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## Review

## Traditional usages, botany, phytochemistry, pharmacology and toxicology of *Polygonum multiflorum* Thunb.: A review



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## ABSTRACT

**Ethnopharmacological relevance:** *Polygonum multiflorum* Thunb., which is known as *Heshouwu* (何首乌 in Chinese) in China. It is traditionally valued and reported for hair-blackening, liver and kidney-tonifying and anti-aging effects as well as low toxicity. The aim of this review is to provide comprehensive information on the botany, traditional uses, phytochemistry, pharmacological research and toxicology of *Polygonum multiflorum*, based on the scientific literature. Moreover, trends and perspectives for future investigation of this plant are discussed. It will build up a new foundation for further study on *Polygonum multiflorum*. **Materials and methods:** A systematic review of the literature on *Polygonum multiflorum* was performed using several resources, including classic books on Chinese herbal medicine and various scientific databases, such as PubMed, SciFinder, the Web of Science, Science Direct, China Knowledge Resource Integrated (CNKI).

**Results:** *Polygonum multiflorum* is widely distributed throughout the world and has been used as a traditional medicine for centuries in China. The ethnomedical uses of *Polygonum multiflorum* have been recorded in many provinces of China and Japan for nine species of adulterants in six families. More than 100 chemical compounds have been isolated from this plant, and the major components have been determined to be stilbenes, quinones, flavonoids and others. Crude extracts and pure compounds of this plant are used as effective agents in pre-clinical and clinical practice due to their anti-aging, anti-hyperlipidaemia, anti-cancer and anti-inflammatory effects and to promote immunomodulation, neuroprotection, and the curing of other diseases. However, these extracts can also lead to hepatotoxicity, nephrotoxicity and embryonic toxicity. Pharmacokinetic studies have demonstrated that the main components of *Polygonum multiflorum*, such as 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucopyranoside and emodin are distributed among many organs and tissues.

**Conclusion:** Therapeutic potential of *Polygonum multiflorum* has been demonstrated in the conditions like Alzheimer's disease, Parkinson's disease, hyperlipidaemia, inflammation and cancer, which is attributed to the presence of various stilbenes, quinones, flavonoids, phospholipids and other compounds in the drug. On the other hand, the adverse effects (hepatotoxicity, nephrotoxicity, and embryonic toxicity) of this plant were caused by the quinones, such as emodin and rhein. Thus more pharmacological and toxicological mechanisms on main active compounds are necessary to be explored, especially the combined anthraquinones (Emodin-8-O-β-D-glucopyranoside, Physcion-8-O-β-D-glucopyranoside, etc.) and the variety of stilbenes.

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## 1. Introduction

*Polygonum multiflorum* (Fig. 1) is one of the most popular traditional Chinese medicines and is an ingredient in many medicines and prescriptions. It has been widely used to treat various diseases that have been commonly associated with aging for many centuries in China. A recent study proved that it can exhibit antioxidative activity (Lv et al., 2007; Wang 2005a; Wang et al., 2008, 2009a), mainly due to its flavonoid and phenolic acid constituents. The pharmacological effects of stilbene in *Polygonum multiflorum* have been reported to promote anti-aging effects (Long and Dougherty, 2003; Lin et al., 2008; Chen et al., 2001a; Chan et al., 2002; Um et al., 2006; Cheung et al., 2014) and hepatoprotective activities (Huang et al., 2007; Liu et al., 1992). Anthraquinones, another main component of this plant, also have many biological activities, such as effects against cancer (Ma et al., 2012; Wang et al., 2011b; Way et al., 2014; Yu, et al., 2013; Liu et al., 2009a; Lin et al., 2006; Tabolacci et al., 2010), developmental anomalies (Yon et al., 2013), and tonic tension (Lim et al., 2014). However, an increasing number of recently published studies have demonstrated the adverse effects of *Polygonum multiflorum*. Some researchers have found that *Polygonum multiflorum* shows not only hepatotoxicity but also a possible drug interaction with warfarin to result in bone marrow suppression. Specifically, the long-term use of *Polygonum multiflorum* may lead to liver and kidney toxicity. The toxicity of emodin has been detailed by the U.S. National Toxicology Program (NTP technical report, 2001). In the current review, we provide a comprehensive overview of the existing knowledge and traditional uses of *Polygonum multiflorum*, including its botany, phytochemistry, pharmacodynamics and potential applications, toxicology and pharmacokinetics.

## 2. Traditional usages

With a wide spectrum of biological and pharmacological effects, *Polygonum multiflorum* has been used as a traditional medicine for many centuries in China. The *Compendium of Materia Medica* (*Ben cao Gang mu*) reported that it exerts liver-tonic and hair-blackening effects. In *Diannan Bencao*, a famous monograph of traditional Chinese medicine, this plant was described to be useful for the treatment of sore scabies, ringworm and pruritus (Lan, 1959). The toxicity of this plant was first described in *Bencao Huiyan* (another famous monograph of traditional Chinese medicine written in China during the Ming dynasty), which described this plant to be of minimal toxicity to humans. In other monographs of *Materia Medica*, such as *Kaibao Bencao*, *Bencao Mengquan*, and *Xinbian Bencao*, this plant was described to be used for the treatment of scrofula, carbuncles, and postpartum and morbid leucorrhoea and to reinforce the kidney and promote anti-aging effects.

The root of this plant is used as the effective agent after its common processing by steaming with black bean (Zhou et al., 2010), rehmannia juice, or a wine- or ginger-black bean mixture (Committee on the Programming of Teaching Material for Higher TCM Education, 1996).

The black bean method (black beans are the dry and mature seeds of *Glycine max* (L.) Merr.) (Yang et al., 2008) is the most commonly used processing method, as described in “Xian Shou Li Shang Xu Duan Mi Fang” (Secret Formulary for Traumatology and Fracture Taught by Immortal), which was written during the Tang Dynasty. This work first proposed that the plant be prepared as follows: “10 lb, cooked with half a catty of black bean”. The book “Sue Shen Liang fang” of the Song Dynasty states that “After a one-day-long immersion, cut the *Polygonum multiflorum* into half-inch-



**Fig. 1.** Whole *Polygonum multiflorum* plant (A); The roots of *Polygonum multiflorum* (B); the roots of *Polygonum multiflorum* Praeparata (C).

thick sections and then mix well with the water of the black bean by placing fleece-flower root layer upon layer with the black bean. This should be followed by steaming until the beans become rotten, removal of the beans, and drying of the root in the shade". The Qing Dynasty "Cheng Fang Qie Yong" proposed that the plant be "mixed seven times with black bean juice" (Yu, 2014). In modern times, the 2010 edition of "Chinese Pharmacopoeia" described the following detailed rules for the *Polygonum multiflorum* processing method: Mix the slices or pieces of *Polygonum multiflorum* thoroughly with black bean juice (Preparation of black bean juice: Boil 10 kg of black bean in a sufficient quantity of water for 4 h and stew to get about 15 kg of juice. Boil the bean residue again in water for about 3 h and stew to get about 10 kg of juice. Combine to get about 25 kg of the black bean juice). Carry out the stewing method in a suitable non-ferrous container until the juice is exhausted or carry out the steaming method, steam it alone or steam it after being mixed with black bean juice to a brown color on all sides, dry in the sun to partial dryness, then cut into slice and dry. For each 100 kg of slice (piece) of *Polygonum multiflorum* use 10 kg of black bean (Editorial Committee of Chinese Pharmacopoeia., 2010).

Steaming is another common preparation method for *Polygonum multiflorum*. In this method, slightly moist *Polygonum multiflorum* is enclosed in boiler and steamed until the drugs both inside and outside are brown, at which point it is removed and desiccated (Zhou et al., 2010; Tian et al., 2007; Li et al., 2012g). In addition, there are other processing methods, including steaming with wine, rehmannia juice and boiling with a black bean-ginger mixture. There are also novel and improved processing methods using modern science and technology, such as fermentation and autoclave steaming. The pressure processing parameters are as

follows: the pressure ranges from 0.08 to 0.25 MPa, the heating time ranges from 4 to 10 h, and the temperature is 120 °C (Li et al., 2012f, 2012g; Du et al., 2012; Sun, 1996c; Liu and Wang, 2013; Xu et al., 2011; Qiu and Zeng, 2006b).

Currently in China, *Polygonum multiflorum* is a well-known traditional herb that is used as the main component of powders, decoctions or infusions for the treatments of leptotrichia (Wang et al., 2001), hyperlipidaemia (Yang et al., 2005), inflammation (Lv et al., 2001), learning and memory obstructions (Liu et al., 2004) and hyp immunity (Ma and Du, 2001) and as an antioxidant and anti-aging compound (Xiao et al., 1993). It has been widely used in clinical and traditional practice. An analysis of dozens of traditional Chinese medicine prescription books, such as "Beijing traditional Chinese medicine prescription anthology", "Ji Shan Tang Fang", "Bi Hua Yi Jing", "Bianque Xin Shu-Shen Fang", "Bu Ju Ji", "Chuai Mo You De Ji", "Dan Xi Xin Fa", and "Gu Fang Hui Jing" revealed 242 prescriptions containing *Polygonum multiflorum*, and the compatible herbs that are most frequently found include *Angelica sinensis*, *Radix rehmanniae*, *Glycyrrhiza*, *Rhizoma Chuanxiong*, and *Radix sileris*. The 2010 edition of the Chinese Pharmacopoeia lists 46 Chinese patent medicines containing *Polygonum multiflorum*, and the compatible herbs that are more frequently described include *Radix rehmanniae*, astragalus, *Angelica sinensis*, *Salviae miltiorrhizae*, and *Radix ophiopogonis*. Table 1 lists subsets of the Chinese patent drugs and decoctions containing *Polygonum multiflorum*.

### 3. Botany

*Polygonum multiflorum*, an herbaceous perennial plant, was originally called *Caulis Polygoni Multiflori* in the book "He Shou Wu Zhuan" written during the Tang dynasty (Li et al., 2003). Its root is tuberous, hypertrophic, oblong and dark brown in color. Its stems are approximately 2–4 m in length with a twine-like appearance, many branches, longitudinal ribs, glabrous and micro-rough skin and exhibit lignification in the lower parts. The leaves are ovate or broadly elliptic and 3–7 × 2–5 cm<sup>2</sup> in size with an acuminate apex and a cordate or subcordate base. Both sides of the leaf are coarse and have entire margins; the petioles are 1.5–3 cm in length; and the ochreas are membranous, oblique, glabrous and 3–5 mm in length. The inflorescences are paniculate, terminal or axillary and approximately 10–20 cm in length; the branches are expansive, with longitudinal ridges and small dense protrusions along the ridge. The bracts are triangular and ovate with small protrusions, and the apex is acute. In addition, each inflorescence contains three to four flowers. The pedicels are 2–3 mm in length and slender, and the perianths are white or greenish and five-parted. The perianth segments are oblong and of non-standard size. The male flowers have eight stamens, and the lower parts of the filaments are wide and very short, exhibit three styles, and have stigmas with a capitulum. The achenes are ovate with three ribs, black-brown, shiny, and approximately 2.5–3 mm in length (Editorial Board of Flora of China, 1998).

This plant is widely cultivated in many provinces of China, including Gansu, Shanxi, Sichuan, Yunnan, Guizhou, and Henan, and other countries, such as Japan. It grows in valley shrubs, hillside forests, gutter rock crevices and other locations with altitudes of 200–3000 m (Editorial Board of Flora of China, 1998; Zhou 1993).

As a widely used traditional Chinese medicine, there are some adulterants of this plant, involving nine species belonging to six families. The original plants are *Pteroxygonum giraldii* Damm et Diels, *P. cillinerve* (Nakai) Ohwi, *P. subertii* L. Henry, *Cynanchum auriculatum* Royle ex Wight, *C. wilfordi* (Maxim) Hemsl., *Stephania cepharantha* Hayata, *Musa basjoo* Sieb. et Zucc, *Dioscorea bulbifera* L. and *Rodgersia aesculifolia* Batal. (Chen et al., 1999a; Cheng and Zhou, 2005a; Zhao et al., 1998; Xia and Li, 2003). Until now, several



**Table 1**  
The traditional and clinical uses of *Polygonum multiflorum* in China.

Preparation name	Compositions	Used	References
Ren Shen Zai Zao pill	Scrophulariae Radix, Ephedrae Herba, Cyperi Rhizome, Angelicae Dahuricae Radix, Polygonum multiflorum, Rehmannia Radix Preparata, Asari Radix et Rhizome and others.	Curing apoplexia, facial paralysis and hemiplegia.	"Beijing traditional Chinese medicine prescription anthology", page 10.
Chan Ling pellet	Angelica Sinensis, Atractylodes Rhizome, Radix Aucklandiae, Polygonum multiflorum, Radix Aucklandiae, Monkshood Root, Rhizome Ligustici, Radix Saposhnikoviae, Angelicae Dahuricae Radix and others.	Curing woman postpartum lochiometra, thoracic and abdominal distension, stabbing hypochondrium pain.	"Beijing traditional Chinese medicine prescription anthology", page 194.
Duo Zi ingots	Lanceolata, Eucommia, Herba Cistanche, Common Anemarrhena Rhizome, Phellodendron Bark, Radix Polygala Tenuifolia, Alisma Orientale, Chinese Yam Root, Glycyrrhiza Uralensis Fisch, Polygonum multiflorum and others.	Curing deficiency of kidney qi, listlessness and ache of waist.	"Beijing traditional Chinese medicine prescription anthology", page 114.
Anti-asthma pill	Seeds of Brassica Alba, Folium Perillae, Liliun Brownie, Apricot Kernel, Radish Seed, Polygonum multiflorum, Radix Asparagi, Fritillaria Cirrhosa, Roots of Common Anemarrhena, Pinellia Ternate, Angelica Sinensis and others.	Curing deficiency syndrome of the lung, cough, dyspnea with cough and Phlegm	"Beijing traditional Chinese medicine prescription anthology", page 139.
Qi Bao Mei Ran pellet	Red Polygonum multiflorum, White Polygonum multiflorum, Red Poria Cocos, White Poria Cocos, Achyranthes Root, Angelica Sinensis, Barbary Wolfberry, Cuscuta Chinensis Lam and Fructus Psoralea.	Curing leukotrichia, lipsotrichia, dysgenesis, metrorrhagia and leukorrhagia, teeth shake, liver and kidney deficiencies	"Compendium of Materia Medica", qing dynasty, vol. 18.
Li Yin He Zhong	decotion	Rehmanniae Radix, Radix Glehniae, Cortex Lycii Radicis, Concha Ostreae, Polygonum multiflorum, White Peony Root, Magnolia Officinalis, Cortex Moutan, Artemisia Annuua, Fructus Setariae Germinates and Fructus Hordei Germinatus.	Curing children with rickets.
"Bi Hua Yi Jing", qing dynasty, vol. 3.			
Pei Tu Yang Yin	decotion	Prepared Polygonum multiflorum, Salvia Miltiorrhiza, Hyacinth Bean, Fructus Setariae Germinates, White Peony Root, Plantain Herb, Lotusty and Porcine Kidney.	Curing consumptive disease, apocleisis, phlegmatic, spontaneous perspiration, night sweat and spermatorrhea.
"Bu Ju Ji", qing dynasty, batch 1, vol. 10.			
Li Pi Yi Ying	decotion	Prepared Polygonum multiflorum, Sea Cucumber, Lotusty, Black Soybean, Rhizoma Dioscorea and Hyacinth Bean.	Curing insufficiency of the spleen, insufficiency of blood, fever due to yin deficiency.
"Bu Ju Ji", qing dynasty, batch 1, vol. 10.			
Qing Ji	decotion	Pinellia Ternate, Grassleaved Sweetflag Rhizome, Sophora Flavescens Ait, Linseed, Radix Saposhnikoviae, Atractylodes Rhizome, Radix Angelica Sinensis, Polygonum multiflorum, Rehmanniae Radix, Dried Ginger, Sixpetal Clematis Root and Carthamus Tinctorius.	Curing scabies and familial benign pemphigus.
"Chuang Yang Jing Yan Quan Shu", song dynasty, vol. 6.			
Ji Yin Hui Chun	decotion	Fresh Polygonum multiflorum, Radix Angelica Sinensis, White Peony Roots, Glycyrrhiza Uralemis Fisch, Raphanus Seed, Plantain Seed, Citrus Aurantium, Tangerine Peel and Simmer Radix Aucklandiae.	Curing dysentery.
"Ci Hang Ji",			

Table 1 (continued)

