

## Review

# *Artemisia frigida* Willd.: Advances in Traditional Uses, Phytochemical Constituents, Extraction and Separation Methods, and Pharmacological Activities

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## Abstract

*Artemisia frigida* Willd. (*A. frigida*), a traditional medicinal herb widely distributed in northern China, Mongolia, and Siberia, has garnered increasing scientific interest due to its diverse phytochemical profile and extensive pharmacological potential. Modern studies have identified a wide range of bioactive compounds in *A. frigida*, including flavonoids, sesquiterpene lactones and phenolic acids. These compounds exhibit various biological activities, such as antioxidant, anti-inflammatory, anticancer, and antimicrobial effects. This review systematically summarizes the research progress on the chemical constituents of *A. frigida* and their extraction and separation methods, including solvent extraction, ultrasonic-assisted extraction, macroporous resin adsorption, and chromatography-based techniques. By integrating traditional knowledge with modern pharmacological evidence, this review provides a scientific foundation for the further development and utilization of *A. frigida* in functional food, pharmaceuticals, and ethnomedicine.

**Keywords:** *Artemisia frigida* Willd.; extraction and separation; bioactive components; pharmacological properties



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## 1. Introduction

Given the considerable toxic side effects associated with many synthetic pharmaceuticals [1], there is growing interest in developing plant-derived therapeutics that offer improved efficacy with reduced toxicity [2]. Traditional Mongolian Medicine (TMM), a vital component of China's rich medical heritage, has played a pivotal role in disease prevention and treatment for thousands of years [3]. Globally, traditional remedies are increasingly adopted as alternative or complementary approaches to conventional medicine [4]. Recognizing their importance, the World Health Organization has emphasized the role of traditional medicine in addressing healthcare needs, particularly in developing regions [5].

*Artemisia frigida* Willd. (*A. frigida*) (Figure 1), commonly known as “Xiaobaihao” in Chinese and “Agei” in Mongolian, is a biennial to perennial herbaceous species belonging to the genus *Artemisia* within the family Asteraceae (Compositae). It is widely distributed throughout China and extends to other regions, including Mongolia, North

America, Siberia, Kazakhstan, and adjacent areas [6,7]. As a traditional Mongolian medicinal herb, *A. frigida* has been used therapeutically for centuries. Both the whole plant and its aerial parts are commonly incorporated into traditional formulations [8], primarily for their hemostatic and anti-edematous properties [9]. *A. frigida* contains a diverse array of bioactive constituents, including flavonoids, sesquiterpenoids, and phenolic acids [10–17]. These compounds have been associated with notable anti-inflammatory [18,19], antioxidant [20–23], and antitumor activities [10,24], highlighting the considerable medicinal potential of *A. frigida*. As a traditional herbal medicine, *A. frigida* has attracted growing scientific interest. This review summarizes recent advances in the traditional uses, bioactive constituents, pharmacological activities, and extraction and isolation techniques of *A. frigida*.



**Figure 1.** *Artemisia frigida* Willd. [21].

## 2. Traditional Ethnomedicinal Uses

As a prominent herb in Traditional Mongolian Medicine, *A. frigida* has a long-standing history of medicinal use and demonstrates considerable potential for further development as a traditional Chinese medicine resource [25]. Traditionally, the entire plant is used, valued for its characteristic bitter flavor and classified in ethnomedicine as possessing cooling, astringent, dull, and desiccating properties. *A. frigida* is believed to exert hemostatic effects, dispel pathogenic wind, promote meridian circulation, and reduce swelling [26–30]. Clinically, it is primarily employed in the treatment of joint swelling and pain, hyperactive kidney fire, menstrual disorders, abscesses, cholecystitis, dysuria, pruritus, eczema, and helminthic infections [8,19,31–33]. It is also frequently prescribed to alleviate systemic symptoms such as irritability, dizziness, cephalalgia, fatigue in the lower back and extremities, and localized swelling or pain in the breasts and limbs [31]. Among nomadic communities in regions such as Siberia and Mongolia, *A. frigida* holds cultural as well as medicinal significance. It is often consumed as *sagaan aya*, a traditional herbal infusion reputed for its antioxidant activity and general health-promoting effects. Beyond its medicinal roles, *A. frigida* is also incorporated into the diet; young shoots are commonly blanched, mixed with cornmeal, and steamed, serving as a seasonal food source with both nutritional and therapeutic value [21,25]. Taken together, *A. frigida*'s ethnomedicinal roles,

dietary integration, and cultural significance position it for structured development as a traditional Chinese medicine resource.

### 3. Extraction and Separation Technologies of Active Compounds in AF

*A. frigida* is rich in phytochemicals and contains multiple classes of constituents. The rational design of extraction and separation workflows is critical for maximizing resource utilization and ensuring quality evaluation. At present, commonly used techniques (Figure 2) for *A. frigida* include solvent extraction (SE), ultrasonic-assisted extraction (UAE), supercritical fluid extraction (SFE), macroporous resin adsorption/enrichment (MAR), high-performance liquid chromatography (HPLC), preparative/semi-preparative HPLC (prep HPLC), column chromatography (CC), and high-performance capillary electrophoresis (HPCE) for rapid analytical separation. The strengths and limitations of these methods as applied are summarized in Table 1. Among them, SFE is regarded as particularly promising for industrial applications due to its scalability, efficiency, and environmentally friendly nature. For separation, MAR shows notable potential because of its reusability, cost-effectiveness, and feasibility for large-scale purification of bioactive compounds.

