The genus *Porana* (Convolvulaceae) - A phytochemical and pharmacological review

Yu Peng^1,2†, Ye Li^1†, Yuanyuan Yang^3, Yuqing Gao^2, Hui Ren^1, Jing Hu^1, Xiaomin Cui^3, Wenjing Lu^1, Hongxun Tao^4* and Zhiyong Chen^1*

^1Shaanxi Academy of Traditional Chinese Medicine, Xi’an, Shaanxi, China, ^2Jiangsu Provincial Key Laboratory of Cardiovascular and Cerebrovascular Medicine, School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu, China, ^3Xi’an Institute for Food and Drug Control, Xi’an, Shaanxi, China, ^4School of Food and Biological Engineering, Jiangsu University, Zhenjiang, Jiangsu, China

There are about 20 species of *Porana* Burm. f. worldwide in tropical and subtropical Asia, Africa and neighboring islands, Oceania, and the Americas. In China, India, and other places, this genus enjoys a wealth of experience in folk applications. Nevertheless, the chemical composition of only five species has been reported, and 59 compounds have been isolated and identified, including steroids, coumarins, flavonoids, quinic acid derivatives, and amides. Pharmacological studies revealed that extracts from this genus and their bioactive components exhibit anti-inflammatory, analgesic, antioxidant, anti-gout, anti-cancer, and anti-diabetic effects. Although this genus is abundant, the development of its pharmacological applications remains limited. This review will systematically summarize the traditional and current uses, chemical compositions, and pharmacological activities of various *Porana* species. Network analysis was introduced to compare and confirm its output with current research progress to explore the potential targets and pathways of chemical components in this genus. We hope to increase understanding of this genus’s medicinal value and suggest directions for rational medicinal development.

**KEYWORDS**
Porana burm. f., traditional use, phytochemistry, network analysis, pharmacological activity

**Abbreviations:** Akt, protein kinase B; COX-2, cyclooxygenase-2; C-T-P, compound-target-pathway; FGF-2, fibroblast growth factor 2; HIF, hypoxia inducible factor; HPLC, high performance liquid chromatography; Ig, intragastric administration; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; Ip, intraperitoneal injection; KEGG, Kyoto Encyclopedia of Genes and Genomes; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MDA, malonic dialdehyde; MSU, monosodium urate; MyD88, myeloid differentiation factor 88; NF-κB, nuclear transcription factor-κB; NO, nitric oxide; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PPI, protein-protein interaction; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TLR2, toll-like receptor 2; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.
1 Introduction

There are more than 20 species of Porana Burm. f. worldwide in tropical and subtropical Asia, Africa and neighboring islands, Oceania, and the Americas. Fifteen species are displayed in Table 1 (for more information, see http://www.plantsoftheworldonline.org or www.theplanetlist.org). The global distribution of Porana plants based on the Global Biodiversity Information Facility (https://www.gbif.org/) and the herbarium diagrams of three mainstream species are shown in Figure 1.

Porana plants are vines, woody, herbaceous, or climbing shrubs. Their ovate leaves are mostly cordate at the base, with petioles. The inflorescence morphology of Porana plants is divided into racemes or panicles, with some single-flower forms. Their bracts are leaflike, small and subulate, or absent. Their corollas are neatly arranged, presenting white, reddish, and some lavender. The ovaries are primarily glabrous. Some are one-celled, containing two ovules, while some are one-to two-celled, containing two to four ovules.

Porana plants are relatively small, sub-globose to oblong, dehiscent in two petals, or not dehiscent. Porana plants usually have only one spherical and glabrous seed (Chen et al., 2004).

The medicinal records of Porana plants are extensive. Porana paniculata Roxb. has been used in folk medicine to treat pain and inflammation in Ayurveda and India (Kumar et al., 2015). Porana sinensis Hemsl. is a direct substitute for commercial Dingdongteng medicinal materials and is known for its therapeutic effect on rheumatoid arthritis and bruises (Ren et al., 2019). According to the National Compendium of Chinese Herbal Medicine, the whole plant of Porana racemosa Roxb. is used to treat colds and indigestion (Guoqiang, 2014), while its stems and roots are used to treat rheumatism (Liu and Li, 1997). Research on the phytochemistry of Porana plants focuses on Porana discifera C.K.Schneid., P. racemosa, P. sinensis, Porana spectabilis Kurz, and Porana duclouxii Gagnep. & Courchet; 59 compounds have been isolated from Porana plants, including 14 steroids, six coumarins, seven flavonoids, six quinic acid derivatives, and three amides (Zhu et al., 2007; Li et al., 2013; Ding et al., 2014; Chen et al., 2015; Xue et al., 2019). Pharmacological studies revealed that the extracts of Porana plants and their bioactive compounds treat arthritis (Dou et al., 2013), gout (Chen et al., 2014; Du et al., 2020), inflammation (Wu et al., 2016; Xue et al., 2019), and cancer (Huang et al., 2019).

| No. | Species | Synonyms | Distribution |
|-----|---------|----------|--------------|
| 1   | Porana acuminata P. Beauv. | Neuropeltis acuminata (P. Beauv.) Benth | West Tropical Africa |
| 2   | Porana densiflora Hallier f | Metaporana densiflora (Hallier f.) N.E. Br | Tanzania |
| 3   | Porana dinetoides C.K. Schneid | Dinetus dinetoides (C.K. Schneid.) Staples | Assam, China South-Central, Myanmar |
| 4   | Porana discifera C.K. Schneid | Poranopsis discifera (C.K. Schneid.) Staples | Assam, China South-Central, Laos, Myanmar, Thailand, Vietnam |
| 5   | Porana duclouxii Gagnep. & Courchet | Dinetus duclouxii (Gagnep. & Courchet) Staples | China South-Central |
| 6   | Porana grandiflora Wall | Dinetus grandiflorus (Wall) Staples | East Himalaya, Nepal, Tibet |
| 7   | Porana henryi Verdc. | Poranopsis sinensis (Hand.-Mazz.) Staples | China South-Central |
| 8   | Porana mairei Gagnep | Dinetus decorus (W.W.Sm.) Staples | Assam, China South-Central, Myanmar |
| 9   | Porana paniculata Roxb | Poranopsis paniculata (Roxb.) Roberty | Assam, Bangladesh, East Himalaya, India, Myanmar, Nepal, Pakistan, Tibet, West Himalaya |
| 10  | Porana parvifolia (K. Afzel.) Verdc | Metaporana parvifolia (K. Afzel.) Verdc | Madagascar |
| 11  | Porana racemosa Roxb | Dinetus racemosis (Roxb.) Sweet | Assam, Bangladesh, China North-Central, China South-Central, China Southeast, East Himalaya, India, Jawa, Laos, Lesser Sunda Is., Myanmar, Nepal, Pakistan, Sulawesi, Thailand, Vietnam, West Himalaya |
| 12  | Porana sinensis Hemsl | Tridynamia sinensis (Hemsl.) Staples | China North-Central, China South-Central, China Southeast, Vietnam |
| 13  | Porana spectabilis Kurz | Tridynamia spectabilis (kurz) Parmar | Andaman Is., Assam, Cambodia, China South-Central, China Southeast, Hainan, Laos, Malaya, Myanmar, Thailand, Vietnam |
| 14  | Porana subrotundifolia De Wild | Paralepisitemon shrensis (Oliv.) Lejoly & Lisowski | Angola, KwaZulu-Natal, Malawi, Mozambique, Northern Provinces, Zambia, Zaire, Zimbabwe |
| 15  | Porana velutina (M. Martens & Galeotti) Hallier f | Porana nutans (Choisy) O’Donell | Mexico Central, Mexico Southwest |
Although *Porana* has a wide range of medicinal uses, and its extracts and bioactive compounds show excellent efficacy, current research remains limited, complicating the investigation of its chemical components, pharmacological activities, quality control, and safety. Therefore, it is critical to perform a systematic literature review on *Porana* to promote rational medicinal development.

### 2 Methodology

An extensive search of studies was conducted from scientific journals (original research, reviews, and short communications), books, and reports from internationally recognized databases (Web of Science, PubMed, ScienceDirect, China National Knowledge Infrastructure, and Google Scholar). The following keywords were selected: “Porana,” “pharmacology,” “ethnopharmacology,” “compound,” “phytotherapy,” “biological activity,” “substitute,” “toxicity,” and “quality control.” The bibliographies of all selected articles were scanned to seek additional relevant articles.

### 3 Traditional uses

The medicinal parts of *P. sinensis* are canes, which have been used to substitute for the endangered traditional Chinese medicine *Dinggongteng* (*Erycibes caulis*) in China (Xue et al., 2017). *Dinggongteng* is a traditional Chinese folk medicine, first recorded in the Supplement to Medica, which recorded the effect of dispelling wind and strengthening the waist (Shang, 2004). The National Collection of Chinese Herbal Medicine, the Dictionary of Chinese Herbal Medicine, and the Chinese Materia Medica have documented *Dinggongteng*, which dispels wind and dampness, relaxes tendons, activates collaterals, reduces swelling, and relieves pain. The traditional clinical
application of Dinggongteng has been to treat rheumatoid arthritis, bruises, and other diseases, according to the 2020 edition of the Chinese Pharmacopoeia. With E. caulis as the main medicinal material, and more than ten Chinese patent medicines have been developed, including Feng Liaoxing Rheumatism Dieda Liquor and Tenghuoqing Capsule (Fan et al., 2021; Peng et al., 2021). Dinggongteng is often combined with Cinnamomi ramulus, Ephedrae herba, Angelicae sinensis radix, and other medicinal materials. Wu et al. (2005) investigated the commercial medicinal materials in Guangxi, the main production area for E. caulis, as well as Shanghai, Jiangsu, Zhejiang, and other places, and found that the wild resources of Erycibe obtusifolia Benth. and Erycibe schmidtii Craib could no longer meet the demand for clinical medication. P. sinensis has already become a mainstream substitute for E. caulis on the market. The widespread application of P. sinensis has promoted the sustainable utilization of the endangered traditional Chinese medicine E. caulis while accumulating evidence for the effectiveness and safety of P. sinensis.

P. racemosa is also a traditional folk medicine of the Dai, Yi, and Tujia nationalities in China, and its whole herb is the medicinal part (Fang et al., 2007). According to the National Compendium of Chinese Herbal Medicine, the whole plant of P. racemosa relieves the surface, eliminates food accumulation, and is primarily used for colds and food accumulation (Editorial Board, 1975). Its stem and root treat rheumatism (Liu and Li, 1997). In the treatment of cold and fever, it is often used in combination with Peucedanum praeruptorum and Periliae fructus, while in the treatment of food accumulation, it is often used in combination with Crataegi fructus and Serissa serissoides (Fang et al., 2007). In Guangxi Province, P. spectabilis is used to treat uterine prolapse, with its whole herb as the medicinal part (Li et al., 1985). P. spectabilis contains scopoletin, ethyl caffeate, and other compounds (Zhu et al., 2001); however, no pharmacodynamic study has been reported. According to the Chinese Materia Medica, the root of Porana mairei Gagnep. relieves cough and asthma (Editorial Board, 2009).

In summary, Porana plants are used as folk medicines. The genus has received increasing attention due to the widespread use of P. sinensis as a substitute for E. caulis.

4 Chemical compositions of Porana plants

Based on literature reports and our previous research, we concluded that the research on the phytochemical constituents of this genus focused on P. discifera, P. racemosa, P. sinensis, P. spectabilis, and P. duclouxii. Fifty-nine compounds have been isolated from Porana species, including 14 steroids, six coumarins, seven flavonoids, six quinic acid derivatives, three amides, and 23 other compounds. These compounds are displayed in Table 2 according to their chemical name, chemical type, and their original plants. The structural formulas of these compounds are shown in Figure 2.

4.1 Steroids

Fourteen steroids have been isolated from Porana species, of which 12 were isolated from P. discifera, including compounds 1–10 (Zhu et al., 2000) and 12–13 (Yu et al., 2003); four were found in P. racemosa, including compounds 11–14 (Liu and Li, 1997; Wang, 2003; Li et al., 2004); two were found in P. sinensis, including compounds 12–13 (Zhang et al., 2006). Compounds 1–10 are phytocycloditerpenes, natural polyhydroxylated compounds with a four-ringed skeleton, usually comprising 27 carbon atoms or 28–29 carbon atoms with the characteristic 7-en-6-ketone on the steroid nucleus (Tarkowska and Strnad, 2016). Phytocycloditerpenes are a class of natural steroids with insect ecdisis activity. They also exhibit extensive pharmacological effects on higher animals, including hypoglycemia, wound repair, and immune regulation (Taha-Salaime et al., 2019; Yusupova et al., 2019). Compounds 1–7 have no anti-inflammatory, sedative, anti-convulsant, or anti-cerebra-hypoxic activities in animal testing with Kunming mice (Zhu et al., 2000). Most steroids reported in Porana species have been found in P. discifera. In this case, several issues need to be addressed. Are these compounds also present in other plants of this genus, and can they be used as the chemical indicators of the Porana Burm.? Answering these questions must address the biological activity of steroids among the pharmacological activities of this genus.

