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*

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(Received May 20, 2023; Revised August 01, 2023; Accepted August 02, 2023)

Abstract: *Platycodon grandiflorum* (Jacq.) A.DC is a perennial single-species herb in the Campanulaceae family, and its dried roots have been widely used for a long time to diffuse the lung, soothe the throat, dispel phlegm, and expel pus as a Chinese traditional medicine. In addition, *P. grandiflorum* compounds are homologous to those in medicines and foods approved by the Ministry of Health of China, and many related foods have been marketed. It has been reported that the glycosides in pentacyclic triterpenoids, also known as saponins, are the main biologically active constituents of *P. grandiflorum*. This article offers a systematic review of recently reported saponins isolated from *P. grandiflorum* over the past decade covering the literature from the beginning of 2017 through the end of 2022 and describes their structural diversity and pharmacological studies. To the best of our knowledge, a total of 74 natural saponins have been isolated to date. For this review, 131 references on saponins were obtained, and the information from these articles is compiled herein. This review may be of interest to pharmacognosists and natural-product chemists. This review provides new ideas for the development and utilization of natural saponins for clinical applications in the future.

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

1. Introduction

The dried roots of *Platycodon grandiflorum* (Jacq.) A.DC, a single perennial herb species, were first described in "Shennong Herbal Classic" and are widely used traditional Chinese medicine

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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.409.2201.2328
Available online: August 15, 2023

[1]. *P. grandiflorum* is prescribed to diffuse the lung, soothing the throat, dispel phlegm, and expel pus, and is mainly used for the treatment of cough and phlegm, chest tightness, sore throat, laryngitis, and lung abscesses [2]. Additionally, it has been discovered that *P. grandiflorum* exerts a therapeutic effect on cardiovascular diseases, diabetes, atherosclerosis, and other diseases [3]. The compounds in *P. grandiflorum* are homologous to those in medicines and foods approved by the Ministry of Health of China [4]. The fresh roots of *P. grandiflorum* are widely used as edible vegetables in South Korea, North Korea, Japan, and Northeast China; therefore, the demand for *P. grandiflorum* is very high in East Asia [5]. The health effects of *P. grandiflorum* are also a focus of attention [6].

In recent years, phytochemical studies of *P. grandiflorum* have garnered considerable attention due to the potent and wide range of pharmacological activities of this plant; these functions include antitumor [7], anti-inflammatory [8], antioxidant [8], hypolipidemic [9], and antidiabetic effects [10]. As early as the beginning of the 20th century, Japanese researchers studied the chemical constituents of *P. grandiflorum*. The glycosides of pentacyclic triterpenoids, also known as saponins, are the main biologically active constituents in *P. grandiflorum* [4]. In addition to saponins, *P. grandiflorum* contains flavonoids, fatty acids, sterols, vitamins, and a variety of essential trace elements needed for the human body [11]. Several excellent reviews on various aspects of the components derived from *P. grandiflorum* have been published in recent decades [5, 12-13]. However, no work has been specifically aimed at pentacyclic triterpenoid saponins from *P. grandiflorum*. As part of our ongoing investigations into the biological compounds in *P. grandiflorum*, a detailed and comprehensive literature survey to summarize previously published structures has been performed. Because all the known structures of *P. grandiflorum* may not have been presented to date, this review presents the most recent research on the phytochemical and pharmacological characteristics of natural saponins isolated from *P. grandiflorum*.

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

2. Phytochemical Studies

A literature survey revealed that oleanane pentacyclic triterpene-type saponins are the main components of *P. grandiflorum* [14]. To date, 75 different kinds of triterpenoid saponins, particularly derived from oleanolic acid, have been isolated from *P. grandiflorum*. More precisely, the structures of triterpenoid saponins can be classified into five categories, including platycodin genins (**1-28**), platyconic acids (**29-39**), polygalacic acids (**40-56**), platyconic acid lactones (**57-65**) and other types of triterpenoids (**67-75**) [15]. For these compounds, the glycosylation positions are located mainly at positions C-3 and C-28, and glycol groups consist mainly of L-rhamnose, D-xylose, D-glucose, L-arabinose, and D-spinose and their derivatives [16].

2.1. Platycodin Genin-Type Saponins

Among all five categories, platycodin genins constitute the largest set of triterpenoids in *P. grandiflorum*. These saponins have characteristics consistent with the parent oleanolic acid, two hydroxymethyl molecules (-CH_2OH) located at the C-4 position, a total of five methyl molecules at the C-25, C26, C-27, C29, and C-30 positions, and a carbonyl group at the C-28 position.

Compounds **1**-**8** were isolated and identified as eight platycodin genin-type saponins by Ishii et al., and among these, Compounds **2**, **3,** and **5** were discovered by the aforementioned group. Notably, the O-acetyl groups at the C-2 or C-3 positions of rhamnose in these three compounds easily reversibly migrate [17]. Compounds **6**-**8** consist of saponin methyl esters, and the difference between them is based on differences in the sugar moiety at the C-4 position [18]. Compounds **9** and **26** are two recently identified compounds in *P. grandiflorum* characterized through spectroscopic and chemical evidence. Two identical CH_2OH moieties are located at the C-4 position of **9**, while CH_3 and CH_2OH groups are located at the C-4 position of **26** [19]. Compounds **10**, **11,** and **28** were purified and identified by He et al., and among these compounds, **11** and **28** were reported for the first time by this group. The biggest difference between these two newly identified saponins is that **11** carries two CH_2OH groups at C-4, while **28** carries two OH groups at the same position [20]. Compounds **12** and **13** were first isolated and identified by Fu et al., and between them, the monosaccharide has been identified as a glucose alcohol acetate on the basis of gas chromatography results [21]. Compound **14**, named deapio-platycoside E, is a disaccharide saponin with different sugar chains at the C-4 and C-28 positions [22]. The structure of Compound **15** is similar to that of **16**, which was first isolated by Choi et al. The difference between Compounds **15** and **16** is that the C-3 substituent in **15** is Glc^3-Glc, while that in **16** is Glc^6-Glc [23,24]. Compounds **17**-**19** were identified as three new compounds purified via silica gel column chromatography. At the C-3 position of **18** and **19,** a linked glucuronic acid (-GlcA) is evident, and an O-acetyl group is located in the 2,3-position of the rhamnose unit [25]. Similarly, the rhamnose in Compound **21** carries an O-acetyl group [26]. The structures of Compounds **22** and **23** are the same, except for the positions of the O-acetyl sugar moiety. Additionally, the C-28 position of Compound **24** consists of a disaccharide, which is different from that of Compound **25** [27,28]. In contrast to Compounds **1**-**26**, both Compounds **27** and **28** harbor two -OH groups attached at the C-4 position [29].

