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Review Article

Anchusa italica Retz.: A Review of Chemical Composition, Pharmacological Effects, and Network Analysis

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Abstract

Anchusa italica Retz., a botanical drug belonging to the *Anchusa* genus of the Boraginaceae family, is a traditional Chinese botanical drug and medicine widely used in Uygur medicine for treating palpitations, insomnia, neurasthenia, hypertension, and other disorders. Recent studies have revealed its diverse chemical constituents and expanded pharmacological understanding. The plant is abundant in oils, triterpenoids, flavonoids, and other bioactive metabolites. Modern pharmacological research indicates that it has multifaceted biological activities, including cardiovascular protection, anti-tumor, antioxidative, anti-viral, anti-bacterial, anti-inflammatory, and neuroprotective properties. Despite the established clinical use of *A. italica* Retz. for cardiovascular protection, no comprehensive review exists to consolidate its pharmacological profile. This study systematically analyzes published research on the chemical constituents and pharmacological activities of the compound, with a particular focus on vasodilatory, cardioprotective, and anti-cancer mechanisms using network pharmacology approaches. The synthesized evidence aims to establish a scientific foundation for clinical translation and facilitate expanded therapeutic applications of this medicinal plant.

Keywords

Anchusa italica Retz., chemical metabolites, pharmacological effects, research progress, network analysis

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Introduction

Cardiovascular diseases (CVDs) and cancer are currently the two leading global public health concerns, particularly affecting the elderly population (Chuwen et al., 2023). Cardiovascular and cerebrovascular diseases generally refer to conditions in which ischemia or hemorrhage occurs in the heart, brain, and other tissues. These diseases are often associated with risk factors such as hypertension, hyperlipidemia, and hyperglycemia, along with issues like blood hyperviscosity and atherosclerosis (Ziqi, 2021). Atherosclerosis is a major contributor to CVDs, with systemic inflammation playing a crucial role in its pathogenesis. Annually, CVDs account for approximately 15 million deaths globally, ranking as a leading cause of mortality (Yanwen, 2022).

Traditional Chinese medicine (TCM) has a long-standing history of disease prevention and treatment in China. Over thousands of years of clinical practice, its effectiveness and safety have been well-established (Tian et al., 2023). TCM exhibits significant advantages in treating CVDs. For instance, its "multi-targeting" approach can induce cell differentiation, promote apoptosis, and mitigate the toxic side effects associated with chemotherapy. Moreover, TCM helps patients boost their immune function and facilitate recovery (Tian et al., 2023).

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Anchusa italica Retz. (Boraginaceae), commonly known as Gaoziwan or Gaoziban (اگــاۋزىۋ in the Uygur vernacular), is a perennial medicinal plant distributed in the Mediterranean region, tropical areas, and the Kashgar and Hetian prefectures of Xinjiang, China (Ketabchi et al., 2011). Listed in the Drug Standard of the Ministry of Health of the People's Republic of China: *Uyghur Medicine* sub-book, this species serves as a key metabolite in Uygur cardiovascular and cerebrovascular botanical drug formulas. It is also featured in classic compound preparations such as compound Gaoziban tablets, Jianxin Hemeier Gaoziban Anbi tablets, and Anshen cow's tongue honey paste (Abbas et al., 2009).

According to Uygur medical theory, Gaoziwan (*A. italica* Retz.) is categorized as having a dampness-heat property. It exerts pharmacological effects, including resolving dampness and tonifying the brain, dispelling cold and strengthening the heart, refreshing the heart and tranquilizing the mind, moistening dryness and exhibiting anti-inflammatory activity, relieving cough, and calming wheezing (China, 2005; Khare, 2008). Modern pharmacological studies have demonstrated that *A. italica* Retz. possesses biological activities such as cardiovascular protection, anti-tumor, anti-inflammatory, antioxidant, anti-viral, anti-bacterial, and neuroprotective effects (Changchun et al., 2018). A statistical analysis demonstrated that Anshen Niushecao honey ointment, with *A. italica* Retz. as the primary ingredient, ranks second in usage frequency among Uygur medicinal formulas for treating tachyarrhythmia. The study further indicated that among 189 single-ingredient Uygur medicines used for tachyarrhythmia, *A. italica* Retz. ranked fourth in usage frequency (Mamuti, 2023).

As a key Uygur ethnic medicine widely used in cardiovascular and cerebrovascular therapy, *A. italica* Retz. has demonstrated pharmacological properties including inhibition of lipopolysaccharide (LPS)-induced inflammation, anti-thrombotic activity, vasodilation, and myocardial protection. Its extracts also exhibit significant cytotoxicity against breast, hepatocellular, colon, lung, prostate, and leukemia cancer cells (Changchun et al., 2018). While extensive research has focused on the pharmacological activities of *A. italica* Retz., studies on its bioactive metabolites remain limited, with most investigations confined to crude extracts. This review systematically summarizes the chemical composition and pharmacological properties of *A. italica* Retz., with a focus on its anti-inflammatory, anti-cancer, vasodilatory, and cardioprotective effects. By applying network pharmacology analysis, this article aims to provide a pharmacological rationale for its use in CVDs and cancer treatment, thereby promoting the translational research and clinical application of *A. italica* Retz.

Methodology

Literature on the traditional uses, phytochemistry, and pharmacology of *A. italica* Retz. was systematically retrieved from scientific databases including Google Scholar, Web of Science, PubMed, ScienceDirect, Wiley, Springer, Baidu Scholar, China National Knowledge Infrastructure (CNKI), Wanfang Data, and J-GLOBAL. Search terms combined "*Anchusa italica* Retz." with "traditional uses," "phytochemistry," and "pharmacology" using Boolean operators (AND). Chemical structures were drawn with ChemDraw 19.0. Active ingredient targets were predicted via the SwissTargetPrediction database (http://swisstargetprediction.ch/). Disease-related targets were identified by querying the GeneCards database (https://www.genecards.org/) with disease-specific keywords. Overlapping targets between active ingredients and diseases were analyzed using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/). Protein–protein interaction (PPI) networks were constructed via the STRING database (https://cn.string-db.org/) and visualized in Cytoscape 3.9.1.

Chemical Composition

The phytochemical profile of *A. italica* Retz. encompasses lipids, triterpenoids, and flavonoids, while its leaves exhibit a distinct elemental composition containing essential minerals (calcium [Ca], potassium [K], magnesium [Mg], sodium [Na]) and trace metals (cadmium [Cd], cobalt [Co], copper [Cu], iron [Fe]). Quantitative analyses reveal potassium as the predominant mineral in fresh biomass (12.8 mg/g), with iron becoming the major constituent in dehydrated material (9.4 mg/g) (Jalali & Fakhri, 2021).

Triterpenoids

A comprehensive literature review identified 55 triterpenoids from *A. italica* Retz., with pentacyclic triterpenoids and oleanane-type triterpenoids predominating. For example, Kuruüzüm-Uz et al. (2010) isolated five triterpenoid metabolites from its methanolic extract: oleanazuroside 1, eanazuroside 2, ursolazuroside 1, ursolazuroside 2, and nigaichigoside. Kuikui et al. (2016) characterized eight triterpenoids from 95% ethanol extracts of the whole plant: 2α,3β,19α,23-tetrahydroxylurs-12-en-28-oic acid-28-β-D-glucopyranoside, 24-hydroxytormentic acid ester glucoside, 24-epi-pinfaensin, 2α,3β,19α-trihydroxyurs-24-oxo-12-en-28-oic acid, oleanolic acid ester glucoside, 2α,3β,21β,23-tetrahydroxyolean-12-en-28-oic acid, oleanazuroside 1, and 2α,3β,19α,23-tetrahydroxylurs-12-en-28-oic acid. Hu et al. (2020) reported 28 triterpenoids from 75% ethanol extracts of *A. italica* aerial parts, while Duan et al. (2022) identified 25 triterpenoids in the dichloromethane fraction via liquid chromatography–tandem mass spectrometry (LC–MS/MS). Collectively, over 50 triterpenoids have been isolated from *A. italica* Retz. (Table 1), with their structures illustrated in Figure 1.

