TMR Publishing Group

TMR Modern Herbal Medicine
homepage: https://www.tmrjournals.com/mhm

A review of the ethnobotanical value, phytochemistry, and pharmacology of *Physalis pubescens* L.

Xin-Ping Cheng [1], Bin Yin [2,3], Qian-Kun Zheng [3], Zhen-Peng Xu[1], Lin-Tao Xu[1], Guang-Cheng Peng[1], Xiao-Ning Wang [1,*], Tao Shen [1,*]

[1]Key Lab of Chemical Biology (MOE), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, Jinan 250012, People's Republic of China;
[2]Poultry Institue, Shandong Academy of Agricultural Science, Jinan 250100, People's Republic of China;
[3]Delisi Industrial Park, Zhucheng 262200, Shandong province, People's Republic of China.

***Corresponding to** Prof. Tao Shen, Key Lab of Chemical Biology (MOE), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan 250012, People's Republic of China. Email: shentao@sdu.edu.cn;
Prof. Xiao-Ning Wang, Key Lab of Chemical Biology (MOE), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan 250012, People's Republic of China. Email: wangxn@sdu.edu.cn.

Peer review information
TMR Modern Herbal Medicine thanks anonymous reviewers for their contribution to the peer review of this work.

Citation
Cheng XP, Yin B, Zheng QK, et al. A review of the ethnobotanical value, phytochemistry, and pharmacology of *Physalis pubescens* L.. *TMR Modern Herb Med*. 2022; 5(3):18.

Executive editor Chao-Yong Wu

Submitted 23 July2022
Accepted 28 August 2022
Available online 1 September 2022

Abstract

Physalis pubescens L. (*P. pubescens*) was widely used for the treatment of inflammation-related diseases, such as sore throat, aphonia, phlegm, heat, and cough in folk medicine. The fruits of *P. pubescens* are commonly consumed as fruit in many areas of the world. In the past few decades, the phytochemistry and pharmacology of *P. pubescens* were extensively investigated. About 170 chemical constituents were purified from *P. pubescens*. The extract and chemical constituents of *P. pubescens* demonstrate diverse pharmacological effects, including anti-oxidation, anti-inflammation, anticancer, antimicrobial activity, immunomodulation, diuretic effect, hypoglycemic, and hypolipidemic in vitro and *in vivo*. Herein, we systematically summarized the ethnomedicinal uses, botanical characterization, distribution, phytochemistry, and pharmacology of *P. pubescens*, and establish the correlation between chemical constituents and pharmacological effects.

Keywords *Physalis pubescens* L.; Phytochemistry; Withanolides; Pharmacology; Anti-Inflammation

TMR
doi: 10.53388/MHM2022B0723001

Highlights

This paper reviewed botanical characterization, distribution, ethnomedicinal uses, phytochemistry, pharmacology and nutrition of *Physalis pubescens* L. and establish the correlation between chemical constituents, pharmacological effects, and ethnomedicinal uses of *P. pubescens.*, which will provide the proofs for the new drug discovery.

Background

The calyxes and fruits of the plants from the genus *Physalis*, commonly known as 'Suan-Jiang' (酸浆) in Chinese, were recorded in 'Shennong's Classic of Materia Medica' (Shen Nong Ben Cao Jing, 神农本草经), and have been adopted for the treatment of respiratory diseases in China for a long history [1]. The well-accepted species for 'Suan-Jiang' is *Physalis alkekengi* var. *franchetii*, which has been recorded in Chinese Pharmacopoeia. However, in some areas of China, *Physalis pubescens* L. (*P. pubescens*) has been used as a substitute for *P. alkekengi* var. *franchetii*, since their similar therapeutic effects against respiratory diseases. *P. pubescens* is an annual herb of the genus *Physalis* (Solanaceae) [2], and has been adopted to treat sore throat, aphonia, phlegm, heat, coughing, and urogenital system diseases in traditional Chinese medicines (TCM) and folk medicine [3]. In addition to its medicinal value, the fruits of *P. pubescens* are also consumed as edible fruit in many areas of the world since their sweet and sour taste, bright color, and high nutrition.

In recent years, the phytochemistry and pharmacology of *P. pubescens* were investigated extensively. About 170 chemical components including flavonoids, steroids, phenylpropanoids, terpenoids, alkaloids, and organic acids, were identified from the stems, leaves, calyxes, and fruits of *P. pubescens*. Its extract and ingredients exerted diverse bioactivities such as anti-oxidation, anti-inflammation, anticancer, antimicrobial, immunomodulation, diuretic, hypoglycemic, and hypolipidemic [4-9]. A review written in Chinese has summarized 125 ingredients extracted and purified from *P. pubescens* before 2017 and briefly described their biological activities [10]. However, in the last five years, great progress has been made in the phytochemistry and pharmacology of *P. pubescens*. Thus, compared with the published review, our review updated chemical constituents recently discovered in *P. pubescens* and totally summarized 170 chemical constituents. Moreover, our review analyzed the relationship between the chemical composition and pharmacological effects in more detail, to correlate its ethnomedicinal uses with its modern phytochemistry and pharmacology. Since the fruits have been consumed in large quantities, the nutritional content of *P. pubescens* has also been mentioned in our review.

Botanical characterization and distribution

P. pubescens is an annual herb with a pubescence-covered stem and usually has many densely hairy branches. The leaves are blade broadly ovate, 3 – 8 cm long, 2 – 6 cm broad, glabrescent or sparsely pubescent, base cordate, often oblique, margin usually unequal dentate, apex acute. Pedicel is 5 – 10 mm in length with densely pubescent. The calyxes are campanulate, densely pilose, lobes lanceolate, acutely pointed. The corollas are light yellow, with purple markings on throat, 6 – 10 mm in diameter. The seeds are nearly disc-shaped and about 2 mm in diameter. The fruits are globose, about 1.2 cm in diameter, yellow or purplish which is edible as fruit. The flowering period lasts from May to November. A picture of *P. pubescens* is shown in Figure 1. In China, *P. pubescens* was mainly distributed in Heilongjiang, Jilin, and Liaoning provinces.

Ethnomedicinal uses

There are more than 120 species of the genus *Physalis* (Solanaceae) in the world, and 5 species and 2 varieties in China, including *Physalis alkekengi* L., *Physalis alkekengi* L.var. *francheti* (Mast.) Makino, *Physalis pubescens* L., *Physalis minima* L., *Physalis angulata* L., *Physalis angulata* L. var. *villosa* Bonati, and *Physalis peruviana* L. (http://www.iplant.cn/info/*Physalis*?t=z). In ancient China, dry calyxes and fruits of *Physalis*, including *P. pubescens*, were usually used as TCM herb 'Suan-Jiang' (酸浆) [1, 3]. Presently, *P. pubescens* has been distinguished from other plants, and named as 'Mao-Suan-Jiang' (毛酸浆). Suan-Jiang was first recorded as a medium-grade herb with the effects of removing heat and clearing the throat in 'Shennong' s Classic of Materia Medica' (神农本草经) arisen in the period of the warring states, the Qin and Han Dynasties (B. C. 475–A. D. 220). Compendium of Materia Medica (本草纲目, A. D. 1578) clearly recorded that

Figure 1 Pictures of *P. pubescens* (fruits and calyxes)

Suan-Jiang had the effects of removing dampness heat and dampness, reducing phlegm, clearing lungs, and treating cough and gangrene. Many well-known classics of TCM, exemplified by Xin Xiu Ben Cao (新修本草, A. D. 659), Zheng Lei Ben Cao (证类本草, A. D. 1097), A Supplement to Compendium of Materia Medica (本草纲目拾遗, A. D. 1765), have also recorded its medicinal uses. It has the functions of clearing away heat, detoxifying, reducing phlegm, and diuresis, thus was used for symptoms such as sore throat, aphonia, phlegm, heat, coughing, and urine negative embolism. In Chinese folks, *P. pubescens* is often used internally to treat phlegm, cough, sore throat, hoarse voice or loss of voice, and unpleasant urination, and externally to treat skin diseases such as scars and eczema. In Dan Xi Cuan Yao (丹溪纂要, A. D. 1484), Yi Xue Zheng Zhuan (医学正传, A. D. 1515), Gui Yang Min Jian Yao Cao (贵阳民间药草, A. D. 1959), it has been recorded as Chinese folk medicines for the treatment of phlegm-heat cough, sore throat, dumb tone, and urination. Moreover, Suan-Jiang was also used as antipyretic and cardiotonic medicine in Japan.

Phytochemistry

The research on chemical composition of *P. pubescens* could be traced back to the 1980s. Until now, 170 chemical components have been isolated from *P. pubescens*, including steroids, flavonoids, phenylpropanoids, terpenoids, *N*-containing compounds, organic acids, and miscellaneous constituents. Withanolides and flavonoid were reported to be characteristic and active chemical constituents.

Steroids

About 52 steroids were isolated and identified from the calyxes, fruits, and aerial of *P. pubescens*. The steroids isolated from this plant could be mainly divided into two types, withanolides and sterols. Compared to sterols, withanolides are the characteristic and predominant bioactive components in *P. pubescens*.

(1) Withanolides Withanolides are a group of naturally occurring C28 steroids based on an ergostane skeleton, in which C-26 and C-22, or C-26 and C-23, are oxidized to form a δ – or γ -lactone [11]. The first withanolide, withaferin A (**2**), was found in the *Withania somnifera* by Lavie in 1965 [12]. Based on the difference in the substituted groups of C-17 side chain, most withanolides can be divided into two types, those containing δ -lactone or δ -lactol (Type A), and those containing γ -lactone or γ -lactol (Type B) side chain (Figure 2). The number of natural Type B withanolides is far fewer than that of Type A. Most of withanolides isolated from *P. pubescens* belong to the Type-A group (**1–39**), except for compounds (**40-41**) belonging to the Types-B group (Table 1). Many withanolides isolated from *P. pubescens* existed in the form of glycosides, e.g. physapubside A (**13**) as monoglycoside, and physapubside B (**14**) as diglycoside. Furthermore, the structures of withanolides from *P. pubescens* also contain some heteroatoms. For instance, (20*S*,22*R*,24*S*,25*S*,26*R*)-15α-acetoxy-6α-chloro-22,26:24,25-diepoxy-4β,5β,26-trihydroxyergost-2-en-1-one (**20**) has a molecule of chlorine (Cl), and (20*S*,22*R*,24*R*,25*S*)-15α-acetoxy-22,26-epoxy-4β,6α-[oxy(2β-hydroxy-2,1-ethanediyl) thio]-5β,24,25,26-tetrahydroxyergost-2-en-1-one (**37**) contains sulfhydryl group. Most remarkably, pairs of interconvertible C-26 epimeric isomers were found from *P. pubescens*, such as 26*S*-physapubescin F (**15a**) and 26*R*-physapubescin F (**15b**), 26*S*-physapubside C (**16a**) and 26*R*-physapubside C (**16b**), and so on.

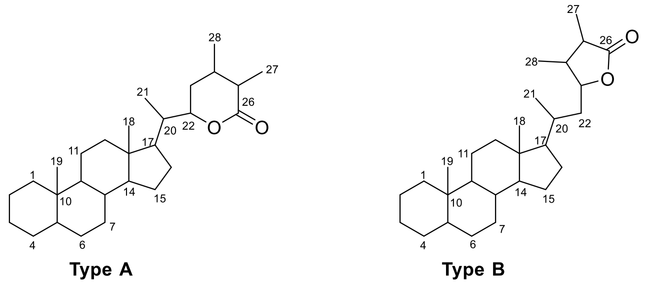
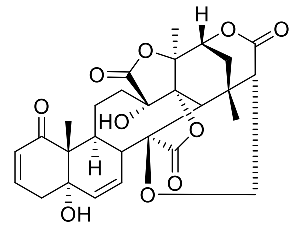


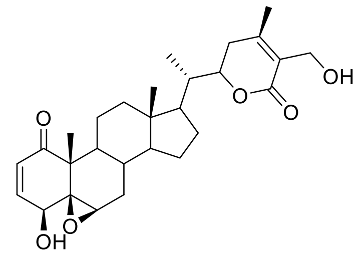
Figure 2 Structures of two important groups of withanolides (Types A and B)

Among these withanolides, physapubescins, which count up to 0.033% of the hairy groundcherry, are considered as representative ingredients of *P. pubescens* [13]. Physapubescins are a group of withanolides which usually contain 24,25-epoxy or ring opening at 24,25-epoxy to form two hydroxyl groups. Since the complexity of their structures, the absolute configuration of physapubescins, such as physapubescin A (**8**) and physapubescin B (**9**), were identified using single-crystal X-ray diffraction analysis or ECD data analysis.

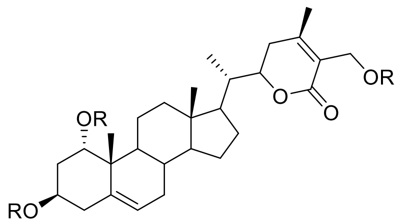
(2) Sterols At present, some sterols have been separated from the *P. pubescens*, exemplified by withapubeside C (**42**), withapubeside D (**43**), alkesterol A (**44**), alkesterol B (**45**), β-sitosterol (**50**), daucosterol (**51**), and stigmasterol (**52**) [14–16]. In addition, (22*E*,24*S*)-5α,8α-epidioxy-24-methyl-cholesta-6,22-dien-3β-ol (**46**) and (22*E*,24*S*)-5α,8α-epidioxy-24-methyl-cholesta-6,9(11),22-trien-3β-ol (**47**) containing peroxidic bond, as well as two glycosides 2α,3β-dihydroxy-5α-pregn-16-en-20-one 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-galactop yranoside (**48**) and (25*R*)-2α-hydroxy-5α-spirostan-3β-yl *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside (**49**) have been isolated from this plant. All structures of steroids from *P. pubescens* were summarized in Figure 3.



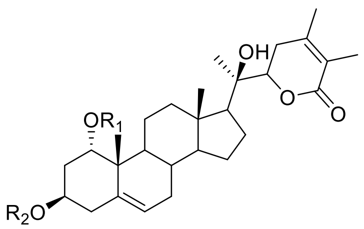
1



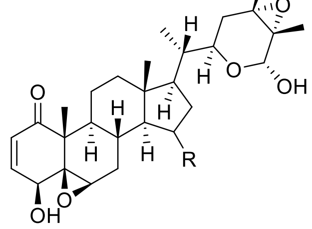
2



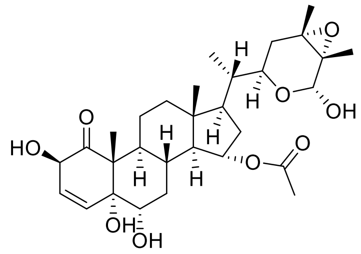
3 R=H
4 R=Ac



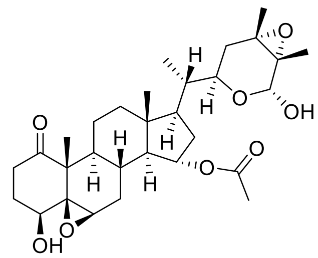
5 R_1=Ac, R_2=H
6 R_1=R_2=H
7 R_1=R_2=Ac



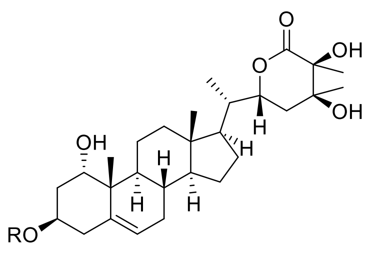
8 R=α -OAc
9 R=β -OAc



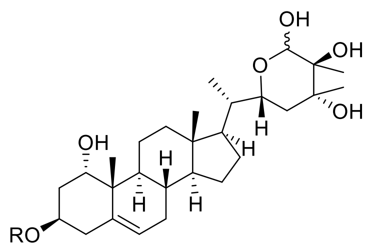
10



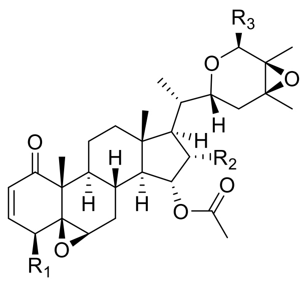
11



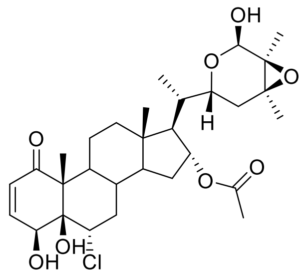
12 R=H
13 R=β -D-Glc
14 R=β -D-Glc-(1-6)- β -D-Glc



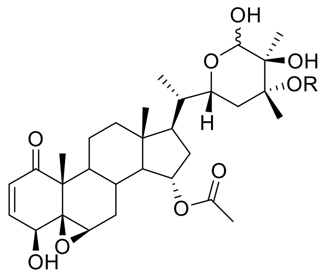
15a R=H (26α -OH)
15b R=H (26β -OH)
16a R=β -D-Glc-(1-6)-β -D-Glc (26α -OH)
16b R=β - D-Glc-(1-6)-β -D-Glc (26β -OH)



