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Triterpenoids from *Cyclocarya paliurus*: structure, biosynthesis, biological activities

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ABSTRACT

Cyclocarya paliurus (Batalin) Iljinskaja, as a unique and rare monocotyledonous plant in Southern China, is a promising and economical Chinese herbal medicine and functional food. People have conducted a number of research on *C. paliurus* because of its rich triterpenoids. However, no comprehensive review has illustrated the composition and pharmacological activity of triterpenoids from *C. paliurus*. This review summarizes 177 triterpenoids from different parts of *C. paliurus*. The structures of compounds were elucidated, and their biosynthesis was inferred. The biological activities of compounds and triterpenoid-rich extracts, including anti-diabetes, antihyperlipidemia, anti-inflammatory, anticancer or cytotoxicity, antioxidation, etc., were discussed. *C. paliurus* can be an important and valuable supplement to the food market. This review provides a reference for the further research and application of *C. paliurus* triterpenoids in the fields of foods and pharmaceuticals.

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1. Introduction

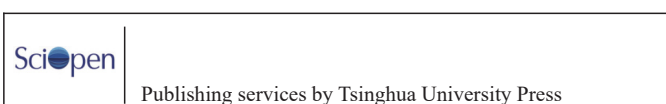
Cyclocarya paliurus (Batalin) Iljinskaja, known as “sweet tea tree” because of the strong sweetness of its leaves, is an endemic species in China^[1-2]. This tree grows in the cloudy and foggy highlands of Southern China, such as Jiangxi, Hunan, Fujian, and Sichuan Provinces^[3-4]. *C. paliurus*, the only species of its genus, belongs to family Juglandaceae^[5]. This plant is also used as a medicinal Chinese herb with the effect of “Qingrejiedu and Shengjinzhike,” and mentioned in the ancient Chinese pharmacopoeia *Zhong Hua Ben Cao*^[6]. *C. paliurus* leaves have high nutritional value and health function, and they have been widely used as a tea drink in China^[7-8]. In 2013, the leaves of *C. paliurus* were approved as a new food material by the National Health Commission of People’s

Republic of China^[9]. The plant’s leaves have been successfully processed into health tea products and have made breakthroughs in industrialization. Large-scale plantations for leaf picking have been established to meet the growing demand for medical leaves or tea production in China^[10]. *C. paliurus* has gained increasing attention given its wide range of bioactivities, such as its antihyperlipidemic^[11], antihyperglycemic^[12], anti-inflammatory^[13-14], antioxidant^[15], anticancer^[16], and hepatoprotective effects^[17]. Empirical studies attribute these activities to the main active components of *C. paliurus* leaves, such as flavonoids, polysaccharides, triterpenoids, steroids, saponins, and phenolic acids^[18].

To understand the research progress and trend of the main active components of *C. paliurus*, we used “*C. paliurus*”/“triterpenoids,” “*C. paliurus*”/“polyphenols,” “*C. paliurus*”/“flavonoids,” and “*C. paliurus*”/“polysaccharides” as keywords to search the Web of Science database. Statistical analysis of relevant literature since 2015 revealed a limited number of studies on triterpenoids (18.4%) in *C. paliurus* compared with those on polysaccharides (44.3%) and flavonoids (25.1%). Chen et al.^[11] summarized 210 active ingredients

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in *C. paliurus*, of which triterpenoids accounted for 65.2%. Therefore, more attention should be given to the research and development of triterpenoids from *C. paliurus*.

Terpenoids are natural compounds formed by isoprene^[19]. The basic nucleus of most triterpenoids is composed of 30 carbon atoms, which can be regarded as the polymerization of 6 isoprene units according to isoprene rules^[20]. Triterpenoids are important secondary metabolites in the plant kingdom and one of the most abundant phytochemical categories; they possess more than 20 000 known structures because their basic skeletons are modified through various ways^[21]. They are widely distributed plant ingredients and generally considered nontoxic^[22]. Terpenoids offer many health-promoting properties, such as antidiabetic^[23], antitumor^[24], and antinociceptive activities^[25]. These compounds exert a strong cytotoxic effect on human cancer cells, and thus, the research on terpenoids has attracted considerable attention^[26]. The search for anticancer agents based on natural terpenoids has become an interesting challenge for chemists^[27]. Previous articles have primarily reviewed polyphenols^[28] and polysaccharides^[29] from *C. paliurus*, and pay little attention to triterpenoids. The current research on triterpenoids from *C. paliurus* mainly centers on the separation, purification, and identification of their biological activity. However, data from these studies are relatively scattered, and no summary has been provided regarding its future application trends, which hinders the development and utilization of triterpenoids from *C. paliurus*. The pentacyclic triterpenoids extracted from *C. paliurus* have wide application prospect in drug and food exploitation, food additives, aquaculture,

and so on. Therefore, an in-depth study of triterpenoids from *C. paliurus* is very important to explore new strategies for the application and promotion of the efficient use of resources.

In this review, we summarize the research progress on the structure, biosynthesis, and biological activity of triterpenoids from *C. paliurus*. The structure-activity relationship of triterpenoids was discussed in depth, and a variety of biological activity mechanisms were systematically summarized. We prospect other potential functions and applications of triterpenoids from *C. paliurus*. This review provides a reference for the further research and application of *C. paliurus* triterpenoids in the fields of functional foods and pharmaceuticals.

2. Structures of triterpenoids from *C. paliurus*

A total of 177 triterpenoids, including triterpenes and their saponins, were isolated from different parts of *C. paliurus* and identified *via* strict identification methods. Triterpene saponins originate from triterpenoid aglycones, and their glucose and/or other sugar molecules are linked to the skeleton through hydroxyl dehydration between sugars and glycans. The triterpenoids found from *C. paliurus* are mainly tetracyclic and pentacyclic triterpenes and their saponins. Tetracyclic triterpenoids include 3,4-seco-damaranes and dammaranes, and pentacyclic triterpenoids consist of oleananes, ursanes, lupinanes, and taraxeranes. Table 1 summarizes the triterpenoids from *C. paliurus*, including their names, molecular formula, and plant organ. Figs. 1-5 show their chemical structures.

Table 1
Chemical structures of triterpenoids from *C. paliurus*.

No.	Compound	Molecular formula	Plant organ	Reference
Dammaranes				
1	Cyclopalitin A	C ₂₇ H ₄₆ O ₃	Stems, leaves	[30]
2	Cyclopalitin B	C ₂₈ H ₄₇ O ₅	Stems, leaves	[30]
3	Cyclocarioside I	C ₂₈ H ₄₇ O ₅	Leaves	[116]
4	Cyclocarioside H	C ₄₃ H ₇₂ O ₁₃	Leaves	[120]
5	Cyclocarioside B	C ₄₂ H ₇₂ O ₁₂	Leaves	[121]
6	Cyclocarioside J	C ₄₁ H ₇₀ O ₁₂	Leaves	[122]
7	Cyclocarioside N	C ₄₄ H ₇₄ O ₁₃	Leaves	[37]
8	Cyclocarioside K	C ₄₁ H ₇₀ O ₁₂	Leaves	[120]
9	Cyclocarioside Z7	C ₄₁ H ₇₀ O ₁₂	Leaves	[34]
10	Cyclocarioside Z8	C ₄₂ H ₇₂ O ₁₂	Leaves	[34]
11	(24 <i>R</i>)-3 <i>β</i> -[(4- <i>O</i> -Acetyl- <i>α</i> - <i>L</i> -arabinopyranosyl) oxy]-25-hydroxy-20,24-epoxydammaran-12 <i>β</i> -yl 6-deoxy- <i>β</i> - <i>D</i> -glucopyranoside	C ₄₃ H ₇₂ O ₁₃	Leaves	[80]
12	Cyclocarioside A	C ₄₃ H ₇₂ O ₁₃	Leaves	[123]
13	Cyclocarioside C	C ₄₂ H ₆₉ O ₁₃	Leaves	[121]
14	Cyclocarioside Z13	C ₄₁ H ₇₀ O ₁₃	Leaves	[124]
15	Cypaliuruside M	C ₄₂ H ₇₂ O ₁₂	Leaves	[125]
16	Cyclocarioside Z ₁₈	C ₄₁ H ₇₀ O ₁₃	Leaves	[126]
17	Cyclocarioside Z ₁₉	C ₄₃ H ₇₂ O ₁₄	Leaves	[126]
18	Cypaliuruside V	C ₄₃ H ₇₂ O ₁₃	Leaves	[56]
19	Cypaliuruside N	C ₃₆ H ₆₂ O ₈	Leaves	[81]
20	Cypaliuruside O	C ₄₀ H ₆₈ O ₁₂	Leaves	[81]
21	Cyclocarioside L	C ₃₈ H ₆₂ O ₁₂	Leaves	[37]
22	Cyclocarioside M	C ₄₀ H ₆₄ O ₁₃	Leaves	[37]
23	Cyclocarioside Z ₁₃	C ₄₂ H ₇₂ O ₁₂	Leaves	[126]
24	Cyclocarioside Z ₁₄	C ₄₁ H ₇₀ O ₁₂	Leaves	[126]

Table 1 (Continued)

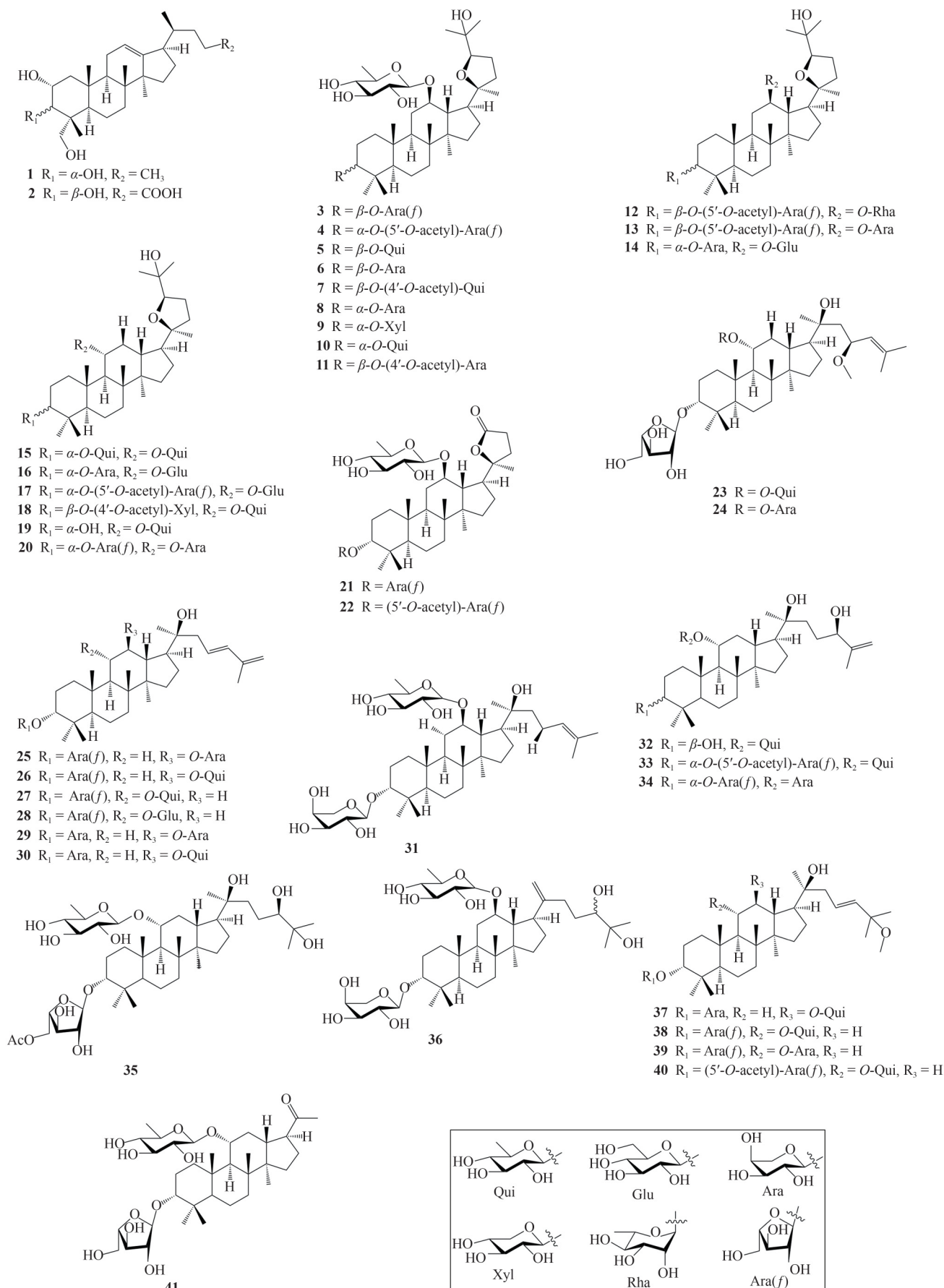
No.	Compound	Molecular formula	Plant organ	Reference
25	Cyclocarioside O	C ₄₀ H ₆₆ O ₁₁	Leaves	[107]
26	Cyclocarioside P	C ₄₁ H ₆₈ O ₁₁	Leaves	[107]
27	Cypaliuraside L	C ₄₁ H ₆₈ O ₁₁	Leaves	[125]
28	Cyclocarioside Z ₁₁	C ₄₁ H ₆₈ O ₁₂	Leaves	[126]
29	Cyclocarioside Z5	C ₄₀ H ₆₆ O ₁₁	Leaves	[34]
30	Cyclocarioside Z12	C ₄₁ H ₆₈ O ₁₁	Leaves	[124]
31	Cyclocarioside Z6	C ₄₁ H ₇₀ O ₁₁	Leaves	[34]
32	Cyclocarioside Z ₉	C ₃₆ H ₆₂ O ₈	Leaves	[126]
33	Cypaliuraside P	C ₄₃ H ₇₂ O ₁₃	Leaves	[81]
34	Cypaliuraside Q	C ₄₀ H ₆₈ O ₁₂	Leaves	[81]
35	Cyclocarioside Z ₁₀	C ₄₃ H ₇₄ O ₁₄	Leaves	[126]
36	3β-(α-L-Arabinopyranosyloxy)-24,25-dihydroxydammar-20-en-12α-yl 6-deoxy-β-D-glucopyranoside	C ₄₁ H ₇₀ O ₁₂	Leaves	[80]
37	Cyclocarioside Q	C ₄₂ H ₇₂ O ₁₂	Leaves	[107]
38	Cyclocarioside Z ₁₅	C ₄₂ H ₇₂ O ₁₂	Leaves	[126]
39	Cyclocarioside Z ₁₆	C ₄₁ H ₇₀ O ₁₂	Leaves	[126]
40	Cyclocarioside Z ₁₇	C ₄₄ H ₇₄ O ₁₃	Leaves	[126]
41	Cyclocarioside Z ₁₂	C ₃₅ H ₅₈ O ₁₁	Leaves	[126]
3,4-Seco-dammaranes				
42	(23E)-(12R,20S)-12,20,25-Trihydroxy-3,4-seco-dammara-4(28),23-dien-3-oic acid	C ₃₀ H ₅₀ O ₅	Leaves	[57]
43	Cyclocariol E	C ₃₁ H ₅₂ O ₅	Leaves	[57]
44	Cyclocariol F	C ₃₂ H ₅₄ O ₅	Leaves	[57]
45	Cyclocariol A	C ₃₁ H ₅₂ O ₅	Leaves	[57]
46	Cyclocariol B	C ₃₁ H ₅₂ O ₅	Leaves	[57]
47	Cyclocariol C	C ₃₀ H ₅₀ O ₅	Leaves	[57]
48	Cyclocariol D	C ₃₀ H ₅₀ O ₅	Leaves	[57]
49	Qingqianliusu L	C ₃₂ H ₅₄ O ₅	Leaves	[31]
50	Qingqianliusu M	C ₃₂ H ₅₄ O ₅	Leaves	[31]
51	Cyclocarin A	C ₃₁ H ₅₀ O ₄	Leaves	[127]
52	Cyclocariol G	C ₃₁ H ₅₀ O ₄	Leaves	[57]
53	Ovalifoliolide B	C ₃₀ H ₄₈ O ₄	Leaves	[57]
54	Cyclocariol I	C ₃₁ H ₅₂ O ₅	Leaves	[128]
55	Qingqianliusu A	C ₃₀ H ₄₈ O ₄	Leaves	[31]
56	Qingqianliusu B	C ₃₀ H ₄₈ O ₄	Leaves	[31]
57	Qingqianliusu C	C ₃₁ H ₅₂ O ₅	Leaves	[31]
58	Qingqianliusu I	C ₃₂ H ₅₄ O ₅	Leaves	[31]
59	Qingqianliusu D	C ₃₁ H ₅₂ O ₅	Leaves	[31]
60	Qingqianliusu E	C ₃₁ H ₅₂ O ₅	Leaves	[31]
61	Qingqianliusu F	C ₃₁ H ₅₂ O ₄	Leaves	[31]
62	Qingqianliusu G	C ₃₀ H ₅₀ O ₄	Leaves	[31]
63	Qingqianliusu H	C ₃₀ H ₄₈ O ₅	Leaves	[31]
64	Pterocaryoside A	C ₃₆ H ₆₀ O ₉	Stems, leaves	[32]
65	Pterocaryoside B	C ₃₅ H ₅₈ O ₉	Stems, leaves	[32]
66	Cyclocarioside D	C ₃₇ H ₆₂ O ₉	Leaves	[127]
67	Cyclocarioside F	C ₃₆ H ₆₀ O ₉	Leaves	[127]
68	Cyclocarioside P	C ₃₆ H ₆₀ O ₉	Leaves	[129]
69	Cyclocarioside Z3 Cyclocarioside Z ₁	C ₃₇ H ₆₂ O ₉	Leaves	[34]
70	Cyclocarioside Z10	C ₃₆ H ₆₀ O ₁₀	Leaves	[104]
71	Cyclocarioside X	C ₃₇ H ₆₂ O ₉	Leaves	[99]
72	Cyclocarioside Y	C ₃₈ H ₆₄ O ₉	Leaves	[99]
73	Cyclocarioside E	C ₃₉ H ₆₆ O ₉	Leaves	[127]
74	Cyclocarioside G	C ₃₈ H ₆₄ O ₉	Leaves	[127]

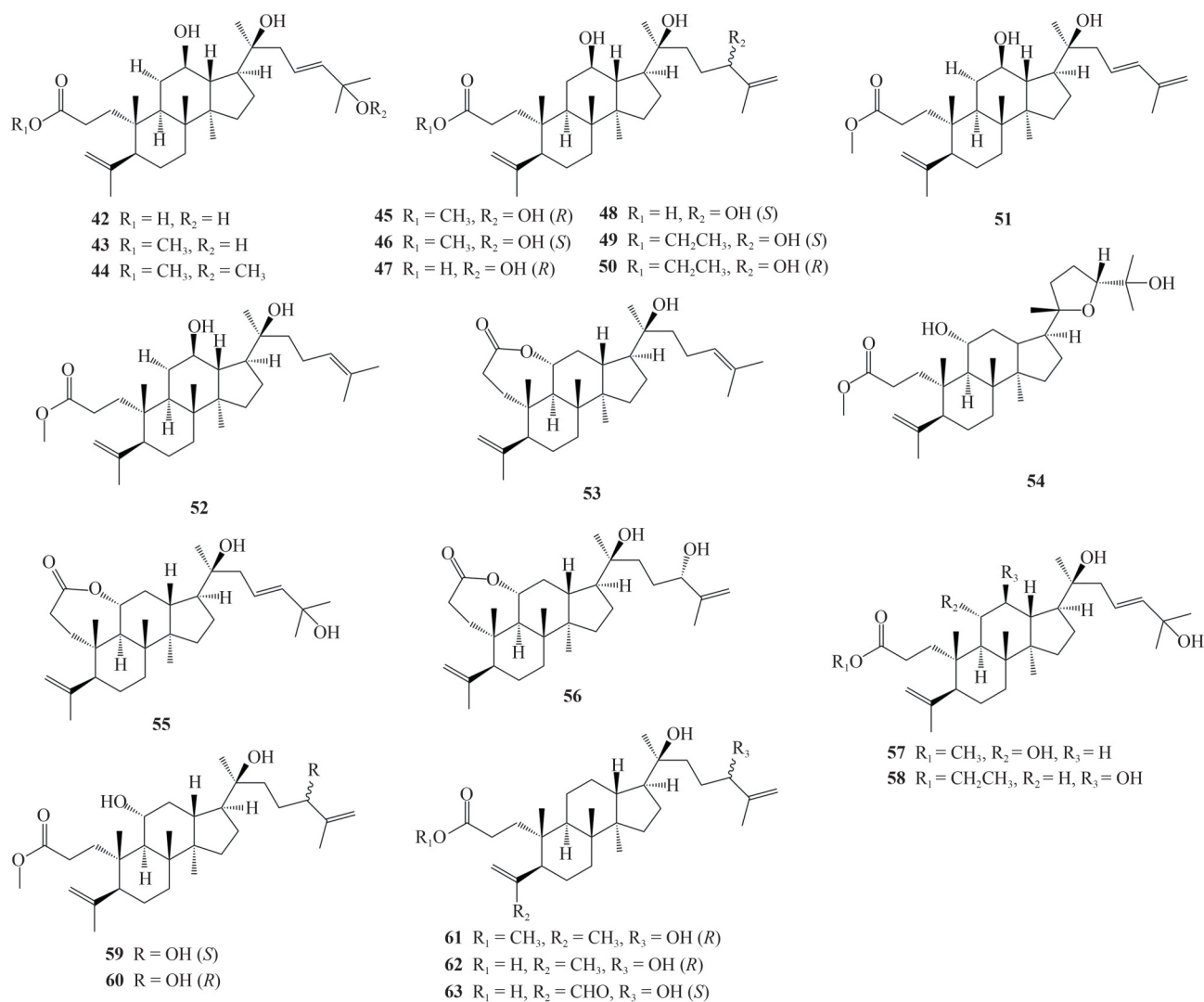
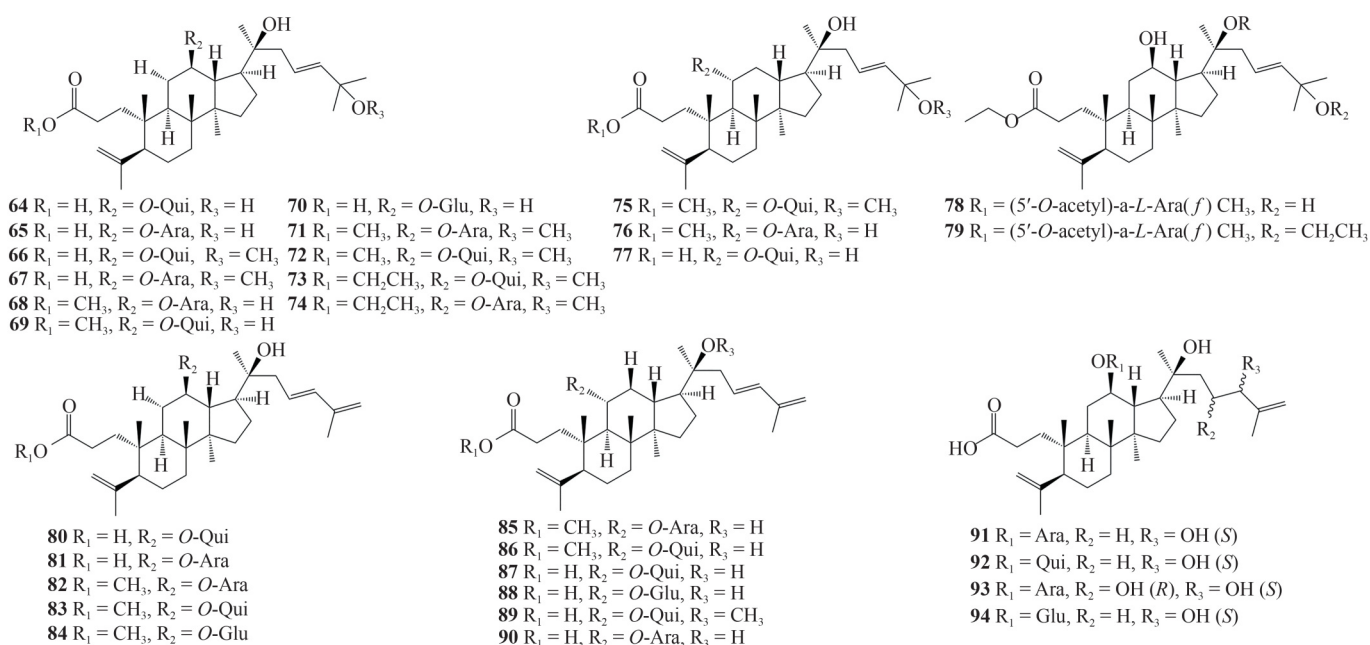
Table 1 (Continued)