2.2. Platyconic Acid-Type Saponins

Only 10 platyconic acid-type saponins have been isolated from *P. grandiflorum* (Compounds **29**-**39**). These saponins are also derived from a parent oleanolic acid. They carry a COOR group; a CH_2OH group at the C-4 position; a total of five methyl groups at the C-25, C-26, C-27, C-29, and C-30 positions; and two carbonyls at the C-4 and C-28 positions.

Compounds **29**-**31** were first isolated by Ishii et al. in 1981. The difference between Compounds **29** and **30** is characterized by moiety at the C-2 position; in Compound **29** an H is the substitute molecule at the C-2 position, but CH_3 is the molecule at the C-2 position in Compound **30.** The C-2 and C-28 positions in **31** consist of a substituted H group and CH_3 group, respectively [22]. Compounds **32**, **33**, **35,** and **36** were simultaneously isolated from *P. grandiflorum* by Choi et al. for the first time [30]. The structures of Compounds **32** and **33** are almost the same, except at the C-2 and C-28 positions of **32,** a CH_3 substitution group is evident. The difference between Compounds **35** and **36** relates to the C-28 position. In Compound **35,** the C-28 position has been substituted with a COOH group, while that in Compound 3**6** has been replaced by a sugar group. Compounds **37**-**39** were first reported in 2010, and the rhamnose moieties in Compounds **37** and 39 are acetylated [25].

2.3. Polygalacic Acid-Type Saponins

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

This type of saponin was isolated from *P. grandiflorum* in 1978 (Compounds **40**-**44**) [25]. Among these compounds, the rhamnose moiety in Compounds **42**-**44** is acetylated, while in the other compounds, the rhamnose moiety is not acetylated. The structures of Compounds **45** and **46** are the same except for the substituents at the C-3 position, and both compounds were first isolated

in 1981 [22]. As the characteristic constituent of *P. grandiflorum* in Chinese pharmacopeia, Compound **47** (platycoside D) is a disaccharide glycoside with seven sugar groups and was first isolated by Nikaido et al. [23]. In contrast to that in Compound **47**, the C-3 position in Compound **48 (**platycoside G3) is replaced with a disaccharide chain [21]. Compounds **49**-**51** share the same structure except for the C-3 sugar chains [25]. Compound **52**, named 3-O-β-D-laminatedibiosyl polygalacic acid, was characterized with a COOH group linked to the C-3 and C-28 positions, respectively [31]. In contrast to that in Compounds **51** and **52**, the rhamnose moiety in Compound **53** is acetylated [32].

2.4. Platyconic Acid Lactone-Type Saponins

Only 9 platyconic acid lactone-type saponins have been isolated from *P. grandiflorum*. These saponins are derived from parent oleanolic acid, with a -CH_2OH group at the C-4 position and OH at the C-2 position; upon dehydration, they form a lactone structure, with a total of five methyl groups at the positions of C-25, C-26, C-27, C-29, and C-30 and two carbonyl groups at the C-23 and C-28 positions.

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

2.5. Other Types of Triterpenoid Saponins

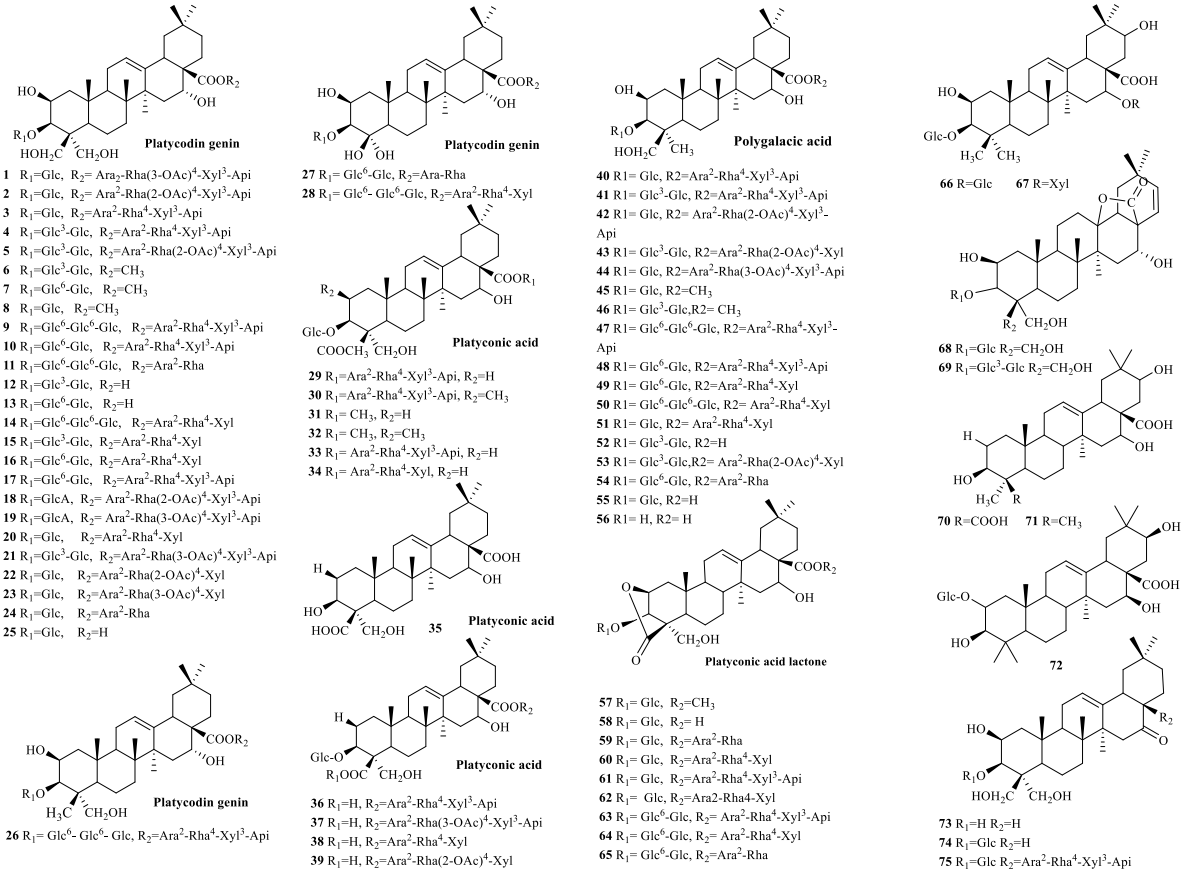
Ten saponins are structured in ways that differ from those described in the four aforemented categories. Compounds **66** and **67** were first isolated from *P. grandiflorum* by Ma et al. in 2013. The difference between them is the sugar moiety (either a Glc group or a Xyl group) located at the C-22 position [34]. The structural feature of Compounds **68** and **69** is based on the lactone ring formed by the COOH group at the C-28 position and an OH group at the C-13 position [35]. The main difference among Compounds **70**-**72** is the substituent groups at the C-4 position, and the differences among Compound **73**-**75** are the substituent groups at the C-3 and C-28 positions [36].