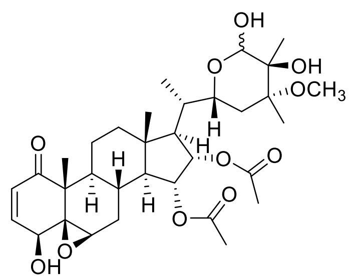
17 R_1=H, R_2=H, R_3=OH
18 R_1=OH, R_2=OAc, R_3=OH
19 R_1=OH, R_2=H, R_3=OCH_3



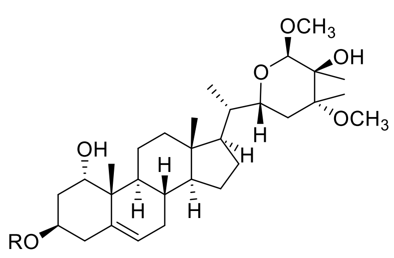
20



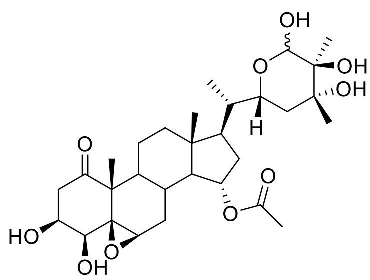
21a R=CH_3 (26α -OH)
21b R=CH_3 (26β -OH)
22a R=H (26α -OH)
22b R=H (26β -OH)



23a 26α -OH
23b 26β -OH

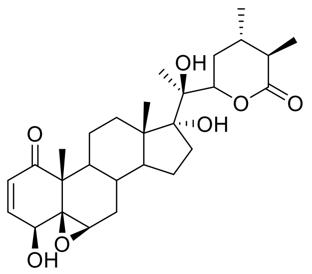


24 R=β -D-Glc-(1-6)-β -D-Glc
25 R=H

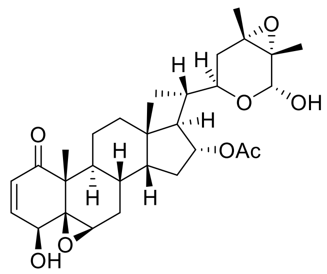


26a 26α -OH
26b 26β -OH

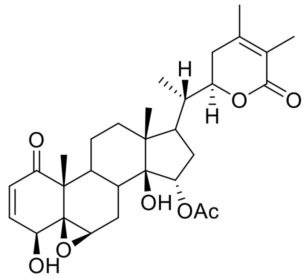
doi: 10.53388/MHM2022B0723001



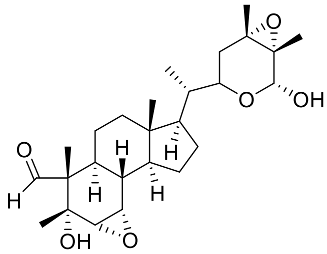
27



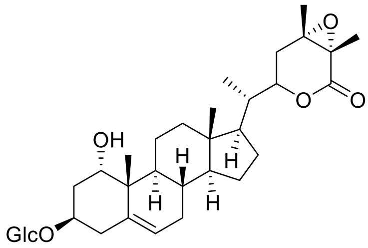
28



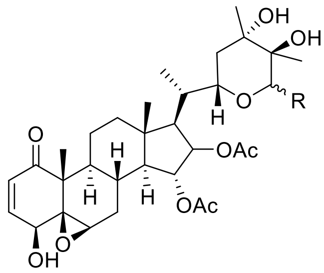
29



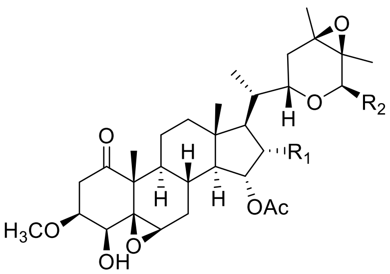
30



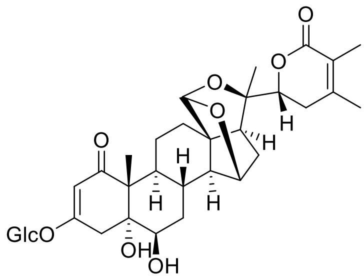
31



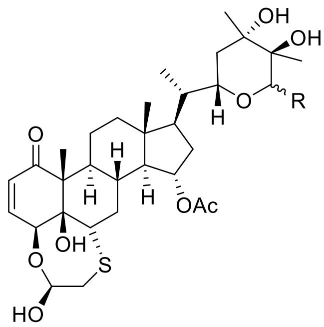
32a R=α -OH
32b R=β -OH



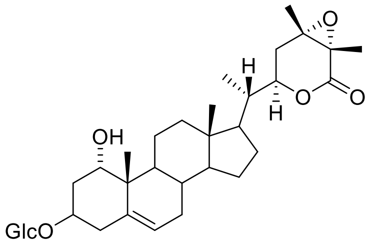
33 R_1=OAc, R_2=OH
34 R_1=OAc, R_2=OCH_3
35 R_1=H, R_2=OH



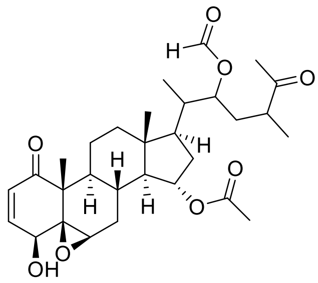
36



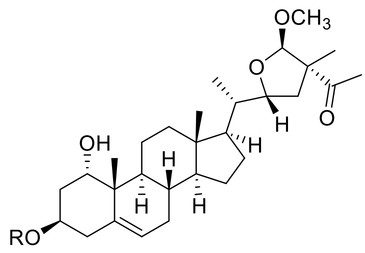
37a R=α -OH
37b R=β -OH



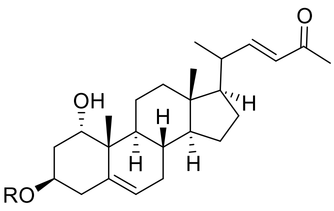
38



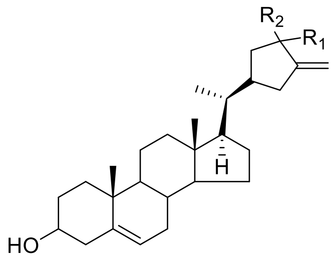
39



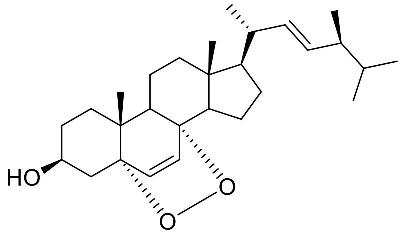
40 R=Gen
41 R=H



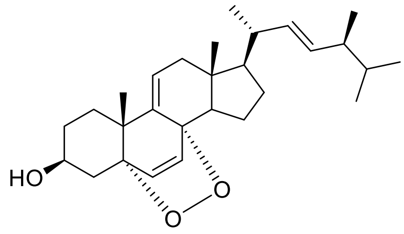
42 R=Glc
43 R=Gen



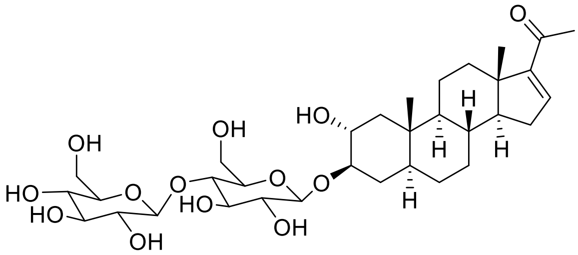
44 R_1=α -CH_3, R_2=β -OH
45 R_1=β -CH_3 ,R_2=α -OH



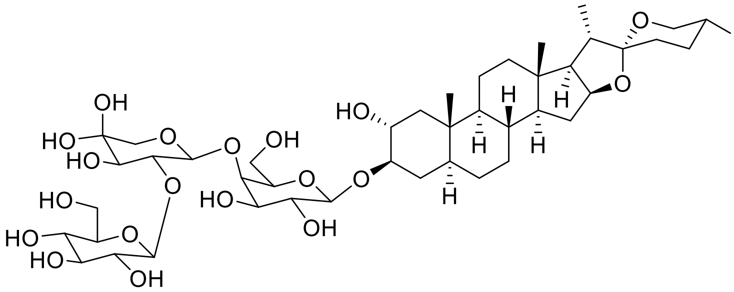
46



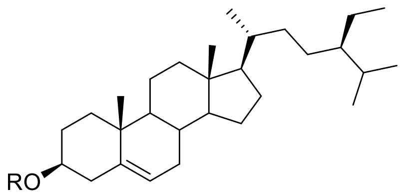
47



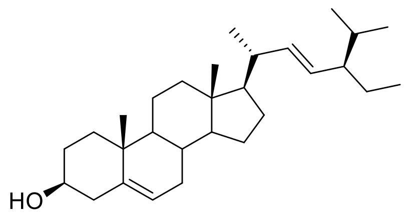
48



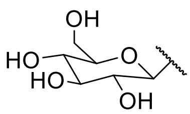
49



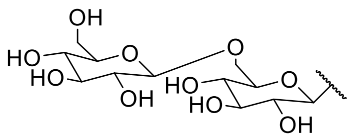
50 R=H
51 R=Glc



52



β -D-glucose (Glc)



gentiobiose (Gen)

Figure 3 Steroids isolated from *P. pubescens*

Flavonoids

About 36 flavonoids have been separated from the calyxes and fruit of *P. pubescens* (Figure 4). These isolated flavonoids are quercetin (**55**) and its derivatives (**56, 59-64, 85**), luteolin (**53**) and its glycoside rutin (**54**), kaempferol glycosides (**67-80**) [1, 14, 17–21]. Moreover, one chalcone [4,4′-dihydroxy-2′-methoxychalcone (**87**)] and one isoflavone [genistein-7-*O*-*β*-D-glucoside-4′-*O*-*α*-L-rhamnose-(1→2)-*β*-D-glucoside (**88**)] were obtained from the fruits and calyxes of this plant [14, 21]. In addition, three flavonol analogues, ombuine (**57**), 3′-methoxy ombuine (**58**), and oxyayanin A (**83**), were obtained from calyxes of *P. pubescens* [19, 22].

Phenylpropanoids

At present, about 31 phenylpropanoids, including simple phenylpropanoids, coumarins, and lignans, have been separated from *P. pubescens* (Figure 5). Among these phenylpropanoids, lignans have the activities of scavenging free radicals and anti-oxidation such as neo-olivil (**98**), nortrachelogenin (**99**), medioresinol (**100**), and pinoresinol (**101**) [1, 17]. Meanwhile, coumarins are also important members of phenylpropanoids from *P. pubescens*, such as imperatorin (**102**), xanthotoxin (**103**), bergapten (**104**), isopimpinellin (**105**), osthol (**106**), (−)-meranzin hydrate (**107**), and auraptenol (**108**) [20]. Furthermore, some phenylpropanoids are substituted by benzoethanol glycoside moiety, for instance, 1′-*O*-*β*-D-(3,4- dihydroxyphenyl)-4′-*O*-caffeoyl glucoside (**118**) and calceolarioside A (**119**).

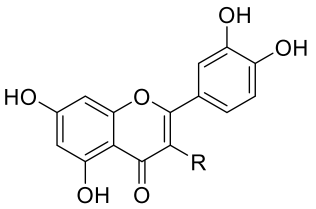
doi: 10.53388/MHM2022B0723001

Terpenoids

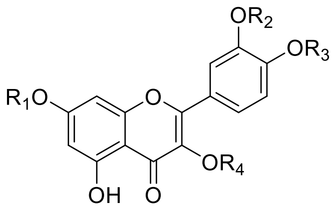
About 16 terpenoids have been discovered, covering sesquiterpenes, triterpenes (Figure 6) [1, 14, 19–22, 24]. Although the amounts of terpenoids isolated from *P. pubescens* were limited, there are still some compounds with distinctive structures. For example, 5-*O*-(*E*-feruloyl) blumenol (**122**) was regarded as the product of esterification reaction between sesquiterpene and phenylpropanoid. Some terpenoids isolated from *P. pubescens* existed in the form of glycosides, such as oleuropein (**120**), pulsatilla saponin A (**124**), pulsatilla saponin D (**125**), and 3,6,11-trimethyl-3-hydroxyl-1,6*E*,10-dodecatriene-8-*O*-*β*-D-glucoside (**126**). Moreover, lubimin (**130**) is a rare vetispirane-type sesquiterpenoid which has been isolated from *P. pubescens* in 2020 [18].

***N*-containing compounds**

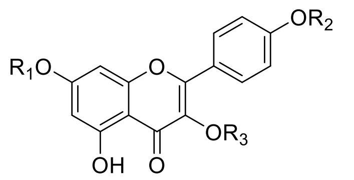
Three *N*-containing compounds have been separated from the roots of *P. pubescens*. (Figure 7), which are two alkaloids, uridine (**137**) and adenosine (**138**), and one amide *N*-*trans*-ferulogltyramine (**136**) [1, 17, 20].



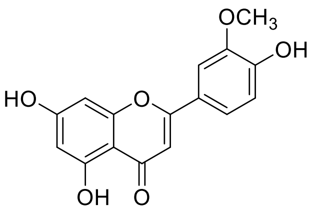
53 R=H
54 R=OGlc-Glc (6→1)



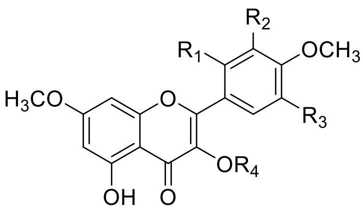
55 $R_1=R_2=R_3=R_4=H$
56 $R_1=R_4=CH_3$, $R_2=R_3=H$
57 $R_1=R_3=CH_3$, $R_2=R_4=H$
58 $R_1=R_2=R_3=CH_3$, $R_4=H$
59 $R_1=R_2=R_4=CH_3$, $R_3=H$
60 $R_1=R_2=R_3=H$, R_4=Glc
61 $R_1=R_2=R_3=H$, R_4=Gal
62 $R_1=R_2=R_3=H$, R_4=Ara
63 $R_1=R_2=R_3=H$, R_4=Rha
64 $R_1=R_2=R_3=H$, R_4= Glc-COO-CHCH-C_6H_5OH
65 $R_1=R_3=R_4=CH_3$, $R_2=H$
66 $R_1=CH_3$, $R_2=R_3=R_4=H$



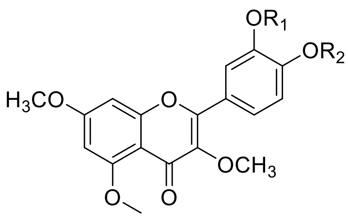
67 $R_1=R_2=R_3=H$
68 $R_1=R_3=H$, $R_2=CH_3$
69 $R_1=CH_3$, $R_2=R_3=H$
70 $R_1=R_3=CH_3$, $R_2=H$
71 R_1=Rha, R_2=H, R_3=Glc
72 R_1=Rha, $R_2=R_3=H$
73 $R_1=R_2=H$, R_3=Rha
74 R_1=Glc, R_2=H, R_3=Glc-Glc (2→1)
75 $R_1=R_2=H$, R_3=Gal
76 $R_1=R_2=H$, R_3=Glc
77 $R_1=R_2=H$, R_3=Rutinose
78 $R_1=R_2=H$, R_3=Sop
79 $R_1=R_2=H$, R_3=Rha-Glc(6→1)
80 R_1=Glc, R_2=H, R_3=Rha



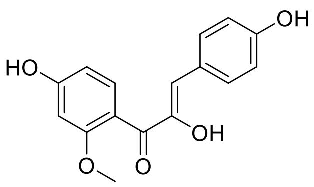
81



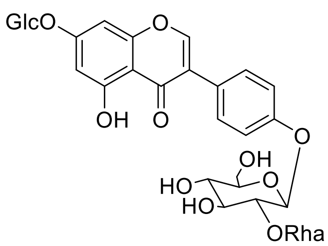
82 R_1=H, $R_2=R_3$=OH
83 $R_1=R_2$=H, R_3=OH, $R_4=CH_3$
84 $R_1=CH_3$, R_2=OH, $R_3=R_4$=H



85 R_1=Glc, R_2=H
86 R_1=H, $R_2=CH_3$

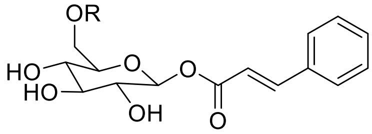


87

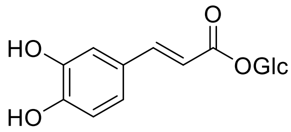


88

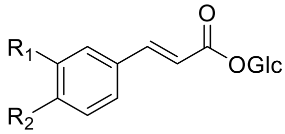
Figure 4 Flavonoids isolated from *P. pubescens*



