REVIEW ARTICLE

A C G publications

Rec. Nat. Prod. X:X (2023) XX-XX

records of natural products

Phytochemical and Pharmacological Studies of Natural Saponins from *Platycodon grandiflorum*

Xinying Du [1,2], Huijiao Li [1,2], Runxiang Zhai [1,2], Kuo Xu [1,2,*] and Xianjun Fu [1,2,*]

[1] *Marine Traditional Chinese Medicine Research Center, Key Laboratory of Marine Traditional Chinese Medicine in Shandong Universities, Shandong Engineering and Technology Research Center on Omics of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China*

[2] *Qingdao Academy of Traditional Chinese Medicine Shandong University of TCM, Qingdao Key Laboratory of Research in Marine Traditional Chinese Medicine, Qingdao Key Technology Innovation Center of Marine Traditional Chinese Medicine's Deep Development and Industrialization, Qingdao 266114, China*

(Received Month Day, 2023; Revised Month Day, 2023; Accepted Month Day, 2023)

Abstract: *Platycodon grandiflorum* (Jacq.) A. DC is a perennial single-species herb of Campanulaceae, whose dried root is widely used to diffuse the lung, soothe the throat, dispel phlegm, and expel pus in Chinese traditional medicine with a long history. Besides, *P. grandiflorum* is also a homology of medicine and food approved by the Ministry of Health of China, and many related foods have come into market. It has been reported that the glycosides of pentacyclic triterpenoids, also known as saponins, are the main biological active constituents of *P. grandiflorus*. This present article offers a systematic review of newly reported saponins from *P. grandiflorus* over the past decade years covering the pieces of literature from the beginning of 2017 through the end of 2022 and describes their structural diversities and pharmacological studies. As far as knowledge, a total of 74 natural saponins and 131 references were updated and compiled in this review, which may be of interest to pharmacognosists and natural product chemists. The review provides new ideas for the development and utilization of platycodon and clinical application in the future.

Keywords: *Platycodon grandiflorum*; platycodin D; pharmacological activity; chemical constitution

1. Introduction

Platycodon grandiflorus (Jacq.) A. DC is the dried root of *Platycodon grandiflorum*, which belongs to perennial single species of herbs. It is first recorded in the "Shennong Herbal Classic" and is a widely used traditional Chinese medicine [1]. *P. grandiflorus* has the functions of diffusing the lung, soothing the throat, dispelling phlegm, and expelling pus, which is mainly used for the treatment of cough and phlegm, chest tightness, sore throat, dumb voice, and abscess of the lung [2]. Additionally, it has been discovered that *P. grandiflorus* also has a good therapeutic effect on

*Corresponding author: E-Mail: xukoworld@126.com (Kuo Xu); xianxiu@hotmail.com (Xianjun Fu)

The article was published by ACG Publications

http://www.acgpubs.org/journal/records-of-natural-products Month-Month 202x EISSN:1307-6167

DOI: http://doi.org/10.25135/rnp.18.17.06.108

Available online: X/X/202X

cardiovascular, diabetes, atherosclerosis, and other diseases [3]. *P. grandiflorum* is also a homology of medicine and food approved by the Ministry of Health of China [4]. The fresh roots of *P. grandiflorus* are widely used as edible vegetables in South Korea, North Korea, Japan, and Northeast China, so the demand for *P. grandiflorus* is very huge in East Asia [5]. The healthcare effects of *P. grandiflorus* are also the focus of attention [6].

In recent years, the phytochemical studies of *P. grandiflorus* have drawn considerable attention, due to their potent and wide range of pharmacological activities in the aspect of anti-tumor [7], anti-inflammatory [8], antioxidant [8], hypolipidemic [9], and anti-diabetic activities [10], etc. As early as the beginning of the 20th century, Japanese researchers studied the chemical constituents of *P. grandiflorus*. It has been previously reported that the glycosides of pentacyclic triterpenoids, also known as saponins, are the main biological active constituents of *P. grandiflorus* [4]. In addition to saponins, *P. grandiflorus* also contains flavonoids, fatty acids, sterols, vitamins, and a variety of essential trace elements for the human body [11]. Several excellent reviews on various aspects of constituents that are derived from *P. grandiflorus* have been published in the past decades [5, 12-13]. However, there is no work specifically aimed at pentacyclic triterpenoid saponins from the *P. grandiflorus*. As part of our ongoing investigations of biological compounds from *P. grandiflorus*, a detailed and comprehensive literature survey disclosed that the previously published structures might not be adequately represented. This review aimed to update the latest research progress on the phytochemical and pharmacological studies of natural saponins from *P. grandiflorum*.

Figure 1. (A) The plant of *P. grandifloras*. (B) The medicinal part of *P. grandifloras*. (C) The pickles of *P. grandifloras*.

2. Phytochemical Study

The literature survey disclosed that saponins of oleanane pentacyclic triterpene-type is the main component of *P. grandiflorus* [14]. Up to date, 75 different kinds of triterpenoid saponins with oleanolic acid mother nuclei have been isolated from *P. grandiflorus*. More precisely, these structures of triterpenoid saponins can be divided into five categories including platycodin genin (**1-28**), platyconic acid (**29-39**), polygalacic acid (**40-56**), platyconic acid lactone (**57-65**) and other types of triterpenoid(**67-75**) [15]. For these compounds, glycosylation positions are mainly located at positions C-3 and C-28, while the glycol groups mainlcontainns L-rhamnose, D-xylose, D-glucose, L-arabinose, and d-spinose, and their derivatives[16].

2.1. Platycodin genin-type saponins

Of all the five categories, Platycodin genins-type triterpenoids occupy the largest number in *P. grandiflorus*. These saponins have the characteristics that the parent nucleus is oleanolic acid, two hydroxymethyls (-CH_2OH) are located at C-4 position, and a total of five methyl at C-25, C26, C-27, C29, and C-30 positions, and a carbonyl at the C-28 position.

Compounds **1**-**8** were isolated and identified as eight Platycodin genin-type saponins by Ishii et al, of which compounds **2**, **3,** and **5** were reported for the first time. Notably, the O-acetyl groups at C-2 or C-3 positions of rhamnose in these three compounds are easily reversibly migrated [17]. Compounds **6**-**8** are three saponin methyl esters, the difference of which is the sugar moiety at C-4 position [18]. Compounds **9** and **26** are two new compounds first identified from *P. grandiflorus* based on spectroscopic and chemical evidence. There are two same CH_2OH moieties located at the

C-4 position of **9**, while a CH_3 and a CH_2OH groups at the C-4 position of **26** [19]. Compounds **10**, **11,** and **28** were purified and identified by He et al., of which **11** and **28** were reported for the first time. The biggest difference between these two new saponins is that **11** has two CH_2OH groups at C-4, while **28** possesses two OH groups at the same position [20]. Compounds **12** and **13** were first isolated and identified by Fu et al, of which monosaccharide was characterized as glucose alcohol acetate detected by gas chromatography [18]. Compound **14**, named as Deapio-platycoside E, is a disaccharide saponin with different sugar chains at the positions of C-4 and C-28 [22]. The structure of compound **15** is similar to that of **16**, which was first isolated by Choi et al. Their difference was that the C-3 substituent of **15** was Glc^3-Glc, while that of **16** was Glc^6-Glc [23,24]. Compounds **17**-**19** were identified as three new compounds purified by silica gel column. The C-3 position of **18** and **19** is linked to a glucuronic acid (-GlcA) and contains an O-acetyl group at the 2,3-position of the rhamnose unit [25]. Similarly, the rhamnose of compound **21** is also substituted by an O-acetyl group [26]. The structures of compounds **22** and **23** are the same, except for the positions of O-acetyl sugar moiety. Additionally, the C-28 position of compound **24** is a disaccharide, which is different from that of compound **25** [27,28]. Different from compounds **1**-**26**, both compounds **27** and **28** have two -OH groups attached to their C-4 position [29].

2.2. Platyconic acid-type saponins

There are only 10 Platyconic acid-type saponins isolated from *P. grandiflorus* (compounds **29**-**39**). These saponins have the characteristics that the parent nucleus is oleanolic acid, a COOR group, and a CH_2OH group are located at C-4 position, and a total of five methyl at the positions of C-25, C-26, C-27, C-29, and C-30, while two carbonyls at the positions of C-4 and C-28.

