

雷公藤生物碱类成分及其药理活性研究进展

刘 莉,闫 君,舒积成,刘建群*

江西中医药大学 现代中药制剂教育部重点实验室,南昌 330004

摘要:雷公藤具有广泛的药理活性,含多种类型有效成分,在中医临床上有着悠久的历史。生物碱类成分是雷公藤的主要有效成分之一,具有免疫抑制、抗炎、镇痛、抗肿瘤、抗 HIV、杀虫、神经保护等多种药理活性。迄今为止,已见报道的雷公藤生物碱类成分超过 160 个,结构丰富多样。本文总结了至今国内外雷公藤生物碱类成分及其药理活性的研究情况,以为该类成分的进一步研究开发提供参考。

关键词:雷公藤;生物碱;药理活性

中图分类号:R284

文献标识码:A

文章编号:1001-6880(2019)12-2170-12

DOI:10.16333/j.1001-6880.2019.12.022

Advance on alkaloids from *Tripterygium wilfordii* and their bioactivities

LIU Li, YAN Jun, SHU Ji-cheng, LIU Jian-qun*

Key Laboratory of Modern Preparation of TCM, Ministry of Education,
Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China

Abstract: *Tripterygium wilfordii* containing many active components had a long history of clinical application in traditional Chinese medicine for its extensive pharmacological activities. Alkaloids, the main active components of *T. wilfordii*, possessed many pharmacological activities, such as immunosuppression, anti-inflammation, analgesia, anti-tumor, anti-HIV, insecticidal, neuroprotection and so on. So far, more than 160 various alkaloids had been isolated from *T. wilfordii*. In this paper, the research progress of alkaloids from *T. wilfordii* were summarized in order to support the further research and development of these components.

Key words: *Tripterygium wilfordii*; alkaloid; bioactivity

雷公藤(*Tripterygium wilfordii* Hook. f.),又名黄藤根、断肠草等,属卫矛科雷公藤属植物,首载于《神农本草经》,主产于我国长江中下游流域,如浙江、福建、安徽等地。雷公藤味苦,性寒,皮有大毒,归肝、肾二经,具有清热解毒、祛风通络、舒筋活血、消肿止痛、杀虫止血等功效,有着悠久的药用历史^[1]。雷公藤用于治疗类风湿性关节炎等自身免疫性疾病疗效显著,常作为治疗风湿顽痹之要药^[2],但其肝、肾和血液系统等毒副作用大,其有效成分通常也为其毒性成分,严重地制约了其临床应用^[3,4]。现代研究表明,雷公藤具有抗炎、抗病毒、抗肿瘤、杀虫等多种药理作用,具有极大的药用价值,值得深入研究。雷公藤的化学成分复杂,主要有

效成分包括生物碱、二萜、三萜和木脂素等^[5-8]。生物碱是雷公藤中一类重要的化学成分,结构丰富多样,具有广泛的药理活性。笔者课题组研究发现经 200℃烘箱煨制后的雷公藤对治疗类风湿性关节炎有着显著的减毒增效作用^[9],并且煨制后,南蛇藤糠酰胺碱、1-去乙酰基雷公藤定碱等生物碱含量显著下降,生物碱为雷公藤抗炎有效成分之一,且毒性较大,因此,生物碱的含量变化可能是雷公藤煨制减毒增效的物质基础^[10,11]。生物碱类成分因其显著的药理活性^[12],一直是现代研究的热点,雷公藤生物碱具有广泛的药理活性,有着极大的研究价值。迄今为止,已见报道的雷公藤生物碱类成分超过 160 个,结构丰富多样。本文系统、全面总结了至今国内外雷公藤生物碱类成分及其药理活性的研究情况,以为该类成分的进一步研究开发提供参考。

1 化学成分

生物碱类成分是雷公藤的主要活性成分之一,

收稿日期:2019-08-27 接受日期:2019-11-27

基金项目:江西省主要学科科学技术带头人资助项目(20182BCB22004);国家自然科学基金(81860686)

*通信作者 Tel:86-791-87118786;E-mail:liu5308@sina.com

迄今为止,雷公藤中已见报道的生物碱类成分共161个(见表1~4),从结构特点来看主要包括两大类:倍半萜大环内酯类生物碱,共92个(化合物**1~92**);倍半萜非大环内酯类生物碱,共58个(化合物**93~150**)。同时雷公藤中还含有少数其他类型生物碱,共11个(化合物**151~161**)。

1.1 倍半萜大环内酯生物碱

倍半萜大环内酯生物碱是雷公藤内含有数量最多的一类生物碱,目前已见报道的雷公藤倍半萜大

环内酯生物碱共92个,从结构特点来看,主要可以将其分为两大类:吡啶环2',3'位与大环相连的倍半萜大环内酯生物碱(**1~69**)及吡啶环3',4'位与大环相连的倍半萜大环内酯生物碱(**70~92**)。倍半萜部分可连基团位置的多样性及可取代基团的复杂性,决定了该类化合物种类的多样性。

1.1.1 吡啶环2',3'位与大环连接

雷公藤所含此类生物碱见表1,对应结构见图1。

表1 雷公藤吡啶环2',3'位与大环连接的生物碱

Table 1 *T. wilfordii* alkaloids, of which pyridine ring 2',3' position connected to macrocyclic

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
1	Tripterygiumine A	C ₅₀ H ₅₇ NO ₂₁	12
2	Tripterygiumine B	C ₄₃ H ₄₉ NO ₁₈	12
3	Tripterygiumine C	C ₄₈ H ₅₁ NO ₁₈	12
4	Tripterygiumine D	C ₃₃ H ₃₉ NO ₁₃	12
5	Tripterygiumine E	C ₃₉ H ₄₅ NO ₁₈	12
6	Tripterygiumine F	C ₄₆ H ₄₉ NO ₁₉	12
7	Tripterygiumine G	C ₄₆ H ₄₉ NO ₁₉	12
8	Tripterygiumine H	C ₂₈ H ₃₇ NO ₁₃	12
9	Tripterygiumine I	C ₄₁ H ₄₇ NO ₁₇	12
10	Tripterygiumine J	C ₃₄ H ₄₃ NO ₁₆	12
11	Tripterygiumine K	C ₃₉ H ₄₅ NO ₁₆	12
12	Tripterygiumine L	C ₄₀ H ₄₆ N ₂ O ₁₇	12
13	Hyponine D	C ₄₇ H ₅₀ N ₂ O ₁₈	12
14	2- <i>O</i> -Benzoyl-2-deacetylmyteine	C ₄₈ H ₅₁ NO ₁₈	12
15	Hexadecacetyluomynine	C ₂₆ H ₃₅ NO ₁₂	12
16	Euojaponine A	C ₄₁ H ₄₇ NO ₁₇	12
17	Neoeuonymine	C ₃₆ H ₄₅ NO ₁₇	12
18	Hyponine C	C ₄₃ H ₄₉ NO ₁₈	12
19	7-(Acetyloxy)- <i>O</i> -11-benzoyl- <i>O</i> -2,11-deacetyl-7-deoxoevovine	C ₄₁ H ₄₇ NO ₁₇	12
20	4-Hydroxy-7-epi-chuchuhuanine E-V	C ₃₆ H ₄₅ NO ₁₇	12
21	Wilforfine F	C ₄₁ H ₄₇ NO ₁₇	12
22	Aquifoliumine E-III	C ₃₆ H ₄₅ NO ₁₇	13
23	Tripterygiumine M	C ₃₉ H ₄₃ NO ₁₆	12
24	Tripterygiumine N	C ₄₄ H ₄₅ NO ₁₉	12
25	Tripterygiumine O	C ₄₆ H ₄₉ NO ₂₀	12
26	Tripterygiumine S	C ₃₉ H ₄₃ NO ₁₉	14
27	Tripterygiumine T	C ₃₂ H ₃₉ NO ₁₆	14
28	Tripterygiumine U	C ₃₄ H ₄₁ NO ₁₆	14
29	Tripterygiumine V	C ₄₃ H ₄₉ NO ₁₉	14

