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Review Article

Recent progress on the traditional Chinese medicines that regulate the blood

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ABSTRACT

In traditional Chinese medicine, the herbs that regulate blood play a vital role. Here, nine herbs including Typhae Pollen, Notoginseng Root, Common Bletilla Tuber, India Madder Root and Rhizome, Chinese Arborvitae Twig, Lignum Dalbergiae Oderiferae, Chuanxiong Rhizoma, Corydalis Tuber, and Motherwort Herb were selected and reviewed for their recent studies on anti-tumor, anti-inflammatory and cardiovascular effects. Besides, the analytical methods developed to qualify or quantify the active compounds of the herbs are also summarized.

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1. Introduction

Traditional Chinese medicine (TCM) has been used clinically for centuries viewed as a major source for new drug discovery. Chemical constituents, mechanism of actions, and clinical evidence have continually drawn thousands of researchers and funding. In traditional medicine theory, the balance of qi and blood is the most important factor for health. Therefore, TCMs that regulate the blood play an important role in treatment. Blood pathology can be divided into three categories in TCM: bleeding, blood stasis, and blood deficiency. Therefore, the herbs that regulate the blood can also be divided into three: those that stop bleeding, those that invigorate the blood, and those that tonify the blood [1]. This review summarizes research from the past 10 years on herbs that regulate the blood, including new mechanisms, usage,

clinical evidence, and analytical methods. Due to the limitations of space and time, only nine herbs were selected in this review: Typhae Pollen, Notoginseng Root, Common Bletilla Tuber, India Madder Root and Rhizome, Chinese Arborvitae Twig, Lignum Dalbergiae Oderiferae, Chuanxiong Rhizoma, Corydalis Tuber, and Motherwort Herb. Some chemical structures of important bioactive compounds from these herbs are shown in Fig. 1.

2. Typhae Pollen (*Typha angustifolia* L., *T. latifolia* L., *T. angustata* Bory et Chaub., *T. orientalis*)

Typhae Pollen traditionally is used to stop bleeding of external traumatic injury, invigorate the blood, and dispel blood stasis [1]. Recent research is as follows.

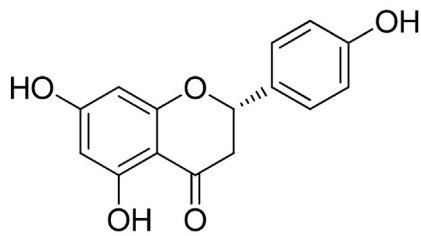
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1. *Typha angustifolia*



(2S)-naringenin

2. *Panax notoginseng*

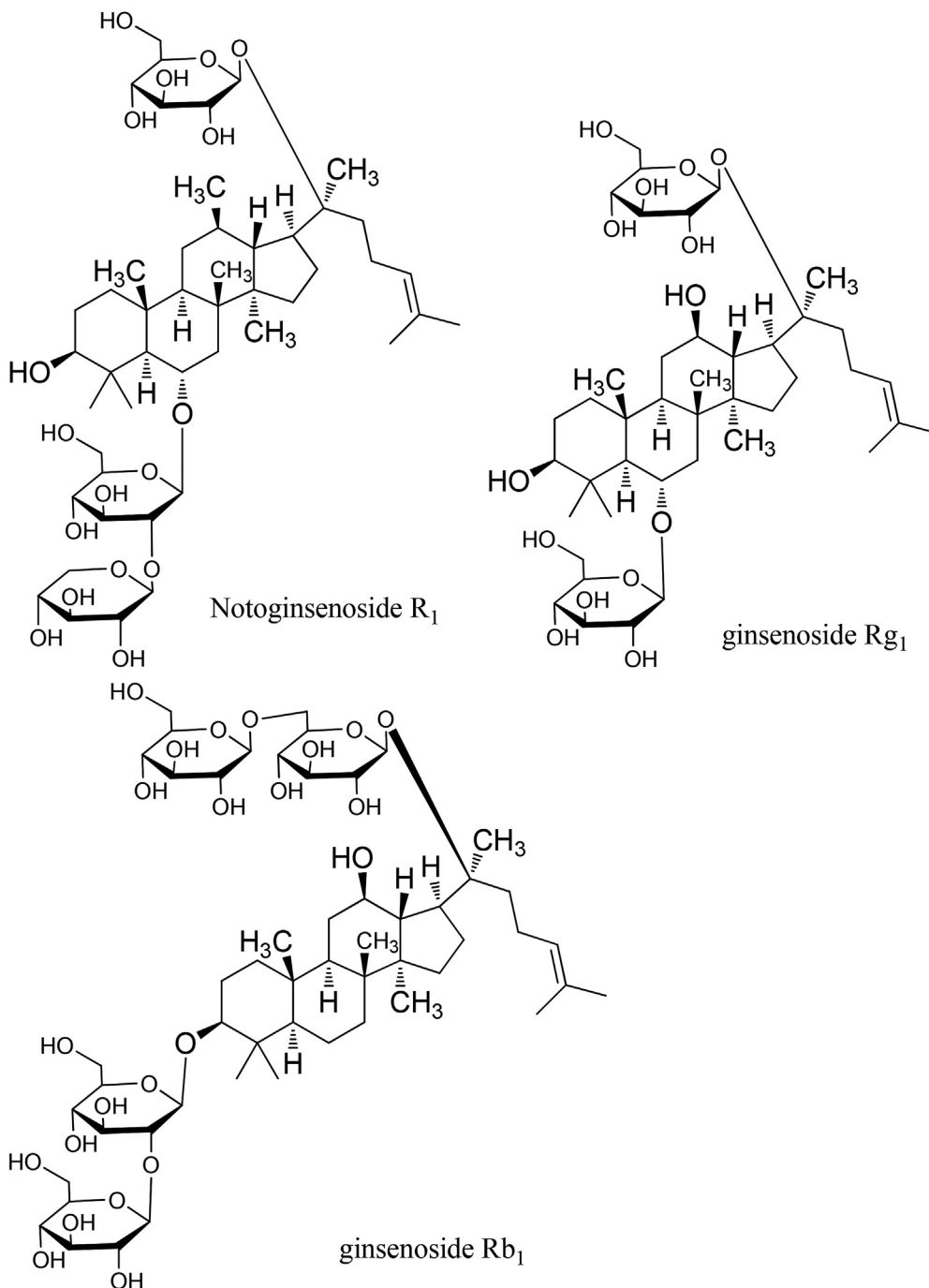
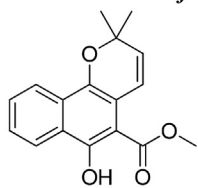
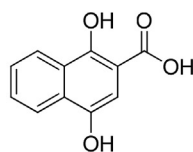


Fig. 1 – Structures of the pure compounds from the herbs that regulate the blood.