Flavonoids

In one study, five major flavonoids from *A. italica* Retz. were analyzed by LC–MS/MS, namely: rutin (1), hesperidin (2),

Table 1. Triterpenoids in *Anchusa italica* Retz.

Sl. No.	Name	References
1	Oleanazuroside 1	Kuruüzüm-Uz et al. (2010)
2	Oleanazuroside 2	Kuruüzüm-Uz et al. (2010)
3	Ursolazuroside 1	Hu et al. (2020), Kuruüzüm-Uz et al. (2010)
4	Ursolazuroside 2	Duan et al. (2022), Hu et al. (2020), Kuruüzüm-Uz et al. (2010)
5	Quercilicoside A	Kuruüzüm-Uz et al. (2010)
6	2α,3β,19α-Trihydroxyurs-24-oxo-12-en-28-oic acid	Kuruüzüm-Uz et al. (2010)
7	Oleanolic acid 3-O-α-L-arabinoside	Kuruüzüm-Uz et al. (2010)
8	2α,3β,21β,23-Tetrahydroxyolean-12-en-28-oic acid	(Kuruüzüm-Uz et al., 2010)
9	2α,3β,19α,23-Tetrahydroxyurs-12-en-28-oic acid	Kuruüzüm-Uz et al. (2010)
10	24-Epi-pinfaensin	Hu et al. (2020), Kuruüzüm-Uz et al. (2010)
11	(2α,3β,21β)-21-(β-D-Glucopyranosyloxy)-23-{[β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl]oxy}-2,3-dihydroxyolean-12-en-28-oic acid	Hu et al. (2020)
12	(2α,3β,21β)-3-{[β-D-Glucopyranosyl(1→2)-β-D-glucopyranosyl]oxy}-21-(β-D-glucopyranosyloxy)-2, 23-dihydroxyolean-12-en-28-oic acid	Hu et al. (2020)
13	(3β,21β)-21-(β-D-Glucopyranosyloxy)-23-{[β-D-glucopyranosyl (1→2)-β-D-glucopyranosyl]-oxy}-3-hydroxyolean-12-en-28-oic acid	Hu et al. (2020)
14	(2α,3β,21β)-2-(β-D-Glucopyranosyloxy)-21-{[β-D-glucopyranosyl (1→2)-β-D-glucopyranosyl]oxy}-3-hydroxyolean-12-en-28-oic acid	Hu et al. (2020)
15	(2α,3β,21β)-3-(β-D-Glucopyranosyloxy)-21-{[β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl]oxy}-2-hydroxyolean-12-en-28-oic acid	Hu et al. (2020)
16	(3β,21β)-21-[(β-d-Glucopyranosyl-(1→2)-β-d-glucopyranosyl)oxy]-3-hydroxyolean-12-en-28-oic acid	Hu et al. (2020)
17	24-Epi-niga-ichigoside F1	Hu et al. (2020)
18	Anserinoside	Hu et al. (2020)
19	3β,19α,23,24-Tetrahydroxyurs-12-en-28-oic acid	Hu et al. (2020)
20	Ziyu-glycoside 1	Hu et al. (2020)
21	Hyptatic acid B	Hu et al. (2020)
22	Laevigin C	Hu et al. (2020)
23	Euscaphic acid	Hu et al. (2020)
24	Officinoterpenoside B	Duan et al. (2022), Hu et al. (2020)
25	Sweriyunnanoside A	Hu et al. (2020)
26	2α,3β-Dihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside	Hu et al. (2020)
27	Anchusosid-5	Duan et al. (2022), Hu et al. (2020)
28	Anchusosid-9	Duan et al. (2022), Hu et al. (2020)
29	Anchusosid-8	Hu et al. (2020)
30	Anchusosid-11	Hu et al. (2020)
31	Maslinic acid	Hu et al. (2020)
32	2α,3β,21β-Trihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside	Hu et al. (2020)
33	Sericoside	Hu et al. (2020)
34	21-O-β-D-Glucopyranosyl-2α,3β,21β,23-tetrahydroxyolean-12- en-28-oic acid	Hu et al. (2020)
35	Tetrahydroxyolean-12-en-28-oic acid-hexahydroxyheptanoic acid	Duan et al. (2022)
36	Dimeric trerpenoid glucoside	Duan et al. (2022)
37	Trihydroxy-oxours-en-oic acid-hexahydroxyheptanoic acid	Duan et al. (2022)
38	Methanetriol-anserinoside	Duan et al. (2022)

(Table 1 continued)

(Table 1 continued)

Sl. No.	Name	References
39	Trihydroxy-oxours-en-oic acid/pinfaensic acid	Duan et al. (2022)
40	Pinfaensic acid-methanetriol-rhamnoside	Duan et al. (2022)
41	Dihydroxy-12-en-28-oic acid- methanetriol	Duan et al. (2022)
42	Dihydroxy-12-en-28-oic acid-glucodise-glucoside	Duan et al. (2022)
43	Dihydroxy-12-en-28-oic acid-2,5-dihydroxyhexaric acid	Duan et al. (2022)
44	Jaligonic acid B	Duan et al. (2022)
45	Tetrahydroxyolean-12-en-28-oic acid/tetrahydroxyurs-12-en-28-oic acid	Duan et al. (2022)
46	Dihydrooleanic acid glucoside-glucoside	Duan et al. (2022)
47	Tetrahydroxyolean-12-en-28-oic acid/tetrahydroxyurs-12-en-28-oic acid	Duan et al. (2022)
48	Isomer of jaligonic acid B	Duan et al. (2022)
49	Trihydroxy-oxours-en-oic acid/epi-pinfaensic acid	Duan et al. (2022)
50	Dihydroxy oleanic acid	Duan et al. (2022)
51	Dihydroxy ursolic acid	Duan et al. (2022)
52	Hydroxy oleanic acid/hydroxy ursolic acid	Duan et al. (2022)
53	Trihydroxy-oxours-en-oic acid/epi-pinfaensic acid	Duan et al. (2022)
54	Tetrahydroxyolean-12-en-28-oic acid/tetrahydroxyurs-12-en-28-oic acid	Duan et al. (2022)

quercetin (3), naringenin (4), and kaempferol (5) (Wang et al., 2020). In another study, researchers isolated three flavonoids from the methanolic extract of oxalis, namely: quercetin-3-(α-rhamnose-(1-6)-β-glucoside) (6), isoquercetin (7), and kaempferol-3-(β-glucoside) (8) (Kuruüzüm-Uz et al., 2010). Duan et al. (2022) also found two flavonoids, trihydroxy-dimethoxyflavone (9) and trihydroxy-trimethoxy flavone (10), in the dichloromethane extract of *A. italica* Retz. Ma Guizhi reported that rutin, kaempferol-3-O-retinoid (11), and narcissoside (12) are the active sites of the total flavonoid of *A. italica* Retz. Astragalin (13) was identified at its dichloromethane and *n*-butanol sites, with the structure shown in Figure 2.

