhibited the expression of nuclear factor-κB (NF-κB), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), and the phosphorylation of inhibitor of NF-κB (IκB). Therefore, the anti-inflammatory effects of A. dahurica in periodontitis might occur via the regulation of pro-inflammatory mediators (Lee et al., 2017). In asthmatic mice, the 70% ethanol extract of A. dahurica root (50 and 100 mg/kg b.w., 5 days) relieved ovalbumin-induced airway inflammation, as evidenced by the reduction of eosinophilia, cytokines (IL-4, IL-5), tumor necrosis factor-α (TNF-α), immunoglobulin E (Ig E) and mucus production by increasing the expression of heme oxygenase-1 (HO-1) (Lee et al., 2011).

5.1.2 Isolated Compounds

What’s more, many compounds isolated from A. dahurica also possess excellent anti-inflammatory properties. For example, the administration of IMP (15, 30 and 60 mg/kg b. w., 7 days), which is the most major ingredient of A. dahurica, significantly inhibited the ear edema of dimethylbenzene-induced mice, acetic acid-induced vascular permeability in mice and ball fralunoma weight cotton pellet-induced granuloma in rats. Further investigation demonstrated that IMP reduced the levels of TNF-α, IL-6, IL-1β, iNOS and COX-2 in LPS-induced Raw 264.7 cells by suppressing the activity of NF-κB via increasing the expression of p65 (C) and IkB (C) and decreasing the level of p65 (N) (Zhang X. et al., 2017). Li et al. isolated 13 coumarins from the root of A. dahurica and evaluated their abilities of anti-allergic inflammation. They found that all these coumarins at a dose of 20 μM for 1 h could reduce the release of histamine in the media for RBL-2H3 cells compared with dinitrophenyl-human serum albumin (DPN-HSA) cells, with oxypeucedanin hydrate (21), bergapten (25) and byakangelicin (41) possessing the strongest property. Moreover, these compounds reduced the secretion of TNF-α, IL-4 and IL-1β, with bergapten and phellopterin (26) exhibiting the most potent effect. The treatment mechanism might be the inhibition of NF-κB signaling (Li and Wu, 2017).

In summary, the related results showed that both crude extracts and active compounds of A. dahurica exhibit significant anti-inflammatory activity, and their mechanism is mainly through inhibiting the expression and release of pro-inflammatory mediators, such as NF-κB, iNOS, COX-2 and TNF-α etc. This activity may link to the traditional uses of A. dahurica root in treating cold, toothache, rhinitis and some skin diseases.

5.2 Anti-Tumor Activity

Modern pharmacological studies have revealed that A. dahurica also exhibits potent anti-tumor effects in multiple cancers, including colon cancer, breast cancer and melanoma. In murine melanoma B16F10 cells, the 70% ethanol extract of A. dahurica root (100 and 200 μg/ml for 24 h) was confirmed to inhibit the growth, migration, invasion and colony formation, while stimulating cell apoptosis via reducing the activity of matrix metalloproteinase-2 (MMP-2) and MMP-9 (Hwangbo et al., 2020). The essential oils from the root of A. dahurica (12.5 μg/ml for 24 h) could suppress the resistance of MCF-7/ADR breast cancer cells to doxorubicin with a fold reversal of 2.09 by inhibiting the expression of ATP-binding cassette subfamily B member1 (ABC1) and decreasing lipid raft stability (Wu et al., 2016). As for colon cancer, the cell apoptosis assay illustrated anti-apoptosis effect of the ethyl acetate extract of A. dahurica root (200 and 250 μg/ml, 48 h) on colon cancer HT-29 cells through p53-independent pathway (Zheng et al., 2016b). Moreover, IMP was reported to significantly inhibited the proliferation at a dose of 150 μM for 12 h in colon cancer.
HCT116 cells, as well as suppressed angiogenesis and tumor growth (50 and 100 mg/kg b. w., 3 times a week, 35 days) in HCT116 xenograft mice by inhibiting hypoxia-inducible factor-1α (HIF-1α) protein synthesis through the mammalian target of rapamycin (mTOR)/ribosomal protein S6 kinase (p70S6K)/eukaryotic initiation factor 4E binding protein-1 (4E-BPI) and mitogen-activated protein kinase (MAPK) signaling pathways (Mi et al., 2017). It could also significantly suppress the growth (IC_{50} = 78 μM), and induce the apoptosis at a dose of 150 μM for 48 h in colon cancer HT-29 cells via upregulating p53 and caspase cascade (Zheng et al., 2016a). In addition, IMP enhanced anokis at doses of 0.1, 0.5 and 1 μg/ml in lung cancer H292 and A549 cells at 24 h after cell detachment and mitigated cancer cachexia at doses of 25 and 50 mg/kg b. w. for 15 days in colorectal adenocarcinoma CT26 tumor-bearing mice (Choochuy et al., 2013; Chen et al., 2020). These results suggested that IMP, the active ingredient of *A. dahurica*, is a new potential candidate for cancer treatment.

Although emerging evidence has demonstrated the anti-tumor effect of *A. dahurica*, several challenges must be overcome in the future. Firstly, the pathogenesis of tumors is complex and the research on the anti-tumor mechanism of *A. dahurica* is not in-depth enough. Furthermore, many studies focused on the crude extracts and could not determine the specific ingredient in *A. dahurica* that was responsible for its anti-tumor activity. Finally, the current studies mainly include *in vivo* and *in vitro* experiments, with a lack of clinical trial data. Future studies are necessary to reveal the anti-tumor effect of *A. dahurica* in clinical trial.