Preparation name	Compositions	Used	References
qing dynasty, vol. 4. Ju Sheng Zi pill	Prepared Radix Rehmanniae, Radix Rehmanniae, Polygonum multiflorum, Achyranthes Root, Cistanche Deserticola, Fructus Dipsaci, Poria Cocos, Seed of Oriental Arborvitae, Morinda Officinalis How, Rhizoma Dioscorea, Radix Dipsaci and others.	Curing feeble pulse, asynodia.	"Dan Xi Xin Fa", yuan dynasty, vol. 3.
Red bean powder Zheng Qi	Polygala Tenuifolium, Polygonum multiflorum Peel, Red bean, Carthamus Tinctorius and Schizonepeta Tenuifolia Briq. decoction	Curing ulcer.  Schizonepeta Tenuifolia Briq, Rhizome of Chuanxiong, Angelica Sinensis, Xia Qu, Radix Paeoniae Rubra, Atractylodes Rhizome, White Atractylodes Rhizome, Tangerine Peel, Red Polygonum multiflorum, Citrus Aurantium, Wrinkled Giant Hyssop and Cassia Twig.	"Gu Fang Jing Hui", qing dynasty, vol. 2. Curing Pregnancy malaria
"Gu Fang Jing Hui", qing dynasty, vol. 3. San Xian pill	Polygonum multiflorum, Atractylodes Rhizome, Foeniculum Vulgare, Cyperus Rotundus, Fructus Toosendan, Concha Ostreae and White Ginger.	Curing epicophosis, dim vision and woman splenic blood disease.	"Pu Ji Fang" qing dynasty, vol. 219.
Gou Pi plaster	Citrus Aurantium, Muscardine Silkworm, Alisma Orientale, Aconite Root, Phellodendron Bark, Polygonum multiflorum, Pinellia Ternate, Myrrha, Cortex Acanthopanax Radices, Achyranthes Root, Platycodon Grandiflorum, Rhizoma Gastrodiae and others.	Curing osphalgia, skelalgia and brachialgia.	Zhao et al. (2011a)
Huo Luo pellet	Tiger bone, Garter Snake, Deinagkistrodon, Radix Clematidis, Polygonum multiflorum, Rhizoma Coptidis, Rhizoma Gastrodiae, Boswellia Carterii, Myrrha, Rhizoma Typhonii, Scutellaria Baicalensis Root, Eucommia Ulmoides, Rhizome of Chuanxiong and others.	Curing rheumatic paralysis, acroanesthesia, low back and leg pain, arthralgia and myalgia, Phlegm heat syndrome.	Li et al. (2012c)
San Shen pill	Prepared Rhizome of Rehmannia, Cortex Moutan, Cynomorium Songaricum, Herba Cistanches, Poria Cocos, Barbary Wolfberry Fruit, White Atractylodes Rhizome, Radix Aconiti Carmichaeli, Rhizome of Chuanxiong, Rhizoma Dioscoreae, Eucommia Ulmoides, Angelicae Sinensis, Polygonum multiflorum and others.	Curing kidney asthenia, aversion to cold, overwork asthma, limb fatigue, lower energizer asthenia cold, hypofunction reproduct.	Zhou. (2010)
Die Da Sun Shang wine	Musk, Boswellia carterii, Native Copper, Carthamus Tinctorious, Pseudo-ginseng, Rhizoma Cyperi, Rhizoma Curcumae, Aristolochiae Lignum, Radix Clematidis, Cynomorium Songaricum, Evodia Rutaecarpa, Polygonum multiflorum, Radix Liquiritiae, Radix Angelicae and others. decoction	Curing traumatic injury.	Yuan et al. (2004)
Wu Mei Shang Yu "Si Sheng Xin Yuan", qing dynasty, vol. 8. Gui Zhi Wu Ling "Si Sheng Xin Yuan", qing dynasty, vol. 7. Yu Feng pellet	decoction	Schisandra Chinensis, Fructus Mume, Fructus Corni, Radix Liquiritiae, Polygonum multiflorum, Herbaceous Peony, Fossil Fragments and Concha Ostreae.	Curing corectasis.
Yu Feng pellet	Rhubarb, Mirabilite, Schizonepeta Tenuifolia Briq, Ephedra Intermedia, Gardenia Jasminoides Ellis, Radix Paeoniae Rubra, Fructus Forsythiae, Radix Liquiritiae, Polygonum multiflorum, Field Mint, Scutellaria Baicalensis Georgi, Rhizoma Gastrodiae and others.	Curing apoplexia.	"Zheng Zhi Bao Jian", mngo, vol. 1.
Yi Gan Ning granule	Herba Hedyotis, Polygonum Filiforme, Mongolian Dandelion Herb, Cortex Moutan Radices, Poria Cocos, White Atractylodes Rhizome, Astragalus Mongholicus, Artemisia Capillaris Thumb, Codonopsis Pilosula, Polygonum multiflorum, Radix Salviae Miltiorrhizae, White Peony Root and Fructus Toosendan	Curing chronic hepatitis, blood stasis blocking collaterals and damp heat toxin accumulation syndrome.	Yang and Zhang (1999) and Wu et al. (2001)

Table 1 (continued)

Preparation name	Compositions	Used	References
He Shou Wu granule	<i>Polygonum multiflorum</i>	Treatment of pregnancy constipation.	Zhu (2011)
Qi Shu	decotion	Astragalus, Radix Codonopsis, Lycium, Donkeyhide Glue, Angelica Sinensis, Polygonum Multiflorum, Cauliss Patholobi, Glycyrrhiza Uralensis.	Treatment of NSCLC patients with leukopenia after Chemotherapy
Xiang and Han, (2013)			
Zi Shen Bu Gan Fang	<i>Polygonum Multiflorum</i> , <i>Polygonatum Canaliculatum</i> , Fructus <i>Ligustri Lucidi</i> , Fructus <i>Lycii</i> .	Anti-aging	Wang (2012b)
Pei Bu Gan Shen Fomula	Fructus broussonetiae, Semen Astragali complanati, Prepared Rhizome of <i>Rehmannia</i> , Prepared <i>Polygonum multiflorum</i> , Glue of Tortoise Plastron, Fructus <i>Lycii</i> , <i>Morinda Officinalis</i> , Radix <i>Achyranthis Bidentatae</i> , Herba <i>Cistanches</i> and others.	Treatment Parkinson's disease and intestinal dysfunction	Chen (2013)
Ren Shen Shou Wu capsule	Radix <i>Ginseng Rubra</i> and Prepared <i>Polygonum multiflorum</i> .	Curing premature graying hair, insomnia, loss of appetite and body weakness due to qi-blood deficiency.	"Chinese Pharmacopoeia", vol. 1.
Tian Ma Shou Wu tablets	Rhizoma <i>Gastrodiae</i> , <i>Polygonum multiflorum</i> , Radix <i>Angelicae</i> , Radix <i>Rehmanniae Praeparata</i> , Radix <i>Salviae Miltiorrhizae</i> , Rhizome of <i>Chuanxiong</i> , Radix <i>Angelicae Sinensis</i> , Stir-baked Fructus <i>Tribuli</i> , Folium <i>Mori</i> , Herba <i>Ecliptae</i> , Fructus <i>Ligustri Lucidi</i> , Radix <i>Paeoniae Alba</i> , <i>Polygonatum Canaliculatum</i> and Radix <i>Liquiritiae</i> .	Curing dizzy, headache, tinnitus, bitter mouth, dry pharynx, soreness and weakness of waist and knees due to the deficiency of liver-yin and kidney-yin. Curing cerebral arteriosclerosis, cluster headache syndrome and alopecia seborrheica.	"Chinese Pharmacopoeia", vol. 1.
Xin Nao Kang capsule	Radix <i>Salviae Miltiorrhizae</i> , Prepared <i>Polygonum multiflorum</i> , Red Paeony Root, Radix <i>Puerariae</i> , <i>Carthamus Tinctorious</i> , Root of <i>Bidentate Achyranthes</i> , Radix <i>Curcumae</i> , Barbary Wolfberry Fruit, Rhizome of <i>Chuanxiong</i> , Rhizoma <i>Alismatis</i> , <i>Polygala Tenuifolia</i> and others.	Curing thoracic obstruction, circumgyration, coronary heart disease, angina pectoris and cerebral arteriosclerosis.	"Chinese Pharmacopoeia", vol. 1.
Xue Zhi Ning Pill	Rhizoma <i>Alismatis</i> , Cassia Seed, Hawthorn and Prepared <i>Polygonum multiflorum</i> .	Curing hyperlipidemia, dizziness, chest tightness and constipated.	"Chinese Pharmacopoeia", vol. 1.
Jiang Zhi Ling tablets	Prepared <i>Polygonum multiflorum</i> , Barbary Wolfberry Fruit, <i>Polygonatum Canaliculatum</i> , Hawthorn and Cassia Seed.	Curing hyperlipidemia, dizziness, premature graying hair.	"Chinese Pharmacopoeia", vol. 1.

methods have been developed to identify and distinguish them, including experiential identification, morphological identification, ultraviolet spectrophotometry, the TLC method, HPLC, gel electrophoresis, HPLC-ESI/MS and ITS2 rDNA sequencing (Chen et al., 1998; Li et al., 1995; Ge et al., 2011; Sun et al., 1996a; Zhang and Shi, 2007a; Zheng et al., 2009; Zheng, 2010).

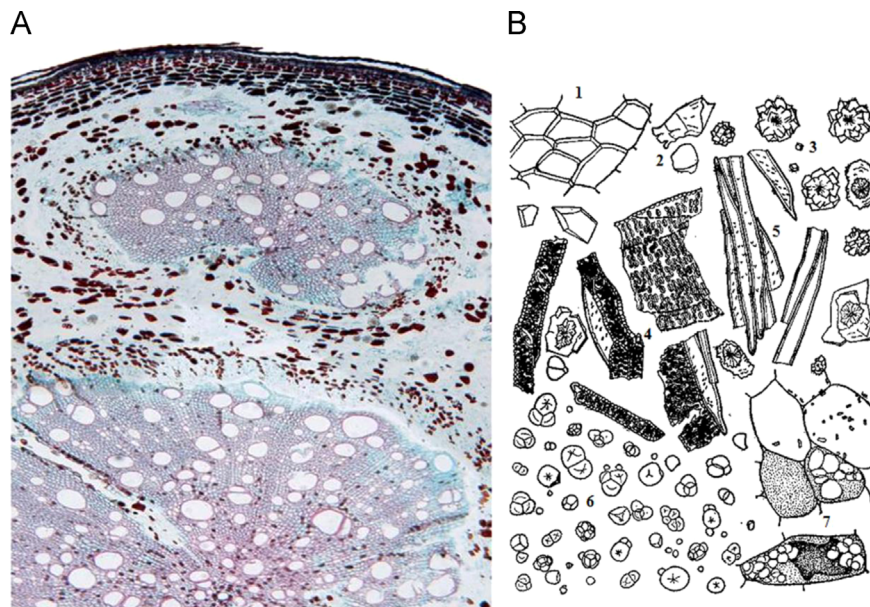
The morphological identification method is regarded as the most popular method for identifying *Polygonum multiflorum*. The fracture plane of *Polygonum multiflorum* is yellowish-brown or reddish-brown and starchy and exhibits a brocaded pattern (abnormal vascular bundle). The cork layer of the root transverse sections shows 2–3 columns of rectangular cells. The phelloderm is a sequence of tangential prolonged cells, the surface view of the cork cells is subpolygonal, and there are decadent epidermal cells on the outside. The phloem is broad and mainly composed of parenchymatous cells, with the brown cells distributed in the parenchyma, and the phloem ray is not obvious. There are several uniquely shaped compound vascular bundles and scattered fiber bundles, with subpolygonal or irregular fibers that are 5–30 µm in diameter with a wall thickness of 2.5 µm. Clusters of calcium oxalate are scattered in the cambium ring. The xylem are more developed, and the vessels are subrounded, primarily bordered, pitted, and 13–101 µm in diameter. The fibers are square and 5–18 µm in diameter with a wall thickness of 2.5 µm. The sequence of wood ray cells is wide but not very obvious, and the majority of the cell walls are thick. The starch granules are fairly abundant with simple spherical granules that are 4–39 µm in diameter. The hilum are stellate or forked, and compound starch granules are common, whereas brown blocks are ubiquitously scattered (Fig. 2). Of the counterfeits of *Polygonum multiflorum*, *Musa basjoo* Sieb. et Zucc has no cork tissue but does have needle-like calcium oxalate crystals. In *Pteroxygonum giraldii* Damm et Diels, the cork cells of are yellowish-

brown, there are fewer vessels in the xylem, and the vessels are primarily reticulate. In this same species, there is a single starch granule that is circular, triangular, oblong or subovate. The hilum is pointed, cleft or cruciate. In the counterfeit species *Dioscorea bulbifera* L, the cork cells are approximately square, and the walls are pale brown. The mucilage cells are oblong, and there are calcium oxalate raphides that are approximately 50 µm in length. The species *P. cillinerve* (Nakai) Ohwi has khaki-coloured sections, and the cork layer of the transverse root sections is composed of a sequence of rectangular cells. The vessels are subrounded and mostly singularly arranged, and these are larger on the outside and become smaller gradually toward the interior. The wood ray is obvious, and there are clusters of calcium oxalate in the wood ray cells. Moreover, none of the counterfeits of *Polygonum multiflorum* have a "brocaded pattern" (Ge et al., 2011; Cheng and Zhou, 2005b; He and Sun, 2010; Guo et al., 2007a; Lu et al., 2012; Sun and Bai, 1996a, 1996b; Xu, 1986).

HPLC is the most widely used method for evaluating the quality and authenticity of *Polygonum multiflorum*. 2,3,5,4'-Tetrahydroxystilbene-2-O-glc in combination with anthraquinone are used as the indicator compounds to characterize the quality of this plant with minimum contents of 1.0% and 0.10%, respectively. The content of the combined anthraquinones is calculated using the amounts of emodin and physcion, and the process is described in the Pharmacopoeia of the People's Republic of China.

#### 4. Phytochemistry

There are many chemical constituents in *Polygonum multiflorum*, including flavones, quinones, and stilbenes. In this section,



**Fig. 2.** Cross section (A) and microscopic structure (B, 1-Cork cell; 2-Brown block; 3-Clusters of calcium oxalate; 4-Vessel; 5-Cork fiber; 6-Starch granules; 7-Brown cell) of *Polygonum multiflorum*.

we describe the major chemical constituents of this plant and their structures (Table 2) (Figs. 3–8).

#### 4.1. Stilbenes

Stilbenes are the main characteristic components in *Polygonum multiflorum*. 2,3,5,4'-Tetrahydroxystilbene-2-O- $\beta$ -D-glucopyranoside (**1**) was first isolated and identified from this plant in 1976 (Yang, 1976), and another two stilbenes, which were identified as 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-(2''-O-monogalloyl esters)-glucopyranoside (**2**) and 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-(3''-O-monogalloyl esters)-glucopyranoside (**3**), were then isolated (Nonaka et al., 1982). 2,3,5,4'-Tetrahydroxystilbene-2,3-di-O- $\beta$ -D-glucopyranoside (**4**) was isolated from the ethyl acetate insoluble fraction of an ethanol extract of the plant (Zhou et al., 1994). Two tetrahydroxystilbenes were isolated from this plant in 2000 and identified as 2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (**5**) (Chen et al., 2000a) and 2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O-acetyl)- $\beta$ -D-glucopyranoside (**6**) (Chen et al., 2000c). Another stilbene, which was identified as 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-xyloside (**7**) (Sun et al., 2013), was isolated from a 70% ethanol extract of *Polygonum multiflorum*. Five stilbene glycosides, which were identified as 2,3,5,4'-tetrahydroxystilbene-2-O-(4''-O- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (**8**), 2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O- $\beta$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (**9**), 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucopyranosyl-4'-O- $\alpha$ -D-glucopyranoside (**10**), 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucopyranosyl-5-O- $\alpha$ -D-glucopyranoside (**11**) and 2,3,5,4'-tetrahydroxystilbene-2-O-(2''-O- $\beta$ -D-fructofuranosyl)- $\beta$ -D-glucopyranoside (**12**), were isolated from *Polygonum multiflorum* in 2013 (Li et al., 2013b). Moreover, resveratrol (**13**), polydatin (**14**) (Xu et al., 2009), rhaponticoside (**15**) (Yi et al., 2007), *cis*-2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucopyranoside (**16**) (Sun et al., 2009) and *cis*-2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (**17**) (Xiao et al., 2002) were also isolated from *Polygonum multiflorum*. Four stilbene derivatives, denoted polygonumosides A–D (**18–21**), were isolated and identified from this plant in 2014 (Yan et al., 2014). Other stilbenes, such as tetrahydroxystilbene-O-(malonyl)-hex, tetrahydroxystilbene-O-deoxyhex and tetrahydroxystilbene-O-(caffeoyl)-hex, were also found in *Polygonum*

*multiflorum*, but their structures have not yet been identified (Qiu et al., 2013).

