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Review Article

Pharmacological and other Bioactivities of the Genus *Polygonum* - A Review

Xiaoxv Dong[1], Jing Fu[1], Xingbin Yin[1], Xuechun Li[1], Bo Wang[2], Sali Cao[1], Jin Zhang[1], Hui Zhang[1], Yang Zhao[1] and Jian Ni*

[1]School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing, 100102, [2]Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

For correspondence:* ***Email:* *njtcm@263.net;* ***Tel:*** *010-84738607*

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Abstract

The genus Polygonum encompasses approximately 300 species widely distributed around the world, among which 120 Polygonum species grow in China. Among the rich species, 81 of them are widely used in traditional Chinese and folk medicines. In recent years, several studies have found that the genus Polygonum posseses a variety of biological activities including antioxidation, antimicrobial, anti-tumor, anti-obesity, etc. However, there are still not enough systemic data on the chemical constituents and their pharmacological effects; hence, it would be useful to review current literature for available pharmacological activites of the genus and as well as its active ingredients. Both in-vitro and in-vivo studies have provided strong evidence for the therapeutic potential of the genus Polygonum. This review collates and examines information on the pharmacological effects of the genus Polygonum as well as its chemical constituents.

Keywords: *Polygonum, Chemical constituents, Pharmacological properties, Flavonoids, Anthraquinones*

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INTRODUCTION

Polygonum is a medicinal large genus of *Polygonaceae*, it falls into about 300 species widely distributed around the world. The genus *Polygonum* contains many medicinal plants, such as *Polygonum multiforum, Polygonum cuspidatum, Polygonum bistorta, Polygonum aviculare, Polygonum tinctorium*, etc [1]. Among the rich species, parts of the plant are recorded in traditional Chinese medicines and folk medicines. Additionally, many chemical constituents have been identified such as flavonoids, anthraquinones, stilbenes, glycolipids and terpenes [2]. For its enormous social and economic implications, it is urgent to understand the mechanisms between the chemical constituents and the pharmacological effects. The primary objectives of this review are to summarize: the pharmacological effects and the main chemical constituents, and their structures.

Antioxidant effect

Most of the genus *Polygonum* have antioxidant and clears the body of excess free radicals [1]. 5,6-dihydropyranobenzopyronean 5,6-dihydro-pyranobenzopyrone (Fig. 1) isolated from *Polygonum amplexicaule* had a strong ability to scavenge oxygen free radicals [3]. Similarly, hydropiperoside B, vanicode A and vanicode E (Fig. 1) isolated from *Polygonum hydropiper* L also exhibited antioxidant activity [4].

Additionally, flavonoids and flavonoid glucoside also exhibited high antioxidant activity. Among these, 2''-O-(3,4,5-trihydroxybenzoyl) quercitrin (galloyl quercitrin) (Fig.1) showed the strongest antioxidant activity [5-7]. *Polygonum aviculare* L. extracts strongly exhibited antioxidant effects by free radical scavenging assays, superoxide radical scavenging assays, lipid peroxidation assays and hydroxyl radical induced DNA strand scission assays [8]. *Polygonum minus* extracts exhibited gastro protective activities. The mechanisms were attributed to the synthesis of antioxidant and PGE2 [9]. Three compounds including gallic acid, catechin, and 2,3,5,4'-tetrahydroxystilbene2-O-β-D-glucoside (Fig. 1) isolated from *Polygonum multiflorum* showed strong antioxidant activity [10]. In addition, the stilbene glycoside from *Polygonum multiflorum* also exhibited strong antioxidant activity by increasing the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) [11]. What is more, the stilbene glycoside (Fig.1) also exerted its antioxidant activity by inhibiting the A/R-mediated elevation of MDA content [12]. Resveratrol and its liposomal isolated from *Polygonum cuspidatum* could protect the dopaminergic neurons, attributing their radical scavenging ability and antioxidant effects which could be attributed their radical scavenging ability and antioxidant effects [13,14]. The methanol and ethyl acetate extracts of *Polygonum tinctorium* also exhibited higher antioxidant activity [15]. *Polygonum maritimum* L. extracts presented a remarkable antioxidant scavenging effects on DPPH radical [16]. Similarly, the MEOH extract of *Polygonum sachalinensis* had antioxidant effects by free radical-scavenging activities [17].