### 5.3 Anti-Oxidant Activity

#### 5.3.1 Crude Extracts

The *A. dahurica* extract exerted significant anti-oxidant activity mainly based on its free radicals scavenging ability (Lee and Woo, 2011; Wang et al., 2017; Liang et al., 2018). Wang et al. (2017) assessed the anti-oxidant activities of different extracts of the root of *A. dahurica* and found that 70% ethanol extract displayed the most powerful anti-oxidant with 50% inhibitory concentration (IC_{50}) of 1.6 ± 0.25 mg/ml using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. Similarly, 70% ethanol extract of *A. dahurica* root exhibited the highest reducing power (IC_{50} = 2.8 ± 0.36 mg/ml) compared with water extract and ethyl acetate extract. Interestingly, they also found that their anti-oxidant activities were improved after fermentation by probiotic bacteria. Lee et al. found that both extracts of *A. dahurica* stem (including leaves) and root exhibited anti-oxidant effect. The DPPH radical scavenging activity of stem [50% effective concentration (EC_{50}) = 243.33 μg/ml] was more powerful than that of root (EC_{50} = 1,161.79 μg/ml), while the xanthine oxidase inhibitory activities of them showed no significant differences with EC_{50} values of 434.66 μg/ml and 435.19 μg/ml, respectively (Lee and Woo, 2011). These results indicated that both the stem and root extracts of *A. dahurica* have certain anti-oxidant effect. Nevertheless, the DPPH analytical method may overestimate the anti-oxidant content and this method cannot test all the analytical properties of the extract. Thus, the anti-oxidant activity cannot be accurately evaluated only by DPPH analysis and it is necessary to try a more precise method to verify it.

#### 5.3.2 Isolated Compounds

In addition to the crude extract of *A. dahurica*, some chemical components from *A. dahurica*, including coumarins, phenols and polysaccharides also possess obvious anti-oxidant activities (Piao et al., 2004; Xu et al., 2011; Bai et al., 2016; Kang et al., 2019; Shu et al., 2020a). For example, Piao et al. identified 11 furanocoumarins from the root of *A. dahurica* and found that 9-hydroxy-4-methoxysperalen (67) and alloisoimperatorin (107) significantly attenuated 2,2-azobis (2-aminoiminopropane)-dihydrochloride (AAPH)-induced renal epithelial cell injury by reducing DPPH radical with IC_{50} of 6.1 and 9.4 μg/ml (Piao et al., 2004). Phenols compounds (289, 290 and 291) from *A. dahurica* root show significant DPPH radical scavenging activities with IC_{50} of 0.36, 0.39 and 0.44 mM (Shu et al., 2020a). Moreover, the polysaccharides ADP1-ADP4 from the root of *A. dahurica* also exhibit powerful anti-oxidant capacity at doses ranging from 62.5 to 500 μg/ml by inhibiting malondialdehyde (MDA) formation and chelating ferrous ion (Fe^{2+}) (Xu et al., 2011). These findings showed that coumarins, phenols and polysaccharides in *A. dahurica* exhibit antioxidant effect. However, *in vitro* experiments used to test anti-oxidant activity are prone to interference and further *in vivo* experiments are required to confirm these results.

### 5.4 Analgesic Activity

*A. dahurica* has been used historically to cure pain-associated diseases, such as headache, toothache, rheumatalgia and supervical ridge pain. Modern molecular pharmacological approaches have demonstrated the analgesic effects of *A. dahurica* root by using multiple pain models and revealed that the analgesic mechanisms are complex. Transient receptor potential vanilloid type 1 (TRPV1) is a therapeutic target for treating various models of pain and is widely expressed in peripheral and central nervous systems (Iftinca et al., 2021). Recently, the researchers indicated that injected subcutaneously with IMP (2.45 mM) could effectively alleviated the acute pain induced by formalin or capsaicin in rats by inhibiting the activity of TRPV1 channel (Chen et al., 2014). Similarly, The water extract of *A. dahurica* root at a dose of 100 mg/kg b. w. for 2 h attenuated the acute pain induced by thermal, formalin and capsaicin in mice through the inhibition of TRPV1 channel (Gao et al., 2019). Moreover, coumarins of *A. dahurica* root (CAD) obviously reduced the nociceptive response at doses 30, 60 and 120 mg/kg b. w. for 4 days in formalin-induced pain models of mice. After intracerebroventricular administration of CAD at dose 6 mg/kg b. w., the latency of mice was significantly prolonged in the hotplate test. Further research suggested that the analgesic site of CAD might be in both peripheral and central nervous systems, and the mechanism might be associated with the synthesis and release of nitric oxide (NO) (Wang H.L. et al., 2009). These findings demonstrated that the extracts of *A. dahurica* root or individual compound may exert analgesic effect by the inhibiting TRPV1 channel and regulating NO level. The root
of *A. dahurica* might have the potential to be effective therapeutic drug for various pains, which was consistent with its traditional use of analgesia.