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

NO.	Name	M.F.	Classification	R1	R2	Ref.
1	Platycodin C	$C_{59}H_{94}O_{29}$	platycodin genin	Glc	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-Xyl^{3}-Api	[17]
2	Platycodin A	$C_{59}H_{94}O_{29}$	platycodin genin	Glc	Ara^{2}-$Rha(2\text{-}OAc)^{4}$-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}-$Rha(2\text{-}OAc)^{4}$-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 methyl ester	$C_{37}H_{60}O_{12}$	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}-$Rha(2\text{-}OAc)^{4}$-Xyl^{3}-Api	[25]
19	Platycodin L	$C_{59}H_{92}O_{30}$	platycodin genin	GlcA	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-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}-$Rha(3\text{-}OAc)^{4}$-Xyl^{3}-Api	[26]
22	Platycoside B	$C_{54}H_{86}O_{25}$	platycodin genin	Glc	Ara^{2}-$Rha(2\text{-}OAc)^{4}$-Xyl	[27]
23	Platycoside C	$C_{54}H_{86}O_{25}$	platycodin genin	Glc	Ara^{2}-$Rha(3\text{-}OAc)^{4}$-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]

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]



1 R_1=Glc, R_2= Ara_2-Rha(3-OAc)^4-Xyl^3-Api
2 R_1=Glc, R_2= Ara^2-Rha(2-OAc)^4-Xyl^3-Api
3 R_1=Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
4 R_1=Glc^3-Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
5 R_1=Glc^3-Glc, R_2=Ara^2-Rha(2-OAc)^4-Xyl^3-Api
6 R_1=Glc^3-Glc, R_2=CH_3
7 R_1=Glc^6-Glc, R_2=CH_3
8 R_1=Glc, R_2=CH_3
9 R_1=Glc^6-Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
10 R_1=Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
11 R_1=Glc^6-Glc^6-Glc, R_2=Ara^2-Rha
12 R_1=Glc^3-Glc, R_2=H
13 R_1=Glc^6-Glc, R_2=H
14 R_1=Glc^6-Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl
15 R_1=Glc^3-Glc, R_2=Ara^2-Rha^4-Xyl
16 R_1=Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl
17 R_1=Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
18 R_1=GlcA, R_2= Ara^2-Rha(2-OAc)^4-Xyl^3-Api
19 R_1=GlcA, R_2= Ara^2-Rha(3-OAc)^4-Xyl^3-Api
20 R_1=Glc, R_2=Ara^2-Rha^4-Xyl
21 R_1=Glc^3-Glc, R_2=Ara^2-Rha(3-OAc)^4-Xyl^3-Api
22 R_1=Glc, R_2=Ara^2-Rha(2-OAc)^4-Xyl
23 R_1=Glc, R_2=Ara^2-Rha(3-OAc)^4-Xyl
24 R_1=Glc, R_2=Ara^2-Rha
25 R_1=Glc, R_2=H

26 R_1= Glc^6- Glc^6- Glc, R_2=Ara^2-Rha^4-Xyl^3-Api

27 R_1= Glc^6-Glc, R_2=Ara-Rha
28 R_1= Glc^6- Glc^6-Glc, R_2=Ara^2-Rha^4-Xyl

29 R_1=Ara^2-Rha^4-Xyl^3-Api, R_2=H
30 R_1=Ara^2-Rha^4-Xyl^3-Api, R_2=CH_3
31 R_1= CH_3, R_2=H
32 R_1= CH_3, R_2=CH_3
33 R_1= Ara^2-Rha^4-Xyl^3-Api, R_2=H
34 R_1= Ara^2-Rha^4-Xyl, R_2=H

35

36 R_1=H, R_2=Ara^2-Rha^4-Xyl^3-Api
37 R_1=H, R_2=Ara^2-Rha(3-OAc)^4-Xyl^3-Api
38 R_1=H, R_2=Ara^2-Rha^4-Xyl
39 R_1=H, R_2=Ara^2-Rha(2-OAc)^4-Xyl