Compounds **29**–**31** were first isolated by Ishii et al. in 1981. The difference between compounds **29** and **30** is that the C-2 position of **29** was substituted by an H, but that of **30** is a CH_3, while the C-2 and C-28 positions of **31** were substituted by an H group and a CH_3 group, respectively [22]. Compounds **32**, **33**, **35,** and **36** were simultaneously isolated from *P. grandiflorus* by Choi et al for the first time [30]. The structures of **32** and **33** is almost the same, except the C-2 and C-28 of **32** substituted by a CH_3 group. The difference between compounds **35** and **36** is that the C-28 position of **35** is substituted by a COOH group, while that of 3**6** is replaced by a sugar group. Compounds **37**-**39** were first reported in 2010, of which **37** and **39**'s rhamnose moiety are acetylated [25].

2.3. Polygalacic acid-type saponins

To date, a total of 17 Polygalacic acid-type saponins have been isolated from *P. grandiflorus*. These saponins have the characteristics that the parent nucleus is oleanolic acid, a CH_3 group and a CH_2OH group are located at C-4 position, a total of six methyl groups at the positions of C-24, C-25, C-26, C-27, C-29, and C-30, while a carbonyl at the position of C-28.

This type of saponin was isolated from *P. grandiflorus* as early as 1978 (compounds **40**-**44**) [25]. Among them, the rhamnose moiety of **42**-**44** is acetylated, while those of the others are not. The structures of compounds **45** and **46** were the same except for the substituents at C-3 position, both of which were first isolated in 1981 [22]. As the characteristic constituent of *P. grandiflorus* in Chinese pharmacopeia, compound **47** (Platycoside D) is a disaccharide glycoLamside with seven sugar groups and is first isolated Nikaido et al [23]. Different from compound **47**, the C-3 position of compound **48** (Platycoside G3) is substituted by a disaccharide chain [21]. The structures of compounds **49**-**51** have the same structures except for the C-3 sugar chains [25]. Compound **52**, named 16-O-β-D-laminatedibiosyl Polygalacic acid, was characterized as a group and COOH group linked to the C-3 and C-28 position, respectively [31]. Different from compounds **51** and **52**, the rhamnose moiety of compound **53** is acetylated [32].

2.4. Platyconic acid lactone-type saponins

There are only 9 Platyconic acid lactone-type saponins isolated from *P. grandiflorus*. These saponins have the characteristics that the parent nucleus is oleanolic acid, -CH_2OH at C-4 position

and OH at C-2 position dehydrated to be a lactone structure, a total of five methyl at the positions of C-25, C-26, C-27, C-29, and C-30, while two carbonyls at the positions of C-23 and C-28.

Compound **57** was characterized as a -Glc group and CH_3 group linked to the C-3 and C-28 position, respectively, which was purified by silica gel chromatography [22]. Compounds **58**-**60** were first reported in 2006, and the main differences between them were the number of sugars at C-28 [33]. The structures of compounds **61**-**64** are very similar. Specifically, the difference between compounds **61** and **62** is that **61** has one more D-apiose at C-28 position than those of **62**, while compound **63** has one more D-apiose than that of compound **64** [30]. The structure of compound **65** was characterized by the disaccharide groups located at both C-3 and C-28 [29].

2.5. Other types of triterpenoids saponins

There are 10 saponins whose structures are difficult to be divided into any of the above four categories. Compounds **66** and **67** were first isolated from *P. grandiflorus* by Ma et al. in 2013. The difference between them was the sugar moiety (a Glc group or a Xyl group) located at C-22 position [34]. The structural feature of compounds **68** and **69** is the lactone ring formed by the COOH group at C-28 and an OH group at C-13 [35]. The main difference of compounds **70**-**72** was the substituent groups at C-4 position, while those of **73**-**75** were the substituent groups at C-3 and C-28 positions [36].

Table 1. Natural saponins isolated from *P. grandiflorus*.

NO.	Name	M.F.	Classification	R1	R2	Ref.
1	Platycodin C	$C_{59}H_{94}O_{29}$	platycodin genin	Glc	Ara^{2}-Rha(3-OAc)^{4}-Xyl^{3}-Api	[17]
2	Platycodin A	$C_{59}H_{94}O_{29}$	platycodin genin	Glc	Ara^{2}-Rha(2-OAc)^{4}-Xyl^{3}-Api	[17]
3	Platycodin D	$C_{57}H_{92}O_{28}$	platycodin genin	Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[17]
4	Platycodin D2	$C_{63}H_{102}O_{33}$	platycodin genin	Glc^{3}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[17]
5	2''-O-acetyl-platycodin D2	$C_{65}H_{104}O_{34}$	platycodin genin	Glc^{3}-Glc	Ara^{2}-Rha(2-OAc)^{4}-Xyl^{3}-Api	[18]
6	3-O-β-D-laminaribiosyl platycodigenin methyl ester	$C_{43}H_{70}O_{17}$	platycodin genin	Glc^{3}-Glc	CH_3	[18]
7	3-O-β-D-gentiobiosyl platycodigenin methyl ester	$C_{43}H_{70}O_{17}$	platycodin genin	Glc^{6}-Glc	CH_3	[18]
8	3-O-β-D-glucopyranosyl platycodigenin methylester	$C_{37}H_{60}O_{12}$	platycodin genin	Glc	CH_3	[18]
9	Platycoside E	$C_{69}H_{112}O_{38}$	platycodin genin	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[19]
10	Platycodin D3	$C_{63}H_{102}O_{33}$	platycodin genin	Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[20]
11	Platycoside G2	$C_{59}H_{96}O_{30}$	platycodin genin	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha	[20]
12	Platycoside K	$C_{42}H_{68}O_{17}$	platycodin genin	Glc^{3}-Glc	H	[21]
13	Platycoside L	$C_{42}H_{68}O_{17}$	platycodin genin	Glc^{6}-Glc	H	[21]
14	Deapio-platycoside E	$C_{64}H_{104}O_{34}$	platycodin genin	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl	[22]
15	Deapio-platycodin D2	$C_{58}H_{94}O_{29}$	platycodin genin	Glc^{3}-Glc	Ara^{2}-Rha^{4}-Xyl	[23]
16	Deapio-platycodin D3	$C_{58}H_{94}O_{29}$	platycodin genin	Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl	[24]
17	Platycodin J	$C_{57}H_{90}O_{29}$	platycodin genin	GlcA	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[25]
18	Platycodin K	$C_{59}H_{92}O_{30}$	platycodin genin	GlcA	Ara^{2}-Rha(2-OAc)^{4}-Xyl^{3}-Api	[25]
19	Platycodin L	$C_{59}H_{92}O_{30}$	platycodin genin	GlcA	Ara^{2}-Rha(3-OAc)^{4}-Xyl^{3}-Api	[25]
20	deapio-platycoside D	$C_{52}H_{84}O_{24}$	platycodin genin	Glc	Ara^{2}-Rha^{4}-Xyl	[26]
21	3''-O-acetyl-platycodin D2	$C_{65}H_{104}O_{34}$	platycodin genin	Glc^{3}-Glc	Ara^{2}-Rha(3-OAc)^{4}-Xyl^{3}-Api	[26]
22	Platycoside B	$C_{54}H_{86}O_{25}$	platycodin genin	Glc	Ara^{2}-Rha(2-OAc)^{4}-Xyl	[27]
23	Platycoside C	$C_{54}H_{86}O_{25}$	platycodin genin	Glc	Ara^{2}-Rha(3-OAc)^{4}-Xyl	[27]
24	Platycoside F	$C_{47}H_{76}O_{20}$	platycodin genin	Glc	Ara^{2}-Rha	[28]
25	3-O-β-D- glucopyranosyl platycodigenin	$C_{36}H_{58}O_{12}$	platycodin genin	Glc	H	[28]
26	Platycoside D	$C_{69}H_{112}O_{37}$	platycodin genin	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[27]

The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products Month-Month 202x EISSN:1307-6167
DOI: http://doi.org/10.25135/mp.18.17.06.108
Available online: X/X/202X

