

Phytochemistry and Pharmacological Activities of *Panax japonicus*: A Comprehensive Review

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Abstract

Background: *Panax japonicus* (*P. japonicus*) belongs to the *Panax* genus of Araliaceae and is used as medicine mainly with the bamboo whiplike rhizome, which has the functions of dispelling blood stasis and hemostasis, attenuating swelling and pain, eradicating phlegm and relieving cough, tonifying, and strength.

Objectives: This review intends to summarize the chemical constituents and pharmacological activities of *P. japonicus* to provide a scientific and systematic basis for better utilization of its rational applications.

Methodology: The literature was searched using PubMed, Baidu Scholar and Science Hub search engines.

Results: The chemistry components isolated from *P. japonicus* are mainly saponins, besides also including polysaccharides, amino acids, volatile oils, inorganic elements, etc. *P. japonicus* exhibits extensive pharmacological activities including anti-inflammatory, antioxidant, lipid lowering activities, and therefore show extensive protective effects on the central nervous system, cardio-cerebrovascular system, digestive system.

Conclusion: This article included a thorough summary of the botany, phytochemistry, and pharmacology of *P. japonicus* and provided evidence for its further research and clinical applications.

Keywords

Panax japonicus (Family Araliaceae), phytochemistry, pharmacological activities, saponins

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Introduction

Panax japonicus C. A. Meyer belongs to the Araliaceae *Panax* family in the plant kingdom (China Pharmacopoeia Commission, 2020). At an elevation of 1,800–2,600 m, it thrives in valley broadleaf forests and is distributed in the south of the Yangtze River basin, east to Japan, and west to the Hengduan Mountains (Jia & Zhang, 2016; Lin et al., 2007). The typical characteristics of *P. japonicus* are the transverse rhizomes in the shape of bamboo whips which can be used as medicine. They have the functions of dispelling blood stasis and hemostasis, attenuating swelling and pain, eradicating phlegm and relieving cough, tonifying, and strength (Song, 1999).

The advancement of technology in separation and identification has allowed for the successful isolation and identification of over 100 compounds (College of Traditional

Chinese Medicine of Nanjing Pharmaceutical University, 1976; He et al., 2019; Ohtani et al., 1989; Wang, 2020; Wu & Yi, 1992; Xiang, 2009; Yang et al., 2014). Modern pharmacological

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research on this plant has demonstrated that its primary ingredients, which include volatile oils, polysaccharides, amino acids, and saponins, have extensive pharmacological effects on the central nervous system, cardio-cerebrovascular system, digestive system, immune system, and so on.

This review intends to summarize the chemical constituents and pharmacological activities of *P. japonicus* to provide a scientific and systematic basis for better utilization of its rational applications.

Methodology

The literature search was conducted using PubMed, Baidu Scholar, and Science Hub search engines. The search was performed using keywords such as *Panax japonicus* and phytochemistry, *Panax japonicus* and pharmacological activities, *Panax japonicus* and cardioprotection, *Panax japonicus* and hepatoprotective, *Panax japonicus* and metabolic system, *Panax japonicus* and obesity, etc. In total, approximately 75 articles on 118 compounds from 1976 to 2023 were compiled. This article aimed to compile literature focused solely on *P. japonicus*.

Botany

P. japonicus is a perennial herbaceous plant that has transverse rhizomes and grows to a height of 30–60 cm. The petiole is slender and 4–9 cm long. The central leaf is obovate or elliptic obovate with 5–15 cm long, 2–5.5 cm wide, base cuneate, rounder or subcordate, margin serrate, double serrate or incised-serrate, glabrous above and sometimes pilose below. Umbel: single terminal, rare few branches; the peduncle is about 12 cm. The flowers are small and in clusters of 20–50. The calyx is cup-shaped with five parts. There are five pale yellow-green petals and an oval triangle. The drupe is berry-shaped, and red when ripe

and often black at the apex. May through June is blooming time, while July through August is fruiting time (Institute of the Academy of Medical Sciences of China, 1979), as shown in Figure 1.

Chemical Constituents

This review identifies over 120 chemical components isolated from *P. japonicus* based on the literature, including saponins, saccharides, amino acids, volatile oils, and inorganic elements.

Saponins

Saponins are considered to be the main bioactive ingredients of *P. japonicus*, and their contents vary with different producing areas. It was reported that the content of saponins in the rhizome of *P. japonicus* was about 5% in China and that in Japan was 23.6%. Up to now, 118 triterpenoid saponins have been isolated from *P. japonicus* (Table 1), which were mainly oleanane type and dammarane type. They could be classified into oleanolic acid (OA), ursolic acid (UA), dammarendiol II (DD-II), protopanaxadiol (PPD), protopanaxatriol (PPT), ocotillol (OCT), and miscellaneous subtypes, as shown in Figures 2 and 3.

Saccharides

Zhao et al. demonstrated that the total saccharide content, reducing sugar content, and total polysaccharide content in *P. japonicus* were 70.011%, 5.819%, and 64.192%, respectively, through 3,5-dinitrosalicylic acid colorimetric method (Zhao et al., 2010). Ohtani et al. isolated two reticuloendothelial system-activating polysaccharides, which were named tochibanan-A and tochibanan-B, from *P. japonicus*. One is β -1,4-galactosan with a molecular weight of about 23,000, and the other is a complex polysaccharide with a molecular weight of about 40,000 containing 7.9%



Figure 1. The Leaves (a), the Fruits (b), and the Rhizomes (c) of *P. japonicus*.

Source: Yuan et al. (2015).

Table 1. The Saponin Constituents from *P. japonicus*.

No.	Compounds	Parts	References
1	Oleanolic acid 28- <i>O</i> - β -D-glucopyranoside	Rhizomes	Cai et al. (1982)
2	28-Desglucosylchikusetsusaponin VIa	Fruits	Yoshizaki et al. (2012)
3	28-Desglucosylchikusetsusaponin VI	Rhizomes	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
4	Chikusetsusaponin II		Lin and Shoji (1979)
5	28-Desglucosylchikusetsusaponin VIa methyl ester		Zhou et al. (2011)
6	28-Desglucosylchikusetsusaponin VIa butyl ester		Liu et al. (2016)
7	Zingibroside R ₁		Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
8	Zingibroside R ₁ methyl ester		Yoshizaki, Devkota, and Yahara (2013)
9	Baisanqisaponin C		Liu et al. (2016)
10	Chikusetsusaponin Ib		Lin et al. (1976)
11	Pseudoginsenoside Rp ₁		Morita et al. (1985)
12	Chikusetsusaponin VIa	Rhizomes, fruits	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013), Yoshizaki et al. (2012)
13	Chikusetsusaponin VIa methyl ester	Rhizomes	Chen et al. (2016), Liu et al. (2016), Zhou et al. (2011)
14	Chikusetsusaponin VIa ethyl ester		Liu et al. (2016)
15	Chikusetsusaponin VIa butyl ester		
16	Chikusetsusaponin VI		Zhou et al. (2011), Morita et al. (1983), Yoshizaki, Devkota, Fujino et al. (2013)
17	Chikusetsusaponin VI methyl ester		Liu et al. (2016), Zhou et al. (2011)
18	Chikusetsusaponin VI	Rhizomes, fruits	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013), Yoshizaki et al. (2012)
19	Chikusetsusaponin VI methyl ester	Rhizomes	Liu et al. (2016), Zhou et al. (2011)
20	Chikusetsusaponin VI ethyl ester		Liu et al. (2016)
21	Chikusetsusaponin VI butyl ester		Liu et al. (2016)
22	Pseudoginsenoside Rt ₁		Cai and Xiao (1984), Chen et al. (2016)
23	Pseudoginsenoside Rt ₁ methyl ester		Chen et al. (2016)
24	Pseudoginsenoside Rt ₁ butyl ester		Liu et al. (2016)
25	Baisanqisaponin A		
26	Baisanqisaponin B		
27	Taibaienoside I		
28	Taibaienoside II		
29	Pjs-4		Cai and Xiao (1984)
30	Hemsgiganoside B		Chen et al. (2016), Zou et al. (2012)
31	Maslinic acid 28- <i>O</i> - β -D-glucopyranoside		Zhao et al. (2010)
32	Cynarasaponin C		Zou et al. (2012)
33	20(S)-Protopanaxadiol		Xu et al. (2015)
34	Ginsenoside F ₂		Chen et al. (2015)
35	Chikusetsusaponin Ia		Lin et al. (1976)
36	Chikusetsusaponin III		Kondo et al. (1969)
37	Chikusetsusaponin FK ₆	Rhizomes, fruits	Yoshizaki, Devkota, Fujino et al. (2013), Yoshizaki, Devkota, and Yahara (2012)
38	Ginsenoside Rd	Rhizomes, leaves	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)

(Table 1 continued)

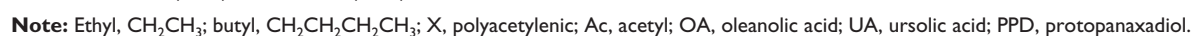
(Table 1 continued)