40 R1= Glc, R2=Ara^2-Rha^4-Xyl^3-Api
41 R1= Glc^3-Glc, R2=Ara^2-Rha^4-Xyl^3-Api
42 R1= Glc, R2= Ara^2-Rha(2-OAc)^4-Xyl^3-Api
43 R1= Glc^3-Glc, R2=Ara^2-Rha(2-OAc)^4-Xyl
44 R1= Glc, R2=Ara^2-Rha(3-OAc)^4-Xyl^3-Api
45 R1= Glc, R2=CH_3
46 R1= Glc^3-Glc,R2= CH_3
47 R1= Glc^6-Glc^6-Glc, R2=Ara^2-Rha^4-Xyl^3-Api
48 R1= Glc^6-Glc, R2=Ara^2-Rha^4-Xyl^3-Api
49 R1= Glc^6-Glc, R2=Ara^2-Rha^4-Xyl
50 R1= Glc^6-Glc^6-Glc, R2= Ara^2-Rha^4-Xyl
51 R1= Glc, R2= Ara^2-Rha^4-Xyl
52 R1= Glc^3-Glc, R2=H
53 R1= Glc^3-Glc,R2= Ara^2-Rha(2-OAc)^4-Xyl
54 R1= Glc^6-Glc, R2=Ara^2-Rha
55 R1= Glc, R2=H
56 R1= H, R2= H

57 R_1= Glc, R_2=CH_3
58 R_1= Glc, R_2= H
59 R_1= Glc, R_2=Ara^2-Rha
60 R_1= Glc, R_2=Ara^2-Rha^4-Xyl
61 R_1= Glc, R_2=Ara^2-Rha^4-Xyl^3-Api
62 R_1= Glc, R_2=Ara2-Rha4-Xyl
63 R_1= Glc^6-Glc, R_2= Ara^2-Rha^4-Xyl^3-Api
64 R_1= Glc^6-Glc, R_2= Ara^2-Rha^4-Xyl
65 R_1= Glc^6-Glc, R_2=Ara^2-Rha

66 R=Glc **67** R=Xyl

68 R_1=Glc R_2=CH_2OH
69 R_1=Glc^3-Glc R_2=CH_2OH

70 R=COOH **71** R=CH_3

72

73 R_1=H R_2=H
74 R_1=Glc R_2=H
75 R_1=Glc R_2=Ara^2-Rha^4-Xyl^3-Api

Figure 2. Chemical structures of natural saponins isolated from *P. grandiflorum*.

3. Pharmacological Studies

A literature survey revealed that previous pharmacological studies of *P. grandiflorum* mainly focused on crude saponin extracts and compounds with biofunctions, such as platycoside D (Compound **3**), which exhibits potent antitumor, anti-inflammatory activity, antioxidant activity, and so on.

3.1. Antitumor Activity

3.1.1. Effects on Cell Apoptosis

There are three main ways to induce apoptosis via *P. grandiflorum* saponin treatment: triggering mitochondrial pathway activation, death receptor pathway activation, and endoplasmic reticulum (ER) stress (Figure 3). By consulting a large number of studies, we found that *P. grandiflorum* saponins induce apoptosis in various cancer cells through their effects on the mitochondrial pathway. The B-cell lymphoma-2 (Bcl-2) family plays a very special role in the mitochondrial apoptosis pathway, as its members can regulate cancer cell apoptosis through complex interactions. This family of proteins are classified into two categories: pro-apoptotic factors and anti-apoptotic factors, with representative members of these factors being Bax and Bcl-2, respectively. A549 cells were used to study the anticancer mechanism of PD action. After PD (Compound **3**) treatment, the cells exhibited obvious apoptosis. Western blotting showed that the protein expression of the proapoptotic factors Bax and Bak in the cells had increased, and the protein expression of the antiapoptotic factors Bcl-2 and Bcl-xl had decreased, resulting in a

decrease in mitochondrial membrane potential and activation of the caspase program, eventually leading to cell death [41]. In cisplatin-resistant A549 cells (A549/DDP cells), PD also upregulate Bax expression and downregulated Bcl-2 expression to induce apoptosis [42]. These results showed that the Bcl-2 family of proteins play important roles in mitochondrial pathway-induced apoptosis. In addition to its effect on lung cancer cells, PD also induced apoptosis by regulating the Bcl-2 family proteins in the mitochondrial pathway in prostate cancer (RC-58T/h/SA#4) cells, human transitional cell carcinoma (5376) cells, rat adrenal pheochromocytoma (PC-12) cells, human breast cancer (MCF-7) cells and human liver cancer (HepG2) cells [43-47]. Reactive oxygen species (ROS) are mainly produced in mitochondria, and excessive ROS levels can lead to mitochondrial dysfunction and activate the mitochondrial apoptosis pathway. Zhang et al. studied the mechanism by which PD induced apoptosis in PC-12 cells and found that after PD treatment, the increase in intracellular ROS levels caused a decrease in mitochondrial membrane potential, which led to cell apoptosis. In another experiment with MG-63 cells, the mechanism underlying PD-induced apoptosis was found to be similar to that identified with PC-12 cells [48].

