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Pharmacology of polygala tenuifolia and its significance in traditional Chinese medicine

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ABSTRACT

Introduction: The dried root of *Polygala tenuifolia* Willd., known as *Polygala Radix*, belonging to the family Polygalaceae, has long been used as a medication to cure a variety of illnesses, including sleeplessness, forgetfulness, sadness, cough, and palpitations. In Southeast Asia, especially China, *Polygala tenuifolia* Willd is a significant industrial and export plant. The benefits of *Polygala tenuifolia's* rhizomes on cognition and nootropics are well-known. As a result, this plant has been used as traditional medicine for many of years.

Methodology: The online databases, including Scopus, web of science, Google Scholar, and PubMed, were searched using different keywords: *Polygala Radix, Polygala tenuifolia*, traditional uses, neuroprotective activity, Chinese herb. The purpose of this review was, therefore, to summarise the previously reported phytochemistry & pharmacological actions of the chosen plant species.

Results: The concentrations of the active ingredients such as tenuifolin, polygalaxanthone III, sibiricose A5, 3,6′-disinapoyl sucrose, and sibiricaxanthone B of *Polygala tenuifolia* Willd. from the primary cultivation regions of China were determined in this study. A wide range of pharmacological actions, including neuroprotective, depressive, hypnotic-sedative, anti-inflammatory, anti-viral, anti-cancer, antioxidant, and antiarrhythmic effects, are present in the isolated components and extracts from *Polygala Radix*.

Discussion: Polygala Radix, the root of *Polygala tenuifolia*, has a variety of therapeutic benefits, especially for neurological disorders. *Polygala tenuifolia* roots also have pharmacological actions associated with anti-inflammatory activity. This review can deepen knowledge of *Polygala Radix* and offer opportunities for further study.

Conclusion: The different chemical compounds isolated from *Polygala Radix* exhibited a wide range of pharmacological actions, such as anti-tumor activity, antioxidant activity, cardiovascular activity, and neuroprotective effects. This review will benefit the researchers to further research on *Polygala Radix* to overcome the limitations.

Introduction

Over the past ten years, traditional oriental herbal remedies have grown in popularity [1,2]. They have a long history of clinical application & their natural origin appears to guarantee that the medications will be successful and nontoxic; that's why they are frequently used for the treatment and prevention of numerous ailments [3]. There are chances to create herbal food items, dietary supplements, and functional foods from each plant employed in such herbal remedies [4,5].

The perennial plant *Polygala tenuifolia* Willd., which is included in each edition of the Chinese Pharmacopoeia, is primarily grown in Shanxi Province in China. Due to its tonic, sedative, and expectorant properties, the root of *Polygala tenuifolia* (*Polygalae Radix*) is the primary source of the traditional Chinese medicine Yuan Zhi [6]. Saponins, oligosaccharide esters, and xanthones from *Polygala Radix* show significant bioactivity and pharmacological effects, including sedation, phlegm expulsion, neuroprotection, coughing cessation, antifungal activity, bioactivity against dementia and tristimania, and others [6]. With almost 50 % of the family's species, Polygala is the most representative genus in the Polygalaceae family. There are more than 600 species in this genus, which includes trees, shrubs, and herbs, having recognized Latin names [7]. They are extensively dispersed all across the planet, with the exception of New Zealand, Polynesia, and the Arctic regions. In China, there are about 39 species. Since more than 2000 years ago,

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Polygala tenuifolia Willd's roots—also known as *Polygala Radix* or "Yuan-Zhi" in Chinese—have been widely used as a traditional Chinese medicine to enhance memory and cognitive function [7,8]. There are various Chinese preparations named as DX-9386, Kami-utan-to etc. where *Polygala tenuifolia* is used as herbs [9]. *Polygala tenuifolia* roots show pharmacological properties linked to anti-inflammatory, anti-cancer, neuroprotective, antidepressant, and sedative-hypnotic actions, according to recent studies [10–14]. Triterpenoids, oligosaccharide esters, and phenolic chemicals, including xanthones, have been discovered in phytochemical research on *Polygala tenuifolia* roots [7,15].

The earliest Chinese pharmacological monograph, Shen Nong's herbal classic, was the first to provide detailed medicinal uses of *Polygala Radix* (PR) [16]. A directory of traditional Chinese medicines in China lists Kai Xin powder, Di Huang Yin Zi, & Gu Yin Jian among the more than 870 Chinese medical formulations that contain PR. These mixtures are frequently used to treat Alzheimer's disease, sleeplessness, anxiety, sadness, irregular menstruation, and early ovarian aging [17,18]. More than 140 chemicals, including saponins, oligosaccharide esters, xanthones, organic acids, and others, have been extracted and identified from *Polygala Radix* with the development of scientific techniques [19, 20]. The PR saponins have been shown to be gastro intestinally toxic, causing animal aphasia, flatulence, and gastrointestinal congestion [21]. Alkaline hydrolysis allows PR to retain its cognitive-enhancing effectiveness while reducing toxicity [22]. The application of PR and the creation of new products are constrained by its toxicity. However, processing or compatibility can change the quality, effectiveness, or toxicity of PR. Additionally, certain oligosaccharide esters and saponins have reduced bioavailability in PR in vivo compared to organic acids [23,24]. Many scientific investigations have been undertaken on this subject, and significant effort has been made to investigate the phytochemistry & potential pharmacological actions of *Polygala Radix* [16]. The pharmacognosy of *Polygala tenuifolia* is as follows:

Kingdom	**Plantae**
Division	**Tracheophyta**
Class	**Rosids**
Order	**Fabales**
Family	**Polygalaceae**
Genus	**Polygala**
Species	**P. tenuifolia**

Phytochemistry

The distinctive components of *Polygala Radix* have been determined to be saponins, xanthones, & oligosaccharide esters. *Polygala Radix* also contains alkaloids, organic acids, flavonoids, fatty acids, resins, and amino acids.

Since long ago, more than 50 saponins have been isolated from PR, and tenuifolin is one of the index components of PR quality control in the Chinese Pharmacopoeia. Pharmacological studies show that saponins exert the functions of relieving excitement, sedation, relieving cough, expelling phlegm, and many others. Triterpene Polygalacic acid, also known as 2β, 3β, 16α, 23, and 23-tetrahydroxy-D12-oleanen-28-oic acid, was created by hydrolyzing triterpene saponins from *Polygala tenuifolia* [7].

One of the key elements of *Polygala Radix* is xanthones. Xanthones have been found to have antifungal, analgesic, anti-cancer, and other properties, according to recent pharmacological studies. According to Chinese Pharmacopoeia, only the dry root of *Polygala Radix* was considered medicinal, while the majority of the aboveground portions were rejected. A new scientific foundation for the logical development and use of *Polygala Radix* resources has been established by Song et al.'s demonstration that the aerial portion of *Polygala Radix* also comprises more active components.

A significant family of *Polygala Radix* chemicals is represented by oligosaccharide esters. Oligosaccharide esters combine glucose or rhamnose with different types of glycosidic bonds to generate oligosaccharides, which are subsequently converted into esters with organic acids. This structure has sucrose as the common mother nucleus. Plants of all kinds produce oligosaccharide esters. However, only Polygalaceae contain sugar esters that contain more than trisaccharide. These elements are thought to be endemic to the Polygalaceae family. So far, 36 oligosaccharide esters have been discovered in this plant. The biological effects of oligosaccharide esters on brain protection, anti-depression, and anti-dementia are significant.