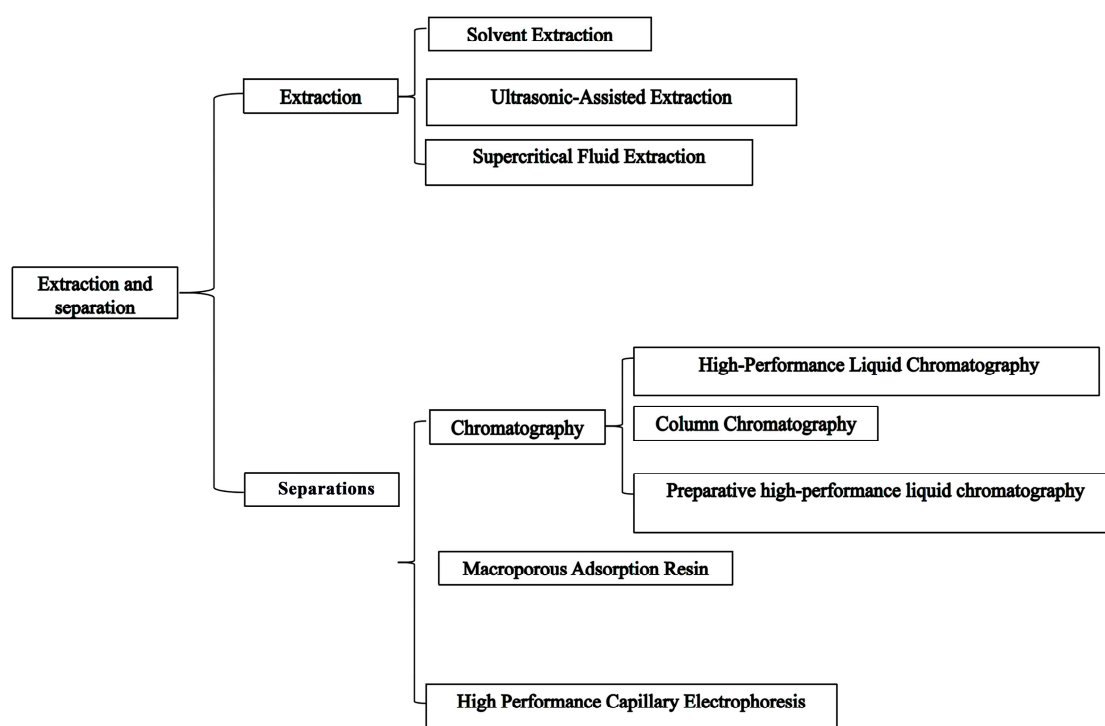


**Figure 2.** Extraction and separation methods applied to *A. frigida*.

**Table 1.** Summary of Key Features and Limitations of Extraction and Separation methods.

| Method | Characteristic                                                                            | Limitations                                                                             | Reference  |
|--------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------|
| SE     | Differential solubility; flexible solvents; cold/hot/reflux; scalable for crude extracts. | Residual solvent risk; low selectivity; possible thermal degradation; time-consuming.   | [34,35]    |
| UAE    | Cavitation enhanced mass transfer; shorter time/low temperature; reduced solvent use.     | Uneven energy distribution; limited industrial scalability; not ideal for all solvents. | [34,36,37] |

**Table 1.** *Cont.*

| Method    | Characteristic                                                                                           | Limitations                                                                              | Reference |
|-----------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------|
| SFE       | High selectivity; low temperature; green solvent; tunable solubility; scalable.                          | High equipment cost; requires high pressure; limited polarity range without co-solvents. | [38–40]   |
| HPLC      | High resolution/selectivity; robust quantitation; broad detectors [UV/DAD/MS].                           | High solvent consumption; not suited for large-scale isolation.                          | [41–43]   |
| MAR       | Adsorptive enrichment; mild conditions; reusable resin.                                                  | Limited specificity; resin fouling over time; requires regeneration.                     | [44,45]   |
| prep-HPLC | High-purity isolation; reproducible fraction collection.                                                 | Time- and solvent-intensive; costly; scale up may be challenging.                        | [46,47]   |
| HPCE      | Mobility-based separation in capillaries; ultra-efficient; minute sample/solvent; fast; UV/LIF/MS-ready. | Low sample capacity; sensitive to pH; complex method optimization.                       | [48,49]   |
| CC        | Versatile; low cost; gram-scale fractionation; customizable gradients.                                   | Labor-intensive; low resolution; inefficient for complex mixtures.                       | [50,51]   |

