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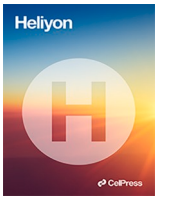

Research article

Iridoids and active ones in *patrinia*: A review

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ABSTRACT

Iridoid is a special class of monoterpenoids, whose basic skeleton is the acetal derivative of antinodilaldehyde with a bicyclic H-5/H-9β, β-cisfused cyclopentan pyran ring. They were often existed in Valerianaceae, Rubiaceae, Scrophulariaceae and Labiaceae family, and has various biological activities, such as anti-inflammatory, hypoglycemic, neuroprotection, and soon. In this review, iridoids from *Patrinia* (Valerianaceae family), and the active ones as well as their mechanisms in recent 20 years were summarized. Up to now, a total of 115 iridoids had been identified in *Patrinia*, among which 48 had extensive biological activities mainly presented in anti-inflammatory, anti-tumor and neuroprotective. And the mechanisms involved in MAPK, NF-κB and JNK signal pathways. The summary for iridoids and their activities will provide the evidence to exploit the iridoids in *Patrinia*.

1. Introduction

Iridoids are a special class of monoterpenoids whose basic parent nucleus is cyclopentano [c] pyran. If cyclopentane is cracked, the seco-iridoids are formed. Since the formation of cyclopentane requires special enzymes, such compounds are found in certain plants, such as Rubiaceae, and Scrophulariaceae. According to the number of carbon atoms of iridoids, iridoids can be divided into C-8 skeleton, C-9 skeleton, C-10 skeleton. C-13, C-14 and C-19 skeletons will be formed when they are combined with other structures. Most iridoid exist in plants as C1–OH and glycosides [1,2]. Up to now, about 800 iridoids have been isolated and identified from natural plants, most of which are iridoid glycosides, only more than 60 non-glycosidic iridoids, and more than 30 seco-iridoids [3].

The iridoids have a variety of pharmacological effects, such as nervous system protection, hypoglycemic, anti-inflammatory, anti-tumor, antiallergic, antioxidant, anti-microbial, antiviral, anticoagulant and antispasmodic effect [1,4,5]. Also, they could help plants resist damage, such as the defense reaction of iridoid glycosides plants against *Cladosporium cucurnerinum* [6]. Therefore, it is focused on the biological activity and mechanism.

Many plants of *Patrinia* genus have high edible and medicinal value. The tender leaves or flower buds of some species of *Patrinia* are

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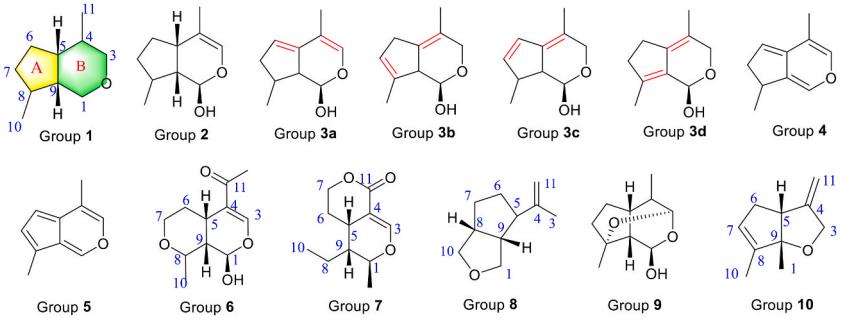


Fig. 1. The basic skeleton of the iridoid terpene from *Patrinia* genus.

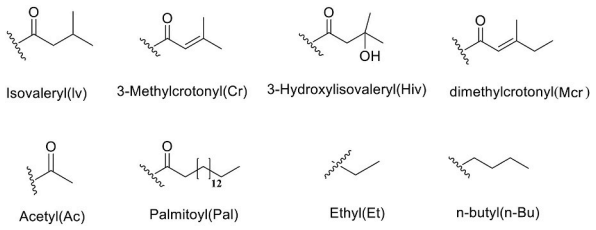


Fig. 2. Structure diagram of iridoid substituents from *Patrinia* genus.

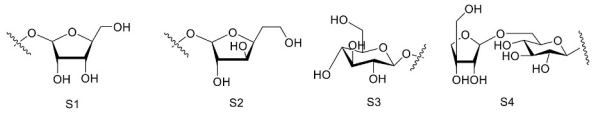


Fig. 3. Sugars of Iridoids from *Patrinia* genus.

cooked and used as vegetables in some regions of China, such as *P. scabiosaefolia* Fisch. ex Trev, *P. villosa* Juss, *P. punctiflora* Hsu et H. J. Wang, etc. [7] Compendium of Materia Medica: "The *Patrinia* is good for discharge of pus and broken blood, so ZhongJing used as well as the ancient prescription gynecology [8]. Modern medical research has confirmed that *Patrinia* has a variety of pharmacological effects such as antibacterial, anti-virus, anti-tumor, sedative, liver protecting and cholagogic, immunity enhancing, and so on [9,10]. The iridoids are one of the main active components of *Patrinia*. Therefore, this review summarizes the structures of iridoids in *Patrinia*, biological activities and action mechanisms in order to provide a basis for their utilization.

2. Iridoids from *patrinia*

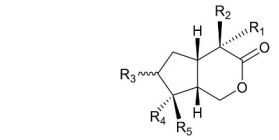
Up to now, 115 iridoids have been isolated and identified from *Patrinia* plants, which the main structure is the cyclopentano [c] pyran type (H-5/H-9β). According to whether cyclopentane and pyran ring contain double bonds, the position and number of double bonds can be divided into five structural types (Fig. 1 Groups 1–5). When cyclopentane splits, it forms seco-iridoids (Fig. 1 Groups 6–8). Some iridoids were formed oxygen bridge at C-3 and C-8, or the pyran ring of iridoid were broken to form Groups 9–10 (Fig. 1), as well as the dimeric iridoids. The substituents on the iridoids are mainly unique to isovaleroxyl, 3-hydroxylisovaleroxyl, 3-methylcrothyl, 3,4-dimethylcrothyl and acetoxyl, ethyl and butyl, etc. (Fig. 2). The iridoids in *Patrinia* exist in free form and glycoside form, and glycoside sugars are mainly β-Glucose and β-apiofuranosyl, etc. (Fig. 3)

2.1. Iridoids with the skeleton of cyclopentano [c] pyran

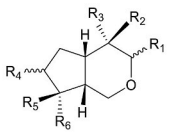
This type generally has substituents at the C-1, C-7, C-8, C-10, and C-11. According to the position and number of double bonds contained in cyclopentane ring (ring A) and pyran ring (ring B), it is divided into non-double-bond iridoids, monoene iridoids, diene iridoids and iridoids with three or four double bonds, and they can be divided into different subtypes according to the difference of double bond positions.