Oils and Fats

Volatile Oils: Kazemi (Kazemi, 2013) obtained 34 volatile oil constituents from the 70% ethanol extract of *A. italica* Retz. flowers using gas chromatography–flame ionization detector (GC–FID) and gas chromatography–mass spectrometry (GC–MS) techniques, and the major constituents were diisobutyl phthalate, dibutyl phthalate, and 6,10,14-trimethyl-2-pentadecanone, which are shown in Table 2.

Fatty Acids: Some researchers analyzed the petroleum ether extracts of *A. italica* Retz. leaves by using the GC–FID technique, and the results showed that the major fatty acids were monounsaturated fatty acids and polyunsaturated fatty acids, including caprylic acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, myristoleic acid, pentadecanoic acid, palmitic acid, palmitoleic acid, heptadecanoic acid, stearic acid, oleic acid, linoleic acid, gamma-linolenic acid, alpha-linolenic acid, arachidic acid, eicosapentaenoic acid, *cis*-8,11,14-twenty-carboxytrienoic acid, *cis*-11,14,17-twenty-carboxytrienoic acid, eicosanoic acid, docosanoic acid, and neuraminic acid (Conforti et al., 2011; Morales et al., 2012).

Other Compounds

In addition to the above compounds, *A. italica* Retz. also contains phenylpropanoids, steroids, and alkaloids. Among them, there are 12 phenylpropanoids, including 9 phenylpropanoids and their derivatives, namely caffeic acid (1), ferulic acid (2), methyl ferulate (3), methyl isoferulate (4), rosmarinic acid (5), methyl rosemary acid (6), oresbiusin A (7), hydroxybenzoic acid (8), and methyl 3,4-dihydroxycinnamate (9) (Duan et al., 2022; Guizhi et al., 2018; Guolian et al., 2018). One coumarin analogue is hydroxycoumarin (10), and two lignans are (−)-butyryl esterin (11) and (−)-epibutyryl esterin (12). Three steroids are β-sitosterol acetate (13), β-sitosterol (14), and carotenoid glycosides (15) (Wen, 2016). An alkaloid is 5-hydroxy-2-pyrrolidone (16), and two other types of compounds were isolated as poly [3-(2,4-dihydroxyphenyl)] glyceric acid (17) and 3-(3,4-dihydroxyphenyl)lactic acid (18), respectively (Qi et al., n.d.; Yuan-Yuan et al., 2017). There are also two monoterpenes: (−)-loliolide (19), (−)-dia-syringaresinol (20). The structures of these compounds are shown in Figure 3. In addition, it has been found that its composition includes polysaccharides, amino acids, and proteins, but it has not yet been determined what kind of polysaccharides, amino acids, and proteins are involved.

Pharmacology Research

Modern pharmacological investigations have revealed that *A. italica* Retz. exhibits diverse pharmacological activities, including

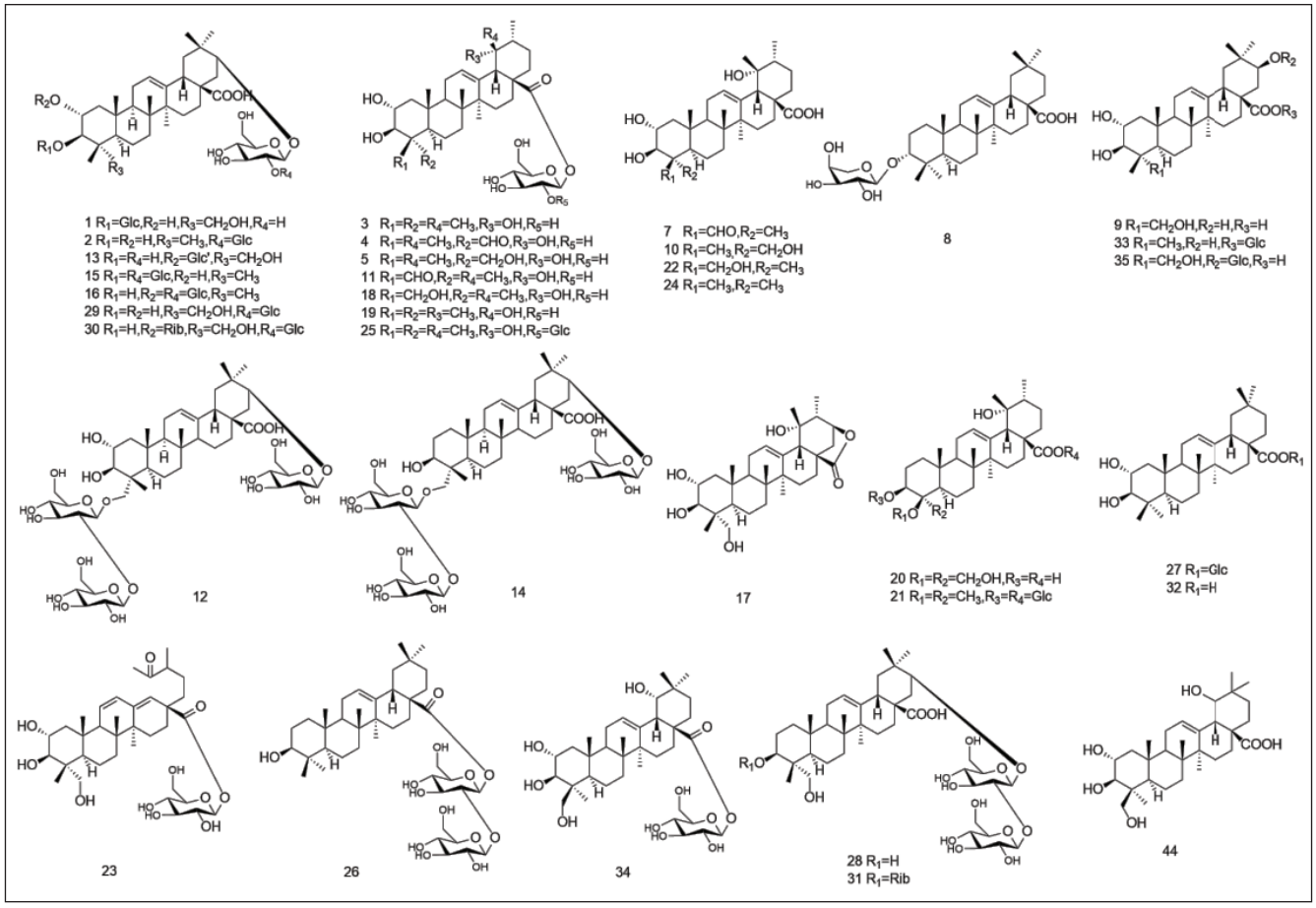


Figure 1. Structural Formula for Some Triterpenoids.