### 5.5 Antiviral and Anti-Microbial Activities

Nowadays, some studies revealed that *A. dahurica* present a wide range of anti-microbial activity. Kwon et al. first isolated eight compounds, including 5,8-di-(2,3-dihydroxy-3-methylbutoxy)-psoralen (75), heracelenol (47), IMP, isomerperatorin (19), phellolpipterin (26), scopoletin (3), byakangelicin (41) and ferulic acid (292) from *A. dahurica* root and evaluated their anti-microbial activities against *Bacillus subtilis*, *Escherichia coli*, *Cladosporium herbarum* and *Aspergillus candidus*. They found that these active constituents displayed good inhibitory effects against *Bacillus subtilis*, *Cladosporium herbarum* and *Aspergillus candidus* with minimum inhibitory concentration (MIC) of 62.5 μg/ml (Kwon et al., 1997). In bioassays of anti-microbial activity, the ethanol extract of *A. dahurica* root showed an inhibition radio of 40% against *Trypanosoma cruzi*, and the water extract of *A. dahurica* exhibited notable effect of anti- *Mycoplasma hominis* with a 50% minimum inhibitory concentration (MIC50) of 3.91 mg/ml, which could be used in treating *Mycoplasma hominis* infection (Schinella et al., 2002; Che et al., 2005). Moreover, the hexane extract of *A. dahurica* root was found to possess anti-microbial activity against *staphylococcus aureus*. From the hexane extract, an anti-microbial compound was isolated by bioassay-guided fractionation and identified as falcarnidil (307). In this study, falcarnidil inhibited the growth of *staphylococcal* strains with MICs ranged from 8 to 32 μg/ml (Lechner et al., 2004).

In addition to the anti-microbial activity, *A. dahurica* also presents significant antiviral effect. In recent years, coumarins from *A. dahurica* were reported to possess significant antiviral property. For example, Lee et al. found that four active furanocoumarins in the root of *A. dahurica*, including isomerperatorin (19), oxypeucedanin (20), oxypeucedanin hydrate (21) and IMP have significant antiviral activity against influenza A (H1N1 and H9N2) viruses. Among them, oxypeucedanin exhibit the most potent antiviral effect with an EC50 of 5.98 ± 0.71 and 4.52 ± 0.39, respectively. Further investigation showed that oxypeucedanin exerts anti-influenza A viruses property by inhibiting the virus infection-induced apoptosis and early stage of the viral replication cycle (Lee, B.W. et al., 2020). Besides, IMP (10, 25 and 50 μM, 30 min) was capable of inhibiting human immunodeficiency virus type 1 (HIV-1) replication in both T cells and HeLa cells infected by HIV-1 via the regulation of transcription factor specificity protein1 (Sp1) (Sancho et al., 2004). As many diseases occur due to the infection of bacteria and viruses. These studies suggested that the root of *A. dahurica* is a rich source of natural anti-microbial and antiviral agents that can prevent and treat some diseases.

### 5.6 Effects on the Cardiovascular System

Cardiovascular diseases are major contributor to global mortality and result in a huge socioeconomic burden. Many studies have declared that *A. dahurica* extract and its active ingredients possess obvious protective role on cardiovascular system. Lee et al. (2015) first reported that 70% methanol extract of *A. dahurica* root (0.03–3.0 μg/ml) markedly relaxed calcium-induced vasoconstriction of aortic rings in a concentration-dependent manner. In high-fat/high-fructose diet (HFFD)-fed rats, IMP at doses of 15 and 30 mg/kg b. w. for 4 weeks significantly reduced blood pressure and heart rate values, and alleviated changes in vascular morphology by regulating the expression of adiponectin receptor 1, endothelial nitric oxide synthase (eNOS) and p47phox (Bunbupha et al., 2021). Meanwhile, IMP displayed a potent vasodilatation role by partially affecting the level of NO in phenylephrine-induced mouse thoracic aorta (IC50 = 12.2 ± 2 ± μmol/L) (Nie et al., 2009). He et al. (2007) found that IMP (1 μM–1 mM) might promote vasodilatation on arteries precontracted by agonists by regulating the calcium channel and competitively antagonizing 5-hydroxytryptamine (5-HT) receptors. Additionally, IMP could also attenuate pathological myocardial hypertrophy and cardiac fibrosis, inhibit transition to heart failure, and prevent cardiac myocyte protein synthesis and cell size induced by angiotensin II. The high dose of IMP (30 μM) was more effective than IMP (10 and 3 μM) and displayed concentration-dependently (Zhang et al., 2010). These scientific reports demonstrated that the root of *A. dahurica* and its active ingredients may control Ca2+ channel, modulate the expression of adiponectin receptor 1, eNOS and p47phox to exert vasodilative and cardioprotective effects. IMP may be responsible for the effects of *A. dahurica* on cardiovascular system.