2.1.1. Iridoids with no double bond in the ring

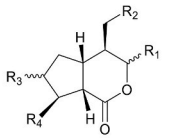
So far, there are twenty-nine iridoids with no double bond in rings (Fig. 4). There are no double bonds in the A and B rings (Group 1). The C-1 and C-3 of the structure can be replaced by hydroxyl groups or carbonyl groups (**1**–**18**, **27**–**29**), C-4, C-8, C-10, C-11



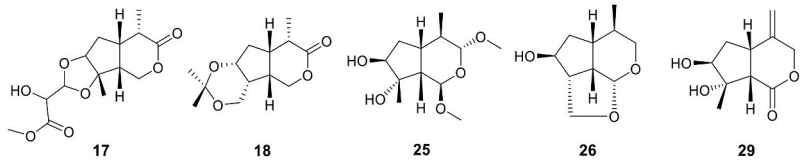
1	R1=H	R2=Me	R3=β-OH	R4=OH	R5=Me
2	R1=Me	R2=H	R3=α-OH	R4=CH_2OH	R5=H
3	R1=H	R2=Me	R3=β-OH	R4=S3	R5=Me
4	R1=Me	R2=H	R3=β-S3	R4=OH	R5=Me
5	R1=H	R2=Me	R3=β-OH	R4=S3	R5=Me
6	R1=Me	R2=H	R3=β-OH	R4=S3	R5=Me
7	R1=H	R2=Me	R3=β-S3	R4=S4	R5=Me
8	R1=Me	R2=H	R3=β-OH	R4=OH	R5=Me
9	R1=H	R2=Me	R3=β-S3	R4=OH	R5=Me
10	R1=OH	R2=Me	R3=β-S3	R4=OH	R5=Me
11	R1=H	R2=Me	R3=H	R4=S3	R5=Me
12	R1=H	R2=Me	R3=H	R4=OH	R5=Me
13	R1=H	R2=Me	R3=H	R4=Me	R5=S3
14	R1=H	R2=Me	R3=α-OH	R4=Me	R5=OH
15	R1=H	R2=Me	R3=α-OH	R4=S3	R5=Me
16	R1=H	R2=H	R3=β-OH	R4=H	R5=Me



19	R1=OH	R2=Me	R3=H	R4=β-OH	R5=Me	R6=S3
20	R1=β-OH	R2=Me	R3=H	R4=β-OH	R5=H	R6=S3
21	R1=β-OH	R2=Me	R3=H	R4=β-OH	R5=Me	R6=OH
22	R1=OMe	R2=Me	R3=H	R4=H	R5=Me	R6=S3
23	R1=β-OH	R2=OH	R3=Me	R4=α-OH	R5=H	R6= $=CH_2$
24	R1=β-OH	R2=OH	R3=Me	R4=β-OH	R5=H	R6=Me

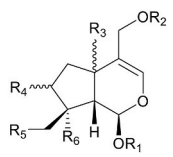


27	R1=H	R2=OS3	R3=H	R4=Me
28	R1=β-OH	R2=H	R3=β-OH	R4=CH_2OH

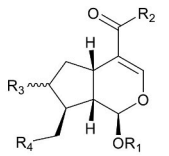


17 **18** **25** **26** **29**

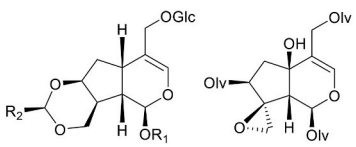
Fig. 4. Iridoid compounds with no double bond inside the ring from *Patrinia* genus.



30	R1=Iv	R2=Iv	R3=β-OH	R4=α-Oiv	R5=Cl	R6=OH
31	R1=Iv	R2=Iv	R3=α-OH	R4=α-OH	R5=Oiv	R6=OH
32	R1=Iv	R2=Iv	R3=β-OH	R4=α-OH	R5=Oiv	R6=OH
33	R1=Iv	R2=Iv	R3=β-H	R4=β-OAc	R5=OAc	R6=OH
34	R1=Iv	R2=Iv	R3=β-H	R4=β-OH	R5=Oiv	R6=OH
35	R1=Iv	R2=Iv	R3=β-H	R4=β-OH	R5=H	R6=H
36	R1=Iv	R2=S3	R3=β-H	R4=β-OH	R5=OH	R6=H
37	R1=Cr	R2=S3	R3=β-H	R4=β-OH	R5=OH	R6=H
38	R1=S3	R2=H	R3=β-H	R4=β-OH	R5=H	R6=H
39	R1=Cr	R2=Iv	R3=β-H	R4=β-OH	R5=Oiv	R6=H
40	R1=Cr	R2=Iv	R3=β-H	R4=α-OH	R5=Oiv	R6=H
41	R1=Iv	R2=Iv	R3=β-H	R4=β-OH	R5=Oiv	R6=H
42	R1=Cr	R2=Iv	R3=β-H	R4=β-OH	R5=OH	R6=H
43	R1=Cr	R2=Iv	R3=β-H	R4=β-OH	R5=OAc	R6=H
44	R1=Cr	R2=Pal	R3=β-H	R4=β-OH	R5=Oiv	R6=H
45	R1=Cr	R2=n-Bu	R3=β-H	R4=β-OH	R5=OH	R6=H
46	R1=Cr	R2=Iv	R3=β-H	R4=β-OH	R5=OHiv	R6=H
47	R1=Cr	R2=H	R3=β-H	R4=β-OH	R5=OH	R6=H
48	R1=Iv	R2=n-Bu	R3=β-H	R4=β-OH	R5=OH	R6=H
49	R1=Mcr	R2=S3	R3=β-H	R4=β-OH	R5=OH	R6=H
50	R1=Cr	R2=S2	R3=β-H	R4=β-OH	R5=OH	R6=H

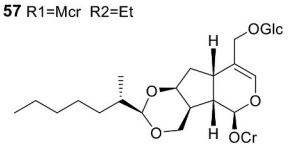


51	R1=S3	R2=OMe	R3=β-OH	R4=H	
52	R1=S3	R2=OMe	R3= =O	R4=H	
53	R1=S3	R2=OH	R3=β-OH	R4=H	
54	R1=Me	R2=H	R3=β-OH	R4=OH	
55	R1=n-Bu	R2=H	R3=β-OH	R4=H	



56	R1=Cr	R2=Et	
57	R1=Mcr	R2=Et	

59



58

Fig. 5. Monoene iridoid from *Patrinia* genus.

polymethyl groups, and are easily oxidized into CH_2OR, –COOH, –COOR and other groups. C-7 is mostly substituted by hydroxyl. When C-7 and C-10 are substituted by hydroxyl at the same time, hydroxyaldehyde condensation can occur with aldehydes to form 1, 3-dioxane ring structure (**17**–**18**). When C-10 and C-1 are simultaneously replaced by hydroxyl, dehydration can occur to form compounds with ether bonds (**26**). The methyl group of C-11 also forms a double bond with C-4 (**29**).

