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# Structural diversity and biological activities of terpenoids derived from *Tripterygium wilfordii* Hook. f.

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Terpenoids, a heterogeneous group of natural products, have garnered considerable attention in the field of drug discovery. This is attributed to their vast diversity, intricate structural features, and extensive biological activities. *Tripterygium wilfordii* Hook. f., a traditional medicinal plant with widespread application in East Asia, is particularly enriched in terpenoids, which can be classified into sesquiterpenoids, diterpenoids, and triterpenoids. The present review provides a comprehensive elaboration of the chemical structures and biological activities of 217 terpenoids isolated from *T. wilfordii*. The purpose is to shed light on their potential in pharmacological research and to stimulate innovative drug discovery as well as clinical applications. These terpenoids display a broad spectrum of biological activities, such as antitumor, anti-inflammatory, immunosuppressive, and other therapeutic effects. Nevertheless, their clinical application is impeded by issues related to toxicity and poor bioavailability. Future research efforts should be concentrated on exploring effective strategies to alleviate toxicity and enhance drug delivery systems. In addition, in-depth investigation into the structure-activity relationships and the identification of new active constituents are crucial for the development of more potent and safer drugs. This review serves as an exhaustive reference for the discovery and development of novel drugs based on the natural active products of *T. wilfordii*, providing valuable insights and guidance for researchers in the relevant field.

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## Introduction

*Tripterygium wilfordii* Hook. f. (*T. wilfordii*), a liana plant belonging to the family Celastraceae, is predominantly distributed throughout East Asia, particularly in China.<sup>1</sup> The roots, leaves, flowers, and fruits of *T. wilfordii* have been extensively utilized in the treatment of autoimmune and inflammatory diseases in China for decades, attributed to their traditional Chinese medicinal properties of being cold in nature, bitter and acrid in taste, distributed in the liver and kidney channels, and also employed as an insecticide.<sup>2</sup> In recent years, terpenoids derived from *T. wilfordii* have garnered significant attention due to their diverse biological activities, including antitumor, anti-inflammatory, and immunosuppressive effects. It is noteworthy that the biological activities of terpenoids are closely related to their structural characteristics. The structural diversity of terpenoids is primarily characterized by the number of isoprene units and the presence or absence of nitrogen atoms. Sesquiterpenoids, diterpenoids, and triterpenoids are the main types of

terpenoids found in *T. wilfordii*, each with distinct structural features and biological activities. The  $\alpha,\beta$ -unsaturated lactone ring of diterpenoids, such as triptolide, is considered a key pharmacophore for their antitumor activity.<sup>3</sup> The quinone structure of triterpenoids, such as celastrol, is directly associated with antioxidant and anti-inflammatory effects.<sup>4</sup> Understanding the relationship between the structure and biological activity of these terpenoids is crucial for the development of new drugs and therapeutic agents. The structural diversity of terpenoids from *T. wilfordii* has been extensively studied to date.<sup>5</sup> These compounds include sesquiterpenoids, diterpenoids, triterpenoids, flavonoids, lignans, steroids, and others, each contributing to the plant's medicinal properties.<sup>4</sup> In this review article, we concentrate on the chemical structure and bioactivity of 217 terpenoids derived from *T. wilfordii*. We hope this article can provide a comprehensive overview and reference for drug development (Scheme 1).

## The chemical constituents of *T. wilfordii*

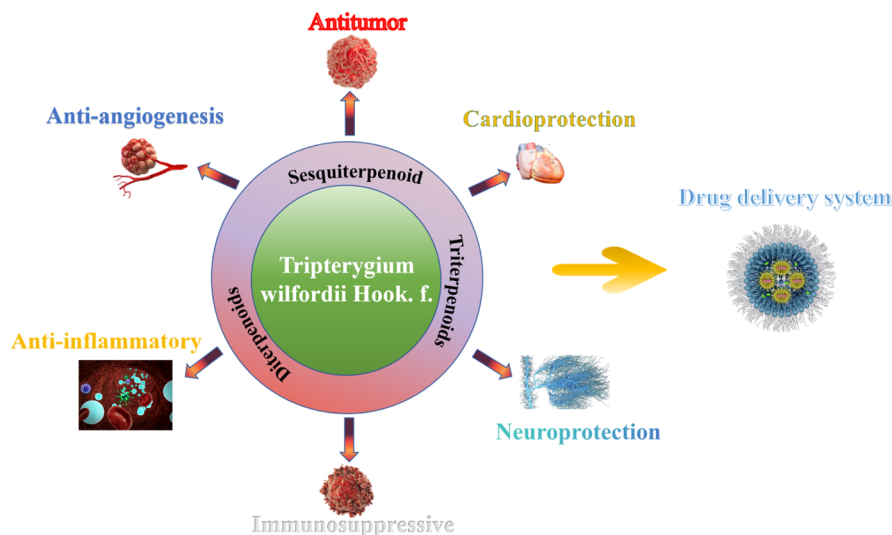
Extensive research has been conducted on the root, leaves, flowers, and fruits of *T. wilfordii*. These compounds can be categorized into various types, including sesquiterpenoids, diterpenoids, triterpenoids, flavonoids, lignans, steroids, and others.<sup>5</sup> In this section, we provide a comprehensive summary