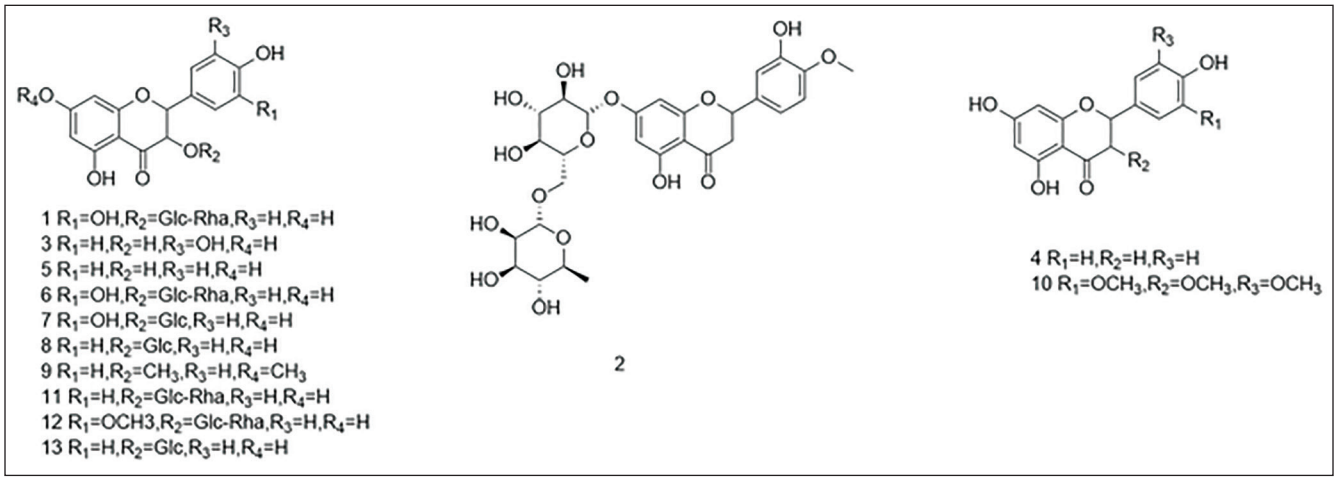


Figure 2. Structural Formula for Flavonoids.

cardiovascular protection, anti-tumor, antioxidant, anti-viral, antibacterial, anti-inflammatory, and neuroendocrine regulatory effects. While these properties have been validated through *in vitro* and *in vivo* experiments, mechanistic studies remain limited to crude extracts, and the specific bioactive metabolites responsible for these effects remain to be further explored.

Table 2. The Volatile Oil Metabolite of the Flower of *Anchusa italica* Retz.

Sl. No.	Name	References
1	(E)-2-Hexanal	Kazemi (2013)
2	(E)-3-Hexen-1-ol	Kazemi (2013)
3	Acetonylacetone	Kazemi (2013)
4	5-Methyl-3-heptanone	Kazemi (2013)
5	Limonene	Kazemi (2013)
6	Nonanal	Kazemi (2013)
7	Safranal	Kazemi (2013)
8	Decanal	Kazemi (2013)
9	3-Methyldodecane	Kazemi (2013)
10	6-Ethyl-1-dodecene	Kazemi (2013)
11	*n*-Tetradecane	Kazemi (2013)
12	Dodecanal	Kazemi (2013)
13	(E)-Geranylacetone	Kazemi (2013)
14	2,4-Cyclohexadienone	Kazemi (2013)
15	β-Ionone	Kazemi (2013)
16	α-(3-Methylbutylidene)-benzeneacetaldehyde	Kazemi (2013)
17	*n*-Pentadecane	Kazemi (2013)
18	2-Metylpentadecane	Kazemi (2013)
19	*n*-Tetradecanal	Kazemi (2013)
20	Benzophenone	Kazemi (2013)
21	Tributyl phosphate	Kazemi (2013)
22	Pentadecanal	Kazemi (2013)
23	2-Heptadecene	Kazemi (2013)
24	Palmitic aldehyde	Kazemi (2013)
25	Hexahydrofarnesylacetone	Kazemi (2013)
26	Diisobutyl phthalate	Kazemi (2013)
27	(E,E)-Farnesylacetone	Kazemi (2013)
28	Dibutyl phthalate	Kazemi (2013)
29	(Z)-Phytol	Kazemi (2013)
30	*n*-Tricosane	Kazemi (2013)
31	*n*-Pentacosane	Kazemi (2013)
32	*bis*(2-Ethylhexyl) phthalate	Kazemi (2013)
33	*n*-Heptacosane	Kazemi (2013)
34	*n*-Nonacosane	Kazemi (2013)

Cardiovascular Protection

As a key Uygur medicinal plant widely used in cardiovascular and cerebrovascular therapy, *A. italica* Retz. has undergone increasingly advanced modern pharmacological investigations. Accumulating evidence indicates that its flavonoid and triterpenoid metabolites are the primary bioactive metabolites underlying its therapeutic effects.

In a murine myocardial infarction model, Wang et al. (2020) demonstrated that *A. italica* total flavonoids (AITF) administered via coronary artery ligation significantly improved survival rates. Treatment with 30 mg/kg and 50 mg/kg AITF reduced myocardial infarction size, suppressed serum levels of pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), and inhibited activation of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway. These findings suggest that AITF exerts cardioprotective effects by attenuating inflammation and modulating the PI3K/Akt/mTOR axis, potentially contributing to improved cardiac function and remodeling.

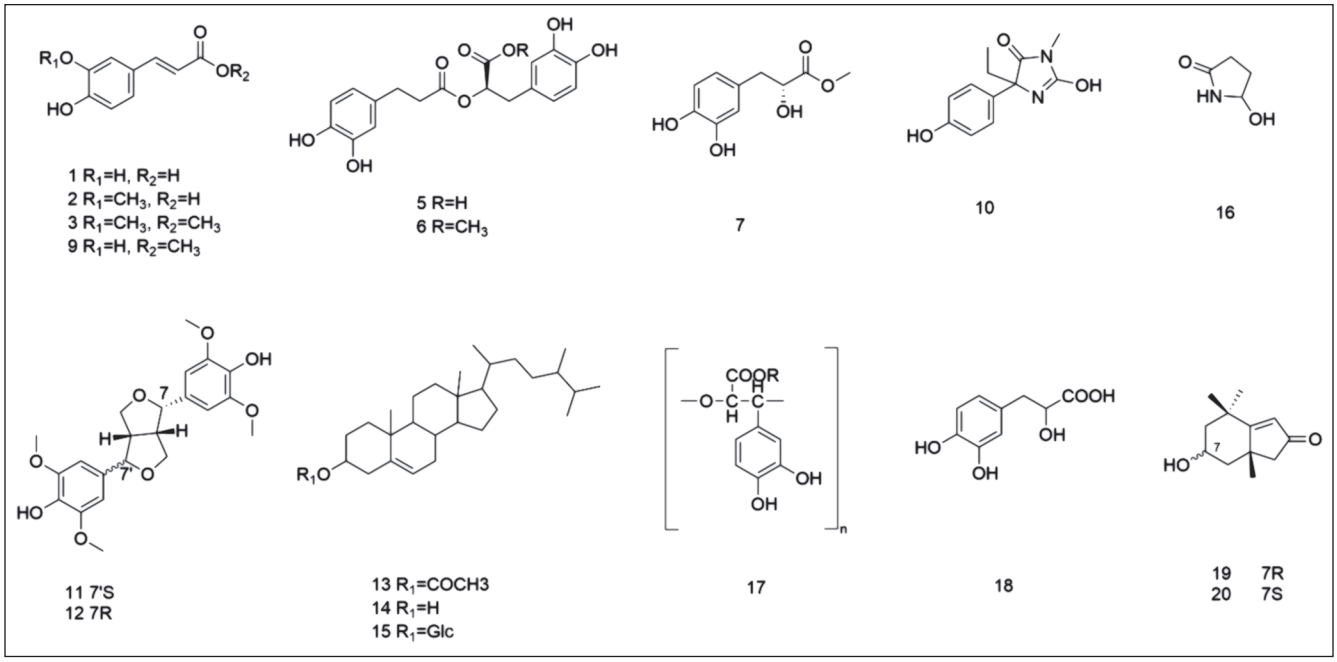


Figure 3. Structural Formulae of Other Compounds.

Experimental studies have confirmed that aqueous and ethanol extracts of *A. italica* Retz. prolong the clotting time in normal mice and reduce thrombus wet weight in rats, indicating their anti-thrombotic potential and preventive effects against vascular occlusion. Xiaodong et al. (2019) reported a dose-dependent vasodilatory effect on rat thoracic aortic rings, demonstrating that this activity is endothelium-independent.