2.1.2. Monoene iridoids

There are 30 monoene iridoids (**30**–**59**) (Group 2) isolated from *Patrinia* (Fig. 5). The double bonds of the iridoid are mainly located

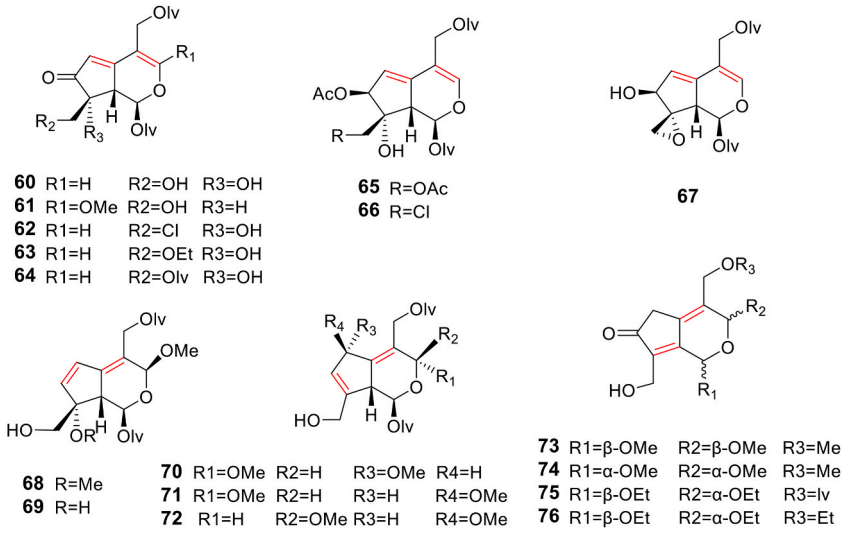


Fig. 6. Diene iridoid from *Patrinia* genus.

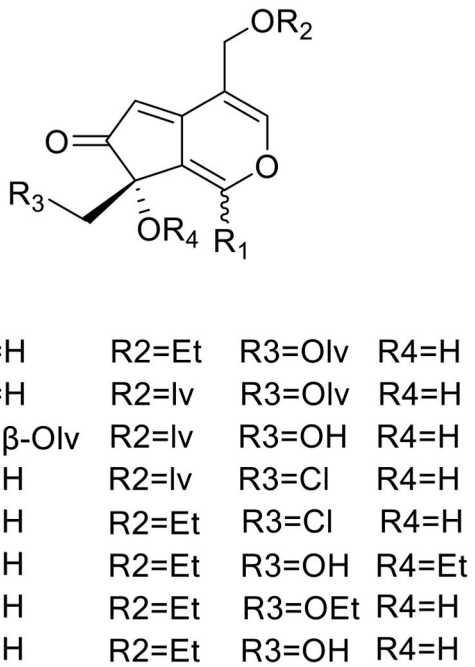


Fig. 7. Triene-type iridoid from *Patrinia* genus.

at C-3 and C-4, and there are oxygen-containing substitutions are found at C-7, C-8, C-10 and C-11. The hydroxyl groups of C-8 and C-10 can be dehydrated to form ethylene oxide, such as compound **59**. Furthermore, C-7 and C-10 can also be condensed with aldehydes to form 1, 3-dioxane structure (**56**–**58**).

2.1.3. Diene iridoids

So far, there are seventeen dienyl-iridoids (**60**–**76**) and their glycosides (Group 3) isolated from the *Patrinia* (Fig. 6). The structures of these iridoids all contain two double bonds, which mainly exist in C-3, 4 and C-5, 6 (**60**–**67**), C-4, 5 and C-6, 7 (**68**–**69**), C-4, 5 and C-7, 8 (**70**–**72**), C-4, 5 and C-8, 9 (**73**–**76**). In the C-10 and C-11, there are oxygen-containing substitutions, or carbonyl substitutions in the C-11, and ethylene oxide (**67**) is formed between C-8 and C-10.

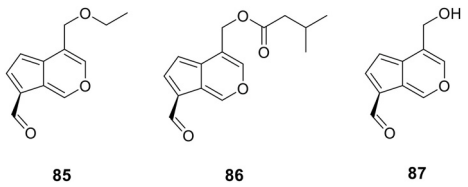


Fig. 8. Tetraene-type iridoid from *Patrinia* genus.

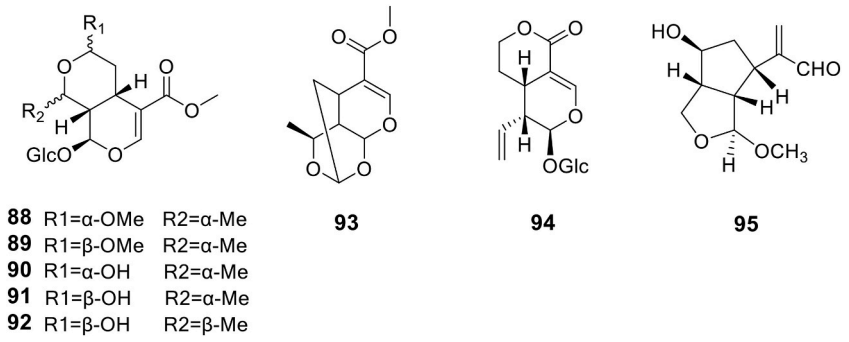


Fig. 9. Seco-iridoids from *Patrinia* genus.