4.2 Coumarins

Three coumarin compounds have been isolated from P. racemosa, including compounds 15–17 (Li et al., 2004). Four coumarin compounds have been found in P. sinensis, including compounds 15–16 (Zhang et al., 2006) and 18–19 (Xue et al., 2019). Three coumarin compounds have been reported in P. discifera, including compounds 15–16 and 20 (Yu et al., 2003). Two coumarin compounds are found in P. spectabilis, including compounds 15–16 (Zhu et al., 2001). The coumarins obtained from Porana plants are simple coumarins, and compounds 15 and 16 have been found in four species; these are thought to be the primary pharmacodynamic substances and chemical indicators of E. caulis (Chen et al., 2014; Chen et al., 2020). Therefore, compounds 15 and 16 are essential for applying P. sinensis as a substitute for E. caulis.
| No | Compounds                                         | Molecular formula | Type       | Plant parts and species | References                              |
|----|--------------------------------------------------|-------------------|------------|-------------------------|-----------------------------------------|
| 1  | β-ecdysterone                                     | C_{27}H_{44}O_{7}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 2  | β-ecdysterone-2-acetate                           | C_{29}H_{46}O_{8}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 3  | β-ecdysterone-3-acetate                           | C_{29}H_{46}O_{8}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 4  | β-ecdysterone-25-acetate                          | C_{29}H_{46}O_{8}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 5  | 2,3-acetonide-β-ecdysterone                       | C_{30}H_{48}O_{7}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 6  | 20,22-acetonide-β-ecdysterone                     | C_{30}H_{48}O_{7}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 7  | 2-deoxy-20-hydroxyecdysone                        | C_{30}H_{48}O_{7}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 8  | 2-deoxyecdysterone-20,22-acetonide                | C_{30}H_{48}O_{7}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 9  | 2-deoxyecdysterone-3-O-β-D-glucopyranoside       | C_{33}H_{54}O_{11} | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 10 | Posterone                                         | C_{21}H_{30}O_{5}  | Steroids   | Aerial parts of *P. discifera* | Zhu et al. (2000)                      |
| 11 | Racemosol                                         | C_{30}H_{50}O       | Steroids   | Whole plants of *P. racemosa* | Li et al. (2004)                       |
| 12 | β-sitosterol                                      | C_{29}H_{48}O       | Steroids   | Stems and roots of *P. racemosa* | Liu and Li, (1997); Yu et al., (2003); Zhang et al., (2006) |
| 13 | β-daucosterol                                     | C_{29}H_{48}O       | Steroids   | Whole plants of *P. racemosa* | Wang, (2003); Yu et al., (2003); Zhang et al., (2006) |
| 14 | Stigmasterol                                      | C_{29}H_{48}O       | Steroids   | Whole plants of *P. racemosa* | Wang, (2003)                           |
| 15 | Scopoletin                                        | C_{10}H_{18}O_{4}   | Coumarins  | Whole plants of *P. racemosa* | Zhu, (2001); Yu et al., (2003); Li et al., (2004); Xue et al., (2019) |
| 16 | Scopolin                                          | C_{16}H_{18}O_{9}   | Coumarins  | Whole plants of *P. racemosa* | Zhu, (2001); Yu et al., (2003); Li et al., (2004); Xue et al., (2019) |
| 17 | Umbelliferone                                     | C_{9}H_{6}O_{3}     | Coumarins  | Whole plants *P. racemosa* | Zhu, (2001); Yu et al., (2003); Li et al., (2004); Xue et al., (2019) |
| 18 | Isoisopoletin                                     | C_{14}H_{10}O_{5}   | Coumarins  | Whole plants *P. racemosa* | Zhu, (2001); Yu et al., (2003); Li et al., (2004); Xue et al., (2019) |
| 19 | 7-O-[(4′′,4′′,8′′-trihydroxyiumyl)-β-D-glucopyranosyl]-6-methoxyocoumarin | C_{26}H_{26}O_{11} | Coumarins  | Whole plants *P. racemosa* | Zhu, (2001); Yu et al., (2003); Li et al., (2004); Xue et al., (2019) |
| 20 | Isofraxidin                                       | C_{11}H_{14}O_{5}   | Coumarins  | Leaves and stems of *P. discifera* | Yu et al. (2003)                       |

(Continued on following page)
| No | Compounds                        | Molecular formula | Type               | Plant parts and species                  | References                  |
|----|----------------------------------|-------------------|--------------------|-----------------------------------------|-----------------------------|
| 21 | Quercetin-3-O-β-D-glucopyranoside| C_{21}H_{20}O_{12} | Flavonoids         | Whole plants of *P. racemosa*           | Li et al. (2004)            |
| 22 | Quercetin-3-O-α-L-rhamnopyranoside| C_{21}H_{20}O_{11} | Flavonoids         | Whole plants of *P. racemosa*           | Li et al. (2004)            |
| 23 | Eupatilin                        | C_{21}H_{18}O_{7}  | Flavonoids         | Whole plants of *P. racemosa*           | Li et al. (2004)            |
| 24 | 4′-Hydroxywogonin                | C_{16}H_{12}O_{6}  | Flavonoids         | Leaves and stems of *P. discifera*      | Yu et al. (2003)            |
| 25 | Quercetin                        | C_{15}H_{10}O_{7}  | Flavonoids         | Whole plants of *P. racemosa*           | Wang, (2003); Yu et al., (2003) |
| 26 | Kaempferol-3-O-β-D-glucopyranoside| C_{21}H_{20}O_{11} | Flavonoids         | Whole plants of *P. racemosa*           | Wang, (2003)                |
| 27 | Rutin                            | C_{20}H_{18}O_{16} | Flavonoids         | Whole plants of *P. racemosa*           | Wang, (2003)                |
| 28 | Chlorogenic acid                 | C_{20}H_{12}O_{5}  | Quinic acid derivatives | Stems of *P. sinensis*              | Chen et al., (2013); Chen et al., (2019); Chen et al., (2020) |
| 29 | 4-O-cafeoylquinic acid           | C_{16}H_{18}O_{9}  | Quinic acid derivatives | Stems of *P. sinensis*              | Chen et al., (2013); Chen et al., (2019); Chen et al., (2020) |
| 30 | 5-O-cafeoylquinic acid           | C_{16}H_{18}O_{9}  | Quinic acid derivatives | Stems of *P. sinensis*             | Chen et al., (2019); Chen et al., (2020) |
| 31 | 3,4-dicaffeoylquinic acid        | C_{22}H_{22}O_{12} | Quinic acid derivatives | Stems of *P. sinensis*             | Chen et al., (2019); Chen et al., (2020) |
| 32 | 4,5-dicaffeoylquinic acid        | C_{22}H_{22}O_{12} | Quinic acid derivatives | Stems of *P. sinensis*             | Chen et al., (2019); Chen et al., (2020) |
| 33 | 3,5-dicaffeoylquinic acid        | C_{22}H_{22}O_{12} | Quinic acid derivatives | Stems of *P. sinensis*             | Chen et al., (2019); Chen et al., (2020) |
| 34 | (E)-N-2-(2,3-dihydroxyphenyl) ethyl cinnamamide | C_{17}H_{17}NO_{3} | Amides | Whole plants of *P. racemosa* | Li et al. (2004) |
| 35 | N-trans-feruloyltryramine        | C_{18}H_{19}NO_{4} | Amides             | Stems of *P. sinensis*                | Zhang et al. (2006)         |
| 36 | N-trans-coumaroyltryramine       | C_{17}H_{17}NO_{3} | Amides             | Stems of *P. sinensis*                | Zhang et al. (2006)         |
| 37 | Methyl β-D-frucopyranoside       | C_{7}H_{14}O_{6}   | Others             | Whole plants of *P. racemosa*          | Zhu et al., (2001); Li et al., (2004) |
| 38 | Syringaresinol-4-O-β-D-glucopyranoside | C_{20}H_{18}O_{13} | Others              | Whole plants of *P. racemosa*          | Zhu et al., (2001); Li et al., (2004) |
| 39 | Poranaiside A                    | C_{20}H_{18}O_{10} | Others             | Roots of *P. duclouxii*               | Ding et al. (2014)          |
| 40 | Poranic acid A                   | C_{20}H_{18}O_{10} | Others             | Roots of *P. duclouxii*               | Ding et al. (2014)          |
| 41 | Poranic acid B                   | C_{20}H_{18}O_{12} | Others             | Roots of *P. duclouxii*               | Ding et al. (2014)          |
| 42 | Disciferitriol                   | C_{15}H_{28}O_{3}  | Others             | Aerial parts of *P. discifera*         | Zhu et al. (2007)           |
| 43 | Cassiachromone                   | C_{13}H_{16}O_{4}  | Others             | Leaves and stems of *P. discifera*     | Yu et al. (2003)            |
| 44 | Vanillic acid                    | C_{8}H_{8}O_{4}    | Others             | Whole plants of *P. racemosa*          | Wang, (2003)                |
| 45 | Ethyl 4′-hydroxy-3′-methoxycinnamate | C_{13}H_{14}O_{4}  | Others             | Whole plants of *P. racemosa*          | Wang, (2003)                |
| 46 | Lupeol                           | C_{30}H_{50}O      | Others             | Whole plants of *P. racemosa*          | Wang, (2003)                |
| 47 | α-amyrin acetate                 | C_{32}H_{58}O_{16} | Others             | Whole plants of *P. racemosa*          | Wang, (2003)                |

(Continued on following page)
4.3 Flavonoids

Six flavonoids have been isolated from *P. racemosa*, including compounds 21–23 (Li et al., 2004) and 25–27 (Wang, 2003). Two flavonoids were found in *P. discifera*, including compounds 24–25 (Yu et al., 2003). Flavonoids are very common in plants. According to reports, no characteristic flavonoid has been found in this genus; this might be due to the lack of reports on the chemical constituents of *Porana* plants. However, several characteristic isoflavones, pterocarps, and rotenoids were identified in *Erycibes* plants (Peng et al., 2021). Based on this, we speculate that flavonoids might be the components differentiating *Porana* from *Erycibes*. Considering flavonoids’ excellent biological activity, exploring such compounds should not be ignored.

4.4 Quinic acid derivatives

Six quinic acid derivatives have been reported in the *Porana* species, including compounds 28–33 (Chen et al., 2013; Chen et al., 2019; Chen et al., 2020), all from *P. sinensis*. Our fingerprint study has revealed that *Porana dinetoides* C.K.Schneid., *P. racemosa*, and *P. duclouxii* also contained quinic acid derivatives (Figure 3). Because many quinic acid derivatives have been detected in fingerprints, this group of compounds can be used as chemical markers for quality control, and this potential deserves further evaluation.

4.5 Amides

Three amides have been isolated from *Porana* plants, among which compound 34 has been found in *P. racemosa* (Li et al., 2004) and compounds 35–36 have been found in *P. sinensis* (Zhang et al., 2006). The chemical structures of the three amides are similar. It was reported that compound 36 has better activity than compound 35 in inhibiting nitric oxide (NO) release from lipopolysaccharide (LPS)-induced RAW 264.7 cells, suggesting that introducing a methoxy group at the two-position reduces the anti-inflammatory activity of these compounds (Zheng et al., 2018).

4.6 Other compounds

Twenty-three compounds were found in *Porana* species, including one lignin (compound 38), one monoterpenoid (compound 55), two sesquiterpenes (compound 42, 54), three triterpenoids (compound 46, 47, 57), one benzoquinone (compound 49), seven phenols (compounds 44, 45, 48, 50, 51, 53, 59), one stilbene (compound 58), five glycosides compounds (compound 37, 39–41, 52), one chromosome (compound 43), and one cyclohexanol (compound 56). There are many phenolic acids and their derivatives in *Porana* plants. Resin glycosides are characteristic of constituents in Convolvulaceae, and three such compounds (compounds 39–41) have been isolated.
from *Porana* plants (Ding et al., 2014). Compounds 39–41 all have a common trisaccharide moiety and (11S)-hydroxytetradecanoic acid or (3S,11S)-dihydroxytetradecanoic acid as the aglycone. These 23 compounds have not shown any regularity. There is no evidence to assess the importance of these compounds regarding quality control or biological activity.

In summary, only five species of *Porana* plants have been reported, with a total of 59 compounds to date. Combined with the literature reports and fingerprints, phenolic acids and coumarins are widely represented in this genus. Phytoecdysteroids and resin glycosides have specific characteristics; however, their distribution is narrow in this genus. This finding suggests that there might be substantial differences in the chemical compositions of these plants, and a phytochemical study of other species needs to be performed urgently.

