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何首乌化学成分及其药理活性的研究进展

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摘要：何首乌(*Pleuropterus multiflorus*)是一种珍贵的多年生中药，为蓼科(Polygonaceae)何首乌属植物，主要分布在四川、云南、贵州以及山西和甘肃南部，可用于治疗肝损伤、癌症、糖尿病、脱发、动脉粥样硬化以及神经退行性疾病。近年来，国际上有报道称摄入何首乌会引起肝损伤，因此，建立何首乌的安全监测和风险管理模型对何首乌的开发利用具有重要意义。对何首乌的化学成分、药理活性及其毒副作用进行了综述，为何首乌的临床应用、科学研究和生产质量控制提供参考。

关键词：何首乌；化学成分；药理活性；综述
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Advances in Chemical Constituents and Pharmacological Activities of *Pleuropterus multiflorus*

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Abstract: *Pleuropterus multiflorum*, known as one of precious perennial Chinese traditional medicine, belonging to *Pleuropterus* genus and Polygonaceae family, distributed mainly in Sichuan, Yunnan, Guizhou and southern Shanxi and Gansu in China. The modern studies showed that *P. multiflorum* could be used for liver injury, cancer, diabetes, alopecia, atherosclerosis, and neurodegenerative diseases as well. In recent years, liver injuries caused by taking *P. multiflorum* have been reported worldwide. Therefore, the model of safety monitoring and risk management of *P. multiflorum* is very important. The chemical constituents and medicinal activities of *P. multiflorum*, including the toxic effects were summarized for the further studies and development, which is beneficial for the strengthening standardization of clinical applications, basic science research, quality control in manufacturing.

Key words: *Pleuropterus multiflorum*; Chemical constituent; Pharmacological activities; Review

Traditional Chinese Medicine (TCM) plays a significant role in Chinese civilization and is widely used in western societies, Asia, Africa and the Middle East now[1]. *Pleuropterus multiflorum* (hereinafter as PM), belonging to *Pleuropterus* genus and Polygonaceae family, is known as one of precious perennial Chinese traditional medicine, also called Heshouwu in China, which is dried root tuber of *P. multiflorum*. It is distributed mainly in provinces of Sichuan, Yunnan, Guizhou and southern Shanxi and Gansu in China. The PM utilization in traditional Chinese at the first time can be traced back to 973 A.D., recorded in Kaibao Bencao, an encyclopedia of medical plants. PM possesses variously pharmacological activities officially listed in the Chinese Pharmacopoeia. There are two forms of PM decoctions in the Chinese

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Pharmacopoeia (2015): Raw Radix *P. multiflorum* (RPM) and *P. multiflorum* Preparata (PMP). PM has been widely used for strengthening bones and muscles, preventing premature graying of the hair and treating seminal emission and menstrual complaints due to their multiple beneficial effects to human body in China. RPM contributes to detoxification and bowel relaxation, while PMP tonifies the liver and kidney, benefits essence of blood and black beard, and relieves hyperlipidemia, fatty liver, and osteoporosis. The modern studies indicated that PM can be used for liver injury, cancer, diabetes, alopecia, atherosclerosis, and neurodegenerative diseases as well. PM is also used in many Chinese medicinal supplements to improve general health. Along with the development of medical values of PM in recent years, it has been prepared as a tonic food and beverage and has become popular in Asia and many other countries. However, liver injuries caused by taking PM have been reported worldwide. More than 130 compounds, including anthraquinones, stilbenes, phenolic acid, phospholipids, flavones and dianthrone derivatives, have been isolated from PM. Anthraquinones and stilbenes might relate to the toxic components.

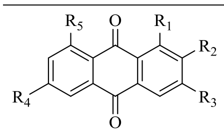
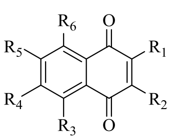
Therefore, this paper summarized the chemical constituents and pharmacological activities of PM to provide a complete overview for the information currently available, which will facilitate further research and exploitation of PM and is beneficial for the strengthening standardization of clinical applications, basic science research, quality control in manufacturing.

1 Chemical constituents

1.1 Anthraquinones

At present, more than 20 anthraquinones had been found from PM, including anthraquinone aglycones, anthraquinone glycosides and anthraquinone methyl ethers (Table 1).