续表 1 (Continued Tab. 1)

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
30	2-Debenzoyl-2-nicotinoylwilforine	C ₄₂ H ₄₈ N ₂ O ₁₈	14
31	9'-O-3-Furoyl-wilfortrine	C ₄₆ H ₄₉ NO ₂₂	12
32	Alatamine	C ₄₁ H ₄₅ NO ₁₈	12
33	Alatusinine	C ₃₈ H ₄₇ NO ₁₉	12
34	Wilforzine	C ₄₁ H ₄₇ NO ₁₇	15
35	Wilforjine	C ₃₆ H ₄₅ NO ₁₇	12
36	Tripterygiumine P	C ₃₅ H ₄₁ NO ₁₅	12
37	Tripterygiumine Q	C ₃₃ H ₃₉ NO ₁₆	12
38	Euonine (Wilformine)	C ₃₈ H ₄₇ NO ₁₈	16
39	Wilfortrine	C ₄₁ H ₄₇ NO ₂₀	17
40	9'-O-Acetyl-7-deacetoxy-7-oxowilfortrine	C ₄₁ H ₄₅ NO ₂₀	18
41	9'-O-Acetylwilfortrine	C ₄₃ H ₄₉ NO ₂₁	18
42	9'-O-Furanoylwilfordine	C ₄₈ H ₅₁ NO ₂₁	18
43	7-O-Benzoyl-5,7-dideacetylWilformine	C ₄₁ H ₄₇ NO ₁₇	18
44	Wilforgine	C ₄₁ H ₄₇ NO ₁₉	17
45	Wilfordine	C ₄₃ H ₄₉ NO ₁₉	17
46	Wilforine	C ₄₃ H ₄₉ NO ₁₈	17
47	Wilfordine	C ₃₆ H ₄₅ NO ₁₈	19
48	Wilformine A	C ₄₅ H ₅₁ NO ₂₀	14
49	Wilformine B	C ₄₃ H ₄₉ NO ₁₉	20
50	Wilformine C	C ₅₀ H ₅₃ NO ₂₀	21
51	Wilformine D	C ₄₃ H ₄₉ NO ₂₁	14
52	Wilformine E	C ₃₆ H ₄₃ NO ₁₈	20
53	Cangorinine E-I	C ₄₃ H ₄₉ NO ₁₈	18
54	Ebenifoline E-II	C ₄₈ H ₅₁ NO ₁₈	18
55	Euonymine	C ₃₈ H ₄₇ NO ₁₈	18
56	Mayteine	C ₄₃ H ₄₉ NO ₁₈	20
57	Tripterygiumine W	C ₄₄ H ₄₇ NO ₁₈	14
58	Wilformine H	C ₄₄ H ₄₇ NO ₂₀	22
59	Hyponine B	C ₄₁ H ₄₇ NO ₁₉	9
60	Hyponine E	C ₄₅ H ₄₈ NO ₁₉	23
61	1-Desacetylwilforgine	C ₃₉ H ₄₅ NO ₁₈	9
62	1-Desacetylwilforine	C ₄₁ H ₄₇ NO ₁₇	22
63	1-Desacetylwilfordine	C ₄₁ H ₄₇ NO ₁₈	9
64	1-Desacetylwilfortrine	C ₃₉ H ₄₅ NO ₁₉	15
65	2-Debenzoyl-2-nicotinoylwilforine	C ₄₂ H ₄₈ N ₂ O ₁₈	15
66	9'-Hydroxy-2-nicotinoylwilforine	C ₄₂ H ₄₈ N ₂ O ₁₉	22
67	Tripfordine A	C ₃₆ H ₄₅ NO ₁₈	21
68	Tripfordine B	C ₃₆ H ₄₅ NO ₁₇	24
69	Triptonine A	C ₄₅ H ₅₄ NO ₂₁	9

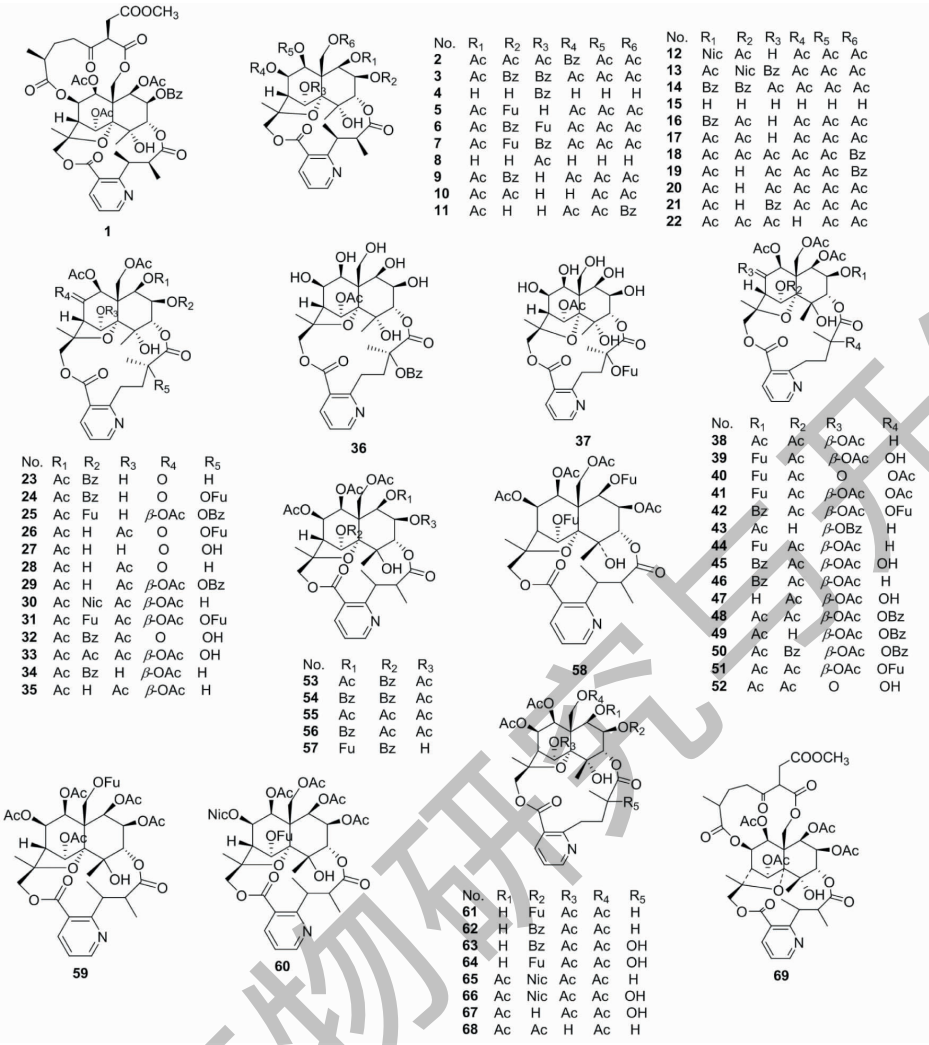


图1 雷公藤吡啶环 2',3'位与大环连接的生物碱结构式

Fig. 1 Structures of *T. wilfordii* alkaloid, of which pyridine ring 2',3' position connected to macrocyclic