In addition to the effect of single-drug use, Zheng et al. found that PD combined with doxorubicin enhanced the anticancer activity of doxorubicin *in vitro*. Further study of the PD mechanism of action revealed that PD upregulated the protein expression of the ASK1, thereby promoting doxorubicin-induced ROS production, leading to the phosphorylation the ASK1 protein and JNK activation, eventually causing JNK-dependent apoptosis in PLC liver cancer cells [49]. In addition, Xuan et al. found that PD attenuated the resistance of HepG2 liver cancer stem cells to 5-fluorouracil, suggesting a new idea for the clinical treatment of tumors [50]. Studying 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 (involving fas) is an important apoptotic pathway. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces tumor cell apoptosis, but some tumor cells are not sensitive to TRAIL. Zhang et al. found that PD enhanced cell sensitivity of TRAIL, which formed a death receptor complex, and then activated Caspase 8, which initiated apoptosis in A549 cells [52]. Huang et al. showed that PD effectively induced apoptosis in the H1975 human lung adenocarcinoma cell line and was thus the first group to provide support for the hypothesized effect of PD. Exploring the mechanism of action the group found that PD promoted the extracellular release of PD-L1 [53]. Specifically, PD functions as a cholesterol-dependent lipid raft regulator to promote PD-L1 loading into extracellular vesicles [54], suggesting new therapeutic ideas for the use of natural products in anticancer treatment. In another study, the number of apoptotic cells was measured by flow cytometry and Western blot analysis. All the results showed that the apoptosis of human gastric cancer cells (AGS cells) caused by PD involved the activation of p38 protein expression [55]. Yu et al. found that PD induced the upregulation of GRP78/Bip and CHOP/GADD153, which play roles downstream of the ER, thereby activating Caspase 4. This finding also indicated that PD induced cancer cell apoptosis mediated through ER pathways [56]. Of course an inextricable link between PD-induced apoptosis and the MAPK pathway was also reported [55,56]. In addition to the common aforementioned pathways, PD has been shown to reduce telomerase activity [57], cause cell vacuole formation [58] and enhance immune responses [59], which are the underlying mechanisms by which PD induces apoptosis. It is also believed that PD does not induce apoptosis through a single pathway but through multiple pathways. Kong et al. measured the expression levels of apoptosis-related proteins by Western blotting. In summary, the experimental results indicated that after PD treatment, PARP was cleaved in the cells, and the levels of cleaved caspase-3 and -8 were increased, increasing fas pathway activation. At the same time, the Bcl-2/Bax ratio was reduced, and the levels of cleaved caspase-3 and caspase-9 were increased, and 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 the main mechanism by which *P. grandiflorum* saponins exert antitumor effects.

3.1.2. Effects on Cell Autophagy

By reading the literature, we found that PD plays a protective role against autophagy-related death in HepG2 cells, and the activation of 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 upregulation of BNIP3 expression in HepG2 cells induced mitochondrial changes, increased the expression of the autophagy-related protein Beclin1, and converted intracellular LC3-I into LC3-II, resulting in autophagy in liver tumor cells. These results prove that autophagy induction is a major approach to induce apoptosis [62]. In another liver cancer cell line called Bel-7402, PD activated the ERK and JNK pathways to induce autophagy [63]. In a study of lung cancer cells, PD upregulated the expression of Atg-3 and Atg-7 to promote the expression of LC3-II and induce autophagy [64]. When the n-butanol fraction of *P. grandiflorum* (Compounds **40** and **41**) was applied to A549 cells, Beclin-1 was upregulated and Blc-2 was downregulated, activating the AMPK pathway to induce autophagy [65]. Notably, treatments with drugs administered in conjunction with traditional medicines targeting a disease may lead to a stronger drug effect. Studies have shown that *P. 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 anticancer application of *P. grandiflorum*.

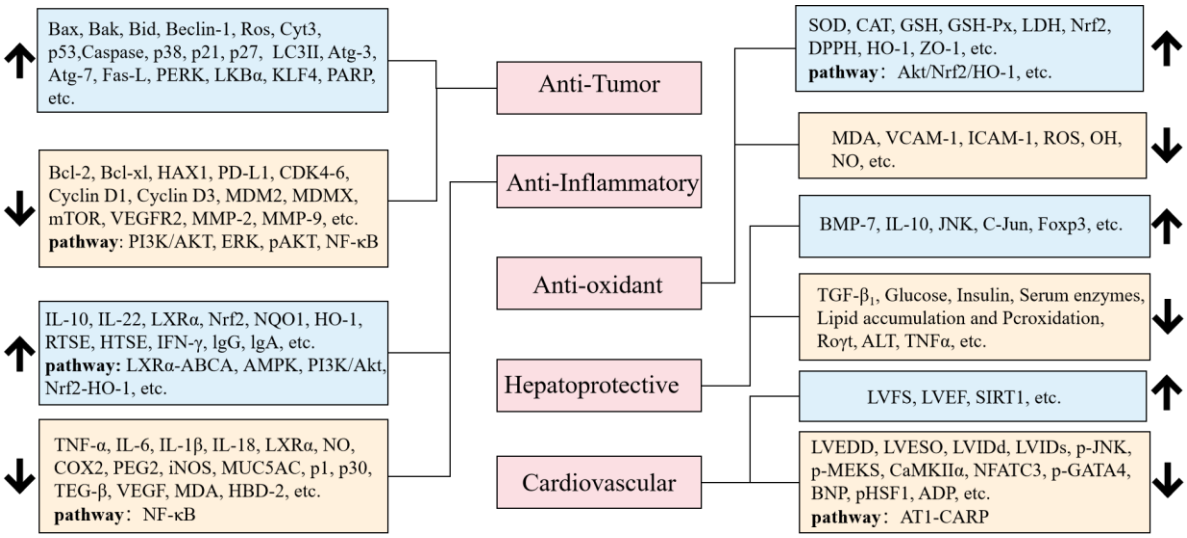


Figure 3. The mechanisms underlying the pharmacological activity of natural saponins isolated from *P. grandiflorum*.

3.1.3. Effects on Cell Cycle Arrest

Zhou et al. first demonstrated that prostate cancer cells were highly sensitive to PD and verified this finding with three different cell lines. All the results showed that fewer adenocarcinoma cell lines tended to be in the S phase. In contrast, the progression of DU185 cells and LNCaP cells, as well as other cells, was blocked in the G0/G1 phase, and PC-3 cells were blocked in G2/M phase [68, 69]. U251 cells and MDA-MB-231 cells also showed the same cell cycle arrest patterns. The difference between the U251 cells and MDA-MB-231 cells is that U251 cells inhibited PI3K/AKT pathway activation [70], while MDA-MB-231 cells inhibited cell proliferation by upregulating MDM2 downstream proteins (p21 and p51) causing cell cycle arrest [71]. Performing cell cytometry, Yi et al. found that total *P. grandiflorum* saponin inhibited the cell cycle of A549 cells in the G0/G1 phase in a dose-dependent manner [72]. Zhao et al. found that PD

also blocked A549 cells in G0/G1 phase, and the mechanism underlying this effect was based on PD inhibition of the expression of downstream the cell cycle regulatory proteins E2F1 and Rb [42]. In this study, the authors found that PD blocked A549/DDP cells in the G2/M phase through the aforementioned mechanism. By reviewing the literature, we found that PD also inhibited PC-3 cell progression in the G2/M phase [68]. In addition, we found that after PD acted on SW620 cells, as the expression of cyclin D1 in these cells decreased in the G1 phase, and the expression of CDK6 also decreased, blocking these cells from entering the S phase [73]. Ma et al. also proved that PD blocked HeLa cells in the G1 phase. The mechanism may be related to the downregulation of overexpressed YAP and TAZ downstream of the Hippo pathway and the upregulation of the expression of the proapoptotic factors Bax, P53, and Caspase-3 [74].