No.	Compound	Molecular formula	Plant organ	Reference
75	Cypaliurisode S	C ₃₈ H ₆₄ O ₉	Leaves	[56]
76	Cypaliurisode H	C ₃₆ H ₆₀ O ₉	Leaves	[125]
77	Cypaliurisode I	C ₃₆ H ₆₀ O ₉	Leaves	[125]
78	Qingqianliusu J	C ₃₉ H ₆₄ O ₁₀	Leaves	[31]
79	Qingqianliusu K	C ₄₁ H ₆₈ O ₁₀	Leaves	[31]
80	Cyclocarioside K	C ₃₆ H ₅₈ O ₈	Leaves	[81]
81	Cyclocarioside I	C ₃₅ H ₅₆ O ₈	Leaves	[107]
82	Cyclocarioside U	C ₃₆ H ₅₈ O ₈	Leaves	[99]
83	Cyclocarioside V	C ₃₇ H ₆₀ O ₈	Leaves	[99]
84	Cyclocarioside W	C ₃₇ H ₆₀ O ₁₀	Leaves	[99]
85	Cypaliurisode B	C ₃₆ H ₅₈ O ₈	Leaves	[125]
86	Cypaliurisode F	C ₃₇ H ₆₀ O ₈	Leaves	[125]
87	Cypaliurisode E	C ₃₆ H ₅₈ O ₈	Leaves	[125]
88	Cypaliurisode J	C ₃₆ H ₅₈ O ₉	Leaves	[125]
89	Cypaliurisode G	C ₃₇ H ₆₀ O ₈	Leaves	[125]
90	Cypaliurisode A	C ₃₅ H ₅₆ O ₈	Leaves	[125]
91	Cyclocarioside J	C ₃₅ H ₅₈ O ₉	Leaves	[120]
92	Cyclocarioside Z2	C ₃₆ H ₆₀ O ₉	Leaves	[34]
93	Cyclocarioside Z9	C ₃₅ H ₅₈ O ₁₀	Leaves	[104]
94	Cyclocarioside Z11	C ₃₆ H ₆₀ O ₁₀	Leaves	[104]
95	Cyclocariol H	C ₃₆ H ₆₀ O ₉	Leaves	[57]
96	Cyclocarioside R	C ₃₆ H ₆₀ O ₁₀	Leaves	[99]
97	Cyclocarioside S	C ₃₆ H ₆₀ O ₁₀	Leaves	[99]
98	Cyclocarioside T	C ₃₇ H ₆₂ O ₁₀	Leaves	[99]
99	Cypaliurisode R	C ₃₆ H ₆₀ O ₉	Leaves	[81]
100	Qingqianliusu N	C ₃₉ H ₆₄ O ₁₀	Leaves	[31]
101	Cyclocarioside Z4	C ₃₅ H ₅₈ O ₉	Leaves	[34]
102	Cyclocarioside III	C ₃₆ H ₆₀ O ₉	Leaves	[33]
103	Cyclocarioside Q	C ₃₆ H ₆₀ O ₁₀	Leaves	[129]
104	(20 <i>S</i> ,24 <i>R</i>)-20,24-epoxy-25-Hydroxy-12β-(α- <i>L</i> -arabinopyranosyloxy)-3,4-seco-dammara-4(28)-en-3-oic acid	C ₃₅ H ₅₈ O ₉	Leaves	[77]
105	Cypaliurisode U	C ₃₅ H ₅₈ O ₉	Leaves	[56]
106	(20 <i>S</i> ,24 <i>R</i>)-20,24-epoxy-25-Hydroxy-12β-(α- <i>L</i> -arabinopyranosyloxy)-3,4-seco-dammara-4(28)-en-3-oic acid methyl ester	C ₃₆ H ₆₀ O ₉	Leaves	[77]
107	(20 <i>S</i> ,24 <i>R</i>)-20,24-epoxy-25-Hydroxy-12β-(β- <i>D</i> -quinovopyranosyloxy)-3,4-seco-dammara-4(28)-en-3-oic acid methyl ester	C ₃₇ H ₆₂ O ₉	Leaves	[77]
108	Cypaliurisode T	C ₃₇ H ₆₂ O ₉	Leaves	[56]
109	Cyclocarioside Z ₂	C ₃₇ H ₆₂ O ₉	Leaves	[99]
110	Cyclocarioside Z ₃	C ₃₈ H ₆₄ O ₉	Leaves	[99]
111	Cypaliurisode C	C ₃₆ H ₆₀ O ₉	Leaves	[125]
112	Cypaliurisode D	C ₃₇ H ₆₂ O ₉	Leaves	[125]
113	Cypaliurisode K	C ₃₈ H ₆₄ O ₉	Leaves	[125]
114	Cyclocarioside II	C ₃₅ H ₅₆ O ₈	Leaves	[33]
115	Cyclocarioside O	C ₃₄ H ₅₄ O ₉	Leaves	[129]
116	20,23,24-Trihydroxy-12α- <i>O</i> -β- <i>D</i> -quinovopyranoside-3,4-secodammara-4(28),25-dien-3-oic acid	C ₃₆ H ₆₀ O ₁₀	Leaves	[56]
117	Cyclocarioside Z1	C ₃₅ H ₅₈ O ₁₀	Leaves	[34]
Oleananes				
118	Oleanolic acid	C ₃₀ H ₄₈ O ₃	Leaves	[130]
119	Hederagenin	C ₃₀ H ₄₈ O ₄	Leaves	[80]
120	Maslinic acid	C ₃₀ H ₄₈ O ₄	Leaves	[130]
121	Arjunolic acid	C ₃₀ H ₄₈ O ₅	Leaves	[130]
122	β-Amyrin	C ₃₀ H ₅₀ O	Leaves	[130]
123	Olean-12-en-1β,3β,28-triol	C ₃₀ H ₅₀ O ₂	Leaves	[77]
124	2α,3β,23-Trihydroxyolean-12-ene	C ₃₀ H ₅₀ O ₃	Stems, leaves	[131]
125	α-Boswellic acid	C ₃₀ H ₄₈ O ₃	Leaves	[131]
126	Octyl ursolate	C ₃₈ H ₅₄ O ₄	Leaves	[126]

Table 1 (Continued)

No.	Compound	Molecular formula	Plant organ	Reference
127	23- <i>trans-p</i> -Coumaroyloxy-2 α ,3 β -dihydroxyplen-12-en-28-acid	C ₃₉ H ₅₄ O ₇	Leaves	[80]
128	3 β ,23,27-Trihydroxy-1-oxo-olean-12-ene-28-oic acid	C ₃₀ H ₄₆ O ₆	Leaves	[37]
129	3 β ,19 α ,23-Trihydroxy-1-oxo-olean-12-en-28-oic acid	C ₃₀ H ₄₆ O ₆	Leaves	[77]
130	1 α ,2 α ,3 β ,23-Tetrahydroxyolean-12-en-28-oic acid	C ₃₀ H ₄₈ O ₆	Leaves	[81]
131	1 α ,3 β ,23-Trihydroxy olean-12-en-28-oic acid	C ₃₀ H ₄₈ O ₅	Leaves	[133]
132	2 α ,3 β ,23-Trihydroxyoleana-11,13(18)-dien-28-oic acid	C ₃₀ H ₄₆ O ₅	Leaves	[128]
133	3 β -Hydroxy-11-oxo-oleana-12-en-28-oic acid	C ₃₀ H ₄₆ O ₄	Stems, leaves	[38]
134	3 β - <i>O-trans</i> -Caffeoyl-morolic acid	C ₃₉ H ₅₄ O ₆	Leaves	[132]
135	3 β ,23-Dihydroxy-1,12-dioxo-olean-28-oic acid	C ₃₀ H ₄₆ O ₆	Leaves	[37]
136	Cyclocaric acid B	C ₃₀ H ₄₆ O ₅	Leaves	[77]
137	Cyclocaric acid A	C ₃₀ H ₄₆ O ₃	Leaves	[134]
138	1 α ,3 β -Dihydroxy-12-oleanen-28-oic acid	C ₃₀ H ₄₈ O ₄	Leaves	[39]
139	1 α ,3 β -Dihydroxy-olean-12-en-28-oic acid	C ₃₀ H ₄₈ O ₄	Leaves	[77]
140	Punicaone	C ₃₀ H ₄₄ O ₄	Leaves	[77]
141	Epikatic acid	C ₃₀ H ₄₈ O ₃	Leaves	[135]
142	2 α -Hydroxyursolic acid	C ₃₀ H ₄₈ O ₄	Leaves	[136]
143	β -Amyrone	C ₃₀ H ₄₈ O	Leaves	[132]
144	Olean-12-en-2 α ,3 β -diol	C ₃₀ H ₅₀ O ₂	Stems, leaves	[38]
145	23-Hydroxy-1-oxo-olean-2,12-dien-28-oic acid	C ₃₀ H ₄₄ O ₄	Leaves	[128]
146	1 α ,3 β -Dihydroxy-1-olean-12-en-28-oic acid	C ₃₀ H ₄₈ O ₄	Leaves	[77]
147	Arjunglucoside II	C ₃₆ H ₅₈ O ₁₀	Leaves	[122]
148	Chebuloide II	C ₃₆ H ₅₈ O ₁₁	Leaves	[80]
149	1-oxo-3 β ,23-Dihydroxyolean-12-en-28-oic acid 28- <i>O</i> - β -D-xylopyranoside	C ₃₅ H ₅₄ O ₉	Leaves	[106]
150	1-oxo-3 β ,23-Dihydroxyolean-12-en-28-oic acid 28- <i>O</i> - β -D-glucopyranoside	C ₃₆ H ₅₆ O ₁₀	Leaves	[81]
151	2 α ,3 β ,23-Trihydroxyurs-12,20(30)-dien-28-oic acid 28- <i>O</i> - β -D-glucopyranoside	C ₃₆ H ₅₆ O ₁₀	Leaves	[128]
Ursanes				
152	Ursolic acid	C ₃₀ H ₄₈ O ₃	Leaves	[130]
153	3 β ,23-Dihydroxy-12-ene-28-ursolic acid	C ₃₀ H ₄₈ O ₄	Stems, leaves	[38]
154	Corosolic acid	C ₃₀ H ₄₈ O ₄	Leaves	[130]
155	Asiatic acid	C ₃₀ H ₄₈ O ₅	Leaves	[77]
156	2 α ,3 α ,23-Trihydroxyurs-12-en-28-oic acid	C ₃₀ H ₄₈ O ₅	Leaves	[37]
157	2 α ,3 α ,6 β ,19 α ,23-Pentahydroxyurs-12-en-28-ursolic acid	C ₃₀ H ₄₈ O ₇	Leaves	[106]
158	2 α ,3 α ,20 β ,23-Tetrahydroxyurs-12-en-28-ursolic acid	C ₃₀ H ₄₈ O ₆	Leaves	[106]
159	19 α -Hydroxy asiatic acid	C ₃₀ H ₄₈ O ₆	Leaves	[106]
160	1 β ,2 α ,3 β ,23-Tetrahydroxyurs-12-en-28-ursolic acid	C ₃₀ H ₄₈ O ₆	Leaves	[106]
161	Actinidic acid	C ₃₀ H ₄₆ O ₅	Leaves	[127]
162	2 α ,3 α ,23-Trihydroxyurs-12,20(30)-dien-28-oic acid	C ₃₀ H ₄₆ O ₅	Leaves	[127]
163	1 β ,2 α ,3 β ,23-Tetrahydroxyurs-12,20(30)-dien-28-ursolic acid	C ₃₀ H ₄₆ O ₆	Leaves	[106]
164	β -Boswellic acid	C ₃₀ H ₄₈ O ₃	Leaves	[130]
165	2 α ,3 β ,23-Trihydroxyurs-11-oxo-12-ene-28-oic acid	C ₃₀ H ₄₆ O ₆	Leaves	[37]
166	2 α ,3 α ,23-Trihydroxy-urs-12-en-28-oic acid 28- <i>O</i> - β -D-glucopyranoside	C ₃₆ H ₅₈ O ₁₀	Leaves	[106]
167	Quadranoside IV	C ₃₆ H ₅₈ O ₁₀	Leaves	[122]
168	2 α ,3 α ,23-Trihydroxy-12, 20(30)-dien-28-ursolic acid 28- <i>O</i> - β -D-glucopyranoside	C ₃₆ H ₅₆ O ₁₀	Leaves	[106]
169	2 α ,3 β ,23-Trihydroxyurs-12,20(30)-dien-28-oic acid β -D-glucopyranoside	C ₃₆ H ₅₆ O ₁₀	Leaves	[137]
170	2 α ,3 β ,22 α -Tirhydroxyurs-12-en-28-oic acid 28- <i>O</i> - β -D-glucopyranoside	C ₃₆ H ₅₈ O ₁₀	Leaves	[81]
Lupinanes				
171	Calenduladiol	C ₃₀ H ₅₀ O ₂	Stems, leaves	[38]
172	Lupeol	C ₃₀ H ₅₀ O	Stems, leaves	[38]
173	Betulonic acid	C ₃₀ H ₄₈ O ₃	Stems, leaves	[38]
174	Betulin	C ₃₀ H ₅₀ O ₂	Stems, leaves	[38]
175	2 α ,3 β -Dihydroxyllupeol	C ₃₀ H ₅₀ O ₂	Stems, leaves	[38]
176	Alphitolic acid	C ₃₀ H ₄₈ O ₄	Stems, leaves	[38]
Taraxerane				
177	Taraxerol	C ₃₀ H ₅₀ O	Leaves	[39]

Fig. 1 Structure of dammaranes from *C. paliurus*.

Fig. 2 Structure of 3,4-seco-dammaranes aglycone from *C. paliurus*.Fig. 3 Structure of 3,4-seco-dammaranes saponins from *C. paliurus*.

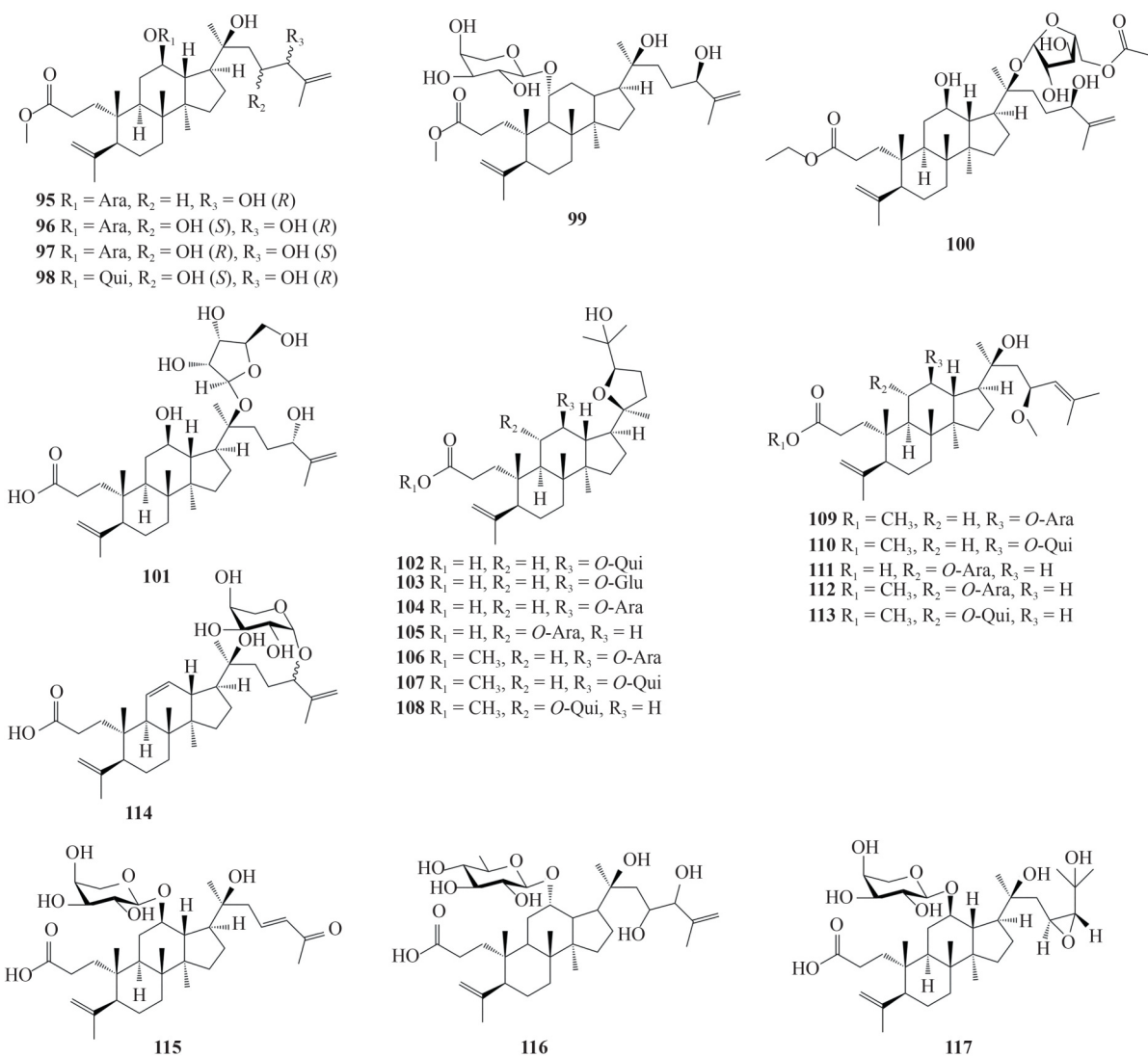
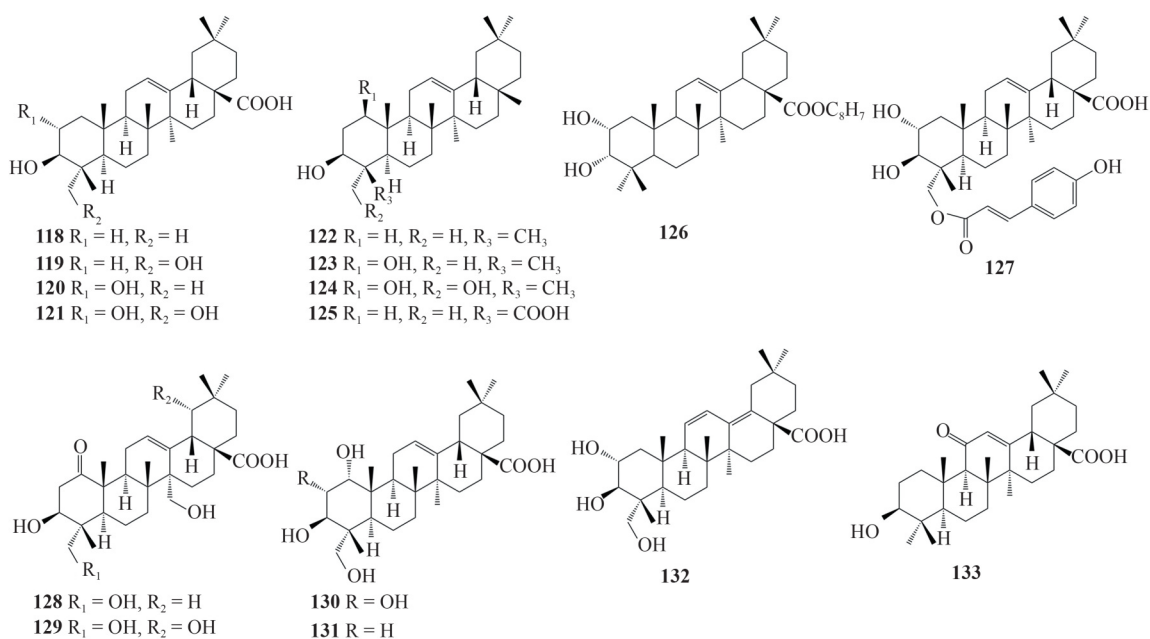


Fig. 3 (Continued)

Fig. 4 Structure of oleananes from *C. paliurus*.