No.	Compounds	Parts	References
39	Gypenoside XVII	Rhizomes	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
40	Notoginsenoside Fe		Yoshizaki, Devkota, Fujino et al. (2013), Zou, Zhu, Meselhy et al. (2002)
41	Notoginsenoside R ₄		Zou, Zhu, Meselhy et al. (2002)
42	Ginsenoside Rb ₁		Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
43	Ginsenoside Rb ₃	Rhizomes,	Yoshizaki, Devkota, Fujino et al. (2013), Yoshizaki, Devkota,
44	Ginsenoside Rc	fruits	and Yahara (2013), Yoshizaki and Yahara (2012a)
45	Chikusetsusaponin VII	Rhizomes	Yoshizaki, Devkota, Fujino et al. (2013)
46	Chikusetsusaponin VI	Rhizomes,	Yoshizaki, Devkota, Fujino et al., (2013), Yoshizaki and Yahara
		fruits	(2012a)
47	Chikusetsusaponin FK ₄	Fruits	Yoshizaki et al. (2012), Yoshizaki and Yahara (2012a)
48	Chikusetsusaponin FK ₅		
49	Notoginsenoside Fa	Rhizomes	Zou, Zhu, Meselhy et al. (2002)
50	Notoginsenoside Fc		
51	Yesaninoside J		
52	Chikusetsusaponin FK ₇	Fruits, leaves	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki and Yahara (2012a)
53	Yesaninoside H	Rhizomes	Zou, Zhu, Meselhy et al. (2002)
54	Chikusetsusaponin FM ₁	Fruits	Yoshizaki and Yahara (2012a)
55	(20R)-Ginsenoside Rh I	Rhizomes	Liu et al. (2016)
56	(20S)-Ginsenoside Rh I		Zhou et al. (2011), Yoshizaki Devkota, Fujino et al. (2013)
57	Ginsenoside Rf		Zhou et al. (2011)
58	Ginsenoside Rg ₂		Lin et al. (1976), Yoshizaki, Devkota, Fujino et al. (2013)
59	Notoginsenoside R ₂		Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
60	20(S)-Protopanaxatriol		Xu et al. (2015)
61	Chikusetsusaponin L ₅	Fruits, leaves	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki and Yahara (2012a)
62	Chikusetsusaponin LM ₁	Leaves	Yoshizaki, Devkota, and Yahara (2013)
63	Chikusetsusaponin LM ₂		
64	Chikusetsusaponin LM ₃		
65	Ginsenoside F ₁		Yahara et al. (2008)
66	Ginsenoside F ₃		Yoshizaki, Devkota, and Yahara (2013)
67	Ginsenoside F ₅		
68	Ginsenoside F ₆		
69	Notoginsenoside R ₆	Rhizomes	Zou, Zhu, Tohda et al. (2002)
70	Ginsenoside Rg ₁	Rhizomes,	Zhou et al. (2011), Morita et al. (1985), Yoshizaki, Devkota,
		fruits	Fujino et al. (2013)
71	Yesaninoside D	Rhizomes	Zou, Zhu, Tohda et al. (2002)
72	Yesaninoside E		
73	Yesaninoside F		
74	Notoginsenoside R ₁	Rhizomes,	Zhou et al. (2011), Yoshizaki, Devkota, Fujino et al. (2013)
		fruits	
75	20-O-Glucosylginsenoside Rf	Rhizomes	Zou, Zhu, Tohda et al. (2002)
76	Ginsenoside Re	Rhizomes,	Yoshizaki and Yahara (2012b), Zou, Zhu, Tohda et al. (2002)
		fruits	
77	6'''-O-Acetyl-ginsenoside Re	Rhizomes	Zhou et al. (2011)

(Table 1 continued)

(Table 1 continued)

No.	Compounds	Parts	References
78	Pseudoginsenoside Rs ₁	Fruits	Yoshizaki and Yahara (2012a)
79	Floralquinoside E		
80	Chikusetsusaponin FK ₁		
81	Chikusetsusaponin L ₁₀	Fruits, leaves	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki and Yahara (2012a)
82	Chikusetsusaponin LM ₄	Leaves	Yoshizaki, Devkota, and Yahara (2013)
83	Chikusetsusaponin LM ₅		
84	Chikusetsusaponin LM ₆		
85	Yesanchinoside R ₁	Rhizomes	Zhou et al. (2011)
86	Yesanchinoside R ₂		
87	Chikusetsusaponin L _{9bc}	Leaves	Yoshizaki, Devkota, and Yahara (2013)
88	Notoginsenoside J	Rhizomes	Zhou et al. (2011)
89	Vinaginsenoside R ₁₅		
90	Chikusetsusaponin L _{9a}	Leaves	Yahara et al. (2008), Yoshizaki, Devkota, and Yahara (2013)
91	Ginsenoside Rh ₄	Rhizomes	Liu et al. (2016)
92	Ginsenoside Rk ₃		Wang (2020)
93	(24S)-Pseudoginsenoside F ₁₁		Zou, Zhu, Tohda et al. (2002)
94	(24S)-Majoroside R ₂		
95	(24S)-Pseudoginsenoside Rt ₄		
96	(24S)-Vinaginsenoside R ₁		
97	(24S)-Vinaginsenoside R ₂		
98	(24S)-Vinaginsenoside R ₆		
99	(24S)-Yesanchinoside A		
100	(24S)-Yesanchinoside B		
101	(24S)-Yesanchinoside C		
102	(24R)-Pseudoginsenoside F ₁₁		Morita et al. (1983)
103	Yesanchinoside I		Zou, Zhu, Meselhy et al. (2002)
104	Notoginsenoside G		Zhou et al. (2011), Zou, Zhu, Meselhy et al. (2002)
105	Yesanchinoside G	Rhizomes	Zou, Zhu, Meselhy et al. (2002)
106	Prosapogenin	Leaves	Dun and Yuan (2006)
107	Chikusetsusaponin FK ₂	Fruits, leaves	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki et al. (2012), Yoshizaki and Yahara (2012a)
108	Chikusetsusaponin FK ₃	Fruits	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki et al. (2012)
109	Chikusetsusaponin LT ₈	Leaves	Yahara et al. (1978)
110	Chikusetsusaponin FT ₄	Fruits	Yoshizaki et al. (2012)
111	Chikusetsusaponin LT ₅	Leaves	Yahara et al. (1978)
112	Chikusetsusaponin FT ₂	Fruits	Yoshizaki et al. (2012)
113	Chikusetsusaponin FT ₃		
114	Chikusetsusaponin LN ₄	Fruits, leaves	Yahara et al. (1978), Yoshizaki et al. (2012)
115	Chikusetsusaponin FH ₂	Fruits	Yoshizaki et al. (2012)
116	Chikusetsusaponin FH ₁		
117	Chikusetsusaponin FT ₁	Fruits, Leaves	Yoshizaki, Devkota, and Yahara (2013), Yoshizaki et al. (2012)
118	Ginsenoside Rh ₈	Fruits	Yoshizaki et al. (2012)



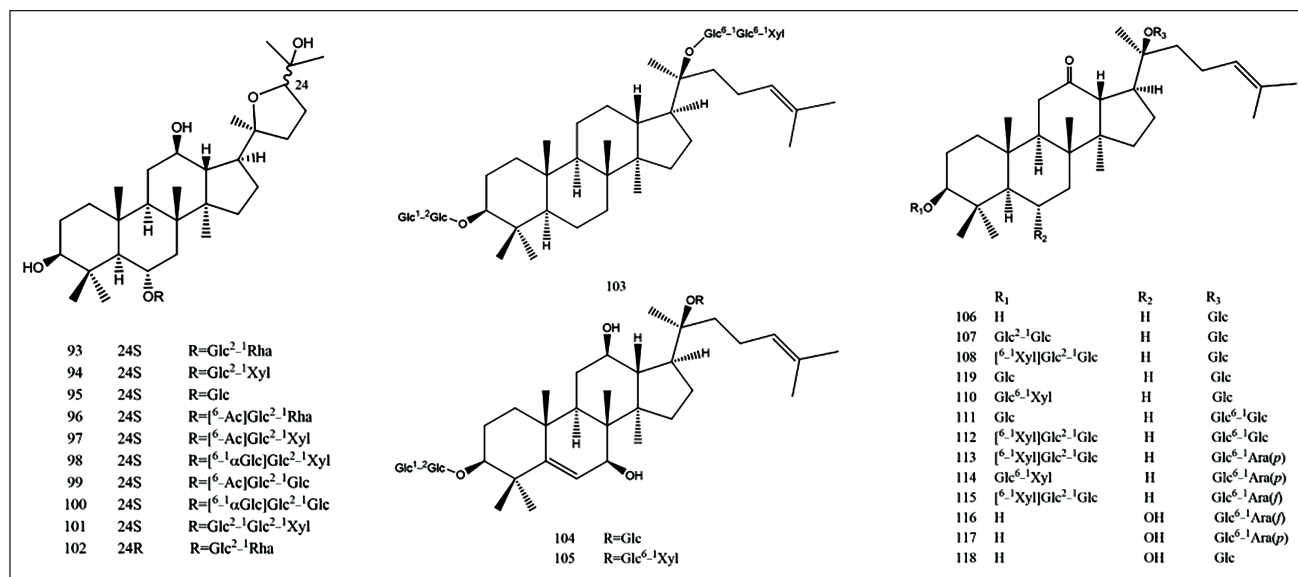


Figure 3. Structures of Compounds 93–102 (OCT-subtype of Dammarane Triterpenoids), 103 (DD-II subtype of Dammarane Triterpenoids), and 104–118 (Miscellaneous).