### 3.1. Solvent Extraction

Solvent extraction (SE) remains one of the most extensively employed methods for isolating bioactive compounds from plant materials due to its simplicity, adaptability, and broad applicability. The technique exploits the differential solubility of phytochemicals in various solvents, enabling selective extraction based on compound polarity and stability [34,52]. Liu et al. [53] applied ethanol reflux extraction to the aerial parts of *A. frigida*, followed by chromatographic separation using polyamide, Sephadex LH-20, silica gel, and C18 columns, ultimately isolating 16 compounds spanning flavonoids, terpenoids, and organic acids. Another study employed 70% ethanol extraction coupled with sequential liquid–liquid partitioning using petroleum ether, ethyl acetate, and saturated n-butanol to fractionate the crude extract. This workflow led to the successful isolation and structural elucidation of ten distinct monomeric constituents from AF [10]. Liu et al. [54] optimized the isolation of quercetin by introducing acidified ethanol (95% ethanol with 1.5 mol/L HCl) under reflux, enhancing extraction efficiency through targeted hydrolysis. Liu [12] used 95% ethanol reflux extraction followed by partitioning with petroleum ether, dichloromethane, and ethyl acetate to generate polarity-based fractions for downstream enrichment and separation. Despite its widespread application, conventional solvent extraction faces limitations such as low efficiency and solvent residue concerns, prompting a growing shift toward greener and more sustainable extraction alternatives.

### 3.2. Ultrasonic-Assisted Extraction

Ultrasound-assisted extraction (UAE) is an efficient and eco-friendly method that uses acoustic cavitation to enhance the release of bioactive compounds from plant tissues. Ultrasonic waves disrupt cell walls, improve solvent penetration, and accelerate mass transfer. Compared to traditional techniques, UAE offers higher yields in less time with lower

solvent use, making it especially suitable for extracting thermolabile or structurally complex phytochemicals [55]. UAE has demonstrated high efficiency in recovering flavonoids from *A. frigida*, particularly when using methanol or ethanol-based solvents. By leveraging acoustic cavitation, UAE disrupts plant cell walls, thereby enhancing mass transfer and accelerating the release of target compounds [3]. Olennikov et al. [21] applied UAE to powdered *A. frigida* using 70% methanol at 50 °C for 60 min, under 100 W ultrasonic power and 35 kHz frequency. The process yielded a total extract of 22.14% after filtration and evaporation under reduced pressure. Zhang et al. [20] employed UAE to obtain total flavonoids from *A. frigida*, using 70% ethanol as the extraction solvent. Following a 24 h soak and ultrasonic treatment, the method achieved an extraction yield of 4.23%, with a recovery rate ranging from 92.0% to 99.6%, demonstrating the efficiency of UAE for isolating flavonoids from traditional Mongolian medicinal herbs. UAE presents significant advantages over traditional extraction techniques, including markedly shortened extraction times and reduced thermal degradation of heat-labile compounds. Moreover, UAE enhances extraction efficiency and minimizes the reliance on organic solvents, thereby offering a highly effective and environmentally sustainable method for the isolation of diverse bioactive constituents [35,56,57].

### 3.3. Supercritical Fluid Extraction

Supercritical fluid extraction (SFE) employs supercritical fluids—most commonly CO<sub>2</sub>, often with polar co-solvents—whose pressure- and temperature-tunable density enables rapid, selective, and low-residue extraction/fractionation of compounds from complex matrices [36,38]. Tang et al. [58,59] optimized supercritical CO<sub>2</sub> extraction of *A. frigida* volatile oil by evaluating pressure, temperature, CO<sub>2</sub> flow and time—identifying 30 MPa, 35–40 °C, 2 h, and 25 m<sup>3</sup>·h<sup>−1</sup> as optimal—and subsequently profiled the SFE-CO<sub>2</sub> oil by GC–MS to determine its constituents and relative abundances. SFE provides a scalable, contamination-free, and environmentally benign alternative widely used in food, nutraceutical, and pharmaceutical purification [60].

### 3.4. High-Performance Liquid Chromatography

High-performance liquid chromatography (HPLC) is a foundational technique in chromatographic analysis, employing a high-pressure delivery system to propel a liquid mobile phase through a column packed with a stationary phase. The interaction between analytes and the stationary phase enables precise separation based on differences in polarity, molecular size, or affinity. As components elute from the column, they are detected for both qualitative identification and quantitative measurement [61]. HPLC has proven instrumental for the separation and quantification of flavonoids. Wang et al. [62] applied HPLC to analyze flavonoid-rich fractions obtained through ethanol extraction and subsequent partitioning. The samples were separated on a C18 reversed-phase column under gradient elution with acetonitrile and 0.2% phosphoric acid aqueous solution at a flow rate of 1.0 mL/min, with detection at 360 nm. This setup enabled efficient resolution of major flavonoid constituents, offering a robust analytical foundation for the pharmacological evaluation and quality control of AF-derived formulations. Tu et al. [63] isolated five major flavonoids from *A. frigida* using HPLC on an EZ0566 column, with a mobile phase of 30% acetonitrile in water, at a flow rate of 5.0 mL/min, and UV detection at 254 nm. The separated compounds were subsequently identified by NMR, confirming the presence of five distinct flavonoid compounds. Sakipova et al. [64] applied HPLC-UV for the quantification of santonin in *A. frigida*. The analysis was performed on a Thermo C18 column (250 mm × 4.6 mm, 5 µm), using a mobile phase composed of water (solvent A) and acetonitrile (solvent B) under a linear gradient from 35:65 to 65:45 (A:B) over 20 min.