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Scheme 1 Graphic illustration of biological activities of terpenoids derived from *T. wilfordii*.

of the names, chemical structures, and subtypes of terpenoids that serve as the major constituents of *T. wilfordii*, highlighting their potential roles in the plant's medicinal properties.

Sesquiterpenoids isolated from *T. wilfordii* are primarily categorized into two groups: nitrogen-containing sesquiterpenoids (compounds 1–50, 51–79) and nitrogen-free sesquiterpenoids (compounds 80–102).<sup>6</sup> The structural types of diterpenoids encompass abietane-type, kaurane-type, and other subtypes (compounds 103–150, 151–185).<sup>7</sup> Triterpenoids, based on their carbon skeleton and substituents, predominantly belong to the friedelane type, oleanane type, ursane type, and related groups (compounds 186–217).<sup>8</sup> The relevant information and chemical structures of terpenoids derived from *T. wilfordii* are depicted in Fig. 1 and Table 1.

### Biological activities of terpenoids

The bioactive constituents extracted from *T. wilfordii*, characterized by diverse skeletal types and structural features, exhibit a broad range of biological activities with potential therapeutic applications. These effects encompass antitumor, anti-inflammatory, immunosuppressive, and neuroprotective properties, among others. In this section, we provide a comprehensive summary of the biological activities of the principal active ingredients derived from *T. wilfordii*, highlighting their significance in the realm of pharmacology.

#### Antitumor activity

A multitude of studies have demonstrated the potent antitumor activity of terpenoids derived from *T. wilfordii*. Triptolide (126), a quintessential abietane-type diterpenoid first isolated from *T. wilfordii* in 1972, has been shown to possess significant, broad-spectrum antitumor effects and diverse sensitizing properties.<sup>35</sup> In recent years, an array of investigations have confirmed triptolide's substantial antitumor activity and therapeutic potential in various cancers, including breast cancer,<sup>3</sup> lung cancer,<sup>35</sup> liver cancer,<sup>35</sup> colon cancer,<sup>36</sup> thyroid cancer, and pancreatic

cancer.<sup>3,36</sup> As a predominant bioactive constituent in *T. wilfordii*, triptolide has been shown to exhibit significant antitumor properties by inducing apoptosis, autophagy, and cell senescence in a wide range of cancer cells, including conventional tumor cells, multidrug-resistant cancer cells, and certain cancer stem cells.<sup>35,36</sup> *In vitro* experiments demonstrated that exposure of prostate cancer cell lines (PC-3, LNCaP, and C4-2) to 50 nM triptolide (126) for 24 h induced autophagy through the CaMKK $\beta$ -AMPK signaling pathway, which subsequently inhibited mTOR activity while activating ULK1 and Beclin 1. *In vivo* validation using a PC-3 xenograft nude mouse model showed that administration of triptolide (0.15 mg per kg per 2 days) for 18 days in combination with the autophagy inhibitor chloroquine resulted in significant tumor growth suppression compared to monotherapy groups.<sup>37</sup> In subsequent *in vivo* studies, administration of triptolide at 1 mg kg<sup>-1</sup> significantly reduced metastatic nodules of SKOV3 xenograft tumors in mice, without causing remarkable systemic toxicity during treatment.<sup>3</sup> The molecular mechanisms of triptolide involved multiple signaling pathways, such as the RPL23-MDM2-p53 signaling pathway, transcription factor 3 activated signaling pathway, Akt/mTOR signaling pathway, NF- $\kappa$ B, vascular endothelial growth factor, and programmed cell death ligand 1.<sup>36,38,39</sup> New dihydroagarofuran sesquiterpene polyol esters, including tripteridine A (80), tripteridine C (12), and tripteridine G (83), have exhibited inhibitory effects on the growth of human tumor cell lines (Huh7, MCF-7, and HCT-116).<sup>15</sup> Cangoring K (76), dimacroregeline C (77), dimacroregeline D (78), and hypoglaunine A (8) have demonstrated potent cytotoxicity against SMMC7721 cells, with 20 h IC<sub>50</sub> values ranging from 0.26 to 9.67  $\mu$ M. This effect was achieved by disrupting the mitochondrial membrane potential.<sup>40</sup> These four constituents, along with hypoterpene D, also showed similar inhibitory effects on LN-229 cells, with IC<sub>50</sub> values ranging from 0.50 to 7.38  $\mu$ M.<sup>14</sup> Triptoquinone E (151) and triptoquinone F (152) have been reported to exhibit significant inhibition on human non-small cell lung cancer cell lines A549, human osteosarcoma cell lines HOS, and human