Source: He et al. (2019) and Xu et al. (2015).

Note: Ac, acetyl; OCT, ocotillol; DD-II, dammarenediol II.

L-arabinose, 87.1% D-galactose, 1.6% D-glucose, and 3.5% galacturonic acid (Ohtani et al., 1989). Yang et al. isolated five kinds of polysaccharides with different molecular weights from *P. japonicus*, and PP1–PP5, and all of them have activities of scavenging free radicals and protecting DNA damage (Yang et al., 2014).

Amino Acids

A large number of amino acids had been obtained from *P. japonicus*, including aspartic acid, glutamic acid, arginine, lysine, valine, leucine, isoleucine, proline, phenylalanine, tyrosine, and histidine. Among them, seven compounds such as methionine, threonine, and phenylalanine are essential for human health, which indicates that *P. japonicus* has high nutritive value (Wu & Yi, 1992; Xiang, 2009).

Volatile Oils

The volatile oils were isolated from *P. japonicus* using steam distillation and identified by gas chromatography–mass spectrometry (GC–MS) as reported in the literature. The volatile oil content of *P. japonicus* was 0.016% (Dun & Yuan, 2006), and the main components were β-santalene and β-farnesene (Zuo & Yuan, 2005).

Pharmacological Activities

Mounting studies have demonstrated that *P. japonicus* exhibits extensive pharmacological effects such as antioxidant, lowering lipid, and anti-inflammation, and therefore show

extensive protective effects on the central nervous system, cardio-cerebrovascular system, digestive system, and so on. We summarized the pharmacological activities in Table 2.

Effects on the Central Nervous System

With aging, the structure and function of the human central nervous system gradually undergo degenerative changes. Several studies have demonstrated that *P. japonicus* confers neuroprotection in naturally aging rats. Saponins from *P. japonicus* (SPJ) can reduce cognitive dysfunction in aged rats by upregulating microglial M1 to M2 polarization, resulting in reduced microglial inflammation and increased microglial autophagy capacity (Pi et al., 2021). Deng et al. indicated that SPJ has antineuroinflammatory effects in aging rats via regulation of the mitogen-activated protein kinase (MAPK) signaling pathway (Deng et al., 2017). And Wan et al. reported that SPJ can reduce age-related apoptosis and promote antioxidant enzyme activities and mitochondrial function (Wan et al., 2020).

Furthermore, substantial studies have found that *P. japonicus* shows therapeutic potential for drug- or disease-induced models by regulating multiple signaling pathways. D-gal-induced animal models are commonly used in brain aging studies. It has been reported that SPJ can ameliorate D-gal-induced neuronal injury and cognitive impairment, which may be related to nuclear factor erythroid 2-related factor 2 (Nrf2) and silent information regulator 1 (SIRT1)-mediated antioxidant pathways (Wang et al., 2015). Chikusetsusaponin IVa, the main monomers of SPJ, was reported to improve sevoflurane or isoflurane-induced cognitive impairment and neuroinflammation through

Table 2. Pharmacological Activities of the *P. japonicus*.

Pharmacological Activity	Compound	Experimental Models	Doses	Results	Target Molecules	References
Neuroprotective activity	Saponins from <i>P. japonicus</i>	Sprague-Dawley rats (18-month-old)	10 and 30 mg/kg	Attenuated aging-induced cognitive impairment	(↑) LC3B, Beclin1, Arg5 (↓) p62	Pi et al. (2021)
		Male Sprague-Dawley rats (18-month-old)	10, 30, and 60 mg/kg, orally for 6 months	Attenuated aging-induced neuroinflammation	(↓) iNOS, COX-2, microglial activation, NF-κB	Deng et al. (2017)
		Sprague-Dawley rats (18-month-old)	10, 30, and 60 mg/kg, orally for 6 months	Conferred neuroprotection in aging rats partly through the modulation of oxidative stress	(↑) SOD, SIRT1, Foxo3a, LC3II, Beclin1, (↓) MDA	Wan et al. (2020)
		Male Wistar rat	50, 100, and 200 mg/kg, orally for 8 weeks	Reduced D-gal-induced oxidative stress and apoptosis	(↑) Nrf2, SIRT1 (100, 200 mg/kg), (↓) MDA, hippocampal neuron damage	Wang et al. (2015)
		Female C57 BL/6J mice (6–8-week-old)	36.5 and 73 mg/kg, orally	Alleviated neurological impairment caused by experimental autoimmune encephalomyelitis	(↓) inflammatory cell infiltration	Wang, J. et al. (2023)
		Male BALB/c mice (6-week-old)	15 and 45 mg/kg, orally for 8 weeks	Alleviated HFD-induced cognitive impairment and depression-like behaviors	(↑) GluA1, GluA2, (↓) NLRP3, Caspase-1, IL-1β	Wang et al. (2021)
Cardioprotective activity	Chikusetsusaponin IVa	Male Sprague-Dawley rat (80-week-old)	30 mg/kg, inject	Improved adolescent spatial memory, ameliorate isoflurane-induced neurotoxicity and cognitive impairment	(↑) SIRT1, p-ERK1/2, (↓) hippocampal neuron apoptosis	Fang et al. (2017)
		Male Sprague-Dawley rats (80-week-old)	30 mg/kg, inject	Alleviated neurological dysfunction in aged rats exposure to sevoflurane	(↓) Caspase-3, NLRP3, IL-18, IL-1β	Shao et al. (2020)
		Male C57BL/6 mice (8–12-week-old), injected streptozotocin to induce diabetes	30, 60, and 120 mg/kg, gavage for 4 weeks	Attenuated cerebral I/R injury in STZ-induced diabetic mice	(↑) AMPK, GSK-3β, PSD95, (↓) infarct size, cell injury after I/R	Duan et al. (2016)
	Chikusetsusaponin V	Sprague-Dawley rats	50 mg/kg, inject	Attenuated CI/R injury	(↑) p-AMPK, SIRT1, PGC-1α, (↓) ROS, mitochondria damage	Zhang et al. (2021)
	Saponins from <i>P. japonicus</i>	Sprague-Dawley rats	50 and 100 mg/kg, orally for 3 days	Exerted cardioprotective effects on MI rats	(↑) SIRT1, (↓) MCP-1, TNF-α, ERK1/2, NF-κB	Wei and Zhang et al. (2014)
		Sprague-Dawley rats	50 and 100 mg/kg, orally for 1 week	Exerted beneficially cardioprotective effects on myocardial ischemia injury rats	(↑) Bcl-2, (↓) Caspase-3, infarct size, cardiac cell death, SOD	He et al. (2012)
		Sprague-Dawley rats (24-month-old)	10 and 30 mg/kg, orally for 6 months	Effectively ameliorate the cardiac aging phenotype and cardiac dysfunction in naturally aging rats	(↑) LC3-II/LC3-I, Beclin1, p-MAPK/AMPK, p-mTOR/m-TOR, (↓) p21, p53, NF-κB, p-MAPK/MAKP	Huang et al. (2023)
	Chikusetsusaponin IVa	BALB/c mice	5 and 15 mg/kg, orally for 20 days	Reduced impairment of isoprenaline-induced cardiac fibrosis in mice	(↑) LC3, Beclin1, p-MAPK/AMPK, (↓) p-mTOR/m-TOR, p-ULK1	Wang et al. (2019)

(Table 2 continued)

(Table 2 continued)