#### 4.2. Quinones

Quinones are the other characteristic components in *Polygonum multiflorum*. Quinones and their derivatives have been isolated and identified, and most of them are anthraquinones. The predominant anthraquinones are emodin-type anthraquinones, including emodin (**22**), aloe-emodin (**23**), chrysophanol (**24**), physcion (**25**), rhein (**26**), 1,6-dimethyl ether-emodin (**27**), emodin-8-methyl ether (**28**), citreorosein (**29**), citreorosein-8-methyl ether (**30**), emodin-3-methyl ether (**31**) fallacinal (**32**), emodin-6,8-dimethylether (**33**) and 2-acetylemodin (**34**) (Sun et al., 2013; Li et al., 2013c; Li and Lin, 1993; Kato and Morita, 1987; Wang et al., 2005b; Chen et al., 1999b; Zuo et al., 2008; Zhang et al., 2006a). There are also many combined anthraquinones in *Polygonum multiflorum*, such as emodin-8-O- $\beta$ -D-glucopyranoside (**35**), physcion-8-O- $\beta$ -D-glucopyranoside (**36**) (Qiu et al., 2013; Li et al., 2013c), emodin-3-methyl ether-8-O- $\beta$ -D-glucopyranoside (**37**) (Li et al., 2006), physcion-8-O-(6'-O-acetyl)- $\beta$ -D-glucopyranoside (**38**) (Sun et al., 2009), emodin-8-O-(6'-O-acetyl)- $\beta$ -D-glucopyranoside (**39**) (Zhang et al., 2006a) and chrysophanol-8-O- $\beta$ -D-glucopyranoside (**40**) (Yang et al., 1998). Two naphthoquinones, namely 6-methoxyl-2-acetyl-3-methyl-1,4-naphthoquinone-8-O- $\beta$ -D-glucopyranoside (**41**) (Chen et al., 2000c) and 2-methoxy-6-acetyl-7-methylglucuronide (**42**) (Li et al., 1993), were also isolated from *Polygonum multiflorum*.

#### 4.3. Flavonoids

Flavonols exist in numerous plants, including *Polygonum multiflorum*. These compounds have antioxidant and free radical scavenging activities (Li et al., 2012e). The flavonols in *Polygonum multiflorum* include tricetin (**43**), rutin (**44**), luteolin (**45**), quercetin (**46**), kaempferol (**47**), isoorientin (**48**), apigenin (**49**), hyperoside (**50**), vitexin (**51**) and quercetin-3-O-arabinoside (**52**) (Xu et al., 2006; Li and Lin, 1993; Chen et al., 2000b, 2001c). In addition, a novel flavonostilbene glycoside was isolated from *Polygonum multiflorum* and identified as polygonflavanol A (**53**) (Chen et al., 2012a).



**Table 2**  
Chemical compounds isolated from *Polygonum multiflorum*.

Classification	NO	Chemical component	Reference
Stilbenes	1	2,3,5,4'-tetrahydroxystilbene-2-O-β-D- glucopyranoside	Yang. (1976)
	2	2,3,5,4'-tetrahydroxystilbene-2-O-β-D-(2''-O-monoalloyl esters)-glucopyranoside	Nonaka et al. (1982)
	3	2,3,5,4'-tetrahydroxystilbene-2-O-β-D-(3''-O-monoalloyl esters)-glucopyranoside	Nonaka et al. (1982)
	4	2,3,5,4'-tetrahydroxystilbene-2,3-di-O-β-D-glucopyranoside	Zhou et al. (1994)
	5	2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O-α-D-glucopyranosyl)-β-D-glucopyranoside	Chen et al. (2000a)
	6	2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O-acetyl)-β-D-glucopyranoside	Chen et al. (2000a)
	7	2,3,5,4'-tetrahydroxystilbene-2-O-β-D-xyloside	Sun et al. (2013)
	8	2,3,5,4'-tetrahydroxystilbene-2-O-(4''-O-α-D-glucopyranosyl)-β-D-glucopyranoside	Li et al. (2013b)
	9	2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O-β-D-glucopyranosyl)-β-D-glucopyranoside	Li et al. (2013b)
	10	2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucopyranosyl-4''-O-α-D-glucopyranoside	Li et al. (2013b)
	11	2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucopyranosyl-5-O-α-D-glucopyranoside	Li et al. (2013b)
	12	2,3,5,4'-tetrahydroxystilbene-2-O-(2''-O-β-D-fructofuranosyl)-β-D-glucopyranoside	Li et al. (2013b)
	13	Resveratrol	Xu et al. (2009)
	14	Polydatin	Xu et al. (2009)
	15	Rhaponticoside	Yi et al. (2007)
	16	Cis-2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucopyranoside	Sun et al. (2009)
	17	Cis-2,3,5,4'-tetrahydroxystilbene-2-O-(6''-O-α-D-glucopyranosyl)-β-D-glucopyranoside	Xiao et al. (2002)
	18	Polygonumosides A	Yan et al. (2014)
	19	Polygonumosides B	Yan et al. (2014)
	20	Polygonumosides C	Yan et al. (2014)
	21	Polygonumosides D	Yan et al. (2014)
Quinones	22	Emodin	Sun et al. (2013); Li et al. (2013); Li and Lin (1993); Kato and Morita (1987); Wang et al. (2005b); Chen et al. (1999b); Zuo et al. (2008); Zhang et al. (2006a)
	23	Aloe-emodin	
	24	Chrysophanol	
	25	Physcion	
	26	Rhein	
	27	1,6-dimethyl ether-emodin	
	28	Emodin-8-methyl ether	
	29	Citreorosein	
	30	Citreorosein-8-methyl ether	
	31	Emodin-3- methyl ether	
	32	Fallacinol	
	33	Emodin-6,8-dimethylether	
	34	2-acetylemodin	
	35	Emodin-8-O-β-D-glucopyranoside	Qiu et al. (2013); Li et al. (2013)
	36	Physcion-8-O-β-D-glucopyranoside	Qiu et al. (2013); Li et al. (2013)
	37	Emodin-3- methyl ether-8-O-β-D-glucopyranoside	Li et al. (2006)
	38	Physcion-8-O-(6''-O-acetyl)-β-D-glucopyranoside	Sun et al. (2009)
	39	Emodin-8-O-( 6''-O-acetyl)- β-D-glucopyranoside	Zhang et al. (2006a)
	40	Chrysophanol-8-O-β-D-glucopyranoside	Yang et al. (1998)
	41	6-methoxyl-2-acetyl-3-methyl-1,4-naphthoquinone-8-O-β-D-glucopyranoside	Chen et al. (2000c)
	42	2-Methoxy-6-acethyl-7-methylglone	Li and Lin (1993)
Flavonoids	43	Tricin	Xu et al. (2006); Li and Lin (1993); Chen et al. (2001c); Chen et al. (2000b)
	44	Rutin	
	45	Luteolin	
	46	Quercetin	
	47	Kaempferol	
	48	Isoorientin	
	49	Apigenin	
	50	Hyperoside	
	51	Vitexin	
	52	Quercetin-3-O-arabinoside	
	53	Polygonflavanol A	Chen et al. (2012a)
Phospholipids	54	Phosphatidyl ethanolamine	Chen et al. (2001c)
	55	Copaene	Chen et al. (2001c)
	56	Eicosane	Chen et al. (2001c)
	57	Hexanoic acid	Chen et al. (2001c)
	58	Hexadecanoic acid methyl ester	Chen et al. (2001c)
	59	Hexadecanoic acid ethyl ester	Chen et al. (2001c)
	60	Octadecanoic acid methyl ester	Chen et al. (2001c)
	61	Octadecanoic acid ethyl ester	Chen et al. (2001c)
	62	Ethyl oleate	Chen et al. (2001c)

Table 2 (continued)

Classification	NO	Chemical component	Reference
	63	Docosanoic acid methyl ester	Chen et al. (2001c)
	64	Tetradecanoic acid ethyl ester	Chen et al. (2001c)
	65	Squalene	Chen et al. (2001c)
	66	1, 2- dihydroxynonadecane- 3	Chen et al. (2000b)
	67	1-O-stearoyl-2-O- $\Delta^{4,7}$ -dodecenoyl-3-O-phosphatidic acid-O- $\beta$ -D-glucoside	Chen et al. (2001b)
	68	1-O-stearoyl-2-O- $\Delta^{4,7}$ -dodecenoyl-3-O-phosphatidic acid-O-(6''-O- $\alpha$ -D-glucoside)- $\beta$ -D-glucoside	Chen et al. (2001b)
Other compounds	69	Catechin	Chen et al. (1999c)
	70	Epicatechin	Chen et al. (1999c)
	71	3-O-galloyl(-)-catechin	Nonaka et al. (1982)
	72	3-O-galloyl(-)-epicatechin	Nonaka et al. (1982)
	73	3-O-galloyl-procyanidin B2	Nonaka et al. (1982)
	74	3,3'-di-O-galloyl-procyanidin B2	Nonaka et al. (1982)
	75	Gallic acid	Li and Lin (1993)
	76	Methyl gallate	Yang et al. (1998)
	77	N-trans-Feruloyl tyramine	Li and Lin (1993)
	78	N-trans-feruloyl-3-methyldopamine	Li and Lin (1993)
	79	Indole-3-(L- $\alpha$ -amino- $\alpha$ -hydroxypropionic acid) methyl ester	Yang et al. (1998)
	80	7-hydroxy-4-methylcoumarin-5-O- $\beta$ -D-glucopyranoside	Yu et al. (2008)
	81	7-hydroxy-3,4-dimethylcoumarin-5-O- $\beta$ -D-glucopyranoside	Yu et al. (2008)
	82	n-butyl- $\beta$ -D-fructopyranoside	Zhang, et al. (2006b)
	83	1,3-dihydroxy-6,7-dimethylxanthone -1-O- $\beta$ -D-glucopyranoside	Zhou et al. (1994)
	84	Daucosterol	Li and Lin (1993); Rao et al. (2009)
	85	4-hydroxybenzaldehyde	Li et al. (2006)
	86	5-carboxymethyl-7-hydroxy-2-methylchromone	Li et al. (2006)
	87	1, 2-propanediol-1-(4-hydroxy-phenyl)	Yamaguchi et al. (1969)
	88	(+)-lyoniresinol-3 $\alpha$ -O- $\beta$ -D-glucopyranoside	Achenbach et al. (1992)
	89	2,3,4,6-tetrahydroxyacetophenone-3-O- $\beta$ -D-glucoside	Yoshizaki et al. (1987); Yoshizaki et al. (1987)
	90	Torachryson-8-O- $\beta$ -D-glucopyranoside	Li et al. (2006)
	91	Torachryson-8-O-(6'-O-acetyl)- $\beta$ -D-glucopyranoside	Sun et al. (2009)
	92	Torachryson-8-O-(6'-O-galloyl)- $\beta$ -D-glucoside	Li and Lin (1993)
	93	$\beta$ -amyrin	Rao et al. (2009)
	94	$\beta$ -sitosterol	Rao et al. (2009)
	95	$\beta$ -Sitosterol-3-O- $\beta$ -D-glucoside	Xu et al. (2006)
	96	2,5-dimethyl-7-hydroxychromone	Liang et al. (2009)
	97	Schizandrin	Chen et al. (1999b)
	98	(S)-2-(2'-hydroxypropyl)-5-methyl-7-hydroxyl chromone-7-O- $\alpha$ -L-fucosyl(1 $\rightarrow$ 2)- $\beta$ -D-glycoside	Zhao et al. (2014)
New compounds after processed	99	2,3-di-hydro-3,5-dihydroxy-6-methyl-4(H)-pyran-4-one	Liu et al. (2007b); Liu et al. (2009c); Liu et al. (2008b).
	100	Hydroxymaltol	
	101	5-Hydroxy methyl-furfuran	
	102	Butanedioic acid	
	103	5-dihydroxy-6-methyl-4(H)-pyran-4-one	

#### 4.4. Phospholipids

*Polygonum multiflorum* is rich in phospholipids and may be associated with the tonic effect of *Polygonum multiflorum*. These phospholipids include phosphatidyl ethanolamine (54), copaene (55), eicosane (56), hexanoic acid (57), hexadecanoic acid methyl ester (58), hexadecanoic acid ethyl ester (59), octadecanoic acid methyl ester (60), octadecanoic acid ethyl ester (61), ethyl oleate (62), docosanoic acid methyl ester (63), tetradecanoic acid ethyl ester (64), squalene (65) (Chen et al., 2001c), 1,2-dihydroxynonadecane-3 (66) (Chen et al., 2000b), 1-O-stearoyl-2-O- $\Delta^{4,7}$ -dodecenoyl-3-O-phosphatidic acid-O- $\beta$ -D-glucoside (67) and 1-O-stearoyl-2-O- $\Delta^{4,7}$ -dodecenoyl-3-O-phosphatidic acid-O-(6''-O- $\alpha$ -D-glucoside)- $\beta$ -D-glucoside (68) (Chen et al., 2001b).

#### 4.5. Other compounds

There are also other components in *Polygonum multiflorum*, and these include the following polyphenolic compounds: catechin (69),

epicatechin (70) (Chen et al., 1999c), 3-O-galloyl(-)-catechin (71), 3-O-galloyl(-)-epicatechin (72), 3-O-galloyl-procyanidin B2 (73), 3,3'-di-O-galloyl-procyanidin B2 (74) (Nonaka et al., 1982), gallic acid (75) (Li and Lin, 1993) and methyl gallate (76) (Yang et al., 1998). Three nitrogenous compounds, namely N-trans-feruloyltyramine (77), N-trans-feruloyl-3-methyldopamine (78) (Li and Lin, 1993) and indole-3-(L- $\alpha$ -amino- $\alpha$ -hydroxypropionic acid) methyl ester (79) (Yang et al., 1998), were also isolated and identified from this plant. Two coumarin glucosides, which were identified as 7-hydroxy-4-methylcoumarin-5-O- $\beta$ -D-glucopyranoside (80) and 7-hydroxy-3,4-dimethylcoumarin-5-O- $\beta$ -D-glucopyranoside (81) (Yu et al., 2008), were also isolated. Furthermore, the following compounds were also isolated from *Polygonum multiflorum*: n-butyl- $\beta$ -D-fructopyranoside (82) (Zhang, et al., 2006b), 1,3-dihydroxy-6,7-dimethylxanthone-1-O- $\beta$ -D-glucopyranoside (83) (Zhou et al., 1994), daucosterol (84) (Li and Lin, 1993; Rao et al., 2009), 4-hydroxybenzaldehyde (85), 5-carboxymethyl-7-hydroxy-2-methylchromone (86) (Li et al., 2006), 1,2-propanediol-1-(4-hydroxy-phenyl) (87) (Yamaguchi et al., 1969), (+)-lyoniresinol-3 $\alpha$ -O- $\beta$ -D-glucopyranoside (88) (Achenbach et al., 1992), 2,3,4,