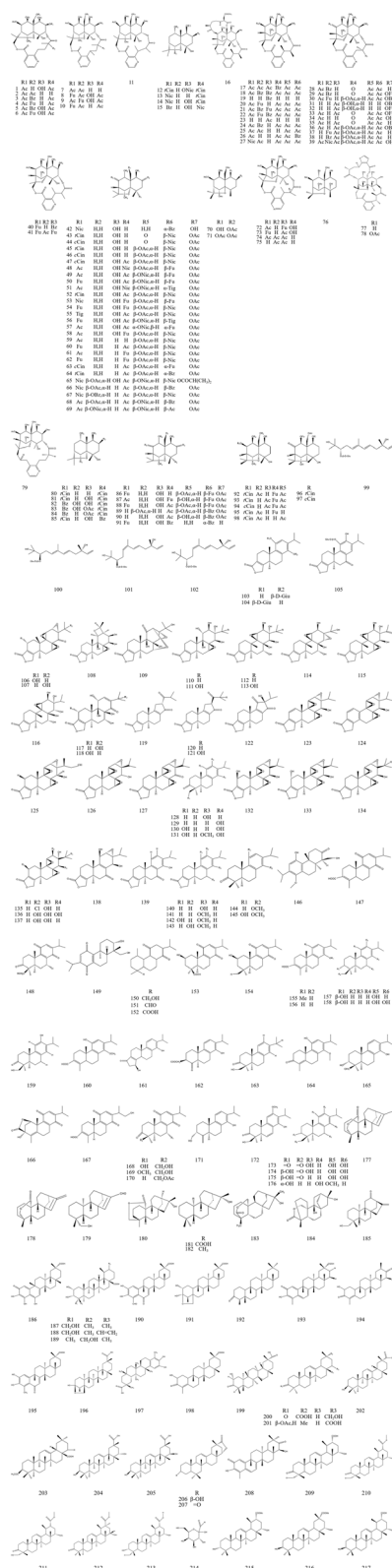


Fig. 1 The chemical structures of diterpenoids derived from *T. wilfordii*.

breast cancer cells MCF-7.<sup>29</sup> Celastrol (**193**), a friedelane-type triterpene derived from *T. wilfordii*, is another promising natural bioactive compound with a broad spectrum of activities