Alkaloids are a common component of plants and exhibit exceptional and unique biological properties. Currently, seven β-carboline-based alkaloids have been identified from *Polygala Radix*. According to studies, β-alkaloids have a large potential for research and use and have properties such as anti-thrombotic, memory improvement, and anti-tumor.

Polygala Radix also includes crucial elements such as volatile oils and organic acids. Ferulic acid, erucic acid, and 3,4,5-trimethoxycinnamic acid were the key constituents that were active, and they had effects that were anticonvulsant, anti-inflammatory, neuroprotective, and anti-amnesic. *Polygala Radix* also includes coumarins, phenylpropanoids & inorganic metal elements, including Zinc, potassium, Calcium, Copper, Iron, Magnesium, and others in addition to the above chemical components.

Little research has been done on the active elements of other portions of *Polygala tenuifolia* Willd., according to a survey of the literature. To aid in the judicious utilization of resources, researchers should examine *Polygala tenuifolia* Willd.'s aboveground components, such as stems & leaves [16].

Chemical constituents

In a study by Son et al., three saponins, ten phenylpropanoid sucrose esters, one benzoic acid sugar ester derivative, two hydroxy benzophenone, four xanthones derivatives, two phenolic derivatives, and two ionones have been extracted from the roots of *Polygala tenuifolia* [15]. After comparing NMR spectra of isolated compounds with reported compounds, the constituents which have been identified are as onjisaponin J, onjisaponin Fg, onjisaponin B, sibiricose A3, sibiricose A5, sibiricose A6, tenuifoliside A, tenuifoliside B, tenuifoliside C, 3,60-disinapoyl sucrose ester, 3-O-(3,4,5-trimethoxy-cinnamoyl),60-O-(p-methoxybenzoyl) sucrose ester, 1-O-(cinnamoyl),3-O-(benzoyl),20-O-(6-O-acetyl-b-d-glucopyranosyl) sucrose ester, polygalatenoside A, polygalaxanthone III, polygalaxanthone IV, 7-O-methylmangiferin, 3,4,5-trimethoxyxanthone, tenuiphenone B, hydrocotoin, p-hydroxybenzoic acid, 3,4,5- trimethoxycinnamic acid methyl ester, blumenol C and 9-epi-blumenol C [15].

Methodology

Searches were conducted through online databases like Scopus, Web of Science, Google Scholar, and PubMed [25]. This article contains all the data about *Polygala tenuifolia* and includes studies and reviews from the years 1992 to 2023. A total of 150 reviews and research publications were studied, and 60 of those were cited. Therefore, the goal of this research was to provide an overview of the previously documented phytopharmacological characteristics of the selected plant species.

Pharmacology

Previous research on PR has shown that it has a wide range of pharmacological effects, including those on the neurological and cardiovascular systems, as well as its anti-inflammatory, antiviral, anti-cancer, and antioxidant characteristics, among others. The effects primarily impact the nervous system. Table 1 lists the major pharmacological effects of *Polygala Radix* [16].

Table 1
Pharmacological effects of *Polygala Radix*.

Pharmacological effect	Chemical moiety	Dose	Animals/cells used for the study	Mechanism of action	Reference
Neuroprotective effects	Tenuifolin	1, 5 10 μM	BV2 cells	Reducing NF-kB signaling pathway activity	[26]
	Senegenin	1, 5 μg/ml	PC12 cells	Reducing neurite outgrowth and boosting MAP2 and Gap-43 expression	[27]
	Onjisaponin B	20, 40 mg/kg/d	C57BL/6 J mice	Inhibition of ROCK2 or Rhoa pathway.	[28]
	3,6′- Disinapoyl sucrose	75, 150 μM	SY5Y cells	reducing NOS hyperactivation, boosting CREB phosphorylation and expression of CRTC1 & BDNF	[29]
	1,3,7- trihydroxyxanthone	0.1–10 μM	Primary culture of rat astrocytes	tPA system modulation and cAMP and ERK pathway activation	[30]
Anti-depressant effects	Tenuifolin	3,6,9 mg/kg	Mice	Increasing 5-HT expression, lowering IDO expression, reducing aching activity	[31]
	Senegenin	4,8 mg/kg	ICR mice	blocking NF-kB and controlling the NLRP3 signal	[32]
	Sibiricose A5	0.53, 13.2, 132 μmol/L	PC12 cells	Ca2+ release inhibition and neurotransmitter release regulation	[33]
	3,6′- Disinapoyl sucrose	1,2,4 mg/kg	Mice	Improvement of 5-HT and NE nerve function	[34]
Cognition enhancing effect	Polygalasaponin XXXII	0.125, 2 mg/kg	Scopolamine induced mice	defending neurons against glutamate and ROS harm, enhancing TrkB phosphorylation, and maintaining LTP	[35]
	Tenuigenin	375 mg/kg	Male rats	nAChR7 expression is being upregulated in the CA1 region of the hippocampus.	[16]
	Polygalacicacid	3,6,12 mg/kg	Mice	regulating cholinergic activity and inflammation in the brain	[36]
Hypnotic sedative effects	Tenuifolin	20,40,80 mg/kg	ICR mice	Increasing GABAergic activity and decreasing noradrenergic activity	[37]
	3,4,5- trimethoxycinnamic acid	2,5,10 mg/kg	Cerebellar granule cells & ICR mice	Modulation of activity of GABA.	[38]
Cardiovascular effects	Senegenin	40, 80 mg/kg	SD rats	Decrease inflammation and expression of HMGB1.	[16]
	3,4,5- trimethoxycinnamic acid	15, 30 μM	Rabbit ventricular myocytes	reducing intracellular Ca2+ transients and preventing calcium channel activity.	[39]
Anti-tumour effects	Polysaccharides	10, 20, 40 mg/kg	OVCAR-3 cells	downregulating the activity of telomerase and inhibiting Bmi-1 at both the protein and mRNA levels	[40]
Anti-viral effects	1,5- anhydro-d-glucitol	10–80 mg/L	Ctenopharyngodon Idella kidney cells	IL-1, TNF, MX1, and MyD88 expression induction	[41]
Anti-inflammatory effects	Tenuifoliside A	5, 10, 40, 80 μM	LPS induced RAW264.7 & murine peritoneal macrophages	NF-B and JNK/MAPK signal inhibition	[42]
Anti-oxidant effects	Oligosaccharide ester fraction	25, 50 mg/kg	Senescence accelerated mice	SOD & GSH-Px content increases, whereas MDA content declines.	[43]

Effect on the nervous system

The main illnesses impacting human health include disorders of the nervous system, such as cerebrovascular disease, Alzheimer's disease, and Parkinson's disease [44]. The neuroprotective properties of *Polygala Radix* have undergone extensive study in contemporary pharmacology. In *Polygala Radix*, saponins are prevalent and show good neuroprotective properties.