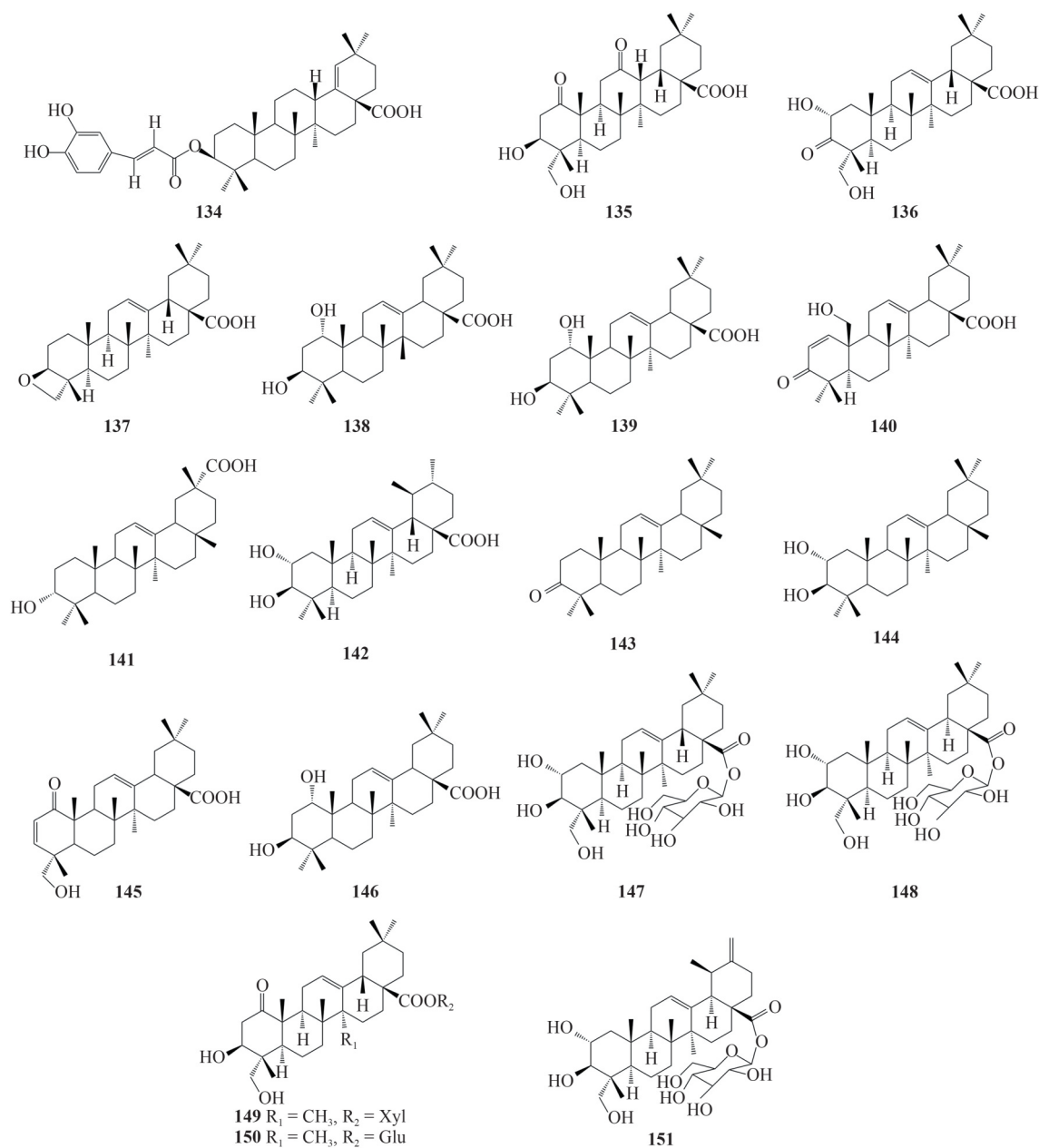
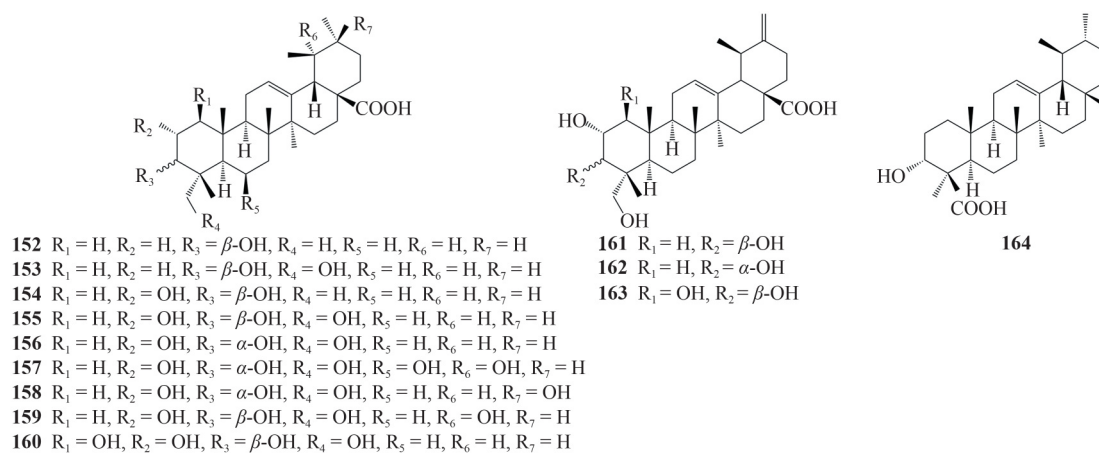


Fig. 4 (Continued)

Fig. 5 Structure of ursanes, lupinane, and taraxerane from *C. paliurus*.

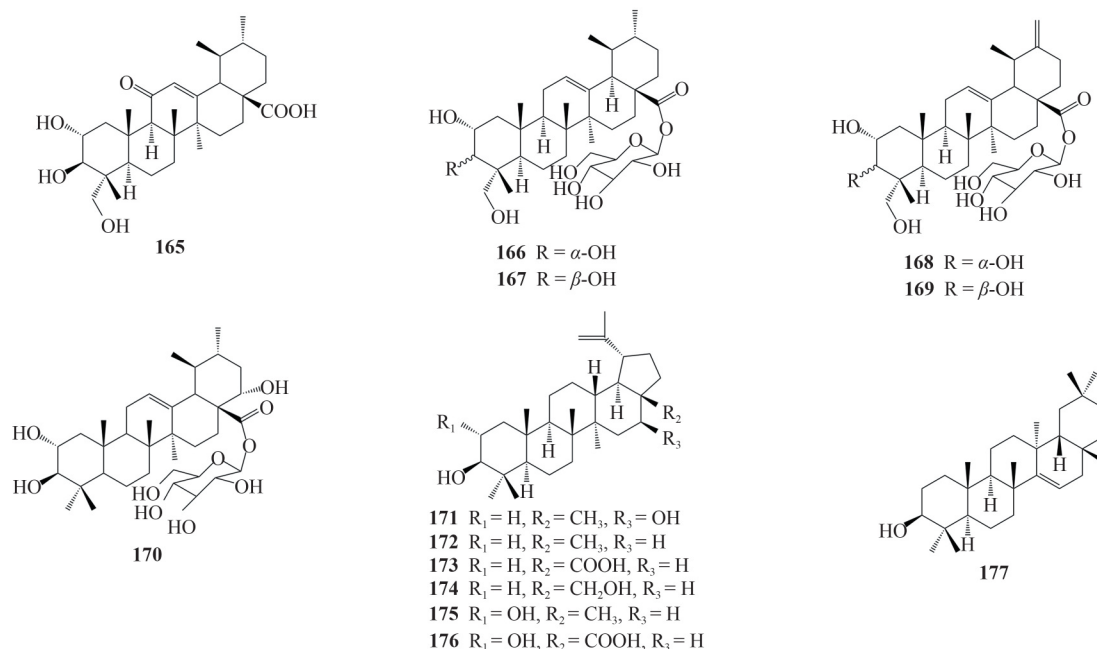


Fig. 5 (Continued)

2.1 Dammaranes

The structural characteristics of dammarane-type triterpenoids include a 6/6/6/5 carbon ring skeleton with a β -type angular methyl at the C-8, 10-position, a β -H at C-13, a β -side chain at C-17, and a configuration that can be R or S at C-20. Compounds **1–41** are dammaranes-type triterpenes, of which compound **2** is dammaranes-type triterpene acid, and compounds **3–41** are dammaranes-type saponins. These substances were first discovered in *C. paliurus*. Cyclopalitins A and B (**1**, **2**) are rare trinordammarane triterpenoids that undergo rearrangement deformation and contain a C-12, C-13 double bond^[30]. Dammarane-type triterpenoids are the main source of sweetness in *C. paliurus*. The sweetness of cyclocariosides I (**3**) and A (**12**) is about 250 and 200 times that of sucrose, respectively. Most dammarane saponins in *C. paliurus* are linked to sugar-containing side chains at C-3, C-11, or C-12, and the sugar units mainly include Qui, Glu, Ara, Xyl, Rha, and Ara(f). Different oxidation methods produce 2 main types of side chains at C-17: the chain and epoxy structures. Based on the analysis of the β -side chain of C-17, C-20, and C-24 oxidative cyclization, compounds **3–22** are called epoxydammarane. Other compounds vary depending on the position and number of double bonds and hydroxyl groups on their side chain. The dammarane-type triterpenes found in ginseng possess hydroxyl substitution at the C-3 and C-12 positions of their skeletons and a C-20 with an *S*-configuration. These triterpenes can be categorized into 2 groups based on hydroxyl substitution at the C-6 position. The first category is derived from 20(*S*)-protopanaxadiol and the second from 20(*S*)-protopanaxatriol. Cyclocarioside Z₉ (**32**) features the basic triterpenoid skeleton of panaxadiol.

2.2 3,4-Seco-dammaranes

3,4-Seco-dammaranes include dammarane-type triterpenoids with a broken chemical bond between C-3 and C-4 of the first 6-carbon ring

of the parent nucleus. Oxidization at the C-3 position results in the formation of a carboxyl group, which forms methyl ester or ethyl ester easily. The double bonds formed at the C-4 and C-28 positions are relatively rare in natural products^[1]. Most of 3,4-seco-dammarane triterpenoids only exist in *C. paliurus*, which indicates that the unusual 3,4-seco-dammarane triterpenoid glycosides can be considered a reliable classification index for *C. paliurus* (Juglandaceae)^[31]. According to the Human Taste Group, pterocaryosides A and B (**64** and **65**, respectively) are approximately 50 and 100 times sweeter than 2% sucrose (a natural sweetener source)^[32]. Compounds **42**, **44**, **47**, and **48** are referred to as 3,4-seco-dammarane triterpene acids, and they are known for the oxidation of their C-3 positions into carboxyl groups. Compounds **64–77**, **80–99**, **102–113**, and **115–117** comprise glycosides that mainly contain glycosyl groups at C-11 or C-12, where sugar units mainly include Ara, Glu, and Qui. In particular, the C-24-linked glycosyl of cyclocarioside II (**114**) on the side chain is Ara^[33]. Compounds **78**, **79**, and **100** are linked to glycosyl Ara(f) at the C-20 position of the side chain. The C-20 side chain of cyclocarioside Z₄ (**101**) is linked to a rare ribose^[34]. The chain structure of 3,4-seco-dammaranes include side chains that are mostly connected to different numbers of hydroxyl groups and double bonds. Dehydration of the hydroxyl groups at the C-23 or C-24 positions of the side chain of cyclocarioside Z₁ (**117**) results in the formation of an epoxy ring^[34]. Cyclocariosides Z₃ and Z₁ (**69**) share the same structure. Compounds **54** and **102–108** possess epoxy side chains, which feature an epoxy furan ring at the C-20 and C-24 positions. Compounds **53**, **55**, and **56** exhibit a rare 3,4-seco-dammarane structure with a seven-membered lactone ring at C-3 and C-11^[35].

2.3 Oleananes

Oleanane-type triterpenoids (β -amyrin-type triterpenoids) are the most common and extensive type of triterpenoid skeleton in the plant kingdom, and they generally exist in the form of aglycones or

glycosides. These triterpenes feature a structure that generally includes 5 six-membered rings, with the A/B, B/C, and C/D rings being *trans*-fused. Oleananes contain 2 types of C/D rings, namely, *cis* and *trans*, and all the C/D rings found in *C. paliurus* are *cis*. Oleanane triterpenoids from *C. paliurus* usually comprise different functional groups at various positions of the skeleton. The skeleton often contains eight methyl substitutions that can be oxidized to form carboxyl groups. The C-28 of compounds **118–121**, **127–140**, **142**, **145**, and **146** is oxidized to carboxyl groups. The oxidized carboxyl groups, such as compounds **13** and **126**, are also often aglyconized, esterified, or lactonized. The carboxyl group of C-28 easily forms glycosides, for example, compounds **147–151**, whose sugar units mainly include Glu and Xyl. Compounds **119**, **121**, **124**, **130–132**, **135**, **136**, **145**, and **147–151** possess C-23 methyl groups that are oxidized to hydroxymethyl groups. According to biosynthetic pathway analysis, the unsaturation of such a structure may originate from the deprotonation of the carbocation after skeleton cyclization. Most oleanane triterpenoids from *C. paliurus* form double bonds between C-12 and C-13 positions. Another feasible phenomenon is the oxidation of the hydroxyl and double bonds at the C-1, C-3, C-11, and C-12 positions to carbonyl groups^[1]. The C-3 of cyclocaric acid A (**137**) possesses a substituent that reacts with the skeleton to form an oxetane ring. However, Wright et al. observed that the compound originally reported as cyclocaric acid A (**37**) was in reality hederagenin (**119**)^[36]. An independent semisynthetic method was conducted, and the results confirmed that “cyclocaric acid A” was not previously isolated from this plant, and the compound originally reported as the isolate was actually hederagenin. Such errors are easy to incur given the similarity of the NMR data combined with the finding of mass spectrometry techniques available at the time.

2.4 Ursanes

Ursane-type triterpenes or α -amyrin-type triterpenes are similar to oleanane-type triterpenes in terms of structure. These compounds possess *trans*-fused A/B, B/C, and C/D rings and a mainly *cis*-fused D/E ring. The main difference in the 8 methyl substitution positions of oleanane and ursanes is the replacement of 2 methyl substitutions at C-20 at the C-19 and C-20 positions, respectively. The C-28 methyl groups of compounds **152–163** and **165** are oxidized to carboxyl groups. The C-24 methyl group of compound **164** is oxidized to a carboxyl group. The C-23 methyl groups of compounds **153**, **155–163**, and **165–169** are oxidized to hydroxymethyl groups. The C-2 carboxyl group of compounds **166–170** forms glycosides with the glycosyl group, in which the sugar unit is mainly Glu. The ursane triterpenoids from *C. paliurus* contain double bonds between C-12 and C-13. C-1, C-2, C-3, C-19, and C-20 are often substituted by hydroxyl groups, with C-1 and C-20 being substituted by β -OH and C-2 and C-19 being substituted by α -OH^[1]. The C-11 position of compound **165** contains a carbonyl group^[37].

2.5 Lupinanes

In the structure of lupine-type triterpenoids, the E ring is a 5-membered carbon ring. In addition, an isopropyl substitution with an α configuration exists at the C-19 position of the E ring. The A/B,

B/C, C/D, and D/E rings are *trans*-arranged. The C-2, C-3, and C-16 positions are usually substituted by a hydroxyl group, and the substituted hydroxyl group at the C-2 position is generally presents an α configuration. Lupine-type triterpenoids skeleton generally contain multiple methyl substitutions. Compound **174** possesses a C-28 methyl group that is oxidized to hydroxymethyl group^[38]. Meanwhile, compounds **173** and **176** possess C-28 methyl groups that are further oxidized to carboxyl groups.

2.6 Taraxeranes

Taraxerane is also known as so-oleanane. Similar to oleanane triterpenoids, taraxeranes have *trans*-arranged A/B, B/C, and C/D rings. However, the double bond in taraxeranes can be found at the C-14 position, and the methyl group at the C-27 position is converted for connection to C-13. To date, only 1 taraxerane triterpenoid has been found in *C. paliurus*^[39].

3. Biosynthesis of triterpenoids from *C. paliurus*

Triterpenoids have complex and diverse structure, which are determined by the diversity of their biosynthetic pathways^[40–41]. Although a number of studies have been conducted on triterpenoids from *C. paliurus*, over the past few decades, the specific biosynthetic pathway is still rarely reported. Here, we have excavated reports related to the biosynthesis of triterpenoids to speculate on their biosynthesis process in *C. paliurus*.

In the early 1950s, studies inferred the similar biosynthesis of all known $C_{30}H_{50}O$ triterpene alcohols; thus, it was proposed the biogenetic isoprene rule, which is a set of dominant principles that can explain the biosynthesis of each triterpene skeleton^[42–43]. Extensive efforts in the separation of natural products have resulted in the discovery of many additional triterpenoids, whose structures can be rationalized through the biogenetic isoprene rule; the results of these efforts provided further support for refining the biogenetic isoprene rule. A few experimental studies have focused on the formation of triterpenoid rings, and the enzymatic cyclization of squalene or oxidized squalene under the law of biosynthesis is the most reliable source of these triterpenoids. In addition, the biogenetic isoprene rule predicts that the product structure is remarkably consistent that the credibility of the newly allocated structure can be evaluated based on its derivation from the biogenetic isoprene rule^[44]. Triterpenoids are mainly synthesized by squalene through the MVA pathway^[45]. Triterpenoids derive from the triterpenoid skeleton, which is produced by multiple cyclization, rearrangement, and degradation reactions involving complex chemical intermediates. Two precursors, namely, squalene and oxidized squalene, produced the triterpenoid skeleton^[46]. Further glycosylation of plant triterpenoid aglycones on hydroxyl or carboxyl groups is catalyzed by UDP-glycosyltransferases (UGTs). Specific saponins are endowed with various properties, such as taste and biological activity, due to differences in the number, type, and position of these glycosyl groups^[47].

The biosynthetic pathway of triterpenoids includes 3 stages: 1) biosynthesis of active isopentenyl phosphate (IPP) and Dimethylallyl pyrophosphate (DMAPP); 2) biosynthesis of triterpene carbocyclic system; 3) complex functionalization process on the ring that can

eventually form a complete triterpene compound. Cyclization of 2,3-oxidosqualene introduces an internal bond into the squalene oxide skeleton to form a predominantly polycyclic molecule that contains varying numbers of 5- and 6-membered rings^[48]. In the biosynthesis of triterpenoids, the oxidosqualene cyclases (OSCs)-catalyzed cyclization cascade involved is characterized by the initial orientation of the 2,3-oxidosqualene backbone in a chair-chair-chair-chair-conformation. Therefore, dammarenyl cation skeletons the first intermediate in the cyclization process of all triterpenoid^[49-50]. According to the biosynthesis analysis, Peng et al.^[30] showed that cyclopaltins A and B (**1** and **2**) may originate from different dammarane precursors, which can be produced by oxidosqualene. Oxidosqualene is cyclized in a boat-chair-chair conformation to form 3- α -OH-dammarenyl and 3- β -OH-dammarenyl cations in a chair-chair-chair conformation^[51-53]. Different types of tetracyclic triterpenoids form the 1,2-migration rearrangement of the C-20 carbocations. The formation of compound **2** involves the multiple 1,2-migration rearrangements of 3- β -OH-dammarane carbocation and multistep oxidation of C-2, C-28, and C-24. Compound **1** form through the multiple 1,2-migration rearrangements and oxidation of 3- α -OH-dammarane carbocation. The functionalization of carbon skeleton mainly is a result of oxidation, such as that of hydroxyl, carbonyl, and carboxylic acids, which can be found in many positions of the molecule^[49]. P450s are monooxygenases that introduce an oxygen atom from molecular oxygen into their substrates, which results in the functionalization of the triterpenoid skeleton^[47]. Dammarane-type

triterpenoid sapogenins usually undergo modifications before glycosylation. The most common sapogenins are modified with small functional groups, such as hydroxyl, ketone, aldehyde, and carboxyl groups, at different positions of the backbone, and may involve more complex side groups^[48]. Compound **32** is formed by 3- β -OH-dammarane-type carbocationic double-bond rearrangement and C-11, C-20, and C-23 oxidation and C-11-OH further linking sugar groups. The oxidosqualene undergoes cyclization to form a C-20 carbocation, which attacks the oxygen atom to form a C-24 carbocation and thereby form a 20,23-furan tetracyclic triterpenoid compound^[54-55]. The 20,23-furan tetracyclic triterpenoids obtained by the boat-chair-chair and chair-chair-chair conformational cyclization are modified at different positions using small functional groups and *via* glycosylated secondary modification to generate compounds **3–10** and **11–22**. The C-3-OH of dammarane-type carbocation is speculated to be oxidized to a carbonyl group, and 20-hydroxydammar 24-en-3-one is converted to intermediate A *via* the Baeyer-Villiger oxidation reaction. The 3,4-seco-dammarane triterpenoid precursor is obtained after hydrolysis, dehydration, and dehydrogenation (Fig. 6)^[56]. The double bond at C-24 of the 3,4-seco-dammarane triterpenoid precursor undergoes a hydration reaction. Given that the hydration reaction is not stereo-controlled reaction, 2 polymers (24R and 24S) are formed^[57]. The 3,4-secodammarane triterpenoids are modified using small functional groups at different positions and secondary modification of glycosylation to form compounds **42–117**.