against multiple complex diseases. It has been found to have positive anti-cancer effects on various cancer types, such as cervical cancer, hepatocellular cancer, prostate cancer, blood cancer, lung cancer, and colon cancer.<sup>4</sup> The anticancer effects of celastrol are primarily achieved through multiple pathways, including inducing apoptosis,<sup>41</sup> causing cell cycle arrest,<sup>41</sup> inhibiting cell proliferation,<sup>42</sup> targeting tumor-promoting inflammation,<sup>43</sup> suppressing angiogenesis,<sup>44</sup> and restraining cell invasion and metastasis.<sup>4,45</sup> The antitumor effects of celastrol are associated with the up-regulation of caspase-3/7/9, E-cadherin, VEGF, bax, IκB, and STAT3, and down-regulation of HER2, *p*-AKT, *p*-ERK, MMP-9, ki-67, TNF-α, IL-6, and other genes involved in signaling pathways.<sup>4,41,42,45</sup> *In vitro* studies showed celastrol (**193**) significantly suppressed proliferation of ovarian cancer A2780 and SKOV3 cells with an 72 h IC<sub>50</sub> of around 2 μM, triggering G2/M phase arrest and apoptosis *via* ROS elevation.<sup>42</sup> *In vitro* studies demonstrated that triptonide (**127**) effectively suppressed proliferation of PaTu8988 and Panc-1 pancreatic cancer cells with an IC<sub>50</sub> of approximately 10.2 nM, inducing G2/M phase cell cycle arrest through activation of the MEKK4-MKK4-p38 signaling axis, accompanied by upregulated p21 expression and reduced CDK3 levels. *In vivo* experiments revealed that administration of 0.15 mg kg<sup>-1</sup> triptonide significantly inhibited tumor growth in PaTu8988 xenograft models without inducing observable systemic toxicity.<sup>37</sup> In addition, tripteridine C (**12**) inhibited the proliferation of HCT-116 colon cancer cells, with an IC<sub>50</sub> value of 5.8 μM. The underlying mechanism was the suppression of the JAK/STAT3 pathway.<sup>15</sup> Triptolidenol (**134**), an epoxy diterpene lactone diterpenoid obtained from *T. wilfordii*, has been shown to significantly suppress cell proliferation, cell migration, and induce cell cycle arrest at the S phase in human renal cell carcinoma through the mechanism of disrupting the NF-κB/COX-2 pathway by targeting ATP-binding sites of IKKβ.<sup>46</sup> Wilforine (**3**) has been detected to re-sensitize MDR cancer cells with 72 h IC<sub>50</sub> values exceeding 40 μM to chemotherapeutic drugs by binding to residues of P-gp such as LEU884, LYS887, THR176, and ASN172, thereby exerting an antitumor effect.<sup>47</sup> Tripterolide (**135**) was demonstrated to effectively inhibit proliferation of A549 and cisplatin-resistant A549/DDP lung cancer cells at an optimal concentration of 200 nM, mechanistically attributed to suppression of AEG-1 expression, subsequent downregulation of MDR-1, and enhanced cisplatin chemosensitivity.<sup>48</sup> Additionally, five triterpenes, including 28-hydroxy-3-oxo-olean-12-en-29-oic acid (**200**), regelin D (**212**), regelindiol B (**216**), 3-acetoxy oleanolic acid (**201**), and regelindiol A (**215**), have exhibited potent activity against HepG2 cells, A549 cells, and Hep3B cell lines, respectively, indicating the potential of these bioactive triterpenes for further investigation in advanced cancers.<sup>13</sup> Table 2 and Fig. 2 provide a concise review of the antitumor effects of TwHF-based therapy, with the anticancer mechanisms of these triterpenoids detailed further in the current literature.

### Anti-inflammatory activity

*T. wilfordii* has demonstrated significant anti-inflammatory effects, which are synergistically produced by its active