Anti-inflammatory effect

The inhibitory effect of ethanol extract of *Polygonum cuspidatum* (PCE) on mouse ear inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) was tested. The results showed PCE significantly reduced the ear edema in a dose-dependent manner [18]. Additionally, the mRNA expressions of TNF-α, IL-6, and C-reactive protein significantly decreased after treatment with the extract of *Polygonum cuspidatum* (containing 20 % resveratrol) [19]. Similarly, well-organized bands of collagen, fibroblasts and hair follicle increased, while the number of inflammatory cells reduced after wound healing rats were treated with the extract from *Polygonum cuspidatum* [20]. Furthermore, *Polygonum cuspidatum* extracts significantly inhibited FCA-induced joint swelling within3 days in FCA-induced adjuvant arthritis model [21]. *Polygonum viviparum* (PV) extracts could inhibit inflammation induced by lipopolysaccharide in RAW 264.7

RAW264.7 macrophages, and the mechanisms were related to might its haem oxygenase-1 induction and activation of the Nrf2 pathway [22]. *Polygonum viscosum* extracts possessed moderate anti-inflammatory activity on raw paw edema induced by carrageenan [23]. Quercetin-3-O-β-D-glucuronide (Fig 1) separated from *Polygonum perfoliatum* significantly suppressed ear edema induced by dimethyl benzene in mice [24]. Two compounds (5-glutinen-3-one, friedelanol) from *Polygonum bistorta* significantly largely suppressed the inflammatory response [25].

Antibacterial and antifungal effect

A fraction isolated from *Polygonum cuspidatum* possessed antibacterial effect against *Streptococcus mutans*, indicating the fraction might be useful for controlling dental biofilms and improving the cariostatic properties of fluoride without increasing its exposure [26]. In addition, the ethyl acetate fraction (polydatin, resveratrol, anthraglycoside B, emodin) the ethyl acetate fraction composed of polydatin, resveratrol, anthraglycoside B, and emodin (Fig. 1) also exhibited a significantly antibacterial effect against three of the five common foodborne bacteria which were *Bacillus cereus, Listeria monocytogenes*, and *Staphylococcus aureus* [27,28]. Through By bioassay-guided separation and analysis of antibacterial activity, the essential oils isolated from *Polygonum bistorta* inhibit *Paenibacillus larvae, Melissococcus plutonius* and *Bacillus subtilis* [29]. *Polygonum punctatum* extracts from the Brazilian medicine plant possessed antifungal effect. The sesquiterpene dialdehyde polygodial (Fig. 1) was the main active constituent [30]. The chloroform extract of *Polygonum aviculare* isolated from *Polygonum aviculare* had a significant antibacterial effect against *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Salmonella paratyphi, Shigella flexner, Staphylococcus aureus, Bacillus subitilis, Streptococcus pyogenes, Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger* [31]. In addition, the gingival index significantly decreased after treatment with *Polygonum aviculare* extracts, indicating they could be useful for the therapy of gingivitis induced by bacteria. The results showed total flavonoids were the effective part of its antibacterial activity [32,33]. *Polygonum orientale* extracts also exhibited antibacterial effect, suggesting the extracts might be useful for controlling bacterial ring rot of potato disease [34]. *Polygonum capitatum*

extracts possessed bacteriostatic and bactericidal properties by evaluated *in vitro* [35]. Tryptanthrin and Kaempferol isolated from *Polygonum tinctorium* L significantly decreased the numbers of *Helicobacter pylori* colonies *in vivo* and *in vitro*, indicating they could be indicated for anti-*H. pylori* therapy [36]. Polygosumic acid (Fig. 1) from *Polygonum viscosum* could inhibit the growth of penicillin-resistant *Escherichia coli* (MIC = 0.05 mg/ml) and methicillin-resistant *Staphylococcus aureus* (MIC = 0.10 mg/ml) [37].