Pharmacological Activity					References	
Compound	Experimental Models	Doses	Results	Target Molecules	References	
Hepatoprotective activity	Chikusetsusaponin V	Male BALB/c mice	5, 15, and 20 mg/kg, orally for 4 days	Attenuated lipopolysaccharide-induced liver injury in mice	(↓) ALT, AST, TNF- α , NF- κ B, p38	Dai et al. (2016)
		C57BL/6 mice (8–10-week-old)	50, 100, and 200 mg/kg	Possessed a positive intervention to hepatocytes damage	(↓) NE, F4/80, HMGB1, IL-1 β , Caspase-1, NLRP3	Liu et al. (2021)
	Saponins from <i>P. japonicus</i>	ICR mice	12.5, 25, and 50 mg/kg, gavage for 30 days	Protected mice from alcohol-induced liver damage	(↑) SOD, GPX, CAT, (↓) reactive oxygen species/free radicals	Li et al. (2010)
		ICR mice	50 and 100 mg/kg, orally for 4 weeks	Alleviated carbon tetrachloride-induced liver fibrosis in mice	(↑) p-AKT/IAKT, p-GSK3 β /GSK3 β , Nrf2, (↓) ALT, AST	Dai et al. (2021)
Intestinal protective activity		BALB/c mice	100 and 300 mg/kg, gavage for 11 weeks	Had a potential protective effect against fatty hepatic fibrosis induced by high-fat diet	(↓) GRP78, CHOP, Coll, α -SMA, TIMP, p-JNK	Yuan et al. (2018)
	Saponins from <i>P. japonicus</i>	Male Sprague-Dawley rat (6-month-old)	10 and 30 mg/kg, inject for 18 months	Modulated URP ^{ER} alterations in colonic tissues of aging rats	(↑) p-eIF2 α , ATF4, (↓) GRP78, IRE1, p-JNK	Dun et al. (2019)
		Male Sprague-Dawley rat (18-month-old)	10 and 30 mg/kg, inject for 6 months	Reversed neuronal loss resulting from α -syn accumulation in the colonic myenteric plexus of aging rats	(↑) NeuN, IRE1, p-eIF2 α , ATF4, (↓) α -syn, GRP78	Guo, Y. et al. (2021)
		Male Sprague-Dawley rat	10, 30, and 60 mg/kg, orally for 20 days	Ameliorated intestinal epithelial tight junction damage in aging rats	(↑) claudin-1, occludin, (↓) IL-1 β , TNF- α , NF- κ B	Dun et al. (2018)
Metabolic activity	Chikusetsusaponin IVa	Male Wistar rat	45, 90, and 180 mg/kg	Possessed insulin secretagogue and hypoglycemic activity	(↑) FSI, (↓) FBG	Cui et al. (2015)
		Male Wistar rat	25, 50, 100, and 200 mg/kg, orally for 14 days	Regulated glucose uptake and fatty acid oxidation	(↑) AMPK, CPT-1, GLUT4	Li, Y. et al. (2015)
Antibesity activity	Saponins from <i>P. japonicus</i>	Male ICR mice (3-week-old)	High-fat diet containing 1 and 3% total chikusetsusaponin, for 9 weeks	Exerted an antiobesity effect in HFD mice	(↓) plasma triacylglycerol, pancreatic lipase activity	Han et al. (2005)
		Male C57BL/6 mice	90 mg/kg, orally for 10 weeks	Alleviated adipose tissue fibrosis and improved obesity	(↑) PPAR γ , PGC-1 α , (↓) TGF β 1	Hu et al. (2022)
	Chikusetsusaponin V	C57BL/6 mice (6-week-old)	25 and 100 mg/kg, gavage for 11 weeks	Alleviated HFD-induced overweight	(↑) HDL-C, (↓) TG, LDL-C, lipid accumulation	Qiu et al. (2021)
	Chikusetsusaponin IVa	Male C57BL/6 mice (4-week-old)	50 and 100 mg/kg, orally for 16 weeks	Improved HFD-induced adipose tissue inflammation in mice	(↓) IL-1 β , TNF- α , CD68, F4/80, NLRP3	Yuan et al. (2017)

(Table 2 continued)

(Table 2 continued)

Pharmacological Activity	Compound	Experimental Models	Doses	Results	Target Molecules	References
Antitumor activity	Chikusetsu-saponin IV and V	HepG2 cancer cell	37.5, 70, 150, 300, and 600 μ M	Shown a potent effect on promoting cell apoptosis in HepG2 cells	($\uparrow$) Caspase-3, Caspase-9, Bax, p21, p53, $\downarrow$) Bcl-2	Zuo et al. (2022)
	Polysaccharides from the rhizomes of <i>P. japonicus</i>	Male Kunming mice	30 and 100 mg/kg, inject	Had antitumor immunostimulatory activity	($\uparrow$) T cells, NK cells, $\downarrow$) IL-4, IL-10	Shu et al. (2018)
Other activity	Chikusetsu-saponin IVa methyl ester	A2780 cell and HEY cell	4, 10, and 20 μ M	Inhibited the migration and invasion of human ovarian cancer cells	($\uparrow$) Bax, $\downarrow$) Cyclin D1, CDK2, CDK6, Bcl-2	Chen et al. (2016)
	Saponins from <i>P. japonicus</i>	Male C57BL/6J mice (8-week-old)	15 and 45 mg/kg, orally for 6 weeks	Alleviated renal ectopic fat deposition to protect renal function in diabetic mice	$\downarrow$) TC, TG, BUN	Wang, T. T. et al. (2023)
		Sprague-Dawley rat (18-month-old)	10 and 60 mg/kg, gavage for 6 months	Ameliorated age-related renal fibrosis	($\uparrow$) MMP2 MMP9, $\downarrow$) α -SMA, TIMP1, TGF- β , Smad2, TNF- α , IL-1 β	Gao et al. (2021)
		DBA 1/J mice	50 and 150 mg/kg, gavage for 10 days	Relieved the symptoms of CIA mice	$\downarrow$) VEGFA, HIF-1 α , IL-1 β , il-17A	Guo et al. (2020)
	Chikusetsusaponin IVa	DBA 1/J mice (6–8-week-old)	50 and 100 mg/kg	Inhibited inflammation and bone destruction in CIA mice	$\downarrow$) STAT3, JAK, IFN- γ , IL-1 β	Guo, X. et al. (2021)

Note: LC3B, microtubule-associated protein light chain 3; Atg5, autophagy-related protein 5; p62, sequestosome 1; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NF- κ B, nuclear factor kappa B; SOD, superoxide dismutase; SIRT1, silent information regulator 1; FOXO3a, forkhead box transcription factor 3a; LC3II, light chain 3-II; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, NOD-like receptor thermal protein domain associated protein 3; Caspase, cysteinyl aspartate specific proteinase; IL-1 β , interleukin-1 β ; ERK, extracellular regulated protein kinases; AMPK, AMP-activated protein kinase; GSK-3 β , glycogen synthase kinase-3 β ; PSD95, postsynaptic density protein-95; PGC-1 α , peroxisome proliferators-activated receptor- γ coactivator-1 α ; MAPK, mitogen-activated protein kinase; ULK, Unc51-like autophagy activating kinase 1; AKT, protein kinase B; ALT, alanine transaminase; AST, aspartate transaminase; TNF- α , tumor necrosis factor alpha; HMGB1, high mobility group protein 1; GRP78, glucose-regulated protein 78; TIMP, tissue inhibitor of metalloproteinase; ATF4, recombinant activating transcription factor 4; FSI, fasting insulin; FBG, fasting blood sugar; CPT-1, carnitine palmitoyl transferase-1; PPAR γ , peroxisome proliferator-activated receptor- γ ; TGF- β , transforming growth factor- β ; IL-10, interleukin-10; CDK2, cyclin dependent kinase; BUN, blood urea nitrogen; MMP, matrix metalloprotein; VEGFA, vascular endothelial growth factor A; HIF-1 α , hypoxia inducible factor-1 α ; CIA, collagen-induced arthritis; STAT3, signal transducers and activators of transcription 3; JAK, Janus kinase.

activation of the SIRT1/extracellular regulated protein kinases (ERK)1/2 pathway and inhibition of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3)/cysteineyl aspartate specific proteinase (caspase)-1 pathway (Fang et al., 2017; Shao et al., 2020). In STZ-induced diabetic rats, Chikusetsusaponin IVa can also prevent cerebral ischemia-reperfusion (I/R) injury via phosphorylating glycogen synthase kinase-3 β (GSK-3 β) through the APN-LKB1 pathway and AMP-activated protein kinase (AMPK) (Duan et al., 2016). Another active component of SPJ is Chikusetsusaponin V, which has been found to alleviate cerebral I/R injury through attenuating oxidative stress and mitochondrial damage, enhancing the deacetylation of peroxisome proliferators-activated receptor- γ coactivator-1 α (PGC-1 α), and activating AMPK and SIRT-1 (Zhang et al., 2021). SPJ could alleviate the neurological impairment caused by experimental autoimmune encephalomyelitis. The mechanism could be associated with modulation of the gut microbiota and nuclear factor kappa B (NF- κ B) pathway (Wang, J. et al., 2023). In addition, SPJ can prevent cognitive deficits and depressive-like behaviors induced by a high-fat diet (HFD) by inhibiting the NLRP3 inflammasome, which increases AMPA receptor expression and influences the CaMKII-CREB pathway (Wang et al., 2021).

Effects on Myocardial Injury

Several studies have found that *P. japonicus* has protective effects on myocardial injury. SPJ can improve myocardial ischemia injury and attenuate myocardial apoptosis through multiple signaling pathways, including NF- κ B, SIRT1, and MAPK. SPJ decreased the serum TNF- α and MCP-1 levels, increased the Bcl-2/Bax expression ratio, and inhibited NF- κ B p65 expression, ERK1/2, and p38 MAPK, and enhanced the SIRT1 protein expression (Wei and Zhang et al., 2014). SPJ can also maintain oxidative and antioxidative balance through Nrf2 pathway (Wei and Yuan et al., 2014), eventually alleviating cardiac cell death and myocardial ischemia injury (He et al., 2012). In naturally aging rats, SPJ can improve cardiac injury through enhancing autophagy and activating AMPK pathway (Huang et al., 2023). Additionally, Chikusetsusaponin IVa alleviated isoprenaline resulted in myocardial fibrosis mediated by up-regulation of p-AMPK and inhibition of p-mTOR, thereby decreasing the phosphorylated ULK1 757 and enhancing autophagy (Wang et al., 2019).