### 5.7 Effects on the Nervous System

IMP might largely contribute to the neuroprotective function of *A. dahurica* and possess significant properties on the nervous system, such as improving memory, antidepressive-like effect and anticonvulsant (Luszczki et al., 2009; Sigurdsson and Gudbjarnason, 2013; Cao et al., 2017). For example, pretreatment with IMP (5, 10 mg/kg b. w., 14 days) exhibited significant amelioration in the mice of LPS-induced poor memory retention by upregulating the level of brain derived neurotrophic factor (BDNF) and inhibiting oxidative stress and inflammation (Chowdhury et al., 2018). In middle cerebral artery occlusion (MCAO) rats, IMP at doses of 5 and 10 mg/kg b. w. reduced the infarct volume and increased the behavior ability. Moreover, IMP (0.612 and 2.56 μM) ameliorated the damage of neural cell lines (SH-SY5Y cells) by anti-apoptosis through increasing the expression of BDNF and phosphorylated-extracellular signal-regulated kinase (p-ERK) (Wang et al., 2013). In the maximal electroshock-induced seizure (MES) test, IMP at a dose of 50 mg/kg b. w. markedly enhanced the anticonvulsant activity of lamotrigine (LTG) in mice by reducing the 50% effective dose (ED50) value by 60% and increased the protective index from 4.90 to 8.96. The MES threshold for IMP administrated alone at 50 and 100 mg/kg were significantly increased by 38% and 68% at 30 min after its administration (Luszczki et al., 2007; Luszczki et al., 2008). In addition to IMP, some other compounds such as phellolpipterin (26) and scopoletin (3) also exhibit neuroprotective effects. Scopoletin (2, 10 and
50 mg/kg b. w.) administration for 2 weeks mitigated anxiety-like symptoms in complete Freund’s adjuvant (CFA)-induced mice by activating γ-aminobutyric acid (GABA_A) receptors and phellodendrin was competitively bind to central nervous system benzodiazepine receptors with IC50 of 0.36 μM (Bergendorff et al., 1997; Luo et al., 2020). Alzheimer’s disease is a common neurodegenerative disease characterized by the formation of β-amyloid plaques and neurofibrillary tangles (Zhang et al., 2020). Marumoto et al. evaluated the inhibitory activities against β-secretase (BACE1) of five furanocoumarins from A. dahurica and found that IMP and byakangelicol (34) exhibit the most excellent properties with IC50 of 91.8 ± 7.5 and 104.9 ± 2.4 μM (Marumoto and Miyazawa, 2010), implying their potential for the treatment of Alzheimer’s disease. However, based on the present study, due to the complexities of the nervous system, IMP is limited to achieve desired therapeutic effects. The combination of IMP with other effective compounds may be a promising direction in clinical trials.

5.8 Hepatoprotective Activity
Several research publications reported the hepatoprotective activities of some active ingredients from A. dahurica. For example, Oh et al. isolated and identified six furanocoumarins, including IMP, isoimperatorin (19), byakangelicol (34), oxypeucedanin (20), byakangelicin (41), and aviprin (78) from the methanol extract of A. dahurica root and validated their cytotoxic effect on tacrine-induced Hep G2 cells. Subsequently, IMP and byakangelicin displayed superior hepatoprotective activities with EC50 values of 36.6 ± 0.98 and 47.9 ± 4.6 μM, respectively. Byakangelicolic and oxypeucedanin exhibited moderate hepatoprotective effects with EC50 values of 112.7 ± 5.35 and 286.7 ± 6.36 μM, respectively (Oh et al., 2002). Meanwhile, IMP at a dose of 100 mg/kg b. w. for 5 days was able to ameliorate acetaminophen overdose-induced acute liver injury in rats as evidenced by the reduced mortality, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in serum and centrilobular hepatic necrosis via stimulating the sirtuin 1 (SIRT1)-farnesoid X receptor (FXR) pathway (Gao et al., 2020). Furthermore, Oral administration of byakangelicin (100 mg/kg b. w., 4 weeks) in mice significantly improved carbon tetrachloride-induced liver fibrosis and damage by inhibiting the deposition of collagen and α-SMA, and decreasing the levels of ALT and AST in serum, which was more effective than that of silibinin. In 4-HNE−induced HepG2 cells, byakangelicin (20 and 40 μmol/L, 24 h) inhibited activation and proliferation of hepatic stellate cells, and prevented the apoptosis of hepatocyte through apoptosis signal regulating kinase-1 (ASK-1)/c-Jun N-terminal kinase (JNK) pathway (Li et al., 2020). The above mentioned results indicated that furanocoumarins in A. dahurica exhibited obvious hepatoprotective activity and may be responsible for the hepatoprotective activity of A. dahurica. However, the molecular mechanism and clinical safety of some coumarins are not clear enough, which hinders the development of coumarins as hepatoprotective drugs. Future research should focus on the precise molecular mechanisms of furanocoumarins in A. dahurica.

5.9 Effects on Skin Diseases
A. dahurica was extensively used as a traditional Chinese medicine in treating skin-associated diseases. In recent years, several studies revealed that A. dahurica has excellent activity on diabetes-induced skin ulcer (Guo et al., 2020; Chao et al., 2021; Hu et al., 2021). Guo et al. (2020) indicated that 10 days treatment with A. dahurica at 1.8 g/kg b. w. significantly promoted would healing and angiogenesis by activating phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and HIF-1α/platelet-derived growth factor-β (PDGF-β) pathways in db/db mice. Moreover, the 70% ethanol extract of A. dahurica root (2.5 mg/ml, 3 days) was reported to improve the adhesion of melanocytes to fibroinectin and stimulate the migration of melanocytes to treat vitiligo (Zhang et al., 2005). Hwang et al. (2016) found that the root of A. dahurica methanol extract (50 μg/ml) and IMP (10, 20 and 40 μM, 2 days) markedly inhibited the insulin-like growth factor-1 (IGF-1)-dependent sebum production by suppressing the phosphorylation of Akt and the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) and sterol response element-binding protein-1 (SREBP-1) in sebocytes, suggesting that they have the potential to be used in the treatment of acne. In addition, IMP and isoimperatorin (19) from A. dahurica root can inhibit melanogenesis by preventing tyrosinase synthesis in B16 melanoma cells and might have the potential to be exploit as a novel whitening agents in cosmetics (Cho et al., 2006). Collectively, the investigations mentioned above could partly support the claim about the traditional use of A. dahurica root for the treatment of skin diseases. The root of A. dahurica is commonly used to treat various skin diseases, such as scabies, carbuncle, sore and pruitus in China and other traditional medicinal systems in Asia, these indications may be promising for future clinical trials.