The flow rate was set at 1.0 mL/min, and detection was carried out at 236 nm. Zhi et al. [65] developed an HPLC method for quantifying chlorogenic acid in *A. frigida*, using a C18 column (250 × 4.6 mm, 5 µm) with a mobile phase of acetonitrile-0.4% phosphoric acid (12:88), a flow rate of 1.0 mL/min, column temperature at 30 °C, and UV detection at 327 nm. This method enabled the accurate determination of chlorogenic acid for quality control of *A. frigida*. HPLC, renowned for its high separation efficiency, enables the resolution of structurally similar compounds and is widely applied in the qualitative and quantitative analysis of active ingredients in traditional Chinese medicine, offering a rapid and reliable method for quality control and pharmacological evaluation.

### 3.5. Column Chromatography

Column chromatography (CC) is a classical and versatile separation technique that exploits differential interactions between sample components and stationary/mobile phases to achieve purification [66]. Borchuluun et al. [67] obtained the volatile oil of *A. frigida* by hydrodistillation and, via silica-gel column fractionation, isolated one new sesquiterpene together with four known sesquiterpenes. Wang et al. [68] isolated two new flavonoid glycosides from *A. frigida* by ethanol reflux extraction and solvent partitioning followed by silica gel/Sephadex LH-20 chromatography. Zhang et al. [69] first applied silica gel column chromatography to the dichloromethane-soluble fraction of *A. frigida*, achieving preliminary fractionation. After TLC-based pooling, they employed successive silica gel and Sephadex LH-20 column chromatography, along with preparative TLC and reversed-phase prep-HPLC, to isolate and purify a novel sesquiterpenolide. Column chromatography remains a classical technique in natural product separation workflows, particularly valued for its simplicity.

### 3.6. Preparative High-Performance Liquid Chromatography

Preparative high-performance liquid chromatography (prep-HPLC), built on classical HPLC principles and employing high-pressure delivery, high-efficiency stationary phases, and sensitive detection, is a robust, broadly applicable, and typically rapid method for large-scale purification of compounds from complex natural-product extracts—and has become a mainstay of natural-product isolation [70,71]. Liu et al. [12] applied ethanol reflux extraction, stepwise solvent partitioning, and successive silica gel/Sephadex/polyamide/macroporous-resin columns, using semi-prep HPLC on key fractions for final purification, and isolated 26 compounds from *A. frigida*. Wang et al. [72] employed silica gel and column chromatography in combination with prep-HPLC to separate the extracts, and isolated and identified 25 compounds. Li et al. [10] employed 70% EtOH reflux extraction, stepwise solvent partitioning and successive columns (silica gel, polyamide, Sephadex LH-20, macroporous resin) with semi-prep HPLC as the final step to obtain ten monomeric compounds from *A. frigida*. Collectively, these studies establish semi-prep/prep HPLC as the pivotal terminal step in *A. frigida* phytochemical workflows, enabling rapid, reproducible purification of numerous constituents for definitive structure elucidation [73,74].

### 3.7. Macroporous Adsorption Resin

Macroporous adsorption resin (MAR) technology is a recently developed method for the purification and enrichment of bioactive compounds. It utilizes the large specific surface area of the resin to physically adsorb target molecules through Van der Waals forces, and achieves effective separation and purification based on differences in adsorption affinity and molecular size, followed by selective elution with appropriate solvents. Hai et al. [75] extracted *A. frigida* using reflux with 95% ethanol, and after concentrating the combined filtrates, the crude total flavonoids were subjected to D101 macroporous resin column

chromatography. Impurities were removed with 20% ethanol, followed by 75% ethanol elution, ultimately yielding 3.2 g of purified total flavonoids. Wang et al. [76] optimized the extraction and purification process of total flavonoids from *A. frigida* using D101 macroporous adsorption resin. Based on orthogonal test design, the optimal conditions were determined as follows: sample concentration of 0.6 mg/mL, sample volume of 4 bed volumes (BV) 20% ethanol for impurity removal, and 60% ethanol for elution. Under these conditions, the yield and purity of total flavonoids reached 85.46% and 65.54%, respectively. Macroporous resin chromatography exhibits excellent purification efficiency for active components from *A. frigida*, offering a rational, stable, and feasible approach.

### 3.8. High-Performance Capillary Electrophoresis

High-performance capillary electrophoresis (HPCE) is an electrophoretic technique that applies high voltage across narrow fused-silica capillaries to separate analytes by differences in effective mobility, delivering ultra-high efficiency [77,78]. Wang et al. and Hai et al. [15,79] both employed HPCE to quantify five flavonoids in AF; Wang et al. established a simultaneous assay and compared contents across different harvest times and plant parts, while Hai et al. evaluated processing conditions and identified 60 °C drying as the optimal procedure. HPCE is a rapid, sensitive, and solvent-sparing platform for quantitative profiling of *A. frigida* flavonoids, effectively supporting process optimization and routine quality control.

The above discussed the separation methods in *A. frigida*. And the separation mechanisms of chromatography and the components suitable for separation are summarized in Table 2. In summary, *A. frigida* extraction and separation technologies range from classical solvent and column-based methods to more advanced approaches such as UAE, SFE, MAR, and prep HPLC, each with distinct advantages and drawbacks. Integrating these complementary techniques offers a promising path toward efficient, scalable, and sustainable workflows that ensure both quality control and future application potential.