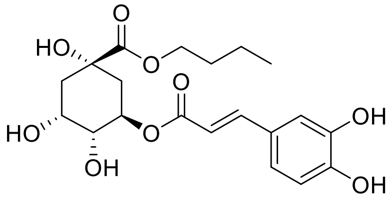
89 R=H
90 R=Glc



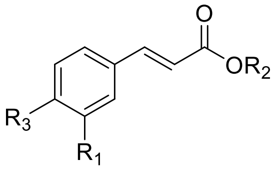
91



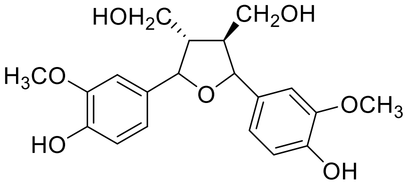
92 R_1=OH, R_2=OCH_3
93 R_1=H, R_2=OH



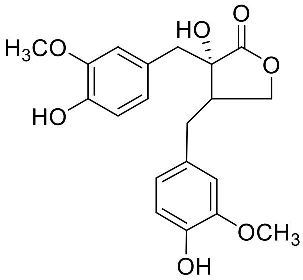
94



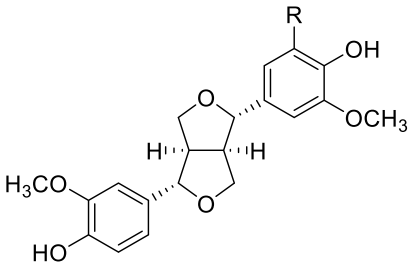
95 R_1=H, R_2=CH_2CH_3, R_3=OH
96 R_1=R_3=H, R_2=CH_3
97 R_1=R_3=OH, R_2=CH_2CH_3



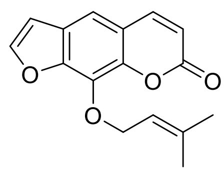
98



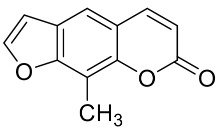
99



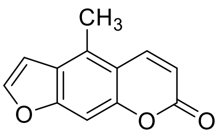
100 R=OCH_3
101 R=H



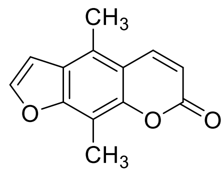
102



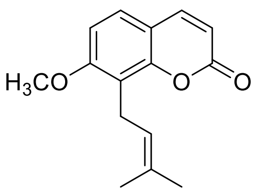
103



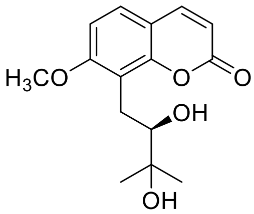
104



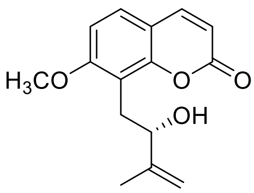
105



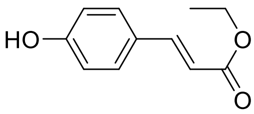
106



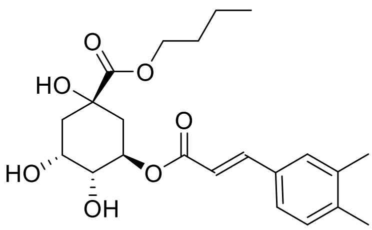
107



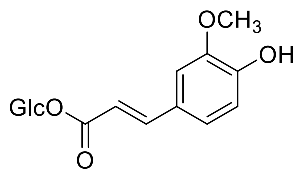
108



109



110



111

doi: 10.53388/MHM2022B0723001

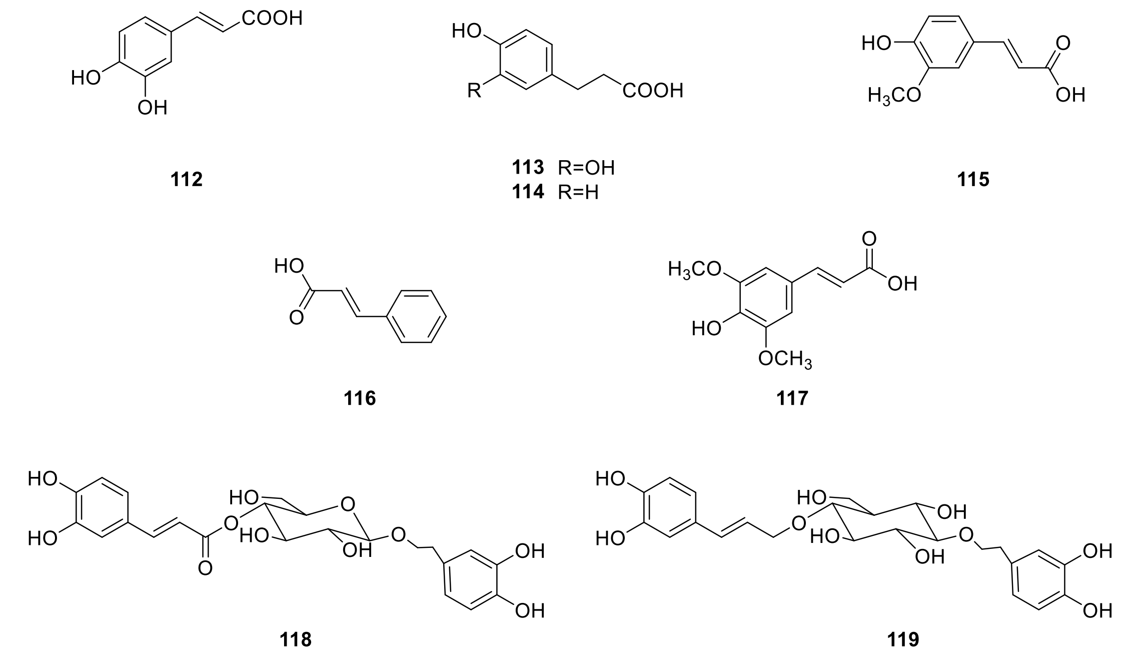


Figure 5 Phenylpropanoids isolated from *P. pubescens*

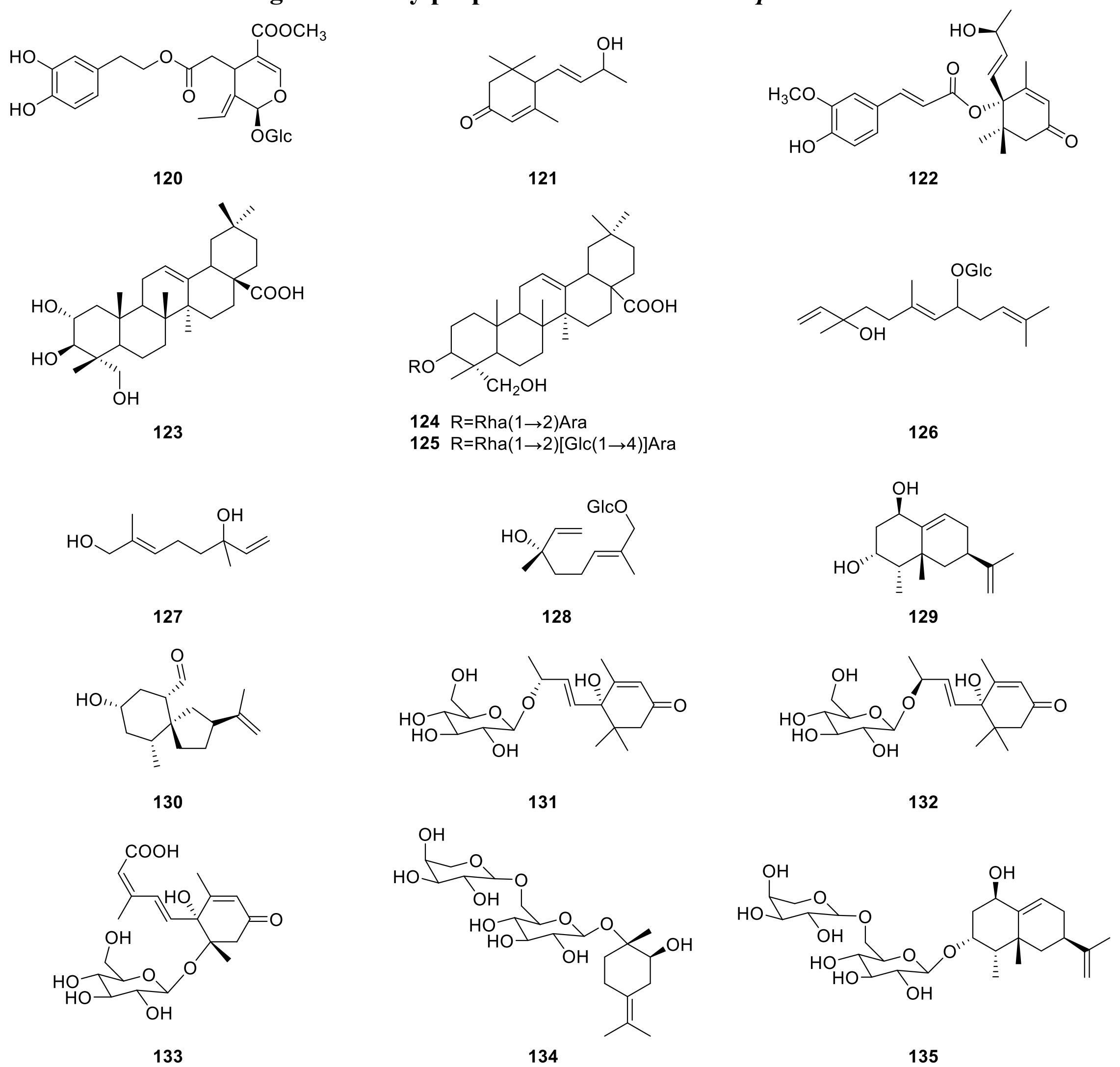
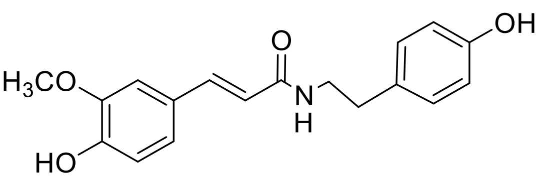
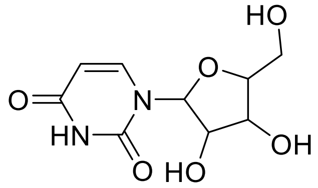


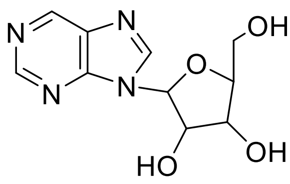
Figure 6 Terpenoids isolated from *P. pubescens*



136

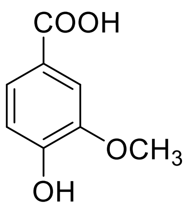


137

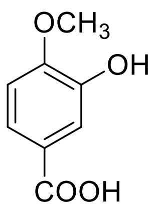


138

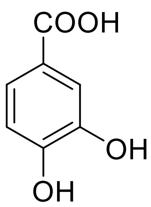
Figure 7 *N*-containing compounds isolated from *P. pubescens*



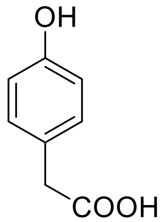
139



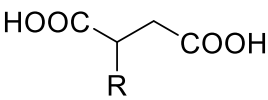
140



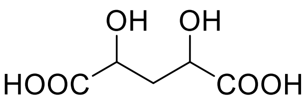
141



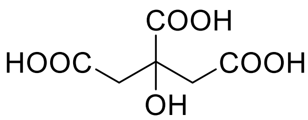
142



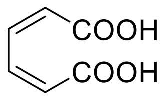
143 R=OH
144 R=H



145



146



147

Figure 8 Organic acid isolated from *P. pubescens*

Organic acids

Natural organic acids from *P. pubescens* are mainly classified as aliphatic organic acids and aromatic organic acids (Figure 8). At present, four aromatic organic acids are isolated from *P. pubescens*, which are 4-hydroyl-3-methoxy benzoic acid (**139**), 3-hydroxyl-4-methoxy benzoic acid (**140**), 3,4-dihydroxy benzoic acid (**141**), and 2-(4-hydroxyphenyl) acetic acid (**142**) [1, 14, 19, 20]. Aliphatic organic acids are dihydroxysuccinic acid (**143**), citric acid (**144**), malic acid (**145**), butanedioic acid (**146**) and *cis*,*cis*-muconic acid (**147**) [19].

Miscellaneous constituents

Plenty of other ingredients have been isolated, such as aromatic compounds (**148-158**), quinones (**159**), heterocyclic compounds (**161-166**), and aliphatic derivatives (Figure 9) [1, 9, 14, 18–22, 25]. Moreover, polyphenols (0.766 g/L) exemplified by tannic acid and pectins were rich in *P. pubescens*. Catechin, salicylic, para-cumaric, and chlorogenic acids are the most abundant phenolic compounds in the juice [26]. The content of oil in juice is very low (1.1 g/L), and most of it is unsaturated fatty acid, which makes *P. pubescens* a healthy fruit [27].

Nutrient content

The fruits of *P. pubescens* are consumed as high-quality fruit for their good taste and rich nutrition in many parts of the world. In Egypt, *P. pubescens* is used by local residents as a good source of vitamin supplements [28]. In Northeast China, it is also used to supplement nutrients, provide minerals, and regulate the body health. The contents of potassium, calcium, magnesium, zinc, copper, iron, phosphorus, and manganese in its juice are higher than the lime, lemon, and orange, suggesting that *P. pubescens* is an important source of these trace elements [29]. There is a high content of natural pigments with anti-oxidation and anti-cancer effects in *P. pubescens* [30].

The fruits of *P. pubescens* contain more than 18 kinds of amino acids, among which the essential amino acid content is distributed as follows: leucine (3.95%), valine (2.75%), lysine (2.58%), threonine (2.54%), phenylalanine (2.23%), isoleucine (1.91%), histidine (1.52%), methionine (1.02%), and tryptophan (0.51%) [31]. Thus, it is a good potential source of essential amino acids such as isoleucine, valine, and tryptophan [(4.2, 3.9, and 3.9) g/100 g protein] [28].