1.1.2 吡啶环 3',4'位与大环连接

雷公藤所含此类生物碱见表2,对应结构见图2

表2 雷公藤吡啶环 3',4'位与大环连接的生物碱

Table 2 *T. wilfordii* alkaloids, of which pyridine ring 3',4' position connected to macrocyclic

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
70	Peritassine A	C ₃₈ H ₄₇ NO ₁₈	25
71	Peritassine B	C ₄₃ H ₄₉ NO ₁₈	23
72	Wilfordinine A	C ₃₆ H ₄₅ NO ₁₇	16
73	Hypoglaunine A	C ₄₁ H ₄₇ NO ₂₀	16
74	Hypoglaunine E	C ₃₉ H ₄₅ NO ₁₉	16
75	Hypoglaunine C	C ₄₃ H ₄₉ NO ₁₉	21
76	Hypoglaunine F	C ₄₀ H ₄₈ NO ₂₀	26
77	Wilfordinine I	C ₄₈ H ₅₁ NO ₁₉	21

续表 2(Continued Tab. 2)

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
78	Wilfordinine J	C ₃₆ H ₄₅ NO ₁₇	20
79	Wilfordinine B	C ₃₈ H ₄₇ NO ₁₉	27
80	Wilfordinine C	C ₄₃ H ₄₉ NO ₁₉	27
81	Isowilfortrine	C ₄₁ H ₄₇ NO ₂₀	19
82	Wilfordsine	C ₄₂ H ₄₉ NO ₁₉	13
83	Wilfordinine E	C ₃₈ H ₄₇ NO ₁₈	16
84	WilfordinineD	C ₄₁ H ₄₇ NO ₁₉	28
85	WilfordinineF	C ₄₃ H ₄₉ NO ₁₈	28
86	WilfordinineG	C ₃₆ H ₄₃ NO ₁₈	28
87	WilfordinineH	C ₄₁ H ₄₇ NO ₂₀	28
88	Isowilfordine	C ₄₃ H ₄₉ NO ₁₈	28
89	WilformineG	C ₄₂ H ₄₈ N ₂ O ₁₈	29
90	Triptordine C	C ₃₆ H ₄₅ NO ₁₇	24
91	HypoglaunineB	C ₄₁ H ₄₈ NO ₂₀	26
92	Triptonine B	C ₄₅ H ₅₄ NO ₂₂	25

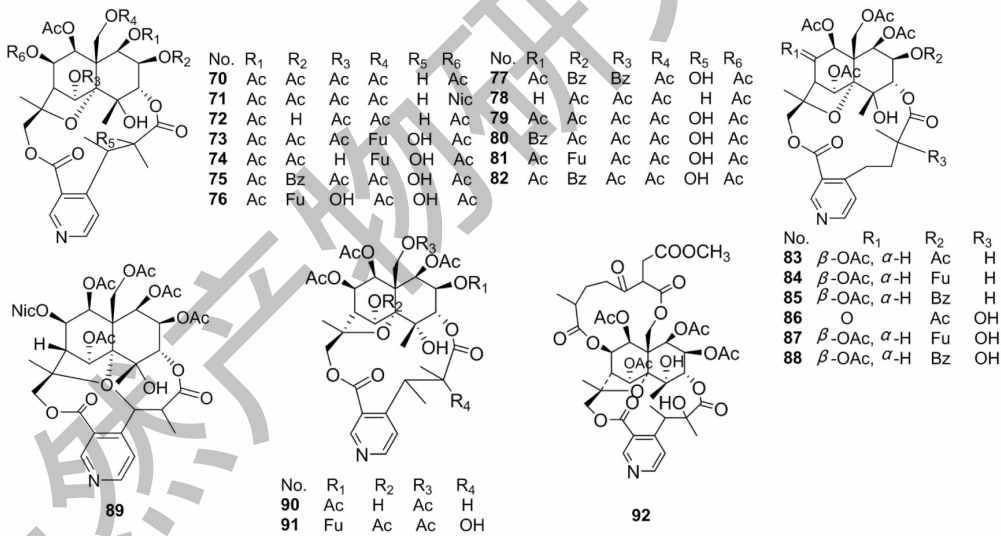


图 2 雷公藤吡啶环 3',4'位与大环连接的生物碱结构式

Fig. 2 Structures of *T. wilfordii* alkaloid, of which pyridine ring 3',4' position connected to macrocyclic

1.2 倍半萜非大环内酯生物碱

倍半萜非大环内酯生物碱是雷公藤中含有的另一类数量极为庞大的生物碱。该类化合物种类的多样性决定于其可连基团位置的多样性及可取代基团的复杂性。雷公藤中所含此类生物碱见表 3, 对应结构见图 3。