**Table 2.** Summary of separation methods.

| Method    | Mechanism               | Application                                                   | Reference |
|-----------|-------------------------|---------------------------------------------------------------|-----------|
| HPLC      | distribution            | chlorogenic acid                                              | [10,80]   |
| MAR       | adsorption              | caffeic acid                                                  | [10,81]   |
| Prep HPLC | distribution            | kaempferol                                                    | [82]      |
| HPCE      | charge-based separation | quercetin                                                     | [15,79]   |
| CC        | adsorption              | 5,7-dihydroxy-3',4',5'-trimethoxy flavone 7-O-β-d-glucuronide | [12]      |

## 4. Active Components in AF

Numerous studies have investigated and identified the major constituents of *A. frigida*. Using the whole plant as a starting material, researchers have systematically isolated and purified its extracts through chromatographic methods, followed by structural elucidation using spectroscopic techniques via ultraviolet (UV) and mass spectrometry (MS). The main active compounds in *A. frigida* are shown in Table 3 and Figure 3.

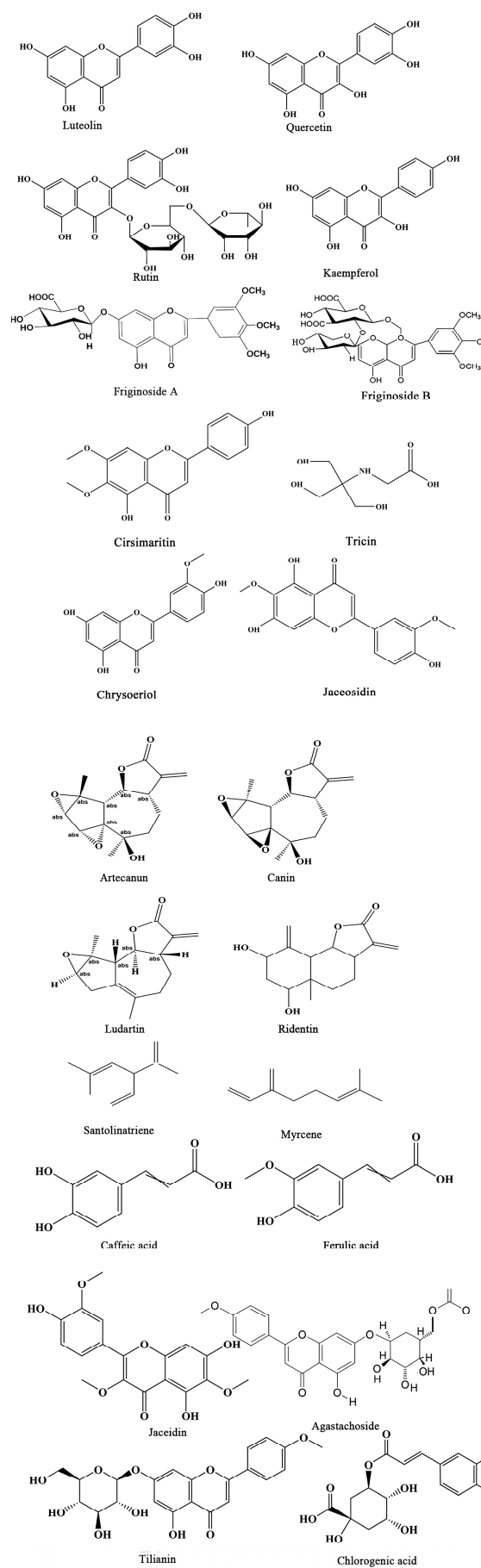


**Figure 3.** The structures of Flavonoids, Sesquiterpenes and Polyphenols in *A. frigida*.

**Table 3.** The main compounds in *A. frigida*.

| Classification | No. | Name             | Reference  |
|----------------|-----|------------------|------------|
| Flavonoids     | 1   | Luteolin         | [9,12,13]  |
|                | 2   | Quercetin        | [9,13]     |
|                | 3   | Rutin            | [20,81]    |
|                | 4   | Kaempferol       | [13,81]    |
|                | 5   | Friginoside A    | [58]       |
|                | 6   | Friginoside B    | [58]       |
|                | 7   | Cirsimaritin     | [12,13]    |
|                | 8   | Tricin           | [12,13,82] |
|                | 9   | Chrysoeriol      | [12,13]    |
|                | 10  | Jaceosidin       | [12,13,82] |
| Sesquiterpenes | 7   | Artecanin        | [81,83]    |
|                | 8   | Canin            | [81,83]    |
|                | 9   | Ludartin         | [83]       |
|                | 10  | Ridentin         | [12,84]    |
|                | 11  | Santolinatriene  | [17,85]    |
|                | 12  | Myrcene          | [85]       |
| Polyphenols    | 13  | Caffeic Acid     | [9,12,80]  |
|                | 14  | Ferulic Acid     | [9,80,81]  |
|                | 15  | Jaceidin         | [12,13]    |
|                | 16  | Agastachoside    | [12]       |
|                | 17  | Tilianin         | [12]       |
|                | 18  | Chlorogenic acid | [66,80,82] |