Effects on the Liver Injury

SPJ has been proven to exert protective effects on liver injury of different models through some important pathways such as anti-inflammation, antioxidation, and regulation of endoplasmic reticulum stress (ERS). It was found that SPJ prevented alcohol-induced liver damage by preventing Kupffer cell activation and decreasing toll-like receptor 4 (TLR4) expression, subsequently alleviating ROS production

and inflammatory insult (Yuan et al., 2013). Chikusetsusaponin V can decrease the lipopolysaccharide (LPS)-induced production of inflammatory cytokines by inhibiting the MAPK/NF- κ B pathway, ultimately improving liver injury (Dai et al., 2016). In addition to regulating the neutrophil extracellular traps, Chikusetsusaponin V also suppresses the high mobility group protein 1 (HMGB1) release and Caspase-1 activation, thereby reducing the neutrophils recruitment and the inflammation as well as the mitochondrial oxidative stress, which contributes to improving the liver damage caused by acetaminophen (Liu et al., 2021).

SPJ also protected liver injury through antioxidant effects. SPJ can directly scavenge oxygen free radicals and upregulate the expression of antioxidation enzymes superoxide dismutase (SOD), Cat, GPX, etc., thereby attenuating alcohol-induced liver injury (Li et al., 2010). SPJ enhanced intracellular antioxidant capacity through regulating protein kinase B (AKT)/GSK-3 β /Nrf2 signaling pathway, thus ameliorating CCL₄-provoked hepatic fibrosis in mice (Dai et al., 2021). Moreover, *P. japonicus* modulates ERS to attenuate hepatic fibrosis by decreasing glucose-regulated protein 78 (GRP78) and CHOP expression (Yuan et al., 2018).

Effects on the Intestine Injury

Recent studies indicate that *P. japonicus* may be an effective treatment for intestinal diseases. SPJ can improve intestinal pathology by regulating the intestinal tight junction barrier and ERS in aged rats. SPJ can downregulate GRP78 and UPR^{ER} alterations, contributing to the myenteric plexus neurons' recovery in aged rats (Dun et al., 2019; Guo, Y. et al., 2021). Additionally, SPJ can remarkably modulate the damage of intestinal epithelial tight junction by upregulating the expression of claudin-1 and occludin, and its mechanism might include the reduction of inflammation, downregulation of NF- κ B, and inactivation of MAPK (Dun et al., 2018).

Effects on the Metabolic System

Research has shown that the ethanolic extract from the roots of *P. japonicus* mainly inhibited α -glucosidase activity (Chan et al., 2010). Six SPJ including Chikusetsusaponin IV, Chikusetsusaponin IVa, Chikusetsusaponin V, Notoginsenoside R1, Ginsenoside Rb1, and Ginsenoside Rd could exhibit α -glucosidase inhibitory effect using a novel assay (Li, S. et al., 2015). Recently, more attention has been paid to Chikusetsusaponin IVa among the above six saponins. It was reported that Chikusetsusaponin IVa can decrease blood glucose levels and increase serum insulin levels in type 2 diabetes mellitus (T2DM) rats (Cui et al., 2015). Chikusetsusaponin IVa has also been proven to decrease the levels of low-density lipoprotein-cholesterol (LDL-C), free fatty acid (FFA), and total cholesterol (TC) in T2DM rats (Li, Y. et al., 2015).

Effects on the Adipose Tissue

Numerous studies have confirmed the effects of *P. japonicus* on adipose tissue. For example, SPJ exerts an antiobesity effect in mice treated with HFD, which is possibly mediated by preventing uptake of dietary fat from the intestines by inhibiting the activity of pancreatic lipase (Han et al., 2005). Hu et al. reported that SPJ could ameliorate obesity and reduce adipose tissue fibrosis via activating peroxisome proliferator-activated receptor- γ (PPAR γ)/PGC-1 α and suppressing transforming growth factor- β 1 (TGF β 1)/Smad2 pathway (Hu et al., 2022). Furthermore, Chikusetsusaponin V significantly alleviated HFD-induced overweight (Qiu et al., 2021). Meanwhile, Chikusetsusaponin IVa inhibited NLRP3 inflammasome and NF- κ B signaling pathway, thereby improving HFD-induced adipose tissue inflammation in mice (Yuan et al., 2017).

Effects on Tumor Cachexia

There is growing evidence that *P. japonicus* can show antitumor activity and improve tumor cachexia in various types of tumor models. Zuo reported that Chikusetsusaponin IV and V promoted HepG2 apoptosis through the p53-mediated apoptosis pathway (Zuo et al., 2022). Also, Shu

reported that polysaccharides isolated from the rhizomes of *P. japonicus* (PSPJ) have antitumor immunostimulatory activity, specifically as follows: PSPJ increased spleen/thymus indexes and splenocyte proliferation induced by ConA/LPS while reduced CD4⁺T cells of mice harboring H22 hepatoma cells. PSPJ decreased the production of immunosuppressive factors in tumor-associated macrophages (Shu et al., 2018). Furthermore, Chikusetsusaponin IVa methyl ester inhibits ovarian cancer cell proliferation, causes cell cycle arrest, promotes apoptosis, as well as inhibits invasion and migration (Chen et al., 2016).

Other Effects

Besides the biological activities described above, *P. japonicus* was reported to have some other pharmacological activities. Wang et al. reported that *P. japonicus* prevented renal cell apoptosis through the Bcl-2/caspase 3 pathway and attenuated renal injury in diabetic mice (Wang, T. T. et al., 2023). SPJ also ameliorated age-related renal fibrosis through inhibiting NF- κ B and TGF- β 1/Smad pathways and enhancing Nrf2 signaling pathway (Gao et al., 2021). Moreover, *P. japonicus* has effects on rheumatoid arthritis via anti-inflammatory and antiangiogenic biological properties. SPJ was reported to modulate the hypoxia inducible factor-1 α (HIF-1) or vascular

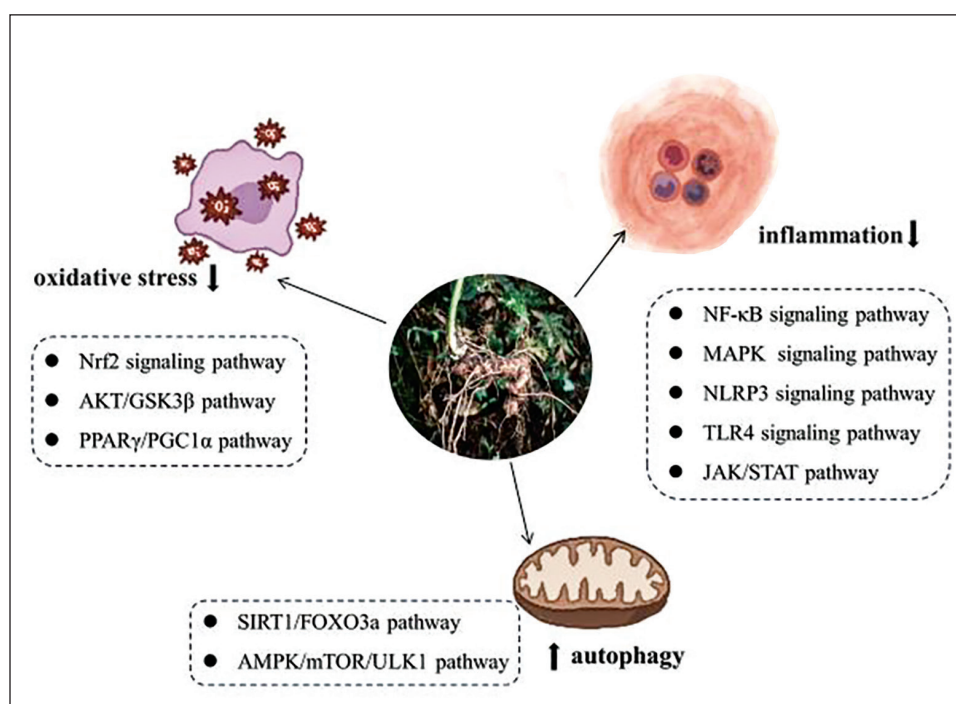


Figure 4. The Mechanisms and Pathways Underlying the Major Pharmacological Activities of *P. japonicus*.

Note: Nrf2, nuclear factor erythroid 2-related factor 2; AKT, protein kinase B; GSK-3 β , glycogen synthase kinase-3 β ; PPAR γ , peroxisome proliferator-activated receptor- γ ; PGC-1 α , peroxisome proliferators-activated receptor- γ coactivator-1 α ; NF- κ B, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; NLRP3, NOD-like receptor thermal protein domain associated protein 3; TLR4, toll-like receptor 4; JAK, Janus kinase; STAT, signal transducers and activators of transcription; SIRT1, silent information regulator 1; FOXO3a, forkhead box transcription factor 3a; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; ULK1, unc-51-like kinase 1.

endothelial growth factor (VEGF) pathways via inhibiting signal transducers and activators of transcription 3 (STAT3) and non-receptor tyrosine kinase, which inhibited angiogenesis and inflammation, and significantly reduced the arthritis indices in collagen-induced arthritis (CIA) mice (Guo et al., 2020). Guo et al. also reported that Chikusetsusaponin IVa attenuated bone destruction and inflammation mediated by Janus kinase (JAK)/STAT pathway in CIA mice, contributing to the clinical treatment of rheumatoid arthritis (Guo, X. et al., 2021).