1.3 其他类型生物碱

雷公藤所含其他生物碱共有以下几种, 如大环

多胺类生物碱。雷公藤所含此类生物碱见表 4, 对应结构见图 4。图 1 ~ 4 生物碱结构式中涉及的一些取代基结构见图 5。

2 药理作用

2.1 免疫抑制

雷公藤的多种生物碱单体均具有免疫抑制作用, 如雷公藤康碱、异雷公藤春碱、雷公藤新碱、雷公藤碱戊、雷公藤吉碱、雷公藤明碱等。雷公藤康碱、

表 3 雷公藤倍半萜非大环内酯生物碱
Table 3 Sesquiterpene non-macrolide *T. wilfordii* alkaloids

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
93	2β,5α,7β-Triacetoxy-11-isobutyryloxy-8α-(3-furancarbonyloxy)-4α-hydroxyl-1β-nicotinoyloxy-dihydroagarofuran	C ₃₆ H ₄₃ NO ₁₅	30
94	1β-Nicotinoyl-2β,5α,7β-triacetoxy-4α-hydroxy-11-isobutyryloxy-8α-furanoyl-dihydroagarofuran	C ₃₆ H ₄₃ NO ₁₅	31
95	Tripterygiumine R	C ₂₈ H ₃₃ NO ₇	12
96	1β,5α,11-Triacetoxy-7β-benzoyl-4α-hydroxy-8β-nicotinoyldihydroag-arofuran	C ₃₄ H ₃₉ NO ₁₂	12
97	Wilforcidine	C ₃₇ H ₃₉ NO ₈	12
98	5α-Benzoyl-4α-hydroxy-1β,8α-dinicotinoyldihydroagarofuran	C ₃₄ H ₃₆ N ₂ O ₈	12
99	Triptersinine Z4	C ₃₂ H ₃₈ NO ₁₂	32
100	Triptersinine Z5	C ₃₂ H ₃₈ NO ₁₂	32
101	Triptersinine Z6	C ₃₅ H ₃₈ NO ₁₃	32
102	Triptersinine Z7	C ₃₆ H ₄₂ NO ₁₁	32
103	Triptersinine Z8	C ₃₆ H ₄₂ NO ₁₁	32
104	Triptersinine Z9	C ₃₅ H ₄₁ NO ₁₃	33
105	Triptersinine Z10	C ₃₅ H ₄₁ NO ₁₃	33
106	Triptersinine Z11	C ₃₅ H ₄₁ NO ₁₃	33
107	Triptersinine Z13	C ₃₅ H ₄₁ NO ₁₃	33
108	Triptersinine Z13	C ₃₅ H ₄₁ NO ₁₃	33
109	Triptersinine Z14	C ₃₅ H ₄₁ NO ₁₃	33
110	Triptersinine A	C ₃₂ H ₃₅ NO ₁₀	16
111	Triptersinine B	C ₃₂ H ₃₅ NO ₁₀	16
112	Triptersinine C	C ₃₄ H ₃₉ NO ₁₁	16
113	Triptersinine D	C ₃₄ H ₃₉ NO ₁₁	16
114	Triptersinine E	C ₃₆ H ₄₁ NO ₁₂	16
115	Triptersinine F	C ₃₂ H ₃₇ NO ₁₃	16
116	Triptersinine G	C ₃₂ H ₃₇ NO ₁₃	16
117	Triptersinine H	C ₃₅ H ₃₇ NO ₁₄	16
118	Triptersinine L	C ₃₂ H ₄₁ NO ₁₂	16
119	Triptersinine M	C ₃₆ H ₄₁ NO ₁₂	34
120	Triptersinine N	C ₃₅ H ₃₇ NO ₁₄	34
121	Triptersinine O	C ₃₅ H ₃₇ NO ₁₄	34
122	Triptersinine P	C ₃₆ H ₄₂ N ₂ O ₁₂	34
123	Triptersinine Q	C ₃₅ H ₄₁ NO ₁₃	34
124	Triptersinine R	C ₃₂ H ₃₇ NO ₁₃	34
125	Triptersinine S	C ₃₂ H ₃₇ NO ₁₃	34
126	Triptersinine T	C ₂₇ H ₃₅ NO ₁₀	34
127	Regelidine	C ₃₅ H ₃₇ NO ₈	29
128	9-O-trans-Cinnamoyl-9-debenzoylregelidine	C ₃₇ H ₃₉ NO ₈	18
129	5α-Benzoyl-4α-hydroxy-1β,8α-dinicotinoyl-dihydroagarofuran	C ₃₄ H ₃₆ N ₂ O ₈	35
130	Wilforsinine A	C ₃₄ H ₃₉ NO ₁₂	30
131	Wilforsinine B	C ₃₄ H ₃₉ NO ₁₁	30

续表 3 (Continued Tab. 3)

编号 No.	化合物 Compound	分子式 Molecular formula	参考文献 Ref.
132	Wilforsinine C	C ₄₀ H ₄₄ N ₂ O ₁₅	30
133	Wilforsinine D	C ₃₆ H ₄₁ NO ₁₃	30
134	Wilforsinine E	C ₄₀ H ₄₂ N ₂ O ₁₃	30
135	Wilforsinine G	C ₄₀ H ₄₂ N ₂ O ₁₃	30
136	Wilforsinine H	C ₃₅ H ₄₀ N ₂ O ₁₃	30
137	2β,6α,12-Triacetox-1β,9β-bis(benzoyl-8β-(β-nicotinoyloxy) -β-dihydroagarofuran	C ₄₁ H ₄₃ NO ₁₃	30
138	1β,2β,5α,8β,11-Pentaacetox-4α-hydroxy-3α(2'-methylbutanoyl) -15-nicotinoyl-7-oxo-dihydroagarofuran	C ₃₆ H ₄₅ NO ₁₇	35
139	Triptersinine U	C ₃₈ H ₄₄ NO ₁₉	26
140	1β,5α,11-Triacetox-7β-benzoyl-4α-hydroxy-8β-nicotinoy-dihydroagarofuran	C ₃₄ H ₃₉ NO ₁₂	35
141	1β,2β,5α,11-Tetraacetox-8α-benzoyl-4α-hydroxy-7β-nicotinoyl-dihydroagarofuran	C ₃₆ H ₄₁ NO ₁₄	35
142	Triptogelin F-1	C ₃₀ H ₃₅ NO ₇	36
143	Triptogelin C-2	C ₃₂ H ₃₇ NO ₉	37
144	Triptogelin C-4	C ₃₀ H ₃₅ NO ₈	38
145	Triptogelin A-10	C ₄₄ H ₄₃ NO ₁₁	37
146	Triptogelin A-5	C ₄₂ H ₄₇ NO ₁₁	37
147	Triptogelin A-6	C ₄₄ H ₄₃ NO ₁₁	37
148	Triptogelin A-7	C ₃₀ H ₃₅ NO ₉	37
149	Triptogelin A-9	C ₄₃ H ₄₉ NO ₁₁	37
150	Triptogelin B-2	C ₃₇ H ₃₉ NO ₉	37

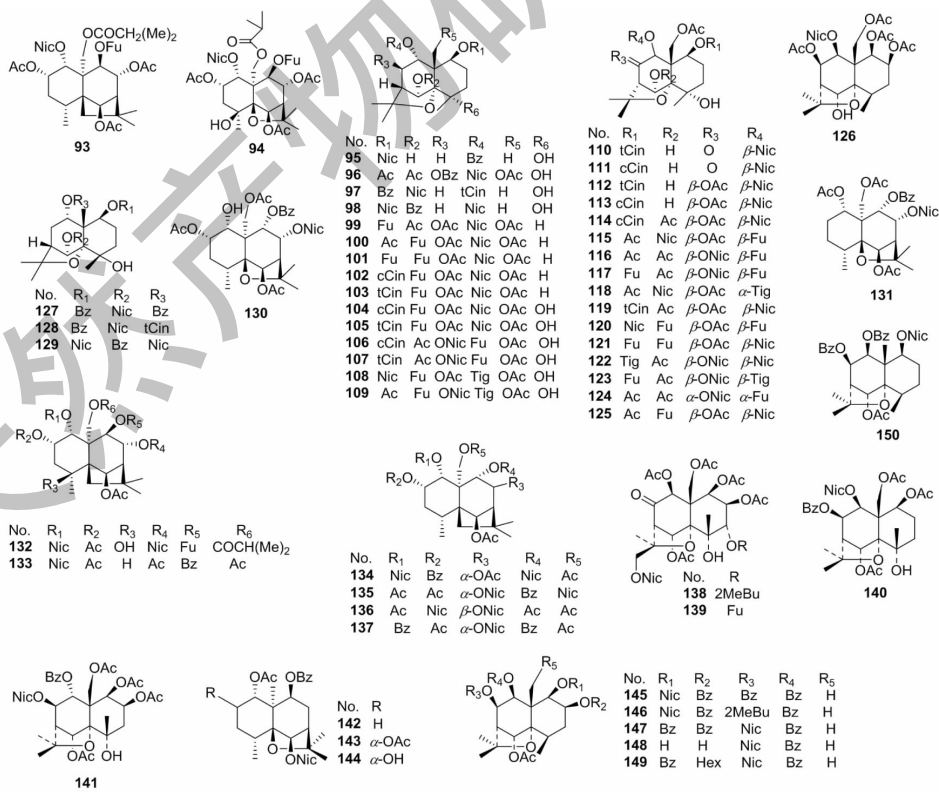


图 3 雷公藤倍半萜非大环内酯生物碱结构式

Fig. 3 Structures of sesquiterpene non-macrolide *Tripterygium wilfordii* alkaloid