#### 4.1. Flavonoids

Flavonoids, which are generally located in plant leaves, flowers, and stems [86], constitute a major class of bioactive compounds, accounting for approximately 10% of its total chemical composition [87,88]. Tu et al. [63] employed HPLC combined with natural bond orbital (NBR) analysis to isolate and identify the principal flavonoids from the aerial parts of *A. frigida*. The major components extracted included: 5,3'-Dihydroxy-3,6,7,4'-tetramethoxyflavone; 5,7,3'-Trihydroxy-6,4'-tetramethoxyflavone; 5,3'-Dihydroxy-6,7,4'-trimethoxyflavone; 5-Hydroxy-3',4'-dimethoxyflavone-7-O- $\beta$ -D-glucuronide; and 5-Hydroxy-3',4'',5'-trimethoxyflavone-7-O- $\beta$ -D-glucuronide. Further investigation by Liu et al. [12], who conducted a comprehensive chromatographic study on the whole herb of *A. frigida*, enabled systematic isolation, purification, and structural elucidation of its flavonoid constituents. The analysis revealed the efficient detection of several key bioactive flavonoids, including jaceosidin, luteolin, kaempferol, triclin, and eupatilin, among others. Two novel flavonoid glucuronides, friginoside A and friginoside B, were also isolated from the n-BuOH fraction of the aerial parts, further enriching the structural diversity of *A. frigida* flavonoids [68]. Olennikov et al. [11] isolated several new flavonoids from the aerial parts of *A. frigida*, including chrysoeriol-7-O-[2''-O-acetyl]- $\beta$ -D-glucopyranoside and jaceosidin-4'-O- $\beta$ -D-glucopyranoside (isojaceoside), alongside 13 previously known flavonoids. Overall, reported yields indicate that the total flavonoid content in *A. frigida* typically accounts for approximately 4–5% of the dry weight [20,82]. These results indicate that flavonoids are

not only structurally diverse but also quantitatively significant constituents, reinforcing their central role in the phytochemical profile of *A. frigida*.

#### 4.2. Sesquiterpenes

Sesquiterpenoids, a class of terpenes composed of three isoprene units and 15 carbon atoms, are widely distributed across the Asteraceae family [89]. Commonly found in essential oils of aromatic plants, these compounds are characterized by their strong fragrance and diverse biological activities. Zhan et al. [69] conducted a phytochemical investigation of *A. frigida* collected from Nanpi County and identified a novel sesquiterpenoid compound:  $1\alpha,3\alpha$ -dihydroxy- $7\beta,11\alpha$ H-germacra-4Z,10 [14]-dien-12,6 $\alpha$ -olide (1). In the same year, Li et al. [90] identified a novel sesquiterpenoid from *A. frigida* collected in Hebei Province, structurally characterized as  $4\alpha,5\alpha$ H, $6\alpha,7\beta,10\beta,11\alpha$ -1,15-dioxoeudesman-12,6-olide. Subsequently, Borchuluun et al. [67] isolated one new and four known sesquiterpenoids—including the newly reported compound Artefrigin—from the essential oil of *A. frigida* harvested in Tongliao, Inner Mongolia. In a separate study, Li et al. [10] reported, for the first time, the isolation and identification of the sesquiterpenoid Roxburghianin B from Altai-sourced *A. frigida*. Several sesquiterpene lactones, including canin, artecanin, ludartin, and 8-deoxycumambrin B, have been successfully isolated from the whole herb of AF [83,84]. Liu et al. [85] identified a total of 101 chemical constituents from the volatile oil of *A. frigida* via GC-MS analysis, among which sesquiterpenes were predominant. Characterized sesquiterpenoid compounds included santolinatriene, myrcene, and 3,3,6-trimethyl-1,5-heptadien-2-ol. Notably, compounds such as santolinatriene and 3,3,6-trimethyl-1,5-heptadien-2-ol were reported for the first time in *A. frigida*, expanding the known sesquiterpene profile of the species. Wang et al. [91] isolated and identified two novel guaianolide-type sesquiterpene lactone glycosides from *A. frigida*, named artemofriginose A and B, thus enriching the sesquiterpene profile of the species.

#### 4.3. Polyphenols

Phenolic compounds, a class of plant secondary metabolites [92], are commonly found in seeds, peels, leaves, and roots. Wang et al. [9,72] extracted *A. frigida* using organic solvents and further separated the constituents via elution chromatography. Structural elucidation of the isolated compounds using spectroscopic techniques led to the identification of 2 phenylpropanoids: caffeic acid and ferulic acid. In a more comprehensive study, Olennikov et al. [21] systematically investigated the phenolic profile of *A. frigida* and, for the first time, identified 12 caffeoylquinic acid derivatives. These included mono-, di-, and tri-ester forms such as 3-O-, 4-O-, and 5-O-caffeoylquinic acid, as well as 3,4-di-, 3,5-di-, and 3,4,5-tri-O-caffeoylquinic acid, among others. Liu et al. [12] identified jaceidin, agastachoside, and tilianin as polyphenolic compounds that were isolated for the first time from *A. frigida*.

Flavonoids, sesquiterpenes, and polyphenols are the main active components of *A. frigida*, reflecting both chemical diversity and pharmacological potential.