3.1.4. Effects on Cell Metastasis

The metastasis of cancer cells is the main cause of death in patients. Controlling cancer cell metastasis has become an antitumor approach in the clinic. Performing Transwell and scratch-wound assays Si et al. proved that PD effectively reduced the migration and invasion rates of BGC823 gastric cancer cells in a dose-dependent manner [75]. According to the literature, Chun et al. [76] first proved that PD inhibited cell migration and invasion by inhibiting the expression of MMP-9 (a proteolytic enzyme associated with cell metastasis). The mechanism was related to the inhibition of the ERK, p38 MAPK, JNK, and PI3K/AKT signaling pathways. In a study of non-small cell lung cancer (A549 and H460 cells), Zhao et al. confirmed this effect and found that PD also inhibited 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]. In OSCC cells, the mechanism was related to the phosphorylation of NF-κB p65, which was confirmed by *in vivo* and *in vitro* experiments. In addition, Cao et al. demonstrated that PD also inhibited the migration and invasion of endometrial cancer cells by regulating KLF4 expression [80]. In addition, Wu et al. found that PD inhibited the NF-κB and JAK2/STAT3 pathways in multiple myeloma cells and enhanced the sensitivity of these cells to BTZ to inhibit their migration and invasion [81].

In addition to the abovementioned antitumor mechanisms, other mechanisms of PD action have been reported. By reading the literature, we found that PD has recently been found to inhibit angiogenesis an achieve antitumor effects in animal studies [81-84]. PD reversed the resistance of acetylase inhibitors (HDACis) in human hepatocellular carcinoma (HCC) cells [85] and was identified as a previously unrecognized Hsp90 inhibitor [86], offering new directions for the treatment of tumor-related diseases. Moreover, Lee et al. found that PD induced apoptosis in highly metastatic breast cancer cells and in mature osteoclasts in mice, inhibiting breast cancer-induced bone destruction [87]. The combination of PD and doxorubicin inhibited glucose metabolism in HeLa cells, which is previously unknown antitumor mechanism [88]. In addition, in the treatment of tumor-related diseases, the inhibition of regulatory feedback loops is limited [89], and the administration of a combination of drugs has become a hot spot in clinical practice. The aforementioned studies reported that PD administered in combination with different drugs exerted different effects on different types of tumor cells [90-92]. Choi et al. found that the antitumor effect of *P. grandiflorum* extract on A549 cells was achieved by inhibiting the expression of mucin 5, subtypes A and C (MUC5AC), which had been induced by acrolein and was related to the inhibition of the ROS-PKCd-MAPK pathway [93]. Chen et al. found a new strategy for PD treatment of bladder cancer by showing that it targeted the LncRNA-XIST/miR-335 axis [94].

Some compounds showed good antitumor effects when they were discovered. For example, Compound **14** inhibited the proliferation of a variety of tumor cells [95].

3.2. Anti-inflammatory Activity

According to the literature we reviewed, since 2001, PD been used to exert anti-inflammatory effects through its inhibition of COX-2 protein activity and subsequent reduction in PEG2 production in rat peritoneal macrophages [96]. Subsequently, Compounds **2**, **3**, **10**, **40**, and **42** exhibited significant anti-inflammatory activity against LPS-induced RAW264.7 cells [97,98].

Wang et al. discovered that in LPS-induced inflammation in bMEc cells, PD exerted anti-inflammatory effects by upregulating the expression of LXRα, which reduced the rate of pro-inflammatory factor release and inhibited the induction of NF-κB pathway activation [99]. In another study, Fu et al. proved that PD exerted an inhibitory effect on inflammation by activating the LXRα-ABCA1 signaling pathway, which disrupted lipid rafts and prevented TLR4 from being transferred to inhibit LPS-induced inflammation in primary rat microglial cells [100]. By upregulating the expression of LXRα, PD also inhibited the inflammatory response of human osteoarthritis chondrocytes that had been induced via IL-1β [101], and it inhibited the LXRα/NF-κB signaling pathway in BV-2 cells that had been induced by Aβ, exerting anti-inflammatory effects [102]. Even in MPP^+-induced BV-2 cells, PD inhibited the LXRα/MyD88/NF-κB signaling pathway, producing an anti-inflammatory effect [103]. Wang et al. utilized IL-13 to induce an inflammatory response in RPMI2650 cells, confirming the anti-inflammatory mechanism of PD, and their findings demonstrated that PD reduced the protein expression of GM-CSF and eotaxin, inhibited p-NF-κB p56 expression in the induced cells, and suppressed MAPK pathway activation [104]. Ye et al. also found that PD inhibited S100A8/A9-induced 4T1 cell inflammation by inhibiting the expression of NF-κB p56 [105]. In addition, studies have found that PD inhibited IAV-induced apoptosis and autophagy in RAW 264.7 cells, thereby inhibiting influenza virus-induced apoptosis and autophagy pathways to inhibit the secretion of inflammatory factors induced by influenza virus infection and ultimately reduced the pathogenesis of influenza virus [106].