doi: 10.53388/MHM2022B0723001

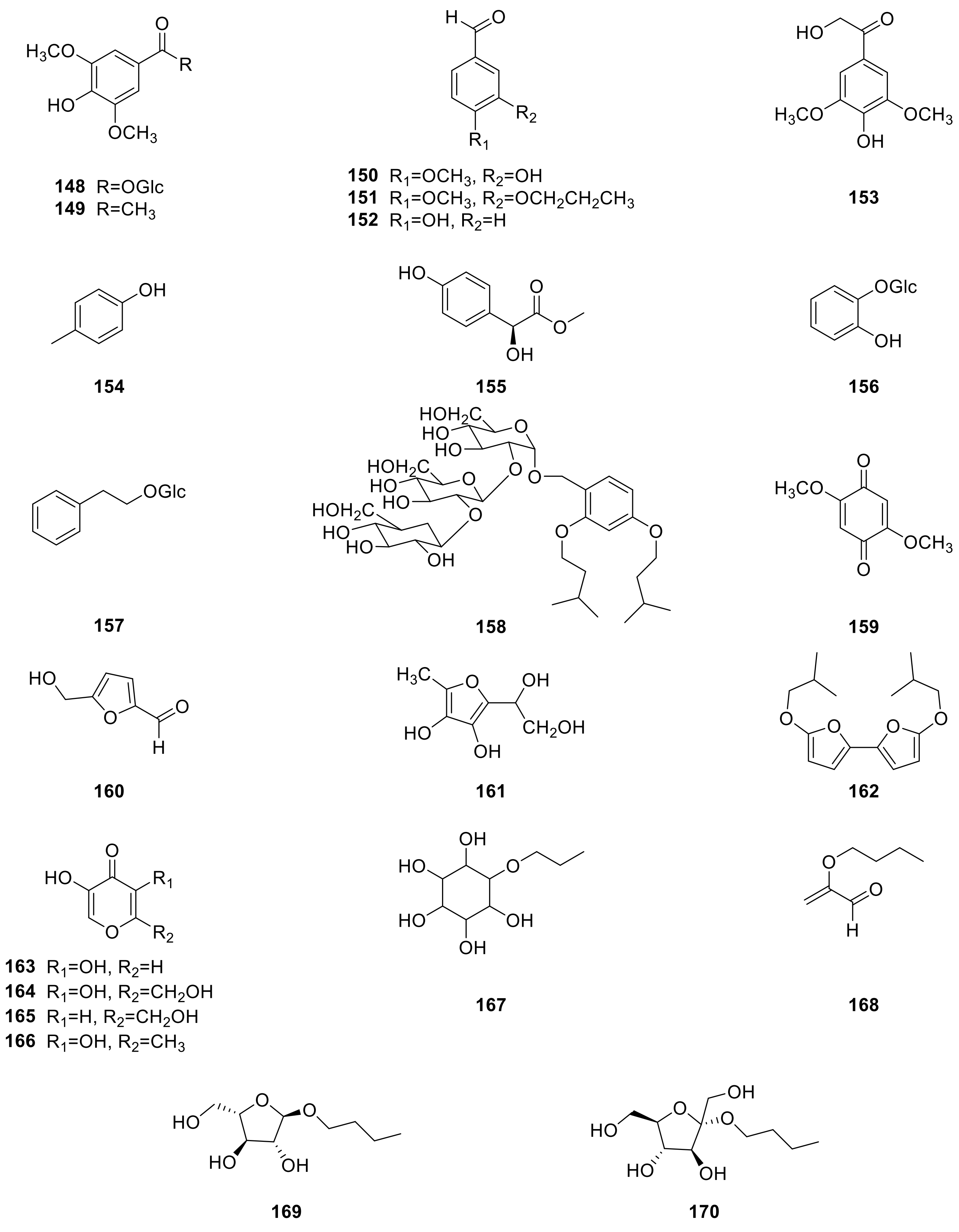


Figure 9 Miscellaneous constituents isolated from *P. pubescens*

Table 1 Chemical constituents isolated from the plant of *P. pubescens*

Classification	No	Chemical ingredient	Part of plant	Ref
Steroids	**1**	physalin P	fruits	[9]
	2	withaferin A	whole plant	[32]
	3	pubesenolide	whole plant	[32]
	4	pubesenolide triacetate	whole plant	[32]
	5	physalolactone B	whole plant	[32]
	6	deacetylphysalolactone B	whole plant	[32]
	7	physalolactone B monoacetate	whole plant	[32]
	8	physapubescin A	calyxes	[22]
	9	physapubescin B	calyxes and fruits	[7, 22, 33–36]
	10	physapubescin C	calyxes and fruits	[22, 33]
	11	physapubescin D	calyxes, fruits, and leaves	[20, 22, 33]
	12	physapubescin E	stems and leaves	[37]
	13	physapubside A	stems and leaves	[37]
	14	physapubside B	stems and leaves	[37]
	15a	26*S*-physapubescin F	stems and leaves	[37]
	15b	26*R*-physapubescin F	stems and leaves	[37]
	16a	26*S*-physapubside C	stems and leaves	[37]
	16b	26*R*-physapubside C	stems and leaves	[37]
	17	physapubescin H	stems and leaves	[37]
	18	physapubescin I	stems, leaves, and fruits	[37, 38]
	19	(20*S*,22*R*,24*S*,25*S*,26*R*)-15*α*-acetoxy-5,6*β*:22,26:24,25-triepoxy-26-methoxy-4*β*-hydroxyergost-2-en-1-one	stems, leaves, and fruits	[37, 39]
	20	(20*S*,22*R*,24*S*,25*S*,26*R*)-15*α*-acetoxy-6*α*-chloro-22, 26:24, 25-diepoxy-4*β*,5*β*,26-trihydroxyergost-2-en-1-one	fruits	[39]
	21a	(20*S*,22*R*,24*S*,25*S*,26*S*)-15*α*-acetoxy-5,6*β*:22,26:diepoxy-24-methoxy-4*β*,25,26-trihydroxy-ergost-2-en-1-one	fruits	[39]
	21b	(20*S*,22*R*,24*S*,25*S*,26*R*)-15*α*-acetoxy-5,6*β*:22,26:diepoxy-24-methoxy-4*β*,25,26-trihydroxyergost-2-en-1-one	fruits	[39]
	22a	(20*S*,22*R*,24*R*,25*S*,26*S*)-15*α*-acetoxy-5,6*β*:22,26-diepoxy-4*β*,24,25,26-tetrahydroxyergost-2-en-1-one	fruits	[39]
	22b	(20*S*,22*R*,24*R*,25*S*,26*R*)-15*α*-acetoxy-5,6*β*:22,26-diepoxy-4*β*,24,25,26-tetrahydroxyergost-2-en-1-one	fruits	[39]
	23a	(20*S*,22*R*,24*S*,25*S*,26Φ)-15*α*,16*α*-diacetoxy-5,6*β*:22,26-diepoxy-24-methoxy-4*β*,25,26*α*-trihydroxyergost-2-en-1-one	leaves	[15]
	23b	(20*S*,22*R*,24*S*,25*S*,26Φ)-15*α*, 16*α*-diacetoxy-5,6*β*:22,26-diepoxy-24-methoxy-4*β*,25,26*β*-trihydroxyerg-ost-2-en-1-one	leaves	[15]
	24	(20*S*,22*R*,24*R*,25*S*,26*R*)-22,26-epoxy-24,26-dimethoxy-1*α*,3*β*,25-trihydroxyergost-5-ene 3-*O*-[*β*-D-glucopyranosyl (1→6)]-*β*-D-glucopyranoside	stems and leaves	[37]
	25	(20*S*,22*R*,24*R*,25*S*,26*R*)-22,26-epoxy-24,26-dimethoxy-1*α*,3*β*,25-trihydroxyergost-5-ene	stems and leaves	[37]
	26a	(20*S*,22*R*,24*R*,25*S*,26*S*)-15*α*-acetoxy-5,6*β*:22,26-	fruits	[39]

		diepoxy-3β,4β,24,25,26-pentahydroxyergost-1-one		
	26b	(20*S*,22*R*,24*R*,25*S*,26*R*)-15α-acetoxy-5,6β:22,26-diepoxy-3β,4β,24,25,26-pentahydroxyergost-1-one	fruits	[39]
	27	philadephicalactones A	calyxes	[14]
	28	virginols A_1	calyxes	[14]
	29	physapubenolide	calyxes	[40]
	30	nic-2	calyxes	[41]
	31	nic-2 lactone	calyxes	[40]
	32	physapubescin K	fruits	[18]
	33	physapubescin L	fruits	[18]
	34	physapubescin M	fruits	[18]
	35	peruvianolide E	fruits	[18]
	36	withapubeside B	Stems	[42]
	37	physapubescin J	fruits	[18]
	38	pubescenin	calyxes	[40]
	39	physapubescin G	stems and leaves	[37]
	40	withapubeside A	stems	[42]
	41	withapubesin	stems	[42]
	42	withapubeside C	stems	[42]
	43	withapubeside D	stems	[42]
	44	alkesterol A	fruits	[43]
	45	alkesterol B	calyxes and fruits	[15, 43]
	46	(22*E*,24*S*)-5α,8α-epidioxy-24-methyl- cholesta-6,22-dien-3β-ol	leaves	[15]
	47	(22*E*,24*S*)-5α,8α-epidioxy-24-methyl-cholesta-6,9(11), 22-trien-3β-ol	leaves	[15]
	48	2α,3β-dihydroxy-5α-pregn-16-en-20-one 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	fruits	[25]
	49	(25*R*)-2α-hydroxy-5α-spirostan-3β-yl *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	fruits	[25]
	50	β-sitosterol	calyxes and fruits	[1, 14, 43, 44]
	51	daucosterol	calyxes and fruits	[1, 14]
	52	stigmasterol	fruits	[16]
Flavonoids	**53**	luteolin	calyxes	[19]
	54	rutin	calyxes	[14]
	55	quercetin	calyxes	[14, 19]
	56	3,7-dimethylquercetin	calyxes	[44]
	57	ombuine	calyxes and fruits	[18, 19]
	58	3′-methoxy ombuine	calyxes and fruits	[22]
	59	3,7,3′-trimethylquercetin	calyxes and fruits	[44]
	60	quercetin-3-*O*-β-D-glucopyranoside	calyxes and fruits	[1, 14]
	61	quercetin-3-*O*-β-D-galactoside	calyxes	[14]
	62	quercetin-3-*O*-β-D-arabinopyranoside	calyxes	[14]
	63	quercetin-3-*O*-α-L-rhamnoside	calyxes	[14]
	64	quercetin-3-*O*-(6′-*O*-*trans*-coumarinoyl)-β-D-glucopyranoside	fruits	[21]
	65	3,7,4′-trimethyl-myricetin	calyxes	[14]

	66	3,5,3′,4′-tetrahydroxyl-7-methoxyflavone	calyxes	[14]
	67	kaempferol	calyxes and fruits	[19]
	68	kaempferide	calyxes	[44]
	69	7-methyl kaempferol	calyxes	[44]
	70	3,7-dimethyl kaempferol	calyxes	[44]
	71	kaempferol-3-glucose-7-rhamnoside	calyxes	[14]
	72	kaempferol-7-*O*-*α*-L-rhamnopyranoside	calyxes	[14]
	73	kaempferol-3-*O*-*α*-L-rhamnoside	calyxes	[14]
	74	kaempferol-7-*O*-*β*-D-glucose-3-*O*-*β*-D-glucosyl-(1→2)-*β*-D- glucoside	calyxes	[14]
	75	kaempferol-3-*O*-*β*-D-galactoside	calyxes	[14]
	76	kaempferol-3-*O*-*β*-D-glucopyranoside	calyxes	[14]
	77	kaempferol-3-*O*-*β*-D-rutinoside	fruits	[21]
	78	kaempferol-3-*O*-*β*-D-sophoroside	calyxes	[14]
	79	kaempferol-3-*O*-*α*-L-rhamnosterin-(1→6)-*β*-D-glucoside	calyxes	[14]
	80	kaempferol-3-*O*-*β*-D-glucoside-7-*O*-*α*-L-rhamnosterin	calyxes	[14]
	81	chrysoeriol	fruits	[1]
	82	3′,5′,5-trihydroxy-3,4′,7-trimethoxyflavone	calyxes	[22]
	83	oxyayanin A	calyxes	[44]
	84	physalis pubescens flavones A	calyxes	[44]
	85	quercetin-3,5,7-trimethyl ether 3′-*O*-*β*-D-glucopyranoside	fruits	[21]
	86	3′,5-dihydroxy-3,7,4′-trimethoxyflavone	calyxes	[14]
	87	4,4′-dihydroxy-2′-methoxychalcone	fruits	[21]
	88	genistein-7-*O*-*β*-D-glucoside-4′-*O*-*α*-L-rhamnose-(1→2)-*β*-D-glucoside	calyxes	[14]
Phenylpropanoid	**89**	*trans*-cinnamoyl *β*-D-glucoside	fruits	[18]
	90	1-*O*-*trans*-cinnamoyl-*β*-D-Glucopyranosyl-(1→6)-*β*-D-glucopyranoside	fruits	[20]
	91	1-*O*-caffeoyl-*β*-D-glucopyranoside	fruits	[1]
	92	1-*O*-*p*-ferulyl-*β*-D-glucopyranoside	fruits	[1]
	93	1-*p*-coumaroyl-*β*-D-glucopyranoside	fruits	[1]
	94	5-*O*-caffeoyl quinic acid butyl ester	fruits	[1]
	95	*E*-ethyl 3-(4-hydroxyphenyl) acrylate	calyxes and fruits	[21, 24]
	96	*E*-methyl cinnamate	calyxes	[24]
	97	ethyl caffeate	fruits	[21]
	98	neo-olivil	fruits	[1]
	99	nortrachelogenin	fruits	[1]
	100	medioresinol	fruits	[1]
	101	pinoresinol	fruits	[1]
	102	imperatorin	fruits	[20]
	103	xanthotoxin	fruits	[20]
	104	bergapten	fruits	[20]
	105	isopimpinellin	fruits	[20]
	106	osthol	fruits	[20]
	107	(−)-meranzin hydrate	fruits	[20]
	108	auraptenol	fruits	[20]
	109	*trans*-*p*-coumaric acid ethyl ester	calyxes	[22]
	110	5-*O*-caffeoylquinic acid butyl ester	fruits	[1]

	111	1-ferulylglucose	fruits	[18]
	112	caffeic acid	fruits	[1]
	113	3,4-dihydroxybenzenepropionic acid	fruits	[20]
	114	*p*-hydroxybenzene propanoic acid	fruits	[20]
	115	ferulic acid	fruits	[45]
	116	cinnamic acid	fruits	[45]
	117	sinapic acid	fruits	[45]
	118	1′-*O*-*β*-D-(3,4-dihydroxyphenyl)-4′-*O*-caffeoyl glucoside	fruits	[1]
	119	calceolarioside A	fruits	[1]
Terpenoids	**120**	oleuropein	fruits	[21]
	121	blumenol A	fruits	[1]
	122	5-*O*-(*E*-feruloyl) blumenol	calyxes	[22, 24]
	123	arjunolic acid	fruits	[1]
	124	pulsatilla saponin A	fruits	[1]
	125	pulsatilla saponin D	fruits	[1]
	126	3,6,11-trimethyl-3-hydroxyl-1,6*E*,10-dodecatriene-8-*O*-*β*-D-glucoside	calyxes	[14]
	127	8-hydroxylinalool	fruits	[18]
	128	betulalbuside A	fruits	[18]
	129	capsidiol	fruits	[18]
	130	lubimin	fruits	[18]
	131	(6*S*,9*R*)-roseoside	fruits	[25]
	132	(6*S*,9*S*)-roseoside	fruits	[25]
	133	(1′*S*,6′*R*)-8′-hydroxyabscisic acid *β*-D-glucoside	fruits	[25]
	134	*p*-menth-4(8)-ene-12-diol 1-*O*-*α*-L-arabinopyranosyl-(1→6)-*β*-D-glucopyranoside	fruits	[25]
	135	1*β*,3*α*-dihydroxy-7*α*-eremophila-9,11-dien-3-*O*-[*α*-L-arabinopyranosyl-(l→6)]-*β*-D-glucopyranoside	fruits	[25]
***N*-containing compounds**	**136**	*N*-*trans*-ferulogltyramine	fruits	[20]
	137	uridine	fruits	[1]
	138	adenosine	fruits	[1]
Organic acids	**139**	4-hydroyl-3-methoxy benzoic acid	fruits and calyxes	[1, 44]
	140	3-hydroxyl-4-methoxy benzoic acid	calyxes	[14]
	141	3,4-dihydroxy benzoic acid	calyxes	[44]
	142	2-(4-hydroxyphenyl) acetic acid	fruits	[20]
	143	dihydroxysuccinic acid	calyxes	[45]
	144	citric acid	calyxes	[45]
	145	malic acid	calyxes	[45]
	146	butanedioic acid	calyxes	[45]
	147	*cis*,*cis*-muconic acid	calyxes	[44]
Miscellaneous constituents	**148**	syringic acid *β*-D-glucopyranosyl ester	fruits	[1]
	149	1-(4-hydroxy-3,5-dimethoxyphenyl) ethanone	fruits	[20]
	150	isovanillin	fruits	[24]
	151	4-methoxy-3-propoxybenzaldehyde	fruits	[9]
	152	*p*-hydroxybenzaldehyde	calyxes	[22, 24]

153	danielone	calyxes and fruits	[22, 24]
154	4-methyl phenol	calyxes	[22, 24]
155	(*S*)-methyl 2-hydroxy-2-(4-hydroxyphenyl) acetate	fruits	[20]
156	pyrocatechol 1-*O*-*β*-D-glucopyranoside	fruits	[20]
157	2-phenylethyl-*O*-*β*-D-glucopyranoside	fruits	[20]
158	*β*-D-glucose-(1-2)-*β*-D-glucose-(1-2-*α*-D-glucose-2,4–diisopentyl-oxybenoside	fruits	[9]
159	2,5-dimethoxybenzoquinoe	fruits	[20]
160	5-hydroxymethylfurfural	fruits	[21]
161	physalis pubescens furansu	calyxes	[44]
162	5,5′-diisobutoxy-2,2′-bifuran	calyxes and fruits	[22, 24]
163	3,5-dihydroxy-pyran-4-one	calyxes	[44]
164	3,5-dihydroxy-2-hydroxymethyl-pyran-4-one	calyxes	[44]
165	5-hydroxy-2-hydroxymethyl-pyran-4-one	calyxes	[44]
166	5-hydroxymaltol	calyxes	[44]
167	5-*O*-propyl-myo-inositol	fruits	[9]
168	*α*-butoxy-acrolein	fruits	[9]
169	butyl-*α*-L-arabinofuranoside	fruits	[18]
170	butyl-*α*-D-fructofuranoside	fruits	[18]

Pharmacology

From the perspective of modern medicine, the diseases which were treated by *P. pubescens* in TCM, such as sore throat, aphonia, phlegm, heat, and coughing, were highly related to inflammation, redox imbalance, and microbial invasion [46]. The extracts and the purified compounds of *P. pubescens* showed anti-inflammation, anti-oxidant, and antibacterial activities. Moreover, they also exerted diverse pharmacological activities, such as anticancer, regulating immunological competence, and antihyperglycemic effects. We focused on the pharmacology effects related to the traditional uses of *P. pubescens*, particularly on the anti-inflammation, anti-oxidant, and antibacterial activities, and try to establish their correlations. Furthermore, pharmacological effects of the extracts and ingredients were also discussed, which was expected to provide a basis for further investigations (Figure 10).

Anti-inflammatory effect

80% ethanol extract of the fruits of *P. pubescens* attenuated acute pyelonephritis. Treatment with ethanol extract of fruits relieved mouse ear edema and rats cotton ball granuloma. Treatment with 0.625 and 1.25 mg/mL ethanol extract significantly decreased the concentration of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) via inhibiting the mRNA and protein levels of nuclear factor-κB (NF-κB) [47]. Moreover, treatment with 0.3 and 0.6 g/kg ethanol extract of the fruits of *P. pubescens* significantly attenuated the kidney inflammation caused by ligation and reduced the accumulation of neutrophils [9]. The extract of crude polysaccharides (POL) from *P. pubescens* fruits ameliorated dextran sulfate sodium salt (DSS)-induced intestinal injury via attenuating the inflammation and oxidative stress in mice. Pretreatment with POL before DSS-stimulation suppressed the neutrophil infiltration and modulated the NF-κB/inducible nitric oxide synthase (iNOS)–cyclooxygenase-2 (COX-2) signal transduction pathway [4].