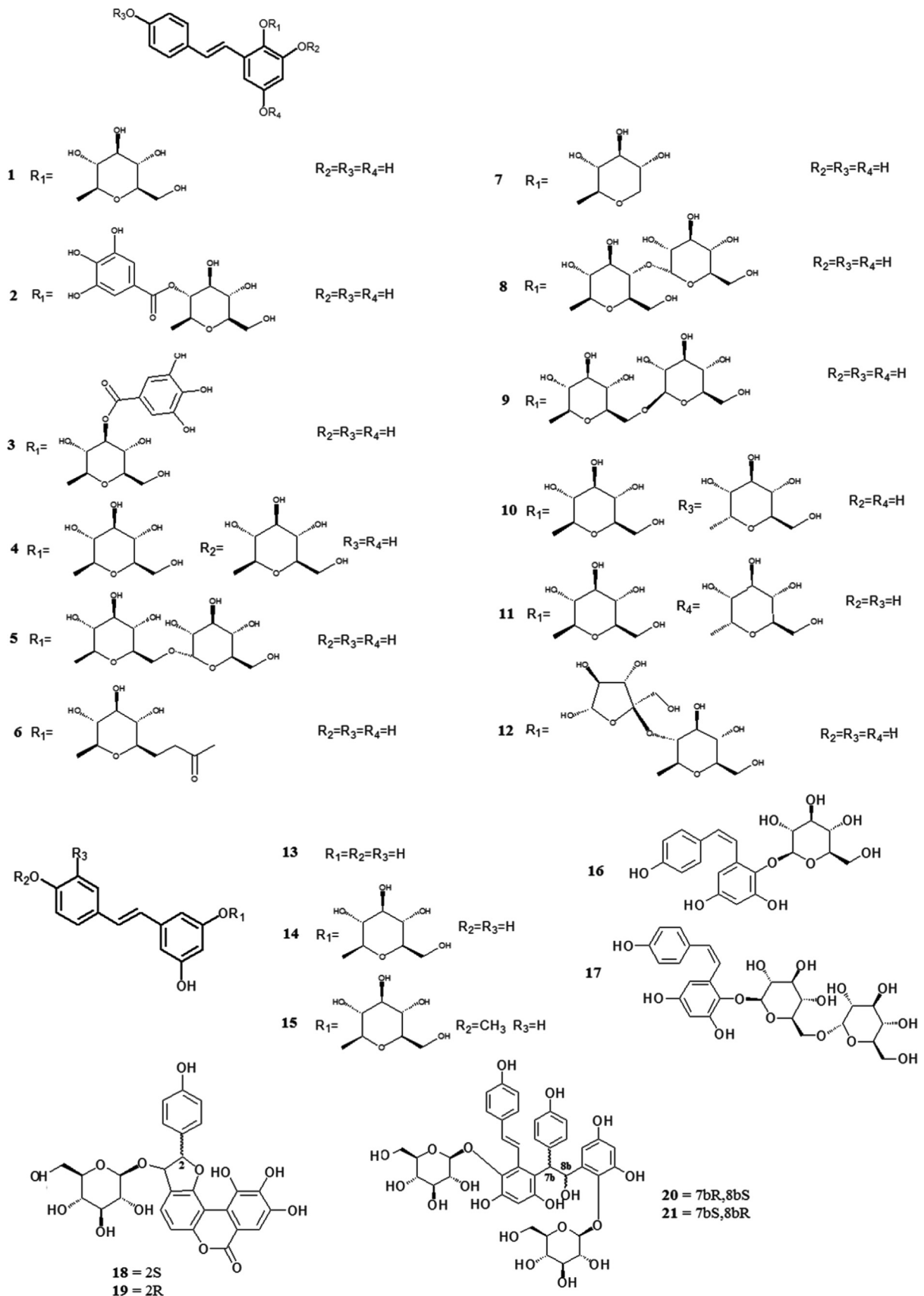
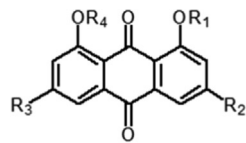


Fig. 3. Chemical structures of stilbenes.



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
22	H	-CH <sub>3</sub>	-OH	H
23	H	H	-CH <sub>2</sub> OH	H
24	H	H	-CH <sub>3</sub>	H
25	H	-CH <sub>3</sub>	-OCH <sub>3</sub>	H
26	H	-CH <sub>3</sub>	-COCH <sub>3</sub>	H
27	-CH <sub>3</sub>	-CH <sub>3</sub>	-OCH <sub>3</sub>	H
28	-CH <sub>3</sub>	-CH <sub>3</sub>	-OH	-CH <sub>3</sub>
29	H	-CH <sub>2</sub> OH	-OH	H
30	H	-CH <sub>2</sub> OH	-OH	-CH <sub>3</sub>
31	H	-OCH <sub>3</sub>	-OH	H
32	H	-CH <sub>2</sub> OH	-OCH <sub>3</sub>	H
33	H	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>

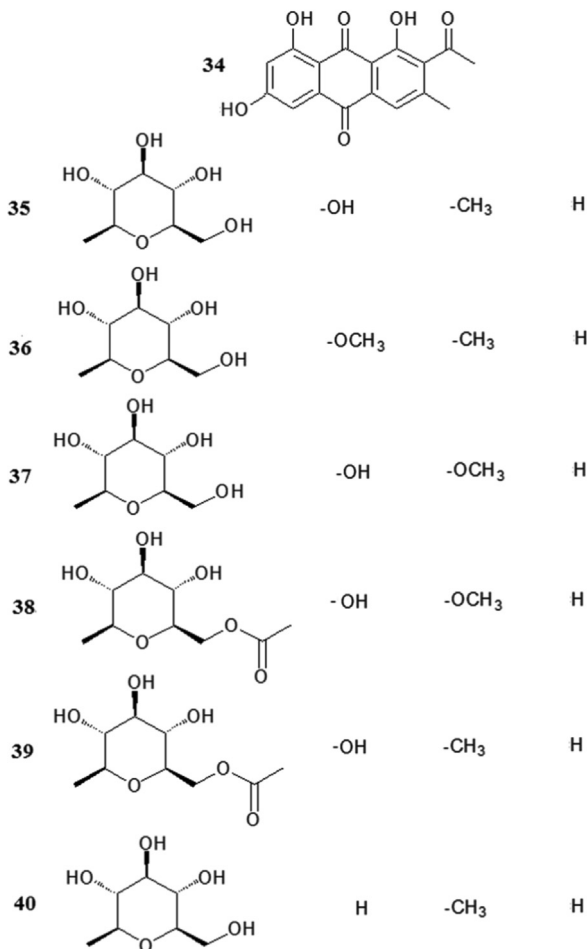


Fig. 4. Chemical structures of quinones.

6-tetrahydroxyacetophenone-3-O- $\beta$ -D-glucopyranoside (**89**) (Yoshizaki et al., 1987), torachryson-8-O- $\beta$ -D-glucopyranoside (**90**) (Li et al., 2006), torachryson-8-O-(6'-O-acetyl)- $\beta$ -D-glucopyranoside (**91**) (Sun et al.,

2009), torachryson-8-O-(6'-O-galloyl)- $\beta$ -D-glucoside (**92**) (Li and Lin, 1993),  $\beta$ -amyrin (**93**),  $\beta$ -sitosterol (**94**) (Rao et al., 2009),  $\beta$ -sitosterol-3-O- $\beta$ -D-glucoside (**95**) (Xu et al., 2006), 2,5-dimethyl-7-hydroxychromone (**96**) (Liang et al., 2009), schisandrin (**97**) (Chen et al., 1999b), (S)-2-(2'-hydroxypropyl)-5-methyl-7-hydroxyl, and chromone-7-O- $\alpha$ -L-fucosyl(1 $\rightarrow$ 2)- $\beta$ -D-glucoside (**98**) (Zhao et al., 2014).

#### 4.6. Changes in the chemical constitution after processing

The chemical constituents in *Polygonum multiflorum* changes after processing, and novel components can be created. The combined anthraquinone content decreases with increased processing. The content of free anthraquinones, such as emodin and physcion, increases with prolonged processing time. The content of D-glucose increases gradually, whereas the D-fructose and sucrose contents decrease gradually, and the content of polysaccharide slightly increases. The content of stilbene glucoside (index component of *Polygonum multiflorum*) is reduced with an increase in the processed time, and the content exhibited the following order: rice wine mixed with steamed > steamed > rice wine and fried > black bean juice products. After processing, the content of tannin decreased, and the antioxidant activity of the gallic acid content increased; however, catechin was almost undetectable after processing for 16 h. Other studies have found that the content of trace elements in fleece-flower root before and after processing changed only slightly (Zhang et al., 2009; Chen et al., 2012d; Fu, 2013; Liu et al., 2008b; Qiu et al., 2006a, 2006b; Wang et al., 2004; Shi, 2003; Liu et al., 2005c; Liu et al., 2009b; Nie and Liu, 2002).

According to a previous study, *Polygonum multiflorum* processing resulted in the production of five ingredients: 2,3-di-hydroxy-3,5-dihydroxy-6-methyl-4(H)-pyran-4-one (**99**), hydroxymaltol (**100**), 5-hydroxyethyl-furfural (**101**), butanedioic acid (**102**), and 5-dihydroxy-6-methyl-4(H)-pyran-4-one (Liu et al., 2007b, 2008c, 2009c). In conclusion, processing has a marked influence on the chemical constituents of *Polygonum multiflorum*, and the fact that the toxicity of *Polygonum multiflorum preparata* is lower than that of the crude drugs may be associated with the decreased levels of some of the components after processing.

## 5. Pharmacodynamics and potential applications

### 5.1. Anti-aging effect

Age is the leading risk factor for many of the most prevalent and devastating diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). AD is a neurodegenerative disease characterized by progressive memory loss and cognitive impairment and is the most common type of dementia in the aging population (Long and Dougherty, 2003). PD is a common progressive neurodegenerative disorder characterized by the loss of specific populations of neurons and the accumulation of protein aggregates in the brain. The disease affects more than 1% of the population over the age of 60, and as the population ages, this frequency is likely to increase (Fahad et al., 2014; Lang and Lozano, 1998; Obeso et al., 2010). The main effect of *Polygonum multiflorum* is anti-aging given that it can be used to treat AD and PD. Specifically, 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside (TSG), one of the effective components of this plant, may be able to treat AD and PD (Li et al., 2010b; Zhang et al., 2010; Su et al., 2014). *Polygonum multiflorum* and TSG may potentially treat AD and PD through the following mechanisms: inhibition of acetylcholinesterase (AChE), neuroprotection, antioxidant activity and cognitive enhancement.



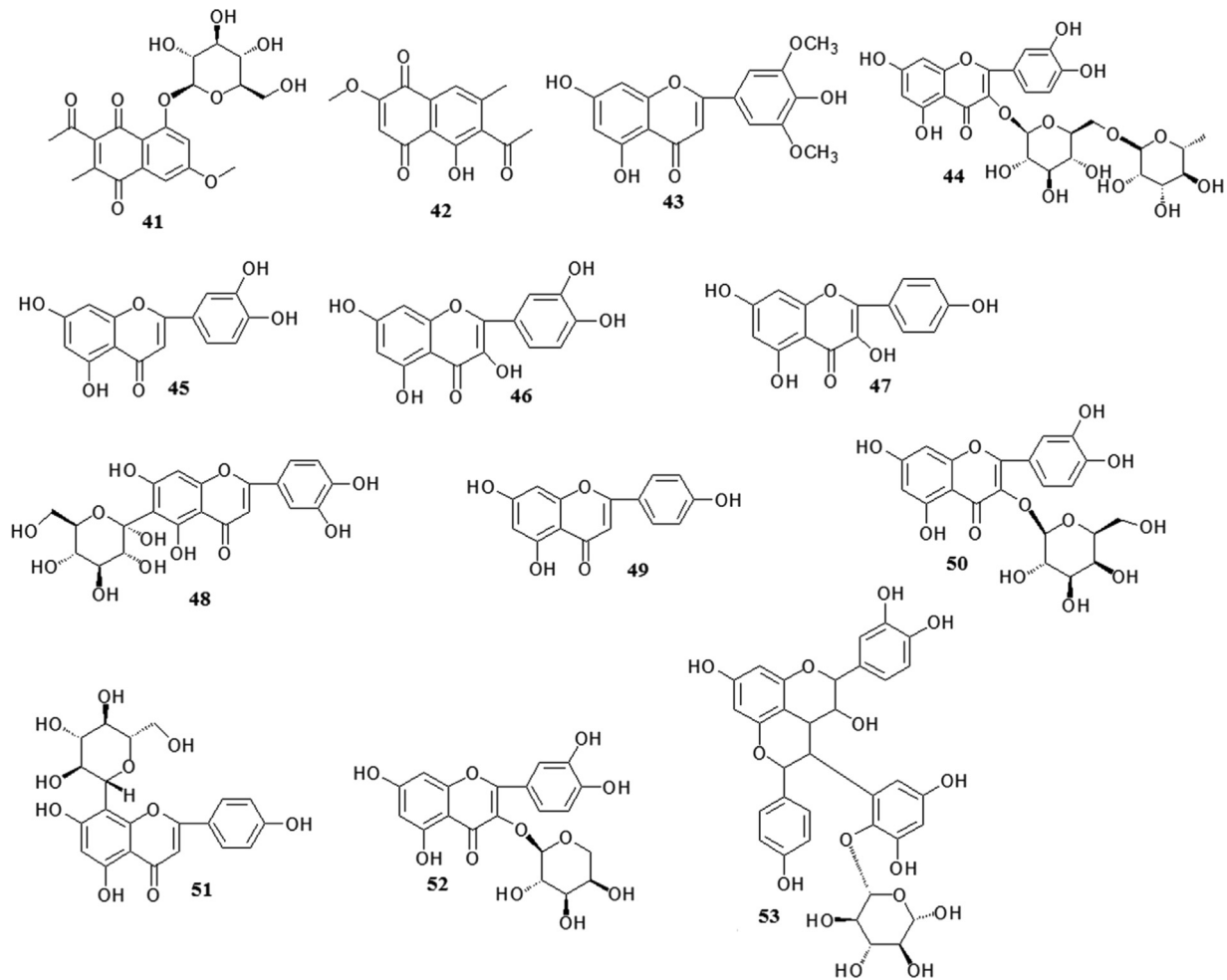


Fig. 5. Chemical structures of flavonoids.

### 5.1.1. AChE inhibition

AChE inhibitors are commonly used to treat AD. TSG can decrease AChE activity and increase the expression of protein phosphatase-2A (PP-2A) and microtubule associated protein-2 (MAP-2) in the hippocampus of model rats following the i.g. administration of 30, 60 and 120 mg/kg/day for 11 weeks (Liu et al., 2008a). Emodin-8-O- $\beta$ -D-glucopyranoside (EG), another effective component of *Polygonum multiflorum*, was tested *in vitro* against AChE I zymogen (extracted from the mice cerebral cortex) at doses ranging from 23.1 to 92.6  $\mu$ mol/mL, and the results indicate that EG can inhibit AChE I activity. In addition, *in vivo* AChE I activity could also be inhibited by EG (0.5–80 mg/kg/day, p.o., once or every day for a period of 15 days), and this inhibition was reversible (Chen et al., 2001a). Previous studies have also demonstrated that *Polygonum multiflorum* extracts can treat insomnia and brain function disorders by inhibiting the activity of AChE. These experiments were conducted on a 96-well plate assay using Ellman's method. The AChE activity inhibition percentages of aqueous and ethanol *Polygonum multiflorum* extracts at doses of 20  $\mu$ g/mL were 59.88 and 47.24, respectively (Lin et al., 2008). *Polygonum multiflorum* aqueous extract, which was administered p.o. to mice for 28 days, obviously improve the cognitive deficits induced by A $\beta$ 25–35 on mice. And, the acetylcholinesterase and GPx activity were increased, the TBARS level was decreased in mice brain after administration for 4 weeks. These effects might be related to the antioxidant activity of *Polygonum multiflorum* (Um et al., 2006).