表 4 雷公藤其他类型生物碱

Table 4 Other type alkaloids from *Tripterygium wilfordii*

编号 No.	化合 Compound	分子式 Molecular formula	参考文献 Ref.
151	2 <i>S</i> ,2' <i>S</i> -Aurantiamideacetate	C ₂₇ H ₂₈ N ₂ O ₄	22
152	Cyclo-(<i>S</i> -Pro- <i>R</i> -Phe)	C ₁₄ H ₁₆ N ₂ O ₂	39
153	Cyclo-(<i>S</i> -Pro- <i>R</i> -Leu)	C ₁₁ H ₁₈ N ₂ O ₂	39
154	Cyclo-(<i>S</i> -Pro- <i>S</i> -Ile)	C ₁₁ H ₁₈ O ₂ N ₂	39
155	(2 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)-2-[(2' <i>R</i>)-2'-Hydroxy tetracosanoyl amino]-1,3,4-octadecanetriol	C ₄₂ H ₈₅ O ₅ N	40
156	(2 <i>S</i> ,3 <i>S</i> ,4 <i>R</i> ,8 <i>E</i>)-2-[(2' <i>R</i>)-2'-Hydroxy pentacosanoyl amino]-8-octadecene-1,3,4-triol	C ₄₃ H ₈₅ O ₅ N ₂	40
157	Celacinnine	C ₂₅ H ₃₁ N ₃ O ₂	9
158	Celalocinnine	C ₂₅ H ₃₁ N ₃ O ₂	9
159	Celabenzine	C ₂₃ H ₂₉ N ₃ O ₂	9
160	Celafurine	C ₂₁ H ₂₇ N ₃ O ₃	21
161	Pyridine-3-carboxylic acid	C ₆ H ₅ NO ₂	41

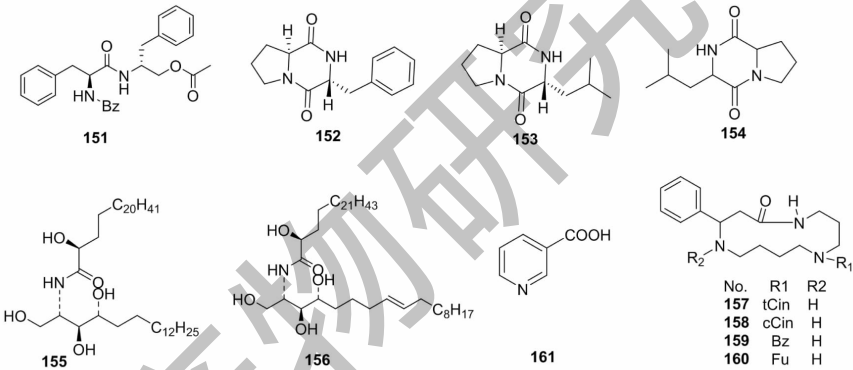


图 4 雷公藤其他类型生物碱结构式

Fig. 4 Structures of other type alkaloids from *Tripterygium wilfordii*

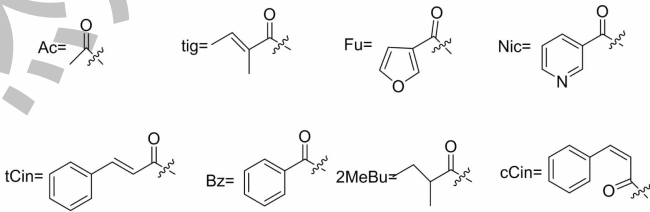


图 5 一些取代基的结构

Fig. 5 The structures of some substituted group

雷公藤明碱、异雷公藤春碱、雷公藤春碱、雷公藤新碱对特异性免疫、非特异性免疫功能均有抑制作用,雷公藤碱戊对 B 细胞功能的多个环节均具有抑制作用。其中雷公藤春碱、雷公藤新碱对体液免疫、细胞免疫、非特异性免疫功能均有抑制作用。Zheng

等^[42]研究发现在一定浓度条件下雷公藤春碱对移植植物抗宿主反应为指标的细胞免疫有一定的抑制作用,雷公藤新碱对 DNCB 所致迟发型超敏反应具有明显的抑制作用,两者均能够明显抑制溶血素抗体的形成、显著降低小鼠碳粒廓清速率,对网状内皮系

统吞噬功能具有抑制作用。Luo 等^[12]研究发现 tripterygiumine Q 对人外周单核细胞具有免疫抑制活性, IC_{50} 值为 $8.67 \mu\text{M}$, 即使在 $100 \mu\text{M}$ 时也没有细胞毒性, 这表明 tripterygiumine Q 可能是开发新免疫抑制剂的新途径。

2.2 抗 HIV

雷公藤中所含的多种生物碱类单体均具有抗 HIV 活性, 如 wilfordine、wilfortrine、hypoglaunine A、hypoglaunine B、triptonine A、triptonine B、cangoronine E-1、euonymine、neoeuonymine、hyponine B 等。Duan^[27]评估了 triptonine A、triptonine B 和几种相关化合物的抗艾滋病毒活性。其中 triptonine B 显示出了有效的抗艾滋病毒活性, $EC_{50} < 0.1 \mu\text{g/mL}$, 其体外治疗指数值 > 1000 。同时雷公藤生物碱类成分 hypoglaunine B、hyponine B、wilfortrine 也具有一定的抗 HIV 病毒活性。Horiuch 等^[24]对 12 种从雷公藤中提取的吡啶生物碱的抗艾滋病毒活性进行了测定, 基于新分离化合物的筛选结果和已知倍半萜吡啶生物碱的先前数据, 提出了这种类型化合物的抗艾滋病毒结构-活性关系: 羧基烷基链在吡啶部分的位置并不重要, 因为 2'-和 4'-取代的化合物都表现出高抗艾滋病毒活性 ($EC_{50} 0.1 \mu\text{g/mL}$); 相反, 在 C-8' (羧丙基侧链) 或 C-9' (羧丁基侧链) 的羟基影响其抗艾滋病毒活性。

2.3 抗肿瘤

雷公藤的部分生物碱类成分还具有抗肿瘤的药理作用。Yue 等^[43]研究发现 wilfortrine 能有效抑制癌细胞增殖, 抑制其侵袭能力。Wilfortrine 治疗后肝癌 HepG2 细胞的凋亡率明显增加, 尤其是早期凋亡率 ($P < 0.05$), 然而, wilfortrine 并没有改变 HepG2 细胞的细胞周期。Wilfortrine 治疗后, Bcl-2 表达明显降低 ($P < 0.05$), 而 Bax 表达较对照组明显增加 ($P < 0.05$)。以上结果表明 wilfortrine 能诱导 HepG2 凋亡, 但对其细胞周期并无影响, 主要通过促进 Bax 表达和抑制抗凋亡蛋白 Bcl-2 表达实现。