Steroids isolated from *P. pubescens* exert anti-inflammatory effects. Withaferin A (**2**) suppressed NF-κB and Akt and thus inhibiting the production of iNOS and NO in RAW 264.7 macrophages induced by lipopolysaccharide (LPS) [48]. Treatment with **2** protected kidneys from the inflammation induced by unilateral uretera obstruction (UUO) via inhibiting the expression of inflammatory factors [49]. Moreover, **2** suppressed the inflammatory disease state in several disease models, such as diabetes, obesity, neurodegenerative disorder, cystic fibrosis, and osteoarthritis [50]. Physapubescin A (**8**), physapubescin I (**18**), and physapubescin M (**34**) were all able to inhibit the production of NO in LPS-induced RAW 264.7 macrophages [18]. Withapubeside A (**40**), withapubeside B (**36**), withapubeside C (**42**), and withapubeside D (**43**) inhibited the production of NO induced by LPS via decreasing the level of iNOS [42].

The anti-inflammatory effects of flavonoids isolated from *P. pubescens* was also extensively studied, such as luteolin (**53**), quercetin (**55**), kaempferol (**67**), and chrysoeriol (**81**). **53** inhibited the LPS, nigericin, and adenosine triphosphate (ATP)-induced nod like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation in J774A.1 macrophages via interfering with ASC oligomerization. Treatment with **53** at doses from 5 to 40 μM suppressed the activation of caspase-1 and the secretion of IL-16 derived by NLRP3 inflammasome in J774 A.1 macrophages [51]. Moreover, **53** exerts anti-inflammatory effects in many animal inflammation models. Treatment with 100 mg/kg **53** suppressed the symptom of ulcerative colitis induced by DSS by regulating the SHP-1 / STAT3 pathway in mice [52]. Similarly, **53** inhibited the inflammation in the ovalbumin (OVA)-stimulated allergic rhinitis rat model [53]. In the diabetic nephropathy mouse model, **53** exerted anti-inflammatory effects via regulating the STAT3 pathway [54]. Treatment with **55** was able to suppress atherosclerosis by inhibiting NLRP3 inflammasome activation [55]. **55** also dose-dependently suppressed oedema and inhibited acute inflammation induced by monosodium urate (MSU) in rats [56]. Moreover, **55** attenuated lung and liver injury by suppressing inflammation induced by LPS and nickel [57–59]. Treatment with **55** exerted an inhibitory effect on systemic inflammation stimulated by LPS in mice [60]. **67** suppressed the inflammation in osteoarthritis via regulating the NF-κB pathway and inflammatory factors [61, 62]. Moreover, **67** showed a therapeutic effect in DSS-induced colitis and cisplatin-induced cardiac dysfunction and injury by suppressing inflammation [63, 64]. Pathogenic microbial invasion is the main cause of inflammation, **67** reduced the expression of TNF-α, IL-1β, IL-8, and IL-18 in human gastric adenocarcinoma AGS cells [65]. The inhibition of **81** on NF-κB, AP-1, and phosphorylation of phosphatidylinositide 3-kinases (PI3K)/Akt and mitogen-activated protein kinase (MAPK) was related to its potent anti-inflammatory effects [66, 67]. Collectively, flavonoids are important sources of anti-inflammatory activity in *P. pubescens*.

Phenylpropanoids from *P. pubescens*, including ethyl caffeate (**97**), pinoresinol (**101**), imperatorin (**102**), xanthotoxin (**103**), and caffeic acid (**112**), showed anti-inflammatory effects. **97** inhibited the activation of NF-κB and the production of iNOS, COX-2, and PGE in vitro or in mouse skin [68]. **101** could significantly reduce levels of IL-6 and COX-2 human intestinal Caco-2 cells [69]. **103** suppressed the production of NO, prostaglandin E2 (PGE2), TNF-α, and IL-6 by downregulating the NF-κB, AP-1, and JAK/STAT3 signaling pathways in LPS-induced RAW 264.7 macrophages [70]. **102** could regulate MRGPRX2 and CamKII/ERK pathway, thus attenuating OVA-induced lung inflammation in mice [71]. **102** also exerted an anti-inflammatory effect in atherosclerosis by regulating the MAPKs signaling pathway [72] and suppressed the iNOS expression and NO production, which was related to its regulating effect of ERK-MAPK/AP1, JAK/STAT, and NF-κB pathway [73–75]. Treatment with **102** attenuated the symptoms of ulcerative colitis by regulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway [76]. **112** inhibited the secretion of TNF-α, IL-6, and IL-1βvia inhibiting NF-κB and MAPKs signaling pathways in the mammary gland [77]. Moreover, **112** suppressed DSS-induced murine ulcerative colitis through deactivating macrophages [78].

Two terpenoids, oleuropein (**120**) and arjunolic acid (**123**), exhibited anti-inflammation activities. **120** protected the kidney from the inflammation after acute injury because of its regulatory effect on TLR4-MyD88-NF-κB/MAPK axis [79]. **120** could suppress the secretion of TNF-α, IL-β, and IL-6 and inflammation-related genes in mice that received LPS injection [80]. Treatment with **123** significantly suppressed the expressions of TNF-α, IL-1β, and IL-6 in serum of complete Freund's adjuvant (CFA)-induced arthritic rats [81].

The anti-inflammatory effects of the calyx and fruit extracts of *P. pubescens* and its constituents have been sufficiently evaluated and verified using diverse models in vitro and *in vivo*. Steroids, flavonoids, terpenoids, and phenylpropanoids are responsible for their anti-inflammatory effects. The mechanism for alleviating inflammation have also been investigated, which was related to inhibition of inflammation-regulating pathways (e.g. NF-κB, AP-1, MAPK, and STAT3). Thus, all of the above data supported the ethnomedical uses of *P. pubescens*f for treating inflammation-related diseases.

Antioxidant effect

The antioxidant capability of hydroalcoholic extracts of the pulp and seeds of *P. pubescens* was evaluated using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging capability assay, and high antioxidant activity of both the pulp (2210.46 μM irgin/g) and seeds (2807.74 μM irgin/g) was observed [82]. The Ferric reducing ability of plasma (FRAP), 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), and superoxide radical scavenging activity of the yellow pigment extracted from *P. pubescens* were 6.11 ± 0.22 mmol/g, 2.80 ± 0.27 mmol/g, and 57281.5 ± 2749.5 U/g, respectively, which indicated that the yellow pigment enables to maintain redox balance [30].

Steroids of *P. pubescens* exhibited antioxidant activity. Withaferin A (**2**) was reported to be a SIRT3 activator that could suppress the oxidative stress stimulated by CCl_4 in mice [83]. The quinone reductase (QR) induction activities of physapubescin A (**8**), physapubescin B (**9**), and physapubescin C (**10**) were 2.41, 2.30, 1.86-fold of control at 10 μM which suggested their antioxidative effect [33].

The antioxidant effects of flavonoids extracted from *P. pubescens* have been investigated extensively. As a Nrf2 activator, luteolin (**53**) alleviates oxidative stress stimulated by ochratoxin A and high blood sugar, thus protecting cells and tissues [84, 85]. Treatment with **53** at doses of 2.5-50 μM protected cells against H_2O_2-induced oxidative stress in human umbilical vein endothelial cells through regulating MAPK/NF-κB [86]. Quercetin (**55**) could also alleviate oxidative stress induced by D-glucose in human hepatoellular carcinomas HepG2 cells via inducing the activity of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and cellular levels of glutathione (GSH) [87]. Kaempferol (**67**) suppressed the oxidative stress induced by different stimulants including Cu^{2+}, clozapine, and radiation in vitro [88–90]. **67** exhibited potential therapeutic effects in lung ischemia-reperfusion injury and skin fibrosis via keeping oxidative balance [91, 92]. Chrysoeriol (**81**) reversed retinal pigment epithelium (RPE) cells dysfunction which is involved in age-related macular degeneration via antioxidant effect, treatment with 2.5-10 μM. **81** significantly suppressed cell death and decreased reactive oxygen species (ROS) stimulated by H_2O_2 [93]. Quercetin (**55**), 3,7,3′-trimethylquercetin (**59**), and kaempferol (**67**) displayed DPPH free radical scavenging ability [19].

Arjunolic acid (**123**) protected uterine tissue against DNA damage, and counteracted ROS induced by As^{3+} in rats via activating endogenous enzymatic antioxidants [94]. Treatment with **123** effectively attenuated oxidative stress-induced I/R injury in rats subjected to middle cerebral artery occlusion [95]. The EC_{50} values of kaempferol-3-*O*-*β*-D-galactoside (**75**), bergapten (**104**), blumenol A (**121**), and caffeic acid (**112**) for scavenging DPPH radical were 0.51, 1.86, 1.47, and 1.75 μg/mL, which indicated that those compounds displayed significant antioxidant effect [17].

Antibacterial effect

Bacterial infestation is an important factor that induces and exacerbates inflammation. The extract of fruits inhibits the proliferation of the standard strain of *Escherichia coli* (ATCC 25922), *Escherichia coli* from hospital, the standard strain of *Staphylococcus aureus* (ATCC 25925), and the clinical isolates of *Staphylococcus aureus* with MICs of 31-125 mg/mL [6]. Besides, flavonoids such as quercetin (**55**), 3,7,3′-trimethylquercetin (**59**), and kaempferol (**67**) exhibited inhibitory effects on different bacterials [19]. Moreover, nortrachelogenin (**99**) inhibited the survival rate of *Escherichia coli* O157 by disorganizing the cytoplasmic membrane [96].

Regulation on immune response

The extract and ingredients of *P. pubescens* also exert regulating effect on the immunological system. The pulp, peel, and seeds extract significantly downregulated cellular immunity in mice through regulating T-lymphocytes. According to the delayed type hypersensitivity (DTH), carbon particle clearance test, and serum agglutination test, 40% ethanol extract had the strongest inhibitory effect against immune response. Besides, two flavonoids extracted from the fruits of *P. pubescens*, luteolin (**53**) and quercetin (**55**) increased the cell viability of natural killer NK-92 cells [97]. Ethyl caffeate (**97**) exerted the effect against arthritis by suppressing the differentiation of CD4+ T cells into Th1 at a dose of 10 μM in vitro [98].

Inhibition of tumor cell proliferation

Flavonoids extracted from *P. pubescens* demonstrate inhibitory effects against cancer cells. Luteolin (**53**) inhibited the progression of carcinogenesis such as cell transformation, metastasis, invasion, and angiogenesis [99], induced apoptotic cancer cells death [100], and blocked the cell cycle arrest [101], thus suppressed the proliferation of various kinds of tumor cells [102]. Treatment with **55** at 50 μM and 75 μM suppressed the growth of human ovarian teratoma PA-1 cells via suppressing PI3k/Akt, Ras/Raf pathways, and epidermal growth factor receptor (EGFR) expression [103]. Similarly, **55** induced apoptosis or cell cycle arrest in human leukemia U937 cells, human breast cancer cells, human cells transformed by human papillomavirus type 16 oncoproteins, and nasopharyngeal carcinoma cells [104–107]. Moreover, the IC_{50} values of kaempferol (**67**) against different cancer cell lines is 19 ± 0.33 μM for human ovarian cancer A2780 cells, 38 ± 3.30 μM for human lung cancer H460 cells, 46 ± 2.70 μM for human skin cancer A431 cells, 45 ± 2.90 μM for human adenocarcinoma HT29 cells, 37 ± 3.5 μM for human mammary epithelial MCF10A cells, 22 ± 2.10 μM for human glioblastoma SJ-G2 cells, and 26 ± 1.30 μM for mouse glioblastoma SMA cells, respectively [108]. The cancer cells growth was suppressed by **67** due to its cell cycle blocking and apoptosis inducing effects [109]. **67** also exerts its anticancer effect through regulating the cyclin-dependent kinase (CDK) 4/CDK6/cyclin D1 pathway in human gallbladder cancer cells [110]. Kaempferide (**68**) induced apoptosis of human lung cancer A549 cells via regulating TGF-β, NF-κB, and MAPK pathways [111]. Chrysoeriol (**81**) could significantly suppress the proliferation of human lung cancer A549 cells with an IC_{50} of 15 μM. The growth of tumor could be suppressed while treated with **81** in xenografted mice models [112]. **81** inhibited the growth of RPMI 8226 and KM3 cell lines via regulating PI3K pathway [113].

Physapubescin B (**9**) inhibited human hepatoellular carcinomas HepG2, human prostate cancer PC3, human ovarian cancer SKOV3, human breast cancer MDA-MB-231, human prostate epithelial RWPE-1, and human prostate cancer Du145 cells with IC_{50} values ranging from 1.8 to 16.0 μM by blocking cancer cells in G2-M phase [7], which was related to its inhibitory effect of STAT3 activation [35]. **9** also promoted the apoptosis and autophagy of cancer cells [114, 115]. Kidney-type glutaminase (KGA) is crucial for energy supply, thus overexpressed in different cancers. Physapubescin I (**20**) showed an inhibition effect on human pancreatic cancer SW1990 cells, human fibrosarcoma HT1080 cells, and human breast cancer MDA-MB-231 cells with IC_{50} 3.34 ±

0.04 μM, 5.04 ± 0.05 μM, and 2.06 ± 0.03 μM by inhibiting the activity of KGA [116]. Similarly, physapubescin A (**8**) was able to inhibit the growth of human non-small cell lung cancer HCC827 cells and human fibrosarcoma HT1080 cells by inhibiting the activity of KGA [117].

As a KGA inhibitor, **21** exhibited inhibitory effects on proliferation of human pancreatic cancer SW1990 and human non-small cell lung cancer HCC827 cancer cells by blocking glutamine metabolism [118]. **21, 26,** and virginols A_1 (**28**) inhibited the growth of four kinds of human cancer cell lines (human renal carcinoma 786-O cells, human renal carcinoma A-498 cells, human clear renal carcinoma Caki-2 cells, and human renal carcinoma ACHN cells). **24** was identified to be the inhibitor of tumor necrosis factor-related apoptosis ligand (TRIL) belonging to the TNF superfamily [39].

Withanolides exemplified by withaferin A (**2**) and 2*α*,3*β*-dihydroxy-5*α*-pregn-16-en-20-one3-*O*-*β*-D-glucopyranosyl-(1→4)-*β*-D-galactopyranoside (**48**) showed inhibitory effect on proliferation of human cancer cells. **2** demonstrated inhibitory effects against cancer cell proliferation, which was verified in several types of cancer [119–121]. 1*β*,3*α*-dihydroxy-7*α*-eremophila-9,11-dien-3-*O*-[*α*-L-arabinopyranosyl-(l→6)]-*β*-D-glucopyranoside (**135**) from the fruit of *P. pubescens*, inhibited the proliferation of human prostate cancer C4-2B cells and human melanoma A375 cells with IC_{50} values of 12.8 and 28.3 μM [25].

Moreover, ethyl caffeate (**97**) inhibited the proliferation, migration and invasion of human ovarian cancer SKOV-3 cells through regulating Akt, ERK, and MAPK [122]. Similarly, nortrachelogenin (**99**) inhibited proliferation of prostate cancer cells through suppressing the membrane localization and activation of growth factor receptors [123]. Pinoresinol (**101**) showed cytotoxic activity and killed human breast cancer MDA-MB-231 cells and human breast cancer MCF-7 cells, which suggested its potential antitumor activity [124]. **101** suppressed the migration, and invasion of human hepatoellular carcinomas HepG2 cells by regulating E-cadherin, vascular cell adhesion molecule-1, and MMP-9 expression [125] and has an inhibitory effect on human ovarian cancer SKOV-3 cells with an IC_{50} of 20 μM [126]. Treatment with 50 μM arjunolic acid (**123**) exerted inhibitory activity against the proliferation of human breast cancer MCF-7 and human cervical cancer Hela cells through regulating ROS, NF-κB, and TNF-α [127]. Pulsatilla saponin A (**124**) caused G2 arrest, differentiation, and apoptosis of myeloma cells by regulating MEK/ERK signaling pathway [128]. Treatment with 20, 50, and 100 nmol/L pulsatilla saponin D (**125**) inhibited the proliferation of human cervical cancer Hela cells with inhibition rates of 47.16%, 17.90%, and 25.28% via regulating the Wnt signaling pathway [129].

Hypoglycemic and hypolipidemic effects

In diabetic rats induced by alloxan monohydrate, administration with the juice of *P. pubescens* exerts antidiabetic and hypolipidemic effects, which are mainly attributed to its antioxidant potential, regulating β cells of the pancreas and insulin production [8]. In streptozocin (STZ)-induced rats, oral administration of 5 mL/kg *P. pubescens* juice significantly decreased the blood glucose and protected against diabetes-induced neurodegenerative complications via inhibiting oxidative stress and inflammation [130]. The polysaccharide was able to inhibit the activity of α-glucosidase in vitro. Meanwhile, it improved the oral glucose tolerance in the diabetic mouse model induced by STZ [131].