In an *in vitro* study, among the 28 triterpenoids isolated from the aerial parts of *A. italica* Retz., compounds 4, 6–17, 21–22, and 26–28 were reported to exhibit protective effects against myocardial cell injury. Specifically, the representative compound 6 significantly suppressed apoptosis and autophagy levels in hypoxia/reoxygenation (H/R)-induced neonatal rat cardiomyocytes (Hu et al., 2020). These findings suggest that triterpenoid compound 6 and its analogs could be the pharmacodynamic substances underlying the cardiovascular benefits of *A. italica* Retz., offering a potential therapeutic strategy for H/R-induced cardiomyocyte injury.

Anti-tumor Effect

A. italica Retz. exhibits cytotoxicity against breast cancer cells (MCF-7), liver cancer cells (HepG2), murine lymphoma cells (WEHI), and bovine kidney cell lines (MDBK), with an IC_{50} exceeding 100 μg/mL (Sahranavard et al., 2009). The dichloromethane extract of *A. italica* Retz. inhibits the proliferation of HL-60 cancer cells *in vitro* (Mulati, 2009). Lone et al. (2013) reported that its flavonoid metabolites showed significant inhibitory activity against the colon cancer cell line (HCT-116), the human lung cancer cell line (A549), the prostate cancer cell line (PC-3), and the leukemia cell line (THP-1). Additionally, *A. italica* Retz. demonstrated potent tumor cell inhibition against human epidermoid cell carcinoma (A-431) and mouse melanoma cells (B16F10). However, current anti-tumor activity assessments are limited to *in vitro* studies, lacking *in vivo* validation. Thus, *in vivo* experiments are required to verify these findings further.

Antioxidant and Neuroprotective Effects

The antioxidant and neuroprotective activities of *A. italica* Retz. ethanol extracts have been comprehensively validated *in vivo*. Oxidative stress, a stress response stemming from an imbalance between oxidative and antioxidant processes in the body, is one of the primary factors contributing to aging and numerous diseases (Peng et al., 2022). This finding indicates the antioxidant efficacy of *A. italica* Retz. ethanol extract. In another study, Khomsi et al. (2022) determined the reducing power, 1,1-diphenyl-2-trinitrophenylhydrazine (DPPH) scavenging ability, and total antioxidant capacity of *A. italica* Retz. root and leaf extracts, revealing significant antioxidant potential.

The central nervous system (CNS) serves as the primary regulatory hub for human physiological processes (Peng et al., 2022). CNS-related pathologies encompass cerebral ischemia, traumatic brain injury, neuropsychiatric disorders, epilepsy, and substance dependence. In a rodent stroke model, Asgharzade et al. (2020) demonstrated that *A. italica* Retz. ethanolic extract attenuated oxidative stress markers

(hippocampal MDA and serum nitric oxide [NO]) while modulating mRNA expression profiles (inducible nitric oxide synthase [iNOS] downregulation; brain-derived neurotrophic factor [BDNF] upregulation). These findings indicate the extract's neuroprotective potential against global cerebral ischemia-reperfusion injury via dual mechanisms: iNOS-mediated anti-inflammatory effects and BDNF-mediated neurotrophic support.

Torki et al. (2018) demonstrated the 14-day intraperitoneal administration of *A. italica* Retz. ethanolic extract ameliorated ischemia-reperfusion-induced cognitive deficits in a rodent stroke model, concomitant with enhanced antioxidant capacity in hippocampal tissue and serum. This intervention exhibited neuroprotective effects against transient global cerebral ischemia-reperfusion injury. Subsequent investigations by Rahimi-Madiseh et al. (2022) revealed the extract's anti-convulsant properties, mechanistically linked to oxidative stress attenuation. Comparative analyses demonstrated a significant elevation of seizure thresholds, augmented antioxidant activity, and reduced MDA/nitrite levels in serum and prefrontal cortex versus controls.

Anti-bacterial Effect

The widespread use of anti-biotics and synthetic anti-microbial drugs has led to an increasing number of drug-resistant strains, making clinical treatment increasingly difficult and seriously threatening public health. *A. italica* Retz., characterized by low toxicity and diverse biological activities, has demonstrated notable anti-microbial activity. Azizi et al. (2016) used *A. italica* Retz. flower extracts and zinc acetate to synthesize zinc oxide nanoparticles for anti-pyretic treatment, and evaluated their anti-bacterial effects. The results showed that the biosynthetic particles containing *A. italica* Retz. extract significantly inhibited pathogenic activity with a broad anti-bacterial spectrum, targeting not only Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus* but also Gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium*.

Xiaoqin et al. (2019) employed the two-fold tube dilution method to screen different extracts of *A. italica* Retz. for anti-microbial activity. The four tested extracts were ethanol, ethyl acetate, *n*-butanol, and water-soluble fractions. All four extracts exhibited inhibitory activity against *B. subtilis*, with the ethyl acetate and water-soluble fractions demonstrating significantly stronger inhibition than the other fractions.

Khomsi et al. (2022) reported that ethanolic extracts of *A. italica* Retz. leaves and roots were evaluated for anti-bacterial activity against four *E. coli* strains, two *Klebsiella pneumoniae* strains, coagulase-negative *Staphylococcus*, and one *Candida albicans* strain. The results showed that all tested strains were inhibited by the extracts, with inhibition zone diameters ranging from 11.00 to 16.00 mm for root extracts and 11.67 to 14.33 mm for leaf extracts.

Anti-inflammatory Activity

Inflammation, an important protective mechanism that organisms have gradually developed during evolution to resist the invasion of foreign pathogens, can, however, induce diseases when it persists or overreacts. These diseases often disrupt people's daily lives and, in severe cases, endanger human safety and health. To explore the anti-inflammatory activity of different extracts of *A. italica* Retz., the effects of ethanol and *n*-butanol extracts of *A. italica* Retz. were observed using a carrageenan-induced rat toe swelling model. The results indicated that within 4 h of inflammation onset, the inhibitory effect of the *n*-butanol extract on inflammation was comparable to that of the dexamethasone acetate group (Xiaoqin et al., 2019).

Duan et al. (2022) demonstrated that the dichloromethane extract of *A. italica* Retz. exhibited a significant inhibitory effect on the LPS-induced inflammatory response. A subsequent mechanistic investigation showed that the extract at a high concentration (50 μg/mL) inhibited the mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), and hemoprotein deposition pathways, while activating the nuclear factor erythroid 2-related factor 2 (Nrf_2)/heme oxygenase-1 (HO-1) pathway. Additionally, LC–MS/MS analysis identified a large number of triterpenoids, suggesting that triterpenoids might contribute to the anti-inflammatory properties of the extract (Duan et al., 2022).

Anti-viral Effect

In addition to the aforementioned activities, *A. italica* Retz. exhibits anti-viral properties. Both aqueous and ethanolic extracts of *A. italica* Retz. demonstrated potency against the influenza virus at concentrations ranging from 2.5 to 80 μg/mL. The anti-viral activity was evaluated by infecting Madin–Darby kidney (MDCK) monolayer cells with the virus. The extracts were added either 1 h before or 1 h after infection. The ethanolic extract showed a more pronounced anti-viral effect compared to the aqueous extract. The anti-viral mechanism may be associated with interference in viral replication and transcription (Ketabchi et al., 2011).