Table 1 Terpenoids isolated from *T. wilfordii*

No	Compounds	Type	Subtype	Ref.
1	Tripfordine A	Sesquiterpenoid	Nitrogen-containing	9
2	Tripfordine B	Sesquiterpenoid	Nitrogen-containing	9
3	Wilforine	Sesquiterpenoid	Nitrogen-containing	9 and 10
4	Wilforgine	Sesquiterpenoid	Nitrogen-containing	9 and 10
5	Wilfordine	Sesquiterpenoid	Nitrogen-containing	11 and 12
6	Wilfortrine	Sesquiterpenoid	Nitrogen-containing	11 and 12
7	Tripfordine C	Sesquiterpenoid	Nitrogen-containing	9
8	Hypoglaunine A	Sesquiterpenoid	Nitrogen-containing	13 and 14
9	Hypoglaunine B	Sesquiterpenoid	Nitrogen-containing	9 and 13
10	Hypoglaunine D	Sesquiterpenoid	Nitrogen-containing	9 and 13
11	Euonymine	Sesquiterpenoid	Nitrogen-containing	9
12	Tripteridine C	Sesquiterpenoid	Nitrogen-containing	15
13	Tripteridine D	Sesquiterpenoid	Nitrogen-containing	15
14	Tripteridine E	Sesquiterpenoid	Nitrogen-containing	15
15	Tripteridine J	Sesquiterpenoid	Nitrogen-containing	15
16	Tripterygiumine A	Sesquiterpenoid	Nitrogen-containing	5 and 16
17	Tripterygiumine B	Sesquiterpenoid	Nitrogen-containing	5
18	Tripterygiumine C	Sesquiterpenoid	Nitrogen-containing	5
19	Tripterygiumine D	Sesquiterpenoid	Nitrogen-containing	5
20	Tripterygiumine E	Sesquiterpenoid	Nitrogen-containing	5
21	Tripterygiumine F	Sesquiterpenoid	Nitrogen-containing	5
22	Tripterygiumine G	Sesquiterpenoid	Nitrogen-containing	5
23	Tripterygiumine H	Sesquiterpenoid	Nitrogen-containing	5
24	Tripterygiumine I	Sesquiterpenoid	Nitrogen-containing	5
25	Tripterygiumine J	Sesquiterpenoid	Nitrogen-containing	5
26	Tripterygiumine K	Sesquiterpenoid	Nitrogen-containing	5
27	Tripterygiumine L	Sesquiterpenoid	Nitrogen-containing	5
28	Tripterygiumine M	Sesquiterpenoid	Nitrogen-containing	5
29	Tripterygiumine N	Sesquiterpenoid	Nitrogen-containing	5
30	Tripterygiumine O	Sesquiterpenoid	Nitrogen-containing	5
31	Tripterygiumine P	Sesquiterpenoid	Nitrogen-containing	5
32	Tripterygiumine Q	Sesquiterpenoid	Nitrogen-containing	5
33	Tripterygiumine S	Sesquiterpenoid	Nitrogen-containing	5
34	Tripterygiumine T	Sesquiterpenoid	Nitrogen-containing	5
35	Tripterygiumine U	Sesquiterpenoid	Nitrogen-containing	5
36	Tripterygiumine V	Sesquiterpenoid	Nitrogen-containing	5
37	1-Desacetylwilforgine	Sesquiterpenoid	Nitrogen-containing	17
38	1-Desacetylwilforine	Sesquiterpenoid	Nitrogen-containing	17
39	9'-Hydroxy-2-nicotinoylwilforine	Sesquiterpenoid	Nitrogen-containing	17
40	Tripterygiumine W	Sesquiterpenoid	Nitrogen-containing	18
41	Wilformine H	Sesquiterpenoid	Nitrogen-containing	18
42	Tripterygiumine R	Sesquiterpenoid	Nitrogen-containing	18
43	Triptersinine A	Sesquiterpenoid	Nitrogen-containing	19
44	Triptersinine B	Sesquiterpenoid	Nitrogen-containing	19
45	Triptersinine C	Sesquiterpenoid	Nitrogen-containing	19
46	Triptersinine D	Sesquiterpenoid	Nitrogen-containing	19
47	Triptersinine E	Sesquiterpenoid	Nitrogen-containing	19
48	Triptersinine F	Sesquiterpenoid	Nitrogen-containing	19
49	Triptersinine G	Sesquiterpenoid	Nitrogen-containing	19
50	Triptersinine H	Sesquiterpenoid	Nitrogen-containing	19
51	Triptersinine L	Sesquiterpenoid	Nitrogen-containing	19
52	Triptersinine M	Sesquiterpenoid	Nitrogen-containing	19
53	Triptersinine N	Sesquiterpenoid	Nitrogen-containing	19
54	Triptersinine O	Sesquiterpenoid	Nitrogen-containing	19
55	Triptersinine P	Sesquiterpenoid	Nitrogen-containing	19
56	Triptersinine Q	Sesquiterpenoid	Nitrogen-containing	19
57	Triptersinine R	Sesquiterpenoid	Nitrogen-containing	19
58	Triptersinine S	Sesquiterpenoid	Nitrogen-containing	19
59	Triptersinine T	Sesquiterpenoid	Nitrogen-containing	19
60	Triptersinine Z4	Sesquiterpenoid	Nitrogen-containing	5 and 19
61	Triptersinine Z5	Sesquiterpenoid	Nitrogen-containing	5 and 19
62	Triptersinine Z6	Sesquiterpenoid	Nitrogen-containing	5 and 19
63	Triptersinine Z7	Sesquiterpenoid	Nitrogen-containing	5 and 19



Table 1 (Contd.)