Treatment of Parkinson's and Alzheimer's disease

Senegenin may improve PC12 cell viability by controlling neurite outgrowth and upregulating the expression of growth-associated protein 43 (Gap-43) and microtubule-associated protein 2 (MAP2), according to recent studies on PC12 cells treated with the A peptide [27]. The anti-inflammatory effects of onjisaponin B at doses of 20 and 40 mg/kg should be investigated as a potential treatment for Parkinson's disease (PD). Onjisaponin B functions by inhibiting nuclear factor-kappa B (NF-B) p65, RhoA, and Rhokinase 2 (ROCK2) protein expression by activating the RhoA/ROCK2 signaling pathway. It also improves antioxidant enzyme activity. Onjisaponin B also has a high molecular mass; therefore, it cannot cross the blood-brain barrier. The administration of metabolite tenuifolin, onjisaponin B, was found to enter the mice's brains and provide a therapeutic effect [28].

In a dose-dependent way, 1,3,7-trihydroxyxanthone, another PR component, could greatly boost the synthesis of brain-derived neurotrophic factor and nerve growth factor (NGF) at both the transcriptional and protein expression levels. As a result, 1,3,7-trihydroxyxanthone may represent a cutting-edge possibility for the treatment of Alzheimer's disease [30]. The primary bioactive chemicals in *Polygala Radix* are oligosaccharide esters, which can be used as an initial basis to create new anti-aging and brain-protecting medications. According to Liu et al., co-treatment with 3,6′-disinapoyl sucrose and tenuifoliside A can reduce Glu-induced nitric oxide synthase (NOS) hyperactivation, increase CREB phosphorylation, and boost the generation of CREB-regulated transcription co-activators (CRTC1) and BDNF [29].

Using chromatographic columns made of diethylaminoethyl cellulose 52 & Sephacryl S-100, *Polygala tenuifolia* rhizomes were first extracted with hot water. PTP70–2, a homogeneous heteropolysaccharide, was identified and had a relative molecular weight of 65.2 kDa by Li et al. The inhibitory effect of 3.08 μM PTP70–2 was much stronger than that of the positive control on lipopolysaccharide (LPS)-induced pro-inflammatory BV2 microglial cells. PTP70–2 significantly lowered the expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6). A novel anti-neuroinflammatory substance called PTP70–2 holds a lot of promise for both treating and preventing Alzheimer's disease [45].

But because there are so many causes that might promote Parkinson's disease or Alzheimer's disease, there are many different and complex signaling pathways. In order to further understand the roles and mechanisms in the pathophysiology of neurodegenerative illnesses, as well as to identify the variables and associated signal molecules that control their neuroprotective effects, more research is required. More research should be done to see if they have any additive and synergistic effects on animal models for mental diseases, as well as to see if they can cross the blood-brain barrier [16].

Anti-depressant effect

In recent years, reports on the antidepressant properties of oligosaccharide esters, organic acid & saponins in *Polygala Radix* have arisen. In 2020, Zhou et al. used behavioral testing and biochemical analysis of brain tissue to assess the anti-depressant effects of PR extracts in behaviourally depressed mice and chronic restraint stress-induced rats. The findings demonstrated that RP could shorten the duration that mice were immobile during a forced swimming test, shorten the period between feeding time and remaining immobile, and increase locomotor activity. Additionally, it might decrease the protein levels of NLRP3, ASC, and cleaved caspase-1, increase the levels of LC3-II and beclin1, regulate the dysfunction of the AMPK-mTOR pathway in the rat prefrontal cortex, and inhibit the expression of pro-inflammatory cytokines. PR extracts' antidepressant effects were attained by encouraging autophagy and reducing neuroinflammation [46].

Dementia

Numerous studies have demonstrated that PR works efficiently to enhance animal learning and memory. The overhead part of *Polygala tenuifolia* was found to exert memory-enhancing results against d-galactose or NaNO2-induced learning and memory impairment in mice by modulating cholinergic activity, inhibiting the formation of IL-1β & malondialdehyde (MDA), increasing the glutathione (GSH) level and superoxide dismutase (SOD) activity, as well as increasing the expression of BDNF and tropomyosin receptor kinase B (TrkB) [47]. The safe range of effective doses was unclear despite the fact that several doses of extracts from *Polygala tenuifolia*'s aerial parts were investigated. Li et al. recognized active chemicals from *Polygala Radix* extracts, among which Onjisaponin B had exhibited a discernible increase in learning and memory by encouraging the destruction of amyloid precursor protein [16,48].

Insomnia

Recent medication epidemiology studies have revealed that PR is a typical Chinese individual remedy for insomnia [49]. The fraction of ethyl acetate in the ethanol extract was determined to be the most beneficial component. When Chen et al. tested the hypnotic activity of PR, and discovered that it may increase sleep duration and rate in mice. Further investigation revealed that mice's hippocampus contained the largest levels of DA and that the eluted fraction of 70 % ethanol in MCI columns had the greatest hypnotic effect [50].

In Chinese herbal formulas, *Polygala Radix* is frequently used to treat insomnia & neurasthenia. Although PR or its active ingredients have hypnotic-sedative effects, not enough research has been done on the mechanism that underlies *Polygala Radix*. The interplay between numerous targets and pathways cannot be fully explained by existing research, nor can it link them together into a functioning mechanism network. Future researchers can investigate PR in depth and find new possible targets as well as signal pathways by using technologies like transcriptomics, genomes, and metabolomics [16].

Anti-inflammatory effect

The development of effective, low-toxicity Traditional Chinese Medicine to prevent & treat ailments brought on by inflammation has a promising future. Kim et al. studied the anti-inflammatory properties of tenuifoliside A and discovered that it suppressed the NF-kB pathway in macrophages by reducing the synthesis of substances that cause inflammation, such as TNF- and IL-1. Additionally, it could interfere with the phosphorylation of JNK in a dose-dependent way and decrease the synthesis of nitric oxide (NO), nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), and cyclooxygenase-2 (COX-2) to act as an anti-inflammatory [42].

Many constituents of *Polygala Radix* exhibit anti-inflammatory action in a variety of ways. These findings have high research value, support PR's traditional usage in treating breast pain, swelling, and sores, and encourage efforts to develop plant's anti-inflammatory properties [16].

Anti-viral activity

Many years of study and practice have demonstrated that TCM has a significant positive impact on viral infection conditions. It is thought that PR has an antiviral impact. The antiviral activity of two substances extracted from PR was subsequently examined in vitro & in vivo by Yu et al. 1,5-anhydro-d-glucitol and 3,4,5-trimethoxycinnamic acid were recognized as the purified substances. The two substances elevated the

levels of immune-related genes like myeloid differentiation factor 88, TNF-, myxovirus, and IL-1 to variable degrees, according to in vitro anti grass carp reovirus tests. 3,4,5 trimethoxy cinnamic acid had better efficiency than 1,5-anhydro-d-glucitol in vivo insecticidal experiments. However, this study didn't possess a positive control, in vivo animal experimentation, and clinical evidence [16,41].

Essentially, a successful antiviral agent must focus on the viral process alone and have no impact on the ongoing cellular processes during viral replication. The virus will, therefore, be unable to access its receptors, which are the functional virus-controlled host cellular receptors. Antiviral substances do not affect healthy cell activity in uninfected cells; they are, therefore, efficient and secure. Interaction with viral envelope proteins that result in the breakdown of the envelope, preventing the virus from attaching to host cells by destroying the cell's covering and the virus's ability to adhere to it, are two of the methods through which saponins work against viruses [51].