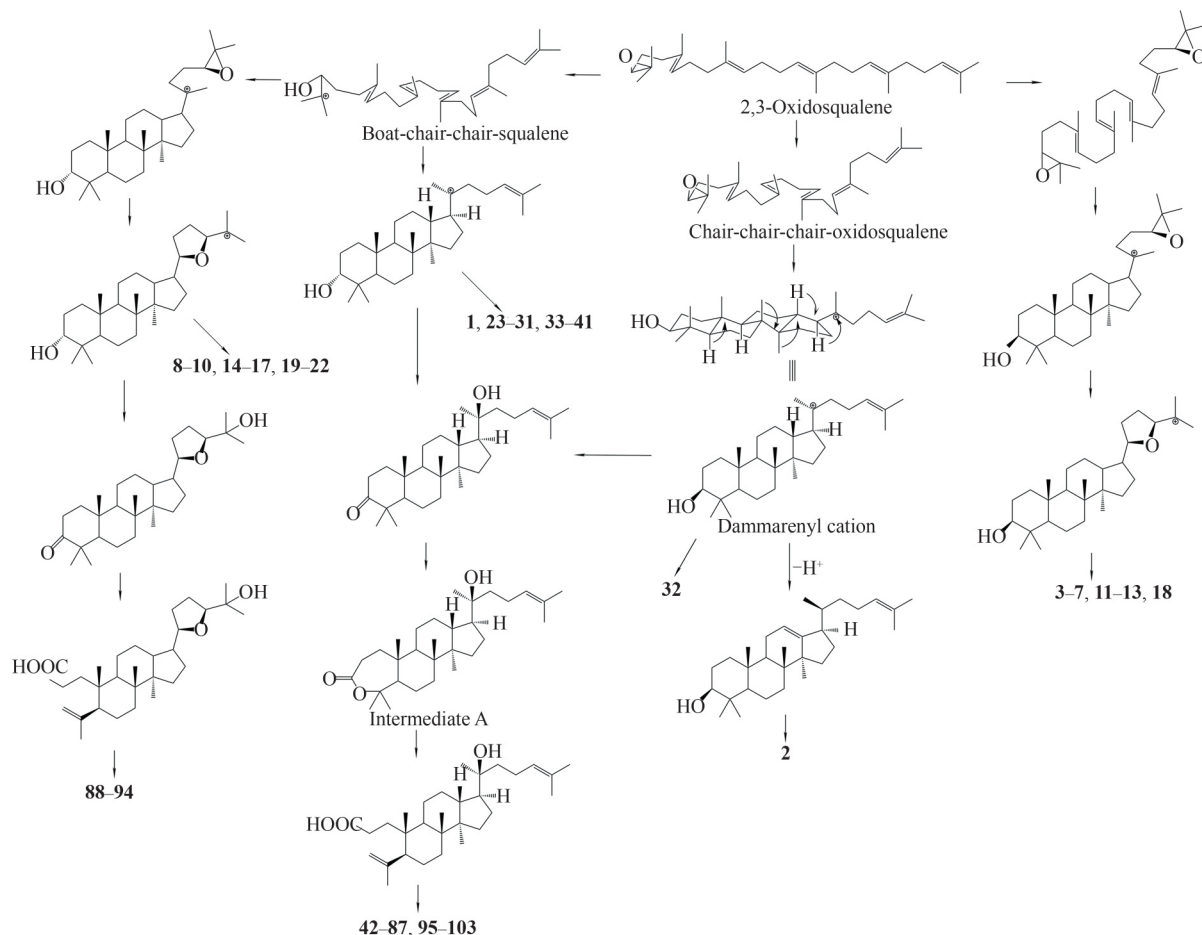


Fig. 6 Biochemical pathways for the synthesis of dammarane from 2,3-oxidosqualene in *C. paliurus*.

Further rearrangement of the dammarane-type carbocation causes the formation of tirucallanyl or the baccharenyl cation. Continued cyclization of baccharenyl cations results in pentacyclic lupanyl cations, whose backbone is commonly found in lupane-type triterpenoids. The 5-membered E-ring of the lupanyl cation is reopened and extended to a 6-carbon ring to form an intermediate cyclization product called germanicyl cation. The germanicyl cation can be further converted to oleanyl (oleanane-type saponin), taraxasterenyl (taraxasterane-type saponin), or ursanyl cation

(ursane-type saponin)^[49,58]. Unsaturated bonds (double bonds) usually form through the deprotonation of carbocations formed after skeleton cyclization (Fig. 7). Single or double unsaturation may occur at different positions of the molecule^[49]. Compounds **118–151** are obtained through deprotonation, oxidation, and glycosylation of oleanyl cation. Saponins are produced by the introduction of specific sugar groups into a specific position of the saponin skeleton through the UGT family^[59]. Two types of ursanyl cation are generated by 2,3-oxidosqualene boat-chair-chair and chair-chair-chair conformational

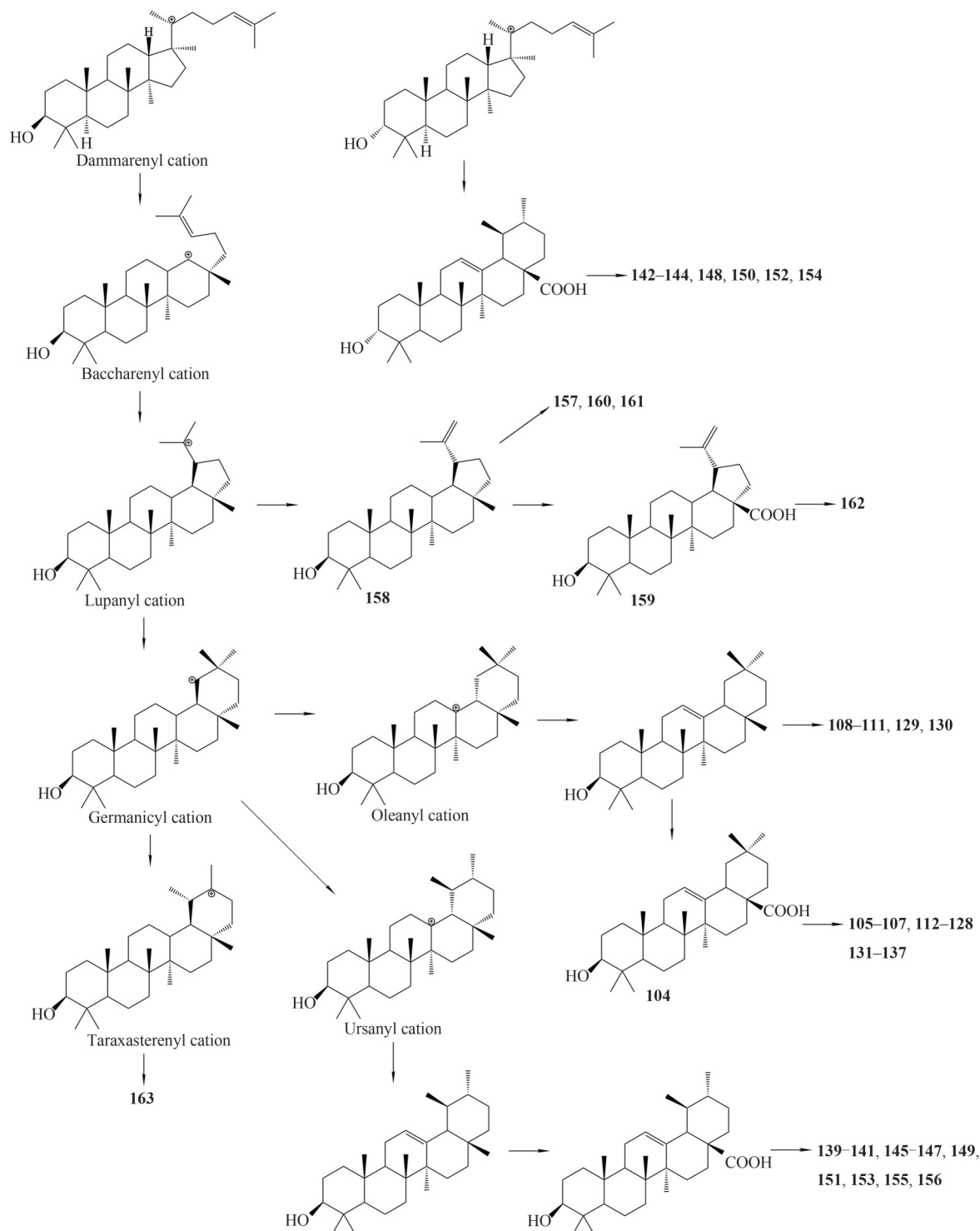


Fig. 7 Biochemical pathways for the synthesis of other triterpenoids from dammarenyl cation in *C. paliurus*.

cyclization, followed by oxidation and glycosylation to generate compounds **156–158**, **162**, **164**, **166**, and **168** and **153–155**, **159–161**, **163**, **165**, **166**, **167**, **169**, **170**, respectively. The lupanyl cation is protonated to form compound **172**, which is then oxidized to compounds **171**, **173–175**. Compound **173** is further oxidized to compound **176**. Compound **177** is obtained *via* the deprotonation and rearrangement of the taraxasterenyl cation. However, further gene and protein studies are needed to verify the accurate biosynthetic pathway of triterpenoids.

4. Biological activity of triterpenoids from *C. paliurus*

C. paliurus has been widely studied because of its antihyperglycemic property. In addition, other pharmacological effects, such as antihyperlipidemia, anticancer, antioxidation, anti-inflammatory, liver protection, and antibacterial properties, have been evaluated^[1]. Triterpenoids or triterpenoid-rich extracts from this plant exhibit rich biological activities, as shown in Table 2. In previous pharmacological studies, the total triterpenoid content of CPAE was 0.05–0.15 mg/g, and that of total triterpenoids in the CPE was 4.39–8.15 mg/g^[60].

Table 2

Bioactivities of triterpenoids from *C. paliurus*.

Compounds/extracts	Dosage uses	Models		Effects	Possible mechanism	References
		<i>In vivo</i>	<i>In vitro</i>			
Anti-hyperglycemic						
Extracts						
EAE	25, 50 and 100 µg/mL	–	α -Glucosidase inhibitory activity	α -Glucosidase activity ↓	–	[126]
CPE	2, 4 and 8 g/kg	HFD and STZ-induced type 2 diabetic rats	–	Insulin level ↑ ; BUN, CREA and GSP ↓	–	[63]
CPE	20, 40 and 80 mg/kg	<i>db/db</i> mice	–	TG, TC, LDH, CK-MB, AST, cTn-I, MDA, and blood glucos ↓ ; SOD, GSH-Px, CAT, TNF- α , IL-1 β , IL-6 ↑	PI3K/Akt	[66]
CPE	1 g/kg; 0.5, 2.5 and 5.0 µg/mL	STZ-induce ICR mice (200 mg/kg)	C2C12 cells	Glucose intake and PI3K ↑ ; p-Akt and p-AS160 ↑	IRS1-PI3K-Akt	[73]
CPE	100, 200 and 500 mg/kg; 100, 200 and 500 µg/mL	Mac-CM-induce rats	3T3-L1 cells	TNF- α , IL-6, MCP-1, and p-IRS-1 ↓ ; p-Akt ↑	IRS1-PI3K-Akt	[138]
TAE	40 and 160 mg/kg; 20 and 5 µg/mL	STZ-induce rats	HK-2 cells	Urinary microalbumin, serum creatinine, blood urea nitrogen, glomerular fibrosis and p-mTOR ↓ ; p-AMPK ↑	AMPK-mTOR	[75]
CPT	40 and 160 mg/kg; 20 and 5 µg/mL	STZ-induce type 1 diabetic rats	H ₂ O ₂ -induced GENCs and HUVECs	Blood glucose, microalbumin, BUN, mesangial, VCAM-1, ICAM-1, and ROCK and Arg2 ↓ ; p-Akt and p-eNOS ↑	ROCK	[76]
CPT	0.25 and 0.5 g/kg; 2, 4 and 8 µg/mL	<i>db/db</i> mice	HepG2 and LO2 cells	IL-1 β , IL-6, and TNF- α ↓	Rho/ROCK/ NF- κ B	[68]
TAE	50 and 200 mg/kg; 15 and 45 µg/mL	STZ-induce rats	Primary hepatocytes	TC, TG,G6Pase, PEPCK, cAMP, p-PKA and p-CREB ↓ ; p-AMPK and p-PDE4B ↑	cAMP/PKA/ CREB	[69]
CPE	0.5 and 1.0 g/kg; 80 and 160 µg/mL	STZ-induce rats	NIT-1	FBG, IRI, MDA, and ROS ↓ ; body weight, FINS, ISI,SOD and GSH-Px ↑	–	[64]
CPE	–	–	α -Glucosidase inhibitory activity	IC ₅₀ = 17.81 µg/mL	–	[139]
TAE	40 and 160 mg/kg; 1, 10, 25, 50 and 100 µg/mL	C57BL/6J mice	HepG2 cells and primary hepatocytes	ALT, AST, TG, TC, blood glucose, and HOMA-IR ↓ ; p-PI3K, p-Akt and p-GSK-3 β ↑	PI3K/Akt/ GSK3 β	[71]
ChE	25, 50 and 100 mg/kg; 0.05, 0.10, 0.15 and 0.20 g/L	ICR male mice	Mice peritoneal macrophages and 3T3-L1 pre-adipocytes	Glucose consumption and uptake ↑ ; p-AMPK ↑ ; IKK β ↓	IRS-1/PI3K/Akt	[83]
Compounds						
112, 77, 88 and 113	–	–	α -Glucosidase inhibitory activity	IC ₅₀ = (24.25 ± 0.39) µmol/L; IC ₅₀ = (65.97 ± 1.62) µmol/L; IC ₅₀ = (2.22 ± 0.13) µmol/L; IC ₅₀ = (175.31 ± 0.86) µmol/L	–	[125]
9, 10, 29, 31, 65, 67, 69, 81, 101 and 117	0.39–100 µmol/L	–	3T3-L1	At 50 µmol/L, consumption of glucose ↑	–	[34]
91 and 92	0.39–100 µmol/L	–	3T3-L1	At 100 µmol/L, consumption of glucose ↑	–	[34]
66, 73, 67, 74, 4 and 51	–	–	α -Glucosidase, lipase, DPP-IV, and aldose reductase inhibitory activity	α -Glucosidase, lipase, DPP-IV, and aldose reductase activities ↓	–	[127]
120 and 162	10 µmol/L	–	HK-2 cells	Fibronectin ↓ ; the inhibition rates were (6.09 ± 0.57)% and (27.66 ± 2.77)%, respectively	–	[128]
151	1 µmol/L	–	HK-2 cells	Fibronectin ↓ ; (17.74 ± 5.83)% inhibition rate	–	[128]

Table 2 (Continued)

Compounds/extracts	Dosage uses	Models		Effects	Possible mechanism	References
		<i>In vivo</i>	<i>In vitro</i>			
119	–	–	HEK-293 cells	11 β -HSD1 ↓ ; IC ₅₀ = (0.16 ± 0.04) μmol/L	–	[80]
104	10 μmol/L	–	C2C12 myoblasts and 3T3-L1 preadipocytes	Glucose uptake ↑	AMPK-p38	[77]
3, 5, 129 and 155	10 μmol/L	–	3T3-L1 preadipocytes	Glucose uptake ↑	–	[77]
121	10 μmol/L	–	Mouse C2C12 myoblasts and 3T3-L1 preadipocytes	Glucose uptake ↑	–	[77]
162 and 120	10 μmol/L	–	HK-2 cells	Fibronectin ↓ ; the inhibition rate was (27.66 ± 2.77)% and (6.09 ± 0.57)%, respectively	–	[128]
169	1 μmol/L	–	HK-2 cells	Fibronectin ↓ ; the inhibition rate was (17.74 ± 5.83)%	–	[128]
35	20, 10, and 5 μmol/L	–	α -Glucosidase inhibitory activity; RAW 264.7 cell	α -Glucosidase, NO, iNOS, NF- κ B, COX-2, IL-6, IL-1 β and TNF- α ↓	NF- κ B	[126]
32, 23, 24, 38, 40, 25, 21, 22 and 6	–	–	α -Glucosidase inhibitory activity; RAW 264.7 cell	α -Glucosidase and NO ↓	–	[126]
39, 16, 17, 4 and 3	–	–	RAW 264.7 cell	NO ↓	–	[126]
28, 41 and 26	–	–	α -Glucosidase inhibitory activity	IC ₅₀ = (290.84 ± 0.99) μmol/L; IC ₅₀ = (578.77 ± 0.94) μmol/L; IC ₅₀ = (274.77 ± 1.13) μmol/L	–	[126]
118, 164, 125, 122, 143 and 134	–	–	Glucosidase and glycogen phosphorylase inhibition activities	Glucosidase and glycogen phosphorylase ↓	–	[132]
19, 20, 3 and 80	–	–	HK-2 cells	Fibronectin ↓	–	[81]
13	–	–	HK-2 cells	Fibronectin and α -SMA ↓ ; E-cadherin expression ↑	EMT	[81]
121	10 μmol/L; 20 and 80 mg/kg	STZ-induce rats	α TC1-6 cells	Glucagon secretion and blood sugar ↓ ; p-EphA1, p-EphA4, p-PI3K, p-Akt, and GLUT4 ↑	PI3K/Akt	[78]
155	10 and 30 mg/kg; 1 and 5 μmol/L	Male SD rats	HK-2	Urinary albumin, blood urea nitrogen, p-Smad3, collagen I, fibronectin and α -SMA ↓ ; LC3 and LAMP1 ↑	–	[82]
136 and 4	2, 5, 10 and 20 μmol/L	–	3T3-L1 pre-adipocytes	Glucose consumption, p-AMPK, p-IRS-1 and p-Akt ↑ ; p-IKK β and p-IRS-1 ↓	IRS-1/PI3K/Akt	[83]
63, 78, 79 and 100	25 mmol/L	–	α -Glucosidase inhibitory activity	IC ₅₀ = (4.97 ± 0.63) μmol/L; IC ₅₀ = (19.62 ± 0.70) μmol/L; IC ₅₀ = (7.08 ± 0.53) μmol/L; IC ₅₀ = (3.76 ± 0.77) μmol/L	–	[31]
Anti-hypolipidemic Extracts						
TAE	200 and 400 mg/kg	HFD-induced rats	–	HDL-C ↑ ; apoB48, MTP, TNF- α , and p-MAPK ↓	TNF- α /p38 MAPK	[89]
CPE	2, 4 and 8 g/kg	HFD and STZ- induced rats	–	TC, TG, LDL-C, and FFA ↓ ; HDL-C ↑	–	[63]
CPE	0.37, 0.75 and 1.50 g/kg	HFD-induced rats	–	TC, TG, LDL-C, MDA, TNF- α and p-MAPK ↓ ; HDL-C, SOD and GSH-Px ↑	–	[90]
ChE	1.5 g/kg; 10, 20 and 50 mg/L	HFD-induced rats	LO2 cells	TC, TG, HMG-CoA, ALT, AST, BUN, CRE, and UA ↓ ; HDL-C ↑	–	[91]
EAE	1.5 g/kg; 10, 20 and 50 mg/L	HFD-induced rats	LO2 cells	TC, TG, ALT, AST, BUN, CRE, and UA ↓ ; HDL-C ↑	–	[91]
BuE	1.5 g/kg; 10, 20 and 50 mg/L	HFD-induced rats	LO2 cells	ALT, AST, BUN, CRE, and UA ↓	–	[91]
CPE	1.5 g/kg; 10, 20 and 50 mg/L	HFD-induced rats	LO2 cells	TC, TG, and HMG-CoA ↓ ; HDL-C ↑	–	[91]
CPE	2, 4 and 8 g/kg	HFD-induced rats	–	Weight gain, food utilization, visceral fat mass, apoB48, LDL-C, TC and TG ↓ ; HDL-C ↑	–	[92]
ChE	2, 4 and 8 g/kg	HFD-induced rats	–	Weight, blood lipid, TNF- α , SREPB 1c, ACC-1 and FAS ↓	–	[95]
TAE	25 and 100 mg/kg; 1, 10, 25, 50 and 100 μg/mL	HFD-induced rats	HepG2 cells	SOD, HO1, HO-1, NQO1 and GSH/GSSG ↑ ; CYP2E1, MDA and PCO ↓	Activating Nrf2	[96]
Compounds						
6, 7, 64, 65, 119, 121, 135, 136, 153, 155 and 156	10 μmol/L	–	Caco-2 cells	ApoB48 ↓	–	[37]

Table 2 (Continued)