3. *Rubia cordifolia*

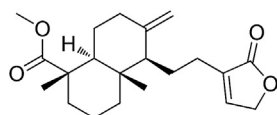


mollugin

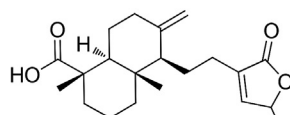


1,4-dihydroxy-2-naphthoic acid

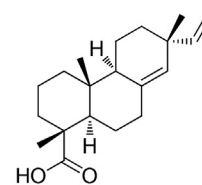
4. *Biota orientalis*



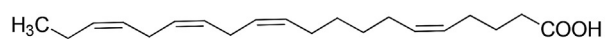
pinusolid



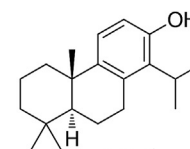
15-methoxypinusolid



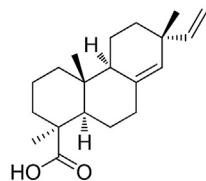
sandaracopimaric acid



Juniperonic acid

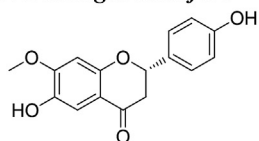


totarol

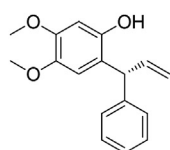


isopimara-8(14),15-dien-19-oic acid

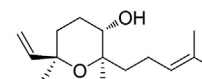
5. *Dalbergia odorifera*



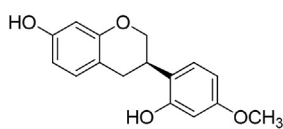
6,4'-Dihydroxy-7-methoxyflavanone



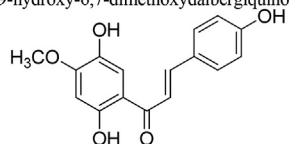
9-hydroxy-6,7-dimethoxydalbergiquinol



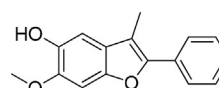
6α-hydroxycyclonerolidiol



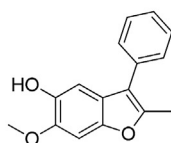
(3R)-vestitol



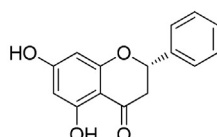
4,2',5'-trihydroxy-4'-methylchalcone



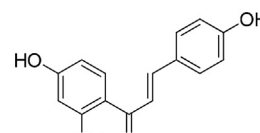
(2R, 3R)-Obtusafuran



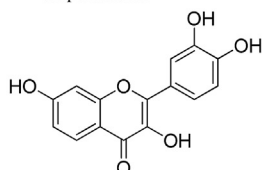
isoparvifuran



(2S)-pinocembrin



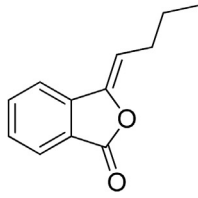
isoliquiritigenin



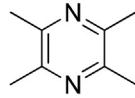
fisetin

Fig. 1 – (continued).

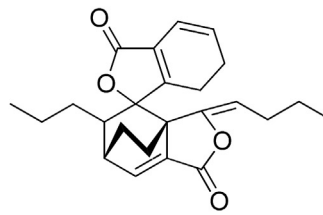
6. *Ligusticum chuanxiong*



butylidenephthalide

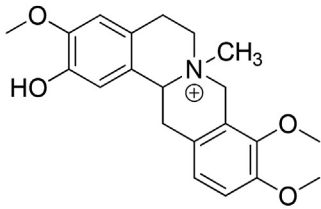


tetramethylpyrazine

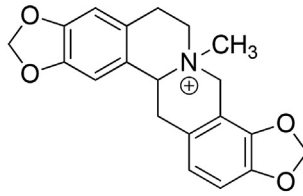


tokinolide B

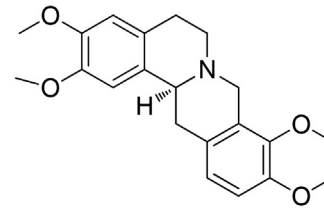
7. *Corydalis yanhusuo*



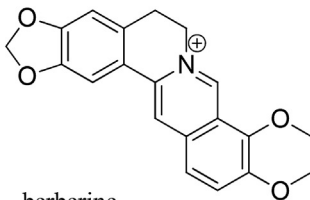
N-methyltetrahydrocolumbamine



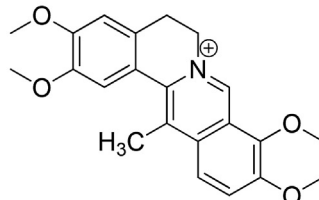
N-methyltetrahydrocoptisine



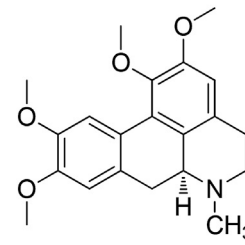
tetrahydropalmatine



berberine

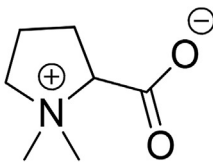


dehydrocorydaline

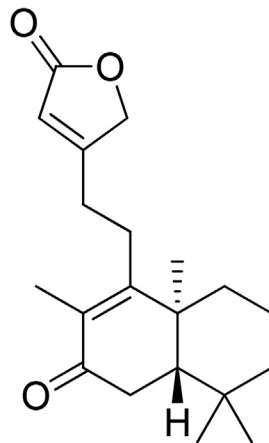


glaucine

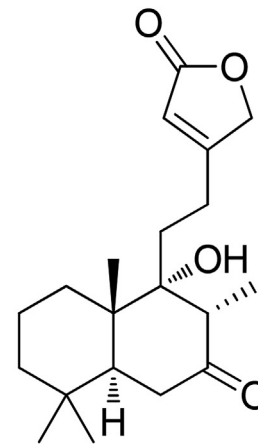
8. *Leonurus heterophyllus*



stachydrine



leoheteronin A



leopersin G

Fig. 1 – (continued).

2.1. Phytoremediation

The recent main focus for this plant is so-called phytoremediation: its ability to remove heavy metal from wetland and recover the soil from heavy metal pollution [2–4].

2.2. Anti-inflammation

The pollen extract (2 µg/mL) may be used for the protection of H₂O₂-induced oxidative damage and dysfunction in MC3T3-E1 osteoblasts, and for the treatment of both acute and chronic inflammatory conditions in carrageenan-induced paw edema studies (500 mg/kg, 250 mg/kg, and 125 mg/kg methanol extract, orally) [5,6]. Dietary supplementation with 10% Typhae Pollen rhizome flour and its combination with prednisolone prevent colonic damage induced by 2,4,6-trinitrobenzenesulfonic acid in rats by improving intestinal oxidative stress, but no synergistic effects were observed [7].

2.3. Cardiovascular effects

(2S)-Naringenin can inhibit proliferation of vascular smooth muscle cells induced platelet-derived growth factor receptor β via a G₀/G₁ arrest and may be valuable for managing atherosclerosis and/or vascular restenosis [8].

3. Notoginseng Root (*Panax notoginseng* (Burk.) F. H. Chen)

Notoginseng Root traditionally is used to stop bleeding and transform blood stasis [1]. There is a lot of research on Notoginseng, therefore, only the recent review articles are summarized as follows.

3.1. Cardiovascular effects

Panax notoginseng saponin (PNS) is one of the most important compounds from roots of the herb *Panax notoginseng*. It has been used as a hemostatic agent to control internal and external bleeding in China for thousands of years. To date, at least 20 saponins have been identified and some of them, including notoginsenoside R₁, ginsenoside Rb₁, and ginsenoside Rg₁, were researched frequently in the area of cardiovascular protection, including the initiation and propagation of atherosclerosis. The mechanism of cardiovascular protection involved anti-oxidation [reduction of oxidized low-density lipoprotein (LDL)], anti-inflammation [reduction of interleukin (IL)-8, IL-1β, matrix metalloproteinase (MMP)-9, MMP-2, nuclear factor (NF)-κB, CD40, IL-6, C-reactive protein, monocyte chemoattractant protein (MCP-1)], and reduction of adhesion monocytes to epithelial cells [intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule-1] [9–11]. Moreover, from 17 randomized clinical trials (17 papers and 1747 participants), oral Notoginseng Root extract, compared with no intervention on the basis of conventional therapy, did not show any significant effect on reducing cardiovascular events, but it could alleviate angina pectoris, including improving the symptoms of angina pectoris, improving electrocardiography, decreasing the recurrence

and duration of angina pectoris, and dose of nitroglycerin. In addition, oral Notoginseng Root extract had a comparable effect to isosorbide dinitrate on angina pectoris [12].

3.2. Anti-diabetes

Recently, hypoglycemic and anti-obesity properties of PNS have been demonstrated. Three major effects of PNS on the factors that are important in the development of diabetes are glucose production, glucose absorption, and inflammatory processes [13].