27	Platycoside P	$C_{53}H_{86}O_{25}$	platycodin genin	Glc^{6}-Glc	Ara^{2}-Rha	[29]
28	Platycoside G1	$C_{64}H_{104}O_{28}$	platycodin genin	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl	[37]
29	Methyl-platycogenate A	$C_{58}H_{92}O_{30}$	platyconic acid	Ara^{2}-Rha^{4}-Xyl^{3}-Api	H	[18]
30	Methyl-2-O-methylplatycogenate A	$C_{59}H_{94}O_{30}$	platyconic acid	Ara^{2}-Rha^{4}-Xyl^{3}-Api	CH_3	[18]
31	Dimethyl-3-O-β-D-glucopyranosyl platycogenate A	$C_{38}H_{60}O_{13}$	platyconic acid	CH_3	H	[18]
32	Dimethyl-2-O-methyl-3-O-β-D-glucopyranosyl platycogenate A	$C_{39}H_{62}O_{13}$	platyconic acid	CH_3	CH_3	[30]
33	Platyconic acid A methyl ester	$C_{58}H_{92}O_{29}$	platyconic acid	Ara^{2}-Rha^{4}-Xyl^{3}-Api	H	[30]
34	Platycoside O	$C_{53}H_{84}O_{25}$	platyconic acid	Ara^{2}-Rha^{4}-Xyl	H	[38]
35	Platyconic acid A	$C_{57}H_{90}O_{29}$	platyconic acid	---	---	[30]
36	Platycogenic acid A	$C_{30}H_{46}O_{8}$	platyconic acid	H	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[30]
37	Platyconic acid B	$C_{59}H_{92}O_{30}$	platyconic acid	H	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-Xyl^{3}-Api	[25]
38	Platyconic acid C	$C_{52}H_{82}O_{25}$	platyconic acid	H	Ara^{2}-Rha^{4}-Xyl	[25]
39	Platyconic acid D	$C_{54}H_{84}O_{26}$	platyconic acid	H	Ara^{2}-$Rha(2\text{-}OAc)^{4}$-Xyl	[25]
40	Polygalacin D	$C_{57}H_{92}O_{27}$	polygalacic acid	Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[17]
41	Polygalacin D2	$C_{63}H_{102}O_{32}$	polygalacic acid	Glc^{3}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[17]
42	2''-O-acetyl Platycoside D	$C_{59}H_{94}O_{28}$	polygalacic acid	Glc	Ara^{2}-$Rha(2\text{-}OAc)^{4}$-Xyl^{3}-Api	[17]
43	3''-O-acetyl Platycoside D2	$C_{65}H_{104}O_{34}$	polygalacic acid	Glc^{3}-Glc	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-Xyl	[17]
44	3''-O-acetyl Platycoside D	$C_{59}H_{94}O_{28}$	polygalacic acid	Glc	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-Xyl^{3}-Api	[17]
45	Methyl-3-O-β-D-glucopyranosyl Polygalaeate	$C_{37}H_{60}O_{11}$	polygalacic acid	Glc	CH_3	[18]
46	Methyl-3-O-β-D-laminaribiosyl Polygalaeate	$C_{43}H_{70}O_{16}$	polygalacic acid	Glc^{3}-Glc	CH_3	[18]
47	Platycoside D	$C_{69}H_{112}O_{37}$	polygalacic acid	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[19]
48	Platycoside G3	$C_{63}H_{102}O_{32}$	polygalacic acid	Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl^{3}-Api	[40]
49	Platycoside H	$C_{58}H_{94}O_{28}$	polygalacic acid	Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl	[21]
50	Platycoside I	$C_{64}H_{104}O_{33}$	polygalacic acid	Glc^{6}-Glc^{6}-Glc	Ara^{2}-Rha^{4}-Xyl	[21]
51	Platycoside J	$C_{52}H_{84}O_{23}$	polygalacic acid	Glc	Ara^{2}-Rha^{4}-Xyl	[21]
52	3-O-β-D-laminaribiosyl Polygalacic acid	$C_{42}H_{68}O_{16}$	polygalacic acid	Glc^{3}-Glc	H	[21]

53	2''-O-acetyl Platycoside D2	$C_{65}H_{104}O_{33}$	polygalacic acid	Glc^3-Glc	Ara^2-Rha(2-OAc)^4-Xyl	[32]
54	Platycoside N	$C_{53}H_{86}O_{24}$	polygalacic acid	Glc^6-Glc	Ara^2-Rha	[24]
55	3-O-β-D-glucopyranosyl Polygalacic acid	$C_{36}H_{58}O_{11}$	polygalacic acid	Glc	H	[25]
56	Polygalacic acid	$C_{30}H_{48}O_6$	polygalacic acid	H	H	[39]
57	Platycoside M-1 methyl ester	$C_{37}H_{56}O_{12}$	platyconic acid lactone	Glc	CH_3	[18]
58	Platycoside M-1	$C_{36}H_{54}O_{12}$	platyconic acid lactone	Glc	H	[33]
59	Platycoside M-2	$C_{47}H_{72}O_{20}$	platyconic acid lactone	Glc	Ara^2-Rha	[33]
60	Platycoside M-3	$C_{52}H_{80}O_{24}$	platyconic acid lactone	Glc	Ara^2-Rha^4-Xyl	[33]
61	Platyconic acid A lactone	$C_{57}H_{88}O_{29}$	platyconic acid lactone	Glc	Ara^2-Rha^4-Xyl^3-Api	[30]
62	Deapio-platyconic acid A lactone	$C_{52}H_{80}O_{25}$	platyconic acid lactone	Glc	Ara^2-Rha^4-Xyl	[30]
63	Platycogenic acid B lactone	$C_{63}H_{98}O_{33}$	platyconic acid lactone	Glc^6-Glc	Ara^2-Rha^4-Xyl^3-Api	[30]
64	Deapio-platyconic acid B lactone	$C_{58}H_{90}O_{29}$	platyconic acid lactone	Glc^6-Glc	Ara^2-Rha^4-Xyl	[30]
65	Platycoside Q	$C_{53}H_{82}O_{25}$	platyconic acid lactone	Glc^6-Glc	Ara^2-Rha	[29]
66	platycodon A	$C_{42}H_{68}O_{16}$	other types	Glc	Glc	[34]
67	platycodon B	$C_{41}H_{66}O_{15}$	other types	Xyl	Xyl	[34]
68	3-O-β-D- glucopyranosyl- 2β, 12α, 16α, 23, 24-penta-Hydroxyoleanane-28(13)-lactone	$C_{36}H_{58}O_{13}$	other types	Glc	CH_2OH	[35]
69	3-O-β-D-glucopyranosyl -3-β-D- glucopyranosyl-2β, 12α, 16α, 23α-tetrahydroxyoleanane-28(13)-lactone	$C_{42}H_{68}O_{17}$	other types	Glc^3-Glc	CH_2OH	[35]
70	Platycogenic acid B	$C_{30}H_{46}O_8$	other types	COOH	COOH	[25]
71	Platycogenic acid C	$C_{30}H_{48}O_6$	other types	CH_3	CH_3	[25]
72	Platycosaponin A	$C_{42}H_{68}O_{16}$	other types	---	---	[25]
73	Platycodonoids A	$C_{29}H_{46}O_5$	other types	H	H	[40]
74	Platycodonoids B	$C_{35}H_{56}O_{10}$	other types	Glc	H	[40]
75	16-OXO-platycodin D	$C_{57}H_{90}O_{28}$	other types	Glc	Ara^2-Rha^4-Xyl^3-Api	[36]