Table 1 Anthraquinones from *Pleuropterus multiflorum*

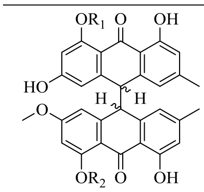
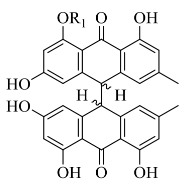
Structure	No.	R_1, R_2, R_3, R_4, R_5	Compound	Reference
	**1**	R_1=R_3=R_5=OH, R_2=H, R_4=CH_3	Emodin	[2]
	2	R_1=R_5=OH, R_2=R_4=H, R_3=CH_2OH	Aloe-emodin	[2]
	3	R_1=R_5=OH, R_2=R_4=H, R_3=CH_3	Chrysophanol	[2]
	4	R_1=R_5=OH, R_2=R_4=H, R_3=COOH	Rhein	[2]
	5	R_1=R_4=R_5=OH, R_2=H, R_3=CH_3	Questin	[3]
	6	R_1=R_4=R_5=OH, R_2=$COCH_3$, R_3=CH_3	2-Acelthylemodin	[2]
	7	R_1=R_5=OH, R_2=H, R_3=CH_2OH, R_4=OCH_3	Fallacinol	[4]
	8	R_1=R_3=R_5=OH, R_2=H, R_4=CH_2OH	Citreorosein	[4]
	9	R_1=R_5=OH, R_2=H, R_3=CH_3, R_4=OCH_3	Physcion	[4]
	10	R_1=R_4=OCH_3, R_2=H, R_3=CH_3, R_5=OH	1,6-Dimethylether emodin	[4]
	11	R_1=R_5=OCH_3, R_2=H, R_3=CH_3, R_4=OH	Emodin-8-methylether	[4]
	12	R_1=R_4=OH, R_2=H, R_3=CH_3, R_5=OCH_3	Citreorosein-8-methylether	[4]
	13	R_1=R_4=R_5=OH, R_2=H, R_3=CH_2CH_3	Emodin-3-ether	[5]
	14	R_1=OH, R_2=H, R_3=CH_3, R_4=R_5=OCH_3	Emodin-6,8-dimethylether	[6]
	15	R_1=R_4=OH, R_2=H, R_3=CH_3,R_5= *O*-*β*-D-glucoside	Emodin-8-*O*-*β*-D-glucoside	[4]
	16	R_1=OH, R_2=R_3=H, R_4=OCH_3, R_5=*O*-*β*-D-glucoside	Physcion-8-*O*-D-glucoside	[4]
	17	R_1=R_4=OH, R_2=H, R_3=CH_2CH_3, R_5=*O*-*β*-D-glucoside	Emodin-3-methyl ether-8-*O*-*β*-D-glucoside	[7]
	18	R_1=R_4=OH, R_2=H, R_3=CH_3, R_5=*O*-*β*-D-glucoside	Physcion-8-*O*-(6′-*O*-acetyl)-*β*-D-glucoside	[8]
	19	R_1=OH, R_2=R_4=H, R_3=CH_3, R_5=*O*-*β*-D-glucoside	Chrysophanol-8-*O*-*β*-D-glucoside	[9]
	20	R_1=R_4=OH, R_2 =H, R_3=CH_3, R_5=*O*-*β*-D-glucoside	Emodin-8-*O*-(6′-*O*-acetyl)-*β*-D-glucoside	[4]
	21	R_1=OCH_3, R_2=OH, R_3=CH_3, R_4=R_5=H	1-Methoxy-2-hydroxy-3-methyl-9,10-anthraquinone	[10]
	**22**	R_1=CH_3, R_2=$COCH_3$, R_3=R_6=OH, R_4=H, R_5=OCH_3	2-Methoxy-6-acetyl-7-methyliuglone	[6]
	23	R_1=$COCH_3$, R_2=CH_3, R_3=R_5=OH, R_4=OCH_3, R_6=*O*-*β*-D-glucoside	6-Methosyl-2-acety-3-methyl-1,4-naphthoquinone-8-*O*-*β*-D-glucoside	[3]

Compound **1** is a possessing anti-cancer activity anthraquinone derived from PM and can dose-dependently inhibit the growth of HepG2 cells, perturb cell cycle progression, down-regulate the expression of genes and proteins related to glycolysis, and trigger intracellular ROS generation[11]. Compound **2** is an active ingredient of Chinese herbs, such as *Cassia occidentalis*, *Rheum palmatum*, *Aloe vera*, and PM, which exhibits many pharmacological effects, including anticancer, antivirus, anti-inflammatory, antibacterial, antiparasitic, neuroprotective, and hepatoprotective activities. Therefore, it can be used to treat various diseases such as influenza virus, inflammation, sepsis, Alzheimer's disease, glaucoma, malaria, liver fibrosis, psoriasis, Type 2 diabetes, growth disorders, and several types of cancers. However, some adverse effects of compound **2** have been reported, especially hepatotoxicity and nephrotoxicity. A poor intestinal absorption, short elimination half-life and low bioavailability of compound **2** have been demonstrated by pharmacokinetic studies[12]. Compound **4** is a major medicinal ingredient isolated from *Rheum palmatum*, *Aloe barbadensis*, *Cassia angustifolia* and PM, which has various pharmacological activities including anti-inflamematory, antitumor, antioxidant, antifibrosis, hepatoprotective and nephroprotective activities[13].

1.2 Dianthrone derivatives

There are 14 dianthrone derivatives had been found from PM[14–16] (Table 2). And 32 new dianthrone derivatives were tentatively characterized in PM using HPLC-UV/LTQ-FT-ICR-MS by Yang[17]. Among of them, compounds **24**−**27** showed moderate cytotoxic effects against KB tumor cell lines[14]. Compound **33** exhibited potential inhibitory effect on UGT1A1 activity[18].