Anti-tumour activity

Yao discovered that polysaccharides could clearly lower transcription and protein levels of the vascular endothelial growth factor (VEGF), CD34, and the epidermal growth factor receptor (EGFR), which resulted in the activation of apoptosis in mice with tumo [52]. When Zhang et al. investigated the anticancer effect of polysaccharides on OVCAR-3 cells, they discovered that polysaccharides, in a dose-dependent manner, limit OVCAR-3 cell growth and colony formation (P 0.05). Additionally, polysaccharides successfully reduced telomerase activity and Bmi-1 protein and gene expression in OVCAR-3 cells. This study lacked a thorough examination of the mechanism of action of polysaccharides in different growth stages of OVCAR-3 cells, as well as a comparison study of positive drugs. In the coming years, flow cytometry could be utilized to further study how polysaccharide affects each growth stage of OVCAR-3 cells [40].

RP02–1, a polysaccharide isolated from *Polygala tenuifolia* Willd., was demonstrated by Bian et al. to be an efficient inhibitor of pancreatic cancer cell growth both in vitro and in vivo. According to mechanism research, RP02–1 reduced the expression of Bcl-2, increased the expression of Bax & Cleaved Caspase 3 in pancreatic cancer cells, causing them to die off in a dose-dependent way. Research on cells revealed that RP02–1 had the biological ability to stop the proliferation of pancreatic cancer cells [16,53].

Yu et al. extracted a polysaccharide from *Polygala tenuifolia* Willd. and demonstrated that this *Polygala tenuifolia* might cause cell apoptosis in human lung cancer cells via activating the FAS/FAS-l-mediated death receptor pathway. They demonstrated that in vitro and in vivo targeting of *Polygala tenuifolia* results in anticancer efficacy and immunoregulation of S180 sarcoma cells [54].

Anti-oxidant activity

When the body is stimulated by oxidation, the overproduction of reactive oxygen species (ROS), in addition to reactive nitrogen free radicals (RNS) can't be eliminated in a timely manner. This damages the homeostasis of the oxidation system and antioxidant system, causes cell or tissue damage, and further promotes the development of numerous acute and chronic diseases. The development of Traditional Chinese Medicine with antioxidant effects has thus become one of the most active areas of research in the field of medicine [16].

Zhang et al. investigated the antioxidant action of aqueous extract of *Polygala tenuifolia* Willd. seedlings and discovered that the aqueous extract significantly improved learning and memory functions decreased MDA content, and increased levels of SOD, catalase (CAT), and total antioxidant capacity [55]. Feifei Xie investigated the antioxidant properties of *Polygala Radix* polysaccharide at various concentrations in vitro and discovered a favorable correlation between *Polygala Radix* polysaccharide concentration and how well it scavenges hydroxyl and DPPH free radicals. The maximal scavenging rates of the hydroxyl and DPPH radicals were 61.3 % & 79.5 %, respectively, at a concentration of 4 mg/mL, demonstrating *Polygala Radix* polysaccharide's favorable in vitro oxidation resistance [16,56].

Cardiovascular activity

3,4,5-trimethoxycinnamic acid inhibits the action of the calcium channel in rabbit ventricular myocytes, exhibiting antiarrhythmic effects [39]. Treatment with senegenin may appear to have protective effects against rat cardiac ischemia reperfusion damage. The mechanism involves the elevation of left ventricular systolic blood pressure (LVSP) while decreasing left ventricular end-diastolic blood pressure (LVEDP), myocardial infarction area, lactate dehydrogenase (LDH) & creatine phosphokinase (CPK) activities, TNF-, IL-6, and iNOS levels, and high-mobility group box protein 1 (HMGB1) expression [57]. Senegenin decreased inflammatory cytokine expression, and this had a protective effect on rat cardiac ischemia reperfusion injury [16].

Immunoadjuvant activity

The *Polygala tenuifolia* root extracts were shown to have significant adjuvant action. Onjisaponins A, E, F, and G were identified as the active components after being isolated from the extract by HPLC. Each onjisaponin was given intranasally to laboratory mice together with the influenza vaccination, and the outcomes were compared to those of animals who received the vaccine alone. Using onjisaponins as adjuvants resulted in a considerable increase in serum HI Ab titers. *Re*-vaccination with the influenza vaccine alone improved both nasal influenza virus antibody IgA & serum HI Ab titers in mice after the primary injection of the influenza vaccine with onjisaponins. These findings suggest that onjisaponins isolated from *Polygala tenuifolia* roots have substantial adjuvant properties when used intranasally with influenza vaccination.

Quil A, a refined combination of Quillaja saponins from the bark of Q. saponaria Molina, has been utilized as an adjuvant for animal vaccinations due to its high adjuvant effect. Quil A has not, however, been used in human vaccinations due to its severe toxicity. Quil A is also thought to have strong hemolytic properties. At 25 g/ml, it has been demonstrated that QS-21, a pure saponin from Quil A, has both powerful adjuvant and hemolytic activity. According to the study's findings, onjisaponins A, E, F & G did not have any hemolytic activity at 100 g/ml and did not even have any at 200 g/ml [58].

SAR of polygala saponins

Saponins are antiviral drugs that block the virus's several pharmacological targets. They also have anti-inflammatory and antithrombotic properties that help to treat the disease's symptoms and clinical consequences. Additionally, saponins have immunostimulatory properties that increase the vaccines' efficacy and safety by extending the duration of the immunogenicity against SARS-CoV-2 & its contagious variants [59].

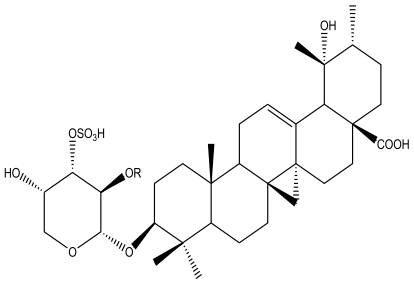
The anti-inflammatory properties of phenolic glycosides & triterpenoid saponins can be used to infer their structure-activity relationship (SAR). According to the SAR of these saponins containing triterpenoid, the presence of the glucose units at the aglycon's C-3 and/or C-28 may be crucial to the inhibitory anti-inflammatory action of these active substances. Additionally, the presence of replacement groups, notably -OH, -OCH3, and -COOH, in structures of phenolic glycosides obviously affects the IC_{50} values. In order to comprehend the structure-activity relationship between the sugar moiety in aglycon & their pharmacological characteristics, particularly in vivo, more research is necessary [60].

When we compare polygala saponins with Quillaja saponins in terms of immunoadjuvant activity, it has been found that Quillaja saponins

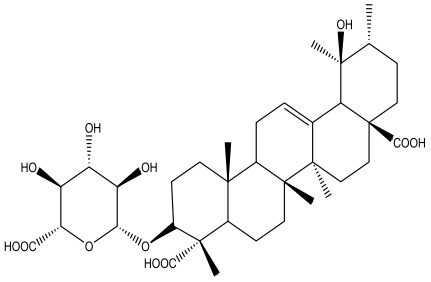
exhibit hemolytic activity along with adjuvant activity, but polygala saponins show no hemolytic activity. The hemolytic activity depends on aglycone moiety and its affinity to bind cholesterol along with the side chain present. The structure of QS-21 contains an aldehyde group at position 23 which is responsible for adjuvant activity. In the case of saponins in other Polygala species like Polygala tenuifolia, a carbonyl group is present in both carboxyl and aldehyde groups associated with hydrogen bonds responsible for adjuvant activity. The studies show that polygala saponins show fewer toxic effects as compared to Quillaja saponins used in animal vaccines due to the difference in moiety attached to the aglycone part of saponins [61].