4. Common Bletilla Tuber (*Bletilla striata* (Thunb.) Reichb. F.)

Common Bletilla Tuber traditionally is used to stop bleeding mainly from the lungs and stomach [1]. Recent research is as follows.

4.1. Biomaterial for drug delivery and wound healing

Satisfactory mechanical features and unique biological functions are expected for the next-generation biomaterials. Several types of polysaccharide from *Bletilla striata* have emerged as new sources for development of biomaterials including drug delivery vehicles and wound healing dressings in varying shapes and sizes. They have demonstrated strong gelling properties, high biocompatibility, and remarkable convenience for processing and modification, as well as response to enzymes produced in special biological niches and/or affinity for carbohydrate receptors on specific cells (Table 1). Besides, a novel mucoadhesive polymer extracted from *Bletilla striata* for ocular delivery of 0.5% levofloxacin in rabbits appears to be a promising candidate as a vehicle for topical ophthalmic drug delivery, especially for antibiotics [14]. In addition, the polysaccharide from Common Bletilla Tuber (100 µL) injection into the subconjunctival space and anterior chamber in rabbits at low concentrations (such as 10 mg/mL) did not have adverse effects [15].

4.2. Anti-inflammation and wound healing

Another study was carried out to evaluate the fibrous root part (FRP), which is usually the discarded and harvested pseudobulb part of *Bletilla striata*. The FRP extracts showed that higher phenolic content was correlated with stronger 2,2-diphenyl-1-picrylhydrazyl scavenging activity, ferric-reducing antioxidant capacity, and tyrosinase inhibition activity, which suggests FRP can be used together with the pseudobulb part [16]. Common Bletilla Tuber polysaccharide hydrogel, prepared by an oxidation and crosslinking method, represents preferable swelling ability, appropriate water vapor transmission rate, and better healing results. The number of infiltrating inflammatory cells and level of tumor necrosis factor (TNF)-α in the Bletilla Tuber polysaccharide hydrogel group are attenuated, whereas secretion of epidermal growth factor is highly elevated [17]. Isolated Common Bletilla Tuber polysaccharide was found to enhance vascular endothelial cell proliferation and vascular endothelial growth factor (VEGF) expression. The

Table 1 – Biomaterials derived from Common Bletilla Tuber.

	BSP	BSPF2	BSPb
	glucomannan-type		
Backbone	<ul style="list-style-type: none"> (1 → 4)-linked β-D-glucopyranosyl residues and (1 → 4)-linked β-D-mannopyranosyl residues Contain cholesteryl succinate 	<ul style="list-style-type: none"> (1 → 4)-linked mannosyl residues and (1 → 4)-linked glucosyl residues (molar ratio of 2:1) About 3/5 of glucosyl residues were branched at O-6 position, and the terminal sugar residues were composed of mannosyl residues. The acetyl content of BSPF2 was estimated to be 2.9% 	<ul style="list-style-type: none"> (1 → 2)-linked α-D-mannopyranose and (1 → 4)-linked β-D-glucopyranose residues.
Content/MW bioactivity	Mannose: glucose = 3.5:1/20 kDa	Mannose: glucose: galactose = 9.4:2.6:1.0/235 kDa BSPF2 significantly induced the spleen cell proliferation in a dose-dependent manner in immunological assay.	Glucose: mannose = 3:1/260 kDa protection against the renal fibrosis effect, probably mediated by down-regulated TGF-βRI, TGF-βRII, and α-SMA in vitro [92]
Refs	[90]	[91]	[92]
	BSP = Bletilla striata polysaccharide; BSPb = Bletilla striata polysaccharide fraction 2; MW = molecular weight; SMA = smooth muscle actin; TGF = transforming growth factor.		

wound healing mechanism could be that Common Bletilla Tuber polysaccharide induces coordinate changes in inducible NO synthase (iNOS), TNF- α , and IL-1 β mRNA levels, and enhances the expression of these cytokines, but has no effect on interferon (IFN)- γ level [18,19].

5. India Madder Root and Rhizome (*Rubia cordifolia* L.)

India Madder Root and Rhizome traditionally is used to stop bleeding, invigorate the blood and dispel blood stasis [1]. Recent research is as follows.

5.1. Anti-inflammation

The plant extracts can elicit over 50% inhibition in NO production in RAW264.7 cells (inhibition > 50% at 100 μ g/mL) [20]. Rat peritoneal macrophages were used to prove that gold nanoparticles embedded in *Rubia cordifolia* matrix had a high therapeutic value relating to the anti-inflammatory characteristics of the nanoparticles by reducing lipopolysaccharide (LPS)-induced NO production [21].

5.2. Anti-tumor effects

Mollugin, a bioactive phytochemical isolated from *Rubia cordifolia* L., has shown preclinical anti-cancer efficacy in various cancer models including MKN45 (gastric cancer cells), MCF-7 (breast cancer cells), A549 (lung cancer cells), HT29 (colon cancer cells), U251MG and U87MG (glioblastoma cells). The suppression of cell viability (glioblastoma, U251MG and U87MG cells) was due to the induction of mitochondrial apoptosis and autophagy. Notably, blockade of autophagy by a chemical inhibitor or RNA interference enhanced the cytotoxicity of mollugin. Further experiments demonstrated that phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin/p70S6 kinase, and extracellular signal-regulated kinase (ERK) signaling pathways participated in mollugin-induced autophagy and apoptosis [22]. In human oral squamous cell carcinoma cells, mollugin induces cell death in a dose-dependent manner in primary (NH4) and metastatic (NH12) oral squamous cell carcinoma cells (IC₅₀ 40–80 μ M, 72 hours). Western blot analysis and reverse transcriptase polymerase chain reaction revealed that mollugin suppressed activation of NF- κ B and NF- κ B-dependent gene products involved in anti-apoptosis (Bcl-2 and Bcl-xl), invasion (MMP-9 and ICAM-1), and angiogenesis (fibroblast growth factor-2 and VEGF). Furthermore, mollugin induced the activation of p38, ERK, and C-Jun N-terminal kinase (JNK) and expression of heme oxygenase (HO)-1 and nuclear factor E2-related factor 2 (Nrf2). Mollugin-induced growth inhibition and apoptosis of HO-1 were reversed by an HO-1 inhibitor and Nrf2 siRNA [23].

5.3. Inhibition of osteoclastogenesis

Rubia cordifolia extract (0.25 mg/mL, containing alizarin 4.8 mg/g extract) was found to inhibit osteoclastogenesis. Apoptosis increased significantly when cells were exposed to

Table 2 – Analytical articles of the herbs that mentioned in this article.