Table 2 Dianthrone derivatives from *Pleuropterus multiflorum*

	No.	R_1, R_1, C_{10}, $C_{10'}$	Compound	Reference
	**24**	R_1=glucoside, R_2=H, C_{10}=αH, $C_{10'}$=αH	Polygonumnolide A1	[14]
	25	R_1=glucoside, R_2=H, C_{10}=βH, $C_{10'}$=βH	Polygonumnolide A2	[14]
	26	R_1=glucoside, R_2=H, C_{10}=βH, $C_{10'}$=αH	Polygonumnolide A3	[14]
	27	R_1=glucoside, R_2=H, C_{10}=αH, $C_{10'}$=βH	Polygonumnolide A4	[14]
	28	R_1=glucoside, R_2=glucoside, C_{10}=αH, $C_{10'}$=αH	Polygonumnolide B1	[14]
	29	R_1=glucoside, R_2=glucoside, C_{10}=βH, $C_{10'}$=βH	Polygonumnolide B2	[14]
	30	R_1=glucoside, R_2=glucoside, C_{10}=βH, $C_{10'}$=αH	Polygonumnolide B3	[14]
	31	R_1=H, R_2=glucoside, C_{10}=H, $C_{10'}$=H	Polygonumnolide E	[15]
	**32**	R_1=glucoside, C_{10}=βH, $C_{10'}$=βH	Polygonumnolide C1	[16]
	33	R_1=glucoside, C_{10}=αH, $C_{10'}$=αH	Polygonumnolide C2	[16]
	34	R_1=glucoside, C_{10}=βH, $C_{10'}$=αH	Polygonumnolide C3	[16]
	35	R_1=glucoside, C_{10}=αH, $C_{10'}$=βH	Polygonumnolide C4	[16]
	36	R_1=H, C_{10}=H, $C_{10'}$=H	*trans*-Emodin dianthrone	[16]
	37	R_1=H, C_{10}=H, $C_{10'}$=H	*cis*-Emodin dianthrone	[16]

1.3 Stilbenes

Forty-two stilbenes (Table 3, 4, Fig. 1) have been isolated from PM[3–4,6,19–33]. Compound **38**, 2,3,5,4′-tetrahydroxystilbene-2-*O*-*β*-D-glucoside (TSG), as the main component of PM was used as a standard compound for appraising PM in the Chinese Pharmacopoeia[34]. Compound **38** is a bioactive natural production with anti-inflammatory and antitumor originnating. It might possess potent anti-breast cancer effect with adriamycin, which may exert a synergistic reduction of cell injury via the inhibition of vascular endothelial growth factor/phosphatidylinositol 3-kinase/Akt pathway[35]. The antioxidant and free radical-scavenging activities of compound **38** even are much stronger than resveratrol[36]. Compound **38** also shown neuroprotective effect in various neurodegenerative diseases and cerebral ischemia such as Alzheimer's disease, Parkinson's disease and cerebral ischemia/reperfusion injury. It can inhibit apoptosis and protect neuronal cells against injury through multifunctional cytoprotective pathways[37]. Compound **38** also has the antiatherosclerosis, anti-inflammatory and anti-cardiac fibrotic effects[38–39]. Compound **38** could delay senescence and treat aging-related diseases, and even more effective than resveratrol in delaying senescence[40]. The moderate inhibitory activities against NO production of compound **69** and **70** had been confirmed by Li in LPS-stimulated RAW264.7 cells[31].