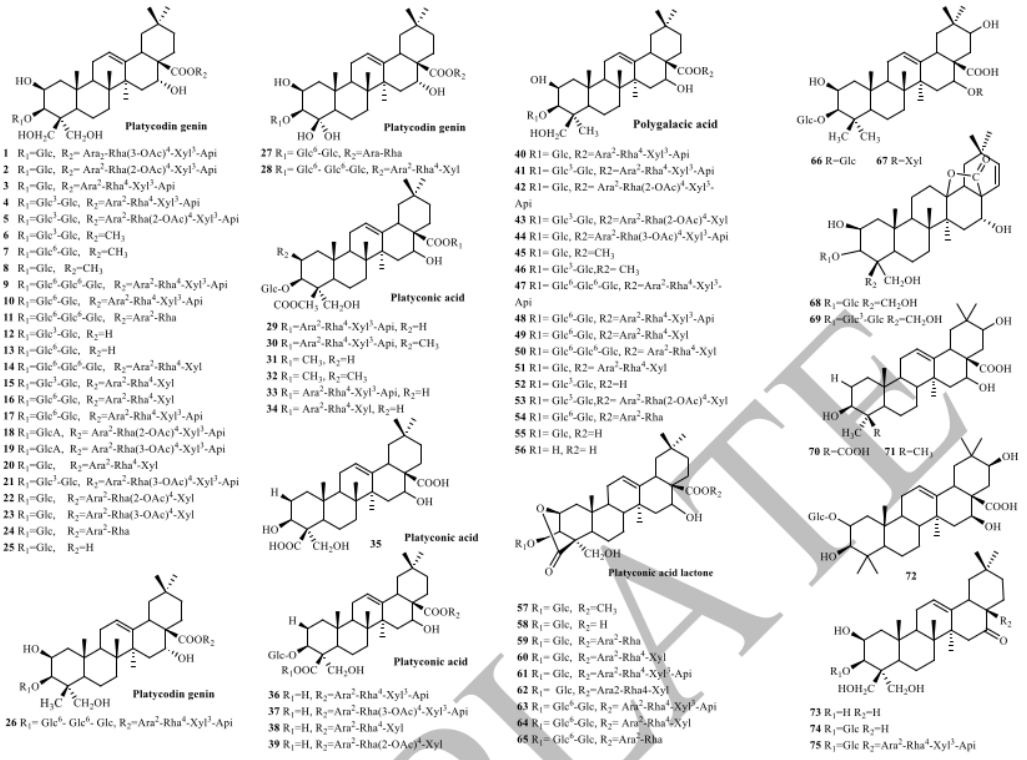

Figure 2. Chemical structure of natural saponins isolated from *P. grandiflorus*.

3. Pharmacological Study

The literature survey disclosed that the previous pharmacological studies of *P. grandiflorum* mainly focus on its crude saponins extract and the indicator components Platycodon D (compound **3**), which exhibited potent anti-tumor, anti-inflammatory activity, antioxidant activity, and so on.

3.1. Anti-tumor activity

3.1.1. Effects on cell apoptosis

There are three main ways to induce apoptosis of *P. grandiflorus* saponins, which are mitochondrial pathway, death receptor pathway, and endoplasmic reticulum (ER) stress pathway (Figure 3). By consulting a large number of kinds of literature, we found that one of the ways that *P. grandiflorus* saponins induce apoptosis of various cancer cells is through the mitochondrial pathway. As we all know, the B-cell lymphoma2 (Bcl-2) family is a very special presence for the mitochondrial apoptosis pathway, which can regulate cancer cell apoptosis through complex interactions. At present, it is divided into two categories: pro-apoptotic factors and anti-apoptotic factors and the representative ones are Bax and Bcl-2. A549 cells were used as the research object to study the anti-cancer mechanism of PD. It was found that after PD (compound **3**) treatment, the cells had obvious apoptosis, western blot showed that the expression of pro-apoptotic factors Bax and Bak protein in the cells increased, and the expression of anti-apoptotic factors Bcl-2 and Bcl-xl protein decreased, resulting in a decrease in mitochondrial membrane potential, and activation of caspase program led to cell death, eventually [41]. For A549 cisplatin-resistant cells (A549/DDP), PD can also up-regulate Bax expression and down-regulate Bcl-2 expression to induce apoptosis [42]. This all shows that the Bcl-2 family plays an important role in mitochondrial pathway-induced

The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products Month-Month 202x EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.18.17.06.108
Available online: X/X/202X

apoptosis. Of course, in addition to lung cancer cells, it can also induce apoptosis by regulating the mitochondrial pathway of Bcl-2 family proteins in prostate cancer cells (RC-58T/h/SA#4), human transitional cell carcinoma cells (5376 cells), rat adrenal pheochromocytoma cells (PC-12 cells), human breast cancer cells (MCF-7) and human liver cancer cells (HepG2 cells) [43-47]. Reactive oxygen species (ROS) are mainly produced in mitochondria, and excessive ROS can lead to mitochondrial dysfunction and activate the mitochondrial apoptosis pathway. Zhang et al. studied the mechanism of PD-induced apoptosis in PC-12 cells and found that after PD treatment, the increase of intracellular ROS level caused the decrease of mitochondrial membrane potential, which led to cell apoptosis. In another experiment with MG-63 cells as the research object, it was also found that the mechanism of PD-induced apoptosis was similar to this [48].

In addition to single drug use, Zheng et al. found that PD combined with doxorubicin can enhance the anticancer activity of doxorubicin *in vitro*. Further study of its mechanism found that PD up-regulated the expression of ASK1 protein after action, thereby promoting doxorubicin-induced ROS to phosphorylate ASK1 protein and activate JNK activation, eventually causing JNK-dependent apoptosis in liver cancer cells (PLC cells) [49]. In addition, Xuan et al. found that PD can inhibit the resistance of HepG2 liver cancer stem cells to 5-fluorouracil, which provides a new idea for the clinical treatment of tumors [50]. For 5637 cells, Li et al. found that PD induced apoptosis not only through the mitochondrial pathway but also through the death receptor pathway [51]. The death receptor pathway (fas) is also one of the important pathways of apoptosis. As we know, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can induce tumor cell apoptosis, but some tumor cells are not sensitive to TRAIL. Zhang et al. found that PD can enhance the sensitivity of TRAIL, form a death receptor complex, and then activate Caspase 8, which initiates the apoptosis process of A549 cells finally [52]. Huang et al. proved that PD can effectively induce apoptosis of human lung adenocarcinoma cell line H1975, which is the first time to verify it. Exploring its mechanism found that PD can promote the extracellular release of PD-L1 [53]. In other words, PD can act as a cholesterol-dependent lipid raft regulator to promote the formation of PD-L1 in extracellular vesicles [54], which provides new therapeutic ideas for natural products used in anti-cancer. In another study, apoptosis was detected by flow cytometry and Western blot analysis. All the results showed that the apoptosis of human gastric cancer cells (AGS cells) caused by PD can activate p38 expression [55]. Yu et al. found that PD can induce the up-regulation of GRP78/Bip and CHOP/GADD153, which play a role in the downstream of ER, thereby activating Caspase 4. This also reflects that PD can induce cancer cell apoptosis through ER [56]. Of course, they were also found to have an inextricable link between PD-induced apoptosis and the MAPK pathway [55.56]. In addition to the above common pathways, studies have found that PD can also reduce telomerase activity [57], cause cell vacuoles [58] and enhance immune response [59], which are the reasons why PD can induce apoptosis. It is also believed that PD does not induce apoptosis through a single pathway but through multiple pathways. Kong et al. detected the expression level of apoptosis-related proteins by Western blot. The experimental results can be summarized as follows: after PD treatment, PARP was cleaved in cells, and the expression of active cleaved caspase-3 and -8 was up-regulated to activate the fas pathway. At the same time, the Bcl-2/Bax ratio was reduced, and the expression of cleaved caspase-3 and-9 was up-regulated, so that PARP was cleaved to activate the mitochondrial pathway, and the expression of P53 protein was inhibited to induce apoptosis [60]. In general, inducing apoptosis is still the main way for *P. grandiflorum* saponins to exert anti-tumor effects.

3.1.2 Effects on cell autophagy

By reading the literature, we found that PD plays a protective autophagy role in HepG2, and the activation of the extracellular signal-regulated kinase (ERK) plays an important role in this process [61]. In another study, Xu et al. found that after PD treatment the up-regulation of BNIP3 expression in HepG2 cells induced mitochondrial changes increased the expression of autophagy-related protein Beclin1, and converted intracellular LC3-I into LC3-II, resulting in autophagy of liver tumor cells. These prove that autophagy is a major way to induce apoptosis [62]. In another liver cancer cell called Bel-7402, PD activates ERK and JNK pathways to induce autophagy [63].