Herb	Objective	Method	Refs
<i>Typha angustifolia</i>	Quantification of 11 major flavonoids in the pollen of <i>Typha angustifolia</i> .	<ul style="list-style-type: none"> HPLC-PDA-MS Apollo C18 column (250 × 4.6 mm, 5 μm), 35 °C Gradient elution of acetonitrile-water and 0.05% formic acid (v/v) Flow-rate of 0.8 mL/min 	[93]
	Determination of nucleosides and nucleobases in the pollen of <i>Typha angustifolia</i> .	<ul style="list-style-type: none"> UPLC-PDA-MS Acuity UPLCHSS T3 column (100 mm × 2.1 mm, 1.8 μm, C18), 35 °C Gradient elution of 5mM ammonium acetate and methanol solution Flow-rate of 0.3 mL/min Total time < 12 min 	[94]
<i>Panax notoginseng</i>	Determine notoginsenoside R ₁ , ginsenoside Rg ₁ , ginsenoside Re and ginsenoside Rb ₁ in samples of <i>P. notoginseng</i>	<ul style="list-style-type: none"> Tchebichef moment method to analyze 3D fingerprint spectra: HPLC-DAD Waters C-18 column (4.6 mm × 250 mm, 5 μm) Gradient elution of acetonitrile-water 	[95]
	Rapid and non-destructive quantification of <i>Panax notoginseng</i> powder containing adulterants	<ul style="list-style-type: none"> Visible and NIR spectroscopy Two calibration methods of partial least square regression and least-squares support vector machines 	[96]
	<ul style="list-style-type: none"> Develop a rapid and precise method to monitor the macroporous resin column chromatography adsorption process in real time 	<ul style="list-style-type: none"> NIR spectra, UV spectra Uninformative variable elimination by partial least squares regression models 	[97]
	<ul style="list-style-type: none"> Quantification of notoginsenoside R₁, ginsenoside Rg₁, ginsenoside Re, ginsenoside Rb₁ and ginsenoside Rd 	<ul style="list-style-type: none"> Direct analysis in real-time MS utilizing a surface flowing mode sample holder 	[98]
	<ul style="list-style-type: none"> Qualitative and quantitative determination of 20(S)-protopanaxatriol saponins and 20(S)-protopanaxadiol saponins in <i>Panax notoginseng</i>, <i>Panax ginseng</i> and <i>Panax quinquefolium</i> 	<ul style="list-style-type: none"> HPLC-ELSD, HPLC-MS Agilent SB-C₁₈ column (250 mm × 4.6 mm, 5 μm) and an Agilent SB-C₁₈ guard column (12.5 mm × 4.6 mm, 5 μm) Gradient elution of acetonitrile and water Flow rate: 1.1 mL/min The Alltech ELSD conditions were optimized as follows: 45 °C of drift tube temperature and 1.2 L/min of nebulizer nitrogen gas flow rate. 	[99] This ref has provided the refs of several analytical methods reported before.
	<ul style="list-style-type: none"> Using chemometrics and its ability to distinguish between different plant parts to help assure the identity and quality of the botanical raw materials and to support the safety and efficacy of the botanical drug products. 	<ul style="list-style-type: none"> HPLC UPLC capillary electrophoresis and NIR spectroscopy 	[100]
<ul style="list-style-type: none"> Dencichine in <i>Panax notoginseng</i> and related species 	<ul style="list-style-type: none"> HPLC-DAD Eprogen Synchropak WAX column (4.6 × 250 mm, 6 μm) 50mM NaH₂ PO₄ aqueous solution isocratic elution 	[101]	
<i>Dalbergia odorifera</i>	<ul style="list-style-type: none"> Quantification of 10 major flavonoids from 60% methanol extract 	<ul style="list-style-type: none"> Reverse-phase liquid chromatography Agilent Zorbax SB-C18 column (250 mm × 4.6 mm, 5 μm) gradient of acetonitrile and 0.3% (v/v) aqueous acetic acid Flow rate of 0.8 mL/min Detected at 275 nm The complete separation was obtained within 55 min for the 10 target compounds. 	[102]
	<ul style="list-style-type: none"> 10 flavonoids: butin, (3R)-4'-methoxy-2',3,7-trihydroxyisoflavanone, liquiritigenin, melanettin, violanone, visticone, formononetin, dalbergin, sativanone and medicarpin 	<ul style="list-style-type: none"> HPLC-ESI-MS parallel with DAD Zorbax SB-C₁₈ column (250 × 4.6 mm, 5 μm) with a Zorbax SB-C₁₈ guard column (20 × 4 mm, 5 μm), 40 °C 	[103]
	<ul style="list-style-type: none"> Qualitative characterization of flavonoids 23 flavonoids, including six isoflavones, six neoflavones, four 		

(continued on next page)

Table 2 – (continued)

Herb	Objective	Method	Refs
	isoflavanones, three flavanones, two chalcones, one isoflavanonol and one pterocarpan	<ul style="list-style-type: none"> • Gradient elution of acetonitrile and 0.3% aqueous acetic acid (v/v) • Flow rate was 0.8 mL/min • Collision-induced dissociations of the [M-H]⁻ ions were studied to clarify the MS behavior of the different types of flavonoids. In negative ion ESI-MS all the flavonoids yielded prominent [M-H]⁻ ions in the first-order mass spectra. Fragments involving losses of CH₃, H₂O, CO, C₂H₂O, and CO₂ were observed in the MS/MS spectra. Each of the seven types of flavonoid showed characteristic MS/MS fragmentation patterns. The isoflavanones, flavanones and chalcones were observed to undergo retro-Diels–Alder fragmentations. The spectra of almost all the neoflavonoids unexpectedly exhibited only [M-H-CH₃]⁻ radical anions as base peaks without any further fragmentation. Substitution positions also remarkably influenced the fragmentation behavior, which could assist in distinction among the flavonoid isomers. The fragmentation rules deduced here could aid in the characterization of other flavonoids of these types. 	
<i>Dalbergia odorifera</i> T. Chen and <i>Scutellaria baicalensis</i> Georgi	<ul style="list-style-type: none"> • Qualitative characterization of 82 flavonoids • Orthogonal parallel separation and accurate molecular weight confirmation 	<ul style="list-style-type: none"> • XTerra MS C(18) column • a home-made Click OEG (Oligo(ethylene glycol)) column, and a Click CD (β-cyclodextrin) column 	[104]
<i>Ligusticum</i> <i>chuanxiong</i> Hort.	<ul style="list-style-type: none"> • Extract ferulic acid, senkyunolide I, senkyunolide H, senkyunolide A, ligustilide and levistolide A from <i>Ligusticum chuanxiong</i> rhizomes. 	<ul style="list-style-type: none"> • High-pressure ultrasound-assisted extraction • The best extraction conditions were as follows: extraction solvent: 40% ethanol; pressure: 10 MPa; particle size: 80 mesh; liquid-to-solid ratio: 100:1; extraction temperature: 70 °C; ultrasonic power, 180 W; and extraction time, 74 min. 	[105]
<i>Ligusticum</i> <i>chuanxiong</i> Hort.	<ul style="list-style-type: none"> • Senkyunolide I metabolites in rats after its intravenous administration. 	<ul style="list-style-type: none"> • UPLC/Q-TOF-MS • The nonmetabolized parent compound and 18 metabolites (methylation, hydration, epoxidation, glucuronidation and glutathione conjugation) from drug-treated samples in rat plasma, urine and bile were identified. 	[106]
	<ul style="list-style-type: none"> • Fingerprint analysis 	<ul style="list-style-type: none"> • Ultra-fast liquid chromatography coupled with DAD 	[107]
Bu-yang-huan-wu-tang (<i>Astragalus membranaceus</i> , <i>Angelica sinensis</i> , <i>Paeonia lactiflora</i> , <i>Ligusticum chuanxiong</i> , <i>Carthamus tinctorius</i> , <i>Amygdalus persica</i> and <i>Pheretima aspergillum</i>)	<ul style="list-style-type: none"> • Cycloartane-type triterpene glycosides of astragaloside I, astragaloside II and astragaloside IV; isoflavones of formononetin, ononin calycosin, calycosin-7-O-β-d-glucoside; ligustilide and paeoniflorin 	<ul style="list-style-type: none"> • LC-ESI-MS/MS • C18 column with gradient elution of methanol/10 mM ammonium acetate buffer-formic acid (100:0.1, v/v) 	[108]
<i>Corydalis yanhusuo</i> W.T. Wang and its formula Jin Ling Zi San (combination of <i>Corydalis Rhizoma</i> and <i>Toosendan</i> <i>Fructus</i>)	<ul style="list-style-type: none"> • Vinegar and wine processing on the content of the main alkaloids of <i>Corydalis Rhizoma</i> was investigated • Eleven alkaloids from <i>Corydalis Rhizoma</i>, namely protopine, α-allocryptopine, 	<ul style="list-style-type: none"> • HPLC-DAD • In the two water decoctions, wine and vinegar processing increased the amount of tertiary alkaloids. • The differences were more pronounced for Jin Ling Zi San, in which case the content of all tertiary alkaloids (protopine, α-allocryptopine, 	[109]