No	Compounds	Type	Subtype	Ref.
64	Triptersinine Z8	Sesquiterpenoid	Nitrogen-containing	5 and 19
65	Wilforsinine C	Sesquiterpenoid	Nitrogen-containing	5 and 20
66	Wilforsinine D	Sesquiterpenoid	Nitrogen-containing	5 and 20
67	Wilforsinine E	Sesquiterpenoid	Nitrogen-containing	5 and 20
68	Wilforsinine G	Sesquiterpenoid	Nitrogen-containing	5 and 20
69	Wilforsinine H	Sesquiterpenoid	Nitrogen-containing	5 and 20
70	Wilforsinine A	Sesquiterpenoid	Nitrogen-containing	21
71	Wilforsinine B	Sesquiterpenoid	Nitrogen-containing	21
72	Hypoglaunine E	Sesquiterpenoid	Nitrogen-containing	13
73	Hypoglaunine F	Sesquiterpenoid	Nitrogen-containing	13
74	Peritassine A	Sesquiterpenoid	Nitrogen-containing	13 and 22
75	Wilfordinine A	Sesquiterpenoid	Nitrogen-containing	13
76	Cangorin K	Sesquiterpenoid	Nitrogen-containing	14
77	Dimacrorregeline C	Sesquiterpenoid	Nitrogen-containing	14
78	Dimacrorregeline D	Sesquiterpenoid	Nitrogen-containing	14
79	Euonine	Sesquiterpenoid	Nitrogen-containing	13 and 22
80	Tripteridine A	Sesquiterpenoids	Nitrogen-free	15
81	Tripteridine B	Sesquiterpenoids	Nitrogen-free	15
82	Tripteridine F	Sesquiterpenoids	Nitrogen-free	15
83	Tripteridine G	Sesquiterpenoids	Nitrogen-free	15
84	Tripteridine H	Sesquiterpenoids	Nitrogen-free	15
85	Tripteridine I	Sesquiterpenoids	Nitrogen-free	15
86	Triptersinine I	Sesquiterpenoids	Nitrogen-free	22 and 23
87	Triptersinine J	Sesquiterpenoids	Nitrogen-free	22 and 23
88	Triptersinine K	Sesquiterpenoids	Nitrogen-free	22 and 23
89	Wilforsinine F	Sesquiterpenoids	Nitrogen-free	5 and 20
90	Triptregelol A	Sesquiterpenoids	Nitrogen-free	22 and 23
91	Triptregelol B	Sesquiterpenoids	Nitrogen-free	22 and 23
92	Triptersinine V	Sesquiterpenoids	Nitrogen-free	5
93	Triptersinine W	Sesquiterpenoids	Nitrogen-free	5
94	Triptersinine X	Sesquiterpenoids	Nitrogen-free	5
95	Triptersinine Y	Sesquiterpenoids	Nitrogen-free	5
96	Triptersinine Z1	Sesquiterpenoids	Nitrogen-free	5
97	Triptersinine Z2	Sesquiterpenoids	Nitrogen-free	5
98	Triptersinine Z3	Sesquiterpenoids	Nitrogen-free	5
99	Triptergosidol A	Sesquiterpenoids	Nitrogen-free	6
100	Triptergosidol B	Sesquiterpenoids	Nitrogen-free	6
101	Triptergosidol C	Sesquiterpenoids	Nitrogen-free	6
102	Triptergosidol D	Sesquiterpenoids	Nitrogen-free	6
103	Tripterycoside A	Diterpenoids	Abietane	24
104	Tripterycoside B	Diterpenoids	Abietane	24
105	Tripterycoside C	Diterpenoids	Abietane	24
106	2 $\alpha$ -Hydroxytriptonide	Diterpenoids	Abietane	24
107	15-Hydroxytriptonide	Diterpenoids	Abietane	24
108	Triptergulide A	Diterpenoids	Abietane	25 and 26
109	Triptergulide B	Diterpenoids	Abietane	25 and 26
110	Triptergulide C	Diterpenoids	Abietane	25 and 26
111	Triptergulide D	Diterpenoids	Abietane	25 and 26
112	Triptergulide E	Diterpenoids	Abietane	25 and 26
113	Triptergulide F	Diterpenoids	Abietane	25 and 26
114	Triptergulide G	Diterpenoids	Abietane	25 and 26
115	Triptergulide H	Diterpenoids	Abietane	25 and 26
116	Triptergulide I	Diterpenoids	Abietane	25 and 26
117	Triptergulide J	Diterpenoids	Abietane	25 and 26
118	Triptergulide K	Diterpenoids	Abietane	25 and 26
119	Tripterlide A	Diterpenoids	Abietane	27
120	Tripterlide B	Diterpenoids	Abietane	27
121	Tripterlide C	Diterpenoids	Abietane	27
122	Tripterlide D	Diterpenoids	Abietane	27
123	Tripterlide E	Diterpenoids	Abietane	27
124	Tripterlide F	Diterpenoids	Abietane	27
125	16-Hydroxytriptolide	Diterpenoids	Abietane	28
126	Triptolide	Diterpenoids	Abietane	2

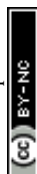


Table 1 (Contd.)