Other Pharmacological Effects

The methanolic extract (200 μg/mL) of *A. italica* Retz. exhibited 57.41% inhibition of hormone-sensitive lipase *in vitro*, demonstrating good inhibitory activity. The inhibition was dose-dependent, with an IC_{50} value of 132.8 μg/mL (Bustanji et al., 2011). The aqueous extract (5%) of *A. italica* Retz. reduced the mean height of rabbit jejunal smooth muscle contraction by 35% compared to normal contraction. In a rat model, where indomethacin was administered to induce gastric damage, extracts from different parts (including oxalis and roots) of *A. italica* Retz. showed anti-ulcerogenic activity (Naema et al., 2010).

Table 3. *Anchusa italica* Retz. Active Ingredients.

Sl. No.	Name	ID
1	Oleanazuroside 1	ST1
2	Oleanazuroside 2	ST2
3	Ursolazuroside 1	ST3
4	Ursolazuroside 2	ST4
5	2α,3β,21β,23-Tetrahydroxyolean-12-en-28-oic acid	ST8
6	24-Epi-pinfaensin	ST10
7	24-Epi-niga-ichigoside F1	ST17
8	3β,19α,23,24-Tetrahydroxyurs-12-en-28-oic acid	ST19
9	Ziyu-glycoside 1	ST20
10	Laevigin C	ST22
11	Euscaphic acid	ST23
12	Maslinic acid	ST32
13	Sericoside	ST34
14	Rutin	T1
15	Hesperidin	T2
16	Quercetin	T3
17	Naringenin	T4
18	Kaempferol	T5
19	Isoquercitrin	T8
20	Prudomestin	T9
21	Isothymonin	T10
22	Nicotiflorin	T11
23	Narcissoside	T12
24	Astragalin	T13
25	β-Sitosterol	Q2
26	Daucosterol	Q3
27	Caffeic acid	Q5
28	Ferulic acid	Q6
29	Methyl 4-hydroxy-3-methoxycinnamate	Q7
30	Isoferulic acid methyl ester	Q8
31	Methyl rosmarinate	Q10
32	Methyl caffeate acid	Q12
33	Syringaresinol	Q14

The ethanolic and *n*-butanol extracts of *A. italica* Retz. prolonged the latency period of coughing in mice, with an effect comparable to that of Gee's syrup, and significantly reduced the number of coughs. These results suggest that the ethanolic and *n*-butanol extracts of *A. italica* Retz. possess anti-tussive properties. Additionally, a rat cough variant asthma (CVA) model was established. The aqueous and *n*-butanol extracts of *A. italica* Retz. inhibited CVA in rats, and the mechanism of action may be associated with the inhibition of the toll-like receptor 4/myeloid differentiation primary response 88/NF-κB (TLR4/MyD88/NF-κB) signaling pathway (Liang et al., 2024; Xiaoqin et al., 2019).

Exploring the Pharmacological Mechanism of Action of *A. italica* Retz. Based on Network Analysis

In summary, some progress has been made in the chemical composition and pharmacological studies of *A. italica* Retz. However, studies on the monomer activity of its chemical constituents are still lacking, and the therapeutic mechanism of the botanical drug, which is commonly used as a cardiovascular botanical drug in Uygur medicine, is still uncertain. Modern pharmacological studies have shown that *A. italica* Retz. also possesses anti-cancer activity, so we explored some

of the pharmacological effects of the active metabolites of *A. italica* Retz. based on network analysis to lay the foundation for its subsequent experimental validation and clinical application.

Results of A. italica Retz. Metabolite Screening and Target Prediction

According to the preliminary literature research, 88 metabolites were obtained or screened for bioactive metabolites through the SwissADME database, which showed "high" based on small intestinal absorption (GI) and two or more "yes" for drug similarity (Cai et al., 2024). As shown in Table 3, a total of 33 active ingredients were obtained, mainly flavonoids and triterpenoids. Then, the corresponding bioactive ingredient targets were obtained from the SwissTargetPrediction database, yielding 369 active ingredient targets.

Disease Targets

The GeneCards database was searched with the keywords "inflammation," "cancer," and "vasodilatation and cardioprotection" to obtain disease targets (Wu et al., 2023). We were able to access 3,922 inflammatory targets, 4,894 cancer targets, and 1,335 vasodilator and cardioprotective targets.

Drug-Disease Common Target Prediction

The obtained active ingredient targets of *A. italica* Retz. were processed with disease targets using Venny 2.1. The intersections were taken and plotted in a Venn diagram, which showed that the active ingredient had 243 intersections with inflammatory targets, 244 targets with cancer, 298 targets with vasodilatation and cardioprotection, and 186 targets with all four intersections, as shown in Figure 4.

Protein–Protein Interaction Network Construction and Key Target Screening

PPI analysis of *A. italica* Retz. metabolite targets with anti-inflammatory, anti-cancer, vasodilator, and cardioprotective intersection targets, as well as the intersection targets of all four, were performed by the STRING database, which yielded a total of 162, 183, 191, and 137 directly or indirectly interacting targets, by utilizing the Cytoscape 3.9.1 software. The anti-inflammatory targets of it were screened with a degree ≥10 to obtain 69 core targets; anti-cancer targets were screened with a degree ≥8 to obtain 52 core targets;