Treating with kaempferol (**67**) enhanced the process of glucose metabolism to protect body from damage from diabetes [132]. **67** promoted β cells survival, insulin secretory function, ameliorates, and insulin sensitivity in type 2 diabetes rats [133, 134]. Administration of **67** at 10 mg/kg attenuated obesity, hyperlipidemia, hyperglycemia, and insulin resistance via activating PPARγ/LXRα /ABCA1 and PPARγ/PI3K/AKT pathways in high-fat-diet rats [135]. In STZ-induced diabetes rats, **67** regulated a series of carbohydrate metabolic enzymes to maintain the blood sugar [136].

Withaferin A (**2**) significantly improved the insulin sensitivity in hepatic metabolic via inhibiting ROS production and inflammation [137, 138]. Moreover, **2** effectively combated STZ-induced type 1 diabetes mellitus (T1DM) through modulating of Nrf2/NF-κB pathway and holding substantial potential for therapy of T1DM [139].

Imperatorin (**102**) significantly reduced obesity, hypertension, dyslipidemia, and increased insulin sensitivity in fat diet-fed rats. Oleuropein (**120**) ameliorated diabetes and relieved diabetes complications since its capability of modulating insulin secretion, repairing islet morphology, activating hepatic AMP-activated protein kinase singling, and improving glucose tolerance and insulin resistance [140]. Treatment with **120** efficiently reduced blood glucose, insulin, and hepatic glycogen levels in gestational diabetes mellitus mice via regulating oxidant and inflammation [141]. Arjunolic acid (**123**) prevented the over-production of ROS, RNS, advanced glycation end products (AGEs), and decrease oxidative damage induced by hyperglycemia in type 1 diabetes [142]. Caffeic acid (**112**) inhibited AGEs formation in vitro, and decreased the inflammatory and oxidative damage in HUVECs exposed to AGEs. **112** markedly decreased lipid accumulation in the liver and the levels of ER stress markers, improved glucose intolerance and insulin sensitivity [143].

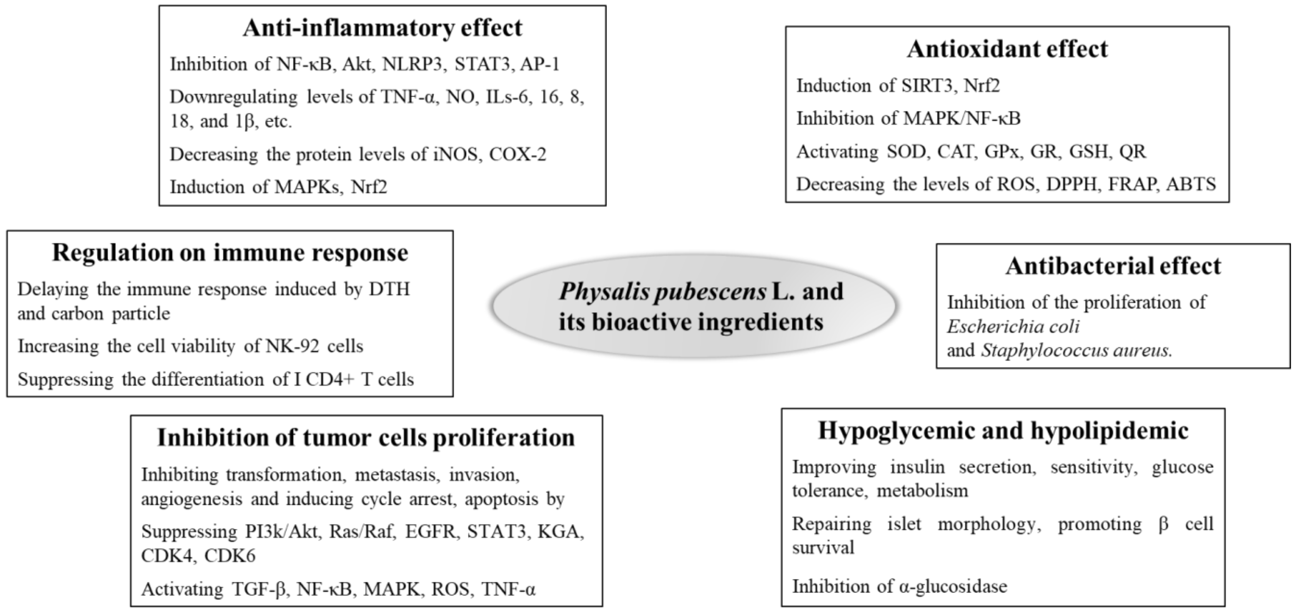


Figure 10 Mechanism of pharmacological activities of *P. pubescens*

Diuretic effect

Treatment with 80% ethanol extract of *P. pubescens* significantly enhanced the urination function of the kidney in rats. The diuretic effect of 0.15, 0.3, and 0.6 g/kg ethanol extract of *P. pubescens* was equivalent to hydro-chlorothiazide in the 1-2 h measurement period and disappeared after 4 hours [9].

Discussion

P. pubescens has been recorded as an important herbal medicinal plant for treating sore throat, aphonia, phlegm, heat, coughing, and urogenital system diseases in TCM and folk medicine for a long history [1, 3, 25]. In the present review, we have summarized the ethnomedicinal use, nutrition, phytochemistry, and pharmacology aspects of *P. pubescens*, which helps to explain its mechanisms of treating the diseases, and thus supports the ethnomedicinal use and establish a basis for future investigations.

The present review summarized 170 constituents including steroids (**1-52**), flavonoids (**53-88**), phenylpropanoids (**89-119**), terpenoids (**120-135**), *N*-containing compounds (**136-138**), organic acids (**139-147**), and miscellaneous constituents (**148-170**), which were derived from calyxes, stems, leaves, and fruits of *P. pubescens*. Of which, steroids, flavonoids, and phenylpropanoids were the main constituents. Those constituents and crude extract exhibited diversity of bioactivities, such as anti-inflammation, anti-oxidation, antibacterial, regulating immunological competence, and diuretic effects which support its ethnomedicinal use [4, 6, 30, 130]. In TCM systems, *P. pubescens* was often used together with other plants of the Solanaceae *Physalis*, but differences in constituents between *P. pubescens* and other plants have been found. Physalins and withaferins which are representative and common compounds in other *Physalis* plants were rarely reported in the phytochemical research of *P. pubescens*. Instead, physapubescins, exemplified by physapubescin A and physapubescin B are rich and representative ingredients in *P. pubescens* [7, 33]. Moreover, compared to other plants of the same genus, *P. pubescens* is more consumed as fruits now.

In the present review, we tried to establish the connection between the modern survey of phytochemistry and bioactivities with the ethnomedicinal use of *P. pubescens*. The diseases of sore throat, aphonia, phlegm, heat, and coughing, are usually accompanied by the inflammation in trachea, throat, or lung [144, 145]. The previous review didn't focus on the anti-inflammatory effect of *P. pubescens*, which is essential for its ethnomedicinal use. The constituents derived from *P. pubescens*, especially steroids, flavonoids, and phenylpropanoids exert anti-inflammatory effects in vitro and *in vivo*. Moreover, inflammation is also closely related to the oxidative stress and infection of bacterial [146, 147]. Active molecules represented by flavonoids and steroids exhibit the potential to scavenge free radicals, maintain redox balance, and attenuate microbial infections. All the observed evidences have indicated that the pharmacological effects supporting the ethnomedicinal use of *P. pubescens* in TCM and folk medicine are produced by flavonoids, steroids, and phenylpropanoids. In addition to respiratory diseases, inflammation is also involved in many chronic diseases, such as neurodegenerative disorders, diabetic nephropathy, heart failure, and so on [148–151]. Among those anti-inflammatory constituents, withaferins and physapubescins exhibited strong anti-

doi: 10.53388/MHM2022B0723001

inflammatory activity as characteristic components of *P. pubescens*, which suggested the potential of *P. pubescens* to be a therapeutic agent for these chronic diseases.

Since long history of ethnomedical application and remarkable therapeutic effects, TCM herbs are an important source for drug discovery and development for various diseases. Besides the pharmacological activities of *P. pubescens* which are closely related to the ethnomedicinal use in TCM and folk medicine, other bioactivities are also discussed in the present review, such as effect on immunological competence, anticancer, antihyperglycemic, antihyperlipidemic, and diuretic effects. Initially, these pharmacological activity studies focused on the extracts of *P. pubescens*, and with continuous in-depth research on the components and pharmacology, a series of components represented by flavonoids, steroids, and phenylpropanoids with those activities have been discovered in *P. pubescens*. Those activities observed in modern research not only confirm the medicinal value of *P. pubescens*, but also broadened his medicinal use, which provides the basis for the further development and utilization of this medicinal herb. Among those activities, anticancer, antihyperglycemic, and antihyperlipidemic effects of *P. pubescens* are more outstanding. The active flavonoids, steroids, and phenylpropanoids possessing above mentioned biological effects are potential lead compounds to explore agents for the therapy of cancer or diabetes.

Moreover, in addition to the medicinal herb, the fruits *P. pubescens* are also consumed as high-quality fruits with good taste and rich nutrition in many areas. Its fruits are excellent supplements of trace elements, especially for zinc and magnesium. The organic acids, such as tartaric acid, malic acid, citric acid, succinic acid, which promote digestion and absorption, were high content in the fruits. In addition, the rich natural pigments in fruits exert antioxidant activity. Taken together, the fruits of *P. pubescens* are excellent fruits with rich trace elements, organic acids, and flavonoids.

Phytochemistry research on *P. pubescens* indicated that the major bioactive constituents of *P. pubescens* are flavonoids, steroids, and phenylpropanoids. In recent decades, much important research has been performed to support its traditional applications. However, problems about *P. pubescens* which need further study and discussion still remains.

(i) The phytochemistry research about *P. pubescens* have been going on for a few decades. However, the understanding of the chemical composition in *P. pubescens* is not sufficient. the further phytochemistry research on *P. pubescens* is needed, especially the research on the water-soluble part of *P. pubescens*, because water decoction is the main method of administration in TCM clinic.

(ii) In folk medicine, *P. pubescens* was totally used with the same pharmacological effect as plants from the genus of *Physalis*, such as *Physalis alkekengi* L. var. *franchetii* (Mast.) Makino. With the development of modern botany, we now know that they are different plants. Further clarifying the similarities and differences between those plants in phytochemical and pharmacological activities is of great significance for the development and utilization of the resources of the medicinal plants.

(iii) *P. pubescens* is a medicinal and edible plant, the fruits of *P. pubescens* are consumed and eaten as fruits in many areas. However, the benefits or therapeutic effects of long-term consumption of *P. pubescens* fruits on the human body have not been fully revealed. More attention is needed for the direction in the future research on *P. pubescens*, which has guiding significance for the food processing of *P. pubescens*.

Data availability or Code availability

Correspondence and requests for materials should be addressed to shentao@sdu.edu.cn (Prof. Tao Shen).

Abbreviations

ABTS, 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid; AGEs, advanced glycation end products ; AP-1, activating protein-1; ARE, antioxidant response element; ATP, adenosine triphosphate; CAT, catalase; CFA, complete freund's adjuvant; CDK, cyclin-dependent kinase; COX-2, cyclooxygenase-2; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DSS, dextran sulfate sodium salt; EGFR, epidermal growth factor receptor; FRAP, ferric reducing ability of plasma; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; HO-1, heme oxygenase-1; IL, interleukin; iNOS, inducible nitric oxide synthase; KGA, kidney-type glutaminase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MSU, monosodium urate; NK, natural killer; NLRP3, nod like receptor family pyrin domain-containing 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; OVA, ovalbumin; PGE2, prostaglandin E2; PI3K, phosphatidylinositide 3-kinases; polysaccharides, POL, polysaccharides; QR, quinone reductase; ROS, reactive oxygen species; RPE, retinal pigment epithelium; SHP-1, src homology 2 domain-containing protein tyrosine phosphatase 1; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; T1DM, type 1 diabetes mellitus; TCM, traditional Chinese medicines; TNF-α, tumor necrosis factor-α.

Acknowledgments

This research was supported by NNSF of China (81673558).

Author contributions

Xin-Ping Cheng, Xiao-Ning Wang, and Tao Shen conceived and designed the review. Xin-Ping Cheng, Bin-Yin, and Qian-Kun Zheng collected and analyzed literatures. Xin-Ping Cheng, Lin-Tao Xu, and Guang-Cheng Peng drafted the manuscript. Xiao-Ning Wang, Zhen-Peng Xu, and Tao Shen revised the manuscript.

Competing interests

The authors declare no competing interests.

References

1. Jia YM. Studies on Chemical Constituents from Berries of *Physalis pubescens* L. Soochow university. 2013. (Chinese)
2. Wen X, Hempel J, Schweiggert RM, Ni YY, Carle R. Carotenoids and carotenoid esters of red and yellow *Physalis* (*Physalis alkekengi* L. and *P. pubescens* L.) fruits and calyces. *J Agr Food Chem*. 2017;65(30): 6140-6151. Doi:10.1021/acs.jafc.7b02514
3. Xu L, Wang R, Yang Y. Study on *Physalis* L. Medicinal plant resources in China. *Chinese Wild Plant Resources*. 2009;28(1):21–23. (Chinese)
4. Zhao X, Liu H, Wu Y et al. Intervention with the crude polysaccharides of *Physalis pubescens* L. mitigates colitis by preventing oxidative damage, aberrant immune responses, and dysbacteriosis. *J Food Sci*. 2020;85(8) 2596–2607. Doi: 10.1111/1750-3841.15330
5. Zimmer TBR, Otero DM, Pedra NS et al. Biological potential of hydroalcoholic extracts of *Physalis pubescens* L. *Biocatalysis and Agricultural Biotechnology*. 2021;31:101895. Doi: 10.1016/j.bcab.2020.101895
6. Zheng JT, Shi JW, Wang F. Study on antibacterial activity of the extract of *Physalis pubescens* L.. *Chinese Journal of Laboratory Diagnosis*. 2010;14 (006):796–797. (Chinese)
7. Ding W, Hu Z, Zhang Z et al. Physapubescin B exhibits potent activity against human prostate cancer in vitro and in *vivo*. *J Agr Food Chem*. 2015;63(43):9504–9512. Doi: 10.1021/acs.jafc.5b03045
8. Hassan AI, Ghoneim M. A possible inhibitory effect of *physalis* (*physalis pubescens* L.) on diabetes in male rats. *World Applied Sciences Journal*. 2013;21(5): 681–688.
9. Zhang SW. Studies on chemical constituents of *Physalis pubescens* L. and its pharmacological activities. *Jilin university*. 2007. (Chinese)
10. Yang BY, Li XM, Liu Y, Kuang HX. Research progress on *Physalis pubescens*. *Chinese Traditional and Herbal Drugs*. 2017;48(14):2979–2988. (Chinese)
11. Zhou LT. Physapubescin B induces apoptosis of human gastric cancer cells through inhibiting JAK2/STAT3 signaling pathway. *Hangzhou normal university*. 2016. (Chinese)
12. Chen LX, He H, Qiu F. Natural withanolides: an overview. *Nat Prod Rep*. 2011;28(4):705–740. Doi:10.1039/c0np00045k
13. Chen L, Xia G, Qiu F et al. Physapubescin selectively induces apoptosis in VHL-null renal cell carcinoma cells through down-regulation of HIF-2α and inhibits tumor growth. *Sci Rep-Uk*. 2016;6(1). Doi: 10.1038/srep32582
14. Yang M. Studies on Chemical Constituents from calyxes of *Physalis pubescens* L. Soochow university. 2013. (Chinese)
15. Xia GY, Ding LQ, Chen LX, Qiu F. Isolation and identification of anti-tumor constituents from *Physalis pubescens* L. *Journal of Shenyang Pharmaceutical University*. 2017;34(9):757–762. Doi:10.14066/j.cnki.cn21-1349/r.2017.09.005 (Chinese)
16. Liu XS. Studies on the chemical constituents of three medicinal plants and the related α-glucosidase inhibitory activity. *Zhejiang university of technology*. 2015. (Chinese)
17. Deng KJ, Zang LL, Lan XH et al. Antioxidant components from cape gooseberry. *J Food Process Pres*. 2016;40(5):893–898. Doi: 10.1111/jfpp.12667
18. Wang G, Xu L, Liu W et al. New anti-inflammatory withanolides from *Physalis pubescens* fruit. *Fitoterapia*. 2020;146(104692). Doi: 10.1016/j.fitote.2020.104692
19. Zhang H, Cheng Z, Li X et al. Chemical constituents in persistent calyx of *Physalis pubescens*. *Chinese Traditional and Herbal Drugs*. 2010;44(11):253–256. (Chinese)
20. Yu SY, Xia GY, Sun JW et al. Isolation and structural characterization of chemical constituents from fruits of *Physalis pubescens*. *Chinese Traditional and Herbal Drugs*. 2018;49(19):4500–4506. (Chinese)
21. Zhu HL, Wang ZZ, Zheng BZ et al. Chemical constituents from berries of *Physalis pubescens*. *Chinese Traditional and Herbal Drugs*. 2016;47(5): 732–735. (Chinese)
22. Ji L. Discovery and action targers of Michael reaction acceptors from two species plants of *Physalis*. *Zhejiang university*. 2013. (Chinese)
23. Deng YX, Lu SF. Biosynthesis and Regulation of Phenylpropanoids in Plants. *Crit Rev Plant Sci*. 2017;36(4):257–290. Doi: 10.1080/07352689.2017.1402852
24. Luo LP, Cheng FQ, Ji L, Yu HY. Chemical constituents of *Physalis pubescens*. *China journal of Chinese materia medica*. 2015;40(22):4424–7. Doi: 10.1080/07352689.2017.1402852
25. Xia G, Huang Y, Xia M et al. A new eremophilane glycoside from the fruits of Physalis pubescens and its

doi: 10.53388/MHM2022B0723001

cytotoxic activity. *Nat Prod Res*. 2017;31(23):2737–44. Doi: 10.1080/14786419.2017.1294176