Compounds/extracts	Dosage uses	Models		Effects	Possible mechanism	References
		<i>In vivo</i>	<i>In vitro</i>			
121	80 mg/kg; 5, 10, 20, 40 and 80 $\mu\text{mol/L}$	HFD-induced rats	Mouse primary hepatocytes	Lipid, TC, TG, ALT, AST, ALP, IL-6, IL-1 β and TNF- α $\downarrow$; p-AMPK/AMPK $\uparrow$	Sirt1 / AMPK	[97]
Anti-inflammatory						
Extracts						
EAE	–	–	RAW 264.7 cell	NO $\downarrow$	–	[99, 126]
CPT	10, 15, 20, 25, 30 $\mu\text{g/mL}$	–	THP-1	IL-1 β $\downarrow$	–	[101]
Compounds						
6, 8, 26, 69, 96, 98 and 83	–	–	RAW 264.7 cells	NO $\downarrow$; IC ₅₀ > 40 $\mu\text{mol/L}$	–	[99]
97, 82 and 84	–	–	RAW 264.7 cells	NO $\downarrow$; IC ₅₀ = (22.30 $\pm$ 0.42) $\mu\text{mol/L}$; IC ₅₀ = (30.77 $\pm$ 0.21) $\mu\text{mol/L}$; IC ₅₀ = (34.57 $\pm$ 0.62) $\mu\text{mol/L}$	–	[99]
71 and 72	10–40 $\mu\text{mol/L}$	–	RAW 264.7 cells	NO, TNF- α , PGE2, and IL-6, COX-2, iNOS, and NF- κB /p65 $\downarrow$	NF- κB	[99]
95, 25, 3 and 4	–	–	RAW 264.7 cells	NO $\downarrow$; IC ₅₀ = (18.53 $\pm$ 0.33) $\mu\text{mol/L}$; IC ₅₀ = (32.88 $\pm$ 0.43) $\mu\text{mol/L}$; IC ₅₀ = (25.78 $\pm$ 0.32) $\mu\text{mol/L}$; IC ₅₀ = (33.25 $\pm$ 0.47) $\mu\text{mol/L}$	–	[99]
153	1–50 $\mu\text{mol/L}$	–	THP-1 cells	IL-1 β , Caspase-1, pro-IL-1 β , pro-Caspase-1, and NLRP3 $\downarrow$	PI3K-AKT-mTOR	[101]
136 and 156	1–50 $\mu\text{mol/L}$	–	THP-1 cells	IL-1 β $\downarrow$	–	[101]
118	5–100 $\mu\text{mol/L}$	–	RAW 264.7 cells	NO, iNOS, IL-6, Keap1, p-ERK1/2, p-P38, and p-JNK1/2 $\downarrow$; P-Nrf2 $\uparrow$	MAPKs-NF- κB -Nrf2	[102]
155	5–100 $\mu\text{mol/L}$	–	RAW 264.7 cells	NO, iNOS, IL-6, p-ERK1/2, p-P38, and p-JNK1/2 $\downarrow$; IL-10 $\uparrow$	MAPKs-NF- κB -Nrf2	[102]
120	5–100 $\mu\text{mol/L}$	–	RAW 264.7 cells	NO, iNOS and IL-6 $\downarrow$; IL-10 $\uparrow$	–	[102]
55, 56, 59, 61, 78 and 79	25 mmol/L	–	Activity against COX-2	The inhibition rates were 12.11%, 15.73%, 10.23%, 20.62%, 17.44% and 35.83%, respectively	–	[31]
Anti-cancer and cytotoxicity						
Extracts						
CPE	–	–	HeLa cell line and HEK293	The growth of HeLa cells $\downarrow$	–	[103]
CPE	–	–	HEK293, HCT-116, HeLa, HepG2, MCF-7, A549 and PANC-1	HeLa: IC ₅₀ = 0.13–0.42 mg/mL, HepG2: IC ₅₀ = 0.25–0.57 mg/mL, PANC-1: IC ₅₀ = 0.52–0.86 mg/mL, A549: IC ₅₀ = 0.35–0.96 mg/mL, HCT-116: IC ₅₀ = 0.44–0.80 mg/mL, HEK-293: IC ₅₀ = 0.21–0.68 mg/mL, MCF-7: IC ₅₀ = 0.22–0.44 mg/mL	–	[140]
Compounds						
96	0.39–100.00 mmol/L	–	MCF-7, PC-3, Du145, NCI- H1975, PC-9, SKVO3 and HepG2	IC ₅₀ = 11.31–29.51 $\mu\text{mol/L}$; MCF-7: IC ₅₀ < 40 μm	–	[104]
68, 69, 81 and 80	0.39–100.00 mmol/L	–	MCF-7	IC ₅₀ < 40 μm	–	[104]
85	0.064–5.000 $\mu\text{mol/L}$	–	Lovo, NCI-H460, T47D	Lovo: IC ₅₀ = (29.21 $\pm$ 2.73) $\mu\text{mol/L}$; NCI-H460: IC ₅₀ = (13.40 $\pm$ 5.17) $\mu\text{mol/L}$; T47D: IC ₅₀ = (37.21 $\pm$ 9.84) $\mu\text{mol/L}$	–	[125]
87	0.064–5.000 $\mu\text{mol/L}$	–	HepG2	IC ₅₀ = (21.12 $\pm$ 4.10) $\mu\text{mol/L}$	–	[125]
86	0.064–5.000 $\mu\text{mol/L}$	–	Lovo, HepG2, HeLa, NCI-H460, T47D	Lovo: IC ₅₀ = (11.86 $\pm$ 0.27) $\mu\text{mol/L}$; HepG2: IC ₅₀ = (4.61 $\pm$ 0.13) $\mu\text{mol/L}$; HeLa: IC ₅₀ = (15.23 $\pm$ 3.88) $\mu\text{mol/L}$; NCI-H460: IC ₅₀ = (5.47 $\pm$ 0.54) $\mu\text{mol/L}$; T47D: IC ₅₀ = (8.65 $\pm$ 1.38) $\mu\text{mol/L}$	–	[125]
89	0.064–5.000 $\mu\text{mol/L}$	–	Lovo, HepG2, NCI-H460	Lovo: IC ₅₀ = (14.10 $\pm$ 0.55) $\mu\text{mol/L}$; HepG2: IC ₅₀ = (9.08 $\pm$ 0.52) $\mu\text{mol/L}$; NCI-H460: IC ₅₀ = (37.02 $\pm$ 1.80) $\mu\text{mol/L}$	–	[125]
113	0.064–5.000 $\mu\text{mol/L}$	–	Lovo, HepG2, HeLa, NCI-H460, T47D	Lovo: IC ₅₀ = (8.96 $\pm$ 0.07) $\mu\text{mol/L}$; HepG2: IC ₅₀ = (9.19 $\pm$ 0.24) $\mu\text{mol/L}$; HeLa: IC ₅₀ = (10.78 $\pm$ 0.85) $\mu\text{mol/L}$; NCI-H460: IC ₅₀ = (6.48 $\pm$ 1.18) $\mu\text{mol/L}$; T47D: IC ₅₀ = (10.76 $\pm$ 1.73) $\mu\text{mol/L}$	–	[125]

Table 2(Continued)

Compounds/extracts	Dosage uses	Models		Effects	Possible mechanism	References
		<i>In vivo</i>	<i>In vitro</i>			
27	0.064–5.000 $\mu\text{mol/L}$	–	HepG2, NCI-H460	HepG2: $\text{IC}_{50} = (28.31 \pm 3.67) \mu\text{mol/L}$; NCI-H460: $\text{IC}_{50} = (39.15 \pm 6.85) \mu\text{mol/L}$	–	[125]
15	0.064–5.000 $\mu\text{mol/L}$	–	HepG2, Hela, NCI-H460, T47D	HepG2: $\text{IC}_{50} = (37.39 \pm 1.92) \mu\text{mol/L}$; Hela: $\text{IC}_{50} = (14.54 \pm 4.77) \mu\text{mol/L}$; NCI-H460: $\text{IC}_{50} = (15.53 \pm 4.11) \mu\text{mol/L}$; T47D: $\text{IC}_{50} = (5.87 \pm 1.59) \mu\text{mol/L}$	–	[125]
68	–	–	ASPC-1, HCT116, HEPG2 and SNU5	ASPC-1: $\text{IC}_{50} = 93.94 \mu\text{mol/L}$; SNU5: $\text{IC}_{50} = 93.54 \mu\text{mol/L}$; HEPG-2: $\text{IC}_{50} = 62.21 \mu\text{mol/L}$; HCT116: $\text{IC}_{50} = 56.62 \mu\text{mol/L}$	–	[129]
75, 4 and 7	5–80 $\mu\text{mol/L}$	–	HepG2	Strongly cytotoxic	–	[56]
30 and 14	–	–	MCF-7	$\text{IC}_{50} < 35 \mu\text{mol/L}$	–	[124]
45	10 $\mu\text{mol/L}$	–	SMMC-7721, BT-549, HCT-116	SMMC-7721: $\text{IC}_{50} = (16.73 \pm 1.02) \mu\text{mol/L}$; BT-549: $\text{IC}_{50} = (15.84 \pm 1.05) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (6.53 \pm 0.5) \mu\text{mol/L}$	–	[57]
67	10 $\mu\text{mol/L}$	–	BT-549, HCT-116	BT-549: $\text{IC}_{50} = (21.64 \pm 1.29) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (4.94 \pm 0.42) \mu\text{mol/L}$	–	[57]
47, 52 and 42	10 $\mu\text{mol/L}$	–	BT-549	$\text{IC}_{50} = (17.78 \pm 1.54) \mu\text{mol/L}$; $\text{IC}_{50} = (21.92 \pm 1.62) \mu\text{mol/L}$; $\text{IC}_{50} = (20.03 \pm 1.38) \mu\text{mol/L}$	–	[57]
43	10 $\mu\text{mol/L}$	–	BT-549, HCT-116	BT-549: $\text{IC}_{50} = (15.61 \pm 0.93) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (8.24 \pm 0.56) \mu\text{mol/L}$;	–	[57]
95	10 $\mu\text{mol/L}$	–	BT-549, HCT-116	BT-54: $\text{IC}_{50} = (20.56 \pm 1.63) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (6.48 \pm 0.45 \text{ m}) \mu\text{mol/L}$	–	[57]
53	10 $\mu\text{mol/L}$	–	SMMC-7721, BT-549	SMMC-772: $\text{IC}_{50} = (21.45 \pm 2.11) \mu\text{mol/L}$; BT-549: $\text{IC}_{50} = (15.69 \pm 1.19) \mu\text{mol/L}$	–	[57]
118, 119 and 121	10 $\mu\text{mol/L}$	–	SMMC-7721	$\text{IC}_{50} = (20.48 \pm 2.18) \mu\text{mol/L}$; SMMC-7721: $\text{IC}_{50} = (19.41 \pm 1.42) \mu\text{mol/L}$; $\text{IC}_{50} = (20.04 \pm 1.92) \mu\text{mol/L}$	–	[57]
30	–	–	MCF-7, PC-9	MCF-7: $\text{IC}_{50} < 35 \mu\text{mol/L}$; PC-9: $\text{IC}_{50} = 75.85 \mu\text{mol/L}$	–	[124]
14	–	–	MCF-7	$\text{IC}_{50} < 35 \mu\text{mol/L}$	–	[124]
121, 119, 136 and 118	–	–	HeLa cell line	Bax, cytochrome c, Caspase-3 and Caspase-9 $\uparrow$; Bcl-2 $\downarrow$	–	[103]
49	–	–	HCT-116	$\text{IC}_{50} = (11.24 \pm 0.22) \mu\text{mol/L}$	–	[31]
50	–	–	BGC-823, MCF-7, HCT-116, and HepG-2	BGC-823: $\text{IC}_{50} = (8.86 \pm 0.38) \mu\text{mol/L}$; MCF-7: $\text{IC}_{50} = (9.19 \pm 0.78) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (8.80 \pm 0.36) \mu\text{mol/L}$; HepG-2: $\text{IC}_{50} = (13.41 \pm 0.90) \mu\text{mol/L}$	–	[31]
57	–	–	BGC-823, HCT-116	BGC-823: $\text{IC}_{50} = (7.69 \pm 0.21) \mu\text{mol/L}$; HCT-116: $\text{IC}_{50} = (9.45 \pm 0.93) \mu\text{mol/L}$;	–	[31]
62 and 78	–	–	BGC-823	$\text{IC}_{50} = (8.47 \pm 0.41) \mu\text{mol/L}$; $\text{IC}_{50} = (9.04 \pm 0.61) \mu\text{mol/L}$	–	[31]
Anti-oxidation						
Extracts						
CPE	–	–	Antioxidant assay	It had significant effects on the scavenging capacity of DPPH and ABTS radical and reducing power	–	[140]
Compounds						
163, 168, 149 and 166	5 mmol/L	–	HepG2 cells; FFA-induce hepatic steatosis	SOD $\uparrow$; MDA $\downarrow$	–	[106]
142	1 mmol/L	–	HepG2 cells; FFA-induce hepatic steatosis	SOD $\uparrow$; MDA $\downarrow$	–	[106]
Hepatoprotective effect						
Compounds						
105	10 $\mu\text{mol/L}$	–	HepG2	Sirt1 activities $\uparrow$	–	[56]
65	20 $\mu\text{mol/L}$	–	HepG2	Sirt1 activities $\uparrow$	–	[56]
25	–	–	RAW 264.7 and HepG2	TNF- α $\downarrow$	–	[107]
Others						
CPT	–	–	<i>Saccharomyces cerevisiae</i> strain Sc131	Filamentous and invasive growth $\downarrow$	–	[108]

Note: –, This item is not mentioned in the reference; HFD, high fat diet; STZ, Streptozotocin.

4.1 Antihyperglycemic

Glucose metabolism disorders can promote diabetes, which is a systemic metabolic disease that impairs organ functions, including those of the heart, liver, and kidney^[9]. Triterpenoids from *C. paliurus* can reduce glucose uptake, regulate blood lipid levels and insulin signaling pathways, reduce oxidative stress levels and β -cell apoptosis, increase insulin synthesis and secretion, and inhibit liver gluconeogenesis and α -glucosidase inhibitor activities, which improve glucose metabolism disorders.

Type 2 diabetes mellitus (T2DM) is the most common metabolic syndrome in the world, and it accounts for more than 90% of diabetes cases^[61]. The rat model of diabetes induced by high fat diet (HFD) and low-dose STZ showed similar metabolic characteristics to human T2DM^[62]. Wang et al.^[63] showed that CPE can reduce the mortality and blood glucose level in T2DM rats, improve insulin sensitivity, and revert the changes in BUN, CREA and GSP levels in rat kidneys. Moreover, CPE can improve insulin level, glucose tolerance, and insulin sensitivity and reduce insulin resistance in DM mice^[64]. Hyperglycemia is a known key driver of oxidative stress and inflammation, which lead to cardiac fibrosis and decreased cardiac function^[65]. Wang et al.^[66] proved that CPE can prevent structural and functional changes in the heart tissue of diabetic mice. This cardioprotective activity is attributed to the antioxidant, antiapoptotic, anti-inflammatory, and antifibrotic activities of CPE. Oral administration of CPE to *db/db* mice prevents cardiac hypertrophy, myocardial fibrosis, and related oxidative stress and inflammation. CPE further reduced the blood lipid levels in treated animals, which resulted in a dose-dependent increase in phosphatidylinositol 3-kinase (PI3K) expression and Akt phosphorylation. These results indicate that the decrease in nuclear factor κ B (NF- κ B) expression may be attributed to CPE-induced changes in the PI3K/Akt pathway activity. In T2DM,

chronic inflammation is the key driver behind the pathogenesis of liver injury^[67]. Jiang et al.^[68] revealed that triterpenoid-enriched fraction from *C. paliurus* (CPT) improved diabetes-induced liver inflammation through the Rho/ROCK/NF- κ B signaling pathway. Triterpenic acids-enriched fraction from *C. paliurus* (TAE) not only improves insulin sensitivity, but also inhibits liver gluconeogenesis and balance systemic glucose homeostasis^[69]. *In vivo* studies have shown that TAE can inhibit the cAMP/PKA/CREB pathway by activating adenosine 5'-monophosphate activated protein kinase (AMPK), and this condition effectively inhibits liver gluconeogenesis and reduces liver glucose production (Fig. 8). Insulin resistance is the main pathophysiological abnormality in patients with NAFLD^[70]. TAE not only reduced liver lipid content but also insulin resistance by upregulating the PI3K/Akt/GSK3 β pathway^[71]. Under insulin stimulation, skeletal muscle undertakes about 75% of glucose uptake^[72]. The mouse muscle cell line C2C12 has been widely used to study the effects of various drugs on glucose transport. CPE treatment promoted glucose uptake and transport of glucose transporter 4 (GLUT4) from the endoplasmic reticulum to the plasma membrane in C2C12 myotubes^[73]. CPE activated the insulin signaling pathway (IRS1-PI3K-Akt) in an insulin-independent manner, which led to increased glucose uptake by inducing GLUT4 translocation in C2C12 cell lines. CPE promotes glucose treatment by improving the insulin sensitivity against inflammatory injury. The involved regulatory mechanism is the positive regulation of the function of insulin receptor substrate-1 (IRS-1) by CPE, which leads to the improvement of phosphatidylinositol 3-kinase (PI3K) signal, as shown by the recovery of Akt phosphorylation in insulin response. Epidemiological studies have shown the gradual development of end-stage renal disease in 30%–50% of diabetic patients^[74]. TAE effectively increases the level of microtubule-associated protein 1 light chain 3 II (LC3II) and the phosphorylation of AMPK and reduced the phosphorylation

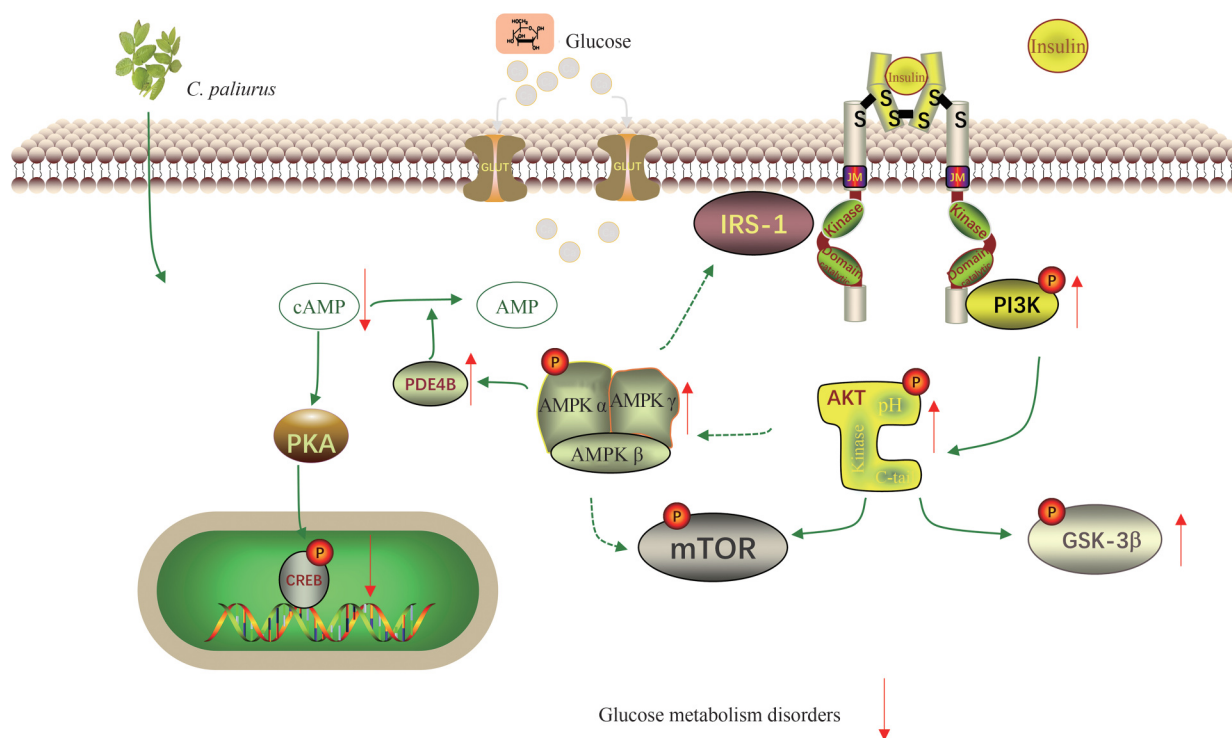


Fig. 8 *C. paliurus* triterpenoid extracts and compounds regulate glucose metabolism disorders.

of its downstream effector mammalian target of rapamycin (mTOR)^[75]. Thus, TAE can prevent diabetic nephropathy (DN) through autophagy and AMPK pathway. Diabetes mellitus (DKD), which originates from endothelial injury, is a serious microvascular complication caused by diabetes. CPT can considerably reduce the excessive activation of Rho-related coiled-coil protein kinase (ROCK) *in vivo* and *in vitro* and inhibit the activity of transforming growth factor- β (TGF- β), which is a key driver of fibrosis^[76]. The possible mechanism is reduction of endothelial to mesenchymal transition (EndMT) by CPT through the inhibition of the ROCK pathway, which prevents the progression of DKD. Although the hypoglycemic activity of *C. paliurus* extract has been recognized to a certain extent, the specific molecular mechanism remains unclear. In addition, further studies must be conducted to determine whether hypoglycemic activity is the overlapping effect of hypoglycemic substances, such as polyphenols, polysaccharides, and triterpenoids, in the extract deserves.

Compound **104** caused the significant enhancement of the glucose uptake ability of C2C12 myotube cells and mouse embryonic fibroblasts 3T3-L1 (3T3-L1) adipocytes under insulin stimulation and the phosphorylation levels of IRS-1, Akt and glycogen synthase kinase-3 β (GSK-3 β) in 3T3-L1 adipocytes under insulin stimulation, and activated the AMPK-p38 pathway^[77]. Compounds **3**, **4**, and **5** also remarkably promoted the insulin-stimulated glucose uptake in 3T3-L1 adipocytes. Therefore, the addition of sugar units can improve the glucose uptake capability of 3,4-seco-dammarane and dammarane triterpenes in 3T3-L1 adipocytes. Compound **121** selectively inhibited glucagon secretion in pancreatic α cells and showed a protective effect on T2DM *in vitro* and *in vivo*^[78]. The mechanism may involve compound **121** promoting the interaction between ephrin-A1 and erythropoietin-producing hepatocellular carcinoma A4 (EphA4), which subsequently activate the PI3K/Akt signaling pathway. The glucose uptake capability of pentacyclic triterpenes requires the presence of 3-hydroxy and 23-hydroxymethyl groups. The overexpression of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) in mouse adipose tissue can lead to insulin-resistant diabetes, which illustrates the importance of selective inhibition of 11 β -HSD1 in key metabolic tissues (especially adipose tissue) for the treatment of type 2 diabetes and metabolic syndrome^[79]. Compound **119** showed a moderate inhibitory effect on mouse 11 β -HSD1 with a half maximal inhibitory concentration (IC₅₀) value of (0.16 $\pm$ 0.04) μ mol/L^[80]. However, compound **120**, which had a similar structure to compound **119**, showed no inhibitory activity against mouse 11 β -HSD1, which indicates that the hydroxyl group on C-3 inhibited the activity. Compound **13** can significantly downregulate the expression of E-cadherin in high-glucose and TGF- β 1 induced HK-2 cells; meanwhile, the expression of α -SMA and fibronectin was significantly up-regulated, which reversed the changes in epithelial-mesenchymal transformation (EMT) and significantly reduced the mRNA levels of snail and twist^[81]. Compound **155** can substantially reduce the urinary protein level of DN rats and activate the autophagy-lysosomal pathway through direct interaction with transforming growth factor beta receptor 1 (TGF- β R1)^[82]. In addition, *in vitro* experiments showed that compound **155** can inhibit the expression of TGF- β R1 and alleviate high glucose (HG) + TGF- β 1-induced renal fibrosis. Compounds **3**, **13**, **19**, and **20** considerably inhibited the level of fibrosis, which indicates that the 20,24-epoxy side chain contributed to the inhibitory effect. Compounds **161** and **162**, with the same skeleton, have different

hydroxyl configurations on C-3, which indicates that α -OH may contribute to antifibrosis. Compound **169**, obtained by the addition of a sugar group to the structure of compound **161**, has evident antihepatic fibrosis effect, which suggests that the access to sugar groups may promote the antifibrosis effect. Compounds **4** and **136** improve glucose uptake and reduce insulin resistance through an insulin-independent pathway^[83]. The improvement of insulin resistance under inflammatory stimulation may be attributed to AMPK activation. Compounds **63**, **88**, and **100** exhibit strong inhibitory activities against glucosidase. Further analysis of their structure and biological activity revealed the desirable antiglucosidase activity of 3,4-seco-dammaranes and oleananes. For the 3,4-seco-dammaranes aglycones, the aldehyde group of the C-4-substituted methyl group of compound **63** is considered the key to inhibiting glucosidase activity. Compound **79**, which possesses a similar structure to compound **78**, has a stronger inhibitory activity. Given that the hydroxyl group of C-25 is replaced by ethoxy, the extension of the side chain can enhance the inhibition of glucosidase. Similar to compounds **78** and **79**, compound **100** has an Ara(f) substitution on the side chain. Ara(f) contributes greatly to the inhibition of 3,4-seco-dammarane saponins in terms of glucosidase activity. Compound **88** lacks a longer side chain but presents the strongest inhibitory activity against glucosidase due to the presence of Glu. Compounds **112** and **113** manifest different glucosidase inhibitory activities due to their varied glycosylation. Therefore, the sugar units affect glucosidase inhibitory activity in the following order: Glu > Ara(f) > Ara > Qui. Compound **118**, as the compound closest to the oleanane-type triterpenoid skeleton, exhibits a strong inhibitory activity against glucosidase. As the carboxyl group at the C-3 position is oxidized to ester (compound **134**) and carbonyl (compound **143**) groups, the glucosidase inhibition activity decreases continuously. For oleanane triterpenoids, modification of the skeleton weakens the glucosidase inhibition activity. Compounds **81** and **91** reveal potential hypoglycemic activity, and they increased the glucose consumption of 3T3-L1 preadipocytes by 27.32% and 29.27% at a dose of 3.125 μ mol/L, respectively^[34]. Therefore, 3,4-seco-dammarane saponins may be the key to the increased glucose consumption of *C. paliurus* by 3T3-L1 preadipocytes. The biological activity of triterpenoids is closely related to their molecular structure. Further research is needed to obtain compounds with a strong hypoglycemic activity and reveal their molecular mechanism and structure-activity relationship.