Anticancer effect

The extracts of *Polygonum hypoleucum* Ohwi possessed inhibitory effects on various tumor cells proliferation. Emodin was thought to be the main effective substances [38]. *Polygonum cuspidatum* extracts exhibited an antiproliferative effect on human lung cancer cells by inducing apoptosis and inhibiting cell growth in A549 and H1650 cell lines [39]. Similarly, resveratrol isolated from *Polygonum cuspidatum* significantly reduced Lewis lung tumor and tumor weight. Furthermore, it also prevented tumor growth and metastasis in lungs by inhibiting DNA synthesis of tumor cells and tumor-induced neovascularization in mice bearing highly metastatic Lewis lung carcinoma tumors [40]. What is more, *Polygonum cuspidatum* extracts significantly inhibited suspension growth, activated caspases, and induced anoikis in hepatocarcinoma cells in a dose- and time-dependent manner [41]. Additionally, *Polygonum cuspidatum* extracts also inhibited the proliferation of oral cancer cells by inducing caspase-dependent apoptosis, suggesting the extracts might be as a promising compound for the effective treatment of oral cancer [42].

Two new flavonoid glucuronides, quercetin-3-O-β-glucuronide and quercetin-3-O-α-rhamnosyl-(1→2)-β-glucuronide (Fig. 1) isolated from *Polygonum amphibium* could induce apoptosis in Jurkat and HL60 cell lines by evaluated in vitro [43]. *Polygonum perfoliatum* extracts possessed cytotoxicity effects against human mammary carcinoma, human colon carcinoma, human hepatocellular carcinoma, human prostate carcinoma, and human erythroleukaemia cells [44]. *Polygonum aviculare* extracts (300, 350 and 400 ng/μl) also exhibited strong inhibitory effects on cell proliferation and induced apopotic cell death in the MCF-7 breast cancer cells [45]. Phenylpropanoid esters of sucrose, vanicoside B and lapathoside A (Fig.1) isolated from *Polygonum lapathifolium* exhibited the inhibitory effects on the EBV-EA induction and anti-tumor-promoting effects on mouse two-stage skin carcinogenesis [46]. The ethyl acetate extract and tryptanthrin (50 mg/kg) from *Polygonum tinctorium* Lour. exhibited anticancer activity on intestinal tumors induced by azoxymethane (AOM) [47].

Antiviral effect

Both ethanol extract and water extract of *Polygonum cuspidatum* significantly increase-d the expression of HBsAg and viral antigens., while inhibited the expression of HBeAg, suggesting *Polygonum cuspidatum* extracts could inhibit HBV in a stable HBV-producing cell line [48].

In addition, emodin isolated from *Polygonum cuspidatum* exhibited the potent antiviral activity by inhibiting CVB4 entry and replication, indicating it could be used as potential antiviral in the post-exposure prophylaxis for CVB4 infection [49]. *Polygonum tinctorium* extracts exhibited fairly strong antiviral effect against HIV-1 (EC_{50} was 0.5 μg/ml) [50]. Similarly, *Polygonum viscosum* extracts also possessed anti-HIV-1 activity. The main effective substances were quercetin 3-O-(6”-feruloyl)-β-D-galactopyranoside (Fig.1) and viscoazulone [51].

Lipid-regulating effect

Polygonum aviculare extracts (PAE) exhibited anti-obesity effects by suppressing lipogenesis in white adipose tissue and increasing antioxidant activity. Besides, its low toxicity in mice and its historical use suggested PAE might be used as a safe anti-obesity pharmaceutical [52]. *Polygonum hypoleucum* Ohwi extracts were found to exhibit favorable effects in alleviating metabolic syndrome, including obesity, hypertriglyceridemia, and the results showed emodin and emodin-8-O-β-D-glucopyranoside (Fig.1) were the main effective substances [53].

Plasma cholesterol, plasma triglyceride and low-density lipoprotein cholesterol increased, while very low-density lipoprotein cholesterol attenuated after treatment with a water-soluble fraction of *Polygonum multiflorum* (PMS), suggesting PMS might be applicable for the treatment of hyperlipidemia disease [54]. In a high fat/cholesterol rabbit model, polydatin from *Polygonum cuspidatum* obviously decreased the serum levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol. Meanwhile, the ratio of TC and the liver coefficient were also reduced [55]. In addition, resveratrol isolated from *Polygonum cuspidatum* could reduce the cholesteryl ester synthesis in

human hepatocytes by inhibiting ACAT activity in a dose-dependent manner [56].