### 5 Pharmacological activities of *Porana* plants

#### 5.1 Network analysis of *Porana* plants

Because the research on this genus is not systematic, to maximize its medicinal value, we first predicted its targets based on its chemical components using network analysis. Using follow-up comparisons with reported pharmacological research results, the pharmacological effects of this genus were explored.
5.1.1 Enrichment of critical targets

The two-dimensional structures of all 59 compounds found in Porana plants were identified in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/search/), their sdf files were downloaded, and they were imported into the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) to predict their targets (Gfeller et al., 2014). After removing the duplicate targets, the potential targets were obtained. We obtained 713 targets in this manner.

5.1.2 The construction and topological parameter analysis of a protein-protein interaction network

All 713 targets obtained in section 5.1.1 were imported into the STRING platform (https://string-db.org/) to construct a PPI network. The topological parameters of the PPI network were calculated and analyzed using Cytoscape 3.6.0. The critical targets were determined with greater values of the degree, closeness centrality, and betweenness centrality than the mean value. This analysis revealed that the mean degree of potential target nodes was 39.5, the mean value of closeness centrality was 0.4326, and the mean value of betweenness centrality was 0.0019. The output was 135 targets with a higher value than the corresponding mean.

5.1.3 Kyoto encyclopedia of genes and genomes pathway enrichment analysis

To explore the related signaling pathways of the 135 targets obtained in Section 5.1.2, the targets were imported into DAVID (https://david.ncifcrf.gov/home.jsp), with the species limited to humans. KEGG pathway enrichment analysis was performed to identify the relevant signaling pathways. After removing specific diseases such as prostate cancer, viral carcinogenesis, glioma, or other irrelevant items, with \( p < 0.01 \) as the screening condition, the top 20 most significant pathways were selected for the subsequent enrichment analysis using R language software (Supplementary Table S1). As shown in Figure 4, the abscissa (enrichment) of the bubble chart represents the ratio of the core targets involved in each pathway to the total number of targets in the pathway; the size of the bubble represents the number of core targets involved in the pathway; the color ranges from red to green, indicating that the \( p \)-value is from small to large, and deeper redness indicates the higher significance of the pathway.

5.1.4 The construction and analysis of the compound-target-pathway network

According to the top 20 pathways of gene enrichment in the KEGG pathway enrichment analysis, the potential targets and the corresponding components enriched in these pathways were outputted. The data table of the C-T-P was imported into Cytoscape 3.6.0 to construct the C-T-P network with a total of 148 nodes (20 pathways, 73 targets, 55 components) and 772 edges. Then the Network Analyzer was used to calculate the topology parameters of the C-T-P network, while a Degree Sorted Circle Layout was applied to lay out nodes. The C-T-P network topology parameters were also analyzed using Network Analyzer, and the results are displayed in Supplementary Table S2. The mean degree of the 55 differentially active components was 7.29, the mean value of closeness centrality was 0.3505, and the mean value of betweenness centrality was 0.0067. Three network topology parameters with 17 components were higher than the corresponding mean value (compounds 1–5, 7, 16–17, 23–25, 34–36, 45, 48, and 50). The mean degree of the 73 potential target nodes was 10.58, the mean value of closeness centrality was 0.3704, and the mean value of betweenness centrality was 0.0048.
centrality was 0.3732, and the mean value of betweenness centrality was 0.0122. Three network topology parameters of 20 targets were higher than the corresponding mean value (MAPK1, PIK3CA, AKT1, MAP2K1, MAPK3, EGFR, MMP2, PRKCA, ESR2, GSK3B, MAPK14, ESR1, PIK3R1, NRAS, SRC, PTGS2, MMP9, TNF, KDR, and ADORA3). The mean degree of the 20 pathways was 18.55, the mean value of closeness centrality was 0.4054, and the mean betweenness centrality was 0.0254. Three network topology parameters of six signaling pathways were higher than the corresponding mean value (PI3K-Akt, HIF-1, estrogen, MAPK, chemokine, and the thyroid hormone signaling pathway).

The results of the network analysis revealed 17 active compounds in *Porana* species, including six steroids, three flavonoids, three amides, two coumarins, and three organic acid esters. In the follow-up quality control study, critical research should be carried out on the actual content of these compounds. Coumarins are widely distributed in *Porana* species, present in *P. sinensis*, *P. racemosa*, *P. discifera*, and *P. spectabilis*. Taking coumarin scopolin as an example, its targets include GSK3B, EGFR, MAPK1, IL2, HSPA8, MMP9, HK1, GAPDH, TNF, ADORA3, acting on PI3K-Akt, HIF-1, estrogen, MAPK, and other signaling pathways. Scopolin promotes the differentiation of osteoblasts and inhibits the decrease of bone mineral density, participating in osteoporosis treatment (Park et al., 2020), possibly associated with the regulation of the estrogen pathway. Intrapertioneal injection of scopolin alleviates the symptoms of adjuvant arthritis in rats by inhibiting inflammatory responses and angiogenesis (Pan et al., 2009); the mechanisms might involve the PI3K-Akt, HIF-1, and MAPK signaling pathways (Park et al., 2015; Qu et al., 2016; Yang et al., 2018).

*Porana* plants are widely used in traditional Chinese and Indian medicine to relieve inflammation and pain and to treat rheumatoid arthritis. Recent studies demonstrated that the PI3K-Akt pathway inhibits apoptosis in chondrocytes, and modulation of the pathway might be a potential target for the therapy of rheumatic arthritis (Malemud, 2015). HIF-1α increases the production of inflammatory cytokines and promotes angiogenesis in rheumatic arthritis patients (Park et al., 2015). We reported that the 40% ethanol extract of *P. sinensis* alleviates rheumatoid arthritis by regulating the PI3K-Akt and HIF-1 signaling pathways (Hu et al., 2022).

*P. racemosa* is another plant in the genus *Porana* with well-documented medicinal applications, which could be used for the treatment of colds. The results of network analysis revealed its primary active components to be scopolin, umbelliferone, eupatilin, and quercetin, which act on AKT1, EGFR, MAPK1, NFkB1, PIK3R1, SRC, TNF, and other targets to regulate PI3K-Akt, MAPK, and the chemokine signaling pathway, indicating the main involvement of inflammatory pathway. MAPK participates in cell proliferation, differentiation, transformation, and apoptosis regulation through phosphorylation of nuclear transcription factors, cytoskeletal proteins, and enzymes (Yeung et al., 2018). PI3K-Akt regulates survival, cell growth, differentiation, cellular

![FIGURE 4](image-url) Analysis of KEGG pathway.
### TABLE 3 Bioactivities of the extracts of *Porana* plants.

| No. | Extracts       | Species          | Part     | Condition                | Quality control                                                                 | Activity                                | Model                      | Results                                                                 | References |
|-----|----------------|------------------|----------|--------------------------|--------------------------------------------------------------------------------|------------------------------------------|---------------------------|-------------------------------------------------------------------------|------------|
| 1   | 40% ethanol extract | *P. sinensis*    | Stem     | 40% ethanol ultrasonic extraction | HPLC, scopolin 20.07 mg/g, chlorogenic acid 33.86 mg/g, scopoletin 7.68 mg/g plant material | Anti-inflammatory and anti-nociceptive activities | In vivo: Xylene-induced ear edema, formalin induced inflammation, carrageenan-induced mice air pouch inflammation in mice, acetic acid-induced writhing, formalin-induced nociception; ig, 143, 285, and 570 mg/kg; positive control: dexamethasone 2 mg/kg, aspirin 200 mg/kg, paracetamol 100 mg/kg | Inhibit the ear swelling, the synthesis of PGE2, reduce the number of writhings, and relieve phase II pain in mice | Chen et al. (2013) |
| 2   | 80% methanol extract | *P. sinensis*    | Stem     | 80% methanol ultrasonic extraction | HPLC, scopolin 1.95 mg/g, chlorogenic acid 2.55 mg/g, scopoletin 0.25 mg/g plant material | Anti-inflammatory activity | In vitro: LPS-induced RAW 264.7 cells, 25, 50, 100 μg/ml | Inhibit LPS-induced RAW 264.7 release of NO, and iNOS, COX-2 and IL-6 mRNA expression | Xue et al. (2017) |
| 3   | 40% ethanol extract | *P. sinensis*    | Stem     | 40% ethanol reflux extraction | HPLC, 5-O-caffeoylquinic acid 13.4628 mg/g, scopolin 12.6935 mg/g, chlorogenic acid 48.5457 mg/g, 4-O-cafeoylquinic acid 8.2953 mg/g, scopoletin 20.9330 mg/g, 3,4-dicaffeoylquinic acid 28.6063 mg/g, 3,5-dicaffeoylquinic acid 13.5660 mg/g, 4,5-dicaffeoylquinic acid 18.3498 mg/g plant material | Anti-inflammatory activity | In vitro: LPS-induced RAW 264.7 cells, 120 μg/ml; positive control: methotrexate 120 μg/ml | In vivo: Collagen-induced arthritis model; ig, 0.6, 0.3, and 0.15 g/kg; positive control: methotrexate 1 mg/kg | Inhibit the release of NO, TNF-α, IL-1β and IL-6 in LPS-induced RAW 264.7 cell; attenuate the severity, pathological changes, and release of cytokines (IL-6 and HIF-1α) during rheumatoid arthritis progression by regulating the PI3K/AKT and HIF-1 pathways | Hu et al. (2022) |
| 4   | 60% ethanol extract | *P. paniculata*   | Whole plants | Cold maceration method | Total flavonoids 59.86 mg/g of quercetin, total phenols 33.34 mg/g of gallic acid | Anti-oxidant Activity | In vitro: DPPH assay, superoxide anion scavenging activity assay, nitric oxide scavenging activity assay, hydrogen peroxide scavenging assay and metal chelating activity, 20, 40, 60, 80 and 100 μg/ml; positive control: L-ascorbic acid, butylated hydroxyanisole, alpha tocopherol, 20, 40, 60 and 100 μg/ml | Present good anti-oxidant activity | Kumar et al. (2015) |
| 5   | 80% methanol extract of ten samples | *P. sinensis*    | Stem     | 80% methanol ultrasonic extraction | HPLC, chlorogenic acid, 4-O-cafeoylquinic acid, 5-O-cafeoylquinic acid, 3,4-dicaffeoylquinic | Anti-oxidant Activity | In vitro: DPPH assay; IC50 211–439 μg/ml; positive control: ascorbic acid, IC50 38.65 μmol/L | Present good DPPH scavenging activity, with IC50 values ranging from 211 to 439 μg/ml | Chen et al. (2020) |

(Continued on following page)
metabolism, and cytoskeletal reorganization of cells. Modification of this pathway is strongly implicated in the pathogenesis of most cancers (Malemud, 2015). The treatment of cancers is not a traditional application of Porana plants. Due to the regulatory effect of compounds on multiple anti-cancer pathways, the genus Porana has excellent application prospects in anti-cancer drugs. The targeting pathway of the chemical constituents of Porana species supports the application of this genus in the treatment of rheumatoid arthritis, colds, and cancer. However, the application of Porana plants in treating these diseases needs to be verified in animal and clinical trials.

5.2 Pharmacological activities of the extracts of Porana plants

For the extracts, various preparation methods lead to significant differences in chemical composition and bioactivities. When reviewing the pharmacological effects of Porana extracts, we focused on the following to facilitate identifying the reasons for the differences in pharmacological effects: plant origin and part, extraction methods, quality control methods, biological activities, and screening models (Table 3). Because in vitro studies of extracts have not considered systemic absorption or metabolism of active compounds, the results of these studies might be biased.