4.2 Antihyperlipidemia

According to the latest “Dietary Guidelines for Chinese Residents 2022” issued by the Chinese Nutrition Society, the prevalences of overweightness and obesity among residents over 18 years old in China have reached 34.3% and 16.4%, respectively^[84]. Obesity, which showed an exponential growth trend, has gradually become a threat to public health. Therefore, urgent action is needed to address the problems of overweightness and obesity. With the support of pharmacological research results, triterpenoids from *C. paliurus* improve lipid metabolism disorders through regulation of blood lipid levels, inhibition of the excessive production of intestinal apolipoprotein B48 (apoB48), promotion of cholesterol excretion, and inhibition of HMG-CoA reductase activity.

Hyperlipidemia, a lipid metabolism disorder, is considered one of the major risk factors for cardiovascular diseases (CVDs), such as atherosclerosis, myocardial infarction, and stroke^[85–86]. The intestine plays a key role in the regulation of dietary fat. ApoB48 is an essential structural protein of chylomicrons (CMs) that transports exogenous fat to blood circulation and other parts of the body^[87]. The excessive production of apoB48 may lead to excessive absorption of exogenous lipids in the intestine, which eventually leads to hyperlipidemia, obesity, and atherosclerosis^[88]. TAE can not only reduce the elevated levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and increase the levels of high-density lipoprotein cholesterol (HDL-C), but also improve dyslipidemia by inhibiting the excessive production of intestinal apoB48^[89]. The underlying mechanism may be related to the downregulation of MTP expression and the TNF- α /p38 MAPK signaling pathway. CPE can restore lipid metabolism disorders in diabetic rats^[63]. CPE showed a significant lipid-lowering effect on hyperlipidemic mice by reducing the TC, TG, and LDL-C levels and increasing the HDL-C levels^[90]. The lipid-lowering effect may be related to the excessive inhibition of apoB48 production, which is mediated by the TNF- α -induced MAPK pathway. Different polar extracts improved lipid metabolism in HFD-induced hyperlipidemia mice, and chloroform fraction from *C. paliurus* (ChE) may increase the activity and mRNA expression level of cholesterol 7 α -hydroxylase (CYP7A1) by promoting the excretion of cholesterol, a bile acid metabolite. In addition, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity, mRNA expression level, and cholesterol biosynthesis were inhibited^[91]. CPE can prevent HFD-induced hyperlipidemia and obesity in SD rats. In addition, CPE treatment can reduce serum TC, TG, LDL-C, free fatty acids (FFAs), and leptin levels, increase HDL-C and adiponectin levels, and substantially reduce body weight gain, visceral fat mass, and fat storage levels^[92]. The early stage of nonalcoholic fatty liver disease (NAFLD) is hepatic steatosis (HS), which is characterized by TG accumulation in the cytoplasm of hepatocytes and increases the susceptibility of the liver to various causes^[93]. HS may result from the imbalance between lipid utilization and output in the liver and between lipid uptake and synthesis^[94]. Therefore, the regulation of related signaling pathways can be a potential strategy to improving HS and blocking the progression of NAFLD. ChE exerts a certain reversal effect on HS, and its mechanism may be related to the reduction of serum non-esterified fatty acids (NEFAs) levels and lipid intake, and inhibition of lipid de novo synthesis in the liver^[95]. ChE can also reduce HFD-induced liver oxidative stress and inflammatory response, which results in the prevention of NAFLD. TAE can improve the antioxidant activity and repair the mitochondrial respiratory chain in HFD-induced rats and FFA-induced HepG2 cells by activating the Nrf2 pathway, which reduces NAFLD^[96]. In addition, studies should further explore the effect and mechanism of triterpenoids from *C. paliurus* extract on antihyperlipidemia activity.

Compound **121** restores impaired autophagy and improves intestinal barrier function by indirectly triggering Sirt1/AMPK-regulated lipid metabolism, which effectively counteracts FFA-induced lipid accumulation and HFD-induced obesity, HS and inflammation, lipid disorders, insulin resistance, and liver injury^[97]. Compounds **119**, **135**, **136**, **153**, **155**, and **156** significantly decreased the oversecretion of apoB48 ($P < 0.05$)^[37]. Further analysis of their structure and biological activity showed that the hydroxymethyl

group at the C-4 position promoted their inhibitory activity. Compounds **6**, **7**, **64**, and **65**, which contain a pyranose group showed stronger inhibitory effects on the excessive secretion of apoB48 than compounds **3**, **4**, **21**, and **22**, which contain a furan sugar group. This finding indicates that the sugar part may have different effects on the compound's inhibitory activity. Compounds **132**, **161**, and **162**, which contain 2 double bonds, and compounds **128** and **165**, which have a- and b-unsaturated ketones, revealed no effect on apoB48 secretion. Therefore, the decrease activity of pentacyclic triterpenoids may be due to the presence of double bonds and a- and b-unsaturated ketones. Further studies are needed to confirm the specific and accurate structure-activity relationship.

4.3 Anti-inflammatory

Inflammation refers to a defense or immune response of the body to external stimuli, and excessive or persistent inflammation can lead to a variety of inflammation-related diseases^[98].

EAE showed a significant inhibitory effect on the release of NO from lipopolysaccharide (LPS)-activated RAW 264.7 cells, and this result is comparable to the inhibitory effect of the positive control dexamethasone^[99]. With in-depth understanding of the pathological mechanism of gout, researchers inferred that the release of IL-1 β can induce the production of proinflammatory cytokines and chemokines by interacting with IL-1R, which leads to the infiltration of neutrophils in the inflammatory site, accompanied with severe pain and swelling^[100]. CPT (10 μ g/mL) can significantly reduce the level of IL-1 β ^[101]. This inspired the development of green and safe anti-inflammatory agents.

Compounds **71**, **72**, **109**, and **110** present significant inhibitory effects on the production of NO and the expressions of cytokines NO, TNF- α , prostaglandin E₂ (PGE₂), and IL-6^[99]. In addition, compound **71** significantly inhibits the expression levels of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and NF- κ B/p65 proteins, which indicates that the compound exerts anti-inflammatory effects by inhibiting the NF- κ B signaling pathway. Therefore, the methoxy group on the side chain is possibly related to the high-efficiency inhibition of endotoxin-activated NO release in RAW 264.7 cells. According to the literature on the inhibitory activity of dammarane-type triterpenoids during NO release, the type of sugar group is important in inhibiting the effect of NO release. The Ara(f)-containing compounds **3**, **4**, and **25** have a weak inhibitory activity. Compound **83**, which has a similar structure to compounds **82** and **84**, has a Qui sugar unit at C-12. Similarly, compound **26** weakly inhibits the release of NO. Qui is speculated to exert a certain inhibitory effect on this activity. Compounds **136**, **153**, and **156** significantly reduce the levels of IL-1 β . Compound **153** can effectively improve NLRP3 inflammasome-mediated gout through PI3K-Akt-mTOR-dependent autophagy^[101]. The inhibition rate of compound **79** on COX-2 reached 35.83, which is half that of the positive control. Compound **78**, which also contains Ara(f) at C-20, showed a certain inhibitory activity on COX-2. C-20 glycosylation is speculated to play an important role in the COX-2 inhibitory activity. Compound **118** significantly inhibited the LPS-induced phosphorylation of P38 mitogen-activated protein kinase (P38), JUN N-terminal kinases 1/2 (JNK1/2), and extracellular regulated protein kinases 1/2 (ERK1/2). Compound **155** considerably reduced the phosphorylation of JNK1/2 and P38, but did not change

the total protein expression levels of JNK1/2, P38, and ERK1/2^[102]. Compounds **118** and **155** mediate the NF- κ B and MAPK pathways together, and compound **120** only mediates the former. Compared with compounds **120** and **155**, compound **118** had the strongest inhibitory effect on LPS-stimulated NO production in RAW 264.7 cells. Such result was observed possible because the C-4 methyl group was not further oxidized to a hydroxymethyl group. More in-depth anti-inflammatory mechanisms and structure-activity relationships await further exploration and discovery.

4.4 Anticancer and cytotoxicity

The cytotoxicity test is the basic content of studies given that *C. paliurus* is a raw material for healthy food. Zhou et al.^[103] investigated the inhibitory activity of CPE leaves from different habitats on HeLa cells, and observed that *C. paliurus* from Anhui and Guizhou populations, which had the highest triterpenoid content, showed the strongest inhibitory effect on HeLa cells. These results provide a basis for the rational selection of suitable planting areas for *C. paliurus* to maximize its function and nutritional value.

Compounds **68**, **69**, and **96** showed extensive cytotoxic effects on cancer cells^[104]. Compounds **118**, **119**, **121**, and **136** significantly reduced the proliferation of HeLa cells by inducing their apoptosis and regulating mitochondrial membrane potential (MMP), reactive oxygen species (ROS) production, and apoptosis-related proteins through the mitochondrial pathway^[103]. RNA sequencing showed that *ACTB*, *ATF4*, *TUBA1B*, and *TUBA1C* genes may be the key genes involved in the apoptosis induced by compounds **119** and **136**. Compounds **15**, **86**, and **113** showed a stronger inhibitory activity against cancer cells than the positive control cisplatin (DDP). Further analysis of their structure and biological activity revealed that the sugar unit Qui connected to C-11 contributes greatly to their anticancer activity. Similarly, compounds **18**, **27**, **75**, **86**, **87**, **89**, **108**, and **133** exhibit anticancer activities to some extent. The presence of ester groups at the C-3 position exerts an important cytotoxic effect. Compounds **50** and **78**, which have ester groups at the C-3 position, exhibit a strong anticancer activity. In addition, the presence of compounds **15**, **86**, and **113**, which also possess a strong anticancer activity, indicates the potential of *C. paliurus* as an anticancer drug. However, the lack of in-depth mechanism research, such as the inhibition of different types of cancer cells, hinders the development of drugs. Thus, further research is urgently needed to fill this clinical transformation gap.

4.5 Others

Cancer, aging, or other diseases are mainly related to the excessive production and accumulation of free radicals^[105]. Therefore, studying antioxidants can result in the effective elimination of the harmful effects of free radicals. CPE had a significant effect on the scavenging capabilities and reducing power of DPPH and ABTS free radicals^[103]. Yang et al.^[106] observed that compounds **142**, **149**, **163**, **166**, and **168** can greatly increase superoxide dismutase (SOD) activities and decrease malondialdehyde (MDA) levels in FFA-induced HepG2 steatosis cells. Compound **142** showed a better potential effect on the inhibition of MDA production than the positive control (vitamin E). Further structural and biological activity analysis

revealed that compounds **160** and **163** have the same chemical skeleton but different C-30 functional group. However, their varying activities suggest that terminal double bonds may be the key to their antioxidant activity. Notably, compounds **161** and **162**, which have double bonds at the end exhibit no antioxidant activity, and this finding indicates that 1-hydroxyl may influence their antioxidant activity. Compounds **65** and **105** showed inhibitory activity against Sirt1, with IC₅₀ values of 20 and 10 μ mol/L, respectively^[56]. Compounds **25**, **26**, and **37** inhibited the activity of TNF- α in LPS-induced mouse peritoneal macrophages (RAW 264.7) and exerted hepatoprotective effects by inhibiting the proliferation of HepG2 cells^[107]. The addition of triterpenoids reduces the filamentous and invasive growth of cells, which is beneficial to redox balance and glycolysis^[108].

In summary, triterpenoids from *C. paliurus* have incalculable health effects. A large number of studies have revealed their antioxidation, antihyperglycemic, antihyperlipidemia, antibacterial, and anti-inflammatory activities. However, the current research usually involves cells, mice, and rats, and related clinical reports are lacking. In addition, further exploration is needed to determine the biological activity and structure-activity relationship of the remaining active substances.

5. Applications of triterpenoids from *C. paliurus*

In traditional Chinese medicine, *C. paliurus* leaves are used for the treatment of hyperglycemia, hyperlipidemia, inflammatory diseases, cancer, DN, and as antioxidants. Triterpenoids are an important contributors to the pharmacological activity of *C. paliurus*, and they have potential applications in the field of food and medicine.

Triterpenoids, which are natural compounds that widely exist in nature, have attracted people's attention due to their various biological and pharmacological activities. However, their application in the clinical drug and food markets is greatly hindered by their low bioavailability, poor targeting, fast metabolism, and other shortcomings. With the development of nanotechnology, the loading of functional small molecules into nanosystems to form targeted delivery systems has become a trend in drug development. Pentacyclic triterpenoids comprise natural amphiphilic products with a rigid skeleton and several polar functional groups, such as hydroxyl, carbonyl, and carboxyl groups. This amphiphilicity enables the assembly of complex nanostructures, which have been widely concerned and applied in various fields^[109]. Chu et al.^[110] utilized Ag⁺-modified chitosan (CS-Ag) nanoparticles (NPs), which resulted in the formation of CS-Ag-L-NPs, to deliver lupeol (**172**). CS-Ag-L-NPs showed good antibacterial activity in an infectious wound model and promoted wound healing. In addition, small-molecule compounds can be used as carriers to assemble NPs through load interaction, which will improve the stability and biological activity of the load. The preparation of asiatic acid (**155**)-caffeic acid phenethyl ester NPs (ASA-CAPE NPs) enabled CAPE to obtain better water solubility, stability, and biological activity^[111]. ASA-CAPE NPs also allowed CAPE to exhibit a good release effect during *in vitro* gastrointestinal digestion. The construction of ursolic acid (**152**)/Tween 80 nanovesicles (V-UA) caused ursolic acid (**152**) not only to act as an active component in the nanovesicle drug delivery system but also a part of the carrier for the stabilization of UA/Tween 80 nanostructures^[112]. Therefore, NP drug delivery systems can not only

reduce the hydrophobicity of certain terpenoids but also improve the precise targeted therapy involving such compound, such as those for antiwound infection and anti-liver disease.

Terpenoids possess many biological activities, such as antioxidation, anticancer, antibacterial, and so on. Therefore, in food production, these compounds can be used as an antioxidant, a bacteriostatic agent, and so on to prolong the preservation of food. soy protein/chitosan-based microsphere (SCM), as a stable biocompatible vehicle of compound **118**, was constructed under acidic conditions and showed high stability and enhanced antibacterial and antioxidant properties^[113]. The potential application of the SCM-OA delivery system was evaluated using microprocessed apples as test materials. The results reveal that the SCM-OA delivery system had evident effects on the reduction of weight loss rate, maintenance of the total phenol content, and inhibition of the browning of microprocessed apples. This past study provides new ideas and a basis for the application of triterpenoids in fruit and vegetable food processing. Triterpenoids can be used not only as antioxidants but also as antibacterial agents in food. Compound **152** is not only present in *C. paliurus*, but is also the main antibacterial active ingredient in blueberry cuticular wax. Compound **152** can inhibit the growth of *Botrytis cinerea* *in vitro* and *in vivo*^[114]. Therefore, this compound has great potential as a fungicide for the control of blueberry gray mold.

The ursolic acid (**152**) water/oil pickering emulsion based on rapeseed oil not only accelerated the digestion process of oil but also improved the bioavailability and bioactivity of ursolic acid (**152**)^[115].

The development of natural compounds as sugar substitutes has been a constant concern in the food industry. The sweetness of *C. paliurus* is mainly attributed to the presence of dammarane-type triterpenoid saponins. Compounds **3** and **12** have a sweetness that is around 200 and 250 times that of sucrose, respectively^[116]. Compounds **64** and **65** are dammarane-type saponins with a sweet taste. Thus, they can be potentially used as natural sweeteners and sugar substitutes in the sweetness test and have great development prospects in the food raw-material market (Fig. 9). Given that compounds **64** and **65** differ only in terms of their glycoside unit,

changing the glycoside unit will affect their perceived sweetness; derivative sugar units with longer or branched may be more effective as sweeteners than **64** or **65**^[32], as observed in other glycoside analogues, such as stevioside and dolomite^[117]. In May 2023, the World Health Organization (WHO) released an updated guide on sugar substitution. WHO recommends not to use nonsugar sweeteners (NSS) to control body weight, because in the long run, replacing free sugars with NSS has no contribution to weight control; long-term use may also have some potential adverse effects, such as the increasing risk of type 2 diabetes, CVD, and death in adults^[118]. Therefore, the triterpenoid saponins from *C. paliurus*, given their certain health benefits, provide prospects, opportunities, and challenges for the development of sugar substitutes. In addition, in-depth studies are required to gain insights into the safety and long-term effects of triterpenoid saponins derived from *C. paliurus* to ensure their sustainable application across various industries.

Compound **120** can act as a growth factor when added to the trout diet. The trout fed with compound **120** showed higher whole-body weight, liver weight, and growth rate of than the control group, which proves the application prospect of terpenoids as feed^[119].

6. Conclusion and prospect

Triterpenoids are important secondary metabolites in the plant kingdom and considered one of the most abundant categories of phytochemicals. Their strong physiological activity provides broad prospect and opportunity for the research and application of *C. paliurus*. Several prospects that need to be addressed may stimulate more far-reaching research work in the future include the following: (1) Despite the emergence of new triterpene compounds, the research on triterpene compounds remains in the stage of extraction, identification, and purification. Therefore, the future challenge is the development of efficient separation and purification methods and accurate structural identification strategies and equipment. (2) The long extraction and purification time and the low yield of secondary metabolites from natural plants have been persistent challenges for researchers. Therefore, other methods, such as fermentation of engineered microorganisms expressing the mevalonate pathway and callus culture, must be developed to increase the yield of triterpenoids. (3) Preliminary studies have shown the important contributions of triterpenoids in terms of hypoglycemic, lipid-lowering, and antioxidant effects and other aspects, but more research on their mechanism of structure and biological activity is still needed. (4) Strong evidence verifying these pharmacological activities is limited. Therefore, virtual docking, animal experiments, and clinical trials are needed to further gain insights into the biological effects, bioavailability, and safety of these triterpenes or saponins. (5) Although some studies focused on the application of triterpenoids from *C. paliurus*, many potential compounds, such as sweet substances and biologically active compounds, wait comprehensive excavation and research. (6) Industries should be encouraged to promote the commercial application of *C. paliurus* triterpenoids in food and medicine. Greater emphasis should be placed on the improvement and upgrading of enterprise standards and regulations. Despite multiple challenges, the great potential for the development of triterpenoids as active ingredients of *C. paliurus* in the field of food and medicine cannot be ignored.

In this review, we have summarized 177 triterpenoids from different parts of *C. paliurus*. We elucidated the structures of these compounds

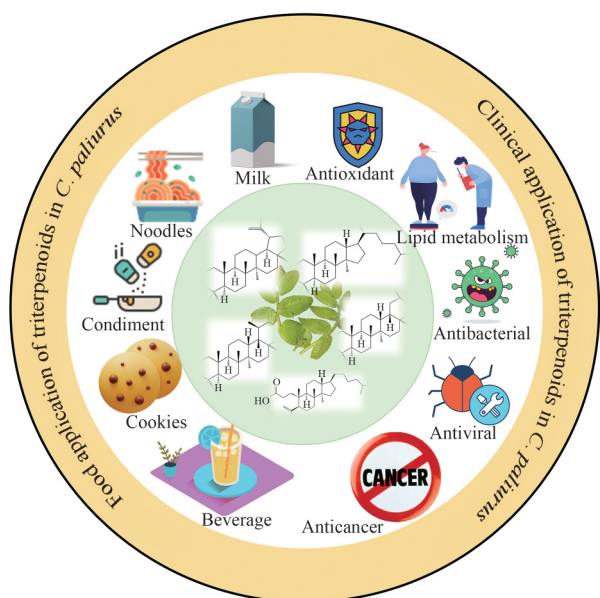


Fig. 9 Future development and application of triterpenoids in *C. paliurus*.

and inferred their biosynthesis. The biological activities of these compounds and triterpenoid-rich extracts were discussed, including antidiabetes, antihyperlipidemia, anti-inflammatory, anticancer or cytotoxicity, antioxidation activities, etc. Applications of related triterpenoids in the fields of food and medicine have been described. *C. paliurus* can be regarded as an important supplement to the food market, and it offers a diverse and invaluable resource for the development and optimization of natural products and new drugs. Further research on the quality control, toxicity studies, and pharmacological activity of triterpenoids from *C. paliurus* is needed to establish a strong theoretical foundation for the market development of this plant.