Conclusion

In this article, we have summarized the botany, phytochemistry, and pharmacological effects of *P. japonicus*. Substantial evidence has shown that the total saponins are the major active ingredient of *P. japonicus*, which have a long history in traditional Chinese medicine because of possessing the functions of dispelling blood stasis and hemostasis, relieving swelling and pain, eliminating phlegm and relieving cough, tonifying, and strength. Mounting studies have demonstrated that *P. japonicus* exhibits extensive pharmacological activities through multiple signal pathways (Figure 4), and therefore shows extensive protective effects on the central nervous system, cardio-cerebrovascular system, and digestive system. But more clinical trial supports are needed to further verify these pharmacological actions of *P. japonicus*. Meanwhile, the available data on the chemical composition of the various parts of *P. japonicus* and their wide range of pharmacological properties are scarce, which makes it more attractive to study it in depth.

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Author Contributions

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Ethical Approval and Informed Consent

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References

- Cai, P., & Xiao, Z. Y. (1984). Studies on the chemical constituents of *Panax japonicus* (II). *Chinese Herbal Medicines*, 15(6), 1–6.
- Cai, P., Xiao, Z. Y., & Wei, J. X. (1982). Studies on the chemical constituents of *Panax japonicus* [First report]. *Chinese Herbal Medicines*, 13(3), 1–2.
- Chan, H.-H., Sun, H.-D., Reddy, M. V. B., & Wu, T.-S. (2010). Potent alpha-glucosidase inhibitors from the roots of *Panax japonicus* C.A. Meyer var. major. *Phytochemistry*, 71(11–12), 1360–1364. <https://doi.org/10.1016/j.phytochem.2010.04.013>
- Chen, J. L., Meng, F. Y., Wang, Z. Z., Zhang, H., Zhu, H. L., Zhao, B. L., Liu, J. P., Ping-Ya, L. I., & University, J. (2015). Content determination of total ginsenosides and 19 monomer ginsenosides or aglycones in tablets of *Panax ginseng* C.A. Meyer cv. silvatica. *Journal of Ginseng Research*, 27(4), 2–5.
- Chen, X., Wu, Q.-S., Meng, F.-C., Tang, Z.-H., Chen, X., Lin, L.-G., Chen, P., Qiang, W.-A., Wang, Y.-T., Zhang, Q.-W., & Lu, J.-J. (2016). Chikusetsusaponin IVa methyl ester induces G1 cell cycle arrest, triggers apoptosis and inhibits migration and invasion in ovarian cancer cells. *Phytomedicine*, 23(13), 1555–1565. <https://doi.org/10.1016/j.phymed.2016.09.002>
- China Pharmacopoeia Commission. (2020). *Chinese pharmacopoeia*. China Medical Science Press.
- College of Traditional Chinese Medicine of Nanjing Pharmaceutical University. (1976). *Chinese herbal medicines-mid*. Jiangsu People's Publishing House.
- Cui, J., Xi, M.-M., Li, Y.-W., Duan, J.-L., Wang, L., Weng, Y., Jia, N., Cao, S.-S., Li, R.-L., Wang, C., Zhao, C., Wu, Y., & Wen, A.-D. (2015). Insulinotropic effect of Chikusetsu saponin IVa in diabetic rats and pancreatic beta-cells. *Journal of Ethnopharmacology*, 164, 334–339. <https://doi.org/10.1016/j.jep.2015.02.032>
- Dai, C., Yusuf, A., Sun, H., Shu, G., & Deng, X. (2021). A characterized saponin extract of *Panax japonicus* suppresses hepatocyte EMT and HSC activation in vitro and CCl4-provoked liver fibrosis in mice: Roles of its modulatory effects on the Akt/GSK3 β /Nrf2 cascade. *Phytomedicine*, 93, 153746. <https://doi.org/10.1016/j.phymed.2021.153746>
- Dai, Y. W., Zhang, C. C., Zhao, H. X., Wan, J. Z., Deng, L. L., Zhou, Z. Y., Dun, Y. Y., Liu, C. Q., Yuan, D., & Wang, T. (2016). Chikusetsusaponin V attenuates lipopolysaccharide-induced liver injury in mice. *Immunopharmacology and Immunotoxicology*, 38(3), 167–174. <https://doi.org/10.3109/08923973.2016.1153109>
- Deng, L.-L., Yuan, D., Zhou, Z.-Y., Wan, J.-Z., Zhang, C.-C., Liu, C.-Q., Dun, Y.-Y., Zhao, H.-X., Zhao, B., Yang, Y.-J., & Wang, T. (2017). Saponins from *Panax japonicus* attenuate age-related neuroinflammation via regulation of the mitogen-activated protein kinase and nuclear factor kappa B signaling pathways.

- Neural Regeneration Research*, 12(11), 1877–1884. <https://doi.org/10.4103/1673-5374.219047>
- Duan, J., Yin, Y., Cui, J., Yan, J., Zhu, Y., Guan, Y., Wei, G., Weng, Y., Wu, X., Guo, C., Wang, Y., Xi, M., & Wen, A. (2016). Chikusetsu saponin IVa ameliorates cerebral ischemia reperfusion injury in diabetic mice via adiponectin-mediated AMPK/GSK-3 β pathway in vivo and in vitro. *Molecular Neurobiology*, 53(1), 728–743. <https://doi.org/10.1007/s12035-014-9033-x>
- Dun, Y. Y., & Yuan, D. (2006). Research progress on chemical constituents of *Panax japonicus*. *Lishizhen Medicine and Materia Medica Research*, 17(10), 3.
- Dun, Y., Cheng, Z., Liu, J., Guo, Y., He, Y., Xiong, Z., Yuan, D., & Zhang, C. (2019). Distinct expression patterns of aging effects on the UPRER signaling pathway in rat colon and regulatory role of saponins from *Panax japonicus*. *International Journal of Clinical and Experimental Pathology*, 12(9), 3279–3289.
- Dun, Y., Liu, M., Chen, J., Peng, D., Zhao, H., Zhou, Z., Wang, T., Liu, C., Guo, Y., Zhang, C., & Yuan, D. (2018). Regulatory effects of saponins from *Panax japonicus* on colonic epithelial tight junctions in aging rats. *Journal of Ginseng Research*, 42(1), 50–56. <https://doi.org/10.1016/j.jgr.2016.12.011>
- Fang, X., Han, Q., Li, S., Zhao, Y., & Luo, A. (2017). Chikusetsu saponin IVa attenuates isoflurane-induced neurotoxicity and cognitive deficits via SIRT1/ERK1/2 in developmental rats. *American Journal of Translational Research*, 9(9), 4288–4299.
- Gao, Y., Yuan, D., Gai, L., Wu, X., Shi, Y., He, Y., Liu, C., Zhang, C., Zhou, G., & Yuan, C. (2021). Saponins from *Panax japonicus* ameliorate age-related renal fibrosis by inhibition of inflammation mediated by NF- κ B and TGF- β 1/Smad signaling and suppression of oxidative stress via activation of Nrf2-ARE signaling. *Journal of Ginseng Research*, 45(3), 408–419. <https://doi.org/10.1016/j.jgr.2020.08.005>
- Guo, Y., Cheng, Z., Liu, J., He, Y., Xiong, Z., Yuan, D., Dun, Y., & Zhang, C. (2021). Protective effects of saponins from *Panax japonicus* on neurons of the colon myenteric plexus in aging rats through reduction of alpha-synuclein through endoplasmic reticulum stress. *Geriatrics and Gerontology International*, 21(1), 85–93. <https://doi.org/10.1111/ggi.13882>
- Guo, X., Ji, J., Jose Kumar Sreena, G. S., Hou, X., Luo, Y., Fu, X., Mei, Z., & Feng, Z. (2020). Computational prediction of antiangiogenesis synergistic mechanisms of total saponins of *Panax japonicus* against rheumatoid arthritis. *Frontiers in Pharmacology*, 11, 566129. <https://doi.org/10.3389/fphar.2020.566129>
- Guo, X., Ji, J., Zhang, J., Hou, X., Fu, X., Luo, Y., Mei, Z., & Feng, Z. (2021). Anti-inflammatory and osteoprotective effects of Chikusetsusaponin IVa on rheumatoid arthritis via the JAK/STAT signaling pathway. *Phytomedicine*, 93, 153801. <https://doi.org/10.1016/j.phymed.2021.153801>
- Han, L.-K., Zheng, Y.-N., Yoshikawa, M., Okuda, H., & Kimura, Y. (2005). Anti-obesity effects of chikusetsusaponins isolated from *Panax japonicus* rhizomes. *BMC Complementary and Alternative Medicine*, 5(1), 9. <https://doi.org/10.1186/1472-6882-5-9>
- He, Y.-M., Ai, K., He, C.-X., Zhang, C.-C., Yuan, D., & Cai, S.-J. (2019). Triterpene saponins in *Panax japonicus* and their ^{13}C -NMR spectroscopic characteristics. *Zhongguo Zhong Yao Za Zhi*, 44(2), 249–260. <https://doi.org/10.19540/j.cnki.cjcm.20181101.016>
- He, H., Xu, J., Xu, Y., Zhang, C., Wang, H., He, Y., Wang, T., & Yuan, D. (2012). Cardioprotective effects of saponins from *Panax japonicus* on acute myocardial ischemia against oxidative stress-triggered damage and cardiac cell death in rats. *Journal of Ethnopharmacology*, 140(1), 73–82. <https://doi.org/10.1016/j.jep.2011.12.024>
- Hu, X. Q., Sun, A., Chen, H. J., Yan, X. Y., Ding, F., Zheng, P., Li, Z., & Yan, Y.-E. (2022). Saponins from *Panax japonicus* alleviate adipose tissue fibrosis and metabolic dysfunction in high-fat-diet-induced obese mice. *Biomarkers*, 27(8), 784–794. <https://doi.org/10.1080/1354750X.2022.2122566>
- Huang, H., Wang, T., Wang, L., Huang, Y., Li, W., Wang, J., Hu, Y., & Zhou, Z. (2023). Saponins of *Panax japonicus* ameliorates cardiac aging phenotype in aging rats by enhancing basal autophagy through AMPK/mTOR/ULK1 pathway. *Experimental Gerontology*, 182, 112305. <https://doi.org/10.1016/j.exger.2023.112305>
- Institute of the Academy of Medical Sciences of China. (1979). *Chinese medicine record*. People's Medical Publishing House.
- Jia, M. R., & Zhang, Y. (2016). *Dictionary of Chinese ethnic medicine*. China Medical Science Press.
- Kondo, N., Shoji, J., Nagumo, N., & Komatsu, N. (1969). Studies on the constituents of *Panax japonicus* rhizoma. II. The structure of chikusetsusaponin IV and some observations on the structural relationship with araloside A. *Yakugaku Zasshi*, 89(6), 846–850. https://doi.org/10.1248/yakushi1947.89.6_846
- Li, Y.-G., Ji, D.-F., Zhong, S., Shi, L.-G., Hu, G.-Y., & Chen, S. (2010). Saponins from *Panax japonicus* protect against alcohol-induced hepatic injury in mice by up-regulating the expression of GPX3, SOD1 and SOD3. *Alcohol and Alcoholism*, 45(4), 320–331. <https://doi.org/10.1093/alcalc/agq034>
- Li, S., Tang, Y., Liu, C., & Zhang, Y. (2015). Development of a method to screen and isolate potential alpha-glucosidase inhibitors from *Panax japonicus* C.A. Meyer by ultrafiltration, liquid chromatography, and counter-current chromatography. *Journal of Separation Science*, 38(12), 2014–2023. <https://doi.org/10.1002/jssc.201500064>
- Li, Y., Zhang, T., Cui, J., Jia, N., Wu, Y., Xi, M., & Wen, A. (2015). Chikusetsu saponin IVa regulates glucose uptake and fatty acid oxidation: Implications in antihyperglycemic and hypolipidemic effects. *The Journal of Pharmacy and Pharmacology*, 67(7), 997–1007. <https://doi.org/10.1111/jphp.12392>
- Lin, T.-D., & Shoji, J. (1979). Constituents of *panax japonicus* rhizoma. VI The structure of Chikusetsu-saponin II, IVC. *Journal of the Chinese Chemical Society*, 26(1), 29–35. <https://doi.org/10.1002/jccs.197900007>
- Lin, T., Kondo, N., & Shoji, J. (1976). Studies on the constituents of *panax japonicus* rhizoma. V. The structures of chikusetsusaponin I, Ia, Ib, IVa and glycoside. *Chemical and Pharmaceutical Bulletin*, 24(2), 253–261. <https://doi.org/10.1248/cpb.24.253>
- Lin, X. M., Xie, L. L., You, J. W., Guo, J., Liao, C. L., & Liu, H. H. (2007). A textual research on the name and origin of *Panax japonicus*. *Journal of Chinese Medicinal Materials*, 30(6), 2.
- Liu, J., Jiang, M., Jin, Q., Wu, Y.-L., Cui, Z.-Y., Cui, B.-W., Shang, Y., Zhan, Z.-Y., Lin, Y.-C., Jiao, J.-Y., Piao, M.-H., Zhang, Z.-H., Sun, R.-H., Nan, J.-X., & Lian, L.-H. (2021). Modulation of HMGB1 release in APAP-induced liver injury: A possible strategy of chikusetsusaponin V targeting NETs