5.10 Other Activities
5.10.1 Regulation of Lipid Metabolism
The 70% ethanol extract of A. dahurica root (800 mg/kg b. w., 4 weeks) significantly reduced the levels of TC and triglyceride (TG) in the livers of hyperlipidemia mice, as well as enhanced the activity of total hepatic lipolysis by upregulating the expression of PPARγ and lipid metabolism related genes-lipase member C (LIPC). Similarly, the levels of TC and TG were decreased by A. dahurica extract (400 μg/ml, 24 h) and IMP (20 μg/ml, 24 h) in 50% fetal bovine serum (FBS)-fed HepG2 cells (Lu et al., 2016). This study suggested the effect of A. dahurica root on the regulation of lipid metabolism and might be developed as a pharmaceutical product against fatty liver and hyperlipemia.

5.10.2 Anti-Diabetic Activity
Phellodendrin (26) isolated from ethyl acetate extract of A. dahurica root at doses of 1 and 2 mg/kg b. w. for 2 weeks significantly decreased the level of blood glucose, TC and TG in high-fat diets (HFD)/streptozotocin (STZ)-induced type II diabetic mice. In 3T3-L1 preadipocytes, the ethyl acetate extract of A. dahurica (25, 50 and 100 μg/ml) and phellodendrin (50 μg/ml, 9 days) induced adipocytes differentiation by increasing the expression of PPARγ, indicating the value of
phellipterin for the development of anti-diabetic drugs through enhancing insulin sensitivity (Han et al., 2018).

5.10.3 Immunoregulatory Activity
A latest study reported that ADP80-2, a water-soluble polysaccharide from A. dahurica root, at doses of 25, 50 and 100 μg/ml for 24 h promoted the phagocytosis of macrophage cells, the release of NO and the generation of cytokines (TNF-α, IL-6 and IL-1β). Moreover, ADP80-2 induced the production of immunoregulation-associated chemokines, including reactive oxygen species (ROS) and NO, in zebrafish embryos (Wang et al., 2021). Another study reported that ADP at doses of 10, 30 and 100 μg/ml activated the immune functions of dendritic cells by targeting toll-like receptor 4 (TLR4), MAPKs and NF-κB (Kim et al., 2013). These studies demonstrated that polysaccharides are mainly responsible for the immunomodulatory function in A. dahurica.

6 PHARMACOKINETICS
Pharmacokinetic studies on A. dahurica mainly focus on the coumarins. Ethanol extract of A. dahurica root was administrated orally at a dose of 4.5 g/kg b. w. to determine pharmacokinetic of nine coumarins, including IMP, isoimperatorin, oxypeucedanin hydrate, bergapten, oxypeucedanin, xanthotoxol, xanthotoxin, isopimpinellin and psoralen in the plasma of rats. The values of half-life time (t1/2) of these compounds were 2.4 ± 0.3, 2.2 ± 0.2, 4.8 ± 2.3, 1.8 ± 0.2, 2.4 ± 0.1, 4.8 ± 1.2, 4.5 ± 1.4, 2.8 ± 0.7 and 2.5 ± 0.7 h, respectively. Among these compounds, the values of maximum plasma concentration (Cmax) of IMP, isoimperatorin, oxypeucedanin hydrate and bergapten (1,017–2,900 ng/ml) were significantly higher than the other five compounds (21–138 ng/ml), which was consistent with their higher contents in A. dahurica (Chen et al., 2015). Xie and colleagues reported the pharmacokinetic profile oxypeucedanin hydrate and byakangelicin in the plasma of mongrel dogs after oral administration of A. dahurica ethanol extract (30 mg/kg b. w.). Oxypeucedanin hydrate reached a Cmax of 4,154.09 ng/ml at 1.71 h (t1/2 3.06 h), and byakangelicin reached a Cmax of 1,474.72 ng/ml at 1.71 h (t1/2 2.77 h) (Xie et al., 2007). Moreover, Hwang et al. (2017) used ultra-performance liquid chromatography-tandem mass spectrometry (UPLC/MS/MS) technology to identify the coumarins from the root of A. dahurica, including oxypeucedanin, IMP and isoimperatorin in the plasma of rats after oral administration (0.5 g/kg b. w.). They found that all the three compounds had rapid oral absorption with the time to reach the peak concentration (Tmax) of 40–75 min. Oxypeucedanin reached a Cmax of 38.5 ng/ml at 43.2 min (t1/2 78.1 min), IMP reached a Cmax of 94.5 ng/ml at 54.0 min (t1/2 59.5 min), and isoimperatorin reached a Cmax of 72.1 ng/ml at 72.0 min (t1/2 63.8 min). Furthermore, it is worth noting that A. dahurica has also been found to affect metabolism of some drugs. The water extract of A. dahurica root (oral dose of 1 mg/kg b. w.) significantly increased the area under the concentration–time curve (AUC), t1/2 and plasma clearance (CL) by 2.5, 2.3 and 0.45 times, respectively after tolbutamide was administrated intravenously in rats, suggesting that A. dahurica delayed elimination of tolbutamide. Moreover, treatment with the root of A. dahurica markedly increased the Cmax by 4 times after oral administration of diazepam in rats, indicating that the first-pass effect of the drug was attenuated. Meanwhile, A. dahurica could also increase the duration of rotorod disruption of diazepam. Mechanistically, A. dahurica interfered the metabolism of tolbutamide and diazepam by inhibiting the activity of cytochrome P450 (Ishihara et al., 2000). These findings implied the potential of A. dahurica to be adjuvant therapy of drugs in some specific diseases.