5.2.1 Anti-inflammatory and analgesic effects

In a previous study, our group adopted the xylene-induced mouse ear swelling model, the formalin-induced inflammation model, and the carrageenan-induced mice air pouch inflammation model to investigate the anti-inflammatory activity of 40% ethanol extracts of P. sinensis (extract 1). We also applied the mouse acetate acid writhing model and the formalin-induced pain model to investigate its analgesic effects (Chen et al., 2013). We found that the oral administration of extract 1 (570 and 285 mg/kg) inhibits ear swelling in mice by 39.0% and 29.5%, respectively, and the induced inflammation in formalin mice by 37.3% and 30.8%, respectively. In the carrageenan-induced mice air pouch inflammation model, extract 1 significantly inhibits the synthesis of PGE2. Extract 1 significantly reduces the number of writhings in mice and relieves phase II pain in the formalin-induced pain model. The 80% methanol ultrasonic extract of P. sinensis (extract 2) inhibits LPS-induced RAW 264.7 release of NO at 25, 50, and 100 μg/ml, with inhibition of iNOS, COX-2, and IL-6 mRNA expression (Xue et al., 2017). However, this

| No. | Extracts            | Species | Part       | Condition               | Quality control                                                                 | Activity                           | Model            | Results                                                                 | References          |
|-----|---------------------|---------|------------|-------------------------|---------------------------------------------------------------------------------|------------------------------------|------------------|------------------------------------------------------------------------|---------------------|
| 6   | 40% ethanol extract P. sinensis | Stem    | 40% ethanol reflux extraction | HPLC, 5-O-cafeoylquinic acid 6.76 mg/g, scopolin 16.97 mg/g, chlorogenic acid 21.53 mg/g, 4-O-cafeoylquinic acid 7.84 mg/g, scopoletin 4.92 mg/g, 3,5-dicaffeyloyquinic acid 12.41 mg/g, 3,6-dicaffeyloyquinic acid 14.94 mg/g, 4,5-dicaffeyloyquinic acid 18.17 mg/g | Anti-gout Activity                  | In vivo: monosodium urate crystal induced gout arthritis, ig. 1.0, 0.5, and 0.25 g/kg; positive control: colchicine 1.5 mg/kg | Regulate the release of inflammatory factors and oxygen free radicals to prevent and treat gouty arthritis by mediating the TLR2-MyD88 signaling pathway | Du et al. (2020)    |
| 7   | 80% methanol extract of ten samples P. sinensis | Stem    | 80% methanol ultrasonic extraction | HPLC, chlorogenic acid, 4-O-cafeoylquinic acid, 5-O-cafeoylquinic acid, 3,4-dicaffeyloyquinic acid, 4,5-dicaffeyloyquinic acid, 3,5-dicaffeyloyquinic acid, scopolin, scopoletin | Anti-gout Activity                  | In vitro: xanthine oxidase inhibitory activity assay; IC50 26.7-45.5 mg/ml; positive control: allopurinol, IC50 0.01 mmol/L | Present good xanthine oxidase inhibitory activity, with IC50 values ranging from 26.7 to 45.5 mg/ml | Chen et al. (2020) |
study lacked a positive control. COX-2 is a critical enzyme that catalyzes the conversion of arachidonic acid to prostaglandins, and this study confirmed the inhibitory effect of extract I on PGE2 synthesis. We reported that 40% ethanol extract of *P. sinensis* (extract 3) inhibits the release of inflammatory mediators (NO, TNF-α, IL-1β, and IL-6) in LPS-induced RAW 264.7 cells (Hu et al., 2022). Extract 3 attenuates the severity, pathological changes, and release of cytokines (IL-6 and HIF-1α) during rheumatoid arthritis progression by regulating the PI3K/Akt and HIF-1 pathways (Hu et al., 2022).

There are many studies on the anti-inflammatory and analgesic efficacy of the extract of *P. sinensis* *in vitro* and *in vivo*. Compared with methotrexate, aspirin, and other positive control drugs, these extracts’ anti-inflammatory and analgesic effects are insignificant. Except for *P. sinensis*, species such as *P. spectabilis* have been recorded for the treatment of chest pain in folk medicine (Li et al., 1985); however, no experimental verification has been reported.

### 5.2.2 Anti-oxidant activity

As a chronic inflammatory autoimmune disease, rheumatoid arthritis is closely related to oxidative stress (Peng et al., 2021). The 60% ethanol extract (extract 4) of *P. paniculata* presented good anti-oxidant activity in DPPH assay, superoxide anion scavenging activity assay, nitric oxide scavenging activity assay, hydrogen peroxide scavenging assay and metal chelating activity (Kumar et al., 2015). In the superoxide anion scavenging assay, extract 4 exhibited more robust activity than the positive control butylated hydroxyanisole. In the hydrogen peroxide scavenging assay, extract 4 (IC$_{50}$ 25.65 μg/ml) performed almost as well as gallic acid (IC$_{50}$ 24.29 μg/ml). Our group also tested ten batches of 80% methanol extract (extract 5) of *P. sinensis*, all of which showed good DPPH scavenging activity, with IC$_{50}$ values ranging from 211 to 439 μg/ml (Chen et al., 2020). However, the above-mentioned test method for anti-oxidant activity is based on chemical reaction *in vitro*, which is far from practical. Therefore, it is necessary to explore the antioxidant activity *in vivo* to clarify the molecular mechanisms of its antioxidant activity.

### 5.2.3 Anti-gout effect

In a previous study, we applied the strategy of network analysis combined with experimental verification to study the mechanism of the 40% ethanol extract of *P. sinensis* (extract 6) against gout. Extract 6 (0.25, 0.5, 1.0 g/g) dose-dependently reduced joint swelling in rats with monosodium urate (MSU) crystal-induced gout arthritis, with decreased serum MDA and IL-1β levels, and increased serum SOD, TGF-β, and IL-4 levels. By mediating the TLR2-MyD88 signaling pathway, it regulates the release of inflammatory factors and oxygen free radicals to prevent and treat gouty arthritis (Du et al., 2020). Because xanthine oxidase is a target for gout treatment, we tested the xanthine oxidase inhibitory activity of ten batches of the 80% methanol extract of *P. sinensis* (extract 7), revealing its good activity, with IC$_{50}$ values ranging from 26.7 to 45.5 mg/ml (Chen et al., 2020). The treatment of gout-related diseases is not traditionally applied to the genus *Porana*. Although the *in vitro* and *in vivo* experiments demonstrated the anti-gout potential of *P. sinensis*, it remains need to be verified by clinical research. In addition, due to the different extraction methods of these extracts, the active components of anti-gout should be clarified in the future.

### 5.2.4 Toxicity

Only acute toxicity of *P. sinensis* has been reported. No mice died with a single intragastric 40% ethanol extract of *P. sinensis* at 5 g/kg. The weights, behaviors, and anatomical examinations showed no apparent abnormalities within 14 days (Chen et al., 2013). However, because it is a medicinal plant, acute toxicity evaluation is insufficient, and chronic toxicity tests and clinical safety evaluations of *Porana* plants need to be performed.

In summary, the current research on the medicinal effects of *Porana* species concentrates on *P. sinensis*. Although *Porana* is widely distributed, its medicinal value is limited. Especially for *P. racemosa*, which enjoys abundant folk medicinal records and good development prospects, its systematic pharmacodynamic and clinical research is lacking. For the pharmacological study of the extract, to clarify its pharmacodynamic components, chemical analysis is required. Some studies have not provided quality control on the extracts, which would affect the reliability of these studies.

### 5.3 Pharmacological activities of the active constituents of *Porana* plants

To further analyze the pharmacological activities of this genus, we followed the pharmacological studies of compounds in this genus and discussed their correlation with the results of our network analysis. The results are summarized in Table 4.

#### 5.3.1 Anti-inflammatory and analgesic effects

The results of long-term folk medicinal and network analysis indicated that anti-inflammatory and analgesic effects are the primary medicinal effects of *Porana* plants. The intraperitoneal injection of scopoletin (compound 15, 1, 5, 10 mg/kg) reduced serum levels of NO, TNF-α, and PGE2 of carrageenan-induced paw edema mice, and the protein expression of iNOS and COX-2 (Chang et al., 2012). Scopoletin reduced the amount of writhing in the mouse acetate writhing model and formalin-induced pain in the late phase. The anti-inflammatory and analgesic effects of scopoletin (10 mg/kg) are equivalent to that of indomethacin (10 mg/kg) (Chang et al., 2012). However, scopoletin was given by intraperitoneal injection, which would limit its application. In the carrageenan-induced mouse model of pleurisy,
| No. | Compounds  | Activities                                      | Dosage                  | Model                          | Positive control                                                                 | Results                                                                                                                                                                                                 | References                                    |
|-----|------------|-------------------------------------------------|-------------------------|-------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| 1   | Scopoletin | Anti-inflammatory and anti-nociceptive activities | Ip: 1, 5, 10 mg/kg      | Acetic acid induced writhing response, formalin test and \(\alpha\)-carrageenan induced paw edema in ICR mice | Indomethacin, ip, 10 mg/kg                                                       | Reduce the levels of NO, TNF-\(\alpha\), PGE2, and the protein expression of iNOS and COX-2 in the serum of carrageenan-induced paw edema mice, reduce the number of writhing in the mouse acetate writhing model, and the formalin-induced pain in the late phase | Chang et al. (2012)                          |
| 2   | Scopoletin | Anti-inflammatory activity                       | Ip: 0.1, 1, 5 mg/kg     | Carrageenan-induced inflammation in the mouse model of pleurisy                 | Dexamethasone, ip, 0.5 mg/kg                                                       | Reduce serum NO, TNF-a and IL-\(\beta\) levels, and inhibit p65, p38 phosphorylation in mouse lungs                                                                                           | Pereira dos Santos Nascimento et al. (2016) |
| 3   | Scopoletin | Anti-inflammatory activity                       | 15, 30, 60 \(\varnothing\)/L | IL-\(\beta\) induced fibroblast-like synoviocytes                          | -                                                                                | Inhibit the production of IL-6, and the phosphorylation of p38, ERK, PKC and CREB                                                                                                                 | Dou et al. (2013)                            |
| 4   | Scopolin   | Anti-inflammatory and anti-nociceptive activities | Ip: 25, 50, 100 mg/kg   | Adjuvant-induced arthritis in rats                                            | Dexamethasone, ip, 2 mg/kg                                                         | Alleviate the symptoms of adjuvant-induced arthritis by inhibiting the expression of IL-6, VEGF and FGF-2 in synovial tissue                                                                         | Pan et al. (2009)                            |
| 5   | Umbelliferone | Anti-inflammatory activity                         | Oral administration: 20, 40 mg/kg | 2,4-dinitrochlorobenzene and house dust mite extract treated mice             | Dexamethasone, oral administration, 1 mg/kg                                          | Reduce ear thickness, spleen size and weight, serum levels of IgG, IgG1, IgG2a, TNF-a, and IL-4, and mast cell infiltration                                                                          | Lim et al. (2019)                            |
| 6   | Isofraxidin | Anti-inflammatory activity                       | 1, 10, 50 \(\varnothing\)/L | IL-\(\beta\) induced inflammatory response in human osteoarthritis chondrocytes | -                                                                                | Block IL-\(\beta\)-stimulated production of NO and PGE2, inhibit the expression of COX-2, iNOS, MMP-1, MMP-3, MMP-13, ADAMTS-4 and -5, suppress IkB-\alpha degradation and NF-\(\kappa\)B activation | Lin et al. (2018)                            |
| 7   | 3,4-dicaffeoylquinic acid | Anti-inflammatory activity | 35, 70, 140 \(\varnothing\)/L | LPS-induced RAW 264-7 cells                                                   | -                                                                                | Inhibit NO/iNOS and PGE2/COX-2 pathways, block the nuclear translocation of NF-\(\kappa\)B                                                                                                        | Xue et al. (2019)                            |
| 8   | 4,5-dicaffeoylquinic acid | Anti-inflammatory activity | Ig: 10, 20 mg/kg          | Acute airway inflammation induced by ammonia liquor in mice                   | Prednisone acetate, Ig, 10 mg/kg                                                   | Reduce the total leukocytes in the bronchoalveolar lavage fluid                                                                                                                               | Wu et al. (2016)                             |
| 9   | Eupatilin  | Anti-inflammatory activity                       | 1, 10, 100 \(\varnothing\)/L | LPS-stimulated macrophages                                                    | -                                                                                | Inhibit the inflammatory modulators and NF-\(\kappa\)B activation                                                                                                                             | Choi et al. (2011)                           |
| 10  | Eupatilin  | Anti-inflammatory activity                       | 1, 2, 5, 10 \(\varnothing\)/L | Murine arthritis model, human rheumatoid synoviocytes                         | -                                                                                | Inhibit TNF-\(\alpha\)-induced IL-6 and IL-\(\beta\) mRNA                                                                                                                               | Kim et al. (2015)                            |