Chinese herbal prescription medicines

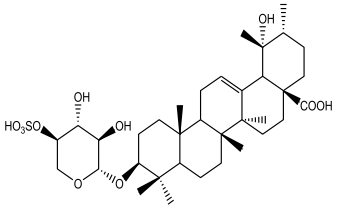
Because of its extensive biological and pharmacological effects, *Polygala Radix* has a long history in China as a traditional medicinal herb (Fig. 1, Fig. 2). Shen Nong's herbal classic, which was composed during the Eastern Han Dynasty, has the first description of *Polygala Radix*. This



A



B

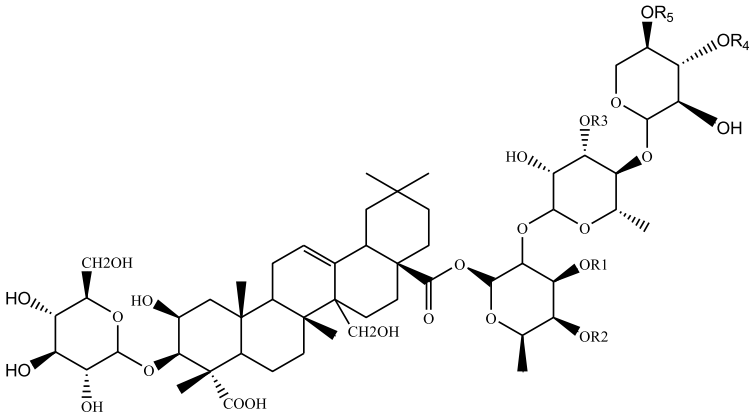


C

A= R = H (Sibiricasaponin B); R = AC (Sibiricasaponin D)

B = Sibiricasaponin A

C = Sibiricasaponin C



R1	R2	R3	R4	R5	Chemical constituent
Rha	MC	Api	H	Gal	Onjisaponin A
H	TC	Api5HMG	H	H	Onjisaponin Gg
Rha	MC	Api	Ara	H	(Z)-Polygalasaponin XXXII
H	TC	Api	Ara	H	Polygalasaponin XXXI
H	MC	Api	H	Gal	(E)-Senegasaponin a
Ara	MC	Api	Gal	H	Myrtifolioside A1
H	H	H	Ara	Gal	Arilloside D

Rha: α-L-rha,nopyranose; MC: (E)-4-methoxy cinnamoyl; Api: β-D-apiofuranosyl; Gal: β-D-galactopyranosyl; TC: (E)-3,4,5-trimethoxy cinnamoyl; Api5HMG: 3-hydroxy-3-methyl-5-pentanoic acid ester-5- β-D-apiofuranosyl; Ara: β-D-arabopyranosyl.

Fig. 1. Chemical structures of Polygala saponins [16].

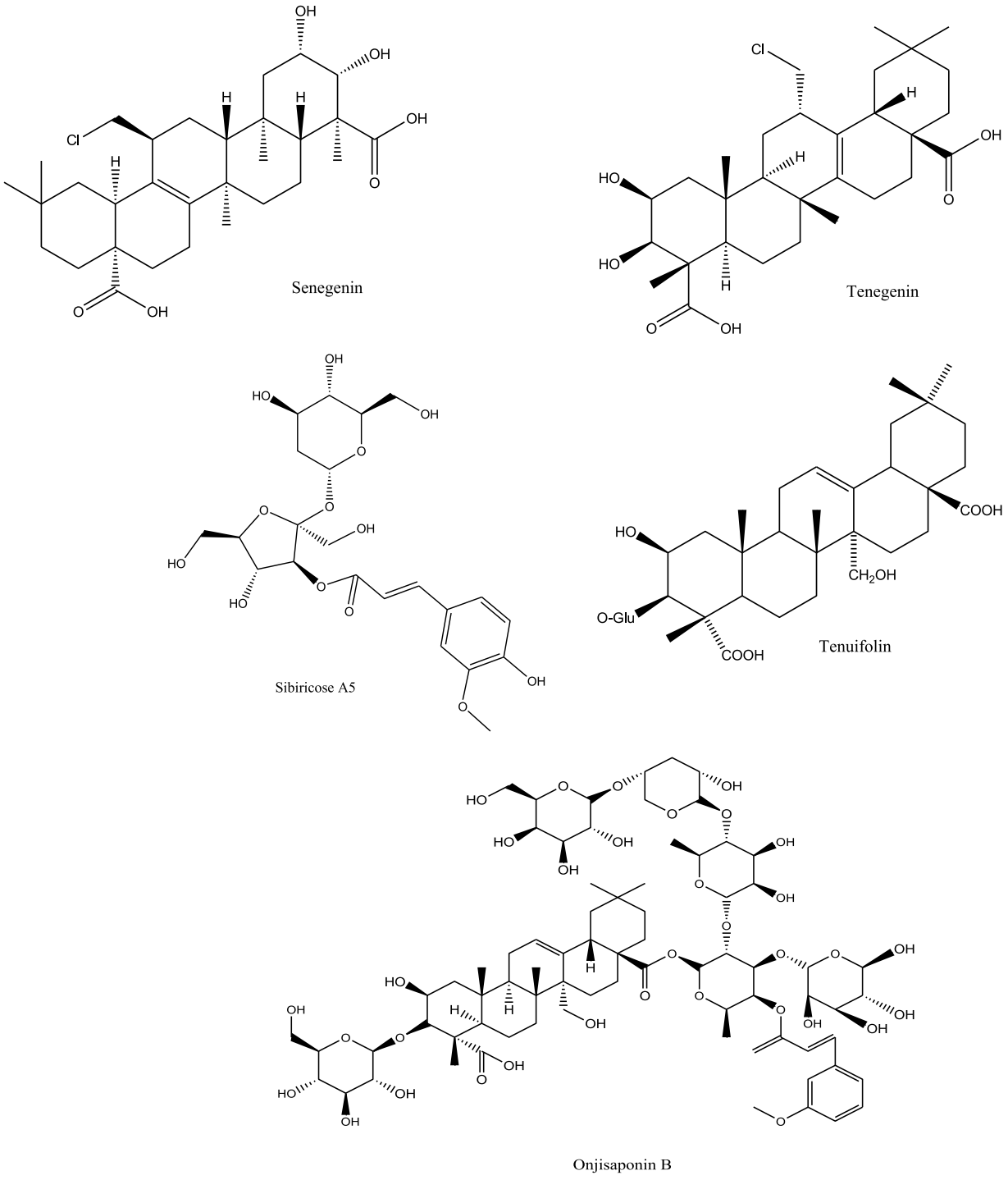


Fig. 2. Chemical Structure of some Chemical Constituents of *Polygala tenuifolia*.

plant was later listed as a potent herbal remedy that can foster intellectual development in the Compendium of Materia Medica, another remarkable traditional Chinese medicine publication [16]. Table 2 lists a few representative traditional Chinese herbal remedies with *Polygala Radix*.

Conclusion

Polygala Radix has been effectively utilized in recent decades and has long been employed in China as a traditional medicine. From *Polygala Radix*, more than 140 products have been extracted and identified. The protective benefits of *Polygala Radix* on the neurological and

Table 2
Chinese medicines containing *Polygala Radix* [9,16].