Table 2 – (continued)

Herb	Objective	Method	Refs
Corydalis yanhusuo W.T. Wang	tetrahydrocolumbamine, coptisine, palmatine, berberine, dehydrocorydaline, dl-tetrahydro-palmatine, THB, corydaline and tetrahydrocoptisine	tetrahydrocolumbamine, tetrahydro-palmatine, tetrahydroberberine, corydaline, tetrahydrocoptisine) was increased by wine processing.	
	• THB, a racemic mixture of (+)- and (–)-enantiomer in rat plasma	<ul style="list-style-type: none"> • Chiral HPLC • Chiral-AD column using methanol:ethanol (80:20, v/v) as the mobile phase at the flow rate 0.4 mL/min. • UV detection was set at 230 nm. • The calibration curves were linear over the range of 0.01–2.5 µg/mL for (+)-THB and 0.01–5.0 µg/ml for (–)-THB, respectively. The lower limit of quantification was 0.01 µg/mL for both (+)-THB and (–)-THB. • Mean plasma levels of (–)-THB were higher at almost all time points than those of (+)-THB. (–)-THB also exhibited greater C(max), and AUC(0–∞), smaller CL clearance and V(d) volume of distribution. 	[110]
	• Optimal extraction condition for extracting quaternary ammonium alkaloid dehydrocorydaline	<ul style="list-style-type: none"> • pH-zone-refining counter-current chromatography with normal phase elution • Chloroform–methanol–water (2:1:1, v/v), in which the lower organic phase containing 10mM triethylamine was used as the mobile phase, while the upper aqueous phase containing 10mM hydrochloric acid was used as the stationary phase. • Recovery for dehydrocorydaline and palmatine was 85 and 86%, respectively. 	[111]
	• Purification of alkaloids	<ul style="list-style-type: none"> • HPLC • Polar-copolymerized stationary phase named C18HCE • About 6.8 mg palmatine (HPLC purity > 98%) and 44.4 mg dehydrocorydaline (HPLC purity > 98%) were rapidly derived from 200 mg crude alkaloid sample, and the recoveries of these two compounds were 76.5 and 81.7%, respectively. 	[112]
	• Quaternary alkaloids in ethanol extract of <i>Corydalis yanhusuo</i>	<ul style="list-style-type: none"> • HPLC-ESI-MS/MS • C18 column • Mobile phase was water (0.2% acetic acid, 0.1% triethylamine, v/v)-acetonitrile (24:76, v/v) • Recovery: 97–105% 	[113]
	• Alkaloids in <i>Corydalis yanhusuo</i>	<ul style="list-style-type: none"> • 2D preparative multi-channel parallel HPLC • off-line mode using the same preparative chromatographic column with pH 3.5 in the first and pH 10.0 in the second separation dimension • 1st: UV; 2nd: UV and MS 	[114]
	• Alkaloids in <i>Corydalis yanhusuo</i>	<ul style="list-style-type: none"> • UPLC-Q-TOF-MS-MS • Sixteen alkaloids were screened out 	[115]
	• Qualitative and quantitative determination of alkaloids in <i>Corydalis yanhusuo</i> .	<ul style="list-style-type: none"> • HPLC-UV and MS • Ten alkaloids, including seven tertiary alkaloids and three quaternary alkaloids, were identified by comparing their retention times, UV and MS spectra with those of authentic compounds. 	[116]
	• Quantification of the 10 alkaloids in <i>Corydalis yanhusuo</i> from methanol and ethyl acetate extract of different origins		
	• Direct determination of dl-tetrahydro-palmatine in <i>Corydalis yanhusuo</i>	<ul style="list-style-type: none"> • l-THP imprinted monolithic precolumn on-line/off-line coupling with reversed-phase HPLC • The l-THP imprinted monolithic column has been prepared by in situ polymerization using 	[117]

(continued on next page)

Table 2 – (continued)

Herb	Objective	Method	Refs
	<ul style="list-style-type: none"> Chiral resolution of the enantiomers of <i>dl</i>-tetrahydropalmatine and THB 	methacrylic acid and ethylene dimethacrylate as functional monomer and cross-linker, respectively. <ul style="list-style-type: none"> HPLC Cellulose tris(3,5-dimethylphenylcarbamate) chiral stationary phases Methanol as mobile phase without any basic additives 	[118]

ELSD = Evaporative Light-scattering Detector.
 DAD = diode array detection; ESI = electrospray Ionization mass spectrometry; HPLC = high-performance liquid chromatography; MS = mass spectrometry; NIR = near infrared; PDA = photodiode array; Q-TOF-MS = quantitative time of flight MS; THB = tetrahydroberberine; THP = tetrahydropalmatine; UPLC = Ultra Performance Liquid Chromatography.

the highest concentration of *Embllica officinalis*, *Hemidesmus indicus*, and *Rubia cordifolia* (2 mg/mL) [24].

5.4. Skin disease treatment

Psoriasis is a chronic inflammatory skin disorder characterized by epidermal keratinocyte hyperproliferation, abnormal differentiation, and inflammatory infiltration. The anthraquinone precursor, 1,4-dihydroxy-2-naphthoic acid, was identified from the ethyl acetate extract and can induce HaCaT keratinocyte apoptosis ($IC_{50} = 38 \mu\text{M}$, 72 hours), via G0/G1 cell cycle arrest through both caspase-dependent and caspase-independent pathways [25]. 1,4-Dihydroxy-2-naphthoic acid has similar apoptotic effects as dithranol, which is commonly used to treat psoriasis in many countries but causes less irritation [25]. The topical application of *Rubia cordifolia* root extract and rose oil obtained from *Rosa* spp. flowers stimulated keratinocyte differentiation in mouse models by skin-barrier-reinforcing properties [26].

6. Chinese Arborvitae Twig (*Biota orientalis* (L.) Endl.)

Chinese Arborvitae Twig traditionally is used to stop bleeding [1]. Recent research is as follows.

6.1. GABA receptor

An ethyl acetate extract of *Biota orientalis* leaves (100 $\mu\text{g/mL}$) potentiated γ -aminobutyric acid (GABA)-induced control current by $92.6 \pm 22.5\%$ in *Xenopus laevis* oocytes expressing GABA(A) receptors ($\alpha_1\beta_2\gamma(2S)$ subtype). Isopimaric acid and sandaracopimaric acid were identified as the compounds responsible for the activity via high-performance liquid chromatography activity profiling. The highest efficiency was reached on α_2 - and α_3 -containing receptor subtypes. In the open field test, intraperitoneal administration of sandaracopimaric acid induced a dose-dependent decrease in locomotor activity in mice (3–30 mg/kg). No significant anxiolytic activity was observed at this dose range [27].

6.2. Inhibition of leukotriene C4 generation

Pinusolide can inhibited 5-lipoxygenase-dependent leukotriene C4 generation in IgE/antigen-induced bone-marrow-derived mast cells in a concentration-dependent manner (1–10 μM) via suppression of calcium influx and JNK phosphorylation [28].

6.3. Anti-inflammation

Pinusolide and its derivative, 15-methoxypinusolidic acid (15-MPA), suppressed NO generation by suppressing iNOS, and exerted anti-inflammatory functions. 15-MPA, not pinusolide, suppressed adipocyte differentiation in a dose-dependent manner (10–200 μM), as revealed by lipid droplet formation and expression of adipogenic genes dependent on peroxisome proliferator-activated receptor- γ , such as adiponectin and adipocyte protein 2 (aP2) [29]. In addition, 15-MPA induced apoptosis in murine microglial cells (12.5–50 μM), presumably via inhibition of cell cycle progression [30]. Moreover, 15-MPA can inhibit LPS-induced iNOS expression and NO production, independent of mitogen-activated protein kinase (MAPK) and NF- κ B in microglial cells [31]. As microglial activation is detrimental in central nervous system (CNS) injuries, these data suggest a strong therapeutic potential of 15-MPA.