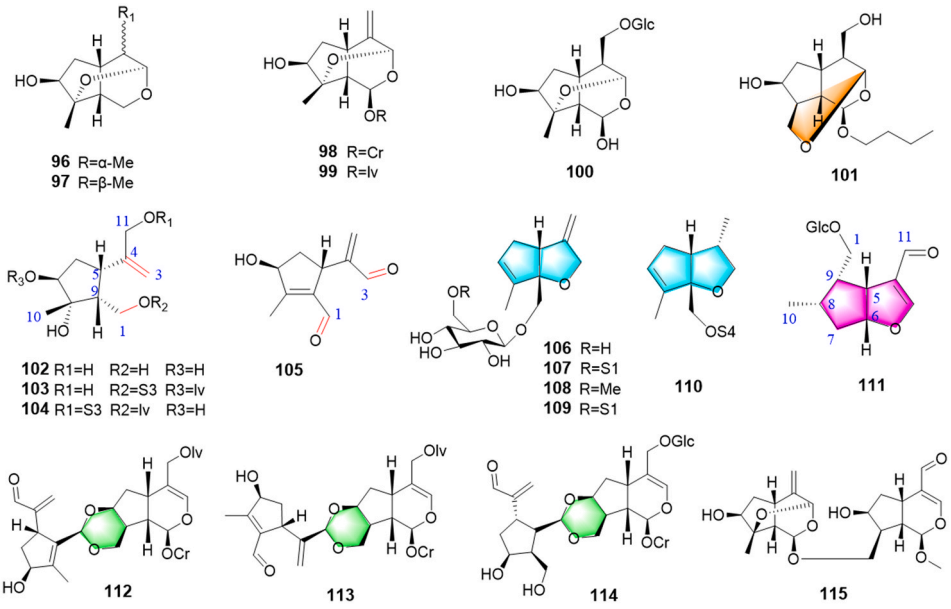


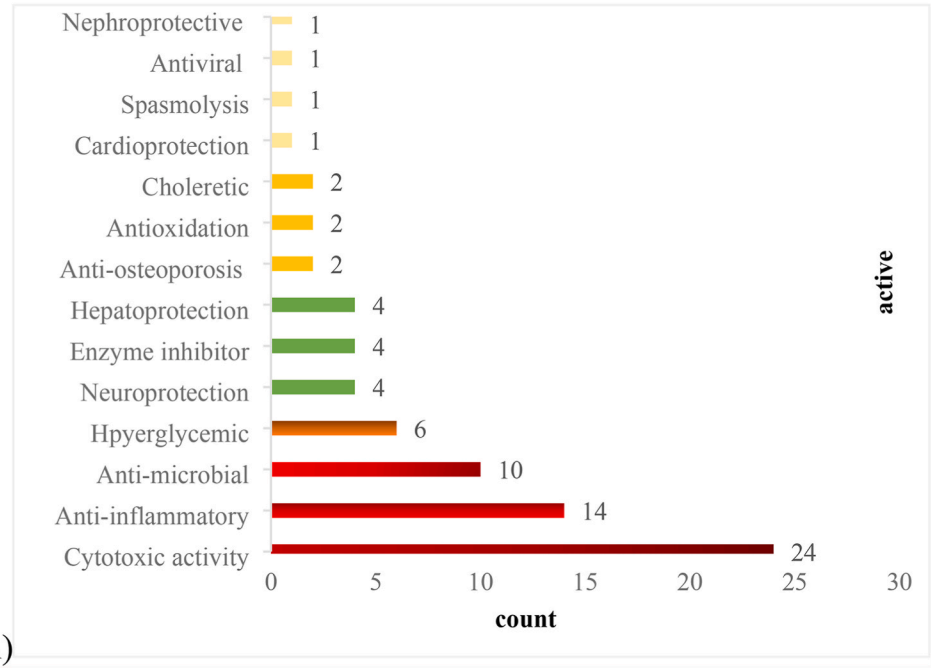
Fig. 10. Other-iridoids from *Patrinia* genus.

2.1.4. *Triene iridoids*

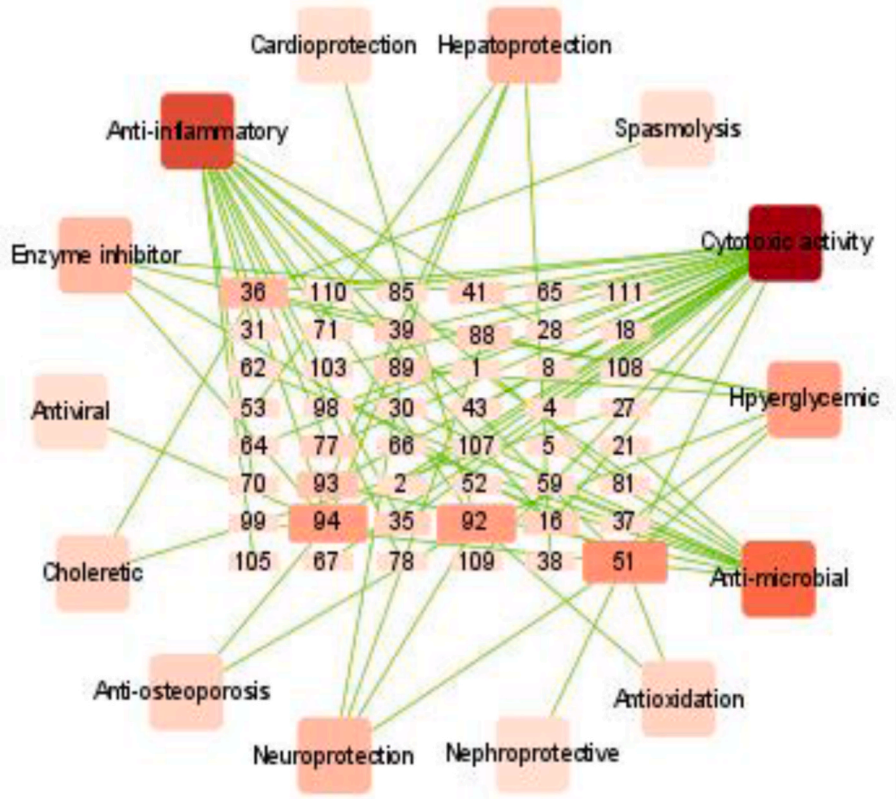
The structure of this kind of iridoid contains three double bonds (Group 4) located at C-3, 4, C-5, 6 and C-1, 9 respectively, of which C-7 is generally carbonyl substitution and C-10 is oxygen substitution. The C-10 can also be replaced by a chlorine atom (**77**–**84**) (Fig. 7).

2.1.5. *Tetraenes iridoid*

The structure of this kind of iridoid contains four double bonds (Group 5) located at C-3, 4, C-5, 6, C-7, 8 and C-1, 9 respectively, and the C-10 is oxidized to aldehyde groups (**85**–**87**) (Fig. 8).



(A)



(B)

(caption on next page)

Fig. 11. (A) Bioactivity of iridoid compounds of the *Patrinia* genus (the length of the column indicates the number of compounds with that bioactivity). (B) A network of relationships of iridoid bioactivity (the black numbers represent the compound No, the size of the inner circle area represents the biological activity abundance of the compound, the outer frame represents the biological activity, and each side line represents the corresponding compound and biological activity).

2.2. Seco-iridoids

The skeletons of seco-iridoids are 7,8-seco-cyclopenta[c]-pyranoid. There are 8 seco-iridoids (**88**–**95**) isolated from *Patrinia* genus (Fig. 9). Most of them mainly C-7 and C-8 cracked, and C-7 is oxidized and combined with C-8 (**88**–**92**). The skeleton of compound **93** is formed by the cyclization of C-7 and C-1 after C-6 and C-7 fracture and oxidation. When C-7 and C-8 crack, C-7 and C-11 are oxidized, and then cyclically combined to form the skeleton of compound **94**. After cracking of pyran ring, C-10 is oxidized to form an oxygen-containing ring with C-1, and usually bicyclic H-8/H-9β, β-*cis*-fused cyclopentane ring system **95**.

2.3. Other iridoids

There are three main types of other iridoids (Fig. 10). (1) There is an oxygen bridge structure in the structure, such as forming an oxygen bridge at C-3 and C-8 or C-3 and C-10 (**96**–**101**). (2) The pyran ring was broken to form compounds **102**–**105**. When the pyran ring is broken, C-2 can be connected with C-9 to form compounds **106**–**110**. When the pyran ring breaks, the C-2 is attached to the C-6, forming the deformed iridoid **111**. (3) The dimeric iridoid is consisted of two iridoids through aldol condensation to form a 1,3-dioxane group (**112**–**114**) or an ether bond (**115**).

3. Active iridoids and their mechanisms in *patrinia* genus

There are 48 iridoids have multiple biological effects, and they are mainly found in the *P. scabiosaefolia*, *P. villosa*, and *P. rupestris*, and their activities mainly focus on antioxidant, anti-inflammatory, hypoglycemic, and cytotoxic effect (Fig. 11, Table 1). Different iridoids have different biological activities and dose-dependent properties due to their different structures or substituents, and each active compound and its activity distribution are listed in Fig. 11 (A, B).

3.1. Anti-inflammatory

Fourteen iridoids **16**, **28**, **31**, **35**, **51**, **70**, **71**, **77**, **78**, **81**, **85**, **92**, **94** and **105** with anti-inflammatory activity have been isolated from the *Patrinia* genus. The anti-inflammatory activity was mainly screened by cell models [16–19,21,22,28–30,53–55,58,72,78] and animal models [31–37,59–61,73]. The cell models were RAW264.7 cell and chondrocyte induced by LPS, and the animal models were colitis mice induced by AKI, UC and DSS (Table 2).