(Continued on following page)
| No. | Compounds                  | Activities             | Dosage       | Model                                           | Positive control                                                                 | Results                                                                 | References              |
|-----|----------------------------|------------------------|--------------|------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------|
| 11  | Quercetin                  | Anti-inflammatory activity | Oral gavage: 30 mg/kg | Collagen-induced arthritis in C57BL/6 mice | Methotrexate, ip, 0.5 mg/kg                                                       | Decrease serum TNF-a, IL-1β, IL-17, and MCP-1 levels                  | Haleagrahara et al. (2017) |
| 12  | Quercetin                  | Anti-inflammatory activity | ip            | Adjuvant-induced arthritis in C57BL/6 mice; mice air pouch model | Dexamethasone                                                                   | Reduce neutrophil infiltration and promote the apoptosis of activated neutrophils by inhibiting neutrophil activities | Yuan et al. (2020)         |
| 13  | β-ecdysterone              | Anti-inflammatory activity | Subcutaneous injection: 0.6, 0.8, 1.0 mg/kg | Monoiodoacetate-induced osteoarthritis in rats; 3-methyladenine, ip, 30 mg/kg, rapamycin, ip, 1 mg/kg | 3-methyladenine-induced apoptosis of chondrocytes, down-regulate PI3K, p-AKT1, p-mTOR, p-p70S6K and caspase-3 expression, activate autophagy in chondrocytes | Inhibit 3-methyladenine-induced apoptosis of chondrocytes, down-regulate PI3K, p-AKT1, p-mTOR, p-p70S6K and caspase-3 expression, activate autophagy in chondrocytes | Tang et al. (2020)        |
| 14  | N-trans-feruloyltryramine  | Anti-inflammatory activity | 6.25, 12.5, 25, 50 µg/ml | LPS-induced RAW 264.7 cells | -                                                                                 | Suppress mRNA expression of COX-2 and iNOS via suppression of AP-1 and JNK signaling pathway | Jiang et al. (2015)       |
| 15  | Scopoletin                 | Anti-gout activity      | Ip: 50, 100, 200 mg/kg; 30, 100, 300 µmol/L | Monosodium urate (MSU) crystal-induced inflammation in mouse air pouch model; MSU crystal-stimulated RAW 264.7 cells | Prednisolone, ip, 10 mg/kg                                                      | Decrease the number of neutrophils and mononuclear phagocytes of monosodium urate (MSU) crystal-induced inflammation in mouse; suppress the secretions of IL-1β, TNF-a, IL-6, PGE2 and NO in MSU crystal-stimulated RAW 264.7 cells, involving the suppression of NF-kB activation and blockade of MAPK signal pathway | Yao et al. (2012)         |
| 16  | Scopoletin                 | Anti-gout activity      | Ig: 4.9 mg/kg | Monosodium urate crystal induced gout arthritis in rats | Colchicine, ig, 1.5 mg/kg                                                      | Inhibit the production of serum MDA, IL-1β, TGF-β1, promote the release of SOD and IL-4, as well as inhibit the expression of TLR2 and MyD88 mRNA in rat joint synovium | Du et al. (2020)          |
| 17  | 3,5-dicaffeoylquinic acid  | Anti-gout activity      | 60, 120, 240, 480, 960 µmol/L | Xanthine oxidase | Allopurinol                                                                      | Exhibit weak xanthine oxidase inhibitory activity                        | Chen et al. (2014)        |
| 18  | Scopoletin                 | Anti-cancer activity    | 3.56, 6.12, 12.5, 25, 50, 100 µmol/L | The normal cell line HCVEpC and the cervical cancer cell lines DoTc2, SiHa, HeLa, and C33A | -                                                                               | Inhibit the growth of DoTc2, SiHa, HeLa, and C33A cells; the apoptotic cell death in HeLa cells has involved the up-regulation of Bax, caspase 3, 8, and 9, the downregulation of Bcl-2, and the blockade of the PI3K/AKT pathway | Tian et al. (2019)        |

(Continued on following page)
| No. | Compounds               | Activities             | Dosage       | Model                                                                 | Positive control                                                                 | References       |
|-----|-------------------------|------------------------|--------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------|
| 19  | Umbelliferone           | Anti-cancer activity   | 5, 25, 100, 150 μmol/L | Human renal carcinoma cells                                        | Reduce cell proliferation and induce apoptotic events by regulating Ki67, MCM2, Bcl-2, CDK2, CyclinE1, CDK4, and CyclinD1 | Wang et al. (2019) |
| 20  | Isofraxidin             | Anti-cancer activity   | 5, 10, 20, 80 μmol/L | Human colorectal cancer cells HT-29 and SW-480 | -                                                                                | Shen et al. (2017) |
| 21  | 5-O-caffeoylquinic acid | Anti-cancer activity   | 1, 10, 50 μmol/L | p53 wild-type A549 and p53-deficient H1299 non-small cell lung cancer cells | Abrogate mitogen-stimulated invasion but not proliferation by the inactivation of p70S6K, dependent signaling pathway | In et al. (2016)  |
| 22  | Chlorogenic acid        | Anti-cancer activity   | 50, 100, 200 μmol/L | U2OS, Saos-2, and MG-63 osteosarcoma cells                         | Inhibit cell proliferation                                                       | Sapio et al. (2020) |
| 23  | Chlorogenic acid        | Anti-cancer activity   | 40 mg/kg      | 4T1 breast cancer tumors in BALB/c mice                            | Participated in the induction of apoptosis, involving the increase of Bax/Bcl-2 ratio, the genes of p53 and caspase-3 | Changizi et al. (2021) |
| 24  | Chlorogenic acid        | Anti-cancer activity   | 250, 1000 μmol/L | HCT116 and HT29 human colon cancer cell lines                      | Inhibit the viability associated with the induction of cell cycle arrest at the S phase and the suppression of extracellular signal related kinase activation | Hou et al. (2017) |
| 25  | Eupatilin               | Anti-cancer activity   | 40, 80, 120, 160, 200, 240, 280, 320 μmol/L | Human malignant glioma cell lines U251MG, U118, T98G, and U87MG | Inhibit the viability and proliferation of glioma cells by arresting the cell cycle at the G1/S phase, and disrupt the structure of the cytoskeleton and affect F-actin depolymerization via the p-LIMK/cofilin pathway | Fei et al. (2019b) |
| 26  | Eupatilin               | Anti-cancer activity   | 12.5, 25, 50 μmol/L | Human prostate PC3, LNCaP cancer cells and prostatic epithelial RWPE-1 cells | Inhibit the proliferation, metastasis and spread of prostate cancer cells through modulation of PTEN and NF-κB pathway | Serttas et al. (2021) |
| 27  | Eupatilin               | Anti-cancer activity   | 2.5, 5, 10, 20, 40 μmol/L, 10, 50 mg/kg | Human esophageal cancer cell line TE1; TE1 xenograft mouse model | Inhibit the Akt and ERK pathways                                                  | Wang et al. (2018b) |
| 28  | 4'-Hydroxywogonin       | Anti-cancer activity   | 0.1, 1, 10 μg/ml | SW620 colorectal cancer cell                                      | Reduce the viability, suppress the proliferation by disrupting PI3K/AKT pathway | Sun et al. (2018) |
| 29  | N-trans-furoxytyramine  | Anti-diabetic activity  | 64, 128, 192, 256, 320 μmol/L | HepG2 and L02 human hepatoma cells | Taxol                                                                              | Gao et al. (2019) |
| 30  | Scopoletin              | Anti-diabetic activity  | 1g, 0.01 g/100 g diet | Streptozotocin induced diabetic mice                             | Metformin, 0.5 g/100 g diet                                                     | Choi et al. (2017) |

(Continued on following page)
intrapерitoneal injection of scopoletin (1 mg/kg) reduced serum NO, TNF-α, and IL-1β levels and inhibited p65, p38 phosphorylation in mouse lungs (Pereira dos Santos Nascimento et al., 2016). Dou et al. (2013) reported that scopoletin (15, 30, 60 μmol/L) significantly inhibited the production of IL-6 in fibroblast-like synoviocytes induced by IL-1β and the phosphorylation of p38, ERK, PKC, and CREB. These findings suggest that scopoletin might play a role by mediating the MAPK/PKC/CREB pathways. It should be noted that this study lacks a positive control. P38 MAPK is relevant to human inflammatory disease, and inhibition of p38 phosphorylation reduces gene expression of many inflammatory mediators (Dou et al., 2013). The regulatory effect of scopoletin on the MAPK signaling pathway is consistent with the results of network analysis. These findings suggest that scopoletin exerts anti-inflammatory and analgesic effects through multiple targets and pathways, indicating its good medicinal potential (Parama et al., 2022). However, due to the instability of scopoletin under physiological media and poor water solubility, its oral bioavailability is only 6.0%, severely restricting its medicinal application (Sakthivel et al., 2022). With the rapid development of pharmaceutical technology, new drug delivery systems have introduced possible applications of scopoletin in recent years. For example, there is a formulation of soluplus-based micelles for scopoletin, which increases its absorption, bioavailability, and tissue distribution 33-fold (Zeng et al., 2017). Pan et al. (2009) reported that intraperitoneal injection of scopolin (compound 16, 50, and 100 mg/kg) alleviated the symptoms of adjuvant-induced arthritis in rats by inhibiting the expression of IL-6, VEGF, and FGF-2 in rat synovial tissue. Li et al. (2019) established an LC-MS/MS method for the simultaneous determination of scopolin and scopoletin in rat biomatrices, while the bioavailability of scopoletin was exceptionally low.

There are also many reports on umbelliferone’s anti-inflammatory and analgesic activities (compound 17) and isofraxidin (compound 20). Oral administration of umbelliferone (20 and 40 mg/kg) for 28 days led to significant decreases in ear thickness, spleen size and weight, and serum levels of IgE, IgG1, IgG2a, TNF-α, and IL-4. There were also decreases in mast cell infiltration on 2,4-dinitrochlorobenzene and house dust mite extract-treated mice (Lim et al., 2019). Umbelliferone reduced the secretion of pro-inflammatory cytokines and chemokines in TNF-α/IFN-γ-treated HaCaT cells via the regulation of the MAPK, IκB-α/NF-κB, and STAT1 signaling pathways (Lim et al., 2019). There are many reports on isofraxidin in the treatment of osteoarthritis (Jin et al., 2018; Wang and Wang, 2021). For example, isofraxidin (1, 10, and 50 μmol/L) blocked IL-1β-stimulated production of NO and PGE2, inhibited the expression of COX-2, iNOS, MMP-1, MMP-3, MMP-13, ADAMTS-4 and -5, and suppressed IL-1β-induced IκB-α degradation and NF-κB activation in human osteoarthritis chondrocytes (Lin et al., 2018); it should be noted that there was no positive control group in this study.

### TABLE 4 (Continued) Bioactivities of the active compounds of *Porana* plants.

| No. | Compounds | Activities | Dosage | Model                  | Positive control                                                                 | Results                                                                                                                                                                                                 | References |
|-----|-----------|------------|--------|------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 31  | Scopoletin| Anti-diabetic activity | Ig: 1 mg/kg | High fructose diet induce type 2 diabetes rats | -                                                                               | Reduce blood glucose, insulin and lipid levels, involving the activation of IRS1, PI3K and AKT phosphorylation                                                                                           | Kalpana et al. (2019) |
| 32  | Scopoletin| Anti-diabetic activity | Ig: 10 mg/kg | Streptorotocin induced diabetes mice | Acarbose, Ig: 10 mg/kg                                                          | Inhibit the activity of α-glucosidase and α-amylase and reduce postprandial blood glucose levels                                                                                                   | Jang et al. (2018) |
| 33  | Scopoletin| Phagocytic activity | 50 μg/ml | Human U937 monocytic cell line | -                                                                               | Enhance the phagocytic activity, which involving the down-regulation of seven genes (CDC42, FGFR1A/FGFR1C, ITGA9, ITGB3, PLCE1, RHOD & RND3) and up-regulation of five genes (DIRAS3, ITGA1, PIK3CA, PIK3R3 & PLCD1) | Alkerashy et al. (2020) |
| 34  | Scopoletin| Anti-fungal activity | 12.5–200 μg/ml | *Candida tropicalis* | Fluconazole, 62.5–1000 μg/ml                                                  | Affect both planktonic and biofilm forms                                                                                                                                                    | Lemos et al. (2020) |
Pharmacokinetic studies demonstrated in vivo its rapid absorption after oral applications (Majnooni et al., 2020).

The HPLC fingerprints of the Porana plants (Figure 3) showed that quinic acid derivatives frequently appear in different Porana species. The anti-inflammatory, analgesic-related pharmacodynamics of chlorogenic acid has been reported in many studies and associated with the NF-κB, MAPK, and JNK/AP-1 signaling pathways; they have also been associated with the downregulation of TNF-α, COX-2, and PGE2 (Bagdas et al., 2020). Xue et al. (2019) applied the method of D101 macroporous resin to track the anti-inflammatory components in P. sinensis; Compounds 31–33 inhibited NO/INOS and PGE2/COX-2 pathways, and the nuclear translocation of NF-κB was also blocked. Wu et al. (2016) reported that compounds 31–33 reduce mouse ammonia liquor-induced acute airway inflammation by reducing the total leukocytes in bronchoalveolar lavage fluid. Among these three compounds, 4,5-dicaffeoylquinic acid exhibited the most potent effect, suggesting that the structure-activity relationship requires further elaboration.

Seven flavonoids have been isolated from Porana species. Eupatilin (compound 23) and quercetin (compound 25) present diverse anti-inflammatory activities. Eupatilin exerts anti-inflammatory effects by regulating NF-κB (Choi et al., 2011), TLR4/MyD88 (Fei et al., 2019a), AMPK (Zhou et al., 2018), and by suppressing osteoclast differentiation (Kim et al., 2015), inhibiting oxidative stress (Ali et al., 2017). Although eupatilin has broad bioactivity, its oral bioavailability is only 2.7% (Wang et al., 2018a). Quercetin is a broad-spectrum anti-inflammatory and analgesic substance without specificity. Considering the folk medicinal application of Porana plants, we only focused on its application in arthritis. Quercetin decreased serum TNF-α, IL-1β, IL-17, and MCP-1 levels in a collagen-induced mouse arthritis model (Haleagrahara et al., 2017). The authors claimed that quercetin produces better activity than methotrexate, which might not be accurate due to the different doses and routes of administration (quercetin, Po with 30 mg/kg; methotrexate, Ip with 0.5 mg/kg). MCP-1 (chemokine ligand 2) has a critical role in inflammation (Singh et al., 2021). These studies confirmed the regulatory effect of Porana plants on the chemokine pathway in network analysis. Yuan et al. (2020) found that quercetin reduces neutrophil infiltration and promotes apoptosis in activated neutrophils; however, this study did not provide the dosage of quercetin and the positive control dexamethasone.