No	Compounds	Type	Subtype	Ref.
127	Triptonide	Diterpenoids	Abietane	2
128	Hinokione	Diterpenoids	Abietane	21
129	Triptonoterpene	Diterpenoids	Abietane	28
130	Triptobenzene A	Diterpenoids	Abietane	20
131	Wilforol F	Diterpenoids	Abietane	7
132	Triptiolide	Diterpenoids	Abietane	28
133	Tripterolide	Diterpenoids	Abietane	28
134	Triptolidenol	Diterpenoids	Abietane	28
135	Tripchlorolide	Diterpenoids	Abietane	28
136	Isotriptetraolide	Diterpenoids	Abietane	28
137	Triptriolide	Diterpenoids	Abietane	28
138	Triptioltonide	Diterpenoids	Abietane	28
139	Triptonolide	Diterpenoids	Abietane	28
140	Triptophenolide	Diterpenoids	Abietane	2
141	Triptophenolide methyl ether	Diterpenoids	Abietane	28
142	Neotriptophenolide	Diterpenoids	Abietane	28
143	Isonotriptophenolide	Diterpenoids	Abietane	28
144	Triptonoterpene methyl ether	Diterpenoids	Abietane	28
145	Neotriptonoterpene	Diterpenoids	Abietane	7
146	Triptonoterpenol	Diterpenoids	Abietane	28
147	Triptoquinone A	Diterpenoids	Abietane	7 and 21
148	Triptoquinone B	Diterpenoids	Abietane	21
149	Triptoquinone C	Diterpenoids	Abietane	28
150	Triptoquinone D	Diterpenoids	Abietane	7 and 29
151	Triptoquinone E	Diterpenoids	Abietane	29
152	Triptoquinone F	Diterpenoids	Abietane	7 and 21
153	Triptoquinone G	Diterpenoids	Abietane	28
154	Triptoquinone H	Diterpenoids	Abietane	21
155	Triptinin A	Diterpenoids	Abietane	20
156	Triptinin B	Diterpenoids	Abietane	20
157	Triptobenzene B	Diterpenoids	Abietane	7
158	Triptobenzene J	Diterpenoids	Abietane	29
159	Triptobenzene M	Diterpenoids	Abietane	7
160	Triptobenzene H	Diterpenoids	Abietane	20
161	Triptobenzene I	Diterpenoids	Abietane	30
162	Triptobenzene Q	Diterpenoids	Abietane	31
163	Triptobenzene R	Diterpenoids	Abietane	31
164	Triptobenzene S	Diterpenoids	Abietane	31
165	Triptobenzene Y	Diterpenoids	Abietane	31
166	Triregelin A	Diterpenoids	Abietane	7
167	Triregelin B	Diterpenoids	Abietane	7
168	Triregelin C	Diterpenoids	Abietane	7
169	Triregelin D	Diterpenoids	Abietane	7
170	Triregelin E	Diterpenoids	Abietane	7
171	Triregelin F	Diterpenoids	Abietane	7
172	Triregelin G	Diterpenoids	Abietane	7
173	Triregelin H	Diterpenoids	Abietane	7
174	Triregelin I	Diterpenoids	Abietane	7
175	Triregelin J	Diterpenoids	Abietane	7
176	Triregelin K	Diterpenoids	Abietane	7
177	Doianoterpene A	Diterpenoids	Kaurane	32
178	Doianoterpene B	Diterpenoids	Kaurane	32
179	Doianoterpene C	Diterpenoids	Kaurane	32
180	Neotripterifordin	Diterpenoids	Kaurane	32
181	Doianoterpene D	Diterpenoids	Kaurane	32
182	Ent-kauranol	Diterpenoids	Kaurane	32
183	Tripterifordin	Diterpenoids	Kaurane	28
184	Tripterinin	Diterpenoids	Kaurane	28
185	Triregelin L	Diterpenoids	Kaurane	7
186	3,4,6-Trihydroxy-2-oxo-1(10),3,5,7-tetraen-23,24-nor-D: A-friedooleana-29-oicacid	Triterpenoids	Friedelane	5
187	2 $\alpha$ ,3 $\alpha$ ,23-Trihydroxyurs-12-en-28-oicacid	Triterpenoids	Friedelane	5
188	2 $\alpha$ ,3 $\alpha$ ,23-Trihydroxyurs-12,20(30)-dien-28-oicacid	Triterpenoids	Friedelane	5

Table 1 (Contd.)