6.4. Anti-tumor effects

Juniperonic acid (Δ -5c, 11c, 14c, 17c-20:4), a polymethylene-interrupted fatty acid, has anti-proliferative activity in Swiss 3T3 cells treated with bombesin, a mitogenic neuropeptide. The eicosapentaenoic acid-like (EPA-like) activity of juniperonic acid may be involved in the pharmacological activity of biota seeds, a psychoactive TCM [32].

6.5. Antifibrotic effects

The antifibrotic effect of 12 diterpenes from the 90% methanolic fraction was evaluated using rat hepatic stellate cell line HSC-T6, by assessing cell proliferation and morphological changes. Among these diterpenes, totarol and isopimara-8,15-dien-19-oic acid (1 μM , 10 μM and 100 μM) dose- and time-dependently reduced cell proliferation and caused different patterns of morphological changes [33].

7. Lignum *Dalbergiae Oderiferae* (*Dalbergia odorifera* T. Chen)

Lignum *Dalbergiae Oderiferae* traditionally is used to stop bleeding, invigorate the blood and dispel blood stasis [1]. Recent research is as follows.

7.1. Osteoclastogenesis

6,4'-Dihydroxy-7-methoxyflavanone (DMF) can inhibit receptor activators of nuclear factor κ -B ligand (RANKL) induced osteoclastogenesis dose-dependently (10–30 μ M). In addition, DMF decreased osteoclast function through disruption of actin ring formation and consequently suppression of the pit-forming activity of mature osteoclasts. Mechanistically, DMF inhibited RANKL-induced expression of NFATc1 (NF of activated T cells, cytoplasmic, calcineurin-dependent 1), and c-Fos via inhibition of the MAPK pathway [34]. 9-Hydroxy-6,7-dimethoxydalbergiquinol (HDDQ) dose-dependently (10–40 μ M) inhibited the early stage of RANKL-mediated osteoclast differentiation in bone marrow macrophages, without cytotoxicity. HDDQ prevented osteoclast differentiation via downregulation of Akt, c-Fos, and NFATc1 signaling molecules [35].

7.2. Antibacterial and antifungal effects

A sesquiterpene, 6 α -hydroxycyclonerolidiol (25 μ L, 20 mg/mL), showed an inhibitory effect on *Candida albicans* (inhibition zone diameter of 9.21 mm) and *Staphylococcus aureus* (inhibition zone diameter of 11.02 mm) by paper disk diffusion [36]. Flavonoids, sativanone, (3R)-vestitone, (3R)-2',3',7'-trihydroxy-4'-methoxyisoflavanone, (3R)-4'-methoxy-2',3,7'-trihydroxyisoflavanone, carthamidin, liquiritigenin, isoliquiritigenin, (3R)-vestitol, and sulfuretin were evaluated for their inhibitory activity against *Ralstonia solanacearum*. (3R)-Vestitol showed the strongest antibacterial activities (inhibition zone diameter of 16.62 mm) [37].

7.3. Anti-inflammation

4,2',5'-Trihydroxy-4'-methoxychalcone inhibited cyclooxygenase-2 and iNOS expression (5–40 μ M), leading to a reduction in cyclooxygenase-2-induced prostaglandin E2 and iNOS-induced NO production in LPS-stimulated murine peritoneal macrophages by inducing the expression of anti-inflammatory HO-1 via the Nrf2 pathway [38]. Neuroinflammation is a key mechanism against infection, injury, and trauma in the CNS. 6,4'-Dihydroxy-7-methoxyflavanone, latifolin, (2R, 3R)-obtusafuran, and isoparvifuran (1–20 μ M) effectively modulates the regulation of antioxidative and anti-inflammatory action, via upregulation of HO-1 in hippocampal neuronal cell line HT22 and BV2 microglia [39,40]. In addition, (2R, 3R)-obtusafuran and latifolin also reduced TNF- α and IL-1 β production [41]. 9-Hydroxy-6,7-dimethoxydalbergiquinol (5–40 μ M) can reduce neurodegenerative diseases caused by neuroinflammation [42]. Ethyl acetate-soluble fraction was found to inhibit LPS-induced NO production in RAW 264.7 cells. (2S)-Pinocembrin was characterized as the most potent inhibitory effect with an IC₅₀ value of 18.1 μ M [43]. Two

flavonoids, 4,2',5'-trihydroxy-4'-methoxychalcone and (2S)-6,7,4'-trihydroxyflavan, along with 14 known flavonoids and two known arylbenzofurans, were isolated from the heartwood of *Dalbergia odorifera*. Of the isolates, eight compounds were found to have a potent protective effect on glutamate-induced oxidative injury in HT22 cells. (2S)-6,4'-Dihydroxy-7-methoxyflavan was the most effective with EC₅₀ 2.85 μ M [44]. Isoliquiritigenin (1–10 μ M) is reported to exert anti-inflammatory effects by effectively inducing HO-1 [45].

7.4. Anti-tumor effects

Methanol extract of the root of *Dalbergia odorifera* showed the strongest MMP inhibitory activity. Fisetin has been characterized as the effective compound via fractionation methods. In addition, fisetin inhibits MMP-1, MMP-3, MMP-7, MMP-9 and MMP-14 more efficiently than a naturally occurring MMP inhibitor tetracycline. Fisetin (10–100 μ M) dose-dependently inhibits proliferation of fibrosarcoma HT-1080 cells and human umbilical vascular endothelial cells (HUVECs), MMP-14-mediated activation of proMMP-2 in HT-1080 cells, invasiveness of HT-1080 cells, and *in vitro* tube formation of HUVECs, suggesting a valuable chemopreventive agent [46].

7.5. Anti-diabetes

Ethyl acetate-soluble fraction had a remarkable inhibitory effect on α -glucosidase. (2S)-Liquiritigenin, (2S)-4',6'-dihydroxy-7-methoxyflavanone, and isoliquiritigenin inhibit yeast α -glucosidases, as shown by ultrafiltration liquid chromatography/mass spectrometry [47]. Besides, 11 isoflavones, medicarpin (1), formononetin (2), mucronulatol (3), (3R)-calussequinone (5), (3R)-5'-methoxyvestitol (6), tectorigenin (7), biochanin A (8), tuberosin (9), calycosin (10), daidzein (11), and genistein (12), as well as a flavone, liquiritigenin (4), from two leguminous plant extracts, the heartwood extract of *Dalbergia odorifera* and the roots extract of *Pueraria thunbergiana* were screened for yeast α -glucosidase inhibitory activity. The IC₅₀ values were calculated as 2.93 mM (1), 0.51 mM (2), 3.52 mM (7) 0.35 mM (8), 3.52 mM (9), 0.85 mM (11), and 0.15 mM (12), while that of reference drug acarbose was calculated as 9.11 mM *in vitro* [48].

7.6. Anti-platelet

Two sesquiterpenes from the essential oil of the heartwood of *Dalbergia odorifera* T. Chen showed anti-platelet activity, but poor antithrombotic activity (10 μ mol/mL of compound, anti-platelet inhibition rate = 51.4%) [49].

8. Chuanxiong Rhizoma (*Ligusticum chuanxiong Hortorum*)

Chuanxiong Rhizoma traditionally is used to invigorate the blood and promote the movement of qi [1]. Modern research indicates that organic acids, phthalides, alkaloids, polysaccharides, ceramides, and cerebrosides are the main components responsible for the bioactivities. The studies before

2012 are summarized in two reviews [50,51]. The most recent 2 years research is as follows.

8.1. K^+ channel blockade

Butylidenephthalide (30–300 μ M) significantly enhanced tension in isolated guinea pig trachea, with a mechanism similar to 4-aminopiridine, a blocker of the Kv1 family of K^+ channels [52].