In conclusion, these results indicated that the pharmacokinetic parameters of single compound and the extract of A. dahurica after oral administration may vary due to dosage form and composition. On the whole, investigations on pharmacokinetics for A. dahurica are relatively limited. Future work should focus more on the pharmacokinetics of A. dahurica in order to better evaluate its clinical efficacy.

7 QUALITY CONTROL
It is well known that quality control of herb medicine plays an essential role in ensuring their safety and efficiency. According to the Chinese pharmacopoeia (the 2020 edition), the content of IMP in the root of A. dahurica must be no less than 0.080%, and the total ash should not exceed 6.0%, which is consistent with the European Pharmacopoeia (the 10th edition). Meanwhile, the Chinese Pharmacopoeia stipulates that the moisture content in A. dahurica should not more than 14.0%, and the European Pharmacopoeia states that the moisture content should less than 12.0%. In addition, according to the description in the Japanese Pharmacopoeia (the 18th edition) and the Korean Pharmacopoeia (the 8th edition), the total ash content, acid-insoluble ash content and ethanol extract should less than 7.0%, 2.5%, more than 25%, respectively. However, the inherent quality of medicinal plants may be affected by geographical conditions, harvest time, cultivation techniques and many other factors (Cheng et al., 2019). For instance, Yang et al. (2020) found that the contents of IMP in different regions of China were variable. Among them, the highest content of IMP was 0.392% in Yangjiaying, Hebei, followed by 0.363% in Xiaoying, Hebei, and the lowest content was 0.093% in Mengzhou, Henan. In addition, TCM usually exert its curative effects through the synergistic effect of multiple components, and it is insufficient to determine the quality of A. dahurica by relying on only a single component for quality control. With the development of analytical techniques, the multi-component determination has been prevalently used in the comprehensive quality control of compounds isolated from A. dahurica. A total of 21 coumarins: IMP, byakangelicin, oxypeucedanin, bergapten, condinilin, osthol, isoimperatorin, scopoletin, xanthotoxol, xanthotoxin, psoralen, isopimpinellin, and afocoumarins A, B, C, D, E, F, G, H, I and some volatile oils have been quantified by different analytical tools. The quantitative analysis of the
Wang Y. J. et al. (2020) indicated that the peak shapes of contaminations can be detected according to the different and the root of other Angelica chemical components. Moreover, the mixing of distinguished by HPLC and pubescens and the roots of other method can also detect the mixing of IMP, byakangelicin and oxypeucedanin, respectively, and they were in different batches of A. dahurica.

Volatile oils  
GC-MS  
22 volatile oils were identified from A. dahurica, main including hexadecanoic acid, ethyl ester (7.32%), a-pinene (8.25%), dodecyl alcohol (13.71%), 1-pentadecanol (6.08%) and elemene (7.54%).

Coumarins  
LC-MS/MS  
9 furanocoumarins have been quantified in the injection of 20 batches of A. dahurica with contents of 3.60–333.33, 0.86–77.48, 1.20–41.74, 3.35–146.84, 1.38–44.51, 3.68–71.82, 21.83–411.03, 9.28–218.73 and 4.11–303.58 μg/g for andafocoumarins A, B, C, D, E, F, G, H, and J.

Volatile oils  
GC-MS  
38 compounds were identified from the essential oils of A. dahurica roots, mainly including a-pinene (44.91%), myrcene (8.72%), terpinen-4-ol (6.01%), cryptone (6.67%), 1-dodecanol (8.43%) and sabinene (3.42%).

Coumarins  
HPLC–ESIMS/MS  
11 coumarins have been quantified in the injection of 12 batches of A. dahurica with contents of 26.1–395.6, 4.2–67.9, 23.1–99.0, 3.1–49.0, 2.6–14.8, 25.6–217.3, 81.3–2079.2, 355.1–1418.6, 312.5–994.8, 0.3–2.2, 364.4–900.4 and 1,327.7–5892.9 μg/g for scopoletin, xanthotoxin, xanthotoxin, psoralen, isoimperatorin, bergapten, oxypeucedanin, IMP, cnidilin, osthole and isoimperatorin.

Bergapten, IMP, cnidilin, osthole and isoimperatorin  
PPLC  
The contents were 181.2–1,152.9, 479.8–1,418.6, 312.5–994.8, 321.3–903.1, 7.3–37.7 and 329.7–723.2 μg/g for bergapten, IMP, cnidilin, osthole and isoimperatorin, respectively, and they were 21 batches of A. dahurica.