- formation. *Frontiers in Pharmacology*, 12, 723881. <https://doi.org/10.3389/fphar.2021.723881>
- Liu, Y., Zhao, J., Chen, Y., Li, W., Li, B., Jian, Y., Sabir, G., Cheng, S., Tuo, Q., Khan, I., & Wang, W. (2016). Polyacetylenic oleanane-type triterpene saponins from the roots of *Panax japonicus*. *Journal of Natural Products*, 79(12), 3079–3085. <https://doi.org/10.1021/acs.jnatprod.6b00748>
- Morita, T., Kasai, R., Kohda, H., Tanaka, O., Zhou, J., & Yang, T. (1983). Chemical and morphological study on Chinese *Panax japonicus* C.A. Meyer (Zhuji-Shen). *Chemical and Pharmaceutical Bulletin*, 31(9), 3205–3209. <https://doi.org/10.1248/cpb.31.3205>
- Morita, T., Tanaka, O., & Kohda, H. (1985). Saponin composition of rhizomes of *Panax japonicus* collected in South Kyushu, Japan, and its significance in oriental traditional medicine. *Chemical & Pharmaceutical Bulletin*, 33(9), 3852–3858. <https://doi.org/10.1248/cpb.33.3852>
- Ohtani, K., Hatono, S., Mizutani, K., Kasai, R., & Tanaka, O. (1989). Reticuloendothelial system-activating polysaccharides from rhizomes of *Panax japonicus*. I. Tochibanan-A and -B. *Chemical & Pharmaceutical Bulletin*, 37(10), 2587–2591. <https://doi.org/10.1248/cpb.37.2587>
- Pi, X.-J., Zhao, Q.-Q., Wang, J.-X., Zhang, X.-L., Yuan, D., Hu, S.-S., He, Y.-M., Zhang, C.-C., Zhou, Z.-Y., & Wang, T. (2021). Saponins from *Panax japonicus* attenuate cognitive impairment in ageing rats through regulating microglial polarisation and autophagy. *Pharmaceutical Biology*, 59(1), 1117–1125. <https://doi.org/10.1080/13880209.2021.1961824>
- Qiu, Y., Yu, H., Hu, Y., Guo, S., Lei, X., Qin, Y., Jian, Y., Li, B., Liu, L., Peng, C., Wang, A., & Wang, W. (2021). Transcriptomic and metabolomic profiling reveal the anti-obesity effects of Chikusetsusaponin V, a compound extracted from *Panax japonicus*. *The Journal of Pharmacy and Pharmacology*, 73(1), 60–69. <https://doi.org/10.1093/jpp/rgaa029>
- Shao, A., Fei, J., Feng, S., & Weng, J. (2020). Chikusetsu saponin IVa alleviated sevoflurane-induced neuroinflammation and cognitive impairment by blocking NLRP3/caspase-1 pathway. *Pharmacological Reports*, 72(4), 833–845. <https://doi.org/10.1007/s43440-020-00078-2>
- Shu, G., Jiang, S., Mu, J., Yu, H., Duan, H., & Deng, X. (2018). Antitumor immunostimulatory activity of polysaccharides from *Panax japonicus* C.A. Mey: Roles of their effects on CD4⁺ T cells and tumor associated macrophages. *International Journal of Biological Macromolecules*, 111, 430–439. <https://doi.org/10.1016/j.ijbiomac.2018.01.011>
- Song, L. R. (1999). *Zhonghua Bencao*. Shanghai Science and Technology Press.
- Wan, J.-Z., Wang, R., Zhou, Z.-Y., Deng, L.-L., Zhang, C.-C., Liu, C.-Q., Zhao, H.-X., Yuan, C.-F., He, Y.-M., Dun, Y.-Y., Yuan, D., & Wang, T. (2020). Saponins of *Panax japonicus* Confer neuroprotection against brain aging through mitochondrial related oxidative stress and autophagy in rats. *Current Pharmaceutical Biotechnology*, 21(8), 667–680. <https://doi.org/10.2174/1389201021666191216114815>
- Wang, D. (2020). Study on saponins from panacis japonici rhizoma. *Food and Drug*, 22(01), 40–42.
- Wang, T., Di, G., Yang, L., Dun, Y., Sun, Z., Wan, J., Peng, B., Liu, C., Xiong, G., Zhang, C., & Yuan, D. (2015). Saponins from *Panax japonicus* attenuate D-galactose-induced cognitive impairment through its anti-oxidative and anti-apoptotic effects in rats. *The Journal of Pharmacy and Pharmacology*, 67(9), 1284–1296. <https://doi.org/10.1111/jphp.12413>
- Wang, J., He, L. Y., Wang, S. Y., Zhao, H., Chen, J., Dong, Y. X., Yasen, S., Wang, L., & Zou, H. Y. (2023). Therapeutic effect of the total saponin from *Panax japonicus* on experimental autoimmune encephalomyelitis by attenuating inflammation and regulating gut microbiota in mice. *Journal of Ethnopharmacology*, 315, 116681. <https://doi.org/10.1016/j.jep.2023.116681>
- Wang, T. T., Huang, X. T., Zhai, K. F., Yu, J. L., Li, J. X., Duan, H., Liu, J. H., Lu, Z. J., Guo, J., & Li, F. (2023). Integrating metabolomics and network pharmacology to investigate *Panax japonicus* prevents kidney injury in HFD/STZ-induced diabetic mice. *Journal of Ethnopharmacology*, 303, 115893. <https://doi.org/10.1016/j.jep.2022.115893>
- Wang, J., Wang, D., Zhou, Z., Zhang, X., Zhang, C., He, Y., Liu, C., Yuan, C., Yuan, D., & Wang, T. (2021). Saponins from *Panax japonicus* alleviate HFD-induced impaired behaviors through inhibiting NLRP3 inflammasome to upregulate AMPA receptors. *Neurochemistry International*, 148, 105098. <https://doi.org/10.1016/j.neuint.2021.105098>
- Wang, L., Yuan, D., Zheng, J., Wu, X., Wang, J., Liu, X., He, Y., Zhang, C., Liu, C., Wang, T., & Zhou, Z. (2019). Chikusetsu saponin IVa attenuates isoprenaline-induced myocardial fibrosis in mice through activation autophagy mediated by AMPK/mTOR/ULK1 signaling. *Phytomedicine*, 58, 152764. <https://doi.org/10.1016/j.phymed.2018.11.024>
- Wei, N., Yuan, D., He, H. B., Xu, Y. Q., Zhang, C. C., Wang, T., Liu, C. Q., & Liu, G. Y. (2014). Saponins from *Panax japonicus* reduces myocardial infarction induced reactive oxygen species production and cardiomyocyte apoptosis via activation of the Nrf-2 pathway. *Advanced Materials Research*, 881–883, 339–346. <https://doi.org/10.4028/www.scientific.net/AMR.881-883.339>
- Wei, N., Zhang, C., He, H., Wang, T., Liu, Z., Liu, G., Sun, Z., Zhou, Z., Bai, C., & Yuan, D. (2014). Protective effect of saponins extract from *Panax japonicus* on myocardial infarction: Involvement of NF- κ B, Sirt1 and mitogen-activated protein kinase signalling pathways and inhibition of inflammation. *The Journal of Pharmacy and Pharmacology*, 66(11), 1641–1651. <https://doi.org/10.1111/jphp.12291>
- Wu, J. Z., & Yi, J. (1992). Comparative study on amino acids and Inorganic elements in four species of *Panax*. *Journal of Guiyang Medical College*, 17(3), 3.
- Xiang, D. (2009). Analysis for content and composition of amino acid in the *Panax japonicus*. *China Brewing*.
- Xu, F.-X., Yuan, C., Wan, J.-B., Yan, R., Hu, H., Li, S.-P., & Zhang, Q.-W. (2015). A novel strategy for rapid quantification of 20(S)-protopanaxatriol and 20(S)-protopanaxadiol saponins in *Panax notoginseng* P. *ginseng* and P. *quinquefolium*. *Natural Product Research*, 29(1), 46–52. <https://doi.org/10.1080/14786419.2014.957698>
- Yahara, S., Kasai, R., & Tanaka, O. (2008). New dammarane type saponins of leaves of *Panax japonicus* C.A. Meyer (1). Chikusetsusaponins L5, L9(a) and L10. *Chemical and Pharmaceutical Bulletin*, 25(8), 2041–2047.
- Yahara, S., Tanaka, O., & Nishioka, I. (1978). Dammarane type saponins of leaves of *Panax japonicus* C.A. Meyer. (2): Saponins of the specimens collected in Tottori-ken, Kyoto-shi,