β-Ecdysterone (compound 1) inhibited 3-methyladenine-induced apoptosis of chondrocytes, downregulated PI3K, p-AKT1, p-mTOR, p-p70S6K, and caspase-3 expression, and activated autophagy in chondrocytes in a rat model of monoiodoacetate-induced osteoarthritis (Tang et al., 2020). N-trans-feruloyltyramine (compound 35) strongly suppressed mRNA expression of COX-2 and iNOS via suppression of AP-1 and the JNK signaling pathway in LPS-induced RAW 264.7 cells (Jiang et al., 2015).

There are several anti-inflammatory and analgesic active ingredients in Porana species, including coumarins, quinic acid derivatives, flavonoids, steroids, and amides. The results of the components (scopoletin, umbelliferone, eupatilin, quercetin, N-trans-feruloyltyramine) pathways (PI3K-Akt, HIF-1, MAPK, chemokine) in our network analysis are consistent with the results of the literature review, which suggests the potential of Porana species in the treatment of arthritis. However, it should be noted that, although components such as scopoletin and eupatilin show good anti-inflammatory and analgesic effects, their bioavailability is relatively low. Further structural modification is needed, or new drug delivery systems should be developed to improve their bioavailability.

5.3.2 Anti-gout effect

Intraperitoneal injection of scopoletin (compound 15, 100, and 200 mg/kg) significantly lowered the number of neutrophils and mononuclear phagocytes of MSU-induced inflammation in a mouse air pouch model. The secretion of IL-1β, TNF-α, IL-6, PGE2, and NO were suppressed by scopoletin (30–300 μmol/L) at the transcriptional level in MSU-stimulated RAW 264.7 cells, mediated by the suppression of NF-κB activation and blockade of the MAPK signal pathway (Yao et al., 2012). In our previous study, we also found that scopoletin (4.9 mg/kg) inhibited the production of serum MDA, IL-1β, and TGF-1β, promoted the release of SOD and IL-4 and inhibited the expression of TLR2 and MyD88 mRNA in rat joint synovium (Du et al., 2020). In another study, we found that 3,4-dicaffeoylquinic acid (compound 31, IC50: 0.32 mmol/L), 4,5-dicaffeoylquinic acid (compound 32, IC50: 0.26 mmol/L), and 3,5-dicaffeoylquinic acid (compound 33, IC50: 0.21 mmol/L) exhibited weak xanthine oxidase inhibitory activity (Positive control: allopurinol, IC50: 0.01 mmol/L) (Chen et al., 2014), partially explaining the phytochemistry of anti-gout activity.

In summary, scopoletin plays an anti-gout role primarily by regulating inflammatory pathways, and quinic acid derivatives have xanthine oxidase inhibitory activity. Due to a large amount of anti-inflammatory, analgesic, antioxidant, and xanthine oxidase-inhibiting ingredients, the genus Porana has excellent application prospects as anti-gout therapies. However, only P. sinensis has been reported to treat acute gouty arthritis. Therefore, the anti-gout efficacy of other species in this genus must be further explored.

5.3.3 Anti-cancer activity

Scopoletin (compound 15) inhibited the growth of cervical cancer cell lines, including DoTc2, SiHa, HeLa, and C33A cells, with the IC50 values ranging from 7.5 to 25 μmol/L. The apoptotic cell death in HeLa cells induced by scopoletin involved the upregulation of Bax, caspase 3, 8, and 9, the downregulation of Bcl-2, and the blockade of the PI3K/Akt pathway. Scopoletin also caused cell cycle arrest at the G2/M phase and inhibited cell migration (Tian et al., 2019).
Umbelliferone (compound 17) exerted anti-cancer effects on various cells and animal models through induction of apoptosis, cell cycle arrest, reduction of cell proliferation, and inhibition of the release of inflammatory factors. For example, treating human renal carcinoma cells with umbelliferone-induced dose-dependent decreases in Ki67, MCM2, Bcl-2, CDK2, CyclinE1, CDK4, and CyclinD1 and an increase in Bax (Wang et al., 2019). Isofraxidin (compound 20, 5–80 μmol/L) significantly hampers cell proliferation, induced cell apoptosis, and decreased the expression of anti-apoptotic protein Bcl-2 in human colorectal cancer cell lines (HT-29 and SW-480). Isofraxidin blocks the Akt pathway via inhibition expression of β-Akt (Shen et al., 2017).

There are many reports on the anti-cancer properties of quinic acid derivatives in *Porana* species. 5-O-caffeoylquinic acid (compound 30) abrogated mitogen-stimulated invasion but not proliferation in p53 wild-type A549 and p53-deficient H1299 NSCLC cells. The anti-invasive activity of 5-O-caffeoylquinic acid in A549 cells might be mediated by the inactivation of the p70S6K-dependent signaling pathway (In et al., 2016). Chlorogenic acid (compound 28) inhibited the proliferation of U2OS, Saos-2, and MG-63 osteosarcoma cells (50, 100, 200 μmol/L) (Sapio et al., 2020). This compound also participates in the apoptosis of 4T1 breast cancer tumors in BALB/c mice, involving the increase of the Bax/Bcl-2 ratio and the genes for p53 and caspase-3 (Changizi et al., 2021); it inhibits the viability of HCT116 and HT29 colon cancer cell lines associated with the induction of cell cycle arrest at the S phase and the suppression of extracellular signal-related kinase activation (Hou et al., 2017). These findings suggest that caffeoylquinic acids exhibit relatively broad anti-cancer activity, with targeted cancer types including lung cancer, osteosarcoma, breast cancer, and colon cancer. Chlorogenic acid inhibits cell proliferation and blocks the cell cycle; however, 5-O-caffeoylquinic acid does not inhibit cell proliferation. As isomers, the difference in antiproliferative effect between these two compounds deserves further explanation.

The flavonoid eupatilin (compound 23) inhibits the viability and proliferation of glioma cells by arresting the cell cycle at the G1/S phase. Eupatilin disrupts the structure of the cytoskeleton and affects F-actin depolymerization via the p-LIMK/cofilin pathway (Fei et al., 2019b). However, this study did not report a proapoptotic effect of eupatilin on glioma, which was inconsistent with other studies. Eupatilin (12.5, 25, 50 μmol/L) inhibits the proliferation, metastasis, and spread of prostate cancer cells through modulation of PTEN and NF-κB signaling (Serttas et al., 2021); it blocks the proliferation of esophageal cancer TE1 cells associated with the inhibition of the Akt and ERK pathways (Wang et al., 2018b). Another flavonoid, 4’-hydroxywogonin (compound 24), reduced the viability and suppressed the proliferation of SW620 colorectal cancer cells angiogenesis by disrupting PI3K/Akt signaling, while the expression of VEGF-A decreased dose-dependently (Sun et al., 2018). Based on this study, it could be presumed that the anti-angiogenic activity of PI3K inhibitors was at least partially mediated by their capacity to reduce VEGF levels.

N-trans-feruloyltyramine (compound 35) inhibits the proliferation of HepG2 cells with an IC₅₀ of 194 ± 0.894 μmol/L, which was significantly lower than the positive control taxol (IC₅₀: 26 ± 0.128 μmol/L) (Gao et al., 2019). Comparing the results on HepG2 and LO2 cells revealed that N-trans-feruloyltyramine might have selective cytotoxic effects.

In summary, there are many anti-cancer active components in *Porana* plants, including coumarins, quinic acid derivatives, and flavonoids. Of these, scopoletin, umbellifereone, chlorogenic acid, and eupatilin have many reports on their anti-cancer activity. These components are widely distributed in nature and are not specific. Since the related research mostly stays at the level of in vitro research, and more in vivo research and clinical studies are needed.

5.3.4 Anti-diabetic activity

In the streptozotocin-induced diabetic mice model, scopoletin (compound 15, 0.01 g/100 g diet) reduced blood glucose and glycated hemoglobin, glucose intolerance, hepatic lipid accumulation and downregulated hepatic gene expression of triglyceride and cholesterol synthesis and inflammation (TLR4, MyD88, NF-κB, TNF-α, and IL-6). These results suggest that scopoletin protects against diabetes-induced steatosis and inflammation by inhibiting lipid biosynthesis and the TLR4-MyD88 pathway (Choi et al., 2017). However, this was a single-dose study with substantial differences in the dosage of the positive control metformin (0.5 g/100 g diet) and scopoletin, which cannot be used for comparison. In another study, scopoletin (1 mg/kg) reduced blood glucose, insulin, and lipid levels in high-fructose diet-induced type 2 diabetes, involving the activation of IRS1, PI3K, and Akt phosphorylation (Kalpana et al., 2019). Scopoletin inhibited the activity of α-glucosidase and α-amylase and reduced postprandial blood glucose levels in streptozotocin-induced diabetes mice. Unfortunately, the IC₅₀ value of scopoletin was 85.12 and 37.36 μmol/L for α-glucosidase and α-amylase, which were lower than acarbose (Jang et al., 2018), indicating that its potential is limited. Another study reported that scopoletin stimulated insulin secretion via a K⁺-ATP channel-dependent pathway in INS-1 pancreatic β cells (Park et al., 2022). Scopoletin could play a role in treating diabetes by stimulating insulin secretion, inhibiting α-glucosidase and α-amylase, and downregulating triglyceride and cholesterol synthesis and inflammation. However, the inhibitory effect of scopoletin on α-glucosidase and α-amylase would be weaker than that of the positive control drug acarbose.

There are many reports on the efficacy and mechanism of chlorogenic acid (compound 28), quercetin (compound 25), and rutin (compound 27) in the treatment of diabetes. For example,
quercetin stimulated insulin secretion (Kitl et al., 2016), alleviated ferroptosis in pancreatic cells (Li et al., 2020), and ameliorated diabetic encephalopathy through the SIRT1/ER stress pathway (Hu et al., 2020). Rutin decreased carbohydrate absorption from the small intestine, inhibited tissue gluconeogenesis, increased tissue glucose uptake, stimulated insulin secretion from beta cells, and protected pancreatic islets against degeneration (Ghorbani, 2017). Chlorogenic acid prevented diabetic nephropathy (Bao et al., 2018), rescued sensorineural auditory function, attenuated insulin resistance, and modulated glucose uptake (Hong et al., 2017).

In summary, many anti-diabetic ingredients are found in *Porana* plants, including coumarins, quinic acid derivatives, and flavonoids. The content of coumarins and quinic acid derivatives is relatively high in the genus *Porana*, suggesting that this genus could be used to treat diabetes. The network analysis shows that the pathways regulated by the chemical compounds of *Porana* plants play an essential role in diabetes treatment. For example, the PI3K/Akt pathway damaged in various body tissues leads to obesity and type 2 diabetes as the result of insulin resistance; in turn, insulin resistance exacerbates the PI3K/Akt pathway, forming a vicious circle (Huang et al., 2018). The progression of diabetes and its complications can be prevented or treated by modulating HIF-1 expression or activity (Catrina and Zheng, 2021). However, apart from the pharmacological or clinical studies of these compounds, there are no reports on the application of *Porana* plants in diabetes treatment; relevant research needs to be performed.

### 5.3.5 Other activities

Alkorashy et al. (2020) used transcriptomic methods to study the effect of scopoletin (compound 15) on the phagocytosis of stimulated U937-derived macrophages. Scopoletin enhanced the phagocytic activity, involving the downregulation of seven genes (CDC42, FCGR1A/FCGR1C, ITGA9, ITGB3, PLCE1, RHOD, and RND3) and upregulation of five genes (DIRAS3, ITGA1, PIK3CA, PIK3R3, and PLCD1). These results provide a basis for applying scopoletin in treating cancer progression and metastasis, autoimmune disorders, pelvic organ prolapse, and cystic fibrosis. ITGB3 is upregulated in pelvic organ prolapse disorders in women, and the downregulation of these genes supports the folk medicinal application of *P. spectabilis* in the treatment of uterine prolapse. Scopoletin also acts as an anti-fungal phytocompound against a multidrug-resistant strain of *Candida tropicalis*, with properties affecting planktonic and biofilm forms of this pathogen (Lemos et al., 2020).