26. Sheikha A, Zaki MS, Bakr AA, Habashy M, Montet D. Biochemical and sensory quality of *Physalis* (*Physalis pubescens* L.) juice. *Journal of Food Processing & Preservation*. 2010;34(3):541–555. Doi: 10.1111/j.1745-4549.2009.00382.x
27. El Sheikha AF, Piombo G, Goli T, Montet D. Main composition of *Physalis* (*Physalis pubescens* L.) fruit juice from Egypt. *Fruits*. 2010;65(4):255–265. Doi: 10.1051/fruits/20 10021
28. Shenstone E, Lippman Z, Van Eck J. A review of nutritional properties and health benefits of *Physalis* species. *Plant Food Hum Nutr*. 2020;75(3):316–325. Doi: 10.1007/s11130-020-00821-3
29. Golubkina NA, Kekina HG, Engalichev MR, Antoshkina MS, Caruso G. Genotypic effect on fruit production and quality, antioxidant content and elemental composition of organically grown *Physalis angulata* L. and *Physalis pubescens* L. *Folia Hortic*. 2018;30(2):367–374. Doi: 10.2478/fhort-2018-0032
30. Wang H, Lin S, Yang X, Rui H, Liang L. Ultrasonic-Assisted Extraction of Natural Yellow Pigment from *Physalis pubescens* L. and Its Antioxidant Activities. *J Chem-Ny*. 2018;2018:1–6. Doi: 10.1155/2018/7861639
31. Feng L, Gao QQ. Analysis of the nutritional components of *Physalis alkekengil* var. francheti and *P. pubescens* L.. *Journal of Anhui Agricultural Sciences*. 2012;(33):91–92+120. (Chinese)
32. Sahai M. Pubesenolide, a new withanolide from *Physalis pubescens*. *Journal of natural products (Washington, D.C.)*. 1985;48(3):474-476. Doi: 10.1021/np50039a021
33. Ji L, Yuan Y, Ma Z et al. Induction of quinone reductase (QR) by withanolides isolated from *Physalis pubescens* L. (Solanaceae). *Steroids*. 2013;78(9):860–865. Doi: 10.1016/j.steroids.2013.05.008
34. Xu J, Wu Y, Lu G et al. Importance of ROS-mediated autophagy in determining apoptotic cell death induced by physapubescin B. *Redox Biol*. 2017;12:198–207. Doi: 10.1016/j.redox.2017.02.017
35. Zhao X, Huang L, Xu W et al. Physapubescin B inhibits tumorgenesis and circumvents taxol resistance of ovarian cancer cells through STAT3 signaling. *Oncotarget*. 2017;8(41):70130–70141. Doi: 10.18632/oncotarget.19593
36. Zeng W, Wang Q, Chen L, Huang L, Zhao X. Anticancer effect of PP31J isolated from *Physalis pubescens* L. in human cervical carcinoma cells. *Am J Transl Res*. 2017;9(5):2466–2472. (Chinese)
37. Xia G, Li Y, Sun J et al. Withanolides from the stems and leaves of *Physalis pubescens* and their cytotoxic activity. *Steroids*. 2016;115:136–146. Doi: 10.1016/j.steroids.2016.09.002
38. Yang K, Wu C, Zheng M et al. Physapubescin I from husk tomato suppresses SW1990 cancer cell growth by targeting kidney-type glutaminase. *Bioorg Chem*. 2019;92:103186. Doi: 10.1016/j.bioorg.2019.103186
39. Chen L, Xia G, He H et al. New withanolides with TRAIL-sensitizing effect from *Physalis pubescens* L. *Rsc Adv*. 2016;6(58):52925–52936. Doi: 10.1039/C6RA07031K
40. Glotter E, Sahai M, Kirson I, Gottlieb He. Physapubenolide and pubescenin, 2 new ergostane-type steroids from *Physalis pubescens* L (SOLANACEAE). *JOURNAL OF THE CHEMICAL SOCIETY-PERKIN TRANSACTIONS 1*. 1985;11:2241–2245. Doi: 10.1039/p19850002241
41. Pan J. Studies on the withanolides. *Heilongjiang University Of Chinese Medicine*. 2015. (Chinese)
42. Xia G, Yao T, Zhang B et al. Withapubesides A–D: natural inducible nitric oxide synthase (iNOS) inhibitors from *Physalis pubescens*. *Org Biomol Chem*. 2017;15(47):10016–23. Doi: 10.1039/C7OB02551C
43. Xu QM, Liu YL, Feng YL Li XR Yang, SL. C28 sterols with a cyclopentane ring at C-22 and 26 from cape gooseberry (berries of *Physalis pubeacens* L.). *J Asian Nat Prod Res*. 2010;12(9):752–759. Doi: 10.1080/10286020.2010.497657
44. Zhang H. Studies on chemical constituents of the persistent calyx of *Physalis pubescens* L. *Soochow university*. 2010. (Chinese)
45. Zhang YL. The effects of refinments of the *Physalis pubescens* L. (Pp) on the immunocompetence. *Northeast foresty university*. 2010. (Chinese)
46. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. *Ther Adv Chronic Dis*. 2016;7(1):34–51. Doi: 10.1177/2040622315609251
47. Chen F, Wang YC, Guan XW et al. Anti-inflammatory effect and mechanism of *Physalis pubescens*. *Drug Evaluation Research*. 2016;39(005):750–755. (Chinese)
48. Oh JH, Lee T, Park J, Kwon TK. Withaferin A inhibits NOS expression and nitric oxide production by Akt inactivation and down-regulating LPS-induced activity of NF-kappa B in RAW 264.7 cells. *Eur J Pharmacol*. 2008;599(1-3):11–17. Doi: 10.1016/j.ejphar.2008.09.017
49. Peddakkulappagari CS, Saifi MA, Khurana A et al. Withaferin A ameliorates renal injury due to its potent effect on inflammatory signaling. *Biofactors*. 2019;45(5):750–762. Doi: 10.1002/biof.1534
50. Logie E, Vanden Berghe W. Tackling Chronic Inflammation with withanolide phytochemicals-A

withaferin A perspective. *ANTIOXIDANTS*. 2020;9(110711). Doi: 10.3390/antiox9111107
51. Lee MN, Lee Y, Wu D, Pae M. Luteolin inhibits NLRP3 inflammasome activation via blocking ASC oligomerization. *J Nutr Biochem*. 2021;92(108614). Doi: 10.1016/j.jnutbio.2021.108614
52. Li B, Zhao D, Du P et al. Luteolin alleviates ulcerative colitis through SHP-1/STAT3 pathway. *Inflamm Res*. 2021;70(6):705-717. Doi: 10.1007/s00011-021-01468-9
53. Dong J, Xu O, Wang J, Shan C, Ren X. Luteolin ameliorates inflammation and Th1/Th2 imbalance via regulating the TLR4/NF-kappa B pathway in allergic rhinitis rats. *Immunopharm Immunot*. 2021;43(3):319–327. Doi: 10.1080/08923973.2021.1905659
54. Zhang M, He L, Liu J, Zhou L. Luteolin attenuates diabetic nephropathy through suppressing inflammatory response and oxidative stress by inhibiting STAT3 pathway. *German Diabetes Association*. 2020;129(10):729-739. Doi: 10.1055/a-0998-7985
55. Li H, Xiao L, He H et al. Quercetin attenuates atherosclerotic inflammation by inhibiting Gal-3-NLRP3 signaling pathway. *Mol Nutr Food Res*. 2021:e2000746. Doi: 10.1002/mnfr.202000746
56. Huang J, Zhu M, Tao Y et al. Therapeutic properties of quercetin on monosodium urate crystal-induced inflammation in rat. *J Pharm Pharmacol*. 2012;64(8):1119–1127. Doi: 10.1111/j.2042-7158.2012.01504.x
57. Huang R, Zhong T, Wu H. Quercetin protects against lipopolysaccharide-induced acute lung injury in rats through suppression of inflammation and oxidative stress. *Arch Med Sci*. 2015;11(2):427–432. Doi: 10.5114/aoms.2015.50975
58. Liu C, Ma J, Xie W et al. Quercetin protects mouse liver against nickel-induced DNA methylation and inflammation associated with the Nrf2/HO-1 and p38/STAT1/NF-kappa B pathway. *Food Chem Toxicol*. 2015;82:19–26. Doi: 10.1016/j.fct.2015.05.001
59. Ma J, Li Z, Xie W, Liu C, Liu S. Quercetin protects mouse liver against CCl4-induced inflammation by the TLR2/4 and MAPK/NF-kappa B pathway. *Int Immunopharmacol*. 2015;28(1):531–539. Doi: 10.1016/j.intimp.2015.06.036
60. Liao Y, Lin J. Quercetin intraperitoneal administration ameliorates lipopolysaccharide-induced systemic inflammation in mice. *Life Sci*. 2015;137:89–97. Doi: 10.1016/j.lfs.2015.07.015
61. Molitorisova M, Sutovska M, Kazimierova I et al. The anti-asthmatic potential of flavonol kaempferol in an experimental model of allergic airway inflammation. *Eur J Pharmacol*. 2021;891(173698). Doi: 10.1016/j.ejphar.2020.173698
62. Zhuang Z, Ye G, Huang B. Kaempferol alleviates the interleukin-1 beta-induced inflammation in rat osteoarthritis chondrocytes via suppression of NF-kappa B. *Med Sci Monitor*. 2017;23. Doi: 10.12659/MSM.902491
63. Park M, Ji GE, Sung M. Dietary Kaempferol Suppresses Inflammation of dextran dulfate dodium-induced colitis in mice. *Digest Dis Sci*. 2012;57(2):355–363. Doi: 10.1007/s10620-011-1883-8
64. Qi Y, Ying Y, Zou J et al. Kaempferol attenuated cisplatin-induced cardiac injury via inhibiting STING/NF-kappa B-mediated inflammation. *Am J Transl Res*. 2020;12(12):8007–8018
65. Yeon MJ, Lee MH, Kim DH et al. Anti-inflammatory effects of Kaempferol on helicobacter pylori-induced inflammation. *Biosci Biotech Bioch*. 2019;83(1):166–173. Doi: 10.1080/09168451.2018.1528140
66. Yoon H, Park CM. Chrysoeriol ameliorates COX-2 expression through NF-kappa B, AP-1 and MAPK regulation via the TLR4/MyD88 signaling pathway in LPS-stimulated murine macrophages. *Exp Ther Med*. 2021;22(7181). Doi: 10.3892/etm.2021.10150
67. Choi DY, Lee JY, Kim MR et al. Chrysoeriol potently inhibits the induction of nitric oxide synthase by blocking AP-1 activation. *J Biomed Sci*. 2005;12(6):949–959. Doi: 10.1007/s11373-005-9028-8
68. Chiang YM, Lo CP, Chen YP et al. Ethyl caffeate suppresses NF-kappa B activation and its downstream inflammatory mediators, iNOS, COX-2, and PGE(2) in vitro or in mouse skin. *Brit J Pharmacol*. 2005;146(3):352-363. Doi: 10.1038/sj.bjp.0706343
69. During A, Debouche C, Raas T, Larondelle Y. Among plant lignans, pinoresinol has the strongest antiinflammatory properties in human intestinal Caco-2 Cells. *J Nutr*. 2012;142(10):1798–1805. Doi: 10.3945/jn.112.162453
70. Lee S, Lee WS, Shin J, Jang DS, Lee KT. Xanthotoxin suppresses LPS-induced expression of iNOS, COX-2, TNF-alpha, and IL-6 via AP-1, NF-kappa B, and JAK-STAT inactivation in RAW 264.7 macrophages. *Int Immunopharmacol*. 2017;49:21–29. Doi: 10.1016/j.intimp.2017.05.021
71. Wang N, Wang J, Zhang Y et al. Imperatorin ameliorates mast cell-mediated allergic airway inflammation by inhibiting MRGPRX2 and CamKII/ERK signaling pathway. *Biochem Pharmacol*. 2021;184(114401). Doi: 10.1016/j.bcp.2020.114401
72. Li W, Yu J, Xiao X et al. Imperatorin reduces the inflammatory response of atherosclerosis by regulating MAPKs signaling pathway in vivo and in vitro. *Int*

Immunopharmacol. 2021;90(107170). Doi: 10.1016/j.intimp.2020.107170
73. Ahmad N, Ansari MY, Bano S, Haqqi TM. Imperatorin suppresses IL-1 beta-induced iNOS expression via inhibiting ERK-MAPK/AP1 signaling in primary human OA chondrocytes. *Int Immunopharmacol*. 2020;85(106612). Doi: 10.1016/j.intimp.2020.106612
74. Singh G, Kaur J, Kaur M, Singh P, Bhatti R. Anti-nociceptive and anti-inflammatory effect of imperatorin: evidences for involvement of COX-2, iNOS, NFκB and inflammatory cytokines. *Int J Neurosci*. 2020;130(2):176-185. Doi: 10.1080/00207454.2019.1667789
75. Li Y, Chen J, Tsai C, Yeh W. Anti-inflammatory property of imperatorin on alveolar macrophages and inflammatory lung injury. *J Nat Prod*. 2019;82(4):1002–1008. Doi: 10.1021/acs.jnatprod.9b00145
76. Luo M, Luo Y. Imperatorin relieved ulcerative colitis by regulating the Nrf-2/ARE/HO-1 pathway in rats. *Inflammation*. 2021;44(2):558–569. Doi: 10.1007/s10753-020-01353-3
77. Zielinska D, Zielinski H, Laparra-Llopis JM et al. Caffeic Acid modulates processes associated with intestinal inflammation. *Nutrients*. 2021;13(5542). Doi: 10.3390/nu13020554
78. Xiang C, Liu M, Lu Q et al. Blockade of TLRs-triggered macrophage activation by caffeic acid exerted protective effects on experimental ulcerative colitis. *Cell Immunol*. 2021;365. Doi: 10.1016/j.cellimm.2021.104364
79. Cui Y, Gao H, Han S et al. Oleuropein attenuates Lipopolysaccharide-induced acute kidney injury in vitro and in vivo by regulating toll-like receptor 4 dimerization. *Front Pharmacol*. 2021;12(617314). Doi: 10.3389/fphar.2021.617314
80. Alsharif KF, Almalki AA, Al-Amer O et al. Oleuropein protects against lipopolysaccharide-induced sepsis and alleviates inflammatory responses in mice. *Iubmb Life*. 2020;72(10):2121–2132. Doi: 10.1002/iub.2347
81. Fan Y, Zhang C, Zheng G et al. Ameliorative and anti-arthritic potential of arjunolic acid against complete Freund's adjuvant-induced arthritis in rats. *Trop J Pharm Res*. 2020;19(9):1933–1939. Doi: 10.4314/tjpr.v19i9.19
82. Zimmer T, Otero DM, Pedra NS, Bona NP, Rui CZ. Biological potential of hydroalcoholic extracts of *Physalis pubescens* L. *Biocatalysis and Agricultural Biotechnology*. 2020;31(3):101895. Doi: 10.1016/j.bcab.2020.101895
83. Gu J, Chen C, Wang J et al. Withaferin A exerts preventive effect on liver fibrosis through oxidative stress inhibition in a Sirtuin 3-dependent manner. *Oxid Med Cell Longev*. 2020;e2452848. Doi: 10.1155/2020/2452848
84. Zhou X, Ru X, Xiao C et al. Sestrin2 is involved in the Nrf2-regulated antioxidative signaling pathway in luteolin-induced prevention of the diabetic rat heart from ischemia/reperfusion injury. *Food Funct*. 2021;12(8):3562–3571. Doi: 10.1039/D0FO02942D
85. Liu M, Cheng C, Li X et al. Luteolin alleviates ochratoxin A induced oxidative stress by regulating Nrf2 and HIF-1 alpha pathways in NRK-52E rat kidney cells. *Food Chem Toxicol*. 2020;141(111436). Doi: 10.1016/j.fct.2020.111436
86. Chen HI, Hu W, Hung M et al. Protective effects of luteolin against oxidative stress and mitochondrial dysfunction in endothelial cells. *Nutr Metab Cardiovas*. 2020;30(6):1032–1043. Doi: 10.1016/j.numecd.2020.02.014
87. Yarahmadi A, Sarabi MM, Sayahi A, Zal F. Protective effects of quercetin against hyperglycemia-induced oxidative stress in hepatic HepG2 cell line. *Avicenna J Phytomed*. 2021;11(3):269–280
88. Kim G, Kim E, Kwon Y, Jang H. Potential mechanism of kaempferol against Cu^{2+}-induced oxidative stress through chelating activity and regulation of nuclear factorerythroid-2-related factor 2 signaling. *Food Sci Biotechnol*. 2012;21(5):1469–1475. Doi: 10.1007/s10068-012-0194-y
89. Bakhshii S, Khezri S, Ahangari R, Jahedsani A, Salimi A. Protection of clozapine-induced oxidative stress and mitochondrial dysfunction by kaempferol in rat cardiomyocytes. *Drug Develop Res*. 2021;82(6):835–843. Doi: 10.1002/ddr.21790
90. Wang J, Li T, Feng J et al. Kaempferol protects against gamma radiation-induced mortality and damage via inhibiting oxidative stress and modulating apoptotic molecules in vivo and vitro. *Environ Toxicol Phar*. 2018;60:128–137. Doi: 10.1016/j.etap.2018.04.014
91. Sekiguchi A, Motegi S, Fujiwara C et al. Inhibitory effect of kaempferol on skin fibrosis in systemic sclerosis by the suppression of oxidative stress. *J Dermatol Sci*. 2019;96(1):8–17. Doi: 10.1016/j.jdermsci.2019.08.004
92. Yang C, Yang W, He Z et al. Kaempferol alleviates oxidative stress and apoptosis through mitochondria-dependent pathway during lung ischemia-reperfusion injury. *Front Pharmacol*. 2021;12(624402). Doi: 10.3389/fphar.2021.624402
93. Kim MH, Kwon SY, Woo S, Seo WD, Kim DY. Antioxidative effects of Chrysoeriol via activation of the Nrf2 signaling pathway and modulation of mitochondrial function. *Molecules*. 2021;26(3132). Doi: 10.3390/molecules26020313
94. Maity M, Perveen H, Dash M et al. Arjunolic acid improves the serum level of Vitamin B-12 and folate in