Neuroprotective effect

The neuroprotective effects of *Polygonum multiflorum* extract (PME) and its two fractions (PME-I, PME-II) were studied in male C57BL/6 mice, the results showed PME-I had neuroprotective effect on damage of the substantia nigral dopaminergic system induced by PQMB in mice, indicating PCE could be beneficial in preventing Parkinson's disease [57]. Pretreatment with hexane extract from *Polygonum multiflorum* significantly decreased glutamate-induced neurotoxicity in a concentration-dependent manner and drastically inhibited glutamate-induced apoptosis [58].

In addition, the ethyl acetate extract from *Polygonum multiflorum* also had neuroprotective effects through both alleviation of extracellular regulated kinase (CRK) and p38 activation with increased activation of cAMP responsive element binding protein (CREB) under oxidative stress [59]. 85 % methanol extracts of *Polygonum cuspidatum* exhibited strong neuroprotective activity by a lipid peroxidation assay *in vitro* and an assay *in vivo* using a transient focal cerebra ischemia model. HPLC analysis for the key compound groups might be stilbene sand anthraquinones [60].

Estrogenic effect

Emodin and emodin 8-O-β-D-glucopyranoside (Fig.1) isolated from *Polygonum cuspidatum* could enhance proliferation of MCF-7 cell, the results demonstrated emodin might be useful for replacement therapy for human menoxenia and postmenopausal diseases [61]. *Polygonum hydropiper* extracts strongly altered the histological structures of both ovary-intact and OVX rats by inducing hyperplasia in places of luminal epithelium and degeneration of endometrial glands [62].

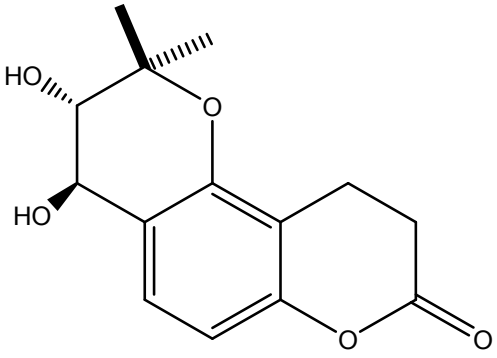
Nine other pharmacological effects

The hexane, ethylacetate and methanol extract of *Polygonum hydropiper* possessed significantly antinociceptive activity on acetic acid-induced writhing in mice [63]. What is more, a compound from the sprout of *Polygonum hydropiper* L. inhibited 70 % of the tyrosinase activity, suggesting it might be a new tyrosinase inhibitor alternative to cosmetic agents [64]. Emotion-8-O-β-D-glucoside (Fig 1) isolated from *Polygonum amplexicaule* Forb. (PAF) significantly promoted cell proliferation and differentiation of osteoblasts *in vitro* [65]. In addition, four anthraquinones and two stilbenes isolated from *Polygonum cuspidatum* also possessed strong inhibition of tyrosinase, indicating it might be useful as skin-whitening agents [66].

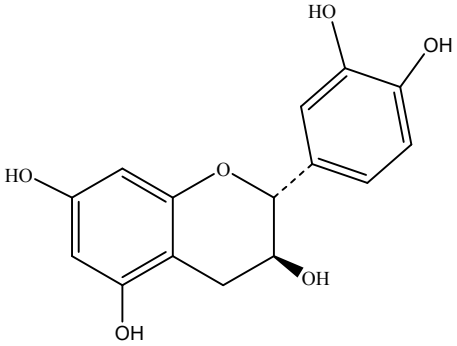
Table 1: Pharmacological effects of the Genus *Polygonum*