The anti-inflammatory effect is mainly achieved by inhibiting the release of pro-inflammatory factors (IL-1, TNF-α, IL-6, IL-11 and IL-8, etc.), and the signaling pathways involved mainly include MAPK, NF-κB, JNK and Nrf2 signaling pathways (Fig. 12). For example, compound **35** inhibits TLR4-MyD88-NF-κB and JNK MAPK signaling pathways, producing anti-inflammatory effects [22]. Compounds **77**, **81** and **105** interfere with the activation of various inflammatory transcription factors such as NF-κB, AP-1, IRF3 and STAT1/3 [55]. Compound **71** inhibited the production of NO and TNF-α and decreased the iNOS protein level in LPS-induced RAW264.7 in a dose-dependent manner [54]. It is worth mentioning that **51** and **92**, which have the most significant anti-inflammatory effects, are iridoid glycosides isolated from *P. villosa*, can synergically inhibit the activation of STAT3/NF-κB [28,78]. Compound **92** by regulating the production of NO and PGE2 in chondrocytes, inhibiting the NF-κB and mTORC1 signaling pathways and activating the PI3K/AKT signaling pathway and autophagy, osteoarthritis is treated [58,72]. Compound **51** also up-regulates the TLR4/NF-κB and Nrf2/HO-1 signaling pathways, down-regulates the expression of proinflammatory enzymes including iNOS and COX-2, and attenuates the LPS-stimulated inflammation of RAW264.7 macrophages [29,30].

Meanwhile, compound **51** has been proved its anti-inflammatory effect in various animal models, such as in the model of cisplatin-induced acute kidney injury in mice, **51** reduces IL-1β, IL-6 and TNF-α, and then inhibit ERK1/2 pathway [31]. In addition, **51** up-regulates the mRNA and protein levels of Sirt1, inhibits NF-κB-P65 acetylation, regulats Sirt1/NF-κB signaling pathway, thereby alleviating the ulcerative colitis induced by DSS in mice [32]. Also, **51** reduces insulin resistance by down-regulating TNF-α/IL-1β-dependent NF-κB activation in PDN rats to inhibit spinal cord inflammation and improve neuropathic inflammation [33–35]. In the instability of mouse osteoarthritis model induced by medial meniscus (DMM), **51** and **92** inhibit NF-κB signal pathway is activated, by reducing the inflammatory mediators in articular cartilage, showing the effect of anti-osteoarthritis [36,37,59]. In the rat model of acute myocardial infarction, **92** and **94** can decrease the levels of LDH and cTnT, and the expressions of IL-6, IL-1β, TNF-α and NF-κB, decrease NF-κB signal pathway and increase the expression of Sirt1 [60,61,73].

3.2. Tumor cytotoxicity

At present, twenty-four compounds **2**, **4**, **8**, **16**, **18**, **35**, **36**, **39**, **41**, **43**, **51**, **64**, **65**, **67**, **77**, **93**, **94**, **98**, **103**, **107–111** with tumor cytotoxic activity have been isolated from the *Patrinia* genus. Cytotoxicity was mainly detected by MTT, and its activity was evaluated by IC_{50} (Table 3). Compounds **94**, **103** and **107–111** have cytotoxicity to MNK - 45 cell line, IC_{50} is 8.7–30.9 μM [14,15]. Compounds

Table 1
Active iridoids in *Patrinia*.

NO.	Compound	Activities	Source	Ref.
1	Patriscabrol	Anti-microbial	*P. rupestris*	[11,12]
2	(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-hydroxy-7-(hydroxymethyl)-4-methylhexahydrocyclopenta[c]pyran-3(1H)-one	Cytotoxic activity	*P. heterophylla*	[13]
4	IsopatriscabrosideI	Cytotoxic activity	*P. scabra*	[14]
5	Patriscabroside II	Anti-microbial	*P. scabra*	[11]
8	Isopatriscabrol	Cytotoxic activity	*P. scabra*	[14,15]
16	6-hydroxy-7-methyl-hexahydro-cyclopenta[c]pyran-3-one	Anti-inflammatory Cytotoxic activity	*P. scabra.*	[16–19,13]
18	1′,3′-dioxane[6,7]cyclopenta[c]pyran-3(1H)-one,hexahydro-2′,2′,4-trimethyl-(4*R*,4a*S*,6*R*,7*R*,7a*S*)	Cytotoxic activity	*P. heterophylla*	[13]
21	3-patriscabrol	Anti-microbial	*P. scabra*	[11]
27	Villoside	Choleretic	*P. villosa*	[20]
28	(4R,5R,7S,8S,9S)-7-hydroxy-8-hydroxymethyl-4-hydroxymethyl-4-methyl-perhydrocyclopent	Anti-inflammatory	*P. scabiosaefaolia*	[21]
30	Rupesin C	Anti-microbial	*P. rupestris*	[11]
31	Patriscabrins E	Anti-inflammatory	*P. scabra*	[16–19]
35	Nardostachin	Anti-inflammatory Cytotoxic activity	*P. scabiosaefolia*	[22,23]
36	Patrinoside	Cytotoxic activity Hpyerglycemic Choleretic Spasmolysis	*P. scabiosaefaolia*	[24,25,20,26]
37	Patrinoside A	Hpyerglycemic	*P. scabiosaefaolia*	[25]
38	Scabroside J	Hepatoprotection	*P. scabiosaefolia*	[27]
39	Patriscabioin A	Enzyme inhibitor Cytotoxic activity	*P. scabiosaefaolia*	[5]
41	Patriscabioin C	Enzyme inhibitor Cytotoxic activity	*P. scabiosaefaolia*	[5]
43	Patriscabioin E	Cytotoxic activity	*P. scabiosaefaolia*	[5]
51	Loganin	Anti-inflammatory Cytotoxic activity Neuroprotection Hpyerglycemic Nephroprotective Antioxidation Enzyme inhibitor	*P. villosa*	[28,29–37,38–46,47,48–51]
52	7-ketologanin	Anti-microbial	*P. rupestris*	[11]
53	Logain acid	Hepatoprotection	*P. villosa*	[27]
59	Rupesin D	Anti-microbial	*P. rupestris*	[11]
62	Rupesin A	Anti-microbial	*P. rupestris*	[11]
64	Patriheterdoid C	Cytotoxic activity	*P. heterophylla*	[52]
65	Acetoxyhydrin	Cytotoxic activity	*P. heterophylla*	[52]
66	Rupesin B	Anti-microbial	*P. rupestris*	[11]
67	Deacetylisovaltrate	Cytotoxic activity	*P. heterophylla*	[52]
70	Patridoid I	Anti-inflammatory	*P. scabiosaefolia*	[53]
71	Patridoid II	Anti-inflammatory	*P. scabiosaefolia*	[54,53]
77	Patriscabrins G	Anti-inflammatory Cytotoxic activity	*P. scabra*	[55,16–19,15]
78	Patriscabrins B	Anti-inflammatory	*P. scabra*	[16–19]
81	Patriscabrins F	Anti-inflammatory	*P. scabra*	[55,16–19]
85	11-ethoxyviburtinal	Anti-inflammatory	*P. rupestris*	[16–19]
88	7α-methoxy-morroniside	Neuroprotection Hpyerglycemic	*P. scabra*	[56,57]
89	7β-methoxy-morroniside	Neuroprotection Hpyerglycemic	*P. scabra*	[56,57]
92	Morroniside	Anti-inflammatory Neuroprotection	*P. villosa*	[28,58, 34, 37,59–61, 62–64, 65, 66–70]