TABLE 6 | Quantitative analysis for the quality control of A. dahurica root.

| Analytes                      | Methods            | Results                                                                 | References       |
|-------------------------------|--------------------|-------------------------------------------------------------------------|------------------|
| IMP, byakangelicin and        | ^H-qNMR            | The contents were 0.093%–0.392%, 0.117%–0.315% and 0.173%–0.353% for IMP, byakangelicin and oxypeucedanin, respectively, and they were in different batches of A. dahurica | Yang et al. (2020) |
| oxypeucedanin                 |                    |                                                                         |                  |
| Volatile oils                 | GC-MS              | 22 volatile oils were identified from A. dahurica, main including       | Sun et al. (2017) |
|                               |                    | hexadecanoic acid, ethyl ester (7.32%), a-pinene (8.25%),              |                  |
|                               |                    | dodecyl alcohol (13.71%), 1-pentadecanol (6.08%) and elemene (7.54%).  |                  |
| Coumarins                     | LC-MS/MS           | 9 furanocoumarins have been quantified in the injection of 20 batches of | Lei Zhang et al. (2017) |
|                               |                    | A. dahurica with contents of 3.60–333.33, 0.86–77.48, 1.20–41.74,    |                  |
|                               |                    | 3.35–146.84, 1.38–44.51, 3.68–71.82, 21.83–411.03, 9.28–218.73 and     |                  |
|                               |                    | 4.11–303.58 μg/g for andafocoumarins A, B, C, D, E, F, G, H, and J.   |                  |
| Volatile oils                 | GC-MS              | 38 compounds were identified from the essential oils of A. dahurica      | Dongying Wang et al. (2020) |
|                               |                    | roots, mainly including a-pinene (44.91%), myrcene (8.72%),            |                  |
|                               |                    | terpinen-4-ol (6.01%), cryptone (6.67%), 1-dodecanol (8.43%) and        |                  |
|                               |                    | sabinene (3.42%).                                                      |                  |
| Coumarins                     | HPLC–ESIMS/MS       | 11 coumarins have been quantified in the injection of 12 batches of A. | Zheng et al. (2010) |
|                               |                    | dahurica with contents of 26.1–395.6, 4.2–67.9, 23.1–99.0, 3.1–49.0, |                  |
|                               |                    | 2.6–14.8, 25.6–217.3, 81.3–2079.2, 355.1–1418.6, 312.5–994.8, 0.3–2.2, |                  |
|                               |                    | 364.4–900.4 and 1,327.7–5892.9 μg/g for scopoletin, xanthotoxin,      |                  |
|                               |                    | xanthotoxin, psoralen, isoimperatorin, bergapten, oxypeucedanin, IMP,  |                  |
|                               |                    | cnidilin, osthole and isoimperatorin.                                  |                  |
| Bergapten, IMP, cnidilin,     | HPLC               | The contents were 181.2–1,152.9, 479.8–1,418.6, 312.5–994.8, 321.3–903.1, | Wang et al. (2007) |
| osthole and isoimperatorin    |                    | 7.3–37.7 and 329.7–723.2 μg/g for bergapten, IMP, cnidilin, osthole    |                  |
|                               |                    | and isoimperatorin, respectively, and they were 21 batches of A. dahurica |                  |
|                               |                    |                                                                         |                  |

compounds isolated from A. dahurica is listed in Table 6. Besides, the fingerprint analysis has also been apply to the quality assessment of A. dahurica. Kang et al. (2008) found that the 13 batches of A. dahurica root from different regions had similar high performance liquid chromatography (HPLC) fingerprints and indicated that fingerprint method could be used for the quality control of A. dahurica. The fingerprint method can also detect the mixing of A. dahurica and the root of other Angelica species and other putative contaminations. Wang Y. J. et al. (2020) indicated that the peak shapes of A. dahurica and the roots of other Angelica species, including A. pubescens and A. sinensis are quite different and can be distinguished by HPLC fingerprints through different chemical components. Moreover, the mixing of A. dahurica and the root of other Angelica species and other putative contaminations can be detected according to the different characteristic peaks from HPLC fingerprints.

8 SAFETY

As a common used medicinal and edible substance, A. dahurica plays an important role in the health of human body. The toxicity investigations on the safety for A. dahurica are relatively lacking, although this plant exhibits extensive pharmacological activities. Zheng et al. (2012) compared the acute toxicity of sulphur fumigated and non-sulphur-fumigated A. dahurica extracts and indicated that both of them belong to non-toxic grade. The 50% lethal dose (LD₅₀) of non-sulphur-fumigated A. dahurica extracts in Kunming mice was 55.5169 g/kg, while the LD₅₀ of sulphur-fumigated A. dahurica extracts in Kunming mice was 89.4420 g/kg, suggesting the safety of A. dahurica and sulphur fumigation could reduce the toxicity of A. dahurica.