Name of preparation	Ingredients	Uses
Ding Zhi pills	Ginseng Radix and Rhizoma, Poria, Glycyrrhizae Radix and Rhizoma, Cinnabaris, *Polygala Radix*, Acori Tatarinowii Rhizoma	Treatment of myopia and forgetfulness, relaxing the nerves, and stimulating the spleen.
Tian Wang Bu Xin pills	Processed Polygalae Radix, Acori Tatarinowii Rhizoma, Angelicae Sinensis Radix, Poria, Schisandra Chinensis Fructus, Codonopsis Radix, Semen Ziziphi Spinosae, Semen Platycladi, Platycodonis Radix, Ophiopogonis Radix, Asparagi Radix, Rehmanniae Radix, Scrophulariae Radix	Treating palpitations, forgetfulness, wet dreams, and insomnia
Yang Xin soup	Angelicae Sinensis Radix, Poria, Fu Shen, Processed Polygalae Radix, Chuanxiong, Glycyrrhizae Radix and Rhizomes, Semen Platycladi, Semen Ziziphi Spinosae, Schisandrae Chinensis Fructus, Pinellia Ternata Radix and rhizomes of ginseng, Ginger Cortex	Nurturing the blood to heal, palpitation & restlessness.
Qi Fu Drink	Ginseng Radix and Rhizoma, Polygalae Radix (processed), Rehmanniae Radix, Angelicae Sinensis Radix, Glycyrrhizae Radix and Rhizoma, and Semen Ziziphi Spinosae	Blood deficiency treatment.
Bai Zi yang Xin pills	Chuanxiong Rhizoma, Polygalae Radix (processed), Semen Platycladi, Codonopsis Radix, Astragali Radix, Radix of Angelica Sinensis Pinellia Ternata, Schisandra Chinensis Fructus, Poria, Semen Ziziphi Spinosae, Cinnamomi Cortex, Glycyrrhizae Radix et Rhizoma, and Cinnabaris	Treating palpitations, sleep issues, daydreaming, and memory loss.
Qiang Yang Bao Shen pills	Semen Astragali Complanati, Psoraleae Fructus, Semen Euryales, Rubi Fructus, Polygalae Radix (processed), Epimedii Folium, Cistanches Herb, and Foeniculi Fructus.	Treating impotence, mental tiredness, and waist acid spermatorrhea brought on by renal deficiency.
Fu Ning Kang tablets	Angelicae Sinensis Radix, Rehmanniae Radix, Paeoniae Radix Rubra, Corni Fructus, Anemarrhenae Rhizoma, Phellodendri Chinensis Cortex, Moutan Cortex, Acori Tatarinowii Rhizoma, Lycii Fructus, Ginseng Radix et Rhizoma, Schisandrae Chinensis Fructus, Cnidh Fructus, Semen Cuscutae, Epimedii Folium, Morinda Officinalis Radix, Cibotii Rhizoma	Treating irregular menstruation, vaginal dryness, emotional distress, and unease brought on by liver and renal insufficiency, as well as disharmony in the vessels that carry blood to and from the uterus.
Fu Mai ding capsules	Astragali Radix, Codonopsis Radix, Polygalae Radix, Chuanxiong Rhizoma, and Mori Fructus	Treating atrial or ventricular premature beats, blood stasis deficiency-related palpitations, and pulse replacement.
Tian Ma Xing Nao capsules	Pheretima, Acori Tatarinowii Rhizoma, Castrodiae Rhizoma, Rehmanniae Radix, Cistanches Herba, and Polygalae Radix	Liver and kidney nourishment, as well as pain relief.
Ling Lian Hua granules	Mushroom powder, Ligustri LucidiFructus, Cardeniae Fructus, Ecliptae Herb, Polygalae Radix, Lilii Bulbus, Leonuri Herba, and Rose Rugosae Flos	Treatment of perimenopausal syndrome involves nourishing yin, calming the mind, and reestablishing heart and kidney connectivity.
DX-9386	Polygala tenuifolia, Panax ginseng, Poria cocos and Acorus gramineus	For the treatment of Alzheimer
Kami-utan-to	Polygala tenuifolia and 12 other herbs	For the treatment of psychoneurological diseases

cardiovascular systems, as well as its anti-inflammatory, antioxidant, and anticancer activity, have all been identified by contemporary pharmacological studies. Both beneficial and harmful *Polygala Radix* components are saponins. Future studies should examine how to balance the effectiveness and potential toxicity of saponins by assessing the effective quantity as compared to the amount that causes toxicity.

Technical challenges still exist in extracting and purifying enough chemical substances, especially saponins and xanthones. Their biological processes and mechanisms of action are still being understood. Another significant obstacle to *Polygala tenuifolia* utilization is quality control. Because of variations in habitat, harvest season, and processing techniques, *Polygala tenuifolia*'s response to treatment is similarly inconsistent. As a result, it is crucial to develop drug quality control standards, define processing parameters, and supply consistent and dependable medicinal materials for usage in medical facilities.

Author's contribution

Akash Garg- Data Collection; Rutvi Agrawal- Writing the manuscript; Rohitas Deshmukh- Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] W.Y. Jiang, Therapeutic wisdom in traditional Chinese medicine: A perspective from modern science, Trends Pharmacol. Sci. 26 (2005) 558–563.
[2] S. Liu, L.Z. Yi, Y.Z. Liang, Traditional Chinese medicine and separation science, J. Sep. Sci. 31 (11) (2008) 2113–2137.
[3] J.L. Tang, B.Y. Liu, K.W. Ma, Traditional Chinese medicine, Lancet 372 (9654) (2008) 1938–1940.
[4] K.Y. Shin, B.Y. Won, H.J. Ha, Y.S. Yun, H.G. Lee, Preclinical Safety of the Root Extract of Polygala tenuifolia Willdenow in Sprague-Dawley Rats and Beagle Dogs, Evid. Based Complement. Alternat. Med. 2014 (2014), 570134.
[5] C.F. Chau, S.H. Wu, The development of regulations of Chinese herbal medicines for both medicinal and food uses, Trends Food Sci. Technol. 17 (6) (2006) 313–323.
[6] J. Liu, A. Liu, F. Mao, Y. Zhao, Z. Cao, N. Cen, et al., Determination of the active ingredients and biopotency in Polygala tenuifolia Willd. and the ecological factors that influence them, Ind. Crops Prod. 134 (2019) 113–123.
[7] M.A. Lacaille-Dubois, C. Delaude, Mitaine-Offer AC. A review on the phytopharmacological studies of the genus Polygala, J. Ethnopharmacol. 249 (2020), 112417.
[8] editorC Delaude (Ed.), Les Polygalaceae Et Leurs Saponines, 1992.
[9] Z.K. Sun, H.Q. Yang, S.D. Chen, Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease, Transl. Neurodegener. 2 (1) (2013) 6.
[10] M.H. Cheong, S.R. Lee, H.S. Yoo, J.W. Jeong, G.Y. Kim, W.J. Kim, et al., Anti-inflammatory effects of Polygala tenuifolia root through inhibition of NF-κB activation in lipopolysaccharide-induced BV2 microglial cells, J. Ethnopharmacol. 137 (3) (2011) 1402–1408.
[11] T. Xin, F. Zhang, Q. Jiang, C. Chen, D. Huang, Y. Li, et al., Extraction, purification and antitumor activity of a water-soluble polysaccharide from the roots of Polygala tenuifolia, Carbohydr. Polym. 90 (2) (2012) 1127–1131.