Pharmacological effect	Plant	Extract/Compound	*In vitro/in vivo*
Antioxidant Activity	*Polygonum amplexicaule*	5,6-dihydropyranobenzopyronean	*In vitro*
	Polygonum hydropiper L	Hydropiperoside B	*In vitro*
		vanicode A	*In vitro*
		vanicode E	*In vitro*
	Polygonum aviculare L.	Ethanol extracts	*In vitro*
	Polygonum minus	Ethyl acetate: methanol=1:1 (V/V)	*In vivo*
	Polygonum multiflorum	Gallic acid	*In vitro*
		Catechin	*In vitro*
		2,3,5,4'-tetrahydroxystilbene2-O-β-D-glucoside	*In vitro*
	Polygonum cuspidatum	Stilbene glycoside	*In vivo*
		Resveratrol	*In vivo*
	Polygonum tinctorium	methanol , ethyl acetate extracts	*In vitro*
	Polygonum maritimum	methanol extract	*In vitro*
	Polygonum sachalinensis	MEOH extract	*In vitro*
Anti-inflammatory activity	*Polygonum cuspidatum*	Ethanol extracts	*In vivo*
		Extracts (containing 20% resveratrol)	*In vivo*
		Ethyl acetate extracts	*In vivo*
	Polygonum viviparum	2-propanol extract	*In vivo*
	Polygonum viscosum	Sesquiterpenes	*In vivo*
		Flavonoid glycoside	*In vivo*
	Polygonum perfoliatum	Quercetin-3-O-β-D-glucuronide	*In vivo*

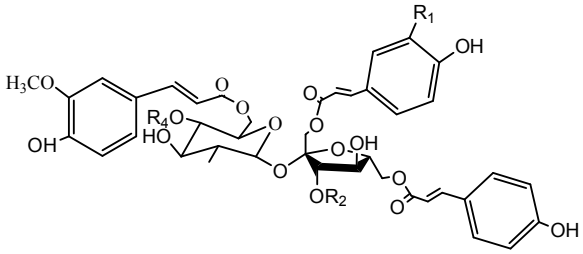
	Polygonum bistorta	5-glutinen-3-one	*In vitro*
		Friedelanol	*In vitro*
Antibacterial and antifungal activities	*Polygonum cuspidatum*	Resveratrol	*In vivo*
		Emodin	*In vivo*
		Physcion	*In vivo*
	Polygonum bistorta	Essential oils	*In vitro*
	Polygonum punctatum	Sesquiterpene dialdehyde polygodial	*In vitro*
	Polygonum aviculare.	Chloroform extract	*In vitro*
	Polygonum orientale	Water extracts	*In vitro / in vivo*
	Polygonum capitatum	Ethanol extracts	*In vivo*
	Polygonum tinctorium	Tryptanthrin , Kaempferol	*In vitro / in vivo*
	Polygonum viscosum	Polygosumic acid	*In vitro*
Pharmacological effect	Plant	Extract/Compound	*In vitro/in vivo*
Anticancer activity	*Polygonum hypoleucum*	Emodin	*In vitro*
	Polygonum cuspidatum	Ethanol extracts	*In vivo*
		Resveratrol	*In vivo*
		Methanol extracts	*In vitro*
	Polygonum amphibium	Glucuronides	*In vitro*
	Polygonum perfoliatum	Methanol extracts	*In vitro*
	Polygonum aviculare	Methanol extracts	*In vitro*
	Polygonum lapathifolium	Phenylpropanoid esters of sucrose	*In vivo*
		vanicoside B	*In vivo*
		Lapathoside A	*In vivo*
	Polygonum tinctorium	Ethyl acetate extracts	*In vitro*
		Tryptanthrin	*In vitro*
Antiviral activity	*Polygonum cuspidatum*	Ethanol extracts	*In vitro*
		Water extracts	*In vitro*
	Polygonum tinctorium	Water extracts	*In vitro*
	Polygonum viscosum	Quercetin 3-O-(6”-feruloyl)-*β-D*-galactopyranoside	*In vivo*
		Viscoazulone	*In vitro*
Lipid-regulating activity	*Polygonum aviculare*	Ethanol extracts	*In vivo*
	Polygonum hypoleucum	Emodin	*In vivo*
		Emodin-8-O-β-D-glucopyranoside	*In vivo*
	Polygonum multiflorum	Water extracts	*In vivo*
	Polygonum cuspidatum	Polydatin	*In vivo*
		Resveratrol	*In vitro*
Neuroprotective activity	*Polygonum multiflorum*	PME-I, PME-II	*In vivo*
		Hexane extracts	*In vitro*
		Ethyl acetate extracts	*In vitro*
	Polygonum cuspidatum	85% methanol extracts	*In vitro / in vivo*
Estrogenic activity	*Polygonum cuspidatum*	Emodin	In vitro
		Emodin 8-*O-β-D*-glucopyranoside	In vitro
	Polygonum hydropiper	Crude root extracts	In vivo
	Polygonum hydropiper	Hexane extracts	In vivo
		Ethyl acetate extracts	In vivo
		Methanol extracts	In vitro
	Polygonum amplexicaule	Emotion-*8-O-β-D*-glucoside	In vitro
	Polygonum cuspidatum	Anthraquinones	In vitro