Table 3 Stilbenes (compounds **38**–**59**) of *Pleuropterus multiflorum*

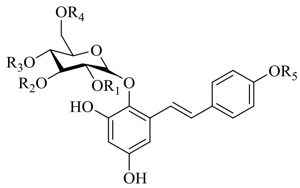
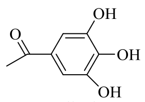
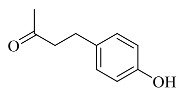
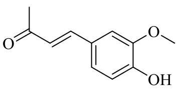
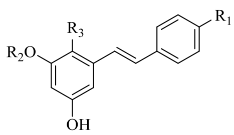
Structure	No.	R_1, R_2, R_3, R_4, R_5	Compound	Reference
	**38**	$R_1=R_2=R_3=R_4=R_5=H$	(E)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-*β*-D-glucoside	[19]
	39	R_1=galloyl, $R_2=R_3=R_4=R_5=H$	(E)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-galloyl)-*β*-D-glucoside	[20]
	40	$R_1=R_2=R_3=R_5=H$, R_4=galloyl	(E)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(6″-*O*-galloyl)-*β*-D-glucoside	[6]
	41	$R_1=R_3=R_4=R_5=H$, R_2=galloyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(3″-*O*-galloyl)-*β*-D-glucoside	[19]
 galloyl	**42**	R_1=galloyl, $R_2=R_3=R_4=R_5=H$	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-feruliacyl)-*β*-D-glucoside	[20]
	43	R_1=*β*-D-fructofurannosyl, $R_2=R_3= R_4=R_5=H$	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-*β*-D-fructofurannosyl)-*β*-D-glucoside	[21]
	44	$R_1=R_2=R_3= R_5=H$, R_4=*α*-D-glucopyranosyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(6″-*O*-*α*-D-glucopyranosyl)-*β*-D-glucoside	[21]
 *p*-coumaryloyl	**45**	R_1=acetyl, $R_2=R_3=R_4=R_5=H$	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-acetyl)-*β*-D-glucoside	[3]
	46	$R_1=R_2=R_3= R_5=H$, R_4=acetyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(6″-*O*-acetyl)-*β*-D-glucoside	[3]
	47	R_1=*p*-coumaryloyl, $R_2=R_3=R_4=R_5=H$	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-*p*-coumaryloyl)-*β*-D-glucoside	[3]
 ferulloyl	**48**	$R_1=R_2=R_4=R_5=H$, R_3=*α*-D-glucopyranosyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(4″-*O*-*α*-D-glucopyranosyl)-*β*-D-glucoside	[21]
	49	$R_1=R_2=R_3=R_4=H$, R_5=*α*-D-glucopyranosyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-4″-*O*-*α*-D-glucopyranosyl-2-*O*-*β*-D-glucoside	[21]
	50	$R_1=R_2=R_3=R_5=H$, R_4=*p*-hydroxybenzoyl	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(2″-*O*-*p*-hydroxybenzoyl)-*β*-D-glucoside	[4]
	51	$R_1=R_2=R_3=R_4=R_5=H$	(*Z*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-*β*-D-glucoside	[22]
	52	$R_1=R_2=R_3=R_5=H$, R_4=*α*-D-glucopyranosyl	(*Z*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-(6″-*O*-*α*-D-glucopyranosyl)-*β*-D-glucoside	[23]
	**53**	R_1=OH, R_2=H, R_3=*O*-rhamnoside	(*E*)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-*β*-*α*-rhamnoside	[24]
	54	R_1=H, $R_2=R_3$=*O*-glucoside	Polygonimitin C	[25]
	55	$R_1=R_2$=H, R_3=*O*-rhamnoside	(E)-2,3,5,4′-Tetrahydroxystilbene-2-*O*-*β*-L-rhamnoside	[24]
	56	R_1=H, R_2=glucoside, R_3=*O*-glucoside	(E)-2,3,5,4′-Tetrahydroxystilbene-2,3-*O*-diglucoside	[25]
	57	R_1=OH, $R_2=R_3$=H	3,5,4′-Trihydroxystilbene/resveratrol	[26]
	58	R_1=*O*-glucoside, $R_2=R_3$=H	3,5,4′-Trihydroxystilbene-4′-*O*-*β*-D-glucoside	[27]
	59	R_1=OH, R_2=glucoside, R_3=H	3,5,4′-Trihydroxystilbene-3-*O*-*β*-D-glucoside	[24]

Table 4 Stilbenes (compounds **60**–**79**) of *Pleuropterus multiflorum*

No.	Compound	Reference	No.	Compound	Reference
60	(*E*)-2,3,6,4′-Tetrahydroxystilbene-2-*O*-*β*-D-glucoside	[4]	**70**	Multiflorumiside I	[31]
61	Rhaponiticin	[28]	**71**	Multiflorumiside J	[31]
62	Multiflorumiside A	[29]	**72**	Multiflorumiside K	[31]
63	Multiflorumiside B	[29]	**73**	Multiflorumiside L	[31]
64	Multiflorumiside C	[29]	**74**	Polygonumoside A (2S)	[32]
65	Multiflorumiside D	[29]	**75**	Polygonumoside B (2R)	[32]
66	Multiflorumiside E	[30]	**76**	Polygonumnoside C (7bR, 8bS)	[32]
67	Multiflorumiside F	[30]	**77**	Polygonumoside D (7bS, 8bR)	[32]
68	Multiflorumiside G	[30]	**78**	Polygonumnolide D	[15]
69	Multiflorumiside H	[31]	**79**	Polygonflavanol A	[33]

1.4 Flavones

There are 26 flavones (Table 5, 6, Fig. 2), one group of important natural compounds, have been isolated from PM[6–7,10,19,20,31,41–46], including rutin, kaempferol, quercetin and their derivatives. Modern medical research shows that flavones have multiple biological activities such as anti-diabetics, antioxidant, anti-cancer, anti-inflammatory activities.