[12] X. Deng, S. Zhao, X. Liu, L. Han, R. Wang, H. Hao, et al., Polygala tenuifolia: a source for anti-Alzheimer's disease drugs, Pharm. Biol. 58 (1) (2020) 410–416.
[13] M.C. Cheng, C.Y. Li, H.C. Ko, F.N. Ko, Y.L. Lin, T.S. Wu, Antidepressant principles of the roots of Polygala tenuifolia, J. Nat. Prod. 69 (9) (2006) 1305–1309.
[14] Y. Yao, M. Jia, J.G. Wu, H. Zhang, L.N. Sun, W.S. Chen, et al., Anxiolytic and sedative-hypnotic activities of polygalasaponins from Polygala tenuifolia in mice, Pharm. Biol. 48 (7) (2010) 801–807.
[15] S.R. Son, Y.S. Yoon, J.P. Hong, J.M. Kim, K.T. Lee, D.S. Jang, Chemical Constituents of the Roots of Polygala tenuifolia and Their Anti-Inflammatory Effects, Plants (Basel, Switzerland) 11 (23) (2022).
[16] X. Zhao, Y. Cui, P. Wu, P. Zhao, Q. Zhou, Z. Zhang, et al., Polygalae Radix: A review of its traditional uses, phytochemistry, pharmacology, toxicology, and pharmacokinetics, Fitoterapia 147 (2020), 104759.
[17] T. Gu, R.H. Wang, T. Wu, Z.H. Ke, H. Yang, D. Wang, Therapeutic effect on mild perimenopausal depression treated with acupuncture at the "thirteen ghost points" and kaixin powder, Zhongguo Zhen Jiu 40 (3) (2020) 267–271.
[18] Z. Zhang, Y. Zhu, C. Zhu, S. Li, Y. Zhao, J. Yang, et al., Effects of Decoction of Dihuang Yinzi on Alzheimer's disease: a systematic review and meta-analysis, Complement. Med. Res. (2023).
[19] H. Wang, J. Gao, D. Zhu, B. Yu, Quality evaluation of Polygala japonica through simultaneous determination of six bioactive triterpenoid saponins by HPLC-ELSD, J. Pharm. Biomed. Anal. 43 (4) (2007) 1552–1556.
[20] S.L. Chen, L.L. Lin, S.B. Chen, D.J. Yang, J.S. Yang, P.G. Xiao, Quantitative Determination of Nine Xanthones in Polygala caudata and Fingerprinting of Polygala L. by HPLC, J. Liq. Chromatogr. Relat. Technol. 28 (18) (2005) 2953–2963.
[21] S.J. Guan, X.P. Yan, J.K. Lin, Study on acute toxicity test of different processed products of Radix polygalae, Zhongguo Zhong Xi Yi Jie He Za Zhi 32 (3) (2012) 398–401.
[22] L. Wen, N. Xia, P. Tang, Y. Hong, Z. Wang, Y. Liu, et al., The Gastrointestinal Irritation of Polygala Saponins and Its Potential Mechanism In Vitro and In Vivo, Biomed. Res. Int. 2015 (2015), 918048.
[23] Y. Chen, X.M. Liu, R.L. Pan, G.N. Wang, Y. Fu, Q. Chang, An LC-MS/MS method for determination of 3,6′-disinapoylsucrose in rat plasma and its application to a pharmacokinetic study, Biomed. Chromatogr. 23 (12) (2009) 1326–1332.
[24] Q. Wang, B.X. Xiao, R.L. Pan, X.M. Liu, Y.H. Liao, L. Feng, et al., An LC-MS/MS method for simultaneous determination of three Polygala saponin hydrolysates in rat plasma and its application to a pharmacokinetic study, J. Ethnopharmacol. 169 (2015) 401–406.
[25] K. Singh, J.K. Gupta, S. Kumar, H. Chopra, S. Kumar, D.K. Chanchal, et al., Pharmacological and Therapeutic Potential of Hordeum Vulgare, Pharmacol. Res. Mod. Chin. Med. (2023), 100300.
[26] S. Chen, J. Jia, Tenuifolin Attenuates Amyloid-β 42-Induced Neuroinflammation in Microglia Through the NF- κB Signaling Pathway, J. Alzheimers Dis. 76 (2020) 195–205.
[27] R. Jesky, H. Chen, The neuritogenic and neuroprotective potential of senegenin against Aβ-induced neurotoxicity in PC 12 cells, BMC Complement. Altern. Med. 16 (1) (2016) 26.
[28] F. Peng, L. Lu, F. Wei, D. Wu, K. Wang, J Tang, The onjisaponin B metabolite tenuifolin ameliorates dopaminergic neurodegeneration in a mouse model of Parkinson's disease, Neuroreport 31 (6) (2020).
[29] X. Liu, D. Wang, R. Zhao, X. Dong, Y. Hu, P Liu, Synergistic Neuroprotective Effects of Two Herbal Ingredients via CREB-Dependent Pathway 7 (2016).
[30] H. Yang, W. Xu, W. Zhao, M. Gu, W. Wang, 1,3,7-Trihydroxyxanthone, derived from Polygalae Radix, a herbal medicine, stimulates the expression of neurotrophic factors in rat astrocyte primary cultures via cAMP- and ERK-dependent pathways, Biomed. Pharmacother. 98 (2018) 762–768.
[31] L-q WANG, S-z ZHU, D-m. LI, Effect of tenuifolin on mental behavior in depression model mice, Chin. J. Public Health 36 (2020) (-4):- 570.
[32] H. Li, S. Lin, T. Qin, H. Li, Z. Ma, S. Ma, Senegenin exerts anti-depression effect in mice induced by chronic un-predictable mild stress via inhibition of NF-κB regulating NLRP3 signal pathway, Int. Immunopharmacol. 53 (2017) 24–32.
[33] Y.H. Leem, S. Oh, 3,4,5-Trimethoxycinnamin acid ameliorates restraint stress-induced anxiety and depression, Neurosci. Lett. 585 (2015) 54–59.
[34] Y. Hu, H.B. Liao, G. Dai-Hong, P. Liu, Y.Y. Wang, K. Rahman, Antidepressant-like effects of 3,6′-disinapoyl sucrose on hippocampal neuronal plasticity and neurotrophic signal pathway in chronically mild stressed rats, Neurochem. Int. 56 (3) (2010) 461–465.
[35] H. Zhou, W. Xue, S-f Chu, Z-z Wang, C-j Li, Y-n Jiang, et al., Polygalasaponin XXXII, a triterpenoid saponin from Polygalae Radix, attenuates scopolamine-induced cognitive impairments in mice, Acta Pharmacol. Sin. 37 (8) (2016) 1045–1053.
[36] C. Guo, J. Shen, Z. Meng, X. Yang, F Li, Neuroprotective effects of polygalacic acid on scopolamine-induced memory deficits in mice, Phytomedicine 23 (2) (2016) 149–155.
[37] Q. Cao, Y. Jiang, S.Y. Cui, P.F. Tu, Y.M. Chen, X.L. Ma, et al., Tenuifolin, a saponin derived from Radix Polygalae, exhibits sleep-enhancing effects in mice, Phytomedicine 23 (14) (2016) 1797–1805.