8.2. Anti-inflammation

The rhizome ethanolic extract (600 mg/kg/day, orally) significantly reduced body weight gain, improved serum lipid profiles (by lowering total cholesterol and LDL-cholesterol but raising high-density lipoprotein-cholesterol), and protected vascular endothelium in ovariectomized rats fed a high-fat diet. It is postulated that this extract could exert its vascular protective effect through multiple targets by: (1) improving serum lipid profiles; (2) reducing the reactive oxygen species (ROS) level in the body via enhancing the hepatic antioxidative activity or antioxidant level to scavenge the ROS generated during postmenopausal hypercholesterolemia; (3) stimulating endothelial-NOS-derived NO production; and (4) counteracting the upregulation of inflammatory cytokine (TNF- α , vascular cell adhesion molecule-1 and ICAM-1) expression so as to reduce endothelial damage [53].

8.3. Neuroinflammation

Microglial cells are the prime effectors in immune and inflammatory responses of the CNS. Negative regulators of microglial activation have been considered as potential therapeutic candidates to target neurodegeneration, such as that in Alzheimer's and Parkinson's diseases. Neuroprotective potential of tetramethylpyrazine (TMP) has been demonstrated in neuropathic animal models. TMP (300–400 μ g/mL) significantly inhibited the A β 25-35 and IFN- γ -stimulated productions of NO, TNF- α , IL-1 β , MCP-1, and intracellular ROS from primary microglial cells, and effectively reduced A β 25-35 and IFN- γ -elicited NF- κ B activation. In organotypic hippocampal slice cultures (OHSCs), TMP significantly blocked A β 25-35-induced ROS generation and phosphorylation of Akt. TMP also inhibited A β 1-42-induced TNF- α and IL-1 β production in primary microglial cells and neuronal death in OHSCs [54]. Butylidenephthalide (25–400 μ M) significantly inhibited the LPS-induced production of NO, TNF- α and IL-1 β in rat brain microglia. In OHSCs, butylidenephthalide clearly blocked the effect of LPS on hippocampal cell death and inhibited LPS-induced NO production in culture medium, suggesting a neuroprotective effect of butylidenephthalide by reducing the release of various proinflammatory molecules from activated microglia [55]. Among 12 phthalides from Chuanxiong Rhizoma, tokinolide B (50 μ M) showed significant inhibitory effects against LPS-induced NO production in LPS-triggered RAW 264.7 macrophages [56].

8.4. Anti-cancer

Chuanxiong Rhizoma extract was shown to have a great effect on ERBB2 gene expression, and synergistically with estrogen,

to stimulate MCF-7 cell growth, which provides important information that may affect clinical treatment strategies among breast cancer patients receiving hormonal or targeted therapies [57]. Chuanxiong Rhizoma alcohol extract (0.183–1.5 mg/mL) can inhibit the proliferation of pancreatic cancer HS 766 T cells and lead to apoptosis via reduced intracellular Ca^{2+} concentration. The cell cycle was blocked in G0/G1 phase, and the cell membrane was damaged [58]. Hypertrophic scarring, a common proliferative disorder of dermal fibroblasts, results from overproduction of fibroblasts and excessive deposition of collagen. Essential oil from the rhizome, prepared as a liposomal formulation, was tested on hypertrophic scars formed in a rabbit ear model. The treatment significantly alleviated hypertrophic scars. The levels of transforming growth factor- β 1, MMP-1, collagen I, and collagen III were evidently decreased, and caspase-3 and -9 levels and apoptotic cells were markedly increased in the scar tissue. The scar elevation index was also significantly reduced. Histological findings exhibited significant amelioration of the collagen tissue, suggesting a potential effective cure for human hypertrophic scars [59].

8.5. Cardiovascular effects

Apolipoprotein-E-deficient mice treated with the extract full of lactones (30 mg/kg and 60 mg/kg) showed significant reduction in lesion size in thoracic segments of the aorta, and decreased serum triglyceride, total cholesterol and LDL-cholesterol levels, as well as expression of CD31, ICAM-1, MCP-1, and NF- κ B in the atherosclerotic plaques [60]. Two new phthalides, chuanxiongdilolides A and B (50 μ M, 25 μ L), showed different degrees of inhibitory effects against butyrylcholine esterase (inhibitory rates: 36% and 21%, respectively) [61]. In ovariectomized rats, the ethanol extract (600 mg/kg/day, orally) reduced body weight gain, improved serum lipid profile, treated nonalcoholic fatty liver disease, and protected the vascular endothelium [62]. All these effects may be associated with antioxidant or vasorelaxant compounds, suggesting a promising natural supplement for postmenopausal women to prevent nonalcoholic fatty liver disease and cardiovascular disease [62]. Ferulic acid (100 mg/kg, intravenously) exerted a neuroprotective effect by regulating the Akt/glycogen synthase kinase-3 β /collapsin response mediator protein-2 signaling pathway, and ameliorated the injury-induced increase of collapsin response mediator protein-2 in focal cerebral ischemia [63]. Ligustrazine (tetramethylpyrazine) not only significantly inhibits L-type calcium current I in a concentration-dependent manner (10 μ M, 20 μ M, 40 μ M and 80 μ M) but also suppresses calcium transient and contraction in the absence and presence of isoprenaline in rabbit ventricular myocytes [64]. A meta-analysis of 25 randomized controlled trials was performed to evaluate the clinical effect of ligustrazine on diabetic nephropathy. The randomized controlled trials included 1645 patients (858 in the treatment group and 787 in the control group). Compared with the control group, ligustrazine injection had a significant therapeutic effect of improving renal function (blood urea nitrogen [BUN] and serum creatinine [SCr] and reducing in urine protein in patients with diabetic nephropathy [65].

9. Corydalis Tuber (*Corydalis yanhusuo* W.T. Wang.)

Corydalis Tuber traditionally is used to invigorate the blood and alleviate pain [1]. The recent research is as follows.

9.1. κ -Opioid receptor agonists

Two *N*-methyltetrahydroprotoberberines, *N*-methyltetrahydrocolumbamine and *N*-methyltetrahydrocoptisine, with κ -opioid receptor agonist activities ($EC_{50} = 220 \mu\text{M}$ and $170 \mu\text{M}$) were isolated using 2D-liquid chromatography with C18HCE (Polarcopolymerized stationary phase) as the first dimension and a strong cation exchange column as the second dimension [66].

9.2. GABA A receptor

Tetrahydropalmatine (THP; 25 mg/kg) given via intraperitoneal injection results in significant anxiolysis and decreased motor movements. Furthermore, flumazenil, 3 mg/kg, does not fully antagonize the effects of THP [67].

9.3. Hyperalgesia

Common chemotherapeutic agents such as oxaliplatin often cause neuropathic pain during cancer treatment. This study found that l-THP (1–4 mg/kg, intraperitoneally) produced a dose-dependent antihyperalgesic effect, involving a dopamine D1 receptor mechanism, in a mouse model of oxaliplatin-induced neuropathic pain [68].

9.4. Acetylcholinesterase inhibition

In a bioassay-guided search for acetylcholinesterase (AChE) inhibitors from Chinese natural resources, eight isoquinoline alkaloids, tetrahydropalmatine, corydaline, protopine, berberine, palmatine, jatrorrhizine, coptisine, and dehydrocorydaline, were isolated from the methanolic extract of the tubers of *Corydalis yanhusuo*. Berberine exhibited the most potent effect ($IC_{50} = 0.47 \pm 0.01$). Structure–activity relationship analysis suggested that aromatization at ring C, as well as substitutions at C-2, C-3, C-9, C-10 and C-13 affect the AChE activity of protoberberine alkaloids [69].