In the study of lung cancer cells, it was also found that PD could up-regulate the expression of Atg-3 and Atg-7 to promote the expression of LC3-II and induce autophagy, finally [64]. When the n-butanol fraction of *platycodon grandiflorum* (compounds **40** and **41**) was applied to A549 cells, it was found that it could also up-regulate Beclin-1 and down-regulate Blc-2 to activate the AMPK pathway to induce autophagy [65]. In terms of traditional Chinese medicine, the guide can guide the treatment of drugs to the disease so that the drugs play a better effect. Studies have shown that *platycodon grandiflorum* has a significant effect on the prevention and treatment of lung cancer [66]. For example, PD can promote cell gap junction communication and lysosomal function, promote autophagy and autophagy degradation, and inhibit cell P-gp expression, thereby exerting a guiding role in the treatment of lung cancer in mice with doxorubicin [67]. Therefore, it is necessary to elucidate the autophagy mechanism of *P. grandiflorum* saponins, which will contribute to the clinical anti-cancer application of *P. grandiflorum*.

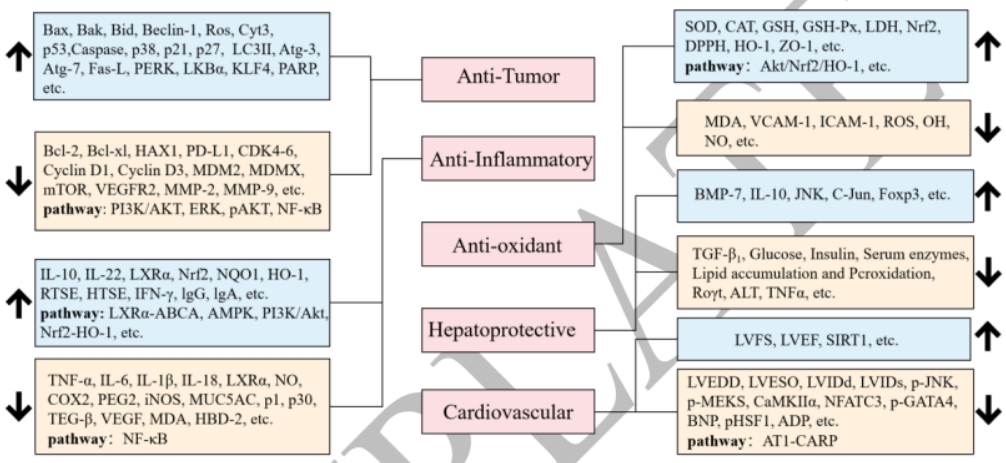

Figure 3. The pharmacological activity mechanism of natural saponins from *P. grandiflorus*.

3.1.3 Effects on cell cycle arrest

Zhou et al. first demonstrated that prostate cancer cells were highly sensitive to PD and verified it with three different cells. All the results showed that the adenocarcinoma cell lines showed a downward trend in the S phase. The difference was that DU185 cells and LNCaP cells were blocked in G0/G1 phase as well as other cells, while PC-3 cells were blocked in the G2/M phase [68, 69]. U251 cells and MDA-MB-231 cells also had the same cycle arrest. The difference between the two is that U251 cells inhibit the PI3K/AKT pathway [70], while MDA-MB-231 cells inhibit cell proliferation by up-regulating MDM2 downstream proteins (p21 and p51) to achieve cycle arrest [71]. Yi et al. found that *P. grandiflorum* total saponins could inhibit the cell cycle of A549 cells in G0/G1 phase in a dose-dependent manner by flow cytometry [72]. After that, Zhao et al. found that PD can also block A549 cells in G0/G1 phase, and the mechanism is that PD inhibits the expression of cell cycle downstream regulatory proteins E2F1 and Rb [42]. In this study, it was also found that for A549/DDP cells, PD blocked their cell cycle in the G2/M phase through this mechanism. By reviewing the literature, we found that PD can also inhibit PC-3 cells in the G2/M phase [68]. In addition, we found that after PD acted on SW620 cells, the expression of cyclin D1 in the cells decreased in the G1 phase, and the expression of CDK6 also decreased, making the cells unable to enter the S phase [73]. Ma et al. also proved that PD can block Hela cells in the G1 phase. The mechanism may be due to the down-regulation of the overexpression of YAP and TAZ the downstream of Hippo pathway and the up-regulation of the expression of pro-apoptotic factors Bax, P53, and Caspase-3, thus causing the G1 phase arrest in Hela cells [74].

3.1.4 Effects on cell metastasis

As we know about tumor diseases, the metastasis of cancer cells is the main cause of death in patients. Controlling cancer cell metastasis has become a clinical anti-tumor method. Si et al. proved that PD could effectively reduce the migration and invasion of gastric cancer BGC823 cells in a dose-dependent manner by the transwell chamber experiment and scratch method [75]. According to the literature, Chun et al. [76] first proved that PD can inhibit cell migration and invasion by inhibiting the expression of MMP-9 proteolytic enzyme associated with cell metastasis). The mechanism was related the inhibition of ERK, p38 MAPK, JNK, and PI3K/AKT signaling pathways. In the study of non-small cell lung cancer (A549, H460), Zhao et al. also confirmed this view and also found that PD can inhibit the expression of p-AKT [77]. In addition, PD reduced the expression of MMP-2 and MMP-9 in OSCC cells [78] and HCCLM3 cells [79]. And for OSCC cells, the mechanism was also related to the phosphorylation of NF-κB p65, which was confirmed by experiments *in vivo* and *in vitro*. In addition, Cao et al. demonstrated that PD can also inhibit the migration and invasion of endometrial cancer cells by regulating KLF4 expression [80]. In addition, Wu et al. also found that PD can inhibit NF-κB and JAK2/STAT3 pathways after acting on multiple myeloma cells, and can enhance the sensitivity of cells to BTZ to inhibit cell migration and invasion [81].

In addition to the above anti-tumor mechanisms, there are some other mechanisms. By reading the literature, PD is currently mainly found through animal experimental studies that it can inhibit angiogenesis to achieve anti-tumor effects [81-84]. It has also been found that PD can reverse the resistance of acetylase inhibitors (HDACi) in human hepatocellular carcinoma cells (HCC cells) [85], or as a new Hsp90 inhibitor [86], which is also a new direction for the treatment of tumor diseases. Moreover, Lee et al. found that PD can induce apoptosis of highly metastatic breast cancer cells and induce apoptosis of mature osteoclasts in mice, which inhibited breast cancer-induced bone destruction [87]. The combination of PD and doxorubicin also showed the effect of inhibiting glucose metabolism in Hela cells which is also a new anti-tumor mechanism [88]. In addition, in the treatment of anti-tumor diseases, the inhibition of feedback regulation has certain limitations [89], and the combination of drugs has become a hot spot in clinical practice. The study also found that PD in combination with different drugs will have different effects on different types of tumor cells [90-82]. Choi et al. also found that the anti-tumor effect of *P. grandiflorum* extract on A549 cells was achieved by inhibiting the expression of mucin 5, subtypes A and C (MUC5AC) induced by acrolein, which was related to the inhibition of ROS-PKCd-MAPK pathway [93]. Chen et al. found a new strategy for PD treatment of bladder cancer, targeting the LncRNA-XIST/miR-335 axis [94].

Some compounds have been found to have good anti-tumor effects when they were discovered. For example, compound **14** has been found to inhibit a variety of tumor cells [95].