异雷公藤春碱、雷公藤康碱对白血病细胞具有抑制作用。Lin 等^[44]用 MTT 法检测雷公藤康碱在体外对 K562 细胞 (红白血病细胞) 及 HL60 细胞 (急性髓性白血病细胞) 的杀伤作用。实验结果显示在 $3.00 \mu\text{g/mL}$ 浓度时, 雷公藤康碱对 K562 细胞的抑制率为 87%, 对 HL60 细胞的抑制率为 90%, 经 Student 检验, 与对照组相比, $P < 0.001$ 。Chen 等^[45]采用 MTT 法, 研究雷公藤总生物碱及倍半萜

类生物碱共 5 种组分对人 CIK 细胞、结直肠癌 HCT116 细胞及肝癌 HepG2 细胞的增殖抑制作用, 以及筛选出的 LGT-ZF1 组分在不同时间点对这 3 种细胞的抑制作用。实验结果显示雷公藤总生物碱及 3 种倍半萜类生物碱组分 (LGT-ZF1、2、3) 具有细胞增殖抑制活性, LGT-ZF1 组分对人 CIK 细胞、HCT116 细胞、HepG2 细胞的抑制效应呈时间剂量依赖性, 同时结果表明 LGT-ZF1 组分具有较好的免疫抑制活性及抗肿瘤作用。

2.4 抗炎

雷公藤总生物碱具有抗炎作用, Zhai 等^[46]采用二甲苯小鼠耳肿胀模型、大鼠棉球肉芽肿、小鼠毛细血管通透性实验法研究雷公藤总生物碱 (ATW) 的抗炎作用, 研究结果表明 ATW 能明显抑制小鼠耳廓肿胀, 抑制棉球肉芽肿的增重, 降低小鼠腹腔毛细血管通透性, 具有抗炎作用。

部分雷公藤生物碱单体也具有抗炎作用, Zhang 等^[47]研究发现雷公藤新碱能够抑制 LPS 诱导的小鼠树突状细胞 (DCs) 成熟与分化, 增加 DCs 抗原吞噬能力, 并抑制其细胞因子分泌, 雷公藤新碱可减轻 DCs 介导的炎症反应。Yang 等^[48]通过对雷公藤次碱 (wilforine) 对脂多糖 (LPS) 诱导的小鼠单核/巨噬细胞系 RAW264.7 细胞炎症模型中炎症因子的影响的观察发现, wilforine 可以抑制 LPS 诱导的 RAW264.7 细胞炎症反应, 其抗炎作用与减少炎症细胞因子 TNF- α 、IL-6 和 NO 的产生有关。Gao 等^[14]通过测量脂多糖诱导的小鼠巨噬细胞系 RAW264.7 产生的一氧化氮来评价多种化合物的抗炎活性发现, 生物碱类成分 9'-O-acetyl-7-deacetoxy-7-oxowilfortrine 及 tripterygiumine S 具有有效的一氧化氮抑制活性, IC_{50} 值在 2.99 至 $28.80 \mu\text{M}$ 范围内, 对 RAW264.7 细胞的生存能力没有任何影响, 化合物 9'-O-acetyl-7-deacetoxy-7-oxowilfortrine、tripterygiumine S, 特别是 9'-O-acetyl-7-deacetoxy-7-oxowilfortrine, 被认为是具有希望的抗炎候选药物。

2.5 镇痛

Zhai 等^[46]采用小鼠温浴法、超声波甩尾法、热板法和扭体法研究 ATW 的镇痛作用, 研究结果表明雷公藤总生物碱对冰醋酸、超声波、热刺激所诱发的小鼠疼痛均有抑制作用, 具有镇痛的药理作用。

2.6 杀虫

雷公藤总生物碱是雷公藤中主要杀虫活性物质, 对鳞翅目、双翅目、鞘翅目等多种昆虫表现出较

强的胃毒、拒食、麻醉、生长发育抑制和种群抑制等多种特异性杀虫作用,是一个很有发展潜力的生物碱杀虫剂。目前已从雷公藤中分离出的生物碱中, wilforgine、wilfordine、wilforine、wilforzine、wilfotrine、euonine 这 6 种生物碱已经确定其确切的杀虫作用。雷公藤生物碱毒杀昆虫的机理是作用于昆虫的神经系统,麻醉昆虫,中毒后昆虫的中肠肠壁细胞遭到破坏,影响其取食和代谢,雷公藤总生物碱引起昆虫的中毒症状依次表现为行动迟缓、停止取食、麻醉、复苏或死亡,复苏后可再次取食、麻醉、复苏或死亡,反复多次,直至死亡,此外,昆虫的呼吸系统也受到一定影响^[49]。

2.7 神经保护

雷公藤中的部分生物碱还具有神经保护作用,Chen 等^[32]测试了 13 种雷公藤叶中分离得到化合物对用 okadaic acid(OKA)处理的 PC12 细胞的神经保护活性。神经生长因子(NGF)用作阳性对照,在 10 μM 时 triptersinines Z4、Z5、Z7、Z8 处理的经 OKA 处理的 PC12 细胞存活率增加,分别从 60.4% \pm 23.0% 增加到 86.2% \pm 25.5%,这几种雷公藤中生物碱显示出适度的神经保护活性,同时活性的比较表明,在 C-4 处没有羟基的化合物比含有这种基团的化合物更有效。

2.8 毒性作用

雷公藤中生物碱类成分具有多种器官毒性,尤其是其肝毒性及对生殖系统的毒性,生物碱类成分的肝毒性最大,能引起肝损伤,破坏红细胞并可导致进行性贫血,甚至诱发肾小管缺氧性损害和严重营养不良^[50]。Zhang 等^[51]研究分析雷公藤柱层析中段和末段组分对小鼠急性毒性和大鼠急性肝损伤的影响发现,雷公藤柱层析中段组分的毒性强于末段组分,毒性物质基础以二萜、生物碱类为主,毒性主要表现为急性肝损伤,毒性成分与毒性存在量效关系。

3 展望

雷公藤治疗类风湿性关节炎等疾病的显著疗效及其广泛的药理活性使其备受国内外研究者关注。目前已从雷公藤中分离得到生物碱类化合物共有 160 多个,其广泛的药理活性显示出了这类成分巨大的研究价值。然而其严重的毒副作用大大制约了其应用,国内外学者为提高其临床应用安全性和有效性进行了大量研究。虽然雷公藤生物碱类成分具有一定的毒副作用,但已有研究表明雷公藤生物碱类成分毒性小于其二萜类成分,且其药效作用显著,