1.5 Phospholipids

Phospholipids were also isolated from PM. Phospholipids are one of the most important constituents of brain tissue and cranial nerve and the main materials

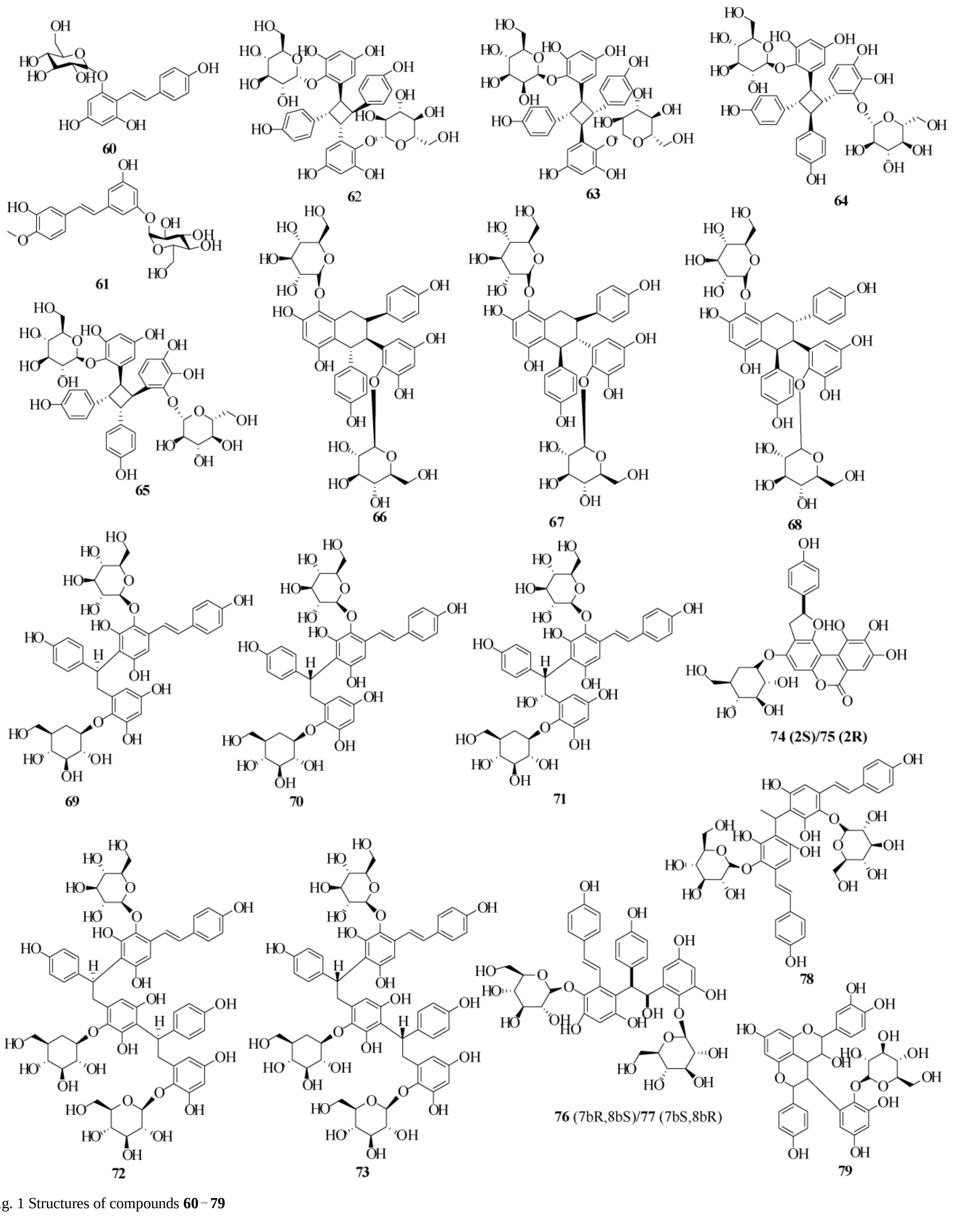


Fig. 1 Structures of compounds **60**–**79**

Table 5 Flavones (compounds **80**–**93**) from *Pleuropterus multiflorum*

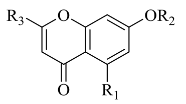
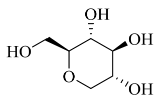
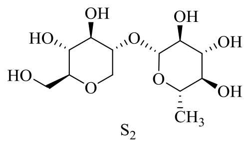
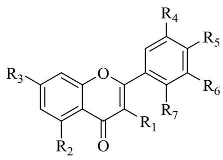
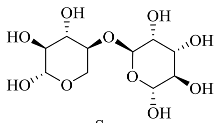
	No.	R_1, R_2, R_3, R_4, R_5, R_6, R_7	Compound	Reference
	**80**	R_1=OH, R_2=H, R_3=CH_3	Noreugenin	[41]
	81	R_1=R_3=CH_3, R_2=H	2,5-Dimethyl-7-hydroxychromone	[31]
	82	R_1=CH_2COOH, R_2=H, R_3=CH_3	5-Carboxymethyl-7-hydroxy-2-methylchromone	[7]
 S_1	**83**	R_1=CH_3, R_2=S_1, R_3=hydroxypropyl	2-(2′-Hydroxypropyl)-5-methylchromone-7-*O*-Glucopyranoside	[32]
 S_2	**84**	R_1=CH_3, R_2=S_2, R_3=hydroxypropyl	(*S*)-2-(2′-Hydroxypropyl)-5-methyl-7-hydroxychromone-7-*O*-*α*-L-fucopyranosyl (1→2)-*β*-D-glucopyranoside	[42]
	**85**	R_1=*O*-galactopyranoside, R_2=R_3=R_4=R_5=OH, R_6=R_7=H	Quercetin-3-*O*-*β*-D-galactopyranoside	[43]
	86	R_1=*O*-arabinoside, R_2=R_3=R_4=R_5=OH, R_6=R_7=H	Quercetin-3-*O*-*β*-D-arabinoside	[43]
	87	R_1=R_2=R_3=R_5=R_6=OH, R_4=R_7=H	Quercetin	[44]
	88	R_1=*O*-glucopyranoside, R_2=R_3=R_4=R_5=OH, R_6=R_7=H	Hyperoside	[41]
 S_3	**89**	R_1=O-S_3, R_2=R_3=R_4=R_5=OH, R_6=R_7=H	Rutin	[44]
	90	R_1=R_7=H, R_2=R_3=R_5=OH, R_4=R_6=OCH_3	Tricin	[6]
	91	R_1=R_2=R_3=R_5=OH, R_4=R_6=R_7=H	Kaempferol	[44]
	92	R_1=R_4=R_6=R_7=H, R_2=R_3=R_5=OH	Apigenin	[10]
	93	R_1=R_4=H, R_2=R_6=OH, R_5=R_7=OCH_3, R_3=*O*-glucopyranoside	Tricin-7-*O*-*β*-D-glucopyranoside	[19]