3.2. Anti-inflammatory activity

According to the literature we reviewed, since 2001, PD has been found to exert anti-inflammatory effects by inhibiting COX-2 protein and subsequently reducing PGG2 production in rat peritoneal macrophages [96]. Subsequently, compounds **2**, **3**, **10**, **40**, and **42** exhibited significant anti-inflammatory activity against LPS-induced RAW2647 cells [97,98]. Wang et al. discovered that in LPS-induced bMEc cell inflammation, PD exerts anti-inflammatory effects by upregulating the expression of LXRα, which reduces the release of pro-inflammatory factors and inhibits its induced activation of NF-κB pathway [99]. In another study, Fu et al. proved that PD exerts an inhibitory effect on inflammation by activating the LXRα-ABCA1 signaling pathway, which disrupts lipid rafts and prevents TLR4 from being transferred to inhibit LPS-induced inflammation in primary rat microglia cells [100]. By up-regulating the expression of LXRα, PD can also inhibit the inflammatory response of human osteoarthritis chondrocytes induced by IL-1β [101] and it can also inhibit the LXRα/NF-κB signaling pathway of BV-2 cells induced by Aβ to exert anti-inflammatory effects [102]. Even for MPP^+ -induced BV-2 cells, PD inhibits the LXRα/MyD88/NF-κB signaling pathway for anti-inflammatory [103]. Wang et al. utilized IL-13 to induce an inflammatory response in RPMI2650 cells, confirming the anti-inflammatory mechanism of PD, which their findings demonstrated that PD reduced protein expression of GM-CSF and

eotaxin, inhibited p-NF-κB p56 expression in induced cells, and suppressed MAPK pathway activation [104]. Ye et al. also found that PD can also inhibit S100A8/A9-induced 4T1 cell inflammation by inhibiting the expression of NF-κB p56 [105]. In addition, more studies have found that PD can inhibit IAV-induced apoptosis and autophagy of RAW 264.7 cells, thereby inhibiting influenza virus apoptosis and autophagy pathways to inhibit the secretion of inflammatory factors induced by influenza virus infection, and ultimately regulate the pathogenesis of influenza virus [106].

Many experiments *in vivo* have demonstrated the potent anti-inflammatory activity of *P. grandiflorum saponins*, particularly in the context of lung inflammation. Wu et al. and Tao et al. have demonstrated that PD exerts a significant protective effect against acute lung injury (ALI), as evidenced by its ability to attenuate pulmonary pathological damage induced by LPS or BLE, reduce the expression of inflammatory mediators in bronchoalveolar lavage fluid, and inhibit NF-κB signaling pathway activation following PD treatment [107,108]. Further research has revealed that PD treatment for ALI also suppresses the IRF3 signaling pathway and induces cholesterol depletion, which disrupts lipid raft formation and impedes TLR4 transportation to lipid rafts, thereby inhibiting inflammation [109]. *P. grandiflorum saponins* have also been shown to have excellent anti-inflammatory effects *in vivo* for carrageenan-induced lung inflammation. The study proved that after drug treatment, the levels of PEG2, TNF-α, and COX-2 in rats, and the paw water caused by modeling were also well inhibited [1]. For cigarette smoke-induced pneumonia in mice, PD also activates the Nrf2-HO-1 pathway and inhibits the activation of the NF-κB pathway [111]. Even for the novel coronavirus pneumonia in the past two years, PD prevents membrane fusion by destroying membrane cholesterol, thereby preventing the entry of SARS-CoV-2 to prevent pneumonia [112]. Studies have substantiated that PD has a significant effect on ovalbumin-induced asthma. They found that PD not only reduces the proportion of macrophage cells and eosinophils in the Mouse airway, inhibits the production of pro-inflammatory factors, but also inhibits NF-κB activation to play a therapeutic role in asthma [113], and it can also inhibit the production of transcription factor Th2 to inhibit airway inflammation in mice [114]. In addition, PD has also been shown to have a significant effect on BLE-induced pulmonary fibrosis [115]. For skin inflammation, studies have found that both PD and crude extracts can significantly reduce the degree of dermatitis in mice [116]. Moreover, Guo et al. studied the effect of PD on dextran sulfate sodium-induced colitis and found that PD reduced the inflammatory response in mice by activating AMPK signaling pathway cells [117]. For inflammation caused by pathogenic microorganisms, studies have found that PD can inhibit the adhesion of Mycoplasma pneumoniae to the host and down-regulate the expression of p1 and p30 to inhibit the development of inflammation [118]. In addition, PD can also inhibit the inflammation of oral mucosal epithelial cells caused by Candida albicans [119]. Undoubtedly, the isolated compounds **27** and **65** were studied for the activity of LPS-induced Raw 264.7 cells to secrete TNF-α. It was found that both compounds showed inhibitory activity at 50 μM and the inhibition rate of Platycoside Q (**65**) was slightly larger, that is, both compounds showed good anti-inflammatory activity [29].

As we all know, the inflammatory response is one of the results of the body's severe immune response, that is, the process of inflammation is the process of immunity. The immune effect of PD is mainly achieved by acting as an adjuvant. Alum is a common adjuvant. To compare the adjuvant activity of PD and Alum, two adjuvants were used to immunize mice to evaluate the antigen-specific cellular and humoral immune responses. PD was found to increase cellular and humoral immune responses and has the potential to serve as an adjuvant for the prevention and treatment of the hepatitis B vaccine [120]. Not only that, but PD can also be used as an adjuvant for the chicken infectious bronchopneumonia vaccine, and experiments have shown that PD can not only improve the chicken's s cellular and humoral immune response but also have no side effects [121]. PD was also added to the Newcastle disease virus recombinant avian influenza vaccine as adjuvant to improve the immunogenicity of the vaccine [122]. In addition, PD can promote the proliferation of mouse spleen lymphocytes and promote the phagocytosis of mouse peritoneal macrophages, thereby enhancing the immune response of Th1 and Th cells in immunized mice [123].

3.3. Anti-oxidant activity

P. grandiflorus saponins have an excellent scavenging effect on free radicals, that is, it has a strong antioxidant capacity, and it is different due to the structure of the aglycone and the number of sugar groups [124]. With the increase in concentration, its ability to scavenge free radicals becomes stronger, and it can be close to the antioxidant capacity of VC at a certain concentration [125]. Wang et al. used oxidized low-density lipoprotein to induce human venous endothelial cells (HUVECs) to study the antioxidant effect of PD, and found that PD could increase the release of NO, reduce the expression of malondialdehyde (MDA), VCAM-1 and ICAM-1, and reduce cell adhesion [126]. PD also activates the Akt/Nfr2/HO-1 signaling pathway to protect cardiomyocytes from injury [127]. When PD acts on hypoxia/glucose deprivation/reperfusion-induced oxidation, Wang et al. found that its role is achieved by regulating the PI3K/Akt/mTOR pathway in cortical neurons [128]. Not only that, but PD also has a good effect on age-dependent endogenous oxidative damage. It can prevent premature aging caused by H_2O_2, mainly by improving mitochondrial biosynthesis [129].

3.4. Hepatoprotective activity

It was found that the anti-hepatic fibrosis effect of PD may be due to the fact that PD reduced TGF-β1 and increased the expression of BMP-7, and inhibited the proliferation and activation of hepatic stellate cells [120]. Other studies have found that PD can achieve anti-hepatic fibrosis by activating JNK and c-Jun cell apoptosis and autophagy in hematopoietic stem cells, which is also considered to be an effective mechanism for anti-hepatic fibrosis [131]. Li et al. first discovered that PD possesses a good protective effect on alcohol-induced liver injury by reducing oxidative stress and inflammatory response [132]. For acetaminophen-induced hepatotoxicity, PD exerts a protective effect by regulating oxidative stress, inflammatory response, and hepatocyte apoptosis associated with the MAPK pathway [133] and the other study proved that CKS also can prevention of ethanol-induced liver injury [134]. For alloxan-induced liver injury, PD has been shown to reduce the phosphorylation of JAK and STAT-3 and reduce the expression of RORγ and Foxp3 to play the role [135]. Other than that, the activities of platycodonoids A (compound **72**), polygalacin D (compound **44**), and PD isolated from *P. grandiflorus* were studied, showing good hepatoprotective activity [25].

3.5. Cardiovascular protection activity

Many studies have shown that *P. grandiflorus* saponins have a good cardiovascular protective effect. Lin et al. studied the effect of PD on cardiac complications caused by hypertension. The results showed that PD could inhibit the transcription and translation of IGF-IIR, thereby inhibiting the expression of PHSF1 and pJNF, and up-regulating the expression of SIRT1, which proved that PD could protect cardiomyocytes from diseases caused by hypertension [136]. In another study, it was also found that the protective effect of PD on myocardium was also related to the inhibition of cardiac fibrosis and the reduction of myocardial hypertrophy [137]. For acute myocardial infarction, PD inhibits left ventricular end-diastolic diameter and left ventricular end-systolic diameter, increases left ventricular short-axis systolic rate and left ventricular ejection frequency, and inhibits AT1-CARP signaling pathway to reduce the reduction of cardiomyocyte apoptosis and finally improve cardiac function [138]. Studies have shown that PD has shown a protective effect on cardiovascular and cerebrovascular in many ways. In order to explore the neuroprotective effect of *P. grandiflorus* saponins, one study explored the effects of five components and demonstrated that PD and 2"-O-acetyl Platycoside D2 (compound **53**) have a good protective effect on the ischemic injury of neurons in the CA1 region *in vitro* and *in vivo* [32].