Many *in vivo* experiments 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. demonstrated that PD exerted a significant protective effect against acute lung injury (ALI), as evidenced by their ability to attenuate pathological pulmonary 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 of ALI suppressed the IRF3 signaling pathway and induced cholesterol depletion, which disrupted lipid raft formation and impeded TLR4 transport to lipid rafts, thereby inhibiting inflammation [109]. *P. grandiflorum* saponins have also been shown to exert highly anti-inflammatory effects *in vivo* on carrageenan-induced inflammation in lungs. The study showed that after drug treatment, the levels of PEG2, TNF-α, and COX-2 in rats and the rat paw edema was also extensively decreased [110]. Against cigarette smoke-induced pneumonia in mice, PD activated the Nrf2-HO-1 pathway and inhibited the activation of the NF-κB pathway [111]. Even for the novel coronavirus pneumonia in the past two years, PD prevented membrane fusion by eliminating membrane cholesterol, thereby preventing the entry of SARS-CoV-2 and subsequent pneumonia [112]. Studies have substantiated the idea that PD exerts a significant effect on ovalbumin-induced asthma. They revealed that PD not only reduced the proportion of macrophage cells and eosinophils in mouse airways and inhibited the production of proinflammatory factors but also inhibited NF-κB activation, playing a therapeutic role in asthma [113]. Moreover, PD inhibited the production of the transcription factor Th2 to inhibit airway inflammation in mice [114]. In addition, PD has been shown to exert a significant effect on BLE-induced pulmonary fibrosis [115]. Studies on skin inflammation have indicated that both PD and crude saponin extracts significantly reduced 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 the mice by activating AMPK signaling pathway cells [117]. With respect to inflammation caused by pathogenic microorganisms, studies have revealed that PD inhibited the adhesion of *Mycoplasma pneumoniae* to host cells and downregulated the expression of p1 and p30 to inhibit the development of inflammation [118]. In addition, PD inhibited the inflammation of oral mucosal epithelial cells caused by *Candida albicans* [119]. Undoubtedly, Compounds **27** and **65** were isolated and their ability to induce LPS-treated Raw 264.7 cells to secrete TNF-α was evaluated. The analysis showed that both of these compounds exhibited inhibitory activity at 50 μM, with the inhibition rate of platycoside Q (**65**) slightly larger; in general, both compounds showed good anti-inflammatory activity [29].

The inflammatory response is a result of a body's severe immune response; that is, inflammation is an immune process. The effect of PD on immune function is achieved mainly

through its role as ab adjuvant. Alum is a common adjuvant. To compare the adjuvant activity of PD and that of alum, the two adjuvants were used to immunize mice, and the antigen-specific cellular and humoral immune responses were evaluated. PD was found to increase cellular and humoral immune responses and showed the potential to be an adjuvant for the vaccine prevention and treatment of hepatitis B infection [120]. In addition, PD can be used as an adjuvant with the chicken infectious bronchopneumonia vaccine, and experiments have shown that PD can not only increased the cellular and humoral immune response in chickens but also exerted no side effects [121]. PD was also administered to the Newcastle disease virus recombinant avian influenza vaccine as an adjuvant, and it increased the immunogenicity of the vaccine [122]. In addition, PD promoted the proliferation of mouse spleen lymphocytes and phagocytosis by mouse peritoneal macrophages, thereby enhancing the immune response of Th1 and Th cells in immunized mice [123].

3.3. Antioxidant Activity

P. grandiflorum saponins exert an excellent scavenging effect on free radicals; that is, they show high antioxidant capacity, but they are different due to the structure of their aglycones and the number of sugar groups they carry [124]. With increased concentration, the ability of PD to scavenge free radicals increases, and it shows antioxidant capacity similar to that of VC at a certain concentration [125]. Wang et al. used oxidized low-density lipoprotein to induce human venous endothelial cells (HUVECs) and study the antioxidant effect of PD; they found that PD increased the release of NO, reduced the expression of malondialdehyde (MDA), VCAM-1 and ICAM-1, and reduced cell adhesion [126]. PD also activated the Akt/Nfr2/HO-1 signaling pathway to protect cardiomyocytes from injury [127]. When PD acted on cells after hypoxia/glucose deprivation/reperfusion-induced oxidation, Wang et al. found that regulated the PI3K/Akt/mTOR pathway in cortical neurons [128]. In addition, PD has exerted good effect on age-dependent endogenous oxidative damage. It prevented premature aging caused by H_2O_2, mainly by increasing mitochondrial biosynthesis rates [129].

3.4. Hepatoprotective Activity

PD reduces hepatic fibrosis, possibly by inducing a reduction in TGF-β1 level, n increase in BMP-7 expression, and the inhibition of hepatic stellate cell proliferation and activation [130]. Other studies have revealed that PD attenuated hepatic fibrosis by activating JNK- and c-Jun-mediated cell apoptosis and autophagy in hematopoietic stem cells, which is considered to be the mechanism underlying the effective attenuation of hepatic fibrosis [131]. Li et al. first discovered that PD exerts a protective effect on alcohol-induced liver injury by reducing oxidative stress and inhibiting the inflammatory response [132]. In response to acetaminophen-induced hepatotoxicity, PD exerts a protective effect by regulating oxidative stress, the inflammatory response, and hepatocyte apoptosis associated with the MAPK pathway [133]. Another study showed that CKS can also prevent ethanol-induced liver injury [134]. For alloxan-induced liver injury, PD has been shown to reduce the phosphorylation of JAK and STAT-3 and thus reduce the expression of RORγ and Foxp3 [135]. In addition, the activities of platycodonoid A (Compound **72)**, polygalacin D (Compound **44**), and PD isolated from *P. grandiflorum* have been studied, and they showed effective hepatoprotection [25].

3.5. Cardiovascular Protection Activity

Many studies have shown that *P. grandiflorum* saponins exert effect cardiovascular protection. Lin et al. studied the effect of PD on cardiac complications caused by hypertension. The results showed that PD inhibited the transcription and translation of IGF-IIR, thereby inhibiting the expression of PHSF1 and pJNF and upregulating the expression of SIRT1, which showed that PD protected cardiomyocytes from diseases caused by hypertension [136]. In another study, the protective effect of PD on the myocardium was found to be related to the inhibition of cardiac

fibrosis and reduction in myocardial hypertrophy [137]. In the acute myocardial infarction context, PD inhibited the left ventricular end-diastolic diameter and left ventricular end-systolic diameter, increased the left ventricular short-axis systolic rate and left ventricular ejection frequency, and inhibited the AT1-CARP signaling pathway to reduce cardiomyocyte apoptosis and increase cardiac function [138]. Studies have shown that PD exerts a protective effect on cardiovascular and cerebrovascular disease in many ways. To explore the neuroprotective effect of *P. grandiflorum* saponins, one study explored the effects of five components and demonstrated that PD and 2"-O-acetyl platycoside D2 (Compound **53**) exerted a protective effect on neurons after CA1 region ischemic injury *in vitro* and *in vivo* [32].