### 5.1.2. Neuroprotective effect

Many studies suggested that JNK played an important role in the mediation of MPP<sup>+</sup>-induced neurotoxicity, and a research demonstrated the TSG could protect against MPP<sup>+</sup>-induced apoptosis in a dose-dependent manner (1, 5 and 10  $\mu$ M) in PC12 cells. The results showed that TSG pretreatment attenuated the expression of the p-JNK, this effect related to the antioxidative ability (blocked the ROS increase) of TSG (Li et al., 2010c). Another study verified that the neuroprotective effects of TSG against MPP<sup>+</sup>-induced damage and apoptosis in PC12 cells (0.1, 1 and 10  $\mu$ M) are likely to be mediated by the activating the PI3K signaling pathway, the stimulation of PI3K activity leads to downstream target Akt phosphorylation and subsequent inhibition of cell apoptosis (Qin et al., 2011). TSG also protected human neuroblastoma SH-SY5Y cells against MPP<sup>+</sup>-induced cytotoxicity (3.125, 6.25, 12.5, 25 and 50  $\mu$ M). The mechanisms underlying this effect may be mediated through (i) its protection of mitochondrial function, (ii) attenuating the accumulation of intracellular reactive oxygen species, (iii) and inhibiting the MPP<sup>+</sup>-induced mitochondrial apoptotic pathway by decreasing the ratio of Bax to Bcl-2 and preventing caspase-3 activation (Sun et al., 2011). These mechanisms were also demonstrated in a study on staurosporine (STS)-induced toxicity in cultured rat hippocampal neurons. The results of the study showed that the administration of 200  $\mu$ M TSG can significantly protect against STS-induced apoptosis in cultured rat hippocampal neurons (Yang et al., 2014). In addition, TSG (5–400  $\mu$ mol/L) significantly promoted cell viability and reduced

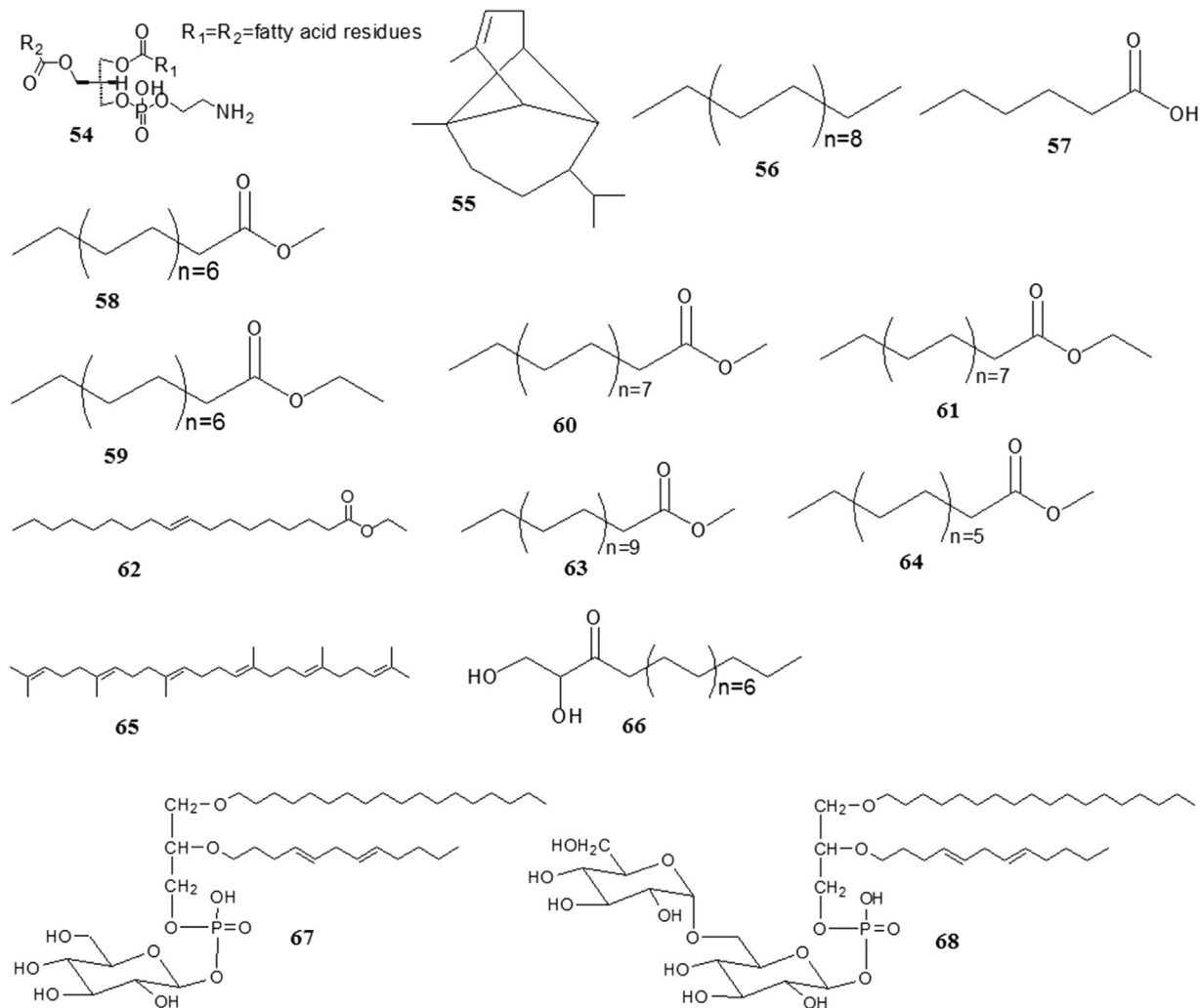


Fig. 6. Chemical structures of phospholipids.

cell membrane damage in  $\beta$ -amyloid 25-35- and  $H_2O_2$ -treated human neuroblastoma SK-N-SH cells. TSG may initially antagonize the cell damage induced by hydrogen peroxide and prevent the subsequent toxicity of amyloid beta protein in nerve cells (Zhang et al., 2004; Xu and Yi, 2013).

*Polygonum multiflorum* ethyl acetate extracts (0.1, 0.5, 1, 3, 5, and 10  $\mu\text{g}/\text{mL}$ ) may exert neuroprotective effects through activation of extracellular regulated kinase (ERK) and p38 via MAPK and the calpain-STEP signaling pathways, and ERK and p38 were major contributing factors to its protection. These extracts may also be used as therapeutic interventions for the treatment of oxidative neuronal death. A previous study showing this effect was conducted by evaluating glutamate-induced oxidative cell death in HT22 hippocampal cells (Kim et al., 2013). An 80% ethanol extract of *Polygonum multiflorum* protected U373 human astrocytes from hydrogen peroxide-induced cell death ( $LC_{50}$ :  $35.2 \pm 1.2 \mu\text{g}/\text{mL}$ ,  $EC_{50}$ :  $< 0.2 \mu\text{g}/\text{mL}$  for hydrogen peroxide). The protective mechanism was mediated by its free radical scavenging and antioxidant capacities (Steele et al., 2013). The hexane extract of *Polygonum multiflorum* also exerts a protective effect against glutamate-induced neurotoxicity in primary cultured cortical neurons. This neuroprotection may be mediated through both DR- and mitochondrial-mediated apoptotic pathways involving DR4, Bcl-2, XIAP, and cIAP-1 (Jang et al., 2013).

The neuroprotective effects of *Polygonum multiflorum* and TSG were also investigated *in vivo*. Treatment with TSG (20 and 40  $\text{mg}/\text{kg}/\text{day}$ , p.o., for 14 days) protected dopaminergic neurons by

preventing MPTP-induced decreases in substantia nigra tyrosine hydroxylase (TH)-positive cells and striatal dopaminergic transporter (DAT) protein levels in mice (Zhang et al., 2013). Another study also demonstrated this neuroprotective effect. This report investigated the degeneration of nigrostriatal dopaminergic neurons induced by a combination of paraquat and maneb (PQMB) in male C57BL/6 mice after the administration of 75% *Polygonum multiflorum* ethanol extract (400 and 800  $\text{mg}/\text{kg}/\text{day}$ , p.o., for 47 days) and the ethanol-soluble (250  $\text{mg}/\text{kg}/\text{day}$ ) and ethanol-insoluble (500  $\text{mg}/\text{kg}/\text{day}$ ) fractions. The results suggested that the neuroprotective effect of the 75% *Polygonum multiflorum* ethanol extract is attributable to a substance(s) in the ethanol-insoluble fraction (Li et al., 2005).

### 5.1.3. Antioxidant effect

Antioxidant and free radical scavenging can also be used to treat AD and PD. A recent study evaluated the protective effect of TSG against D-galactose-induced aging in mice (42, 84 and 168  $\text{mg}/\text{kg}$ , p.o., for 8 weeks). The results suggested that TSG is able to improve the memory ability and regulated the body weight of D-galactose induced aging mice through reducing the levels of ROS, NO and IGF-1 and increasing the levels of superoxide dismutase (SOD),  $Ca^{2+}$  and Klotho protein in the serum (Zhou et al., 2013). Another study also proved that TSG (20 and 40  $\text{mg}/\text{kg}/\text{day}$ , p.o., for 42 days) can increase SOD and glutathione peroxidase (GSH-Px) activities in the serum and organs and decrease the content of 2-thiobarbituric acid-reactive substances

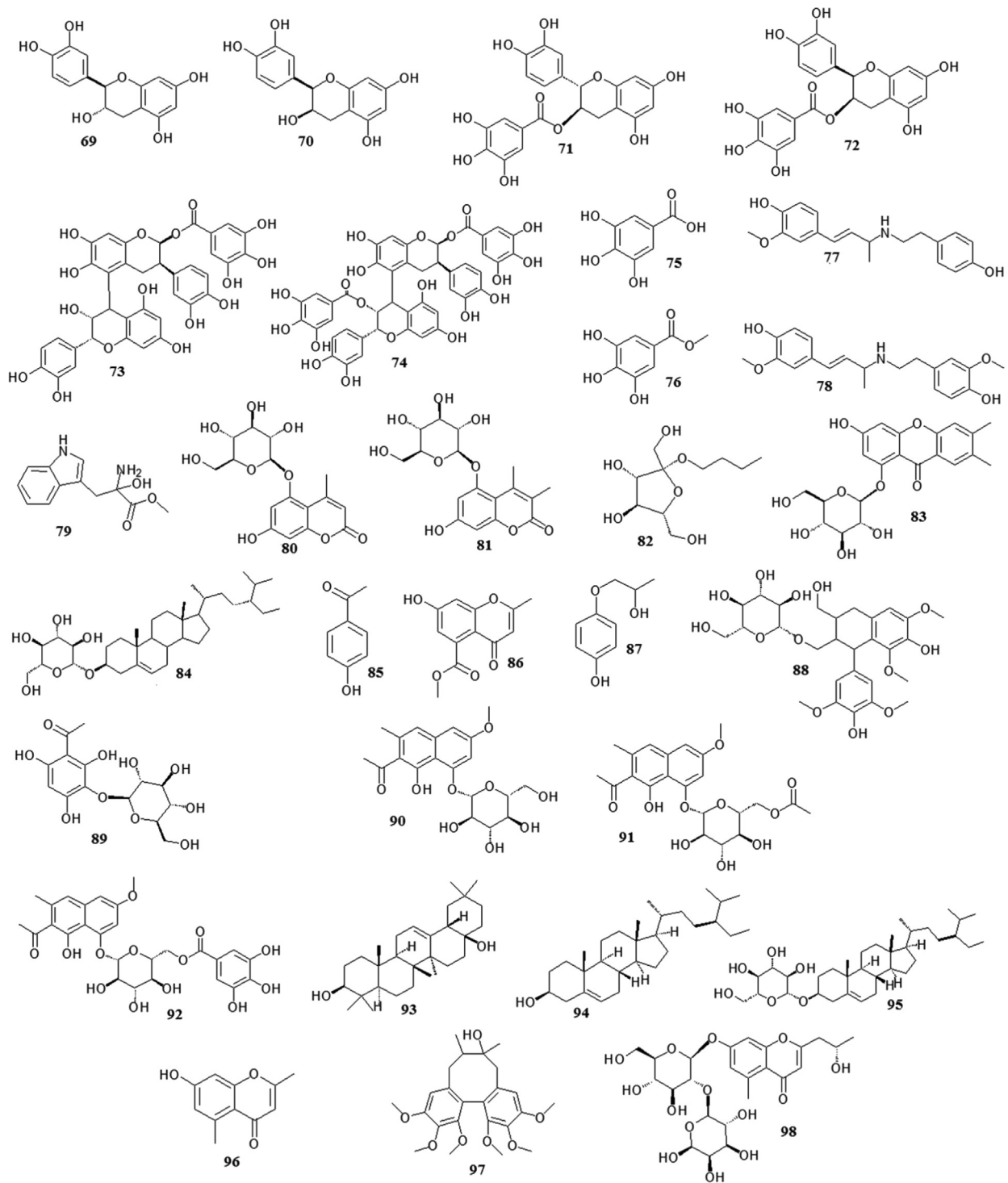


Fig. 7. Chemical structures of other compounds.

(TBARS) in a D-galactose-induced mouse model of dementia (Lv et al., 2007). However, TSG also has anti-melanogenic activity at doses ranging from 60  $\mu$ M to 240  $\mu$ M through a mechanism that is likely mediated through the non-competitive inhibition of tyrosinase, the down-regulation of the expression of melanogenic proteins, and a reduction of tyrosinase/tyrosinase-related protein 1 complex formation (Cheung et al., 2014).

In addition, extracts of *Polygonum multiflorum* also have antioxidant capacities. *Polygonum multiflorum* extract (70% ethanol extract, 0.32 g crude drugs/kg/day, p.o., 5 days/week, for 4 weeks) has anti-aging effects in a mouse model of D-galactose-induced subacute

aging. The mechanism for this effect may be mediated by decreases in the levels of LPF in the brain and kidney and enhancements in the activities of  $\text{Na}^+/\text{K}^+$ -ATPase in the heart and SOD in the liver (Song et al., 2003). Another study showed that mice exhibit a better shuttle avoidance response, fewer vacuoles, less lipofuscin in the hippocampus, and lower MDA concentrations in the brain after being fed *Polygonum multiflorum* extracts (2.5 g/kg/day, p.o., for 18 weeks; 50% ethanol, 95% ethanol, or aqueous). Consequently, these effects promote improved learning and memory abilities (Chan et al., 2002), which may be due to the antioxidant phytochemicals of the extracts (Chan et al., 2003).

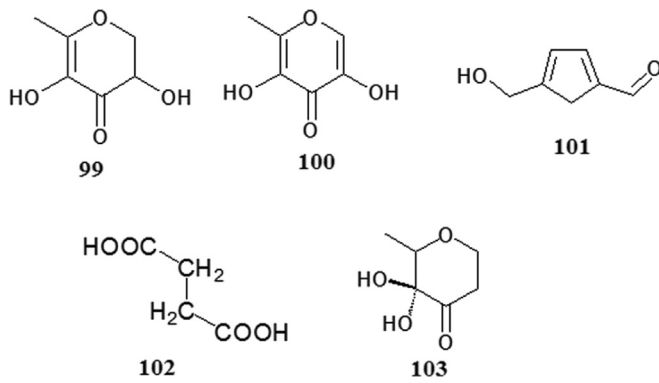


Fig. 8. Chemical structures of new compounds after processed.

#### 5.1.4. Enhanced cognition

TSG can treat AD by enhancing learning and memory abilities. A previous study has shown that TSG (1 and 5  $\mu\text{M}$ ) promotes an ERK-dependent differentiation of PC12 cells, directly enhances ERK1/2 activation and intracellular calcium level in hippocampal neurons. TSG-mediated enhancement of ERK1/2 phosphorylation is involved in the facilitation of hippocampal long-term potentiation (LTP) by TSG, the processes may be involved in the effect of TSG on hippocampal LTP including the ERK–CREB pathway and modulation of the response to the NMDA receptor by calcium/calmodulin-dependent protein kinase II (CaMKII) activity. This effect may contribute to the enhancement of learning and memory observed in animal models (Wang et al., 2011a). This effect was verified in AD-like APP transgenic mice of different ages treated with TSG (120 and 240  $\mu\text{mol/kg/day}$ , p.o., for 4, 10 and 16 months). The results showed that TSG can significantly improve the learning-memory abilities (Zhang et al., 2006c).

#### 5.2. Immunomodulating effect

The immunomodulating effect of *Polygonum multiflorum* is mainly due to its polysaccharides and anthraquinone glycosides. A polysaccharide fraction was purified from *Polygonum multiflorum Praeparata*, which is composed of rhamnose, arabinose, xylose and glucose at a molar ratio of 1.64:1.00:1.34:6.06. This fraction increased the levels of serum IL-2 and hematological parameters, enhanced the antioxidant profiles, and promoted the haematopoiesis of splenocytes by up-regulating the expression of EPOR and GATA-1 proteins in a cyclophosphamide (Cy)-induced mouse anemia model (20, 40 and 80 mg/kg/day, for 7 days, intraperitoneal). This result indicated that the polysaccharide fraction is a potential immunomodulatory agent (Chen et al., 2012b). Another polysaccharide extracted from *Polygonum multiflorum* was administered orally at doses of 0.4, 0.8 and 1.6 g/kg/day to mice for 10 days. Moreover, the results reflected that this fraction inhibited the Cy-induced weight loss of immune organs, decreased the number of blood cells, increased the phagocytic percentage and phagocytic index in peritoneal macrophages, increased the contents of serum hemolysin and the esterase-positive rate of T-lymphocytes, and enhanced the ConA-induced proliferation of splenic T-lymphocytes (Ge and Liu, 2007). A previous investigation also showed that the polysaccharide extracted from *Polygonum multiflorum Praeparata* exerts immunomodulatory effects (mice, 100, 200 and 400 mg/kg/day, p.o., for 7 days) (Zhang et al., 2008). These findings demonstrate that polysaccharides from *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* have immunomodulatory effects; however, the structure and composition of these immunomodulatory polysaccharides have not been clarified. Similar findings were also observed for anthraquinone glycoside extracted from *Polygonum multiflorum*. This compound, when used *in vitro* at doses ranging from 31.25 to 125  $\mu\text{g/mL}$ , (i) significantly accelerated T and B lymphocyte

proliferation and mixed lymphocyte reaction, (ii) improved macrophage phagocytosis, (iii) increased tumour necrosis factor (TNF) secretion and the activity of natural killer (NK) cells, (iv) and antagonized the restraining effect of the lymphocyte helper/suppressor ratio induced by mitomycin (MitC) (Sun et al., 2006).