### 6 Conclusion

The genus *Porana* is abundant in natural resources and is widely distributed in Asia, Africa, Oceania, America, and other regions. In China and India, this genus has several medicinal records. Currently, only the chemical composition, efficacy, and quality control of *P. sinensis* have been systematically reported, while the medicinal value of other species in this genus has not yet been explored. Therefore, we systematically reviewed this genus’s traditional and current use, chemical compositions, and pharmacological activities. We applied network analysis to predict the key targets and pathways of chemical components in this genus to clarify the research status of *Porana* species and highlight the directions for the rational medicinal development of this genus.

Regarding chemical components, only five species of genus *Porana* have been reported, with 59 compounds isolated and identified, including steroids, coumarins, flavonoids, quinic acid derivatives, and amides. Combined with the fingerprints (Figure 3), coumarins and quinic acid derivatives are widely distributed in this genus, while steroids have only been reported in *P. discifera*. Because the research on chemical constituents is the forerunner of medicinal value development, the phytochemical study of other species in this genus needs to be performed.

In terms of pharmacological effects, the extracts of *Porana* plants exhibit anti-inflammatory, analgesic, antioxidant, and anti-gout activities. However, studies on the pharmacological effects of *Porana* plants are focused on *P. sinensis*, and there are few pharmacological studies on other species. Especially for plants with extensive folk medicinal records (such as *P. racemosa*), detailed pharmacodynamic research needs to be performed. The chemical constituents of *Porana* present anti-inflammatory, analgesic, anti-gout, anti-cancer, and diabetes treatment activities. Gout and diabetes treatment are not the traditional medicinal applications of *Porana* plants. However, this genus contains chemical substances with appropriate biological activities. Therefore, we speculate that this genus has the potential to develop in the direction of anti-gout and anti-diabetes. Future research needs to investigate different species’ anti-gout and anti-diabetic efficacy, explain their mechanism of action, and systematically elucidate their active components.

Network analysis showed that steroids, flavonoids, amides, coumarins, and other components maybe be relevant for anti-inflammatory, analgesic, anti-gout, anti-cancer, and diabetes treatment activities of *Porana* plants. Their targets include GSK3B, EGFR, MAPK1, IL2, HSPA8, MMP9, HK1, GAPDH, TNF, ADORA3, and their pathways include PI3K-Akt, HIF-1, estrogen, and MAPK. The enriched targets and pathways are consistent with the results of our literature review.

In summary, *Porana* plants are abundant in natural resources and are widely recorded in folk medicine; nevertheless, the study of their medicinal value is limited. Research on the systematic chemical constituents of this genus is urgently needed. Anti-inflammatory, analgesic, anti-gout, anti-cancer, and diabetes treatments are critical directions for future study.
Author contributions
YP and YL: original and final drafting, editing, revision, and figure editing; YY, YG, HR, JH, and WL: figures, tables and review of the literature; XC: network analysis; HT and ZC: revised the draft and final editing.

Funding
This work was financially supported by the National Natural Science Foundation of China [grant numbers 81973419]; Key Research and Development Program of Shaanxi [grant number 2019ZDLSF04-07, 2022SF-315]; Shaanxi Administration of Traditional Chinese Medicine Projects [grant number 2022-SLKH-YQ-003, 2021-PY-003].

Acknowledgments
Thanks for all institutions that provided the funding.

References
Ali, M. Y., Seong, S. H., Reddy, M. R., Seo, S. Y., Chot, J. S., and Jung, H. A. (2017). Kinetics and molecular docking studies of 6-formyl umbelliferone isolated from Angelica decursiva as an inhibitor of cholinesterase and BACE1. Kinetics and molecular docking studies of 6-formyl umbelliferone isolated from Angelica decursiva as an inhibitor of cholinesterase and BACE1. Molecules 22 (10), 1608. doi:10.3390/molecules22101604
Alkorashy, A. I., Doghish, A. S., Abulsoud, A. I., Ewees, M. G., Abdelghany, T. M., Elshafty, M. M., et al. (2020). Effect of scopoletin on phagocytic activity of U937-1604. doi:10.1007/s00125-020-2532-3
Bagdas, D., Guo, Z., Meade, J. A., Cam, B., Cinklis, N., and Gurun, M. S. (2020). Pharmacologic overview of chlorogenic acid and its metabolites in chronic pain and inflammation. Curr. Neuropharmacol. 18 (3), 216–228. doi:10.2174/1570159X1766691211118109
Bao, L., Li, J., Zha, D., Zhang, L., Gao, P., Yao, T., et al. (2018). Chlorogenic acid prevents diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF-κB pathways. Int. Immunopharmacol. 54, 245–253. doi:10.1016/j.intimp.2017.11.021
Catrina, S. B., and Zheng, X. (2021). Hypoxia and hypoxia-inducible factors in diabetes and its complications. Diabetesologia 64 (4), 709–716. doi:10.1007/s00125-021-05380-z
Chang, T.-N., Deng, J.-S., Chang, Y.-C., Lee, C.-Y., Jung-Chun, L., Lee, M.-M., et al. (2012). Ameliorative effects of scopoletin from Cinnamomum chinensis against inflammation pain and its mechanisms in mice. Evidence-Based Complementary Altern. Med. 2012, 1–10. doi:10.1155/2012/595603
Changizi, Z., Moslehi, A., Rohani, A. H., and Eidi, A. (2021). Chlorogenic acid induces 4T1 breast cancer tumor’s apoptosis via p53, Bax, Bcl-2, and caspase-3 signaling pathways in BALB/c mice. J. Biochem. Mol. Toxicol. 35 (2), e22642. doi:10.1002/jbt.22642
Chen, X., Xu, J., and Liang, S. (2004). Porana“ in Flora of China. Beijing: Science Press.
Chen, Z., Liao, L., Yang, Y., Zhang, Z., and Wang, Z. (2015). Different fingerprinting strategies to differentiate Porana sinensis and plants of Erycibe by high-performance liquid chromatography with diode array detection, ultra high performance liquid chromatography with tandem quadrupole mass spectrometry, and chemometrics. J. Sep. Sci. 38 (2), 231–238. doi:10.1002/jssc.201400861
Chen, Z., Liao, L., Zhang, Z., Wu, L., and Wang, Z. (2013). Comparison of active constituents, acute toxicity, anti-necroptotic and anti-inflammatory activities of Porana sinensis Hemsl., Erycibe obtusifolia Benth. and Erycibe schmidtii Craib. J. Ethnopharmacol. 150 (2), 501–506. doi:10.1016/j.jep.2013.08.039
Chen, Z., Tao, H., Liao, L., Zhang, Z., and Wang, Z. (2014). Quick identification of xanthine oxidase inhibitor and antioxidant from Erycibe obtusifolia by a drug discovery platform composed of multiple mass spectrometric platforms and thin-layer chromatography bioautography. J. Sep. Sci. 37 (16), 2253–2259. doi:10.1002/jssc.201400342
Chen, Z., Wang, M., Yang, Y., Cui, X., Hu, J., Li, Y., et al. (2020). Promotion of a quality standard for Porana sinensis Hemsl. based on the efficacy-oriented Effect-Constituent Index. Biomed. Chromatogr. 34 (2), e14726. doi:10.1002/bmc.14726
Chen, Z., Zhang, M., Yang, Y., Du, X., Zhang, Z., and Li, Y. (2019). Qualitative and quantitative analysis of Porana sinensis Hemsl. by UHPLC-Q-Exactive MS, TLC autorigraphic method and DART-MS. Phytochem. Anal. 30 (3), 311–319. doi:10.1002/pca.2814
Choi, E.-J., Lee, S., Chae, J.-R., Lee, H.-S., Jun, C.-D., and Kim, S.-H. (2011). Eupatilin inhibits lipopolysaccharide-induced expression of inflammatory mediators in macrophages. Life Sci. 88 (25–26), 1121–1126. doi:10.1016/j.lfs.2011.04.011
Choi, R. Y., Ham, J. R., Lee, H. I., Cho, H. W., Choi, M. S., Park, S. K., et al. (2017). Scolepotrin supplementation ameliorates osteoarthritis and inflammation in diabetic mice. Phytother Res. 31 (11), 1795–1804. doi:10.1002/ptr.5925
Ding, W.-B., Zhang, D.-G., Liu, C.-J., Li, G.-H., and Li, Y.-Z. (2014). Resin glycosides from Porana duclosii. J. Asian Nat. Prod. Res. 16 (2), 135–140. doi:10.1080/10286020.2013.864281
Dou, Y., Tong, B., Wei, Z., Li, Y., Xia, Y., and Dai, Y. (2013). Scolepotrin suppresses IL-6 production from fibroblast-like synoviocytes of adjuvant arthritis rats induced by IL-1β stimulation. Int. Immunopharmacol. 17 (4), 1037–1043. doi:10.1016/j.intimp.2013.10.011
Du, X., Zhao, L., Yang, Y., Zhang, Z., Hu, J., Ren, H., et al. (2020). Investigation of the mechanism of action of Porana sinensis Hemsl. against gout arthritis using network pharmacology and experimental validation. J. Ethnopharmacol. 252, 112606. doi:10.1016/j.jep.2020.11.2606
Editorial Board, C.M.M (2009). Chinese Materia Medica. Shanghai: Shanghai Scientific & Technical Publishers.
Editorial Board, N.C.C.H.M (1975). National Compendium of Chinese herbal medicines. Beijing: People’s Medical Publishing House.
Fan, L., Wu, L., Yu, X.-H., Chen, Y.-B., Liu, L., and Li, S.-G. (2021). The ethnopharmacology, phytochemistry, pharmacology and toxicology of the genus Erycibe (Convolvulaceae). J. Ethnopharmacol. 278, 114312. doi:10.1016/j.jep.2021.114312

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note
All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.998965/full#supplementary-material
Fang, Z., Zhao, H., and Zhao, J. (2007). *Tujia medicinal records*. Beijing: China Medical Science and Technology Press.

Fei, X., Chen, C., Kai, S., Fu, X., Man, W., Ding, B., et al. (2019a). Eupatilin attenuates the inflammatory response induced by intracerebral hemorrhage through the TLR4/MyD88 pathway. *Int. Immunopharmacol*. 76, 105837. doi:10.1016/j.intimp.2019.105837

Fei, X., Wang, J., Chen, C., Ding, B., Fu, X., Chen, W., et al. (2019b). Eupatilin inhibits glioma proliferation, migration, and invasion by arresting cell cycle at G1/S phase and disturbing the cell cycle basket structure. *Cancer Manag. Res*. 11, 4781–4797. doi:10.2147/CMA.S207257

Gao, X., Wang, C., Chen, Z., Chen, Y., Santhanam, R. K., Xue, Z., et al. (2019). Effects of *N*-trans-feruloyltyramine isolated from laba garlic on antioxidant, cytotoxic activities and H2O2-induced oxidative damage in HepG2 and L02 cells. *Food Chem. Toxicol.* 130, 130–141. doi:10.1016/j.fct.2019.05.021

Göller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., and Zoete, V. (2014). SwissTargetPrediction: A web server for target prediction of bioactive small molecules. *Nucleic Acids Res*. 42 (W1), W32–W38. doi:10.1093/nar/gku293

Ghorbani, A. (2017). Mechanisms of antibiotic effects of flavonoid rutin. *Biomed. Pharmacother*. 86, 305–312. doi:10.1016/j.biopha.2017.10.001

Guoqiang, W. (2014). “Dinggongteng,” in *The compilation of national Chinese herbal medicine*. 3rd edition (Beijing: People’s Medical Publishing House).

Haleugrahara, N., Miranda-Hernandez, S., Alim, A. M., Hayes, L., Bird, G., and Kerheesaa, N. (2017). Therapeutic effect of quercitin in collagen-induced arthritis. *Biomed. Pharmacother*. 90, 38–46. doi:10.1016/j.biopha.2017.03.026

Hong, B. N., Nam, Y. H., Woo, S. H., and Kang, T. H. (2017). Cholegenic acid rescues sensorineural auditory function in a diabetic animal model. *Neurosci. Lett*. 640, 64–69. doi:10.1016/j.neulet.2017.01.030

Hou, N., Liu, N., Han, J., Yan, Y., and Li, J. (2017). Cholegenic acid induces reactive oxygen species generation and inhibits the viability of human colon cancer cells. *Anticancer Drugs* 28 (1), 59–66. doi:10.CAD.00000000000430

Hu, J., Zhao, L., Li, N., Yang, Y., Qu, T., Ren, H., et al. (2022). Investigation of the active ingredients and pharmacological mechanisms of *Panax notoginseng* S. C. Zhen. Against rheumatoid arthritis using network pharmacology and experimental validation. *PLoS One* 17 (3), e0264786. doi:10.1371/journal.pone.0264786

Hu, T., Shi, J.-J., Fang, J., Wang, Q., Chen, Y.-B., and Zhang, S.-J. (2020). Quercetin inhibits diabetic retinal neovascularization by targeting TLR4/MD-2 axis to prevent osteoarthritis development. *Int. J. Biol. Sci*. 48 (5), 1907–1912. doi:10.4155/fmc.15.55

Jin, J., Yu, X., Hu, Z., Tang, S., Zhong, X., Xu, J., et al. (2018). Isofraxidin targets cells. *Biomed. Pharmacother*. 1016/j.cbi.2015.03.029

Jin, J., Yu, X., Hu, Z., Tang, S., Zhong, X., Xu, J., et al. (2018). Isofraxidin inhibits inflammatory chemokines in hact cells and dhc/dh-induced atopic dermatitis symptoms in mice. *Int. Immunopharmacol*. 76, 105837. doi:10.1016/j.intimp.2019.105830

Lin, J., Li, X., Qu, W., Yan, Y., Chen, K., Xue, X., et al. (2018). Isofraxidin inhibits interleukin-1β induced inflammatory response in human osteoarthritis chondrocytes. *Int. Immunopharmacol*. 64, 238–245. doi:10.1016/j.immuni.2018.09.003

Liu, K., Li, S. (1997). Study on the chemical constituents of Huangwulong. *Human J. Traditional Chin. Med.* 13 (6), 46.