Table 6 Flavones (compounds **94**–**105**) from *Pleuropterus multiflorum*

No.	Compound	Reference	No.	Compound	Reference
94	Catechin	[20]	**100**	3,3′-Di-*O*-galloyl proanthocyanidin B2	[20]
95	(−)-3-*O*-Galloyl-(−)-catechin	[20]	**102**	Proanthocyanidins	[35]
96	epicatechin	[20]	**102**	Epigallocatechin gallate	[46]
97	(−)-3-*O*-Galloyl-(−)-epicatechin	[20]	**103**	Proanthocyanidin B1	[45]
98	Vitexin	[44]	**104**	Proanthocyanidin B2	[46]
99	3-*O*-Galloyl proanthocyanidin B2	[20]	**105**	(−)-gallocatechin gallate	[46]

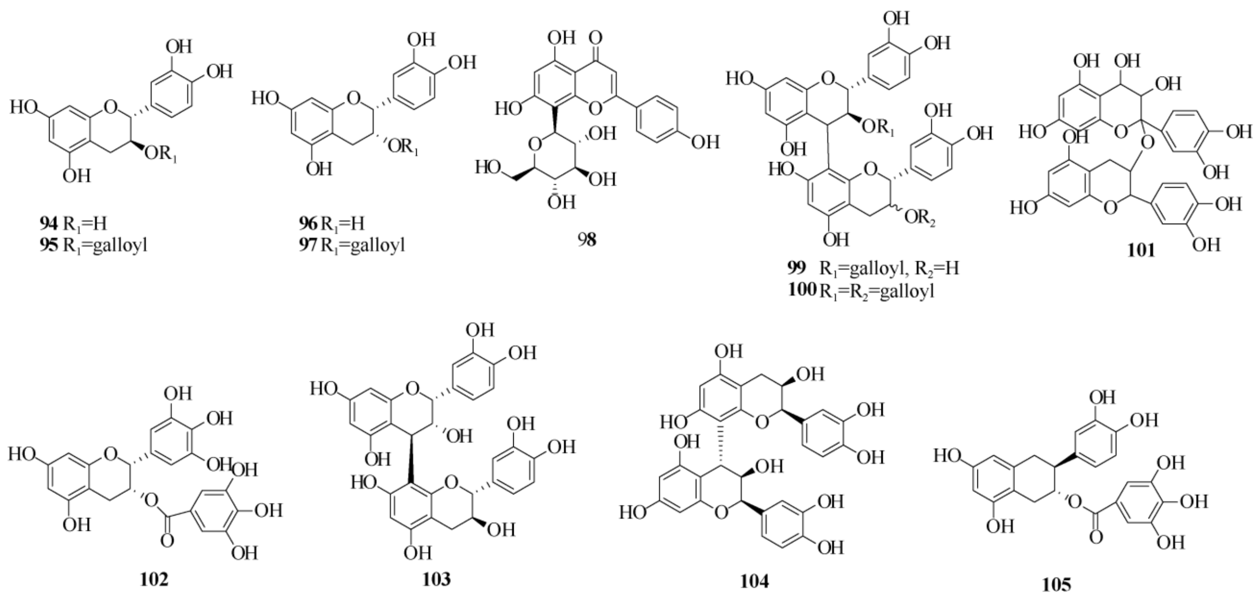


Fig. 2 Structures of compounds **94**–**105**

of cytomembrane synthesized by erythrocyte and other cells of organisms. Phospholipids from PM included phosphatidyl choline, phosphatidyl ethanolamine, lysophosphatidyl choline, phosphatidiyl glycerol, 7-hydroxy-4-methyl coumarin-5-*O*-glucoside, 7-hydroxy-3,4-dimethyl coumarin-5-*O*-glucoside and phosphatedylinositol. A new aliphatic ketone, 1,2-dihydroxynonadecone-3, was confirmed from chloroform section of Radix Polygoni Multiflori Preparata[4]. Two new phospholipids, 1-*O*-stearoyl-2-*O*-D-$\Delta^{4',7'}$-dodecenoyl-3-*O*-phosphatodic acid-*O*-*β*-D-glucoside and 1-*O*-stearoyl-2-*O*-D-$\Delta^{4',7'}$-dodecenoyl-3-*O*-phosphatodic acid-*O*-(6′-*O*-*α*-D-glucose)-*β*-D-glucoside were isolated from Radix Polygoni Multiflori Preparata[33]. Other phospholipids from Radix Polygoni Multiflori Preparata, including dodecane, eicosane, hexanoic acid, hexadecanoic acid methyl ester, hexadecanoic acid ethyl ester, octadecanoic acid methyl ester, octadecanoic acid ethyl ester, ethyl oleate, docosanoic acid methyl ester, methyl palmitate, ethyl palmitate, tetradecanoatic acid ethyl ester, diphosphatidiyl glycerol, copaene and squalene[15].

1.6 Other chemical compounds

Additionally, *β*-sitosterol, gallic acid, torachrysone-8-*O*-*β*-D-glucopyranoside, daucosterol, torachrychrysone-8-*O*-(6′-*O*-acetyl)-*β*-D-glucopyranoside, *N*-*trans*-feruloyl tyramine, *N*-*trans*-feruloyl-3-methyldopamine, schizandrin, indole-3-(L-*α*-amino-*α*-hydroxypropionicacid)-methyl ester, 7-hydroxyl-4-methylcoumarin-5-*O*-*β*-D-glucopyranoside, 7-hydroxyl-3,4-methylcoumarin-5-*O*-*β*-D-glucopyrano-side, 1,3-dihydroxyl-6,7-dimethyl xanthine-1-*O*-*β*-oxymethyl-7-hydroxyl-2-methyl chromone, *β*-amtrin were and 1,2-dihydroxylnonadecanone-3, were isolated from PM[3,14,42].

2 Pharmacological activities

2.1 Anti-aging and antioxidant activities