(*continued on next page*)

Table 1 (*continued*)

NO.	Compound	Activities	Source	Ref.
		Hpyerglycemic Anti-osteoporosis Antioxidation Cardioprotection		
93	Sarracenin	Cytotoxic activity Anti-microbial Hepatoprotection	*P. rupestris*	[23,11,71]
94	Sweroside	Anti-inflammatory Cytotoxic activity Anti-osteoporosis Antiviral Enzyme inhibitor Hepatoprotection	*P. scabra*	[72,14,15,73,27,69,70,74–77]
98	Patriheterdoid B	Cytotoxic activity	*P. heterophylla*	[52]
99	Rupesin E	Anti-microbial	*P. rupestris*	[11]
103	Patrinioside	Cytotoxic activity	*P. scabra*	[14,15]
105	8,9-didehydro-7-hydroxydolichodial	Anti-inflammatory	*P. villosa*	[16–19]
107	Scabroside H	Cytotoxic activity	*P. scabra*	[15]
108	Patriridosides G	Cytotoxic activity	*P. scabra*	[15]
109	Patriridosides H	Cytotoxic activity	*P. scabra*	[15]
110	Patriridosides I	Cytotoxic activity	*P. scabra*	[15]
111	Patriridosides D	Cytotoxic activity	*P. scabra*	[15]

Table 2
Iridoids with anti-inflammatory activity in *Patrinia*.

NO.	Compound	Activities	IC_{50}(μM)	Source	Ref.
16	6-hydroxy-7-methyl-hexahydro-cyclopenta[c]pyran-3-one	Anti-inflammatory (RAW264.7)	——	*P. scabra.*	[16–19]
28	(4R,5R,7S,8S,9S)-7-hydroxy-8-hydroxymethyl-4-hydroxymethyl-4-methyl-perhydrocyclopent	Anti-inflammatory	10	*P. scabiosaefaolia*	[28]
31	Patriscabrins E	Anti-inflammatory (RAW264.7)	14.7–17.8	*P. scabra*	[16–19]
35	Nardostachin	Anti-inflammatory (RAW264.7, BV2)	——	*P. scabiosaefolia*	[22]
51	Loganin	Anti-inflammatory	——	*P. villosa*	[28,29–37]
70	Patridoid I	Anti-inflammatory (RAW264.7,BMMCs)	8.7 , 13.6	*P. scabiosaefolia*	[53]
71	Patridoid II	Anti-inflammatory (RAW264.7, BMMCs)	41.7 , 46.9 14.1 , 17.6	*P. scabiosaefolia*	[54,53]
77	Patriscabrins G	Anti-inflammatory (RAW264.7)	24.6	*P. scabra*	[55,16–19]
78	Patriscabrins B	Anti-inflammatory (RAW264.7)	14.7–17.8	*P. scabra*	[16–19]
81	Patriscabrins F	Anti-inflammatory (RAW264.7)	35.5	*P. scabra*	[55,16–19]
85	11-ethoxyviburtinal	Anti-inflammatory (RAW264.7)	14.1	*P. rupestris*	[16–19]
92	Morroniside	Anti-inflammatory (RAW264.7)	——	*P. villosa*	[34,28,58,37,59–61]
94	Sweroside	Anti-inflammatory	——	*P. scabra*	[73]
105	8,9-didehydro-7-hydroxydolichodial	Anti-inflammatory (RAW264.7)	26.48	*P. villosa*	[16–19]

2, **16**, **18**, **36**, **39**, **41** and **43** show dose-dependent cytotoxicity to human leukemia cells (HL-60, K562 and Jurkat) [5,13,24]. Other compounds also have strong cytotoxicity to human cervical cancer HeLa cells [14,15] and gastric cancer cells [52,79] (SGC-7901). Among various cell activity evaluation results, compounds **39** and **43** have the strongest cytotoxicity IC_{50} of 1.4 and 1.2 μM to HL-60 cells. In addition, compound **39** has strong cytotoxicity to human liver cancer cells (SMMC-7721) and colon cancer cells (SW480), equivalent to cisplatin (DDP) [5]. The IC_{50} values of compounds **98**, **64**, **65**, **67** and **35** on prostate cancer PC-3M cells and human gastric cancer SGC-7901 cells were all 13 μM below [52,23]. By analyzing the structural characteristics of these compounds with strong cytotoxicity, it is speculated that monoene and diene iridoids and acetyl substitution may be the main reason for the strong cytotoxicity of these iridoids.

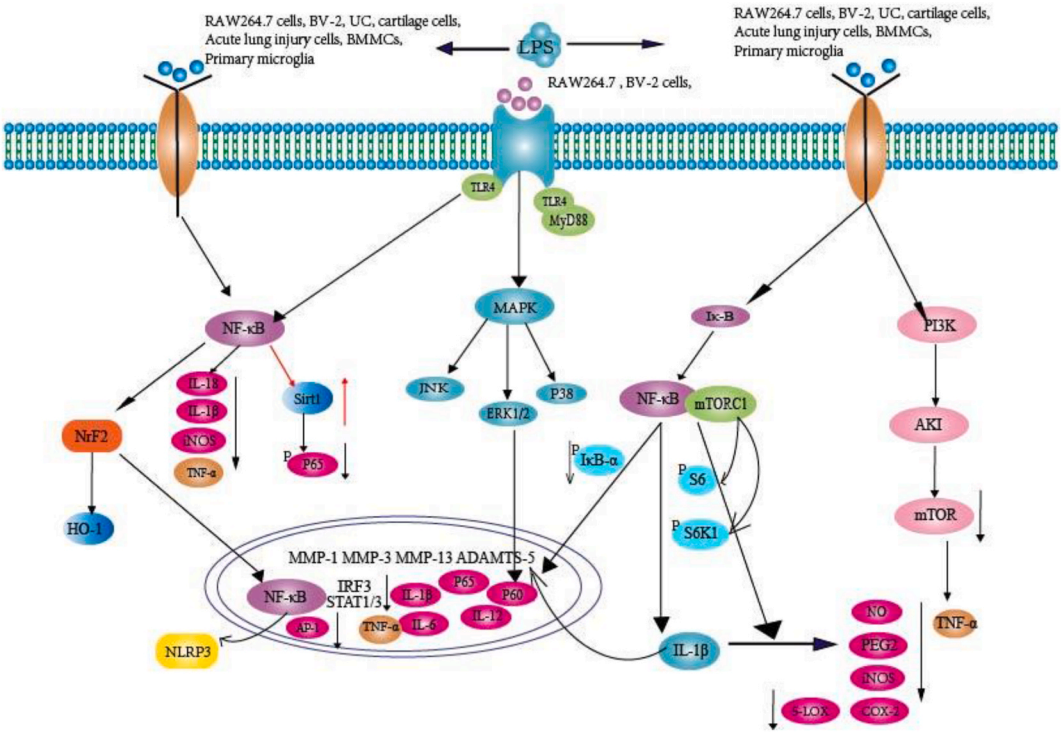


Fig. 12. Anti-inflammatory mechanism of active iridoid in *Patrinia* genus. nitric oxide (NO), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1*β*), activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2),5-lipoxygenase(5-LOX), inducible nitric oxide synthase (iNOS), interferon regulatory factor 3(IRF3), polyclonal antibody to sirtuin 1(Sirt1),mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), p38, lipopolysaccharide (LPS), reactive oxygen species (ROS), nuclear factor erythroid 2-related factor 2 (Nrf2). Note: → (up-regulate), → (down-regulate).