9.5. Drug addiction/dopamine receptor

l-Isocorypalmine (tetrahydrocolumbamine, l-ICP), a monodemethylated analog of l-tetrahydropalmatine, acts as a D₁ partial agonist and a D₂ antagonist to produce its *in vivo* effects. Administration of l-ICP (10 mg/kg) before cocaine once a day for 5 days reduced cocaine-induced locomotor sensitization on Days 5 and 13 after 7 days of withdrawal. Pretreatment with l-ICP before cocaine daily for 6 days blocked cocaine-induced CPP, while l-ICP itself did not cause preference or aversion, which suggests that l-isocorypalmine is a promising agent for treatment of cocaine addiction [70]. Formalin-evoked spontaneous nociceptive responses (licking behavior) were inhibited significantly by giving (intralingival) the total alkaloids of *Corydalis yanhusuo* in a single dose of 150 mg/kg.

Subsequently, an online comprehensive 2D biochromatography method with a silica-bonded human serum albumin column in the first dimension and a monolithic ODS column in the second screened 13 bioactive components in *Corydalis yanhusuo*: protopine, tetrahydrocolumbamine, glaucine, tetrahydropalmatine, corydaline, palmatine, berberine, dehydrocorydaline, canadine, tetrahydrocoptisine, fumaricine, columbamine, and dehydrocorybulbine [71].

9.6. Dopamine receptor

Bioactivity-guided fractionation of *Corydalis yanhusuo* has resulted in the isolation of eight known isoquinoline alkaloids: tetrahydropalmatine, isocorypalmine, stylophine, corydaline, columbamine, coptisine, 13-methylpalmatine, and dehydrocorybulbine. The isolated compounds were screened for their binding affinities at the dopamine D₁ receptor. Isocorypalmine had the highest affinity ($K_i = 83\text{nM}$). The structure–affinity relationships of these alkaloids are discussed [72].

9.7. Pain

Oral administration of a single dose of the extracts of *Corydalis yanhusuo* and *Angelica dahuricae* (low dose: 3.25 g raw herbs; high dose: 6.5 g raw herbs) significantly decreased pain intensity in humans in a dose-dependent manner, which may have clinical value for treating mild to moderate pain [73].

9.8. Cardiovascular effects

l-THP (20 mg/kg) exerted cardioprotective in rat myocardial ischemia-reperfusion injury by activating the phosphatidylinositol 3-kinase/Akt/endothelial NOS/NO pathway, increasing expression of hypoxia-inducible factor-1 α and VEGF, depressing iNOS-derived NO production in myocardium, decreasing accumulation of inflammatory factors, including TNF- α and myeloperoxidase, and lessening the extent of apoptosis [74]. Alcohol extract (200 mg/kg/day or 50 mg/kg/day) from the rhizome significantly improved heart function and prevented cardiac hypertrophy, with parallel reductions in myocardial fibrosis, as demonstrated by reduced left ventricular (LV) collagen volume fraction CVF and reduced levels of type I collagen on pressure-overloaded cardiac hypertrophy induced by transverse abdominal aorta constriction in rats [75]. Administration of ethanol extract *Corydalis yanhusuo* (50 mg/kg/day, 100 mg/kg/day or 200 mg/kg/day for 8 weeks in a rat heart failure model) led to a significant reduction in infarct size, LV/body weight ratio, lung/body weight ratio, inhibition of neurohormonal activation, and improvement in cardiac function, as demonstrated by lower LV end-diastolic pressure and elevated $+/-dp/dt(\text{max})$, suggesting a cardioprotective effect [76]. The extract from *Corydalis yanhusuo* (200 mg/kg or 100 mg/kg) also exerted a protective effect in a myocardial ischemia/reperfusion injury rat model by inhibition of myocardial apoptosis through modulation of the Bcl-2 family [77].

9.9. Anti-inflammation

Dehydrocorydaline (6–24 μM) reduced the viability of macrophage-derived RAW264.7 cells and primary

macrophages in the presence of LPS by inhibiting the elevation of mitochondrial membrane potential and inducing ATP depletion in LPS-stimulated macrophages [78]. THP inhibited LPS-induced IL-8 production in a dose-dependent manner by blocking MAPK phosphorylation in the human monocytic cell line, THP-1 [79].

9.10. Anti-tumor effects

The ethanol extract (50–200 µg/mL) inhibited MCF-7 cell proliferation by inducing G2/M cell cycle arrest, which might be mediated by inducing ROS formation, decreasing $\Delta\Psi_m$, and regulating cell-cycle-related protein expression [80]. The quaternary protoberberine alkaloids and the tertiary protoberberine alkaloids exhibited potent aromatase binding activities (extract 2 mg/mL; pure compound 100 µM). The quaternary ammonium group and the methyl group at C-13 position of tertiary protoberberine alkaloids might be necessary for the activity [81]. Both extract and its active compound berberine significantly suppressed the VEGF-triggered ERK1/2 pathways upregulation of MMP-2 at both mRNA and protein levels [82]. The extract (3–30 µg/mL) inhibited the migration and invasion of MDA-MB-231 cells *in vitro*, involving the activation of p38 and inhibition of ERK1/2 and stress-activated protein kinase/JNK MAPK signaling [83]. Glaucine (3.125–50 µM) inhibits P-glycoprotein and MRP1-mediated efflux and activates ATPase activities of the transporters, indicating that it is a substrate and inhibits P-glycoprotein and multidrug resistance protein 1 (MRP1) competitively. Furthermore, glaucine suppresses expression of ABC transporter genes. It reverses the resistance of MCF-7/ADR to adriamycin and mitoxantrone effectively [84].

9.11. Motherwort Herb (*Leonurus heterophyllus* Sweet)

Motherwort Herb traditionally is used to invigorate the blood and regulate menses [1]. Recent research is as follows.

9.12. Neurite outgrowth-promoting effect

Four new spirocyclic nortriterpenoids, leonurusoleanolide A, leonurusoleanolide B, leonurusoleanolide C, and leonurusoleanolide D, were isolated from the methanol extract of the fruits of Motherwort Herb. Mixtures of all four nortriterpens significantly enhanced the neurite outgrowth of PC12 cells treated with nerve growth factor, at concentrations of 1–30 µM [85].

9.13. Cardiovascular effects

Alkaloid extract from Motherwort Herb at 7.2 mg/kg or 14.4 mg/kg induced significantly decreasing neurological deficit scores and reduced the infarct volume in rats with focal cerebral ischemic injury. At these two doses, the myeloperoxidase content was significantly decreased in ischemic brain as compared with a control group. The extract at 14.4 mg/kg significantly decreased the NO level as well as the apoptosis ratio of nerve fiber compared with the control group [86]. Stachydrine (10^{-8} – 10^{-5} M), a major constituent to promote blood circulation and dispel blood stasis, ameliorates HUVEC

injury induced by anoxia–reoxygenation, and its putative mechanisms are related to inhibition of anoxia–reoxygenation and tissue factor expression [87]. Two new cyclic non-peptides (100 µM), cycloleonoripeptide E, cyclo (-Ala-Pro-Ile-Val-Ala-Ala-Phe-Thr-Pro-), and cycloleonoripeptide F, cyclo (-Gly-Tyr-Pro-Leu-Pro-Phe-Tyr-Pro-Pro-), have been isolated from the fruits of Motherwort Herb, and show moderate vasorelaxant effects on rat aorta [88].

9.14. AChE inhibition

Seventy percent ethanol extract of the aerial parts of Motherwort Herb showed significant AChE inhibitory activity. Bioassay-guided fractionation and repeated column chromatography led to the isolation of new labdane-type diterpenoids, leoheteronin F, and six known compounds. Leoheteronin A ($IC_{50} = 11.6 \mu M$) and leopersin G ($IC_{50} = 12.9 \mu M$) with a 15,16-epoxy group at the side chain were found to be potent inhibitors of AChE [89]. In addition, analytical reports regarding these nine herbs are also summarized in Table 2 [93–118].

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