In addition to the protective effect on the heart, it has a good effect on some vascular diseases. Studies have shown that PD has a good effect on atherosclerosis and found that PD combined with simvastatin has a synergistic effect on the treatment of atherosclerosis, which provides molecular evidence for the first time for the treatment of atherosclerosis with PD [139]. Naturally, there are studies that have shown that PD in the anti-atherosclerosis, also the role of cholesterol-lowering,

two diseases are very potential drug candidates [140]. Studies have found that PD can resist atherosclerosis partly because PD can increase NO concentration, reduce the expression of cell adhesion molecules in endothelial cells induced by OX-LDL, and the adhesion of endothelial cells to monocytes [141]. Similarly, because PD prevents platelet aggregation and activation, reduces arterial thrombosis, and can impair hemostasis, PD is considered to be an effective antithrombotic drug [142].

3.6. Other activities

It was previously reported that the protective effect of PD on cisplatin-induced nephrotoxicity has been studied at both cellular and animal levels. At the cellular level, studies using HEK-293 cells found that PD can regulate oxidative stress, apoptosis, and inflammatory responses in the cell [143]. Another study used mouse experiments to verify the effect of PD on cisplatin-induced nephrotoxicity. It was found that the renal injury of mice treated with PD showed signs of improvement, which further verified the protective effect of PD on the kidney [144].

In recent years, it was found that PD has a good spermicidal effect. Researchers have found that PD has an instantaneous killing effect on sperm and can quickly kill sperm [145]. For PD, mainly destroys the sperm membrane, especially the sperm head membrane, causing the sperm to lose activity, thereby causing late sperm apoptosis [146,147]. Leng et al. found that *P. grandiflorus* saponins can protect against testicular dysfunction induced by heat stress, which also depends on the regulation of the MAPK signaling pathway [148]. The results confirmed that PD has the potential as a spermicide, and in the future may be used as a clinical spermicide to achieve the contraceptive effect.

Many studies have shown that *P. grandiflorus* saponins exhibit a good inhibitory effect on obesity. Zhao et al. found that the lipid metabolism of obese rats treated with *P. grandiflorus* saponins was controlled, resulting in a decrease in IDI cholesterol and a significant decrease in calorie intake, demonstrating that *P. grandiflorus* saponins may be a candidate drug for the treatment of obesity and hyperlipidemia [10]. Further studies have found that PD can induce the activation of the AMPK pathway to up-regulate the expression of AMPKα, reduce the expression of other related adipogenic factors, and finally improve lipid metabolism to control obesity [149,150]. On the other hand, PD can also achieve the effect of obesity by inhibiting lipid accumulation [151]. For crude saponins, Han et al. also found that it can be one of the activities of pancreatic lipase and inhibit the decrease of intestinal sucrase activity, thereby reducing the absorption of dietary fat [152].

For UV radiation or pigmentation and pigmentation, studies have found that PD may be a good inhibitor of melanin production because it can inhibit cAMP signal on melanin production and melanocyte dendrites play an inhibitory effect [153]. PD can also participate in the activation of β-catenin and the differentiation of osteoblasts, regulate the process of osteogenic differentiation, and provide a new idea for the treatment of osteoporosis [154]. PD was also found to induce apoptosis of immortalized human keratinocytes HaCaT cells at the transcriptome level [155]. PD is also a potential drug for the treatment of osteoporosis because PD can inhibit NF-κB and ERK and p38 MAPK pathways induced by NF-κB ligand (RANKL) receptor activators, thereby inhibiting osteoclast differentiation [156]. In mice tail flick, writhing, and formalin tests, PD showed a strong anti-nociceptive effect, that is, a certain analgesic effect, but the study had shown that this effect is not mediated by opioid receptor stimulation [157].

In addition, the anti-respiratory syncytial virus, herpes simplex virus 1, and influenza A virus activity of the extracted *P. grandiflorus* saponins compounds (compounds **9**, **10**, **11**, **28**, and **48**) were tested. It was found that except for the weak anti-respiratory syncytial virus activity of compound **10**, the activity of other compounds was moderate [16].

4. Discussion

P. grandiflorus, as traditional Chinese medicine, is widely used in the clinical treatment of lung diseases. In recent years, the activity studies of *P. grandiflorus* mainly focus on anti-tumor activity and anti-inflammatory activity. So far, saponins, polysaccharides, flavonoids, and other components have been isolated from *P. grandiflorus*.

In this paper, we reviewed the saponin components isolated from *P. grandiflorus* in recent years, and its extensive pharmacological activity, especially the activity of PD, was summarized and described for the future pharmacological activity of *P. grandiflorus* research and clinical development and utilization to provide a theoretical basis.

According to the literature we retrieved, the research on *P. grandiflorus* has penetrated into all aspects, but there are still some shortcomings at this stage. First of all, the research on the components of *P. grandiflorus* is mainly focused on the polysaccharides and saponins, but there are relatively few studies on the flavonoids, polyphenols, and other components of *P. grandiflorus*. However, studies have found that, like saponins, polyphenol compounds have good potential anti-inflammatory activity [158]. Secondly, the current study mainly aimed at more *P. grandiflorus* extract, and the pharmacological activity of its monomer components to PD-based, but the content of PD in *P. grandiflorus* is relatively small, so the current study is somewhat one-sided. For other monomer components, we should also pay more attention and explore. Third, it may be because the medicinal part of *P. grandiflorus* is the root, so the current components are mainly separated from the root part. Of course, the extract of pharmacological activity research is also based on the root extract. Therefore, we think it is necessary to study different parts of *P. grandiflorus*. Of course, some studies have explored the extract activity of the aboveground parts of *P. grandiflorus* and obtained good feedback [159]. It is worth noting that modern studies have shown that saponins are the main active ingredients of *P. grandiflorus*, but *in vivo,* studies have found that these compounds have low bioavailability and few pharmacokinetic studies *in vivo*. Therefore, the metabolism *in vivo* of saponins should be widely studied [160].

In general, as a medicinal and edible Chinese herbal medicine, *P. grandiflorus* has a wide range of clinical applications and small toxic and side effects and has excellent clinical development potential. Various studies on it can provide a more reliable scientific basis for the subsequent sustainable development and utilization of *P. grandiflorus*.

Acknowledgments

This work was supported by the Key R&D Program of Shandong Province (No. 2021CXGC010510), the Shandong Provincial Natural Science Foundation (No. ZR2022YQ71 and ZR2022LZY026), the Key Discipline Construction Project of National Administration of Traditional Chinese Medicine (Marine Traditional Chinese Medicine), Shandong Province Key Discipline Construction Project of Traditional Chinese Medicine (Marine Traditional Chinese Medicine), Shandong Province Traditional Chinese Medicine High-level Talent Cultivation Project, and Youth Innovation Team of Shandong University of Traditional Chinese Medicine.