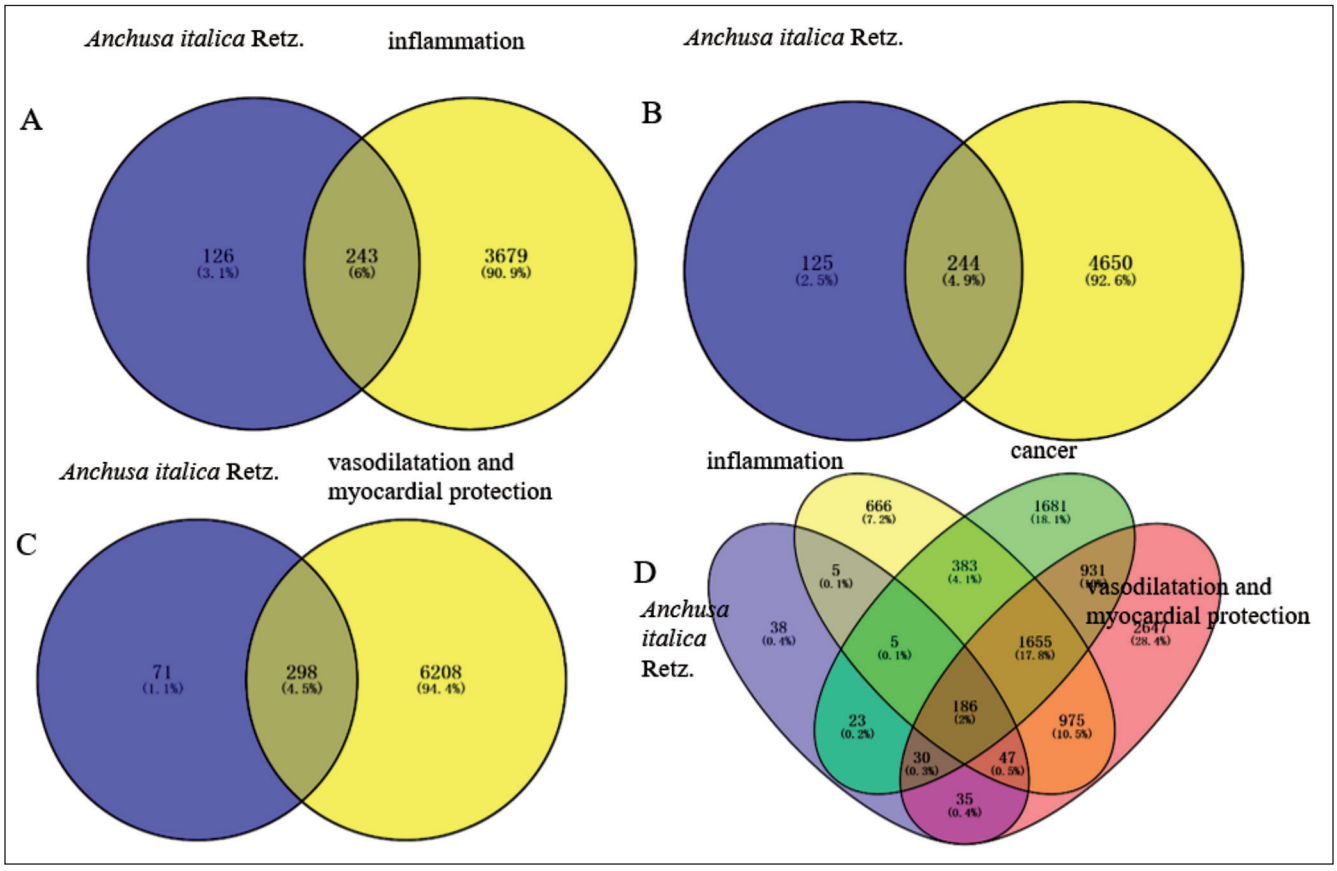


Figure 4. Venn Diagram of Drug-Disease Common Targets. (A) Intersection of Active Ingredients with Inflammatory Targets 290. (B) Intersection of Active Ingredients with Cancer Targets 307. (C) 256 Targets of Active Ingredient Intersection with Vasodilation and Myocardial Protection. (D) 181 Targets at the Intersection of the Four.

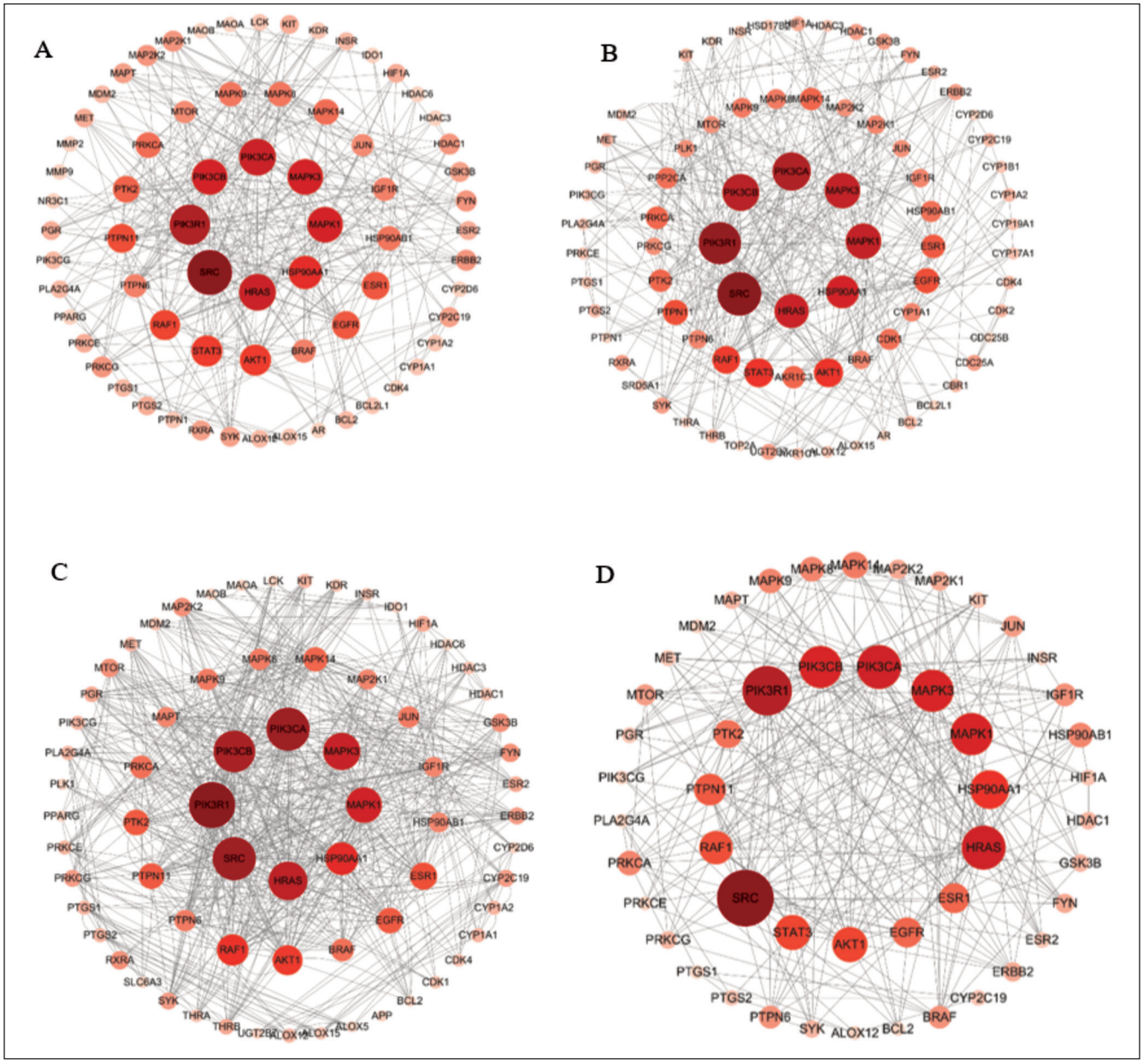


Figure 5. Protein–Protein Interaction (PPI) Network Diagram of *Anchusa italica* Retz.-Protein Interaction of Disease. The Nodes are Sorted by Degree Value. The Larger the Node, the Darker the Color, the Higher the Degree Value, and Vice Versa. Nodes Represent Different Targets, the Connections Between Nodes Represent the Interaction Between them, and the Size of Nodes Represents the Different Possibilities of Binding with *A. italica* Retz. (A) Protein–Protein Interaction (PPI) Network Diagram of Drug Inflammation. (B) Drug-Cancer PPI Network Diagram. (C) Drug-Vasodilator and Myocardial Protection PPI Network Map. (D) Drug-PPI Network Diagram of the Intersection of the Four.

vasodilatation and myocardial protection were screened with a degree ≥7 to obtain 70 core targets; and the PPI targets of the four intersections were screened with a degree ≥8 to obtain 66 core targets, as shown in Figure 5. The larger the value of the degree, the more targets associated with this target are proven to be, and the greater its research significance is, so the core target proteins, such as SRC, PIK3RI, MAPK1, PIK3CB, PIK3CA, and STAT3, were screened and found to be related to the disease.

Construction of the Traditional Chinese Medicine-Active Ingredient-Target-Pathway Network

The targets involved in the seven pathways enriched by Kyoto Encyclopedia of Genes and Genomes (KEGG) were compared and analyzed with those of the active ingredients of TCM, and finally, 15 active chemical metabolites and 20 main targets were obtained. The graph drawn with Cytoscape 3.9.1 software is shown in Figure 6 (E).