PM could significantly reduce the activities of malondialdehyde (MDA), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in serum from D-galactose induced acute senescence rats, while improve the activities of glutathione peroxidase (GSH-px), superoxide dismutase (SOD)[47]. PM shown a protective effect on skin aging of mice, which could relate to increasing the dermis thickness of aging mice, reducing the level of insulin and IGF-1, and promoting the expression of collagen fibers[48]. Xu found that the extract of PM improved the activity of SOD in rat heart and brain tissues, reduced the content of lipid peroxide and lipofuscin and showed significant antioxidant effects and a protective effect on the peroxidation damage of heart and brain tissues[49].

2.2 Improve immunity

The polysaccharide of *P. multiflorum* (PPM) significantly inhibited cyclophosphamide-induced weight loss of immune organs and the decrease in the number of blood cells in mice and potentiated the immunelogical function in immunosuppressed mice. It significantly increased the phagocytic percentage and phagocytic index, the contents of serum hemolysin, the esterase positive rate of T-lymphocytes and Con A-induced proliferation of splenic T-lymphocytes, which indicated that PPM had the function of enhancing immunity[50].

2.3 Dyslipidemia regulation

The findings of a clinical study on 50 hyperlipidemia patients demonstrated that the lipid-owering effect of PM may be related to regulating action of the genes involved in cholesterol synthesis and lipoprotein metabolism[51].

2.4 Neuroprotective activity

The therapeutic effect of PM on neurodegenerative diseases is quite obvious and widely recognized[52]. An investigation about therapeutic activity of PM in Alzheimer’s disease (AD) by Chen et al. shown that the scores for the Ability of Daily Living Scale and the Mini-Mental State Examination were significantly improved in the treatment group compared with the Chinese herb and western medicine control groups[53]. In a randomized, piracetam-controlled, single-center clinical trial, PM was evaluated as monotherapy for vascular dementia (VaD). The results shown that the total clinical effective rate was 71.25% and that the herbal medicinal had obvious therapeutic effect on VaD, with no relative adverse drug reactions[54].

2.5 Hepato-protective activity

In vitro and *vivo* models, the hepatoprotective effects of ethanolic extract of PM were related to regulating the redox state in liver injury through Nrf2 activation and controlling hepatic bile acid homeostasis in obstructive cholestasis, through bile acid transporter expression modulation[55]. The study of *P. multiflorum* water extract (PMW) by Wei et al. suggested that PMW accelerated bile acid enterohepatic circulation and changed the composition of intestinal Bas lead to activation of Fxr-Fgf15 signal in intestines and further inhibition of the expression of Cyp7a1 in the liver[56].