Majnooni, M. B., Pakhri, S., Shokohohina, T., Mosjarrab, M., Kazemi Afsakoti, S., and Farzaei, M. H. (2020). Isofraxidin: Synthesis, biosynthesis, isolation, pharmacokinetic and pharmacological properties. *Molecules* 25 (9), 2040. doi:10.3390/molecules25092040

Malemud, C. J. (2015). The PI3K/AKT/mTOR pathway: A fruitful target for inducing cell death in rheumatoid arthritis? *Future Med. Chem.* 7 (9), 1137–1147. doi:10.4155/fmc.15.55

Pan, R., Dai, Y., Gao, X., and Xia, Y. (2009). Scopolin isolated from *Erycibe obtusifolia* Benth stems suppresses adjuvant-induced rat arthritis by inhibiting inflammation and angiogenesis. *Int. Immunopharmacol*. 9 (7-8), 859–869. doi:10.1016/j.intimp.2009.02.019

Parana, D., Girisa, S., Khatooon, E., Kumar, A., Alqatami, M. S., Abbas, M., et al. (2022). An overview of the pharmacological activities of scopoletin against different chronic diseases. *Pharmacol. Res*. 179, 106202. doi:10.1016/j.phrs.2022.106202

Park, E., Kim, J., Jin, H.-S., Choi, C. W., Choi, T. H., Choi, S., et al. (2020). Scopolitin attenuates osteoradon bone loss in ovariectomized mice. *Nutrients* 12 (11), 3565. doi:10.3390/nu12113565

Park, J. E., Kim, S. Y., and Han, J. S. (2022). Scopoletin stimulates the secretion of insulin via a KATP channel-dependent pathway in INS-1 pancreatic beta cells. *J. Pharm. Pharmacol*. 74, 1274–1281. doi:10.1111/jphp.14143

Park, S. Y., Lee, S. W., Kim, H. Y., Lee, W. S., Hong, K. W., and Kim, C. D. (2015). HMGB1 induces angiogenesis in rheumatoid arthritis via HIF-1α activation. *Int. Immunol*. 45 (4), 1216–1227. doi:10.1093/intimm/dix4908

Peng, Y., Hao, T., Yang, Y., Gao, Y., Ren, H., Hu, J., et al. (2021). Chemical compositions, pharmacological activities, quality control studies of Erycibe plants, and the development of their substitutes. *Phytother. Res*. 35 (8), 4049–4074. doi:10.1002/ptr.7070

Pereira dos Santos Nascimento, M. V., Arruda-Silva, F., Gobbo Luz, A. B., Baratto, B., Venzke, D., Mendes, B. G., et al. (2016). Inhibition of the NF-κB and p38 MAPK pathways by scopoletin reduce the inflammation caused by carrageenan in the mouse model of pleurisy. *Immunopharmacol. Immunotoxicol*. 38 (5), 344–352. doi:10.3109/08929973.2016.1203929

Qu, Y., Wu, J., Deng, J.-X., Zhang, Y. P., Liang, W. Y., Jiang, Z. L., et al. (2016). MicroRNA-126 alleviates ferroptosis of pancreatic β cells in type 2 diabetes. *Nutrients* 12 (10), 2954. doi:10.3390/nu12102954

Ren, H., Yang, Y., Cui, X., Hu, J., Meng, X., and Chen, Z. (2019). Recent advances and prospects of Panax sinensis. *Res. Pract. Chin. Med*. 33 (3), 81–86.

Sachthivel, K. M., Vishnupriya, S., Priya Dharshini, L. C., Rasmi, R. R., and Ramesh, B. (2022). Modulation of multiple cellular signalling pathways as targets for anti-inflammatory and anti-tumor necrosis action of Scopolitin. *J. Pharm. Pharmacol*. 74 (2), 147–161. doi:10.1111/jphp.14047
Chlorogenic acid activates ERK1/2 and inhibits proliferation of osteosarcoma cells. J. Cell. Physiol. 235 (4), 3741–3752. doi:10.1002/jcp.29269

Serttas, R., Koroglu, C., and Erdogan, S. (2021). Eupatilin inhibits the proliferation and migration of prostate cancer cells through modulation of PTEN and NF-κB signaling. Anticancer Agents Med. Chem. 21 (3), 372–382. doi:10.2174/187152020666620081113549

Shang, Z. (2004). Supplement to Medicina: Anhui Science and Technology Press.

Shen, P., Wang, H.-G., Li, M.-M., Ma, Q.-Y., Zhou, C.-W., Pan, F., et al. (2017). Isoliquiritigenin inhibited proliferation and induced apoptosis via blockage of Akt pathway in human colorectal cancer cells. Biomed. Pharmacother. 92, 78–85. doi:10.1016/j.biopha.2017.05.065

Singh, S., Anshita, D., and Ravichandiran, V. (2021). MCP-1: Function, regulation, and involvement in disease. Int. Immunopharmacol. 101, 107598. doi:10.1016/j.intimp.2021.107598

Sun, D., Zhang, F., Qian, J., Shen, W., Fan, H., Tan, J., et al. (2018). 4′-hydroxywogonin inhibits colorectal cancer angiogenesis by disrupting PI3K/Akt signaling. Chem. Biol. Interact. 296, 26–33. doi:10.1016/j.cbi.2018.09.003

Taha-Salame, L., Davidovich-Rikanati, R., Sadeh, A., Abu-Nassar, J., Marzouk-Kheredin, S., Yahyaa, Y., et al. (2019). Phytoecdysteroid and clerodane content in three wild Ajuga species in Israel. J. BUON 24 (3), 997–1002.

Wang, W., and Wang, B. (2021). Isofraxidin inhibits receptor activator of nuclear factor-κB ligand-induced osteoclastogenesis in bone marrow-derived macrophages isolated from Sprague-Dawley rats by regulating NF-κB/NFATc1 and Akt/NFATc1 signaling pathways. Cell Transplant. 30, 0963689721990302. doi:10.1177/0963689721990302

Wang, X., Huang, S., Xin, X., Ren, Y., Weng, G., and Wang, P. (2019). The antitumor activity of umbelliferone in human renal cell carcinoma via regulation of the p110γ catalytic subunit of PI3K. Acta Pharmacol. Sin. 69 (1), 111–119. doi:10.2478/aps-2018-0004

Wang, X., Ren, J., Zhu, S., Ren, G., Wang, L., Chen, X., et al. (2018a). Pharmacokinetics and tissue distribution of eupatilin and its metabolite in rats by an HPLC-MS/MS method. J. Pharm. Biomed. Anal. 159, 113–118. doi:10.1016/j.jpba.2018.06.037

Wang, X., Zhu, Y., Zhu, L., Chen, X., Xu, Y., Zhou, Y., et al. (2018b). Eupatilin inhibits the proliferation of human esophageal cancer TE1 cells by targeting the Akt-GSK3β and MAPK/ERK signaling cascades. Oncol. Rep. 39 (6), 2942–2950. doi:10.3892/or.2018.6390

Wu, L., Zhu, E., Zhang, Z., and Wang, Z. (2005). Investigating original plant of Caulis Erycibes in Guangxi and identifying mainstream variety of Caulis Erycibes in market. Chin. Traditional Herb. Drugs 36 (9), 1398–1408.

Wu, Q.-z., Zhao, D.-x., Xiang, J., Zhang, M., Zhang, C.-f., and Xu, X.-h. (2016). Antitussive, expectorant, and anti-inflammatory activities of four caffeoylquinic acids isolated from Tussilago farfara. Pharm. Biol. 54 (7), 1117–1124. doi:10.3109/13888092.2015.1075048

Xue, Q., Fan, H., Li, K., Yang, L., Sun, L., and Liu, Y. (2017). Comparative evaluations on phenolic antioxidants of nine adulterants and anti-inflammation of four alternatives with their original herb Erycibe schmidtii. Rsc Adv. 7 (81), 51151–51161. doi:10.1039/c7ra10767f

Xue, Q., Yin, P., Li, K., Fan, H., Yang, L., Cao, X., et al. (2019). Identification of bioactive phenolics from Porana sinensis Hemsl. stem by UPLC-QTOF-MS/MS and the confirmation of anti-inflammatory indicators using LPS-induced RAW264.7 cells. Inflammopharmacology 27 (5), 1055–1069. doi:10.1007/s10787-018-00558-1

Yang, G., Chang, C.-C., Yang, Y., Yuan, L., Xu, L., Ho, C.-T., et al. (2018). Reveratrol alleviates rheumatoid arthritis via reducing ROS and inflammation, inhibiting MAPK signaling pathways, and suppressing angiogenesis. J. Agric. Food. Chem. 66 (49), 12953–12966. doi:10.1021/acs.jafc.8b06547

Yao, X., Ding, Z., Xia, Y., Wei, Z., Luo, Y., Feleder, C., et al. (2012). Inhibition of monosodium urate crystal-induced inflammation by scopoletin and underlying mechanisms. Int. Immunopharmacol. 14 (4), 454–462. doi:10.1016/j.intimp.2012.07.024

Yeung, Y. T., Aziz, F., Guerrero-Castilla, A., and Arguelles, S. (2018). Signaling pathways in inflammation and anti-inflammatory therapies. Curr. Pharm. Des. 24 (14), 1449–1484. doi:10.2174/13816128128666181031656004

Yu, R., Xu, Q., Bogan, L., and Zhang, G. (2003). Chemical constituents of Prunus discifera. Nat. Prod. Res. Dev. 15 (5), 405–407.

Yuan, K., Zhu, Q., Lu, Q., Jiang, H., Zhu, M., Li, X., et al. (2020). Quercetin alleviates rheumatoid arthritis by inhibiting neutrophil inflammatory activities. J. Nutr. Biochem. 84, 108454. doi:10.1016/j.jnutbio.2020.108454

Yusupova, U. Y., Usmanov, D., and Ramazonov, N. S. (2019). Phytoecdysteroids from the plant diastlius heleneae. Chem. Nat. Compd. 55 (2), 393–394. doi:10.1007/s10590-019-02701-y

Zeng, Y.-C., Li, S., Liu, C., Gong, T., Sun, X., Fu, Y., et al. (2017). Sulposul micelles for improving the oral bioavailability of scopoletin and their hypooricemic effect in vivo. Acta Pharmacol. Sin. 38 (3), 424–433. doi:10.1038/aps.2016.126

Zhang, C., Zhang, Z., Zhang, M., and Wang, Z. (2006). Studies on chemical constituents in stems of Porana sinensis Hemsl. Chin. Pharm. J. 41 (2), 94–96. doi:10.3321/j.issn:1001-2494.2006.02.004

Zheng, X., Chen, F., Liang, Q., Lu, Y., and Zhou, G. (2018). Amide constituents from the root of Lycium yunnanense kuang and their anti-inflammatory activity. Nat. Prod. Res. 30, 603–609. doi:10.1080/13546808.2018.140412

Zhou, K., Cheng, R., Liu, B., Wang, L., Xie, H., and Zhang, C. (2018). Eupatilin ameliorates dextran sulphate sodium-induced colitis in mice partly through promoting AMPK activation. Phytomedicine. 46–56. doi:10.1016/j.phymed.2018.04.033

Zhu, W., Yang, X., He, H., and Hao, X. (2000). Phytoecdysteroids from the root of Hedychium yunnanense and Porana discifera, and the structural revision of two sesquiterpenoids from Laggera pterodonta. Chin. Pharm. J. 41 (2), 94–96. doi:10.3321/j.issn:1001-2494.2006.02.004

Zhu, W., Yang, X., He, H., and Hao, X. (2000). Phytoecdysterones from Porana discifera. Acta Bot. Yunnanica 22 (3), 351–357. doi:10.3969/j.issn.2095-0845.2000.03.018

Zhu, W., Yin, C., Wang, S., Zuo, G., and Hao, X. (2001). Chemical constituents of Porana spectabilis Kurz. Nat. Prod. Res. Dev. 13 (5), 1–4. doi:10.13633/j.1001-6880.2001.0501