3.3. Neuroprotective effect

At present, four iridoids **51**, **88**, **89** and **92** with neuroprotective effects have been isolated from *Patrinia* genus. Neuroprotective mechanisms include regulation of MAPK, JNK, PI3K/Akt and Nrf2 signaling pathways [39–46,56,62–64] (Table 4). The neuroprotective effects of compound **51** have been extensively studied in both cellular and animal models. Cell models such as PC12 cells and HT-22 cells. The animal model has the brain, spinal cord and gastrocnemius muscle of SMAΔ7 mice. Such as, in a*β*25-35 and MPTP-induced PC12 cells, compound **51** inhibits a*β*25-35-induced cell death, inhibits NF-κB-dependent inflammatory pathways, PI3K/Akt/mTOR and JNK signaling pathways, and promotes MAPK phosphorylation, thereby enhancing neuroprotective effects [39,40]. Compound **51** exerts a neuroprotective effect on H_2O_2-induced apoptosis by inhibiting the phosphorylation of JNK, p38 and ERK 1/2 MAPKs and thereby reducing the expression of the Bcl-2/Bax ratio [41]. In addition, compound **51** can also have a strong specific inhibitory effect on BACE1 and effectively prevent AD [42–45]. In fibroblasts of SMA patients, compound **51** up-regulated the levels of SMN, FL-SMN2 and Gemins, producing neuroprotective effects. In NSC34 cells with SMN deletion, **51** activates the expression of protective signals such as SMN, *p*-Akt, *p*-GSK-3*β*, *p*-CREB, BDNF and Bcl-2, and has neuroprotective effect on SMN deficient neurons [46]. Compound **92** protects HT-22 cells from OGD/R by regulating Nrf2/HO-1 signaling pathway [62], and it also attenuates neuropathic pain by activating GLP-1 receptors in the spinal cord [63].

In addition, compound **51** up-regulated the expression of SMN and *p*-Akt, reduced motor neuron degeneration in the brain, spinal cord and gastrocnemius of the animal model SMAΔ7 mice [46].

3.4. Hpyerglycemic and improving diabetes symptoms

At present, six compounds **36**, **37**, **51**, **88**, **89**, **92** with anti-diabetes activity have been isolated from *Patrinia* genus. The main mechanisms of hypoglycemic activity include regulating MAPK, *p*-Akt/GLUT4 signal pathways (Table 5). Compounds generally affect the GLUT4 translocation and increase glucose uptake by regulating the expression of genes and corresponding proteins associated with insulin signaling pathways, thereby improving T2DM [80]. For example, compounds **36** and **37** isolated from *P. scabra* could active PI-3K/AKT pathway, inhibit NF-κB pathway, MAPK pathway, and improve oxidative stress, which showed multipathways on improving IR [25,57]. Compounds **88** and **89** can inhibit the STAT3 promoter activity of HepG2 cells induced by IL-6 [65]. Compound **92** can treat diabetes induced osteoporosis by inhibiting AGE-RAGE signal and activating Glo1 [47].

Multiple animal experiments have shown that compound **51** can promote glucose uptake in HepG2 cells [81]. In addition, **51** can

Table 3
Iridoids with cytotoxic activity in the *Patrinia*.

NO.	Compound	Activities	IC_{50}(μM)	Source	Ref.
2	(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-hydroxy-7-(hydroxymethyl)-4-methylhexahydrocyclopenta[c]pyran-3(1H)-one	Cytotoxic activity (HL-60, K562, Jurkat)	—— 51.32,30.4,51.36	*P. heterophylla*	[13]
4	IsopatriscabrosideI	Cytotoxic activity (HeLa)	24.9	*P. scabra*	[14]
8	Isopatriscabrol	Cytotoxic activity (HeLa)	14.4,24.5	*P. scabra*	[14, 15]
16	6-hydroxy-7-methyl-hexahydro-cyclopenta[c]pyran-3-one	Cytotoxic activity (HL-60)	81.18	*P. scabra.*	[13]
18	1′,3′-dioxane [6,7]cyclopenta[c]pyran-3(1H)-one,hexahydro-2′,2′,4-trimethyl-(4*R*,4a*S*,6*R*,7*R*,7a*S*)	Cytotoxic activity (HL-60 K562 Jurkat)	55.21,62.64,59.13	*P. heterophylla*	[13]
35	Nardostachin	Cytotoxic activity (PC-3)	6.22	*P. scabiosaefolia*	[23]
36	Patrinoside	Cytotoxic activity (HL-60)	45.38	*P. scabiosaefaolia*	[24]
39	Patriscabioin A	Cytotoxic activity (HL-60, SMMC-7721, SW480)	1.4,7.2,7.1	*P. scabiosaefaolia*	[5]
41	Patriscabioin C	Cytotoxic activity (HL-60)	9.9	*P. scabiosaefaolia*	[5]
43	Patriscabioin E	Cytotoxic activity (HL-60)	1.2	*P. scabiosaefaolia*	[5]
51	Loganin	Cytotoxic activity (BXPC3)	——	*P. villosa*	[38]
64	Patriheterdoid C	Cytotoxic activity (SGC-7901 PC-3)	12.8,9.28	*P. heterophylla*	[52]
65	Acetoxyhydrin	Cytotoxic activity (SGC-7901 PC-3)	2.49,5.29	*P. heterophylla*	[52]
67	Deacetylisovaltrate	Cytotoxic activity (SGC-7901 PC-3)	0.842,2.55	*P. heterophylla*	[52]
77	Patriscabrins G	Cytotoxic activity (HeLa, MNK-45)	24.6,8.7	*P. scabra*	[15]
93	Sarracenin	Cytotoxic activity (A375, SGC-7901, HeLa)	74.91,75.73,67.8	*P. rupestris*	[23]
94	Sweroside	Cytotoxic activity (MNK-45)	11.2	*P. scabra*	[14, 15]
98	Patriheterdoid B	Cytotoxic activity (SGC-7901 PC-3)	10.4,12.6	*P. heterophylla*	[52]
103	Patrinioside	Cytotoxic activity (MNK-45)	23.8	*P. scabra*	[14, 15]
107	Scabroside H	Cytotoxic activity (MNK-45)	9.4	*P. scabra*	[14]
108	Patriridosides G	Cytotoxic activity (MNK-45)	8.7	*P. scabra*	[15]
109	Patriridosides H	Cytotoxic activity (MNK-45)	9.4	*P. scabra*	[15]
110	Patriridosides I	Cytotoxic activity (MNK-45)	30.9	*P. scabra*	[15]
111	Patriridosides D	Cytotoxic activity (MNK-45)	15.6	*P. scabra*	[15]

Table 4
Iridoids with neuroprotective activity in *Patrinia*.