The water extract of *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* significantly increased the serum IgM level in rats after oral administration at a dose of 30 g/kg for 90 days (Hu et al., 2009). After treatment with the water extract of *Polygonum multiflorum* at doses of 2 and 4 mg/mice/day (i.p. injection, 7 days), the ConA- and LPS-induced lymphocyte proliferation in mouse splenocytes and the function of antibody-secreting cells were enhanced (Qin et al., 1990). The enhancement effects of ConA and LPS were also observed in mouse spleen lymphocytes after treatment with *n*-butanol, ethyl acetate and chloroform extracts at dosages of 50, 100 and 200  $\mu\text{g/mL}$  (Deng et al., 2008).

#### 5.3. Anti-hyperlipidaemia effect

Dyslipidemia is characterized by increased total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels and by decreased high-density lipoprotein cholesterol (HDL-C) levels (Toth, 2010). Recently, the effects of TCM have been increasingly demonstrated to be helpful for hyperlipidemic patients. More than 50 TCM formulas have been used to treat hyperlipidaemia. *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* are the commonly used herbs in these formulas (Xie et al., 2012). The anti-hyperlipidaemia effect of *Polygonum multiflorum* was mainly due to the antioxidant function of certain ingredients, such as TSG, polysaccharides and anthraquinones.

TSG (30 and 60 mg/kg/day, p.o., for 28 days) can remarkably decrease the levels of serum TC, TG, LDL-C, and malondialdehyde (MDA). TSG was also shown to decrease the TC/high-density lipoprotein cholesterol (HDL-C) ratio and to markedly increase the levels of serum HDL-C, nitric oxide (NO) and SOD (Wang, 2005a; Wang et al., 2009a). These results were verified by another study through an experimental hyperlipidemic rat model treated with TSG (90 and 180 mg/kg/day, p.o., for 7 days) (Gao et al., 2007). Calreticulin, vimentin, HSP 70, lipocortin 1, and Apo A-I are proteins that may be molecular targets responsible for the TSG-induced atherogenesis suppression (Yao et al., 2013). The anti-hyperlipidaemia effect of *Polygonum multiflorum* polysaccharides in mice were investigated through its administration at doses of 50 and 200 mg/kg/day for 28 days. The results showed that the serum levels of TC, TG and AI were significantly decreased, whereas the HDL-C, LPL, HL and LA levels were significantly increased (Zhai et al., 2010). In addition, a previous study investigated the mechanism underlying the lipid regulation activity of the major chemical components of *Polygonum multiflorum* in LO2 cells. The results showed that TSG increased the content of cholesterol 7 $\alpha$ -hydroxylase (CYP7A) and subsequently promoted the lipolysis of cholesterol. TSG also showed the best LDL-reducing effect. Moreover, emodin inhibited 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and diacylglycerol acyltransferase 1 (DGAT1), which are key enzymes in the synthesis of TC and TG. Physcion increased the content of hepatic triglyceride lipase (HTGL), subsequently boosting the lipolysis of triglycerides. At the same time, physcion showed the best VLDL-reducing effect (Wang et al., 2014). Another study investigated the anti-hyperlipidemic effect in the combined hyperlipidaemia rat model by treatment with emodin alone (75, 150 and 300 mg/kg/day, p.o., for 4 weeks). The result showed that emodin may be effective for the prevention and treatment of combined hyperlipidaemia model rats. The mechanisms may be mediated by increases in the anti-oxidative effects of blood SOD and GSH-PX and reductions in the blood MDA levels (Wu, 2008).



The extracts of *Polygonum multiflorum* also exert anti-hyperlipidaemia effects. A previous study using mice to evaluate the reductions in the blood lipid contents induced by different *Polygonum multiflorum* extracts obtained through different methods, including supercritical fluid extraction (SFE), systematic solvents (petroleum benzene, ethyl acetate, *n*-butanol, 75% ethanol and water) and ethanol precipitation after water extraction, showed that the SFE extract was active (0.5 to 1.25 g/kg, p.o., one administration) (Li et al., 2008). Water extracts of both *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* reduced the total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) contents in the rat blood. Moreover, the two extracts showed dose-dependent TC- and triglyceride (TG)-decreasing effects in liver tissue samples (0.405, 0.81, and 1.62 mg/kg/day for *Polygonum multiflorum*; 0.81, 1.62, and 3.24 mg/kg/day for *Polygonum multiflorum Praeparata*, p.o., for 24 days) (Li et al., 2012b). Another study used hepatic steatosis L02 cells to compare the relative activities of *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* extracts (extracted with water or 50% ethanol; all extracts at doses of 10, 20, 40, 80 and 100 µg/mL). The results showed that the intracellular contents of TG and TC were increased from  $16.50 \pm 1.29$  mmol/L to  $34.40 \pm 1.36$  mmol/L and from  $5.07 \pm 1.80$  mmol/L to  $11.79 \pm 0.54$  mmol/L, respectively, in steatosis L02 cells. The water extract of *Polygonum multiflorum* showed markedly higher TG- and TC-regulation effects than the *Polygonum multiflorum Praeparata* water extract (Wang et al., 2012a).

#### 5.4. Hepatoprotective effect

The compounds and extracts of *Polygonum multiflorum* exert hepatoprotective effects via the actions of anthraquinones and polysaccharides, among others. More research studies have investigated the hepatoprotective effects of anthraquinones compared with those of polysaccharides.

Emodin (30 and 50 mg/kg, p.o., one administration) was isolated and exhibited hepatoprotective effects on carbon tetrachloride (CCl<sub>4</sub>)- as well as D-galactosamine (D-GalN)-induced liver damage in rats. The histopathological examination also clearly showed that emodin reduced lymphocyte cells, Kupffer cells, ballooning degeneration, cell necrosis and hyaline degeneration following CCl<sub>4</sub>- and D-galactosamine-induced damage (Lin et al., 1996). Treatment with emodin (20, 30 and 40 mg/kg, p.o., one administration) significantly lessened the observed toxicity by protecting the acetaminophen-induced alterations in various blood and tissue biochemical variables in rats 24 h after administration, and the protective effect was dose-dependent (Bhadauria, 2010). The protective effect of emodin may be related to anti-inflammatory and anti-oxidant activities. In turn, these mechanisms were mediated by blockade of TLR4/MD2 complex expression on the cell surface of macrophages, which led to the deactivation of MAPKs and NF-κB signaling pathways, and the inhibition of TNF-α production (Yin et al., 2014). Rhein (10, 20 and 40 mg/kg, p.o., one administration) can reduce the levels of glutamate-pyruvate transaminase (GPT), glutamate-oxaloacetic transaminase (GOT), creatinine (CREA), urea nitrogen (UREA) and reactive oxygen species (ROS) in acetaminophen-induced hepatotoxicity and nephrotoxicity rats. The histopathological damage of the liver and kidney were also significantly ameliorated by rhein treatment (Zhao et al., 2011b).

Antioxidant activity tests have been performed, and a homogeneous polysaccharide with a molecular weight of  $6.1 \times 10^2$  kDa was identified at concentrations of 0.1–1.5 mg/mL. The free radical scavenging activity of this polysaccharide was exhibited in the order: superoxide anion (IC<sub>50</sub> 0.47 mg/mL) > hydrogen peroxide (IC<sub>50</sub> 0.60 mg/mL) > hydroxyl radical (IC<sub>50</sub> 0.93 mg/mL), and this polysaccharide also displayed better effects on inhibiting the formation of advanced glycation end products (AGEs) (Lv et al., 2014).

Many studies have investigated the hepatoprotective effect of *Polygonum multiflorum* extracts. The methanol extract of this plant (1–1000 µg/mL) promoted the expression of hepatocyte growth factor (HGF) for hepatic non-parenchymal cells. Consequently, the proliferation of stellate cells was inhibited, and the proliferation of primary liver cells was increased. Moreover, the phagocytic activity of Kupffer cells was enhanced, as determined using fluorescein-labelled *Escherichia coli* as the target. Using dimethylnitrosamine-induced liver cirrhosis mice, the methanol extract of *Polygonum multiflorum* at 20, 23, 30, 37, and 44 mg/kg/day (p.o., for 25 days) was to promote the expression of HGF that stimulates the proliferation of hepatocyte enhances the regenerative potential of liver to reverse dimethylnitrosamine-induced liver damage (Huang et al., 2007). Both *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* extracts (water-extracted, 15 g/kg/day, p.o., for 8 days) can be used to treat the hepatic lipid accumulation caused by prednisone acetate-, carbon tetrachloride- or thioacetamide-induced liver damage in mice (Liu et al., 1992). Moreover, these extracts attenuated liver damage by reducing lipid peroxidation as well as by positively modulating inflammation (Lee et al., 2012).

#### 5.5. Anticancer effect

The compounds of *Polygonum multiflorum* also possess anti-cancer effects. The main effective substances are thought to be anthraquinones, such as emodin and aloe-emodin. The anti-cancer effects of anthraquinones have been studied in different tumour cell lines and in pre-clinical animal models. The main identified mechanisms underlying the anti-cancer effects involve the induction of apoptosis and the activation of the PI3K/AKT/mTOR pathways.

##### 5.5.1. Effects on apoptosis

Apoptosis is generally triggered through two major pathways. One is the death receptor-induced extrinsic pathway, which includes ligands and their receptors, such as FAS, TNF, TRAIL, caspases and Bcl2. The other pathway is the mitochondria-apoptosome-mediated intrinsic pathway, which includes key effector caspases-8, -9 and -10. Emodin is characterized as a strong apoptotic agent. Emodin has been shown to significantly inhibit the growth of HepG2 cells, as evidenced by an IC<sub>50</sub> of  $36 \pm 2.6$  µg/mL (Liu et al., 2003). Emodin at a concentration of 50 µM arrests liver cancer Huh7, Hep3B, and HepG2 cells in the G<sub>2</sub>/M phase, this effect was accompanied by induced cyclin A, cyclin B, Chk2, Cdk2 and P27 expression and down regulated Cdc25c and P21 expression in time-dependent fashion. This result demonstrated that emodin can regulate common gene expression or suppression in different liver cancer cells and the potential biological pathways activated by emodin (Hsu et al., 2010). Aloe-emodin, another anti-apoptotic agent found in this plant, inhibited the growth of human cervical cancer cells (HeLa cells) at the G<sub>2</sub>/M phase in a dose-dependent manner at concentrations between 2.5 and 40 µmol/L. This effect was associated with decreased cyclin A and cyclin-dependent kinases 2 (CDK2) expression and increased cyclin B1 and CDK1 expression. Aloe-emodin had a down regulatory effect on the expression of c-myc in human cervical cancer cells through the PKCα pathway (Guo et al., 2007a). Aloe-emodin also inhibited T24 human bladder cancer cell viability, inducing G<sub>2</sub>/M arrest and apoptosis at doses of 5, 10, 25 and 50 µM. Furthermore, aloe-emodin could increase the accumulation of p53, enhancing the expression of p21, Fas, Bax and cytochrome c, and decreasing Bcl-2 before leading to apoptosis (Lin et al., 2006). Moreover, this treatment (10, 20, 30, 40 or 50 µM) induced cell death through S-phase arrest and caspase-dependent pathways in human tongue

squamous cancer SCC-4 cells (Chiu et al., 2009) and exhibited cytotoxic effects against neuroblastoma cells (SJ-N-KP) (Pecere et al., 2000) and B16-F10 melanoma cells (Tabolacci et al., 2010).

*In vivo*, emodin (40 mg/kg/every 3 days, i.p. injection, 39 days) significantly reduced the colon tumour volume (46%) and tumour weight (42%). These effects were mediated by inducing cell morphological changes and G2/M phase arrest, decreasing the percentage of viability, increasing ROS and Ca<sup>2+</sup> production, and inducing the loss of the mitochondrial membrane potential in human colon cancer cells (LS1034). Apoptosis was also confirmed by DAPI staining, and these effects were concentration-dependent (Ma et al., 2012). In another mouse experiment examining gallbladder tumors induced by an injection of human gallbladder cancer SGC996 cells, emodin (50 mg/kg/day, i.p. injection, 18 days) exerted significant antitumor effects by enhancing the apoptosis of gallbladder cancer cells (Wang et al., 2011b).

### 5.5.2. Effect on the PI3K/AKT/mTOR pathway

Improper regulation of PI3K/AKT pathways has been reported in many human cancers (Fresno Vara et al., 2004). A previous study demonstrated that aloe-emodin (2.5, 5, 10, 20, 40 and 80  $\mu$ M) can reduce the cytotoxicity of the pro-inflammatory cytokine tumour necrosis factor (TNF) in L929 mouse fibrosarcoma and U251 human glioma cell line through a mechanism involving the induction of autophagy and the blockade of ERK activation. Emodin (1, 5, 10, 20 and 40  $\mu$ M in the HeLa cell line) induces apoptosis, and the anti-apoptotic effect of CK2 is partially mediated by targeting the phosphorylation and up-regulation of AKT. This is the mechanism of action associated with the PI3K/AKT pathway, the deregulation of which has been linked numerous times to malignant transformation (Birgitte et al., 2007).

*In vivo*, an i.p. injection of emodin (25 and 50 mg/kg /day, 5 days per week, for 4 weeks) has also shown significant antitumor effects in head and neck squamous cell carcinomas induced by FaDu-pFLAG-CMV or FaDu-pFLAG-TWIST1 cells in mice. The anti-cancer mechanism of emodin is hypothesized to be an inhibition of TWIST1 expression by inhibiting the  $\beta$ -catenin and Akt pathways, up regulating E-cadherin mRNA and protein expression and down regulating vimentin mRNA and protein expression (Way et al., 2014).

Emodin has also been found to exhibit cytotoxic effects against HepG2 cells (Yu, et al., 2013), the prostate cancer cell lines LNCaP and PC-3, the lung cancer cell line A549, the colon cancer cell line HCT-15, the bone cancer cell line MG-63 (Masaldan and Iyer, 2014) and the esophageal cancer cell lines EC-109 (Liu et al., 2009a).

### 5.6. Anti-inflammatory effects

*Polygonum multiflorum* also exerts anti-inflammatory effects. The main effective substances associated with this effect are believed to be TSG and emodin. The anti-inflammatory effects of TSG and emodin have been associated with antioxidant activity and an inhibition of the pro-inflammatory transcription factor NF- $\kappa$ B. TSG (60 and 120 mg/kg/day, p.o., for 7 days) significantly ameliorated colon damage (induced by acetic acid), inhibited the increase in myeloperoxidase (MPO) activity induced by acetic acid, depressed MDA and NO levels, and enhanced SOD activity in mice (Wang et al., 2008). TSG (50  $\mu$ M) attenuated the LPS-mediated induction of pro-inflammatory factors in microglia by reducing iNOS protein expression and the TNF- $\alpha$ , IL-6, and NO levels. TSG also increased apoptosis, caspase-3 cleavage, and the lactate dehydrogenase (LDH) levels. Another effect of TSG was found to be a reduction in the binding of NF- $\kappa$ B to its DNA element in LPS-stimulated BV-2 cells (Huang et al., 2013).

In another experiment, TSG inhibited mouse ear and paw edema with a percentage of inhibition of 87% after oral administration at a dose of 9.2 mg/kg. This percentage was 56% after oral administration at a dose of 12.8 mg/kg. The mechanism underlying these effects is likely related to the suppressed cyclooxygenase-2 (COX-2) gene expression or directly inhibited COX-2 enzyme activity in RAW264.7 macrophage cells (Zhang et al., 2007b). TSG also showed beneficial effects on acetic acid-induced experimental colitis in mice following intragastric administration at 10, 30, or 60 mg/kg for 7 days and exerted beneficial effects on acetic acid-induced experimental colitis by upregulating the PPAR- $\gamma$  mRNA and protein levels and inhibiting the NF- $\kappa$ B pathway. These effects in turn decreased the expressions of the downstream inflammatory mediators TNF- $\alpha$ , IL-6 and COX-2 and MDA content (Zeng et al., 2011). A study showed that administrations of emodin (1, 2, and 4 mg/kg, i.p., one administration) could lessen the LPS-induced mammary gland injury and inflammatory cell infiltration, decrease the myeloperoxidase (MPO) activation in the mammary gland, down-regulate the expression and production of TNF- $\alpha$ , IL-6, and interleukin-1 beta (IL-1b) in a dose dependent manner. The anti-inflammatory mechanism was inhibited by the activation of NF- $\kappa$ B and MAPKs signal pathways (Li et al., 2013a). The *Polygonum multiflorum* extract (70% ethanol extract, p.o., 0.58, 1.15, 2.30, 4.60 and 9.20 g/kg, for 3 days) exhibited strong anti-inflammatory activity based on edema severity and vasopermeability in a mouse model of inflammation and in the response of mice to pain induced by acetate acid. The mechanism was proposed to be related to its immunosuppressive effects (Lv et al., 2001).