因而通过一些技术手段实现对雷公藤生物碱类成分的减毒增效有着极大的研究价值。例如通过炮制降低其毒性,从降毒效果来看,煨制、米醋蒸制和药汁制可能具有较好前景^[52],其中本课题组发现煨制能使雷公藤中 20 余种生物碱类成分发生变化^[9],能实现治疗类风湿性关节炎的减毒增效作用,但仍存在物质变化机理及规律不明、作用机制不清,对其变化产物研究不足等问题。同时目前对雷公藤生物碱类成分的研究主要集中在倍半萜类生物碱及吡啶生物碱的研究,针对从雷公藤中分离出的大环多胺类生物碱研究较少,目前从植物中分离得到的大环多胺类生物碱不足 50 个,且对其报道多为其合成方面,其药理活性方面研究严重不足,具有较大的潜在研究价值。

综上所述,雷公藤中生物碱类化学成分含量丰富,具有广泛的药理活性,特别是免疫抑制、抗炎、镇痛、抗肿瘤、抗 HIV、杀虫、神经保护等,具有广阔的应用前景。随着研究的不断深入,针对雷公藤生物碱结构与活性之间、活性与活性之间的相关研究,可为了解药物作用机理、毒性机制、优化先导化合物结构、阐释传统中药作用机制提供研究基础,亦可为实现其临床用药奠定基石。

参考文献

- 1 Gao W, et al. The research on the transcript of *Tripterygium wilfordii* [J]. Word J Tradit Chin Med(世界中医药), 2012, 7:560-562.
- 2 Liu JQ, et al. Thermal analysis of *Tripterygium wilfordii* and its counterfeits [J]. J China Pharm(中国药房), 2016, 30: 4269-4271.
- 3 Liu JQ, et al. Effects of microwave processing on the toxicity and chemical composition of *Tripterygium wilfordii* [J]. Lishizhen Med Mater Med Res(时珍国医国药), 2014, 25:344-345.
- 4 Liu JQ, et al. Thermal stability and decomposition kinetics of triptolide and triptonide [J]. Nat Prod Res Dev(天然产物研究与开发), 2015, 27:1416-1420.
- 5 Liu JQ, et al. Three new abietane-type diterpene glycosides from the roots of *Tripterygium wilfordii* [J]. Fitoterapia, 2017, 120:126-130.
- 6 Yang RK, et al. Isolation and identification of chemical constituents from ethyl acetate and water in *Tripterygium wilfordii* [J]. J Chin Pharm(中国药房), 2019, 30:638-641.
- 7 Liu JQ, et al. Study on chemical constituents and thermal stability of *Tripterygium wilfordii* [J]. Chem Ind Forest Prod(林产化学与工业), 2017, 37(2):72-78.

- 8 Liu JQ, et al. Study on thermal stability of two active components of *Tripterygium wilfordii* [J]. Jiangxi Med J (江西中医药), 2016, 47(11): 62-64.
- 9 Liu JQ, et al. A method of processing *Tripterygium wilfordii*: CN104306426A [P]. 2015-01-28.
- 10 Liu JQ, et al. Effects of tanning on the chemical constituents of *Tripterygium wilfordii* based on UPLC-Q-TOF MS [J]. J Chin Mass Spectr Soc (质谱学报), 2018, 39: 573-582.
- 11 Liu JQ, et al. Study on chemical composition changes of *Tripterygium wilfordii* [J]. Strait Pharm J (海峡药学), 2018, 30(4): 38-40.
- 12 Luo Y, et al. Nitrogen-containing dihydro- β -agarofuran derivatives from *Tripterygium wilfordii* [J]. J Nat Prod, 2014, 77: 1650-1657.
- 13 Lu J. Discovery of chemical constituents with awakening reductase-inducing activity in *Tripterygium wilfordii* [D]. Zhejiang: Zhejiang University (浙江大学), 2011: 1-92.
- 14 Gao C, et al. Anti-inflammatory sesquiterpene pyridine alkaloids from *Tripterygium wilfordii* [J]. Fitoterapia, 2015, 105: 49-54.
- 15 Ya L, et al. Sesquiterpene alkaloids from *Tripterygium wilfordii* (Hook.): A nuclear magnetic resonance study of 1-desacetylwilfordine, 1-desacetylwilfortrine, and 2-debenzoyl-2-nicotinoylwilforine [J]. Can J Chem, 1990, 68: 371-374.
- 16 Wang C, et al. Anti-inflammatory sesquiterpene derivatives from the leaves of *Tripterygium wilfordii* [J]. J Nat Prod, 2012, 76(1): 85-90.
- 17 Guo H, et al. Separation and simultaneous determination of seven bioactive components in *Tripterygium wilfordii* Hook. f. and *Tripterygium* preparations by micellar electrokinetic capillary chromatography [J]. Electrophoresis, 2019, 40: 547-554.
- 18 Cai T, et al. Untargeted analysis of sesquiterpene pyridine alkaloids from the dried roots of *Tripterygium wilfordii* using high-performance liquid chromatography/electrospray ionization tandem mass spectrometry [J]. Rapid Commun Mass Spectrom, 2015, 29: 965-972.
- 19 Li CX, et al. Advances in research on anti-inflammatory immunomodulatory active monomers of *Tripterygium wilfordii* [J]. Chin J Chin Mater Med (中国中药杂志), 2014, 39: 4159-4164.
- 20 Duan H, et al. Immunosuppressive sesquiterpene alkaloids from *Tripterygium wilfordii* [J]. J Nat Prod, 2001, 64: 582-587.
- 21 Su P, et al. Identification and functional characterization of diterpene synthases for triptolide biosynthesis from *Tripterygium wilfordii* [J]. Plant J, 2018, 93(1): 50-65.
- 22 Lv H, et al. The genus *Tripterygium*: a phytochemistry and pharmacological review [J]. Fitoterapia, 2019, 137: UNSP 104190.
- 23 Fu Q, et al. Rapid and simultaneous analysis of sesquiterpene pyridine alkaloids from *Tripterygium wilfordii* Hook. f. Using supercritical fluid chromatography-diode array detector-tandem mass spectrometry [J]. J Supercrit Fluids, 2015, 104: 85-93.
- 24 Horiuchi M, et al. Tripterdines A-C, sesquiterpene pyridine alkaloids from *Tripterygium wilfordii*, and structure anti-HIV activity relationships of *Tripterygium* alkaloids [J]. J Nat Prod, 2006, 69: 1271-1274.
- 25 Yu L, et al. Simultaneous detection of *Tripterygium wilfordii* sesquiterpene alkaloids by microemulsion electrokinetic chromatography coupled with large volume sample stacking [J]. Microchem J, 2019, 148: 449-455.
- 26 Gao C, et al. Chemical constituents from the roots of *Tripterygium wilfordii* and their cytotoxic activity [J]. J Asian Nat Prod Res, 2017, 19: 725-731.
- 27 Duan H, et al. Sesquiterpene alkaloids from *Tripterygium hypoglauca* and *Tripterygium wilfordii*: a new class of potent anti-HIV agents [J]. J Nat Prod, 2000, 63: 357-361.
- 28 Duan H, et al. Sesquiterpene alkaloids from extracts of *Tripterygium wilfordii* [J]. Chem Pharm Bull, 1999, 47: 1664-1667.
- 29 Luo Y, et al. Dihydroagarofuran derivatives from the dried roots of *Tripterygium wilfordii* [J]. J Nat Prod, 2011, 75(1): 98-102.
- 30 Xu J, et al. Terpenoids from *Tripterygium wilfordii* [J]. Phytochemistry, 2011, 72: 1482-1487.
- 31 Wang X, et al. Immunosuppressive sesquiterpenes from *Tripterygium wilfordii* [J]. Chem Pharm Bull, 2005, 53: 607-610.
- 32 Chen FY, et al. Neuroprotective dihydroagarofuran sesquiterpene derivatives from the leaves of *Tripterygium wilfordii* [J]. J Nat Prod, 2018, 81: 270-278.
- 33 Chen FY, et al. Dihydroagarofuran sesquiterpenoids esterified with organic acids from the leaves of *Tripterygium wilfordii* [J]. Fitoterapia, 2019, 137: 104185.
- 34 Wang C, et al. Bioactive sesquiterpene polyol esters from the leaves of *Tripterygium wilfordii* [J]. Fitoterapia, 2014, 96: 103-108.
- 35 Duan HQ, et al. Sesquiterpene polyol esters from *Tripterygium wilfordii* [J]. Phytochemistry, 2001, 56: 341-346.
- 36 Takaishi Y, et al. Sesquiterpene esters from *Tripterygium wilfordii* [J]. Phytochemistry, 1992, 31: 3943-3947.
- 37 Takaishi Y, et al. Sesquiterpene polyol esters from *Tripterygium wilfordii* var. *regelii* [J]. Phytochemistry, 1991, 30: 1567-1572.
- 38 Takaishi Y, et al. Structures of sesquiterpene polyol esters from *Tripterygium wilfordii* var. *regelii* [J]. Phytochemistry,