### 5. Pharmacological Properties

#### 5.1. Anti-Inflammatory Activity

Pharmacological studies conducted both domestically and internationally have demonstrated that *A. frigida* exhibits potent anti-inflammatory activity, primarily due to its rich content of flavonoid compounds [93]. Wang et al. [62] using HPLC, identified five flavonoids with confirmed anti-inflammatory activity in the total flavonoid extract of *A. frigida*. In a subsequent investigation, Wang et al. [94] isolated and purified flavonoid and biflavonoid glycosides from the n-butanol fraction of *A. frigida*, which showed marked

anti-inflammatory effects in a carrageenan-induced mouse paw edema model. Similarly, Tu et al. [63] demonstrated that total flavonoids from *Artemisia leucophylla* (50 mg/kg) significantly inhibited formalin-induced paw swelling in rats. Moreover, our previous work [95,96] revealed that aqueous extracts of *A. frigida*—prepared via ultrasonic extraction with distilled water—exhibited potent anti-inflammatory activity. Among several solvent fractions, the ethyl acetate extract displayed the most pronounced effect. Xue et al. [19] further reported that *A. frigida* extract effectively suppressed mouse paw edema, with mechanistic studies indicating that its anti-inflammatory action involves downregulation of pro-inflammatory cytokines and mitigation of inflammatory mediator overproduction in affected tissues. Total flavonoids from *A. frigida* exhibited dose-dependent anti-inflammatory effects by inhibiting leukotriene B4 (LTB4) biosynthesis, reducing intracellular calcium mobilization, and enhancing cAMP levels in rat peritoneal leukocytes [97]. Collectively, the anti-inflammatory activity of *A. frigida*, particularly its flavonoid constituents, is mediated primarily through the suppression of pro-inflammatory cytokine expression, modulation of intracellular calcium signaling, and enhancement of cAMP-mediated anti-inflammatory pathways.

### 5.2. Antitumor Effects

Several studies have demonstrated the potential antitumor properties of *A. frigida*, particularly attributed to its sesquiterpene lactones and flavonoid constituents. Li et al. [10] isolated ten compounds from *A. frigida*, among which flavonoids were dominant. One compound, 3,5-dihydroxy-6,7,3',4'-tetramethoxyflavone, showed significant cytotoxicity against HepG2 cells with an  $IC_{50}$  of  $34.58 \pm 2.42$   $\mu\text{g/mL}$ . Chen et al. [98] evaluated the effects of five sesquiterpene lactones isolated from *A. frigida* on the proliferation of human tumor cells using the MTT colorimetric assay. Dehydrocostuslactone (I) exhibited significant inhibitory activity against HeLa, T-98, HLE, and HMV-1 cells, while dihydrodehydrocostuslactone showed moderate antiproliferative effects. In summary, *A. frigida* contains sesquiterpene lactones with measurable in vitro antitumor activity, and these findings offer valuable references for the development of natural antitumor agents.

### 5.3. Antioxidant Activity

In recent years, increasing attention has been paid to the antioxidant potential of *A. frigida* due to its abundance of flavonoids and phenolic acids. Olennikov et al. [21] systematically investigated the antioxidant activity of *A. frigida* herbal tea, identifying 59 polyphenolic compounds, including caffeoylquinic acids and flavonoids. Using DPPH and ORAC assays, the extract exhibited high antioxidant capacity with an  $IC_{50}$  value of 12.63  $\mu\text{g/mL}$  and an ORAC value of 2918.8  $\mu\text{mol TE/100 mL}$ . Even after simulated gastrointestinal digestion, the antioxidant effect was only slightly reduced, indicating excellent bioavailability and stability. Further supporting these findings, Hai et al. [75] evaluated the total flavonoids extracted from *A. frigida* and demonstrated that they possess strong radical scavenging activities in vitro. Compared with standard antioxidants like vitamin C and rutin, *A. frigida* flavonoids showed superior capacity in neutralizing DPPH $\cdot$ , superoxide anion ( $O_2^{\cdot-}$ ), and hydroxyl radicals ( $\cdot\text{OH}$ ), with dose-dependent effects across a concentration range of 60–600  $\mu\text{g/mL}$ . The study also identified 9 key flavonoid compounds by HPLC, including luteolin and methoxylated derivatives, contributing to the observed antioxidative effects. Zhang et al. [20] evaluated the hydroxyl radical scavenging ability of flavonoid extracts from *A. frigida* using the Fenton reaction and found that the scavenging capacity increased with the rising content of flavonoid compounds. In addition to polyphenols, alkaloids from *A. frigida* have also demonstrated potent antioxidant effects. Wu et al. [99] investigated the scavenging ability of *A. frigida* alkaloids using Fenton-induced hydroxyl

radical systems, auto-oxidation of pyrogallol for superoxide radicals, and  $\text{H}_2\text{O}_2$  reaction systems. The results indicated significant scavenging effects on  $\cdot\text{OH}$ ,  $\text{O}_2^{\cdot-}$ , and  $\text{H}_2\text{O}_2$ , with clear dose–response relationships. These results further underscore the potential of *A. frigida* flavonoids as natural antioxidants with strong activity and significant application prospects in functional foods and pharmaceuticals.