### 5.7. Other pharmacological effects

In addition to the pharmacological effects described above, *Polygonum multiflorum* and its ingredients have other pharmacological effects, such as increased hair-fiber length, anti-brain infarct activity, and anti-thromboembolic disorders. Some of these effects are discussed briefly below.

Torachryson-8-O- $\beta$ -D-glucoside, a recently discovered compound in *Polygonum multiflorum*, induced a strong increase in the proliferation of dermal papilla cells and increased the hair-fiber length significantly at doses of 10 and 20  $\mu$ M (Sun et al., 2013). TSG (10 and 20 mg/kg/day, p.o., for 56 days) ameliorated diabetic nephropathy in rats. The therapeutic mechanisms of TSG on diabetic nephropathy involved in inhibiting oxidative stress, inflammation, and the expression of TGF- $\beta$ 1, which partly mediated by activation of SIRT1. These effects occur in part via the activation of SIRT1 (Li et al., 2010a). TSG has been shown to attenuate reactive oxygen/nitrogen species (ROS/RNS) formation and to protect against ischemia/reperfusion injury. The neuroprotective effect of TSG is caused by multifunctional cytoprotective pathways (Wang et al., 2009b). TSG (30, 60, 120 mg/kg/day) was administered to rats for 30 days in a cardiac remodeling study. In this context, TSG prevented cardiac remodeling induced by pressure overload in rats. The underlying mechanisms may be related to a decrease in the angiotensin II level, an antioxidant effect of the tested compound, the suppression of transforming growth factor- $\beta$ 1 expression, and the inhibition of extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase activation (Xu et al., 2014). Another study indicated that TSG exerted potent anti-platelet activity against collagen-induced aggregation. TSG is likely to exert protective effects in platelet-associated thromboembolic disorders by modulating human platelets (Xiang et al., 2014).

Importantly, emodin (IC<sub>50</sub> was 200  $\mu$ M) seriously blocks both the binding of SARS-CoV S protein to angiotensin-converting enzyme 2 (ACE2) and the infectivity of S protein-pseudotyped retrovirus to Vero E6 cells. Therefore, emodin may be considered a potential lead therapeutic to treat SARS (Ho et al., 2007). Another study revealed

that co-treatment with emodin ( $1 \times 10^{-5}$  and  $1 \times 10^{-4}$   $\mu\text{g/ml}$ ) significantly prevented ethanol-induced developmental anomalies in cultured mouse fetuses by modulating hypoxia and antioxidant enzymes and attenuating the enhanced levels of TNF- $\alpha$  and caspase 3 in cultured embryos (Yon et al., 2013). Emodin (1  $\mu\text{M}$  to 10  $\mu\text{M}$ ) also inhibited tonic tension in a concentration- and time-dependent manner by suppressing the PKC $\delta$ -mediated inhibition of myosin phosphatase in isolated rat thoracic aortas (Lim et al., 2014).

A study that investigated the cerebrovascular protective effects of *Polygonum multiflorum* against ischemic brain injury used an *in vivo* photothrombotic mouse model. Hexane, ethyl acetate and methanol extracts of *Polygonum multiflorum* (100 mg/kg) were administered i.p. 30 min prior to ischemic insult. The result showed that the hexane extracts induced a significant reduction in infarct volume and subsequent neurological deficits compared with the other extracts. This cerebroprotective effect is primarily mediated via an eNOS-dependent mechanism (Lee et al., 2014).

### 5.8. Clinical application

*Polygonum multiflorum* is not usually used as a single herb for clinical application but shows better therapeutic effects when used in combination with other herbs. A previous study investigated the effect of Buyanghuanwu Pill Jiajian Fang (BPJF, composed of *Radix astragali*, *Angelica sinensis*, *Ligusticum wallichii*, *Radix Paeoniae alba*, peach kernel, safflower, *Lumbricus*, *Fructus Psoraleae*, and *Cistanche salsa*) on patients suffering from PD. Sixty patients with PD were randomly divided into the treatment group (BPJF+Madopar group,  $n=30$ ) or the control group (Madopar group,  $n=30$ ) and treated for 3 months. The total effective rate of the treatment group was 87.5%, whereas that of the control group was 77.5%, and this difference was significant (Zhang, 2008). Another study observed the effect of Qishu decoction (contains *Astragalus*, prepared Rhizome of *rehmannia*, *Radix codonopsis*, lyceum, donkey-hide glue, *Angelica sinensis*, *Polygonum multiflorum*, *Caulis Spatholobi*, and *Glycyrrhiza uralensis*) on the treatment of NSCLC patients with leukopenia after chemotherapy. Two-hundred-forty patients with NSCLC were randomly divided into the treatment group (Qishu decoction group  $n=120$ ) or control group (Leucogen and Batilol tablet group, both  $n=120$ ). Both groups were treated for 10 days. The total effective rate in the treatment group was 91.5%, whereas that for the control group was 72.8%. This result suggested that the Qishu decoction can greatly improve bone marrow depression, promote blood-producing functions and recover leukocytes, thereby benefiting NSCLC patients (Xiang and Han, 2013). The He shou wu and Rou cong rong decoction (composed of *Polygonum multiflorum*, *Cistanche salsa*, *Radix Astragali preparata*, *Ligusticum wallichii*, *Angelica sinensis*, and *Salviae miltiorrhizae*) was demonstrated to enhance immunoregulation and improve the clinical symptoms in a study of 34-year-old inpatients with kidney deficiency and blood stasis KDBS (Chen et al., 2006). The Shou wu ji li formula decoction (composed of *Polygoni multiflori preparata*, stir-baked *Fructus tribuli*, *Angelica sinensis*, *Fructus ligustri lucidi*, *Ecliptae herba*, *Rehmannia glutinosa libosch*, duckweed, *Fructus Xanthii*, *Clematis chinensis*, *Radix sileris*, *Semen Astragali Complanati*, and *Radix Glycyrrhizae preparata*) combined with the Kaliziran tincture formula was effective for treating blood deficiency and wind sheng-type vitiligo, and there were fewer adverse reactions. The mechanism of action may be through an increase in tyrosinase activity and modulation of the immune system. This combination was found to change the white spots in vitiligo to become darker (Bai, 2013). *Polygonum multiflorum* is used widely in clinical practice, and there are many studies similar to those mentioned above; we therefore do not list all of the studies in this manuscript.

### 5.9. Summary of pharmacological effects

*Polygonum multiflorum* exerts a wide spectrum of pharmacological effects, including anti-aging, immunologic, anti-hyperlipidaemia, neuroprotective, anti-cancer and anti-inflammatory effects (Table 3). Based on these pharmacological effects, we can conclude that the extracts and the compounds from this plant can prevent or treat certain diseases, such as hyperlipidaemia, inflammation/infection, cancer and AD. However, there are insufficient data for these chemical compounds and their pharmacological effects. Therefore, it is necessary and important to investigate the pharmacological effects and molecular mechanisms of these chemical compounds based on our modern understanding of these diseases' pathophysiology.

## 6. Toxicology

The number of reports on the adverse effects of *Polygonum multiflorum* has recently increased. Some researchers have found that *Polygonum multiflorum* shows not only hepatotoxicity and kidney toxicity, particularly in long-term use, but also a possible drug interaction with warfarin to result in bone marrow suppression.

### 6.1. Hepatotoxicity

The adverse hepatic effects of *Polygonum multiflorum* have been reported commonly in China and other countries (Niu 1996; Ye 1996; Dong et al., 2014), and acute toxic hepatitis was the most frequently reported (Park et al., 2001; Min et al., 2008; Jung et al., 2011). A study that evaluated the hepatotoxicity of the aqueous and acetone extracts of *Polygonum multiflorum* and *Polygonum multiflorum Praeparata* on mice (5, 10, and 20 g/kg/day, p.o., for 28 days) indicated that the hepatotoxicity of the aqueous decoction was much higher than that of the acetone extract. Moreover, the hepatotoxicity of the acetone extract of *Polygonum multiflorum* was considerably higher than that of *Polygonum multiflorum Praeparata* (Wu et al., 2012). Another study established the "dose-time-toxicity" relationship of the hepatotoxicity caused by administration of a single dose of the water-extracted and ethanol-extracted components of *Polygonum multiflorum* to mice. The water-extracted components (from 5.5 to 30.75 g/kg) and the ethanol-extracted components (from 8.5 to 24.5 g/kg) caused obvious damage to the liver organization, resulting in significantly increased ALT and AST serum levels, and this effect was dose-dependent (Huang, et al., 2011). Other studies have demonstrated that *Polygonum multiflorum Praeparata* also exerts side effects on the rat liver; however, the toxicity was less than that obtained with *Polygonum multiflorum* (Li et al., 2012d; Hu et al., 2006a, 2006b, 2007).

Emodin and rhein, the major components of *Polygonum multiflorum*, have been demonstrated to exert concentration- and time-dependent toxic effects on human liver (L-02) cells. Emodin at a concentration of 30  $\mu\text{M}$  led to significant apoptosis in a time-dependent manner, as determined by morphological changes in the drug-treated cells (Li et al., 2012a). An *in vitro* study suggested the occurrence of time- and dosage-dependent (in the range of 6.25–50  $\mu\text{mol/L}$ ) toxic effects of rhein on L-02 cells (Sun et al., 2010).

### 6.2. Nephrotoxicity

Emodin at a concentration of 40  $\mu\text{M}$  displayed apoptotic/necrotic effects in a dose- and time-dependent manner on human proximal tubular epithelial (HK-2) cells. Cell cycle analysis revealed that the HK-2 cells were locked in G1 phase, and the observed apoptosis was mediated through the induction of a



**Table 3**  
Pharmacological effects of *Polygonum multiflorum*.

Pharmacological effects	Detail	Active extract/fraction/compound	Effective concentration/dose/pattern	Study model	Reference
Anti-aging effect	Increase the activities of SOD and GSH-Px	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	20 and 40 mg/kg/day, po., for 42 days	<i>in vivo</i>	Liu et al. (2008a)
	Inhibit AChE I activity	Emodin-8-O- $\beta$ -D-glucopyranoside	0.5–80 mg/kg/day, po., once or 15 days	<i>in vivo</i>	Chen et al. (2001a)
	Decrease the AChE activity	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	30,60 and 120 mg/kg/day, ig., for 11 weeks	<i>in vivo</i>	Lin et al. (2008)
	Preventive effect against cognitive deficits	Water extract	The experimental diet was based on the RAIN 76 formula, and comprised either 0.5% or 1% <i>Polygonum multiflorum</i> water extract, po., for 28 days	<i>in vivo</i>	Um et al. (2006)
	Protect against MPP <sup>+</sup> -induced apoptosis	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	1, 5 and 10 $\mu$ M	<i>in vitro</i>	Li et al. (2010c)
	Protect against MPP <sup>+</sup> -induced apoptosis	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	0.1, 1 and 10 $\mu$ M	<i>in vitro</i>	Qin et al. (2011)
	Protected human neuroblastoma SH-SY5Y cells against MPP <sup>+</sup> -induced cytotoxicity promoted cell viability and reduced cell membrane damage	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	3.125, 6.25, 12.5, 25 and 50 $\mu$ M	<i>in vitro</i>	Sun et al. (2011)
		2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	5–400 $\mu$ mol/L	<i>in vitro</i>	Zhang et al. (2004); Xu and Yi (2013)
	Neuroprotective effect	Ethyl acetate extract	0.1, 0.5, 1, 3, 5, 10 $\mu$ g/mL	<i>in vivo</i>	Kim et al. (2013)
	Protect U373 human astrocytes	80% ethanol extract	LC <sub>50</sub> was 35.2 $\pm$ 1.2 $\mu$ g/mL, EC <sub>50</sub> was < 0.2 $\mu$ g/mL for hydrogen peroxide	<i>in vitro</i>	Steele et al. (2013)
	Inhibition of apoptosis of primary cortical neurons	Hexane extract	0.1, 0.5, 1, 5 and 10 $\mu$ g/mL	<i>in vitro</i>	Jang et al. (2013)
	Neuroprotective effects	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	20 and 40 mg/kg/day, po., for 14 days	<i>in vivo</i>	Zhang et al. (2013)
	The neuroprotective effect was attributable to some substance (s) Included in the ethanol-soluble fraction.	75% ethanol extract	400 and 800 mg/kg/day, po., for 47 days.	<i>in vivo</i>	Li et al. (2005)
	Against D-galactose-induced aging	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	42, 84 and 168 mg/kg, po., for 8 weeks	<i>in vivo</i>	Zhou et al. (2013)
	Antioxidant effect	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	20 and 40 mg/kg/day, po., for 42 days	<i>in vivo</i>	Ly et al. (2007)
	Antimelanogenic activity	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	60 $\mu$ M to 240 $\mu$ M	<i>in vitro</i>	Cheung et al. (2014)
		Ethanol extract	0.32 g crude drugs/kg/day, po., 5 days/week, for 4 weeks	<i>in vivo</i>	Song et al. (2003)
		50% ethanol, 95% ethanol, or water extracts	2.5 g/kg/day, po., for 18 weeks	<i>in vivo</i>	Chan et al. (2002)
		2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	1 and 5 $\mu$ M	<i>in vitro</i>	Wang et al. (2011a)
	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	120, 240 $\mu$ mol/kg/day, po., for 4, 10 and 16 months	<i>in vivo</i>	Zhang et al. (2006c)	
Immunomodulating effect	Immunomodulatory effects	Polysaccharide fraction	20, 40 and 80 mg/kg/day, intraperitoneal, for 7 days	<i>in vivo</i>	Chen et al. (2012b)
	Immunomodulatory effects	Polysaccharide fraction	0.4, 0.8 or 1.6 g/kg/day, po., for 10 days	<i>in vivo</i>	Ge et al. (2007)
	Immunomodulatory effects	Polysaccharide fraction	100, 200 and 400 mg/kg/day, po., for 7 days	<i>in vivo</i>	Zhang et al. (2008)
	Accelerate T and B lymphocytes proliferation	Anthraquinone glycoside	31.25–125 $\mu$ g/mL	<i>in vitro</i>	Sun et al. (2006)
	Increased of serum IgM	Water extract of <i>Polygonum multiflorum</i> and <i>Polygonum multiflorum Praeparata</i>	30 g/kg, po., for 90 days	<i>in vivo</i>	Hu et al. (2009)
	Enhance antibody Secreting cells' function	Water extract	2 mg or 4 mg /mice/day, intraperitoneal injection, for 7 days.	<i>in vivo</i>	Qin et al. (1990)
ConA and LPS enhancement	<i>n</i> -butanol, ethyl acetate and chloroform extracts	50, 100 and 200 $\mu$ g/mL	<i>in vitro</i>	Deng et al. (2008)	
Anti-hyperlipidaemia effect	Decrease the levels of TC, TG, LDL-C, MDA and TC/HDL-C, HDL-C, NO and SOD.	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	30, 60 mg/kg/day, po., for 28 days	<i>in vivo</i>	Wang (2005a); Wang et al. (2009a)



Table 3 (continued)