- 1991,30:3027-3031.
- 39 Cao Y, et al. Study on chemical constituents of *Tripterygium* [J]. Chin J Chin Mater Med (中国中药杂志), 2011, 36: 1028-1031.
 - 40 Chen Y, et al. Ceramides from *Tripterygium wilfordii* [J]. J Cent China Nor Univ; Nat Sci (华中师范大学学报: 自然科学版), 2005, 39: 225-227.
 - 41 Chen Y, et al. Study on the phenolic composition of *Tripterygium wilfordii* [J]. J South-Central Univ Nation (中南民族大学学报), 2005, 24(1): 8-10.
 - 42 Zheng YL, et al. Immunostatic effects of *Tripterygium wilfordii* and triptolide [J]. Acta Pharm Sin (药科学报), 1989, 24: 568-572.
 - 43 Yue M, et al. Effect of wilfortrine on human hepatic cancer HepG2 cell proliferation potential *in vitro* [J]. Genet Mol Res, 2015, 14: 15349-15355.
 - 44 Lin W, et al. Studies on the sesquiterpene alkaloids from *Tripterygium wilfordii* [J]. Acta Pharm Sin (药科学报), 2001: 116-119.
 - 45 Chen GB, et al. Inhibition of proliferation of human CIK, HCT116 and HepG2 cells by *Tripterygium* alkaloids components [J]. Mod Tradit Chin Med (现代中医药), 2014, 34(3): 76-78.
 - 46 Zhai KD, et al. Experimental study on the efficacy of total alkaloids from *Tripterygium wilfordii* [J]. Chin J Clin Pharmacol (中药药理与临床), 2011, 27(1): 33-36.
 - 47 Zhang W, et al. Effects of triptolide on the maturation and differentiation of mouse bone marrow dendritic cells induced by LPS and the secretion of inflammatory factors [J]. Chin J Immu (中国免疫学杂志), 2019, 35: 298-301.
 - 48 Yang LN, et al. Effects of *Tripterygium wilfordii* on inflammatory factors induced by lipopolysaccharide in RAW264. 7 cells [J]. Chin J Hosp Pharm (中国医院药学杂志), 2014, 34: 1164-1167.
 - 49 Tang LH. Study on pharmacology and anticoagulant effect of *Tripterygium wilfordii* [J]. Chin J Hyg Insect Equip (中华卫生杀虫药械), 2018, 24: 292-295.
 - 50 Tian YG, et al. Overview of hepatotoxicity studies on *Tripterygium wilfordii* in recent 20 years [J]. China J Chin Mater Med (中国中药杂志), 2019, 44: 3399-3405.
 - 51 Zhang H, et al. Acute toxicity of middle and last components of column chromatography in *Tripterygium wilfordii* [J]. Mod Chin Med (中国现代中药), 2019, 21: 296-302.
 - 52 Jiang QY, et al. Progress in research on effect of processing on toxicity, activity and constituent of *Tripterygium wilfordii* [J]. Chin J Exp Tradit Med Form (中国实验方剂学杂志), 2018, 24: 216-221.
-
- (上接第 2070 页)
- 10 Smith SB, Crager SE, Mogil JS. Paclitaxel-induced neuropathic hypersensitivity in mice: Responses in 10 inbred mouse strains [J]. Life Sci, 2004, 74: 2593-2604.
 - 11 Cliffer KD, Siuciak JA, Carson SR, et al. Physiological characterization of taxol-induced large-fiber sensory neuropathy in the rat [J]. Ann Neurol, 1998, 43(1): 46-55.
 - 12 Dina OA, Chen X, Reichling D, et al. Role of protein kinase cepsilon and protein kinase a in a model of paclitaxel-induced painful peripheral neuropathy in the rat [J]. Neurosci, 2001, 108: 507-515.
 - 13 Authier N, Gillet JP, Fialip J, et al. Description of a short-term taxol-induced nociceptive neuropathy in rats [J]. Brain Res, 2000, 887: 239-249.
 - 14 Prasad AS, Bao B, Beck FW, et al. Zinc-suppressed inflammatory cytokines by induction of a20-mediated inhibition of nuclear factor-kappab [J]. Nutrition, 2011, 27: 816-823.
 - 15 Liu F, Ma F, Kong G, et al. Zinc supplementation alleviates diabetic peripheral neuropathy by inhibiting oxidative stress and upregulating metallothionein in peripheral nerves of diabetic rats [J]. Biol Trace Elem Res, 2014, 158: 211-218.
 - 16 Huang ZZ, Li D, Liu CC, et al. Cx3cl1-mediated macrophage activation contributed to paclitaxel-induced drg neuronal apoptosis and painful peripheral neuropathy [J]. Brain Behav Immun, 2014, 40: 155-165.
 - 17 Ochi-ishi R, Nagata K, Inoue T, et al. Involvement of the chemokine ccl3 and the purinoceptor p2x7 in the spinal cord in paclitaxel-induced mechanical allodynia [J]. Mol Pain, 2014, 10: 53.
 - 18 Zhang H, Li Y, de Carvalho-Barbosa M, et al. Dorsal root ganglion infiltration by macrophages contributes to paclitaxel chemotherapy-induced peripheral neuropathy [J]. J Pain, 2016, 17: 775-786.
 - 19 Simonetti M, Agarwal N, Stosser S, et al. Wnt-fzd signaling sensitizes peripheral sensory neurons via distinct noncanonical pathways [J]. Neuron, 2014, 83: 104-121.
 - 20 Endo Y, Beauchamp E, Woods D, et al. Wnt-3a and dickkopf-1 stimulate neurite outgrowth in ewing tumor cells via a frizzled3- and c-jun n-terminal kinase-dependent mechanism [J]. Mol Cell Biol, 2008, 28: 2368-2379.