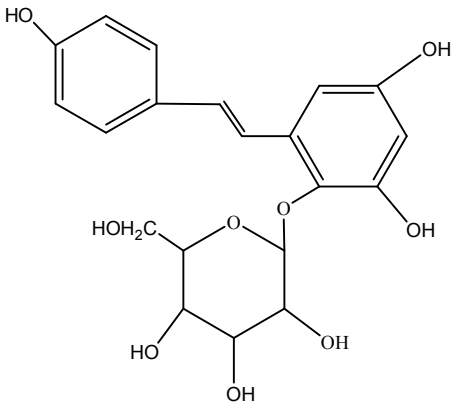
5,6-dihydropyranobenzopyrone



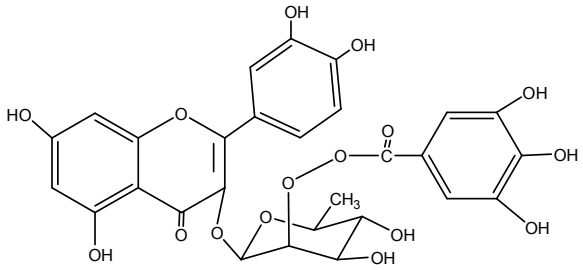
Catechin



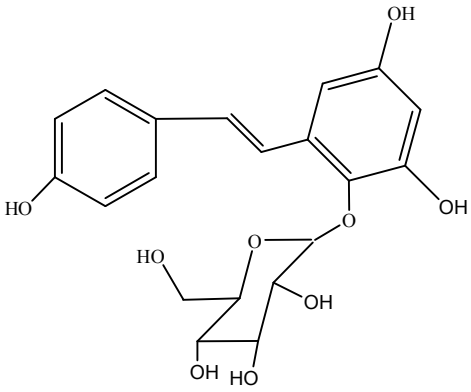
hydropiperoside B R_1= OCH_3, R_2= *trans-p*-courmaroyl, R_3= Ac, R_4= H
vanicode A. R_1= R_4= H, R_2= *trans-p*-courmaroyl, R_3= Ac
vanicode E. R_1= H, R_2= *trans-p*-courmaroyl, R_3= R_4= Ac



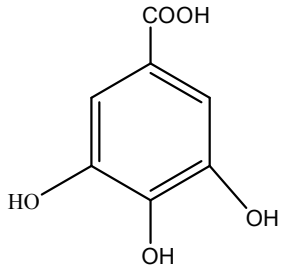
2,3,5,4'-tetrahydroxysti-lbene2-O-β-D-glucoside



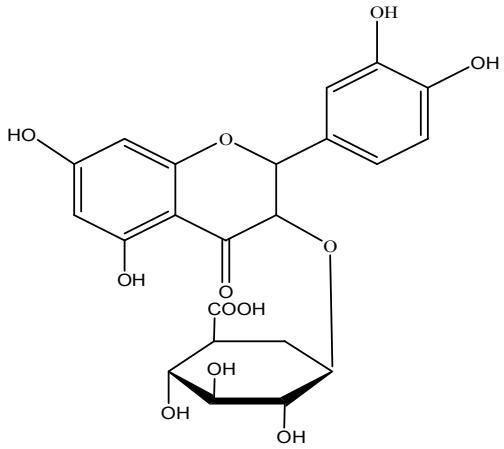
2''-*O*-(3,4,5-trihydroxybenzoyl) quercitrin (galloyl quercitrin)