NO.	Compound	Activities	Source	Ref.
51	Loganin	Neuroprotection	*P. villosa*	[39–46]
88	7α-methoxy-morroniside	Neuroprotection	*P. scabra*	[56]
89	7β-methoxy-morroniside	Neuroprotection	*P. scabra*	[56]
92	Morroniside	Neuroprotection	*P. villosa*	[62–64]

Table 5
Iridoids that can improve diabetes and its complications in *Patrinia*.

NO.	Compound	Activities	Source	Ref.
36	Patrinoside	Hpyerglycemic	*P. scabiosaefaolia*	[25,57]
37	Patrinoside A	Hpyerglycemic	*P. scabiosaefaolia*	[25,57]
51	Loganin	Hpyerglycemic	*P. villosa*	[48,49,81]
88	7α-methoxy-morroniside	Hpyerglycemic	*P. scabra*	[65]
89	7β-methoxy-morroniside	Hpyerglycemic	*P. scabra*	[65]
92	Morroniside	Hpyerglycemic	*P. villosa*	[47]

treat diabetic nephropathy by reducing the level of AGE in serum and kidney of diabetic mice, down-regulating the expression of AGE receptor mRNA and protein in kidney and inhibiting the AGE pathway [48]. Compound **51** not only decreased the blood glucose of diabetic testicular lesion mice, but also increased the activity of testicle-specific marker enzyme, decreased the apoptosis rate of GC-2 cells induced by AGEs, improved oxidative stress, and inhibited p38 MAPK phosphorylation, thus improving the pathological injury of diabetic mice testicular lesion [49].

Table 6
Other active iridoids in *Patrinia*.

NO.	Compound	Activities	Source	Ref.
1	Patriscabrol	Anti-microbial	*P. rupestris*	[12,20]
5	Patriscabroside II	Anti-microbial	*P. scabra*	[12]
21	3-patriscabrol	Anti-microbial	*P. scabra*	[12]
27	Villoside	Choleretic	*P. villosa*	[71]
30	Rupesin C	Anti-microbial	*P. rupestris*	[12]
36	Patrinoside	Choleretic Spasmolysis	*P. scabiosaefaolia*	[71,82]
38	Scabroside J	Hepatoprotection	*P. scabiosaefolia*	[11]
39	Patriscabioin A	Enzyme inhibitor (AChE)	*P. scabiosaefaolia*	[5]
41	Patriscabioin C	Enzyme inhibitor (AChE)	*P. scabiosaefaolia*	[5]
51	Loganin	Nephroprotective Antioxidation Enzyme inhibitor (TYR)	*P. villosa*	[31,50,51,66]
52	7-ketologanin	Anti-microbial	*P. rupestris*	[12]
53	Logain acid	Hepatoprotection	*P. villosa*	[11]
59	Rupesin D	Anti-microbial	*P. rupestris*	[12]
62	Rupesin A	Anti-microbial	*P. rupestris*	[12]
66	Rupesin B	Anti-microbial	*P. rupestris*	[12]
92	Morroniside	Anti-osteoporosis Antioxidation Cardioprotection	*P. villosa*	[34,67–70,74]
93	Sarracenin	Anti-microbial	*P. rupestris*	[12,26]
94	Sweroside	Anti-osteoporosis Antiviral Enzyme inhibitor (TYR) Hepatoprotection	*P. scabra*	[11,27,70,74–77]
99	Rupesin E	Anti-microbial	*P. rupestris*	[12]

3.5. Other activities

In addition, 18 other active compounds (Table 6) were obtained from 4 species of *Patrinia* genus, including Anti-microbial and antiviral (11), Hepatoprotective (4), Enzyme inhibitor (4), Antioxidant (2), Anti-osteoporosis (2), Choleretic (2), Spasmolysis (1), Nephroprotective (1) and Cardioprotective (1), among which, Compounds **51**, **92** and **94** contain multiple activities. The main mechanisms include the regulation of JAK2/STAT3, Nrf2/HO-1, Akt, ERK, NF-κB, JNK signaling pathways [11,12,20,26,27,50,51,66–71,74–77,82]. For example, compound **51** activates AKT signal in proximal renal tubular cells [31] or inhibits JAK2/STAT3 and activates Nrf2/HO-1 signal pathway [50], it can also reduce the production of tyrosinase, TRP-1 and TRP-2 proteins in melanin cells, while up regulating ERK phosphorylation and down regulating CREB phosphorylation and tyrosinase gene expression [51]. In addition, it also prevents H_2O_2 induced oxidative damage of HaCaT keratinocytes [66]. Compound **92** reduced the activity of CK-MB, LDH, α-HBDH and AST in AMI rats, and reduced the expression of NF-κB in myocardium [67]. More, **92** significantly up-regulated *p*-Nrf2, activated SOD and NQO1, significantly regulated the level of apoptosis related proteins through p38 and JNK pathways, and reduced H_2O_2 induced oxidative damage and apoptosis of ovarian GCs [68]. It can also reduce ROS accumulation by regulating Keap1/Nrf2, inhibiting oxidative stress [69], or activating Nrf2/HO-1 signaling pathway [34]. Both **92** and **94** can up-regulate MC3T3-E1, BMSCs and ALP, respectively, promote osteoblast differentiation, reduce osteoclast differentiation, activate mTORC1/PS6 and p38 signaling pathways, and prevent OVX-induced osteoporosis in mice [70,74–76]. **94** inhibits Akt and ERK signaling pathways, inhibits somatic pigmentation in a dose-dependent manner, and regulates the expression of ERK1/2 and melanase [77]. In addition, compound **94** is also an inhibitor of viral protein R [27]. Compounds **53**, **38** and **94** have protective effects on APAP induced HepG2 cell damage [11].

It is worth mentioning that compounds **52** and **59**, compounds **1**, **5**, **21**, **62**, **66**, **99**, **93**, and compounds **1**, **30**, **59** have significant inhibitory effects on *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*, respectively [12]. The antibacterial activity of compound **1** was stronger than that of the positive drug garcinoic acid [20]. Both **27** and **36** can promote biliary secretion, and their anticholinergic effects are related to their hemiacetal structures [71].

4. Concluding remarks and prospects

Iridoids are widely distributed in *Patrinia* genus, mainly in different species such as *P. scabra, P. villosa* and *P. scabra* [83]. It has anti-inflammatory, neuroprotective, anti-tumor, antifungal, viral and other biological effects. At present, iridoid extracts are also sold as health products [84]. Due to the special semi-acetal structure, cyclopene ethers are particularly unstable, and they degrade to open rings under physical and chemical conditions. Therefore, it also hinders the study of its activities and functions. In recent years, with the continuous improvement of extraction methods and storage conditions, more and more iridoid compounds have been found, and their functions have become a new hotspot of natural products. However, most of the researches on iridoids are still confined to the determination of their structures and the analysis of their activities. There is a lack of systematic research on the structure-activity

relationship and biological activities of iridoids. Therefore, through the analysis and comparative study of the structure and function of the known iridoid, the main active groups and characteristics of iridoid can be better inferred, and also provide effective data support for chemical modification and new drug development.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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