9 CONCLUSION AND FUTURE PERSPECTIVES

In this review, we summarized the traditional uses, phytochemistry and pharmacology activities of A. dahurica according to ancient classics and modern researches, and it will provide a new insight for future exploration of A. dahurica. The root of A. dahurica has been widely used to treat cold fever, headache, toothache and cold-damp pain in ancient and modern China. Meanwhile, the root of A. dahurica has a predominant therapeutic effect in diseases such as abnormal leucorrhrea, sore, as well as skin ulcer. Interestingly, A. dahurica root exerts dual functions as medicine and food, which has been widely used as condiment or healthcare product. Up to now, more than 300 compounds have been isolated and identified from A. dahurica. Among these constituents, coumarins and volatile oils represent the main active ingredients and IMP (22) is the most principal and representative compound of A. dahurica. It is expected that more compounds of these categories will be discovered in the future studies. Moreover, researches have shown that both crude extracts and active components of A. dahurica possess a wide range of pharmacological activities, including anti-inflammatory, anti-tumor, anti-oxidation, analgesic activity, antiviral and anti-microbial effects, effects on the cardiovascular system, neuroprotective function, hepatoprotective activity, effects on skin diseases and so on. These modern pharmacological studies supported most traditional uses of A. dahurica root as folk medicine. However, gaps still exist in the systematic research on A. dahurica.

Firstly, the chemical constituents and pharmacological studies of the aerial part are limited, although the roots of A. dahurica have been studied extensively in recent decades. Current studies of A. dahurica most focused on the crude extracts and some coumarins such as IMP, byakangelicin, phellopterin and scopoletin, but these investigations are insufficient. Studies have shown that the aerial part of A. dahurica also has certain pharmacological activities, such as anti-oxidation (Lee and
Woo, 2011), and thus might have medicinal relevance for some aging-related diseases. Therefore, more extensive studies of other compositions and other parts of *A. dahurica* are necessary. Secondly, many pharmacological studies on the crude extracts or active components are not in-depth enough. These pharmacological activities need to be further confirmed by animal experiments *in vivo* and combined with clinical applications. This direction will provide a solid basis for developing novel drug-lead compounds in the future study. For example, the minimum effective dose (MED) of IMP in two kidney one clip renovascular hypertensive rats (2KIC-RHR) was 6.25 mg/kg, and it exhibited obvious hypotensive effect after continuous administration for 2 weeks. The proposed clinical dose of IMP is 100 mg/d per person, that is, 1.67 mg/kg. Moreover, the LD<sub>50</sub> of IMP in rats was 3188.7 mg/kg, indicating that IMP has a wide safety range and a great possibility of clinical application (Zhu et al., 2013).

Thirdly, most studies on the pharmacological activities of *A. dahurica* concentrated on uncharacterized crude extracts, and this makes it difficult to clarify the connections between bioactivities and isolated compounds. Further systematic pharmacological studies of the compounds isolated from *A. dahurica* are quite considerable. Additionally, the exact mechanisms of many pharmacological activities, such as anti-oxidant and antiviral activities of the crude extract or compounds from *A. dahurica* remain unclear; thus, further studies to better reveal the precise molecular mechanisms of the pharmacological activities of this herb seem to be necessary.

Fourthly, there were multiple processing methods of *A. dahurica* root in ancient China, such as stir-baking with *Polygonati Rhizoma*, immersing into wine and immersing into rice. Different processing methods may affect the chemical constituents and pharmacological activities of *A. dahurica* root, resulting in different clinical applications, but there are few studies on the influences of processing methods of *A. dahurica* root. Hence, investigations on the processing methods may be one of the main directions of *A. dahurica* root in the future researches.

Finally, *A. dahurica* root is usually used prescribed with other traditional herbs, such as *Atractyloides lancea* and *Xanthium sibiricum* to treat specific diseases. However, only a few studies reveal the effects of synergy or antagonism have been reported. Therefore, the roles on drug-interaction between certain herbs and *A. dahurica* seem to be a new direction that worth further exploration.

In conclusion, the root of *A. dahurica* is an important edible medicinal herb with extensive pharmacological activities and great values in medicine and food. However, more in-depth and comprehensive studies on clinical utility are needed to determine its safety and availability. Until now, multiple compounds have been discovered in *A. dahurica*, but what we have done is far from enough. Moreover, the precise molecular mechanisms of these active ingredients in some diseases still worth further study. Consequently, systematic studies on phytochemistry and bioactivities of *A. dahurica* will undoubtedly be the key direction of future research. This review should provide an important reference for the development and application of *A. dahurica*.

**AUTHOR CONTRIBUTIONS**

Study concepts and design: JY; Literature search: HZ, MW, and TL; Manuscript preparation and revision: HZ, Y-LF, and J-JW. All authors have participated sufficiently in the study and approved the final version.

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**SUPPLEMENTARY MATERIAL**

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Baek, N. I., Ahn, E. M., Kim, H. Y., and Park, Y. D. (2000). Furanocoumarins from *A. dahurica* and other parts of *A. dahurica* are necessary. Therefore, more extensive studies of other compositions and other parts of *A. dahurica* are necessary. Secondly, many pharmacological studies on the crude extracts or active components are not in-depth enough. These pharmacological activities need to be further confirmed by animal experiments *in vivo* and combined with clinical applications. This direction will provide a solid basis for developing novel drug-lead compounds in the future study. For example, the minimum effective dose (MED) of IMP in two kidney one clip renovascular hypertensive rats (2KIC-RHR) was 6.25 mg/kg, and it exhibited obvious hypotensive effect after continuous administration for 2 weeks. The proposed clinical dose of IMP is 100 mg/d per person, that is, 1.67 mg/kg. Moreover, the LD<sub>50</sub> of IMP in rats was 3188.7 mg/kg, indicating that IMP has a wide safety range and a great possibility of clinical application (Zhu et al., 2013).

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