In addition to the protective effect on the heart, PD exerts an ameliorating effect on some vascular diseases. Studies have shown that PD exerts an attenuating effect on atherosclerosis and that PD combined with simvastatin exerts a synergistic therapeutic effect on atherosclerosis, providing the first molecular evidence for the PD treatment of atherosclerosis [139]. Naturally, some studies that have shown that PD plays an anti-atherosclerosis role, as well as a role in lowering cholesterol; two conditions in which PD shows very high potential as a drug candidate [140]. Studies have revealed that PD can induce cell resistance to atherosclerosis partly because PD increases the NO concentration and reduces the expression of cell adhesion molecules in endothelial cells exposed to OX-LDL and the adhesion of endothelial cells to monocytes [141]. Similarly, because it prevents platelet aggregation and activation, PD reduces arterial thrombosis and can impair hemostasis; therefore, PD is considered to be an effective antithrombotic drug [142].

3.6. Other Activities

It has been previously reported that PD confers protection against cisplatin-induced nephrotoxicity at both the cellular and animal levels. At the cellular level, studies using HEK-293 cells revealed that PD regulated oxidative stress, apoptosis, and inflammatory responses [143]. Another study reported that mouse experiments verified the effect of PD on cisplatin-induced nephrotoxicity. Moreover, renal injury in mice treated with PD showed signs of improvement, which verified the protective effect of PD on the kidney [144].

In recent years, PD has shown a good spermicidal effect. Researchers have found that PD exerts an instantaneous killing effect on sperm [145]. PD mainly destroys the sperm membrane, especially the sperm head membrane, causing the sperm to lose activity and causing late sperm apoptosis [146,147]. Leng et al. found that *P. grandiflorum* saponins protect against testicular dysfunction induced by heat stress, an outcome that depended on MAPK signaling pathway regulation [148]. The results of these studies confirmed that PD shows potential as a spermicide, and in the future, it may be used as a clinical spermicide to achieve contraceptive effects.

Many studies have shown that *P. grandiflorum* saponins exhibit a inhibitory effects on obesity. Zhao et al. found that the lipid metabolism of obese rats treated with *P. grandiflorum* saponins was controlled, resulting in a decrease in IDI cholesterol and a significant decrease in calorie intake, demonstrating that *P. grandiflorum* saponins may be a candidate drug for the treatment of obesity and hyperlipidemia [10]. Additional studies have revealed that PD induced the activation of the AMPK pathway to upregulate the expression of AMPKα, reduce the expression of other related adipogenic factors, and ultimately increased lipid metabolism to control obesity [149,150]. Moreover, PD also reduced obesity by inhibiting lipid accumulation [151]. Han et al. found that crude saponins may show pancreatic lipase activity and inhibit the decrease in intestinal sucrase activity, thereby reducing the absorption of dietary fat [152].

After UV radiation increased pigmentation, PD showed an inhibitory effect on melanin production by suppressing cAMP signaling during melanin production, and melanocyte dendrites also played an inhibitory role [153]. PD contributed to the activation of β-catenin, the differentiation of osteoblasts, and the regulation of osteogenic differentiation, providing new ideas for the treatment of osteoporosis [154]. PD has also been found to induce the apoptosis of HaCaT immortalized human keratinocyte cells at the transcriptome level [155]. PD is also a potential drug for the treatment of osteoporosis because it can inhibit the NF-κB, ERK and p38 MAPK pathways induced by NF-κB ligand (RANKL) receptor activators, thereby inhibiting osteoclast differentiation

[156]. In mouse tail flick, writhing, and formalin tests, PD showed strong anti-nociceptive effects, via an analgesic effect, and the study indicated that this effect was not mediated by opioid receptor stimulation [157].

In addition, the effects against respiratory syncytial virus, herpes simplex virus 1, and influenza A virus infection by extracted *P. grandiflorum* saponin compounds (Compounds **9**, **10**, **11**, **28**, and **48**) were evaluated. Except for weak effect of Compound **10** on respiratory syncytial virus activity, the antiviral activity of these compounds was found to be moderate [16].

4. Discussion

In this paper, we reviewed the saponin components isolated from *P. grandiflorum* in recent years, and their extensive pharmacological activity, especially the activity of PD, was summarized. The future of *P. grandiflorum* saponin pharmacological activity research and a theoretical basis for the clinical development and utilization of these compounds were described.

According to the literature we retrieved, research on *P. grandiflorum* has been extensive, but there are still some shortcomings at this stage of research. First, research on the components of *P. grandiflorum* has mainly focused on polysaccharides and saponins, but relatively few studies on flavonoids, polyphenols [158], and other components have been reported. Second, pharmacological studies to date have been aimed mainly at *P. grandiflorum* extracts and monomer components, such as platycodin D; however, the content of PD in *P. grandiflorum* is very low [159], so recent studies offer limited promise for the use of PD. Therefore, we should pay more attention and explore other monomer components. Third, the components studied to date are mainly extracted from the roots of *P. grandiflorum* [160], and it is necessary to study other parts of *P. grandiflorum*. Notably, natural saponins are considered the main active ingredients in *P. grandiflorum*, but *in vivo* studies have revealed that these compounds show low bioavailability, and few pharmacokinetic studies performed *in vivo* have been reported Therefore, the metabolism of saponins *in vivo* needs to be extensively studied.

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), High Level Traditional Chinese Medicine Key Disciplines of the State Administration 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.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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