Pharmacological effects	Detail	Active extract/fraction/compound	Effective concentration/dose/pattern	Study model	Reference
	Decrease the levels of TC, TG, LDL-C, MDA and TC/HDL-C, HDL-C, NO and SOD.	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	90, 180 mg/kg/day, po., for 7 days	<i>in vivo</i>	Gao et al. (2007)
	Decrease the TC, TG and AI levels.	<i>Polygonum multiflorum</i> polysaccharides	50 and 200 mg/kg/day, po., for 28 days	<i>in vivo</i>	Zhai et al. (2010)
	Lipid regulation activity	major chemical components from <i>Polygonum multiflorum</i> (Emodin, Physcion and 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside)	50 $\mu$ M to 300 $\mu$ M	<i>in vitro</i>	Wang et al. (2014)
	Anti-hyperlipidemic effect	Emodin	75, 150 and 300 mg/kg/day, po., for 4 weeks	<i>in vivo</i>	Wu et al. (2012)
	Reduce blood lipid effect	SFE, systematic solvents (petroleum benzin, ethylacetate, <i>n</i> -butanol, 75 % ethanol and water) and ethanol-precipitation after water-extraction extracts.	0.5 to 1.25 g/kg, po., for once	<i>in vivo</i>	Li et al. (2008)
	TC-lowering effects, reduce LDL-C	Water extracts	0.405, 0.81, 1.62 mg/kg/day for <i>Polygonum multiflorum</i> , 0.81, 1.62, 3.24 mg/kg/day for <i>Polygonum multiflorum Praeparata</i> , po., for 24 days	<i>in vivo</i>	Li et al. (2012b)
Hepatoprotective effect	Increase the intracellular contents of TG and TC	Water and 50% ethanol extracts	10, 20, 40, 80 and 100 $\mu$ g/mL	<i>in vitro</i>	Wang et al. (2012a)
	Hepatoprotective effects	Emodin	30 and 50 mg/kg, po.	<i>in vivo</i>	Lin et al. (1996)
	Hepatoprotective effects	Emodin	20, 30 and 40 mg/kg, po., one administration	<i>in vivo</i>	Bhadauria et al. (2010)
	Hepatoprotective and renal protection	Rhein	10, 20 and 40 mg/kg, po., for once	<i>in vivo</i>	Zhao et al. (2011b)
	Antioxidant activity	Homogeneous polysaccharide	IC <sub>50</sub> values were 0.47, 0.6 and 0.93 mg/mL for superoxide anion scavenging, hydroxyl radical scavenging, and hydroxyl peroxide scavenging	<i>in vitro</i>	Lv et al. (2014)
	Promote the expression of HGF	Methanol extract	1–1000 $\mu$ g/mL	<i>in vitro</i>	Huang et al. (2007)
	Increases the expression of HGF messenger RNA in liver tissue	Methanol extract	20, 23, 30, 37, and 44 mg/kg/day, po., for 25 days.	<i>in vivo</i>	Huang et al. (2007)
Anticancer effect	Treatment the hepatic lipid accumulation	Water extracted	15 g/kg/day, po., for 8 days	<i>in vivo</i>	Liu et al. (1992)
	Inhibit the growth of HepG2 cells	Emodin	IC <sub>50</sub> was 36 $\pm$ 2.6 $\mu$ g/ml	<i>in vitro</i>	Liu et al. (2003)
	Arrests liver cancer Huh7, Hep3B, and HepG2 cells in G2/M phase,	Emodin	50 $\mu$ M	<i>in vitro</i>	Hsu et al. (2010)
	Anti-cervical cancer	Aloe-emodin	2.5 and 40 $\mu$ mol/L	<i>in vitro</i>	Guo et al. (2007b)
	Anti-bladder cancer	Aloe-emodin	5, 10, 25 and 50 $\mu$ M	<i>in vitro</i>	Lin et al. (2006)
	Anti-tongue squamous cancer	Aloe-emodin	10, 20, 30, 40 and 50 $\mu$ M	<i>in vitro</i>	Chiu et al. (2009)
	Exhibited cytotoxic effects against neuroblastoma cells	Aloe-emodin	ED50 of 7 $\mu$ M	<i>in vitro</i>	Pecere et al. (2000)
	Exhibited cytotoxic effects against B16–F10 melanoma cells	Aloe-emodin	IC50 values of 60 $\mu$ M	<i>in vitro</i>	Tabolacci et al. (2010)
	Anti-colon cancer	Emodin	40 mg/kg/every 3 days, intraperitoneal injection, for 39 days	<i>in vivo</i>	Ma et al. (2012)
	Anti-gallbladder cancer	Emodin	50 mg/kg/day, intraperitoneal injection, for 18 days	<i>in vivo</i>	Wang et al. (2011)
	Reduce the cytotoxicity of fibrosarcoma and U251 human glioma cell lines.	Aloe-emodin	2.5, 5, 10, 20, 40 and 80 $\mu$ M	<i>in vitro</i>	Birgitte et al. (2007)
	Anti-apoptotic effect	Emodin	1, 5, 10, 20 and 40 $\mu$ M	<i>in vitro</i>	Birgitte et al. (2007)
Anti-head and neck squamous cell carcinoma	Emodin	25 and 50 mg/kg/day, 5 days per week, intraperitoneal injection, for 4 weeks	<i>in vivo</i>	Way et al. (2014)	
Exhibited cytotoxic effects against HepG2 cells	Emodin	30–120 $\mu$ M	<i>in vitro</i>	Yu, et al. (2013)	
Anti-prostate cancer, lung cancer, colon cancer, bone cancer	Emodin	GL <sub>50</sub> ( $\mu$ M)—LNCaP(10), PC-3(36.4), A549 (21.7), HCT-15(33.1), MG-63(50)		<i>in vitro</i>	Masaldan and Iyer (2014)
Anti-esophageal cancer	Emodin	2.5,5,0,10,0,20,0 $\mu$ g/mL		<i>in vitro</i>	Liu et al. (2009a)

Table 3 (continued)

Pharmacological effects	Detail	Active extract/fraction/compound	Effective concentration/dose/pattern	Study model	Reference
Anti-inflammatory effects	Ameliorated colon damage	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	60 and 120 mg/kg/day, po., for 7 days	<i>in vivo</i>	Wang et al. (2008)
	Attenuates proinflammatory factors in microglia	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	50 $\mu$ M	<i>in vitro</i>	Huang et al. (2013)
	Inhibited mouse ear edema and rat paw edema	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	9.2 mg/kg for inhibited mouse ear edema, 12.8 mg/kg for inhibited rat paw edema	<i>in vivo</i>	Zhang et al. (2007b)
	Beneficial effects on colitis	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	intra-gastric administered 10, 30, 60 mg/kg for 7 days	<i>in vivo</i>	Zeng et al. (2011)
	Increased in LPS-induced mouse mastitis	Emodin	1, 2, and 4 mg/kg, i.p., one administration	<i>in vivo</i>	Li et al. (2013a)
	Exhibited intensive anti-inflammation effect	Ethanol extract	po., 0.58 g/kg, 1.15 g/kg, 2.30 g/kg, 4.60 g/kg and 9.20 g/kg, for 3 days	<i>in vivo</i>	Lv et al. (2001)
Promote hair growth	Increase in the proliferation of dermal papilla cells and increased hair-fiber length	Torachryson-8-O- $\beta$ -D-glucoside	10 and 20 $\mu$ M	<i>in vitro</i>	Sun et al. (2013)
Ameliorates diabetic Nephropathy	Alleviation of oxidative stress injury and overexpression of COX-2 and TGF- $\beta$ 1, partially via activation of SIRT1	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	10 and 20 mg/kg/day, po., for 56 days	<i>in vivo</i>	Wang et al. (2009b)
Treatment SARS	Blocked the S protein and ACE2	Emodin	IC <sub>50</sub> was 200 $\mu$ M	<i>in vitro</i>	Ho et al. (2007)
Prevent cardiac remodeling	Prevent cardiac remodeling	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	30, 60, 120 mg/kg/day	<i>in vivo</i>	Xu et al. (2014)
Anti-platelet activity	Anti-platelet activity	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside	10 and 50 $\mu$ M	<i>in vitro</i>	Xiang et al. (2014)
Prevented developmental anomalies	Prevented developmental anomalies in cultured mouse fetus induced by ethanol	Emodin	$1 \times 10^{-5}$ and $1 \times 10^{-4}$ $\mu$ g/ml	<i>in vitro</i>	Yon et al. (2013)
Inhibit tonic tension	Inhibit tonic tension through suppressing PKC $\delta$ -mediated inhibition of myosin phosphatase	Emodin	1 $\mu$ M to 10 $\mu$ M	<i>in vitro</i>	Lim et al. (2014)
Cerebrovascular protective effects	Against ischemic brain injury	Hexane extracts, ethyl acetate extracts and methanol extracts of <i>Polygonum multiflorum</i>	100 mg/kg	<i>in vivo</i>	Lee et al. (2014)

caspase 3-dependent pathway (Wang et al., 2007a). Rhein also induced the apoptosis of HK-2 cells at a dose of 40  $\mu$ M. However, the toxicity of rhein was weaker than that of emodin (Da et al., 2009). Another study demonstrated that emodin, rhein and physcion can significantly inhibit the proliferation of HK-2 cells with IC<sub>50</sub> values of 130.65, 82.97 and 76.02  $\mu$ mol/L, respectively (Wang et al., 2007c). The suppression of the phosphorylation of ERK through the MAPK/ERK signal pathway and alterations in the proportions of lipid moieties may lead to the impairment of the outer mitochondrial membrane in renal tubular epithelial cells. This effect can in turn cause the release of cytochrome c and lead to apoptosis, inducing a decline in the reabsorption of low-molecular-weight compounds in the renal tubule, aminoaciduria and glucosuria (Wang, 2007b).

### 6.3. Other toxicities

Emodin induces embryonic toxicity in mouse blastocysts at doses of 25, 50 and 75  $\mu$ M. The injury in mouse blastocysts occurs via the intrinsic apoptotic signaling processes, impairing subsequent embryonic development (Chang et al., 2012). Moreover, the adverse effects of *Polygonum multiflorum* can be observed not only in the liver and kidney but also in the lung. An ethanol extract of *Polygonum multiflorum* was found to exert toxic effects in the rat lung after repeated intra-gastric administration for 28 days at a dosage of 40 g/kg (Li et al., 2013b). Emodin and rhein also showed mutagenicity in TK gene mutation analysis at the concentrations of 80 and 120  $\mu$ g/mL (Zhu et al., 2011). In addition, a previous study compared the acute toxicity of different components of *Polygonum multiflorum* on mice. The acute toxicity of dual extraction components was stronger than that of the ethanol- and/or water-

extracted components, and the maximum tolerated doses (MTD) were 20.0, 98.4 and 78.0 g/kg, respectively (Huang et al., 2010).

## 7. Pharmacokinetics

In pharmacokinetic experiments, rats were administered *Polygonum multiflorum* extracts. After the tissues were extracted with methanol, the metabolites were identified by LC-MS/MS. TSG, the main component of *Polygonum multiflorum*, was rapidly absorbed into the body fluids, widely distributed throughout the body and quickly eliminated. TSG was mainly distributed in the liver and lung but hardly penetrated the blood-brain and blood-testicle barriers (Lv et al., 2011). Emodin was found predominantly in the liver and brain (Lin et al., 2012). Another study evaluated the pharmacokinetic behaviors of typical constituents of different types of processed *Polygonum multiflorum* after oral administration in rats by LC-MS/MS. The results showed that the bioavailability of gallic acid improved, and the absorption of TSG, polydatin and emodin from the processed product in rats was reduced compared with that obtained with the raw product (Zhang et al., 2013). Some studies have found that stilbene glucoside and emodin were rapidly converted to glucuronide conjugates in rats after oral administration (Sun 2004; Liu et al., 2011). Further pharmacokinetic studies indicated that the AUC, C<sub>max</sub> and T<sub>1/2</sub> of emodin were increased after stilbene glucoside treatment, and the glucuronidation of the emodin levels was significantly inhibited. This phenomenon may be attributed to the inhibition of UGT1A8 mRNA expression by stilbene glucoside (Ma et al., 2013).

## 8. Future perspectives and conclusions

*Polygonum multiflorum* is one of the most important and frequently used traditional Chinese herbal medicines because it exhibits anti-aging, immunologic, anti-hyperlipidaemia, neuroprotective, anti-cancer, and anti-inflammatory effects, among others. Quinones and stilbenes are considered to be the major constituents with pharmacological effects. However, some aspects need to be further investigated.

Many recent studies have investigated the effective constituents of *Polygonum multiflorum* from different geographical areas. HPLC-fingerprint chromatography is usually used to compare the differences in *Polygonum multiflorum* from different geographical areas (Wu et al., 2006; Luo et al., 2008; Liu et al., 2007a; Cai et al., 2011; Xue et al., 2004; Zhang et al., 2003). These studies have only focused on the differences in the contents of common components but have ignored differences in the more minor components in these plants, which is crucially important for *Polygonum multiflorum* not only in terms of quality but also clinical use. The combined anthraquinones are used as indicator compounds to characterize the quality of this plant, which should have a minimum content of 0.10%, as delineated in the Pharmacopoeia of the People's Republic of China; this percentage is calculated based on the amounts of emodin and physcion. However, chryso-phenol-8-O- $\beta$ -D-glucopyranoside and other combined anthraquinones (Yang et al., 1998) are also found in *Polygonum multiflorum*. Therefore, the development of a method to accurately measure the amount of the combined anthraquinones requires further investigation. Although we summarized 102 ingredients in this plant, this number is quite limited at present, and future research on the chemical composition of the plant should be more precise.

In traditional Chinese medicine, *Polygonum multiflorum* is commonly used with other herbs. However, modern experiments have validated that this plant alone exhibits significant pharmacological effects. Therefore, it is important to investigate the molecular mechanisms of *Polygonum multiflorum* combined with other herbs based on traditional uses. Second, the pharmacological effects of some traditional uses of *Polygonum multiflorum* have been validated in recent studies, but these studies were primarily conducted *in vitro*. Thus, the effects of these compounds need to be verified *in vivo*. Third, to date, approximately 100 chemical compounds have been isolated from this plant; however, the pharmacological effects of only a few of the ingredients, such as 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucopyranoside, resveratrol, polydatin, emodin, and physcion, have been studied. Some stilbenes and quinones, the major components of *Polygonum multiflorum*, have not been sufficiently researched in terms of their pharmacological effects, and this is also true for emodin glycosides, physcion glycosides, and some stilbenes, among others.

The number of reports of the adverse effects of *Polygonum multiflorum*, such as hepatotoxicity, nephrotoxicity, and embryonic toxicity, is increasing. The primary toxicity among these is hepatotoxicity, which is of wide concern worldwide. However, the identity if the component(s) that causes hepatotoxicity remains unclear. Some studies have shown that free anthraquinones, such as emodin and physcion, were the main hepatotoxicants (Li et al., 2012a; Sun et al., 2010). Other studies have demonstrated that the hepatotoxicity of the water extract was stronger than that of the ethanol and acetone extracts of *Polygonum multiflorum* (Wu et al., 2012; Huang et al., 2011). Moreover, the hepatotoxicity of *Polygonum multiflorum* was also stronger than that of *Polygonum multiflorum Praeparata*. The emodin and physcion contents increased after processing of this herb (Zhang et al., 2003; Chen et al., 2012c; Liu et al., 2005a; Zhou 2005; Liu et al., 2005b), and the contents of these components in the ethanol and acetone

extracts of this herb were higher than those of the water extract. Thus, the above-described results appear to be contradictory.

Another issue is that *Polygonum multiflorum* exhibits both hepatoprotection and hepatotoxicity, which appears to be contradictory. Based on an examination of the literature, we speculate that the possible reasons are as follows. The first is the size of the administered dose. High doses are more likely to result in liver toxicity, and low doses may show liver protection. The second is the length of the delivery time: long-term drug delivery can easily show liver toxicity, whereas short-term drug delivery may result in liver protection. Third, a study revealed that TSG and physcion likely attenuated the cytotoxic effect of emodin (Yu et al., 2011); therefore, the different experimental results may be due to the different TSG, physcion and emodin ratios in the herbs. Fourth, TSG and emodin are also hepatoprotective due to their antioxidant activity. Thus, this issue requires further study.

In conclusion, *Polygonum multiflorum* is one of the most popular traditional Chinese medicines, and it is an ingredient of many patent medicines or prescriptions. It has been widely used to treat various diseases commonly associated with aging in China for many centuries. Modern research demonstrated that *Polygonum multiflorum* have therapeutic potential in the conditions like Alzheimer's disease, Parkinson's disease, hyperlipidaemia, inflammation and cancer attributed to the presence of various stilbenes, quinones, flavonoids, phospholipids and other compounds present in the drug. The adverse effects (hepatotoxicity, nephrotoxicity, and embryonic toxicity) of this plant were due to the quinones, such as emodin and rhein. Thus more pharmacological and toxicological mechanisms on main active compounds are necessary to be explored, especially the combined anthraquinones (such as emodin-8-O- $\beta$ -D-glucopyranoside, Physcion-8-O- $\beta$ -D-glucopyranoside, etc.) and the variety of stilbenes.

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