Conflict of interest

Jianhua Xie is an editorial board member for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare there is no conflict of interest.

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References

- [1] Z.L. Chen, Y.Q. Jian, Q. Wu, et al., *Cyclocarya paliurus* (Batalin) Iljinskaja: botany, ethnopharmacology, phytochemistry and pharmacology, *J. Ethnopharmacol.* 285 (2022) 114912. <https://doi.org/10.1016/j.jep.2021.114912>.
- [2] L.M. Xie, M.Y. Shen, R. Huang, et al., Apoptosis of colon cancer CT-26 cells induced polysaccharide from *Cyclocarya paliurus* and its phosphorylated derivative via intrinsic mitochondrial passway, *Food Sci. Hum. Wellness.* 12(5) (2023) 1545-1556. <https://doi.org/10.1016/j.fshw.2023.02.002>.
- [3] Y. Yu, H.B. Zhu, M.Y. Shen, et al., Sulfated *Cyclocarya paliurus* polysaccharides exert immunomodulatory potential on macrophages via Toll-like receptor 4 mediated MAPK/NF- κ B signaling pathways, *Food Sci. Hum. Wellness.* 13(1) (2024) 115-123. <https://doi.org/10.26599/FSHW.2022.9250009>.
- [4] Y. Liu, Q. Liang, D.B. Tang, et al., Development of suspension culture technology and hormone effects on anthocyanin biosynthesis for red *Cyclocarya paliurus* cells, *Plant Cell, Tissue Organ. Cult.* 149(1/2) (2022) 175-195. <https://doi.org/10.1007/s11240-021-02215-y>.
- [5] L.P. Zhu, S.Y. Fang, X.C. Lu, et al., Structurally diverse glycosides with α -glucosidase inhibitory properties from water extract of the leaves of *Cyclocarya paliurus*, *Fitoterapia* 167 (2023) 105473. <https://doi.org/10.1016/j.fitote.2023.105473>.
- [6] X.X. Zhang, Y.L. Ji, L.P. Zhu, et al., Arjunolic acid from *Cyclocarya paliurus* ameliorates diabetic retinopathy through AMPK/mTOR/HO-1 regulated autophagy pathway, *J. Ethnopharmacol.* 284 (2022) 114772. <https://doi.org/10.1016/j.jep.2021.114772>.
- [7] L. Liang, Y.C. Liu, Y.X. Liu, et al., Untargeted metabolomics analysis based on HS-SPME-GC-MS and UPLC-Q-TOF/MS reveals the contribution of stem to the flavor of *Cyclocarya paliurus* herbal extract, *LWT-Food Sci. Technol.* 167 (2022) 113819. <https://doi.org/10.1016/j.lwt.2022.113819>.
- [8] L. Zhang, Y. Liu, Z.J. Zhang, et al., Physiological response and molecular regulatory mechanism reveal a positive role of nitric oxide and hydrogen sulfide applications in salt tolerance of *Cyclocarya paliurus*, *Front. Plant Sci.* 14 (2023) 1162. <https://doi.org/10.3389/fpls.2023.1211162>.
- [9] X. Wang, L. Tang, W.X. Ping, et al., Progress in research on the alleviation of glucose metabolism disorders in type 2 diabetes using *Cyclocarya paliurus*, *Nutrients* 14(15) (2022) 3169. <https://doi.org/10.3390/nu14153169>.
- [10] X.R. Zheng, C.L. Liu, M.J. Zhang, et al., First report of leaf blight of *Cyclocarya paliurus* caused by *Nigrospora sphaerica* in China, *Crop Prot.* 140 (2021) 105453. <https://doi.org/10.1016/j.cpro.2020.105453>.
- [11] Y.M. Shao, T.T. Li, C.E. Wu, et al., A review on extraction and biological activities of triterpenoid from *Cyclocarya paliurus*, *Food Rev. Int.* 40(5) (2023) 1374-1394. <https://doi.org/10.1080/87559129.2023.2213307>.
- [12] X.H. Zheng, H.B. Xiao, J.N. Chen, et al., Metabolome and whole-transcriptome analyses reveal the molecular mechanisms underlying hypoglycemic nutrient metabolites biosynthesis in *Cyclocarya paliurus* leaves during different harvest stages, *Front. Nutr.* 9 (2022) 851569. <https://doi.org/10.3389/fnut.2022.851569>.
- [13] R. Gui, Y.K. Wang, J.P. Wu, et al., *Cyclocarya paliurus* leaves alleviate hyperuricemic nephropathy via modulation of purine metabolism, antiinflammation, and antifibrosis, *J. Funct. Foods* 103 (2023) 105485. <https://doi.org/10.1016/j.jff.2023.105485>.
- [14] H.Y. Lu, M.Y. Shen, Y. Chen, et al., Alleviative effects of natural plant polysaccharides against DSS-induced ulcerative colitis via inhibiting inflammation and modulating gut microbiota, *Food Res. Int.* 167 (2023) 112630. <https://doi.org/10.1016/j.foodres.2023.112630>.
- [15] Y.Y. Zhu, X.H. Li, C.Y. Da, et al., Effects of *Cyclocarya paliurus* (Batal.) extracts on oxidative stability and sensory quality in meat products (frankfurters), *Foods* 11(22) (2022) 3721. <https://doi.org/10.3390/foods11223721>.
- [16] W.C. Tu, R.H. Luo, E. Yuan, et al., Triterpene constituents from the fruits of *Cyclocarya paliurus* and their anti-HIV-1IIB activity, *Nat. Prod. Res.* 37(11) (2022) 1787-1796. <https://doi.org/10.1080/14786419.2022.2120874>.
- [17] L. Zhong, X.J. Peng, C.T. Wu, et al., Polysaccharides and flavonoids from *Cyclocarya paliurus* modulate gut microbiota and attenuate hepatic steatosis, hyperglycemia, and hyperlipidemia in nonalcoholic fatty liver disease rats with type 2 diabetes mellitus, *Int. J. Diabetes. Dev. C.* 43(2) (2022) 317-327. <https://doi.org/10.1007/s13410-022-01080-5>.
- [18] Y.P. Tong, X. Li, Z.P. Zhu, et al., Extraction and identification of antioxidant ingredients from *Cyclocarya paliurus* (Batal.) Iljinsk using UHPLC-Q-Orbitrap-MS/MS-based molecular networking, *J. Chem.* 2022 (2022) 1-14. <https://doi.org/10.1155/2022/8260379>.
- [19] W.Y. Wang, D.Y. Huang, Y.B. Yu, et al., A modular approach for the synthesis of natural and artificial terpenoids, *Angew. Chem. Int. Ed.* 62(37) (2023) e202307626. <https://doi.org/10.1002/anie.202307626>.
- [20] P. Darshani, S. Sen Sarma, A.K. Srivastava, et al., Anti-viral triterpenes: a review, *Phytochem. Rev.* 21(6) (2022) 1761-1842. <https://doi.org/10.1007/s11101-022-09808-1>.
- [21] R.K. Joshi, Bioactive usual and unusual triterpenoids derived from natural sources used in traditional medicine, *Chem. Biodivers.* 20(2) (2023) e202200853. <https://doi.org/10.1002/cbdv.202200853>.
- [22] M. Gleńsk, M.K. Dudek, A. Rybacka, et al., Triterpenoids from strawberry *Fragaria $\times$ ananassa* Duch. cultivar Senga Sengana leaves, *Ind. Crops Prod.* 169 (2021) 113668. <https://doi.org/10.1016/j.indcrop.2021.113668>.
- [23] J.H. Ma, D. Hu, L.L. Deng, et al., Pentacyclic triterpenoids from *Sabia discolor* Dunn and their α -glucosidase inhibitory activities, *Molecules* 27(7) (2022) 2161. <https://doi.org/10.3390/molecules27072161>.
- [24] J.J. Cui, Y.S. Han, B. Zhou, et al., Ursane and 24-noroleanane-type triterpenoids with anti-HIV activity from the twigs and leaves of *Antirhea chinensis*, *Chem. Biodivers.* 19(10) (2022) e202200716. <https://doi.org/10.1002/cbdv.202200716>.
- [25] P. Matos, M.T. Batista, A. Figueirinha, A review of the ethnomedicinal uses, chemistry, and pharmacological properties of the genus *Acanthus* (Acanthaceae), *J. Ethnopharmacol.* 293 (2022) 115271. <https://doi.org/10.1016/j.jep.2022.115271>.
- [26] N. Bhardwaj, A. Sharma, N. Tripathi, et al., New cycloartane triterpenoids from *Dysoxylum malabaricum* and their cytotoxic evaluation, *Steroids* 200 (2023) 109315. <https://doi.org/10.1016/j.steroids.2023.109315>.
- [27] J.C. Wei, H.H. Huang, N.F. Zhong, et al., Euphorfistrines A-G, cytotoxic and AChE inhibiting triterpenoids from the roots of *Euphorbia fischeriana*, *Bioorg. Chem.* 116 (2021) 105395. <https://doi.org/10.1016/j.bioorg.2021.105395>.
- [28] J.J. Zhao, Z.T. Wang, D.P. Xu, et al., Advances on *Cyclocarya paliurus* polyphenols: extraction, structures, bioactivities and future perspectives, *Food Chem.* 396 (2022) 133667. <https://doi.org/10.1016/j.foodchem.2022.133667>.

- [29] M.U. Kakar, M. Naveed, M. Saeed, et al., A review on structure, extraction, and biological activities of polysaccharides isolated from *Cyclocarya paliurus* (Batalin) Iljinskaja, *Int. J. Biol. Macromol.* 156 (2020) 420-429. <https://doi.org/10.1016/j.ijbiomac.2020.04.022>.
- [30] W.W. Peng, S.M. Zhao, C.J. Ji, et al., Cyclopalitins A B, nortriterpenoids from aerial parts of *Cyclocarya paliurus*, *Phytochem. Lett.* 31 (2019) 114-117. <https://doi.org/10.1016/j.phytol.2019.03.017>.
- [31] Z.L. Chen, Q. Wu, J. Wu, et al., Qingqianlianus A-N, 3,4-seco-dammarane triterpenoids from the leaves of *Cyclocarya paliurus* and their biological activities, *Arabian J. Chem.* 16(1)(2023) 104441. <https://doi.org/10.1016/j.arabjc.2022.104441>.
- [32] E.J. Kennelly, L.N. Cai, L.N. Long, et al., Novel highly sweet seco-dammarane glycosides from *pterocarya paliurus*, *J. Agric. Food. Chem.* 43 (1995) 2602-2607. <https://doi.org/10.1021/jf00058a009>.
- [33] R.G. Shu, C.R. Xu, L.N. Li, et al., Cyclocarioside II, cyclocarioside III: two seco-dammarane triterpenoid saponins from *Cyclocarya paliurus*, *Planta Med.* 61 (1995) 551-553. <https://doi.org/10.1055/s-2006-959369>.
- [34] H.H. Sun, J. Tan, W.Y. Lü, et al., Hypoglycemic triterpenoid glycosides from *Cyclocarya paliurus* (sweet tea tree), *Bioorg. Chem.* 95 (2020) 103493. <https://doi.org/10.1016/j.bioorg.2019.103493>.
- [35] H. Fuchino, T. Satoh, M. Yokochi, et al., Chemical and petroleum engineering chemical evaluation of *Betula* species in Japan. v. constituents of *Betula ovalifolia*, *Chem. Pharm. Bull.* 46(1) (1998) 169-170. <https://doi.org/10.1248/cpb.46.169>.
- [36] M.E. Wright, J. Byrd, C. He, et al., Synthesis of cyclocaric acid A and comparison to material from *Cyclocarya paliurus*, *J. Nat. Prod.* 77(11) (2014) 2566-2569. <https://doi.org/10.1021/np500575q>.
- [37] Z.F. Wu, F.C. Meng, L.J. Cao, et al., Triterpenoids from *Cyclocarya paliurus* and their inhibitory effect on the secretion of apolipoprotein B48 in Caco-2 cells, *Phytochemistry* 142 (2017) 76-84. <https://doi.org/10.1016/j.phytochem.2017.06.015>.
- [38] W.W. Peng, Z.Y. Zhang, C.J. Ji, et al., Chemical constituents from the aerial part of *Cyclocarya paliurus* (Batal.) Iljinsk (Juglandaceae), *Biochem. Syst. Ecol.* 78 (2018) 110-112. <https://doi.org/10.1016/j.bse.2018.04.012>.
- [39] B.S. Cui, S. Li, Chemical constituents from leaves of *Cyclocarya paliurus*, *Zhong Cao Yao* 43 (2012) 2132-2136. <https://doi.org/10.11926/jtsb.3820>.
- [40] H.A. Noushahi, A.H. Khan, U.F. Noushahi, et al., Biosynthetic pathways of triterpenoids and strategies to improve their biosynthetic efficiency, *Plant Growth Regul.* 97(3) (2022) 439-454. <https://doi.org/10.1007/s10725-022-00818-9>.
- [41] X.T. Zhang, M.J. Zheng, A.M. Fu, et al., Natural sesquiterpenoids, diterpenoids, sesterterpenoids, and triterpenoids with intriguing structures from 2017 to 2022, *Chin. J. Chem.* 41(22) (2023) 3115-3132. <https://doi.org/10.1002/cjoc.202300275>.
- [42] L. Ruzicka The isoprene rule and the biogenesis of terpenic compounds, *Experientia* 9(10) (1953) 357-367. <https://doi.org/10.1007/bf02167631>.
- [43] A. Eschenmoser, L. Ruzicka, O. Jeger, et al., Eine stereochemische interpretation der biogenetischen isoprenregel bei den triterpenen, *Helv. Chim. Acta* 38(7) (1955) 1890-1904. <https://doi.org/10.1002/hlca.19550380728>.
- [44] R. Xu, G.C. Fazio, S.T. Matsuda, On the origins of triterpenoid skeletal diversity, *Phytochemistry*. 65(3) (2004) 261-291. <https://doi.org/10.1016/j.phytochem.2003.11.014>.
- [45] L.Y. Yang, Y.Y. Gu, J.Q. Zhou, et al., Whole-genome identification and analysis of multiple gene families reveal candidate genes for theasaponin biosynthesis in *Camellia oleifera*, *Int. J. Mol. Sci.* 23(12) (2022) 6393. <https://doi.org/10.3390/ijms23126393>.
- [46] J.J. Chen, Z. Zhang, Y. Wang, et al., Transcriptome analysis of *Antrodia cinnamomea* Mycelia from different wood substrates, *Mycobiology* 51(1) (2023) 49-59. <https://doi.org/10.1080/12298093.2023.2175434>.
- [47] H. Seki, K. Tamura, T. Muranaka, P450s and UGTs: key players in the structural diversity of triterpenoid saponins, *Plant Cell Physiol.* 56(8) (2015) 1463-1471. <https://doi.org/10.1093/pcp/pcv062>.
- [48] J.M. Augustin, V. Kuzina, S.B. Andersen, et al., Molecular activities, biosynthesis and evolution of triterpenoid saponins, *Phytochemistry* 72(6) (2011) 435-457. <https://doi.org/10.1016/j.phytochem.2011.01.015>.
- [49] J. Vincken, L. Heng, A. Groot, et al., Saponins, classification and occurrence in the plant kingdom, *Phytochemistry* 68(3) (2007) 275-297. <https://doi.org/10.1016/j.phytochem.2006.10.008>.
- [50] D.R. Phillips, J.M. Rasbery, B. Bartel, et al., Biosynthetic diversity in plant triterpene cyclization, *Curr. Opin. Plant Biol.* 9(3) (2006) 305-314. <https://doi.org/10.1016/j.pbi.2006.03.004>.
- [51] J. Ryu, J. Park, J. Eun, et al., A dammarane glycoside from Korean red ginseng, *Phytochemistry* 44 (1997) 931-933. [https://doi.org/10.1016/S0031-9422\(96\)00661-9](https://doi.org/10.1016/S0031-9422(96)00661-9).
- [52] W. Ma, M. Mizutani, K.E. Malterud, et al., Saponins from the roots of *Panax notoginseng*, *Phytochemistry* 52 (1999) 1133-1139. [https://doi.org/10.1016/S0031-9422\(99\)00364-7](https://doi.org/10.1016/S0031-9422(99)00364-7).
- [53] A. Chakravarty, T. Sarkar, K. Masuda, et al., Bacopaside I and II two pseudojubilogenin glycosides from *Bacopa monniera*, *Phytochemistry* 58 (2001) 553-556. [https://doi.org/10.1016/S0031-9422\(01\)00275-8](https://doi.org/10.1016/S0031-9422(01)00275-8).
- [54] W. Aalbersber, Y. Sing, Dammarane triterpenoids from *Dysoxylum richii*, *Phytochemistry* 30 (1991) 921-926. [https://doi.org/10.1016/0031-9422\(91\)85280-D](https://doi.org/10.1016/0031-9422(91)85280-D).
- [55] A. Rouf, Y. Ozaki, M. Rashid, et al., Dammarane derivatives from the dried fruits of *Forsythia suspensa*, *Phytochemistry* 56 (2001) 815-818. [https://doi.org/10.1016/S0031-9422\(01\)00028-0](https://doi.org/10.1016/S0031-9422(01)00028-0).
- [56] L.P. Zhu, H.M. Yang, X. Zheng, et al., Four new dammarane triterpenoid glycosides from the leaves of *Cyclocarya paliurus* and their SIRT1 activation activities, *Fitoterapia* 154 (2021) 105003. <https://doi.org/10.1016/j.fitote.2021.105003>.
- [57] Y.J. Chen, L. Na, J.P. Fan, et al., Seco-dammarane triterpenoids from the leaves of *Cyclocarya paliurus*, *Phytochemistry* 145 (2018) 85-92. <https://doi.org/10.1016/j.phytochem.2017.10.013>.
- [58] S. Lodeiro, Q. Xiong, W.K. Wilson, et al., An oxidosqualene cyclase makes numerous products by diverse mechanisms a challenge to prevailing concepts of triterpene biosynthesis, *J. Am. Chem. Soc.* 129 (2007) 11213-11222. <https://doi.org/10.1021/ja073133u>.
- [59] T. Biswas, U.N. Dwivedi, Plant triterpenoid saponins: biosynthesis, *in vitro* production, and pharmacological relevance, *Protoplasma*. 256(6) (2019) 1463-1486. <https://doi.org/10.1007/s00709-019-01411-0>.
- [60] W. Liu, Y. Wu, Y.L. Hu, et al., Effects of *Cyclocarya paliurus* aqueous and ethanol extracts on glucolipid metabolism and the underlying mechanisms: a meta-analysis and systematic review, *Front. Nutr.* 7 (2020) 605605. <https://doi.org/10.3389/fnut.2020.605605>.
- [61] Y.N. Chao, T.W. Gu, Z. Zhang, et al., The role of miRNAs carried by extracellular vesicles in type 2 diabetes and its complications, *J. Diabetes*. 15(10) (2023) 838-852. <https://doi.org/10.1111/1753-0407.13456>.
- [62] A. Ghasemi, S. Jeddi, Streptozotocin as a tool for induction of rat models of diabetes, *Excli. J.* 22 (2022) 274-294. <https://doi.org/10.17179/excli2022-5720>.
- [63] Q.Q. Wang, C.H. Jiang, S.Z. Fang, et al., Antihyperglycemic, antihyperlipidemic and antioxidant effects of ethanol and aqueous extracts of *Cyclocarya paliurus* leaves in type 2 diabetic rats, *J. Ethnopharmacol.* 150(3) (2013) 1119-1127. <https://doi.org/10.1016/j.jep.2013.10.040>.
- [64] L.C. Zhao, X. Wang, J.X. Li, et al., Effect of *Cyclocarya paliurus* on hypoglycemic effect in type 2 diabetic mice, *Med. Sci. Monit.* 25 (2019) 2976-2983. <https://doi.org/10.12659/msm.913368>.
- [65] N.F. Sangweni, P.V. Dlodla, R.A. Mosa, et al., Lanosteryl triterpenes from *Protosorus longifolia* as a cardioprotective agent: a mini review, *Heart Fail Rev.* 24(1) (2018) 155-166. <https://doi.org/10.1007/s10741-018-9733-9>.
- [66] Y. Wang, X.J. Zheng, L.Y. Li, et al., *Cyclocarya paliurus* ethanol leaf extracts protect against diabetic cardiomyopathy in db/db mice via regulating PI3K/Akt/NF- κ B signaling, *Food Nutr. Res.* 64 (2020) 4267. <https://doi.org/10.29219/fnr.v64.4267>.
- [67] J.Y. Kim, S.H. Lee, E.H. Song, et al., A critical role of STAT1 in streptozotocin-induced diabetic liver injury in mice: controlled by ATF3, *Cell Signalling* 21(12) (2009) 1758-1767. <https://doi.org/10.1016/j.cellsig.2009.07.011>.
- [68] C.H. Jiang, Y.T. Wang, Q.M. Jin, et al., *Cyclocarya paliurus* triterpenoids improve diabetes-induced hepatic inflammation via the Rho-kinase-dependent pathway, *Front. Pharmacol.* 10 (2019) 811. <https://doi.org/10.3389/fphar.2019.00811>.
- [69] J.J. Cao, R.D. Zheng, X.Y. Chang, et al., *Cyclocarya paliurus* triterpenoids suppress hepatic gluconeogenesis via AMPK-mediated cAMP/PKA/CREB pathway, *Phytomedicine* 102 (2022) 154175. <https://doi.org/10.1016/j.phymed.2022.154175>.
- [70] Y.X. Zhang, J. Hai, M. Cao, et al., Silibinin ameliorates steatosis and insulin resistance during non-alcoholic fatty liver disease development partly through targeting IRS-1/PI3K/Akt pathway, *Int. Immunopharmacol.* 17(3) (2013) 714-720. <https://doi.org/10.1016/j.intimp.2013.08.019>.
- [71] X. Zheng, M.G. Zhao, C.H. Jiang, et al., Triterpenic acids-enriched fraction from *Cyclocarya paliurus* attenuates insulin resistance and hepatic