20230511173843854092237176205312

ORIGINALITY REPORT

17%
SIMILARITY INDEX

PRIMARY SOURCES

1	Xinying Du, Xinhai Cui, Xiaowen Sun, Hui Li, Kuo Xu, Xianjun Fu. "Platycodin D-Induced Immunotoxicity in RAW 264.7 Macrophages via Oxidative Stress-Mediated Apoptosis", Natural Product Communications, 2023 Crossref	150 words — 2%
2	www.acgpubs.org Internet	125 words — 1%
3	xb.njucm.edu.cn Internet	119 words — 1%
4	Shengnan Zhang, Xiaoyun Chai, Guige Hou, Fenglan Zhao, Qingguo Meng. "Platycodon grandiflorum (Jacq.) A. DC.: a review of phytochemistry, pharmacology, toxicology and traditional use", Phytomedicine, 2022 Crossref	103 words — 1%
5	www.science.gov Internet	103 words — 1%
6	docksci.com Internet	85 words — 1%
7	res.mdpi.com Internet	54 words — 1%
8	bio-bigdata.hrbmu.edu.cn Internet	

46 words — 1%

9 Chun-Xiao Yan, Ya-Wen Wei, Hui Li, Kuo Xu, Run-Xiang Zhai, De-Chuan Meng, Xian-Jun Fu, Xia Ren. "Vitex rotundifolia L. f. and Vitex trifolia L.: A review on their traditional medicine, phytochemistry, pharmacology", Journal of Ethnopharmacology, 2023 — 42 words — 1%
Crossref

10 samnuingoclinh.net — 37 words — < 1%
Internet

11 "Chromatographic Fingerprint Analysis of Herbal Medicines Volume III", Springer Nature, 2015 — 35 words — < 1%
Crossref

12 Le Zhang, Yingli Wang, Dawei Yang, Chunhong Zhang, Na Zhang, Minhui Li, Yanze Liu. "Platycodon grandiflorus – An Ethnopharmacological, phytochemical and pharmacological review", Journal of Ethnopharmacology, 2015 — 29 words — < 1%
Crossref

13 Peng Zhang, Qian Wei, Xiaolong Yuan, Kuo Xu. "Newly Reported Alkaloids Produced by Marine-Derived Penicillium Species (Covering 2014–2018)", Bioorganic Chemistry, 2020 — 26 words — < 1%
Crossref

14 www.frontiersin.org — 24 words — < 1%
Internet

15 www.mdpi.com — 24 words — < 1%
Internet

16 Yeon Hee Choi, Dae Seok Yoo, Mi-Ran Cha, Chun Whan Choi, Young Sup Kim, Sang-Un Choi, Kang Ro Lee, Shi Yong Ryu. " Antiproliferative Effects of Saponins from the Roots of on Cultured Human Tumor Cells ", Journal of Natural Products, 2010
Crossref
22 words — < 1%

17 Yunhe Fu, Zhuoyuan Xin, Bin Liu, Jiaxin Wang, Jingjing Wang, Xu Zhang, Yanan Wang, Fan Li. "Platycodin D Inhibits Inflammatory Response in LPS-Stimulated Primary Rat Microglia Cells through Activating LXRα–ABCA1 Signaling Pathway", Frontiers in Immunology, 2018
Crossref
20 words — < 1%

18 Ying Zhang, Yi Zhang, Jun Liang, Hai-Xue Kuang, Yong-Gang Xia. "Exploring the effects of different processing techniques on the composition and biological activity of Platycodon grandiflorus (Jacq.) A.DC. by metabonomics and pharmacologic design", Journal of Ethnopharmacology, 2022
Crossref
18 words — < 1%

19 Lee-Fong Yau, Hao Huang, Tian-Tian Tong, Long-Bo Bai, Guo-Yuan Zhu, Yuanyuan Hou, Gang Bai, Zhi-Hong Jiang. "Characterization of deglycosylated metabolites of platycosides reveals their biotransformation after oral administration", Food Chemistry, 2022
Crossref
16 words — < 1%

20 downloads.hindawi.com
Internet
15 words — < 1%

21 Chao Wang, Wenfeng Ding, Ming Zhao, Gang Lin, Shiqi Peng. "Studies on the Large Scale Synthesis and Anti-tumor Activity of YSL", Preparative Biochemistry and Biotechnology, 2003
Crossref
14 words — < 1%

22	link.springer.com Internet	14 words — < 1%
23	Chen, Tong, Jin Gao, Pengjun Xiang, Yongde Chen, Jing Ji, Peng Xie, Hui Wu, Wei Xiao, Yidan Wei, Shumin Wang, Li Lan, Hui Ji, and Tianhua Yan. "Protective effect of platycodin D on liver injury in alloxan-induced diabetic mice via regulation of Treg/Th17 balance", International Immunopharmacology, 2015. Crossref	13 words — < 1%
24	Sahdeo Prasad. "Regulation of signaling pathways involved in lupeol induced inhibition of proliferation and induction of apoptosis in human prostate cancer cells", Molecular Carcinogenesis, 12/2008 Crossref	13 words — < 1%
25	www.science.org Internet	13 words — < 1%
26	Basem Abdellatif, Mostafa Shibl, Tamer Khattab, John Tadrous, Tarek ElFouly, Nizar Zorba. "Caching Through the Skies: The Case of LEO Satellites Connected Edges for 6G and Beyond", Institute of Electrical and Electronics Engineers (IEEE), 2023 Crossref Posted Content	12 words — < 1%
27	Changcun Bai, Tingting Wei, Lingyue Zou, Na Liu, Xiaoquan Huang, Meng Tang. "The apoptosis induced by CdTe quantum dots through the mitochondrial pathway in dorsal root ganglion cell line ND7/23", Journal of Applied Toxicology, 2022 Crossref	12 words — < 1%
28	Lu, Phong. "Mitochondrially Targeted p53 and p53-BH3 Fusion for High-Grade Serous Ovarian	12 words — < 1%

Cancer Gene Therapy", The University of Utah, 2023
ProQuest

29	spgykj.com Internet	11 words — < 1%
30	www.dovepress.com Internet	11 words — < 1%
31	acgpubs.org Internet	10 words — < 1%
32	biotechnologyforbiofuels.biomedcentral.com Internet	10 words — < 1%
33	e-sciencecentral.org Internet	10 words — < 1%
34	pubmed.ncbi.nlm.nih.gov Internet	10 words — < 1%
35	tcm.cmu.edu.tw Internet	10 words — < 1%
36	www.wjgnet.com Internet	10 words — < 1%
37	Jun - nan Hu, Jing Leng, Qiong Shen, Ying Liu, Xin - dian Li, Shi - han Wang, Hui - ping Li, Zi Wang, Ying - ping Wang, Wei Li. "Platycodin D suppresses cisplatin - induced cytotoxicity by suppressing ROS - mediated oxidative damage, apoptosis, and inflammation in HEK - 293 cells", Journal of Biochemical and Molecular Toxicology, 2020 Crossref	9 words — < 1%
38	Le-Le Zhang, Mu-Yang Huang, Yong Yang, Ming-Qing Huang, Jia-Jie Shi, Liang Zou, Jin-Jian Lu.	9 words — < 1%

"Bioactive platycodins from Platycodonis Radix: phytochemistry, pharmacological activities, toxicology and pharmacokinetics", Food Chemistry, 2020
Crossref

39	ruor.uottawa.ca Internet	9 words — < 1%
40	www.aging-us.com Internet	9 words — < 1%
41	www.researchsquare.com Internet	9 words — < 1%
42	"Sweeteners", Springer Science and Business Media LLC, 2018 Crossref	8 words — < 1%
43	Marie-Aleth Lacaille-Dubois, Clément Delaude, Anne-Claire Mitaine-Offer. "A review on the phytopharmacological studies of the genus Polygala", Journal of Ethnopharmacology, 2020 Crossref	8 words — < 1%
44	Xianghai Ren, Xiaoyu Xie, Baoxiang Chen, Liang Liu, Congqing Jiang, Qun Qian. "Marine Natural Products: A Potential Source of Anti-hepatocellular Carcinoma Drugs", Journal of Medicinal Chemistry, 2021 Crossref	8 words — < 1%
45	dx.doi.org Internet	8 words — < 1%
46	idus.us.es Internet	8 words — < 1%
47	pdffox.com Internet	8 words — < 1%

48	spandidos-publications.com Internet	8 words — < 1%
49	www.cjter.com Internet	8 words — < 1%
50	www.hindawi.com Internet	8 words — < 1%
51	www.j3.jstage.jst.go.jp Internet	8 words — < 1%
52	Liliane Eustache Okoumassoun, Caterina Russo, Francine Denizeau, Diana Averill-Bates, Dr. Janet E. Henderson. "Parathyroid hormone-related protein (PTHrP) inhibits mitochondrial-dependent apoptosis through CK2", Journal of Cellular Physiology, 2007 Crossref	7 words — < 1%
53	www.ncbi.nlm.nih.gov Internet	7 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	OFF