[38] C.I. Lee, J.Y. Han, J.T. Hong, Oh K-W. 3,4,5-Trimethoxycinnamic acid (TMCA), one of the constituents of Polygalae Radix enhances pentobarbital-induced sleeping behaviors via GABAAergic systems in mice, Arch. Pharmacal Res. 36 (10) (2013) 1244–1251.
[39] Z. Zhao, M. Fang, D. Xiao, M. Liu, N. Fefelova, C. Huang, et al., Potential Antiarrhythmic Effect of Methyl 3,4,5-Trimethoxycinnamate, a Bioactive Substance from Roots of Polygalae Radix: Suppression of Triggered Activities in Rabbit Myocytes, Biol. Pharm. Bull. 36 (2) (2013) 238–244.
[40] F. Zhang, X. Song, L. Li, J. Wang, L. Lin, C. Li, et al., Polygala tenuifolia polysaccharide PTP induced apoptosis in ovarian cancer cells via a mitochondrial pathway, Tumour Biol. 36 (4) (2015) 2913–2919.
[41] X.B. Yu, G.L. Liu, B. Zhu, K. Hao, F. Ling, G.X. Wang, In vitro immunocompetence of two compounds isolated from Polygala tenuifolia and development of resistance against grass carp reovirus (GCRV) and Dactylogyrus intermedius in respective host, Fish Shellfish Immunol. 41 (2) (2014) 541–548.
[42] K.S. Kim, D-S Lee, G.S. Bae, S.J. Park, D-G Kang, H.S. Lee, et al., The inhibition of JNK MAPK and NF-κB signaling by tenuifoliside A isolated from Polygala tenuifolia in lipopolysaccharide-induced macrophages is associated with its anti-inflammatory effect, Eur. J. Pharmacol. 721 (1) (2013) 267–276.
[43] P. Liu, Y. Hu, D-H Guo, B.R. Lu, K. Rahman, L-H Mu, et al., Antioxidant activity of oligosaccharide ester extracted from Polygala tenuifolia roots in senescence-accelerated mice, Pharm. Biol. 48 (7) (2010) 828–833.
[44] Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 18 (5) (2019) 459–480.
[45] J. Li, J. Zhong, H. Chen, Q. Yu, C Yan, Structural characterization and anti-neuroinflammatory activity of a heteropolysaccharide isolated from the rhizomes of Polygala tenuifolia, Ind. Crops Prod. 155 (2020), 112792.
[46] Y. Zhou, M. Yan, R. Pan, Z. Wang, X. Tao, C. Li, et al., Radix Polygalae extract exerts antidepressant effects in behavioral despair mice and chronic restraint stress-induced rats probably by promoting autophagy and inhibiting neuroinflammation, J. Ethnopharmacol. 265 (2021), 113317.
[47] D. Zhang, X. Wang, R. Li, L. Wang, Z. Zhou, Q. Fu, et al., Extract of the Aerial Part of Polygala tenuifolia Attenuates d-Galactose/NaNO2-induced Learning and Memory Impairment in Mice, Planta Med. 86 (18) (2020) 1389–1399.
[48] X. Li, J. Cui, Y. Yu, W. Li, Y. Hou, X. Wang, et al., Traditional Chinese Nootropic Medicine Radix Polygalae and Its Active Constituent Onjisaponin B Reduce β-Amyloid Production and Improve Cognitive Impairments, PLoS One 11 (3) (2016), e0151147.
[49] F.P. Chen, M.S. Jong, Y.C. Chen, Y.Y. Kung, T.J. Chen, F.J. Chen, et al., Prescriptions of Chinese Herbal Medicines for Insomnia in Taiwan during 2002, Evid.-Based Complement. Altern. Med. 2011 (2011), 236341.
[50] L.H. Chen, D.P. Xu, J.M. Kong, M.H. Yao, D. Zhang, L. Gu, et al., Separation and identification of the hypnotic active ingredients of Polygala tenuifolia Willd, Baozhuang Yu Shipin Jixie 34 (2018) 119–122.
[51] P. Sharma, A. Tyagi, P. Bhansali, S. Pareek, V. Singh, A. Ilyas, et al., Saponins: Extraction, bio-medicinal properties and way forward to anti-viral representatives, Food Chem. Toxicol. 150 (2021), 112075.
[52] H. Yao, P. Cui, D. Xu, Y. Liu, Q. Tian, F. Zhang, A water-soluble polysaccharide from the roots of Polygala tenuifolia suppresses ovarian tumor growth and angiogenesis in vivo, Int. J. Biol. Macromol. 107 (2018) 713–718.
[53] Y. Bian, H. Zeng, H. Tao, L. Huang, Z. Du, J. Wang, et al., A pectin-like polysaccharide from Polygala tenuifolia inhibits pancreatic cancer cell growth in vitro and in vivo by inducing apoptosis and suppressing autophagy, Int. J. Biol. Macromol. 162 (2020) 107–115.
[54] S. Yu, X. Dong, H. Ji, J. Yu, A Liu, Antitumor activity and immunomodulation mechanism of a novel polysaccharide extracted from Polygala tenuifolia Willd. evaluated by S180 cells and S180 tumor-bearing mice, Int. J. Biol. Macromol. 192 (2021) 546–556.
[55] D. Zhang, Y. Wang, X. Wang, L. Wang, R. Li, M.F Fang, Antioxidant effect of aqueous extract of Polygala tenuifolia Willd. seedlings on D-galactose aging mice, Zhongguo Zhongyao Zazhi 34 (2019) 4322–4326.
[56] X. Feifei, Effects of Anti-fatigue in Vivo and Anti-oxidant in Vitro of Polysaccharides from Polygala tenuifolia Willd.on Exhaustive Exercise Mice, J. Sci. Tech. Food Indust. 42 (6) (2021) 332.
[57] H.Y. Li, Y.F. Chi, Effects of senegenin pretreatment on myocardial ischemia-reperfusion injury and HMGB1 expression in rats, Zhongchengyao 41 (2019) 1165–1168.
[58] T. Nagai, Y. Suzuki, H. Kiyohara, E. Susa, T. Kato, T. Nagamine, et al., Onjisaponins, from the root of Polygala tenuifolia Willdenow, as effective adjuvants for nasal influenza and diphtheria-pertussis-tetanus vaccines, Vaccine 19 (32) (2001) 4824–4834.
[59] D. Mieres-Castro, F. Mora-Poblete, Saponins: Research Progress and Their Potential Role in the Post-COVID-19 Pandemic Era, Pharmaceutics 15 (2) (2023).
[60] L.B. Vinh, M. Heo, N.V. Phong, I. Ali, Y.S. Koh, Y.H. Kim, et al., Bioactive Compounds from Polygala tenuifolia and Their Inhibitory Effects on Lipopolysaccharide-Stimulated Pro-inflammatory Cytokine Production in Bone Marrow-Derived Dendritic Cells, Plants (Basel, Switzerland) 9 (9) (2020).
[61] G.S. Katselis, A. Estrada, D.K. Gorecki, B. Barl, Adjuvant activities of saponins from the root of Polygala senega L, Can. J. Physiol. Pharmacol. 85 (11) (2007) 1184–1194.