#### 5.4. Other Biological Activities

In recent years, *A. frigida* has been found to possess various other biological activities in addition to its significant antioxidant, anti-inflammatory, and antitumor properties, highlighting its potential value for further development and application. Essential oil extracted from *A. frigida* was tested against a panel of bacterial and fungal strains, including *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, showing moderate to strong antimicrobial activity [100]. The antimicrobial effect was primarily attributed to major volatile constituents such as 1,8-cineole, and camphor, which are known to compromise microbial membrane integrity. In addition to antimicrobial properties, *A. frigida* essential oil also exhibits promising insecticidal activity. Liu et al. [101] analyzed the volatile composition of *A. frigida* essential oil and identified 1,8-cineole, camphor, and borneol as the predominant components. These compounds demonstrated significant fumigant toxicity against *Sitophilus zeamais* and *Liposcelis bostrychophila*, two common storage pests. These results suggest that *A. frigida* essential oil may serve as a potential botanical pesticide. Yan et al. [102] evaluated the hemostatic effects of *A. frigida* extracts obtained through different extraction methods and from various polarity-based fractions in mice. The results showed that the n-butanol and ethyl acetate fractions of *A. frigida* significantly shortened both bleeding time and coagulation time in mice. Moreover, the decoction extract demonstrated superior efficacy compared to the mixed plant decoction, suggesting that the hemostatic activity may be attributed to glycosidic compounds with relatively high polarity present in *A. frigida*. Zhao et al. [103] revealed that *A. frigida* extract modulates the immune response in loach by significantly altering the expression of multiple immune-related miRNAs, which in turn regulate key innate immune pathways including Toll-like receptor (TLR), NOD-like receptor (NLR), and RIG-I-like receptor (RLR) signaling, as well as pathways involved in apoptosis, endocytosis, and cytokine interactions. More recently, dehydrovomifoliol, an active constituent isolated from *A. frigida*, was shown to exhibit protective effects against nonalcoholic fatty liver disease (NAFLD) [95]. *A. frigida* has been shown to exert notable anti-inflammatory, antioxidant, and antitumor effects, mainly linked to its flavonoids and sesquiterpenes. It also displays antimicrobial, insecticidal, hemostatic, and immunomodulatory activities, highlighting its potential for further medicinal and practical applications (Table 4).

**Table 4.** Active compounds of *A. frigida* with reported pharmacological activities and targets.

| Compound                                    | Pharmacology      | Mechanism                                                     | Reference |
|---------------------------------------------|-------------------|---------------------------------------------------------------|-----------|
| total flavonoids                            | anti-inflammatory | cytokine regulation, LTB4 inhibition, increase in cAMP levels | [19,97]   |
| 3,5-Dihydroxy-6,7,3',4'-tetramethoxyflavone | antitumor         | induction of cytotoxicity (HepG2 cells)                       | [10]      |
| sesquiterpene lactones                      | antitumor         | strong antiproliferative effect                               | [98]      |

**Table 4.** *Cont.*

| Compound                              | Pharmacology     | Mechanism                                                                                                                                 | Reference |
|---------------------------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| caffeoylquinic acids                  | antioxidant      | Radical scavenging activity and high ORAC values                                                                                          | [21]      |
| total flavonoids                      | antioxidant      | Strong scavenging of DPPH, superoxide ( $O_2^{\cdot-}$ ), hydroxyl radicals (OH)                                                          | [75]      |
| flavonoid extracts                    | antioxidant      | Hydroxyl radical scavenging                                                                                                               | [20]      |
| 1,8-cineole, camphor                  | antimicrobial    | disruption of microbial membrane integrity ( <i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> )                                     | [100]     |
| 1,8 cineole, camphor, borneol         | insecticidal     | fumigant toxicity against storage pests ( <i>Sitophilus zeamais</i> , <i>Liposcelis bostrychophila</i> )                                  | [101]     |
| n-Butanol and ethyl acetate fractions | hemostatic       | Shortening of bleeding and coagulation times in mice                                                                                      | [102]     |
| crude extracts                        | Immunomodulatory | Regulation of immune-related miRNAs; modulation of TLR, NLR, RLR pathways; influence on apoptosis, endocytosis, and cytokine interactions | [103]     |

## 6. Conclusions

*A. frigida* exhibits considerable medicinal promise, attributable to its chemically diverse repertoire of bioactive constituents—including flavonoids, sesquiterpenoids, and phenolic acids. Supported by both its long-standing traditional use and emerging pharmacological evidence, *A. frigida* is increasingly recognized as a valuable candidate for the development of natural therapeutic agents. Nevertheless, several challenges remain before its broader application can be realized. Current pharmacological studies are largely limited to in vitro or preclinical models, with insufficient clinical validation to substantiate therapeutic claims. Systematic investigations into toxicity and safety are also scarce, leaving uncertainties regarding long-term use and dosage. In addition, the complexity of its phytochemical profile highlights the need for rigorous standardization of extraction, separation, and quality-control procedures to ensure reproducibility and efficacy. To fully harness its potential, future research should integrate multidisciplinary approaches: optimizing extraction and separation technologies, conducting comprehensive safety evaluations, and advancing clinical studies that can translate laboratory findings into evidence-based healthcare applications. Moreover, given its broad pharmacological spectrum and rich phytochemical profile, *A. frigida* holds substantial application potential not only in medicine but also in the fields of nutraceuticals, cosmeceuticals, and functional foods. These multidisciplinary intersections merit deeper exploration to support its translational development from traditional remedies to modern healthcare product.

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