the process of the attenuation of arsenic induced uterine oxidative stress. *Biol Trace Elem Res*. 2018;182(1):78–90. Doi: 10.1007/s12011-017-1077-0
95. Yaidikar L, Thakur S. Arjunolic acid, a pentacyclic triterpenoidal saponin of Terminalia arjuna bark protects neurons from oxidative stress associated damage in focal cerebral ischemia and reperfusion. *Pharmacol Rep*. 2015;67(5):890–895. Doi: 10.1016/j.pharep.2015.02.003
96. Lee H, Ji YR, Ryoo ZY et al. Antibacterial mechanism of (-)-Nortrachelogenin in Escherichia coli O157. *Curr Microbiol*. 2016;72(1):48–54. Doi: 10.1007/s00284-015-0918-3
97. Hasyam AMM, Nor NM, Adman LHM et al. Effects of apigenin, Luteolin, and Quercetin on the Natural Killer (NK-92) cells proliferation: a potential role as immunomodulator. *Sains Malays*. 2021;50(3):821–828. Doi: 10.17576/jsm-2021-5003-22
98. Xu S, Zuo A, Guo Z, Wan C. Ethyl caffeate ameliorates collagen-induced arthritis by suppressing Th1 immune response. *J Immunol Res*. 2017;2017(7416792). Doi: 10.1155/2017/7416792
99. Birt DF, Hendrich S, Wang WQ. Dietary agents in cancer prevention: flavonoids and isoflavonoids. *Pharmacol Therapeut*. 2001;90(2-3):157–177. Doi: 10.1016/S0163-7258(01)00137-1
100. Rauf A, Imran M, Butt MS et al. Resveratrol as an anti-cancer agent: A review. *Crit Rev Food Sci*. 2018;58(9):1428–1447. Doi: 10.1080/10408398.2016.1263597
101. Martin KR. Targeting apoptosis with dietary bioactive agents. *Exp Biol Med*. 2006;231(2):117-129. Doi: 10.1177/153537020623100201
102. Wruck CJ, Claussen M, Fuhrmann G et al. Luteolin protects rat PC12 and C6 cells against MPP plus induced toxicity via an ERK dependent Keapl-Nrf2-ARE pathway. *JOURNAL OF NEURAL TRANSMISSION-SUPPLEMENT*. 2007;(72):57–67. Doi: 10.1007/978-3-211-73574-9_9
103. Dhanaraj T, Mohan M, Arunakaran J. Quercetin attenuates metastatic ability of human metastatic ovarian cancer cells via modulating multiple signaling molecules involved in cell survival, proliferation, migration and adhesion. *Arch Biochem Biophys*. 2021;701(108795). Doi: 10.1016/j.abb.2021.108795
104. Lee T, Kim OH, Kim YH et al. Quercetin arrests G2M phase and induces caspase-dependent cell death in U937 cells. *Cancer Lett*. 2006;240(2):234–242. Doi: 10.1016/j.canlet.2005.09.013
105. HERTOG M, HOLLMAN P, KATAN MB, KROMHOUT D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. *Nutr Cancer*. 1993;20(1):21–29. Doi: 10.1080/01635589309514267
106. Choi JA, Kim JY, Lee JY et al. Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. *Int J Oncol*. 2001;19(4):837–844. Doi: 10.3892/ijo.19.4.837
107. Ong CS, Tran E, Nguyen T et al. Quercetin-induced growth inhibition and cell death in nasopharyngeal carcinoma cells are associated with increase in Bad and hypophosphorylated retinoblastoma expressions. *Oncol Rep*. 2004;11(3):727–733.
108. Hong NTP, Sakoff JA, Vuong QV, Bowyer MC, Scarlett CJ. Comparative cytotoxic activity between kaempferol and gallic acid against various cancer cell lines. *DATA IN BRIEF*. 2018;21:1033–1036. Doi: 10.1016/j.dib.2018.10.121
109. Zhu L, Xue L. Kaempferol suppresses proliferation and induces cell cycle arrest, apoptosis, and DNA damage in breast cancer cells. *Oncol Res*. 2019;27(6):629–634. Doi: 10.3727/096504018X15228018559434
110. Liu Z, Yao G, Zhai J, Hu D, Fan Y. Kaempferol suppresses proliferation and induces apoptosis and DNA damage in human gallbladder cancer cells through the CDK4/CDK6/cyclin D1 pathway. *Eur Rev Med Pharmaco*. 2021;25(3):1311–1321. Doi: 10.26355/eurrev_202102_24836
111. Li H, Li S, Luo Y et al. Kaempferide induces G0/G1 phase arrest and apoptosis via ROS-mediated signaling pathways in A549 human lung cancer cells. *Nat Prod Commun*. 2020;15(7). Doi: 10.1177/1934578X20935226
112. Wei W, He J, Ruan H, Wang Y. In vitro and in *vivo* cytotoxic effects of chrysoeriol in human lung carcinoma are facilitated through activation of autophagy, sub-G1 cell cycle arrest, cell migration and invasion inhibition and modulation of MAPK/ERK signalling pathway. *J Buon*. 2019;24(3):936–942
113. Yang Y, Zhou X, Xiao M et al. Discovery of chrysoeriol, a PI3K-AKT-mTOR pathway inhibitor with potent antitumor activity against human multiple myeloma cells in vitro. *J Huazhong U Sci-Med*. 2010;30(6):734–740. Doi: 10.1007/s11596-010-0649-4
114. Dai C, Shen L, Jin W, et al. Physapubescin B enhances the sensitivity of gastric cancer cells to trametinib by inhibiting the STAT3 signaling pathway. *Toxicol Appl Pharm*. 2020;408:e115273. Doi: 10.1016/j.taap.2020.115273
115. Xu J, Wu Y, Lu G et al. Importance of ROS-mediated autophagy in determining apoptotic cell death induced by physapubescin B. *Redox Biol*. 2017;12:198–207. Doi: 10.1016/j.redox.2017.02.017
116. Yang K, Wu C, Zheng M et al. Physapubescin I from husk tomato suppresses SW1990 cancer cell growth by

doi: 10.53388/MHM2022B0723001

targeting kidney-type glutaminase. *Bioorg Chem*. 2019;92(103186). Doi: 10.1016/j.bioorg.2019.103186
117. Cheng L, Wu C, Zhu L, Li H, Chen L. Physapubescin, a natural withanolide as a kidney-type glutaminase (KGA) inhibitor. *Bioorg Med Chem Lett*. 2017;27(5):1243–1246. Doi: 10.1016/j.bmcl.2017.01.057
118. Wu C, Zheng M, Gao S et al. A natural inhibitor of kidney-type glutaminase: a withanolide from *Physalis pubescens* with potent anti-tumor activity. *ONCOTARGET*. 2017;8(69):113516–113530. Doi: 10.18632/oncotarget.23058
119. Woo SM, Min K, Kim S et al. Axl is a novel target of withaferin A in the induction of apoptosis and the suppression of invasion. *Biochem Bioph Res Co*. 2014;451(3):455–460. Doi: 10.1016/j.bbrc.2014.08.018
120. Devi PU, Utsumi H, Takata M, Takeda S. Enhancement of radiation induced cell death in chicken B lymphocytes by withaferin A. *Indian J Exp Biol*. 2008;46(6):437–442.
121. Malik F, Kumar A, Bhushan S et al. Reactive oxygen species generation and mitochondrial dysfunction in the apoptotic cell death of human myeloid leukemia HL-60 cells by a dietary compound withaferin A with concomitant protection by N-acetyl cysteine. *Apoptosis*. 2007;12(11):2115–2133. Doi: 10.1007/s10495-007-0129-x
122. Lee HN, Kim J, Kim JH et al. A mechanistic study on the anti-cancer activity of ethyl caffeate in human ovarian cancer SKOV-3 cells. *Chem-Biol Interact*. 2014;219:151-158. Doi: 10.1016/j.cbi.2014.05.017
123. Peuhu E, Paul P, Remes M et al. The antitumor lignan Nortrachelogenin sensitizes prostate cancer cells to TRAIL-induced cell death by inhibition of the Akt pathway and growth factor signaling. *Biochem Pharmacol*. 2013;86(5):571–583. Doi: 10.1016/j.bcp.2013.05.026
124. Lopez-Biedma A, Sanchez-Quesada C, Beltran G, Delgado-Rodriguez M, Gaforio JJ. Phytoestrogen (+)-pinoresinol exerts antitumor activity in breast cancer cells with different oestrogen receptor statuses. *Bmc Complem Altern M*. 2016;16(350). Doi: 10.1186/s12906-016-1233-7
125. Zhang Y, Zhao H, Di Y et al. Antitumor activity of Pinoresinol in vitro: inducing apoptosis and inhibiting I HepG2 invasion. *J Funct Foods*. 2018;45:206–214. Doi: 10.1016/j.jff.2018.04.009
126. Ning Y, Fu YL, Zhang QH, Zhang C, Chen Y. Inhibition of in vitro and in *vivo* ovarian cancer cell growth by pinoresinol occurs by way of inducing autophagy, inhibition of cell invasion, loss of mitochondrial membrane potential and inhibition Ras/MEK/ERK signalling pathway. *J Buon*. 2019;24(2):709–714.
127. Manna S, Dey A, Majumdar R et al. Self assembled arjunolic acid acts as a smart weapon against cancer through TNF- alpha mediated ROS generation. *HELIYON*. 2020;6:e034562. Doi: 10.1016/j.heliyon.2020.e03456
128. Ye B, Zhou Y, Liu Y et al. Pulsatilla saponin A induces apoptosis and differentiation of myeloma Cells. *Anti-Cancer Agent Me*. 2021;21(7):919–926. Doi: 10.2174/1871520620666200721125036
129. Wang B, Chen W, Zhang X, Yin L. Antiproliferative effect of pulsatilla saponin D on cervical cancer cells and its relationship with Wnt signaling pathway. *The Chinese Journal of Clinical Pharmacology*. 2019; 35(21):2732-2735. Doi:10.13699/j.cnki.1001-6821.2019.21.023 (Chinese)
130. Ali AM, Essawy AR, Hamed E, Moneim A, Attaby FA. The ameliorative role of *Physalis pubescens* L. against neurological impairment associated with streptozotocin induced diabetes in rats. *Metab Brain Dis*. 2021;(5). Doi: 10.1007/s11011-021-00730-7
131. Chen X, Li X, Zhang X et al. Antihyperglycemic and antihyperlipidemic activities of a polysaccharide from *Physalis pubescens* L. in streptozotocin (STZ)-induced diabetic mice. *Food Funct*. 2019;10(8):4868–4876. Doi: 10.1039/C9FO00687G
132. Alkhalidy H, Moore W, Wang Y et al. The flavonoid Kaempferol ameliorates Streptozotocin-induced diabetes by suppressing hepatic glucose production. *Molecules*. 2018;23:e23389. Doi: 10.3390/molecules23092338
133. Zhang Y, Zhuo F, Liu D. Flavonol Kaempferol Promotes Beta Cell Survival, Insulin Secretory Function and Ameliorates Hyperglycemia in a Mouse Model of Type 2 Diabetes. *Diabetes*. 2010;591: A677–A677
134. Moore W, Alkhalidy H, Mcmillan R et al. Small molecule Kaempferol prevents Type 2 diabetes by promoting insulin sensitivity and reducing hpatic gluconeogenesis. *Diabetes*. 2014;631:A504–A505.
135. Tang H, Zeng Q, Tang T, Wei Y, Pu P. Kaempferide improves glycolipid metabolism disorder by activating PPAR gamma in high-fat-diet-fed mice. *Life Sci*. 2021;270:e119133. Doi: 10.1016/j.lfs.2021.119133
136. Krishnan B, Ganesan AR, Balasubramani R et al. Chrysoeriol ameliorates hyperglycemia by regulating the carbohydrate metabolic enzymes in streptozotocin-induced diabetic rats. *FOOD SCIENCE AND HUMAN WELLNESS*. 2020;9(4):346–354. Doi: 10.1016/j.fshw.2020.05.014
137. Abu Bakar MH, Azmi MN, Shariff KA, Tan JS. Withaferin A protects against high-fat diet-induced obesity via attenuation of oxidative stress, inflamm-

ation, and insulin resistance. *Appl Biochem Biotech*. 2019;188(1):241–259. Doi: 10.1007/s12010-018-2920-2

138. Batumalaie K, Amin MA, Murugan DD, Sattar MZA, Abdullah NA. Withaferin A protects against palmitic acid-induced endothelial insulin resistance and dysfunction through suppression of oxidative stress and inflammation. *Sci Rep-Uk*. 2016;6:e27236. Doi: 10.1038/srep27236
139. Tekula S, Khurana A, Anchi P, Godugu C. Withaferin-A attenuates multiple low doses of Streptozotocin (MLD-STZ) induced type 1 diabetes. *Biomed Pharmacother*. 2018;106:1428–1440. Doi: 10.1016/j.biopha.2018.07.090
140. Zheng S, Huang K, Tong T. Efficacy and mechanisms of oleuropein in mitigating diabetes and diabetes complications. *J Agr Food Chem*. 2021;. Doi: 10.1021/acs.jafc.1c01404
141. Zhang Z, Zhao H, Wang A. Oleuropein alleviates gestational diabetes mellitus by activating AMPK signaling. *Endocr Connect*. 2021;10(1):45–53. Doi: 10.1530/EC-20-0466
142. Manna P, Sil PC. Arjunolic acid: beneficial role in type 1 diabetes and its associated organ pathophysiology. *Free Radical Res*. 2012;46(7):815–830. Doi: 10.3109/10715762.2012.68 3431
143. Kim HM, Kim Y, Lee ES, Huh JH, Chung CH. Caffeic acid ameliorates hepatic steatosis and reduces ER stress in high fat diet-induced obese mice by regulating autophagy. *Nutrition*. 2018;55-56:63–70. Doi: 10.1016/j.nut.2018.03.010
144. Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *New Engl J Med*. 2019;381(13):1248–1256. Doi: 10.1056/NEJMra1900475
145. Wang Q, Jin S. Research progress of endogenous mediators regulate lung inflammation resolution. *Chemistry of Life*. 2011; 31(1):72–77 (Chinese)
146. O'Dwyer DN, Ashley SL, Gurczynski SJ et al. Lung microbiota contribute to pulmonary inflammation and disease progression in pulmonary fibrosis. *Am J Resp Crit Care*. 2019;199(9):1127–1138. Doi: 10.1164/rccm.201809-1650OC
147. Barnes PJ. Oxidative stress-based therapeutics in COPD. *Redox Biol*. 2020;33:e101544. Doi:10.1016/j.redox.2020.101544
148. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener*. 2020;9(1):42. Doi: 10.1186/s40035-020-00221-2
149. Komada T, Muruve DA. The role of inflammasomes in kidney disease. *Nat Rev Nephrol*. 2019;15(8):501–520. Doi: 10.1038/s41581-019-0158-z
150. Williams BM, Cliff CL, Lee K, Squires PE, Hills CE. The Role of the NLRP3 Inflammasome in Mediating Glomerular and Tubular Injury in Diabetic Nephropathy. *Front Physiol*. 2022;13:e907504. Doi: 10.3389/fphys.2022.907504
151. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. *Nat Rev Cardiol*. 2020;17(5):269–285. Doi: 10.1038/s41569-019-0315-x