2.6 Renal-protective activity

TSG from PM plays a concentration-dependent protective role in ameliorating the progression of an adriamycin (AD)-induced focal segmental glomerulosclerosis (FSGS) through activation of the Nrf2-Keap1 antioxidant pathway. TSG has the capacity of blocking angiotensin II (ANG II) signaling. In the streptozotocin (STZ)-induced diabetes model TSG was demonstrated the beneficial effect of therapy on renal damage though the inhibition of the RAS effectively to prevent renal injury in diabetic nephronpathy[57].

2.7 Cardiovascular system

Tetrahydroxystilbene glucoside could induce relaxation of the superior mesenteric artery through an endothelium-dependent pathway that involves the inhibition of COX-2 activity and decreased in TXA2 and through an endothelium-independent pathway *via* opening of a voltage-dependent K^+ channel, blockade of Ca^{2+} influx and release of intracellular Ca^{2+}[58]. The cardioprotective effects of TSG have been demonstrated. TSG protected murine hearts against ischemia/reperfusion injury *in vivo* and *in vitro* by activating the Notch1/Hes1 signaling pathway and attenuating ER stress-induced apoptosis[59].

2.8 Anti-inflammatory and antibacterial activity

Lu et al.[60] reported that ethanol extract of *P. multiflorum* (PME) had a significantly anti-inflamematory effect. Chin et al.[61] found that TSG of PM could reduce periodontitis, gene expression of TNF-*α*, interleukin-1 IL (IL-1) and IL-6, and inhibit the activation of NK-kB *in vivo* and *in vitro*. Studies found that PM had the function of inhibiting human dysentery bacillus and mycobacterium tuberculosis. Especially, the anthraquinone derivatives of PM had inhibitory effect on bacteria, fungal influenza viruses and pathogens, such as paratyphoid rod 901, diphtheria bacillus, staphylococcus aureus, paratyphoid bacillus B, hemolytic streptococcus B and bacillus anthracis. Study confirmed that Raw Radix *P. multiflorum* had the effect of fighting staphylococcus aureus, while *P. multiflorum* preparata had the effect of fighting staphylococcus albicans. And steamed and wine *P. multiflorum* preparata had a better effect against diphtheria bacillus.

2.9 Other effects

A study on diabetes-related bone loss in mice shown that PMW significantly alleviated mouse body weight loss and hyperglycemia, and elevated serum levels of insulin, osteocalcin and bone-alkaline phosphatase. PMW might relieve diabetes-related bone disorders through regulating osteoclast-related genes and PM may be used as a preventive agent for diabetes-induced bone loss[62]. At the same time, tetra hydroxy stilbene glucoside from PM was also demonstrated the protected against diabetes-induced osteoporosis in mice with streptozotocin-induced hyperglycemia[63]. A study on PME in high-fat diet-induced obese mice demonstrated that PME might relieve obesity by inhibition of adipogenesis and lipogenesis and lipolysis and fatty acid oxidetion[64].

3 Toxic effects

Although there are many reports referred to the toxicity of PM, especially for liver adverse reactions, mechanism of toxicity remains unclear. Liver injuries caused by PM have been reported and the incidences have increased in recent years[65–66]. Although the hepatotoxic chemicals attributing to the hepatic lesions of PM remain in dispute, the hepatotoxicity of emodin has been well documented in many studies[67–70]. Luteolin was reported to cause cytotoxicity in primary rat hepatocytes at dosages of 50 μmol/L or lower levels of concentration[71]. Apigenin was found to can significantly increase the accumulation of lipid droplets and cause fatty liver disease[72]. He et al.[73] screen 25 ingredients in PM by a computational toxicology approach. Emodin, chrysophanol, rhein, danthron, aloe emodin, physcion, and apigenin could cause variable degrees of liver injury recorded in the literature. Emodin 8-glucoside, physcion-8-*O*-D-glucopyranoside, and luteolin were reported to possess potential hepatotoxicity. For the other 14 hepatotoxic ingredients, although direct evidence focused on their hepatotoxicity was not available, none of them was reported to be potential hepato-protector. Liu et al. hypothesized tannin, as another major component in PM, was one of the reasons for the induced liver damage[74]. While the components of PM responsible for the hepatotoxic effects have not yet been identified now, even many of the reports are contradictory, and the mechanism involved in PM-induced liver damage are not comprehensive. Although many reports referring to toxicity of PM especially for liver adverse reactions have been reported, it might possible that PMW usage in TCM still keep safe currently, except high dose of HSW usage in a long term[75].

4 Conclusions

PM is an important medical plant wildly used in traditional Chinese medicine. There are abundant anthraquinones, stilbenes, flavones, phospholipids and dianthrone derivatives from PM. At present these studies on PM mainly aimed at the medicinal effects, mechanisms and quality control. TSG, as the main component of PM, not only has many medicinal activities, but also has great potential exploitation for medicines. And with the concern about liver injury induced by PM, the model of safety monitoring and risk management of PM is very important based on quality control as one of the major safety problems in TCM drug safety concerns. The comprehensive knowledge of PM by strengthening standardization of clinical applications, basic science research, quality control in manufacturing is significance. Measures should also be encouraged and implemented to promote healthy development of the TCM industry.

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