- and Niigata-ken. *Chemical and Pharmaceutical Bulletin* 26 (10), 3010–3016.
- Yang, X., Wang, R., Zhang, S., Zhu, W., Tang, J., Liu, J., Chen, P., Zhang, D., Ye, W., & Zheng, Y. (2014). Polysaccharides from *Panax japonicus* C.A. Meyer and their antioxidant activities. *Carbohydrate Polymers*, 101, 386–391. <https://doi.org/10.1016/j.carbpol.2013.09.038>
- Yoshizaki, K., & Yahara, S. (2012a). New triterpenoid saponins from fruits specimens of *Panax japonicus* collected in Kumamoto and Miyazaki prefectures (1). *Chemical & Pharmaceutical Bulletin*, 60(3), 354–362. <https://doi.org/10.1248/cpb.60.354>
- Yoshizaki, K., & Yahara, S. (2012b). New triterpenoid saponins from leaves of *Panax japonicus* (3). Saponins of the specimens collected in Miyazaki Prefecture. *Natural Product Communications*, 7(4), 491–493. <https://doi.org/10.1177/1934578X1200700419>
- Yoshizaki, K., Devkota, H. P., & Yahara, S. (2013). Four new triterpenoid saponins from the leaves of *Panax japonicus* grown in southern Miyazaki Prefecture (4). *Chemical & Pharmaceutical Bulletin*, 61(3), 273–278. <https://doi.org/10.1248/cpb.c12-00794>
- Yoshizaki, K., Devkota, H. P., Fujino, H., & Yahara, S. (2013). Saponins composition of rhizomes, taproots, and lateral roots of Satsuma-ninjin (*Panax japonicus*). *Chemical & Pharmaceutical Bulletin*, 61(3), 344–350. <https://doi.org/10.1248/cpb.c12-00764>
- Yoshizaki, K., Murakami, M., Fujino, H., Yoshida, N., & Yahara, S. (2012). New triterpenoid saponins from fruit specimens of *Panax japonicus* collected in Toyama Prefecture and Hokkaido (2). *Chemical & Pharmaceutical Bulletin*, 60(6), 728–735. <https://doi.org/10.1248/cpb.60.728>
- Yuan, C., Liu, C., Wang, T., He, Y., Zhou, Z., Dun, Y., Zhao, H., Ren, D., Wang, J., Zhang, C., & Yuan, D. (2017). Chikusetsu saponin IVa ameliorates high fat diet-induced inflammation in adipose tissue of mice through inhibition of NLRP3 inflammasome activation and NF- κ B signaling. *Oncotarget*, 8(19), 31023–31040. <https://doi.org/10.18632/oncotarget.16052>
- Yuan, D., Wan, J. Z., Dai, Y. W., Zhang, C. C., & Wang, T. (2013). Hepatoprotective effects of saponins from *Panax japonicus* against alcohol-induced liver injury via inhibition of toll-like receptor-4 mediated signaling pathway. *Acta Pharmacologica Sinica*, 34, 96–97.
- Yuan, D., Xiang, T., Huo, Y., Liu, C., Wang, T., Zhou, Z., Dun, Y., Zhao, H., & Zhang, C. (2018). Preventive effects of total saponins of *Panax japonicus* on fatty liver fibrosis in mice. *Archives of Medical Science*, 14(2), 396–406. <https://doi.org/10.5114/aoms.2016.63260>
- Yuan, D., Zhang, C. C., Wang, T., Cai, S. J., & Liao, C. L. (2015). *Basic and applied research on rhizoma Panax japonicus*. Science Press.
- Zhang, T., Li, Z., Qin, Z., Cao, Y., Shan, T., Fang, Y., Tang, L., Jia, N., Jia, J., Jin, Z., Xu, T., & Li, Y. (2021). Neuroprotection of Chikusetsu saponin V on transient focal cerebral ischemia/reperfusion and the underlying mechanism. *Phytomedicine*, 84, 153516. <https://doi.org/10.1016/j.phymed.2021.153516>
- Zhao, H. X., Yuan, D., Yu-Min, H. E., Jiang, M. J., Jia, L. L., & Zhang, C. C. (2010). Quantitative determination of *Panax japonicus* polysaccharide by DNS method. *Science and Technology of Food Industry*, 6, 327–329.
- Zhou, M., Xu, M., Wang, D., Zhu, H.-T., Yang, C.-R., & Zhang, Y.-J. (2011). New dammarane-type saponins from the rhizomes of *Panax japonicus*. *Helvetica Chimica Acta*, 94(11), 2010–2019. <https://doi.org/10.1002/hlca.201100085>
- Zou, H., Zhao, H., Qiu, K., Cui, X., & Ping, Y. (2012). Study on saponins of *Panax japonicus* rhizome. *World Chinese Medicine*, 7, 65–66.
- Zou, K., Zhu, S., Meselhy, M. R., Tohda, C., Cai, S., & Komatsu, K. (2002). Dammarane-type saponins from *Panax japonicus* and their neurite outgrowth activity in SK-N-SH cells. *Journal of Natural Products*, 65(9), 1288–1292. <https://doi.org/10.1021/np0201117>
- Zou, K., Zhu, S., Tohda, C., Cai, S., & Komatsu, K. (2002). Dammarane-type triterpene saponins from *Panax japonicus*. *Journal of Natural Products*, 65(3), 346–351. <https://doi.org/10.1021/np010354j>
- Zuo, R., & Yuan, D. (2005). Research on chemical constituents and biological activities of rhizoma of *Panax japonicus*. *Lishizhen Medicine and Materia Medica Research*, 16, 838–841.
- Zuo, T., Zhang, Z., Jiang, P., Zhang, R., Ni, D., Yuan, Y., & Zhang, S. (2022). Characterization of chikusetsusaponin IV and V induced apoptosis in HepG2 cancer cells. *Molecular Biology Reports*, 49(6), 4247–4255. <https://doi.org/10.1007/s11033-022-07259-7>