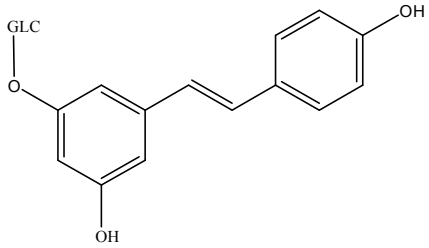
The stilbene glycoside



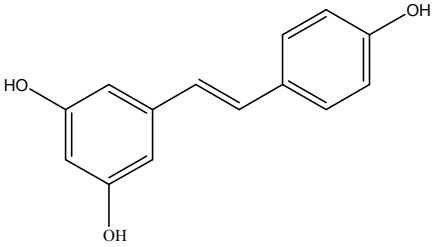
Gallic acid



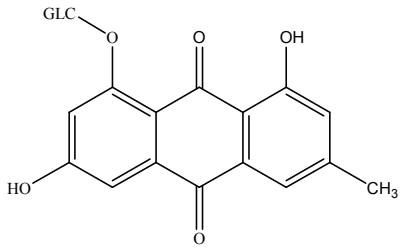
Quercetin-3-O-β-D-glucuronide



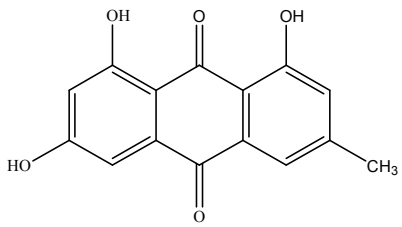
Polydatin



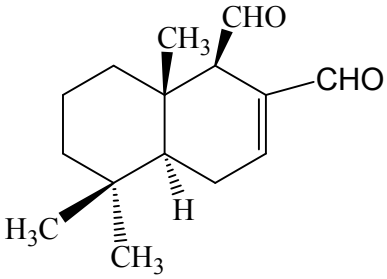
Resveratrol



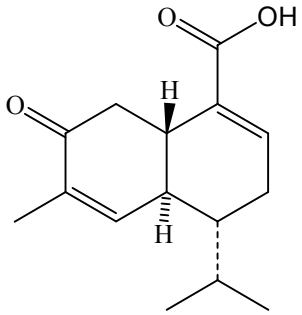
Anthraglycoside B



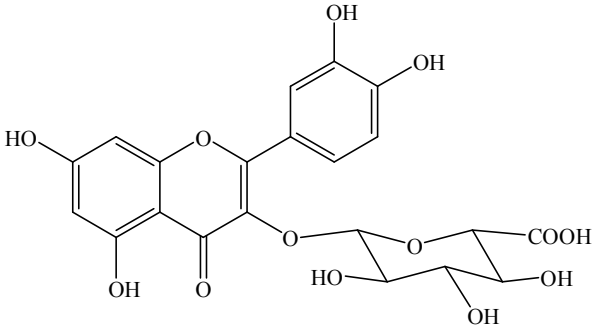
Emodin



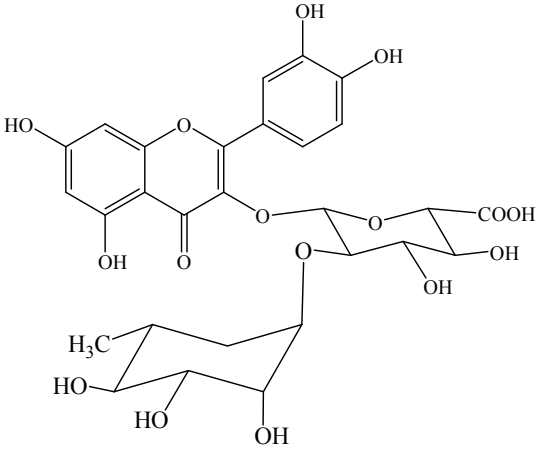
Polygodial



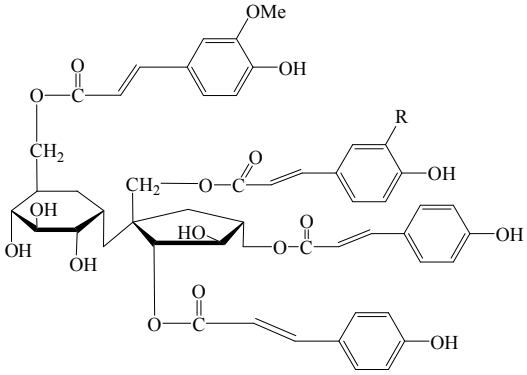
Polygosumic acid



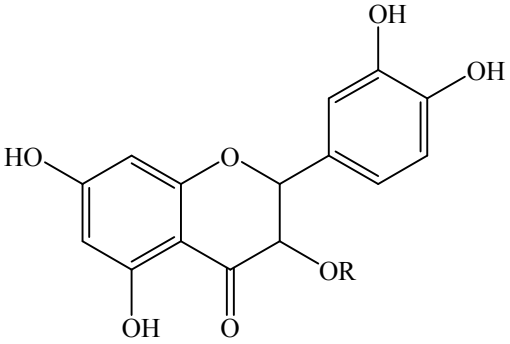
Quercetin-3-*O*-*β*-glucuronide



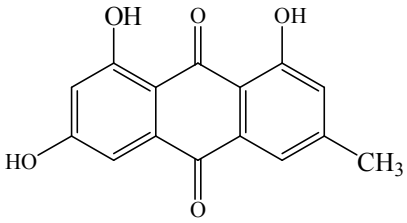
Quercetin-3-*O*-*α*-rhamnosyl-(1→2)-*β*-glucuronide



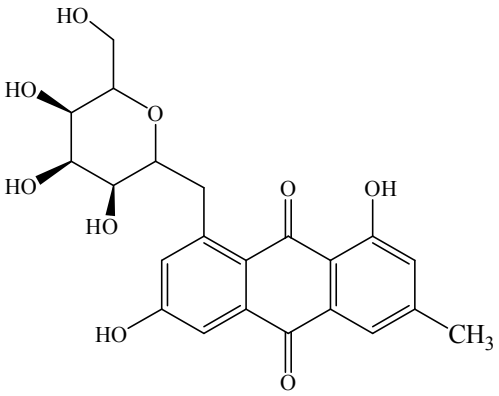
Vanicoside B R=H
Lapathoside A R=OMe



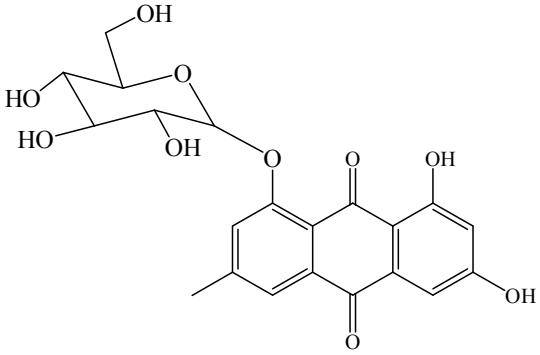
R=(6”-feruloyl)-*β*-*D*-galactopyranosyl
Quercetin3-O-(6”-feruloyl)-*β*-*D*-galactopyranoside



Emodin



Emodin-8-*O*-*β*-*D*-glucopyranoside



Emotion-8-*O*-*β*-*D*-glucoside

Fig 1: Some compounds found in the genus *Polygonum*

CONCLUSION

To the best of our knowledge, the chemical composition of the genus *Polygonum* is rich, and a variety of biological activity have also been reported have been studies by modern investigations, such as antioxidation, antimicrobial, anticancer, antivirus, etc (Table 1). While, there are not enough systemic data for the pharmacokinetics and toxicity of the genus *Polygonum*.

This paper dedicated to compiling many active ingredients and intricate mechanisms of genus *Polygonum*. However, many comprehensive mechanisms still need to be investigated. In order to clarify the structure-activity relationship of the genus *Polygonum*. The main chemical constituents and their structures are shown in Fig 1). Considering the fact that the genus *Polygonum* spreading the world, only 27 % of them have been widely investigated, the genus *Polygonum* still remains to be a potential resource to research.

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