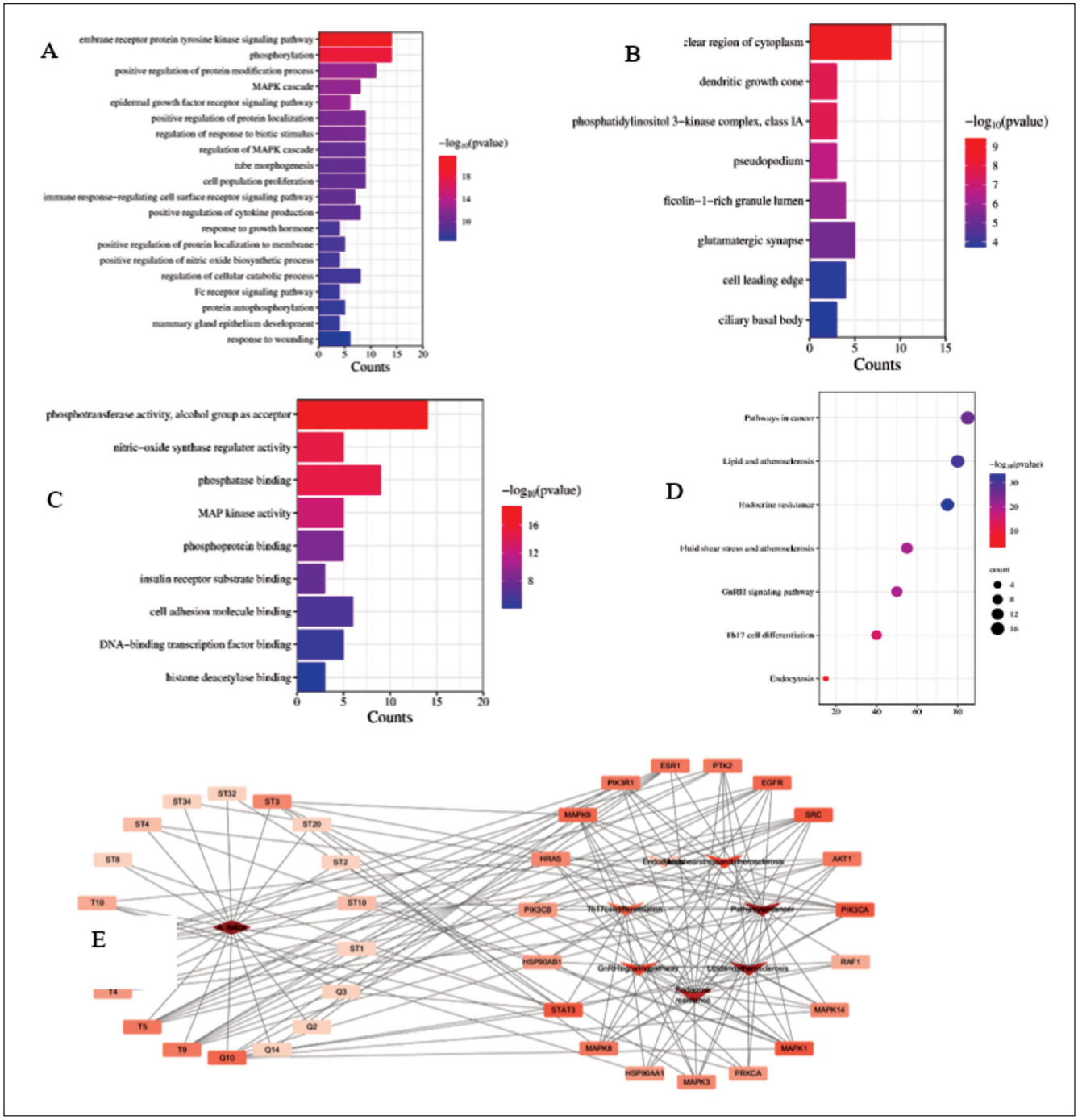


Figure 6. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Analyses of *Anchusa italica* Retz. with Four Core Targets at the Intersection of Anti-inflammatory, Anti-cancer, Vasodilatory, and Cardioprotective. (A) Analysis of the Biological Process. (B) Analysis of Cell Metabolites. (C) Analysis of Molecular Function. (D) Bubble Diagram of the KEGG Pathway. (E) Medicine-active Ingredient-Target-Pathway Network Diagram.

Conclusion

As a specialty botanical drug of Xinjiang, *A. italica* Retz. has a long history of folk medicine. Summarizing the review, up to now, a total of 86 compounds, mainly triterpenoids, flavonoids, volatile oils, and some phenolic acids, have been found, with cardiovascular, anti-inflammatory, antioxidant, and neuroprotective pharmacological effects. Although all the studies on *A. italica* Retz. have made some progress, research on the activity of single compounds of its chemical constituents is still weak. The studies on pharmacological effects are also mainly focused on cardiovascular and

cerebrovascular biological activities, and there is a large research gap in other pharmacological effects. Meanwhile, as one of the preferred botanical drugs in Uygur medicine for the treatment of cardiovascular and cerebrovascular diseases, its therapeutic mechanism still needs to be further explored. In this article, the anti-inflammatory, anti-cancer, vasodilatory, and cardioprotective effects of the active constituents of *A. italica* Retz. were investigated on the basis of network pharmacological analysis. The active constituents were found to be mainly triterpenoids and flavonoids, which may be the main active metabolites of *A. italica* Retz., and which may also play a role in both cancer and cardiovascular protection. It may provide the material basis for these two major diseases, but further experimental verification is needed. Therefore, the metabolites of *A. italica* Retz. can actually be further studied and developed. Whether further modification of its active ingredients can yield better effects against diseases may provide new ideas for developing new drugs. In the future, it is necessary to deepen the research on the chemical composition and pharmacological effects of *A. italica* Retz. on the basis of modern technology and advanced scientific research techniques to promote the further development and clinical application of *A. italica* Retz.

Abbreviations

AITF: *Anchusa italica* total flavonoids; Akt: Protein kinase B; ARRIVE: Animal Research: Reporting of *In vivo* Experiments; BDNF: Brain-derived neurotrophic factor; CNS: Central nervous system; CNKI: China National Knowledge Infrastructure; CVA: Cough variant asthma; CVDs: Cardiovascular diseases; DPPH: 1,1-Diphenyl-2-trinitrophenylhydrazine; GC–FID: Gas chromatography–flame ionization detector; GC–MS: Gas chromatography–mass spectrometry; GI: Gastrointestinal; GO: Gene Ontology; GSH-PX: Glutathione peroxidase; H/R: Hypoxia/reoxygenation; HO-1: Heme oxygenase-1; IACUC: Institutional Animal Care and Use Committee; IC_{50}: Half maximal inhibitory concentration; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; iNOS: Inducible nitric oxide synthase; KEGG: Kyoto Encyclopedia of Genes and Genomes; LC–MS/MS: Liquid chromatography–tandem mass spectrometry; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MDA: Malondialdehyde; MDCK: Madin–Darby canine kidney; mTOR: Mammalian target of rapamycin; MyD88: Myeloid differentiation primary response 88; NF-κB: Nuclear factor-kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; PI3K: Phosphoinositide 3-kinase; PPI: Protein–protein interaction; SOD: Superoxide dismutase; TCM: Traditional Chinese medicine; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor-alpha.

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Authors' Contributions

Conceptualization, W.G.; methodology, L.C.; software, W.G.; formal analysis, W.G.; investigation, L.C.; resources, X.X.; data curation, X.X. and C.L.; writing – original draft preparation, W.G.; writing – review and editing, W.G.; visualization, X.X.; supervision, M.D. and L.C.; project administration, M.D. and L.C. All authors have read and agreed to the published version of the manuscript.

Declaration of Conflicting Interest

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

Ethical Approval and Informed Consent

This experiment was approved by the Experimental Animal Ethics Committee of Xinjiang Medical University (Ethics Batch Number: IACUC-20220301-04) and the date, March 1, 2022, of this approval. Experimental compliance was in accordance with The Animal Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines.

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