- steatosis via PI3K/Akt/GSK3 β pathway, *Phytomedicine* 66 (2020) 153130. <https://doi.org/10.1016/j.phymed.2019.153130>.
- [72] S.C. Pal, N. Méndez Sánchez, Insulin resistance and adipose tissue interactions as the cornerstone of metabolic (dysfunction)-associated fatty liver disease pathogenesis, *World J. Gastroenterol.* 29(25) (2023) 3999–4008. <https://doi.org/10.3748/wjg.v29.i25.3999>.
- [73] G. López Lluch, H. Yoshitomi, R. Tsuru, et al., *Cyclocarya paliurus* extract activates insulin signaling via Sirtuin1 in C2C12 myotubes and decreases blood glucose level in mice with impaired insulin secretion, *PLoS One* 12(8) (2017) e0183988. <https://doi.org/10.1371/journal.pone.0183988>.
- [74] K. Umanath, J.B. Lewis, Update on diabetic nephropathy: core curriculum 2018, *Am. J. Kidney Dis.* 71(6) (2018) 884–895. <https://doi.org/10.1053/j.ajkd.2017.10.026>.
- [75] X.X. Zhang, C.H. Jiang, Y. Liu, et al., *Cyclocarya paliurus* triterpenic acids fraction attenuates kidney injury via AMPK-mTOR-regulated autophagy pathway in diabetic rats, *Phytomedicine* 64 (2019) 153060. <https://doi.org/10.1016/j.phymed.2019.153060>.
- [76] R. Yang, S.S. Xu, X.X. Zhang, et al., *Cyclocarya paliurus* triterpenoids attenuate glomerular endothelial injury in the diabetic rats via ROCK pathway, *J. Ethnopharmacol.* 291 (2022) 115127. <https://doi.org/10.1016/j.jep.2022.115127>.
- [77] Z.J. Fang, S.N. Shen, J.M. Wang, et al., Triterpenoids from *Cyclocarya paliurus* that enhance glucose uptake in 3T3-L1 adipocytes, *Molecules* 24(1) (2019) 187. <https://doi.org/10.3390/molecules24010187>.
- [78] C.Q. Fang, Y. Teng, Y.T. Wang, et al., Arjunolic acid from *Cyclocarya paliurus* selectively inhibits glucagon secretion from α cells and ameliorates diabetes via ephrin-A1 and EphA4 interaction, *J. Funct. Foods* 99 (2022) 105323. <https://doi.org/10.1016/j.jff.2022.105323>.
- [79] C.L. Zhang, M.Z. Xu, C.H. He, et al., Discovery of 1'-(1-phenylcyclopropane-carbonyl)-3H-spiro[isobenzofuran-1,3'-pyrrolidin]-3-one as a novel steroid mimetic scaffold for the potent and tissue-specific inhibition of 11 β -HSD1 using a scaffold-hopping approach, *Bioorganic Med. Chem. Lett.* 69 (2022) 128782. <https://doi.org/10.1016/j.bmcl.2022.128782>.
- [80] H. Yan, X. Li, W. Ni, et al., Phytochemicals from the leaves of *Cyclocarya paliurus* and their 11 β -HSD1 enzyme inhibitory effects, *Chem. Biodivers.* 18(1) (2020) e2000772. <https://doi.org/10.1002/cbdv.202000772>.
- [81] Y. Liu, X.X. Zhang, S.S. Xu, et al., New triterpenoids from the *Cyclocarya paliurus* (Batalin) Iljinskaja and their anti-fibrotic activity, *Phytochemistry* 204 (2022) 113434. <https://doi.org/10.1016/j.phytochem.2022.113434>.
- [82] X.X. Zhang, Y. Liu, S.S. Xu, et al., Asiatic acid from *Cyclocarya paliurus* regulates the autophagy-lysosome system via directly inhibiting TGF- β type I receptor and ameliorates diabetic nephropathy fibrosis, *Food Funct.* 13(10) (2022) 5536–5546. <https://doi.org/10.1039/d1fo02445k>.
- [83] K.N. Zhu, C.H. Jiang, Y.S. Tian, et al., Two triterpenoids from *Cyclocarya paliurus* (Batal) Iljinsk (Juglandaceae) promote glucose uptake in 3T3-L1 adipocytes: the relationship to AMPK activation, *Phytomedicine* 22(9) (2015) 837–846. <https://doi.org/10.1016/j.phymed.2015.05.058>.
- [84] S. Zhou, Z.Y. Li, H.Z. Song, et al., Recent advances in tea seeds (*Camellia Sinensis* (L.) O. Kuntze): active ingredients, health effects, and potential applications, *Trends Food Sci. Technol.* 141 (2023) 104192. <https://doi.org/10.1016/j.tifs.2023.104192>.
- [85] T.Y. Wu, N. Tien, C.L. Lin, et al., Influence of antipsychotic medications on hyperlipidemia risk in patients with schizophrenia: evidence from a population-based cohort study and *in vitro* hepatic lipid homeostasis gene expression, *Front. Med.* 10 (2023) 7977. <https://doi.org/10.3389/fmed.2023.1137977>.
- [86] V.H. Jeremy, S. Duval, L. Russell V, et al., Association of cardiovascular disease risk factors with socio-demographics and health beliefs among a community-based sample of african americans in minnesota, *Mayo Clinic Proceedings* 97(1) (2022) 46–56. <https://doi.org/10.1016/j.mayocp.2021.08.027>.
- [87] A. Gugliucci, Triglyceride-rich lipoprotein metabolism: key regulators of their flux, *J. Clin. Med.* 12(13) (2023) 4399. <https://doi.org/10.3390/jcm12134399>.
- [88] N. Mena Vázquez, R. Redond Rodríguez, J. Rioja, et al., Postprandial hyperlipidemia: association with inflammation and subclinical atherosclerosis in patients with rheumatoid arthritis, *Biomedicines* 10(1) (2022) 133. <https://doi.org/10.3390/biomedicines10010133>.
- [89] Z.F. Wu, T.H. Gao, R.L. Zhong, et al., Antihyperlipidaemic effect of triterpenic acid-enriched fraction from *Cyclocarya paliurus* leaves in hyperlipidaemic rats, *Pharm. Biol.* 55(1) (2017) 712–721. <https://doi.org/10.1080/13880209.2016.1267231>.
- [90] Y.L. Ma, C.H. Jiang, N. Yao, et al., Antihyperlipidemic effect of *Cyclocarya paliurus* (Batal.) Iljinskaja extract and inhibition of apolipoprotein B48 overproduction in hyperlipidemic mice, *J. Ethnopharmacol.* 166 (2015) 286–296. <https://doi.org/10.1016/j.jep.2015.03.030>.
- [91] C.H. Jiang, Q.Q. Wang, Y.J. Wei, et al., Cholesterol-lowering effects and potential mechanisms of different polar extracts from *Cyclocarya paliurus* leave in hyperlipidemic mice, *J. Ethnopharmacol.* 176 (2015) 17–26. <https://doi.org/10.1016/j.jep.2015.10.006>.
- [92] X.M. Yao, Z. Lin, C.H. Jiang, et al., *Cyclocarya paliurus* prevents high fat diet induced hyperlipidemia and obesity in Sprague-Dawley rats, *Can. J. Physiol. Pharmacol.* 93 (2015) 677–686. <https://doi.org/10.1139/cjpp-2014-0477>.
- [93] H. Tilg, A.R. Moschen, Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis, *Hepatology* 52(5) (2010) 1836–1846. <https://doi.org/10.1002/hep.24001>.
- [94] C. Postic, J. Girard, The role of the lipogenic pathway in the development of hepatic steatosis, *Diabetes Metab.* 34 (2008) 643–648. [https://doi.org/10.1016/S1262-3636\(08\)74599-3](https://doi.org/10.1016/S1262-3636(08)74599-3).
- [95] Z. Lin, Z.F. Wu, C.H. Jiang, et al., The chloroform extract of *Cyclocarya paliurus* attenuates high-fat diet induced non-alcoholic hepatic steatosis in Sprague Dawley rats, *Phytomedicine* 23(12) (2016) 1475–1483. <https://doi.org/10.1016/j.phymed.2016.08.003>.
- [96] M.G. Zhao, X.P. Sheng, Y.P. Huang, et al., Triterpenic acids-enriched fraction from *Cyclocarya paliurus* attenuates non-alcoholic fatty liver disease via improving oxidative stress and mitochondrial dysfunction, *Biomed. Pharmacother.* 104 (2018) 229–239. <https://doi.org/10.1016/j.biopha.2018.03.170>.
- [97] X. Zheng, X.G. Zhang, Y. Liu, et al., Arjunolic acid from *Cyclocarya paliurus* ameliorates nonalcoholic fatty liver disease in mice via activating Sirt1/AMPK, triggering autophagy and improving gut barrier function, *J. Funct. Foods* 86 (2021) 104686. <https://doi.org/10.1016/j.jff.2021.104686>.
- [98] L. Xiong, K.H. Ouyang, Y. Jiang, et al., Chemical composition of *Cyclocarya paliurus* polysaccharide and inflammatory effects in lipopolysaccharide-stimulated RAW264.7 macrophage, *Int. J. Biol. Macromol.* 107 (2018) 1898–1907. <https://doi.org/10.1016/j.ijbiomac.2017.10.055>.
- [99] W. Liu, S.P. Deng, D.X. Zhou, et al., 3,4-Seco-dammarane triterpenoid saponins with anti-inflammatory activity isolated from the leaves of *Cyclocarya paliurus*, *J. Agric. Food Chem.* 68(7) (2020) 2041–2053. <https://doi.org/10.1021/acs.jafc.9b06898>.
- [100] A.K. So, F. Martinon, Inflammation in gout: mechanisms and therapeutic targets, *Nat. Rev. Rheumatol.* 13(11) (2017) 639–647. <https://doi.org/10.1038/nrrheum.2017.155>.
- [101] D.X. Lou, X.G. Zhang, C.H. Jiang, et al., 3 β ,23-Dihydroxy-12-ene-28-ursolic acid isolated from *Cyclocarya paliurus* alleviates NLRP3 inflammasome-mediated gout via PI3K-AKT-mTOR-dependent autophagy, *Evid. -Based Compl. Alt. Med.* 2022 (2022) 1–15. <https://doi.org/10.1155/2022/5541232>.
- [102] Y. Han, C. Yuan, X. Zhou, et al., Anti-inflammatory activity of three triterpene from *Hippophae rhamnoides* L. in lipopolysaccharide-stimulated RAW264.7 cells, *Int. J. Mol. Sci.* 22(21) (2021) 12009. <https://doi.org/10.3390/ijms222112009>.
- [103] M.M. Zhou, S.Y. Quek, X.L. Shang, et al., Geographical variations of triterpenoid contents in *Cyclocarya paliurus* leaves and their inhibitory effects on HeLa cells, *Ind. Crops Prod.* 162 (2021) 113314. <https://doi.org/10.1016/j.indcrop.2021.113314>.
- [104] H.H. Sun, W.Y. Lü, J. Tan, et al., Cytotoxic triterpenoid glycosides from leaves of *Cyclocarya paliurus*, *Nat. Prod. Res.* 35(21) (2020) 4018–4024. <https://doi.org/10.1080/14786419.2020.1756801>.
- [105] T. Landete Castillejos, A. Rossetti, A.J. Garcia, et al., From a general anti-cancer treatment to antioxidant or deer osteoporosis: the consequences of antler as the fastest-growing tissue, *Anim. Prod. Sci. SI* (2022) AN22176. <https://doi.org/10.1071/an22176>.
- [106] H.M. Yang, Z.Q. Yin, M.G. Zhao, et al., Pentacyclic triterpenoids from *Cyclocarya paliurus* and their antioxidant activities in FFA-induced HepG2 steatosis cells, *Phytochemistry* 151 (2018) 119–127. <https://doi.org/10.1016/j.phytochem.2018.03.010>.
- [107] Y.R. Wang, B.S. Cui, S.W. Han, et al., New dammarane triterpenoid saponins from the leaves of *Cyclocarya paliurus*, *J. Asian Nat. Prod. Res.* 20(11) (2018) 1019–1027. <https://doi.org/10.1080/10286020.2018.1457653>.
- [108] Y.H. Chen, X. Zhang, M. Zhang, et al., A transcriptome analysis of the ameliorate effect of *Cyclocarya paliurus* triterpenoids on ethanol stress in

- Saccharomyces cerevisiae*, World J. Microbiol. Biotechnol. 34(12)(2018) 182. <https://doi.org/10.1007/s11274-018-2561-1>.
- [109] Z.C. Shi, X.Q. Huang, Y.N. Zhao, et al., Construction of a novel ursolic acid-based supramolecular gel for efficient removal of iodine from solution, Environ. Res. 235 (2023) 116617. <https://doi.org/10.1016/j.envres.2023.116617>.
- [110] W.H. Chu, P. Wang, Z. Ma, et al., Lupeol-loaded chitosan-Ag⁺ nanoparticle/sericin hydrogel accelerates wound healing and effectively inhibits bacterial infection, Int. J. Biol. Macromol. 243 (2023) 125310. <https://doi.org/10.1016/j.ijbiomac.2023.125310>.
- [111] Y.Q. Liu, K.K. Liu, X.L. Wang, et al., Co-assembling nanoparticles of asiatic acid and caffeic acid phenethyl ester: characterization, stability and bioactivity *in vitro*, Food Chem. 402 (2023) 134409. <https://doi.org/10.1016/j.foodchem.2022.134409>.
- [112] C.H. Yuan, W.W. Fan, T.F. Zhou, et al., Ligand-free high loading capacity ursolic acid self-carried nanovesicles enable hepatocyte targeting *via* absorbing apolipoproteins, Int. J. Pharm. 638 (2023) 122931. <https://doi.org/10.1016/j.ijpharm.2023.122931>.
- [113] S.N. Gao, M.Y. Yang, Z.S. Luo, et al., Soy protein/chitosan-based microsphere as stable biocompatible vehicles of oleanolic acid: an emerging alternative enabling the quality maintenance of minimally processed produce, Food Hydrocoll. 124 (2022) 107325. <https://doi.org/10.1016/j.foodhyd.2021.107325>.
- [114] R.L. Liu, L.P. Zhang, S.Y. Xiao, et al., Ursolic acid, the main component of blueberry cuticular wax, inhibits *Botrytis cinerea* growth by damaging cell membrane integrity, Food Chem. 415 (2023) 135753. <https://doi.org/10.1016/j.foodchem.2023.135753>.
- [115] Y.G. Liu, H.P. Xia, S.Y. Guo, et al., Effect and mechanism of edible oil co-digestion on the bioaccessibility and bioavailability of ursolic acid, Food Chem. 423 (2023) 136220. <https://doi.org/10.1016/j.foodchem.2023.136220>.
- [116] R.G. Shu, C.R. Xu, L.N. Li, Studies on the sweet principles from the leaves of *Cyclocarya paliurus* (Batal.) Iljinsk, Acta Pharmacol. Sin. 30(10) (1995) 757-761. <https://doi.org/10.16438/j.0513-4870.1995.10.008>.
- [117] H. Yamada, M. Nishizawa, Syntheses of sweet tasting diterpene glycosides, baiyunoside and analogs, Tetrahedron 48(15) (1992) 3021-3044. [https://doi.org/10.1016/S0040-4020\(01\)92246-X](https://doi.org/10.1016/S0040-4020(01)92246-X).
- [118] World Health Organization, WHO advises not to use non-sugar sweeteners for weight control in newly released guideline, 2023, available from <https://www.who.int/news/item/15-05-2023-who-advises-not-to-use-non-sugar-sweeteners-for-weight-control-in-newly-released-guideline>.
- [119] M. Fernández Navarro, J. Peragón, F.J. Esteban, et al., Maslinic acid as a feed additive to stimulate growth and hepatic protein-turnover rates in rainbow trout (*Onchorhynchus mykiss*), Comp. Biochem. Physiol. C: Toxicol. Pharmacol. 144(2) (2006) 130-140. <https://doi.org/10.1016/j.cbpc.2006.07.006>.
- [120] B.S. Cui, S. Li, New triterpenoid saponins from the leaves of *Cyclocarya paliurus*, Chin. Chem. Lett. 26(5) (2015) 585-589. <https://doi.org/10.1016/j.ccl.2014.11.033>.
- [121] Z.Y. Jiang, X.M. Zhang, J. Zhou, et al., Two new triterpenoid glycosides from *Cyclocarya paliurus*, J. Asian Nat. Prod. Res. 8(1/2) (2006) 93-98. <https://doi.org/10.1080/10286020500480217>.
- [122] Y. Liu, M.Q. Zhang, X.L. Li, et al., Study on chemical constituents of *Cyclocarya paliurus*, J. Asian Nat. Prod. Res. 16(2) (2013) 206-209. <https://doi.org/10.1080/10286020.2013.825254>.
- [123] D.J. Yang, Z.C. Zhong, Z.M. Xie, Studies on the sweet principles from the leaves of *Cyclocarya paliurus* (Batal.) Iljinskaya, Acta Pharmacol. Sin. 27(11) (1992) 841-844. <https://doi.org/10.16438/j.0513-4870.1992.11.008>.
- [124] H.H. Sun, H. Zhu, J.P. Wu, et al., Two new triterpenoid glycosides from leaves of *Cyclocarya paliurus*, Nat. Prod. Res. 36(20) (2021) 5277-5282. <https://doi.org/10.1080/14786419.2021.1931182>.
- [125] X.L. Zhou, S.B. Li, M.Q. Yan, et al., Bioactive dammarane triterpenoid saponins from the leaves of *Cyclocarya paliurus*, Phytochemistry 183 (2021) 112618. <https://doi.org/10.1016/j.phytochem.2020.112618>.
- [126] C.G. Li, S.P. Deng, W. Liu, et al., α -Glucosidase inhibitory and anti-inflammatory activities of dammarane triterpenoids from the leaves of *Cyclocarya paliurus*, Bioorg. Chem. 111 (2021) 104847. <https://doi.org/10.1016/j.bioorg.2021.104847>.
- [127] S. Li, B.S. Cui, Q. Liu, et al., New triterpenoids from the leaves of *Cyclocarya paliurus*, Planta Med. 78(3) (2012) 290-296. <https://doi.org/10.1055/s-0031-1280403>.
- [128] Y. Liu, G.T. Zheng, X.X. Zhang, et al., Two new triterpenoids from the leaves of *Cyclocarya paliurus* (Batalin) Iljinskaja, Nat. Prod. Res. 36(15) (2021) 3938-3944. <https://doi.org/10.1080/14786419.2021.1900845>.
- [129] T.Y. Xuan, J. Tan, H.H. Sun, et al., Cyclocarioside O-Q, three novel seco-dammarane triterpenoid glycosides from the leaves of *Cyclocarya paliurus*, Nat. Prod. Res. 35(1) (2019) 167-173. <https://doi.org/10.1080/14786419.2019.1616722>.
- [130] T. Li, X.C. Shangguan, Z.P. Yin, et al., The separation and identification of triterpenoids from leaves of *Cyclocarya paliurus*, Acta Agriculturae Universitatis Jiangxiensis 35(5) (2013) 1048-1054. <https://doi.org/10.13836/j.jjau.2013184>.
- [131] T. Fouri, F.A. Snyder, Pentacyclic triterpene with anti-inflammatory and analgesic activity from the roots of *Commiphora merkeri*, J. Nat. Prod. 52(5) (1989) 1129-1131. <https://doi.org/10.1021/np50065a034>.
- [132] J. Li, Y.Y. Lu, X.J. Su, et al., A Norsesquiterpene lactone and a benzoic acid derivative from the leaves of *Cyclocarya paliurus* and their glucosidase and glycogen phosphorylase inhibiting activities, Planta Med. 74(3) (2008) 287-289. <https://doi.org/10.1055/s-2008-1034309>.
- [133] F. Fullas, M. Wani, M. Wall, et al., Triterpenes from the combined leaf and stem of *Lithospermum carolinense*, Phytochemistry 43(6) (1996) 1303-1305. [https://doi.org/10.1016/S0031-9422\(96\)00422-0](https://doi.org/10.1016/S0031-9422(96)00422-0).
- [134] R.J. Zhong, R.G. Shu, X.L. Ni, et al., Studies on the chemical structure of cyclocaric acid A, Acta Pharmacol. Sin. 31(5) (1996) 398-400. <https://doi.org/10.16438/j.0513-4870.1996.05.014>.
- [135] R.G. Shu, Y.F. Liu, J. Chen, et al., Studies on the triterpenoids of *Cyclocarya paliurus* (Batal.) Iljinsk, J. Chinese Med. Mat. 28(7) (2005) 558-559. <https://doi.org/10.13863/j.issn1001-4454.2005.07.013>.
- [136] R.J. Zhong, L.N. Li, Y.H. Gao, et al., Pentacyclic triterpenoids from roundwingfruit *Cyclocarya* (*Cyclocarya paliurus*), Zhong Cao Yao 27(7) (1996) 387-389. <https://doi.org/10.3321/j.issn:0253-2670.1996.07.001>.
- [137] J.C. Shu, J.Q. Liu, G.X. Chou, et al., Two new triterpenoids from *Psidium guajava*, Chin. Chem. Lett. 23(7) (2012) 827-830. <https://doi.org/10.1016/j.ccl.2012.05.018>.
- [138] C.H. Jiang, N. Yao, Q.Q. Wang, et al., *Cyclocarya paliurus* extract modulates adipokine expression and improves insulin sensitivity by inhibition of inflammation in mice, J. Ethnopharmacol. 153(2) (2014) 344-351. <https://doi.org/10.1016/j.jep.2014.02.003>.
- [139] Y.J. Li, G.Z. Wan, F.C. Xu, et al., Screening and identification of α -glucosidase inhibitors from *Cyclocarya paliurus* leaves by ultrafiltration coupled with liquid chromatography-mass spectrometry and molecular docking, J. Chromatogr. A 1675 (2022) 463160. <https://doi.org/10.1016/j.chroma.2022.463160>.
- [140] M.M. Zhou, P. Chen, Y. Lin, et al., A comprehensive assessment of bioactive metabolites, antioxidant and antiproliferative activities of *Cyclocarya paliurus* (Batal.) Iljinskaja leaves, Forests 10(8) (2019) 625. <https://doi.org/10.3390/f10080625>.