No	Compounds	Type	Subtype	Ref.
189	2 $\alpha$ , 3 $\alpha$ , 24-Trihydroxyurs-12-en-28-oic acid	Triterpenoids	Friedelane	5
190	Demethylzeylasteral	Triterpenoids	Friedelane	8
191	Orthophenic acid	Triterpenoids	Friedelane	8
192	Polpunic acid	Triterpenoids	Friedelane	8
193	Celastrol	Triterpenoids	Friedelane	8
194	Triptocalline A	Triterpenoids	Friedelane	8
195	Wilforol A	Triterpenoids	Friedelane	8
196	Salaspermic acid	Triterpenoids	Friedelane	16
197	Wilforic acid A	Triterpenoids	Friedelane	28
198	Wilforic acid B	Triterpenoids	Friedelane	28
199	Wilforic acid C	Triterpenoids	Oleanane	28
200	28-Hydroxy-3-oxo-olean-12-en-29-oic acid	Triterpenoids	Oleanane	13
201	3-acetoxy oleanolic acid	Triterpenoids	Oleanane	13
202	3-Epikatonol acid	Triterpenoids	Oleanane	8
203	3 $\beta$ -Acetyl-oleanolic acid	Triterpenoids	Oleanane	33
204	Triptotriterpenic acid A	Triterpenoids	Oleanane	16
205	Triptotriterpenic acid B	Triterpenoids	Oleanane	8
206	Wilforide A	Triterpenoids	Oleanane	8
207	Wilforide B	Triterpenoids	Oleanane	8
208	22 $\beta$ -Hydroxytingenone	Triterpenoids	Ursane	8
209	Demethylregelin	Triterpenoids	Ursane	8
210	Regelin	Triterpenoids	Ursane	8
211	Regelin C	Triterpenoids	Ursane	8 and 13
212	Regelin D	Triterpenoids	Ursane	8 and 13
213	Triptocallic acid A	Triterpenoids	Ursane	8
214	Dulcioic acid	Triterpenoids	Ursane	34 and 12
215	Regelindiol A	Triterpenoids	Ursane	10 and 13
216	Regelindiol B	Triterpenoids	Ursane	10 and 13
217	Triptotriterpenic acid C	Triterpenoids	Ursane	10

constituents, including sesquiterpenoids, diterpenoids, and triterpenoids. Particularly in China, *T. wilfordii* is widely recognized for its therapeutic potential in treating rheumatoid arthritis, a common autoimmune disease.<sup>50</sup> Network pharmacology studies have identified key genes such as AKT1, TNF- $\alpha$ , IL-6, CXCL8, MMP9, PTGS2, CASP3, and JUN, which are

involved in the inflammatory response and are modulated by Triptolide (126) with a concentration of 50 nM for 24 h during renal injury. This diterpenoid has been reported to inhibit proliferation, induce apoptosis, and regulate the cell cycle in immunoglobulin A nephropathy mesangial cells, highlighting its molecular mechanisms.<sup>51</sup> Furthermore, triptolide has been

Table 2 Antitumor activity of key terpenoids from *T. wilfordii*

Compound	Type	Model	Mechanism	Dose/IC50	Ref.
Triptolide (126)	Diterpenoid	PC-3 (prostate cancer) Nude mouse with PC-3 cell tumor	Modulates autophagy, LC3B activation	50 nM in vitro 0.15 mg kg <sup>-1</sup> intraperitoneal injection	37
Celastrol (193)	Triterpenoid	A2780 (ovarian cancer cells) Nude mouse with A2780 cell tumor	G2/M phase arrest and apoptosis ROS elevation	2 $\mu$ M in vitro 2 mg kg <sup>-1</sup> intraperitoneal injection	42
Triptonide (127)	Diterpenoid	PaTu8988 (pancreatic cancer) Female NOD/SCID mouse with PaTu8988 cell tumor	MAPK pathway suppression	10 nM in vitro 5 mg kg <sup>-1</sup> intraperitoneal injection	49
Triptoquinone E (151)	Diterpenoid	A549 (lung cancer)	Cytotoxicity	35 $\mu$ M in vitro	29
Wilforine (3)	Sesquiterpenoid	MDR cancer cells	P-gp inhibition	40 $\mu$ M in vitro	47
Hypoglaunine A (8)	Sesquiterpenoid	SMMC7721 (liver cancer)	Mitochondrial disruption	0.29 $\mu$ M in vitro	40
Tripteridine C (12)	Sesquiterpenoid	HCT-116 (colon cancer)	Cytotoxicity	5.8 $\mu$ M in vitro	15
Triptolidenol (134)	Diterpenoid	768-O (renal cancer)	IKK $\beta$ /COX-2 blockade	87 nM in vitro	46
Cangorin K (76)	Sesquiterpenoid	LN-229 (glioblastoma)	Cytotoxicity	0.5 $\mu$ M in vitro	40
Triptoquinone F (152)	Diterpenoid	MCF-7 (breast cancer)	Cytotoxicity	4.5 $\mu$ M in vitro	29
Triphlorolide (135)	Diterpenoid	A549 and A549/DDP (lung cancer)	AEG-1 inhibition	200 nM in vitro	48



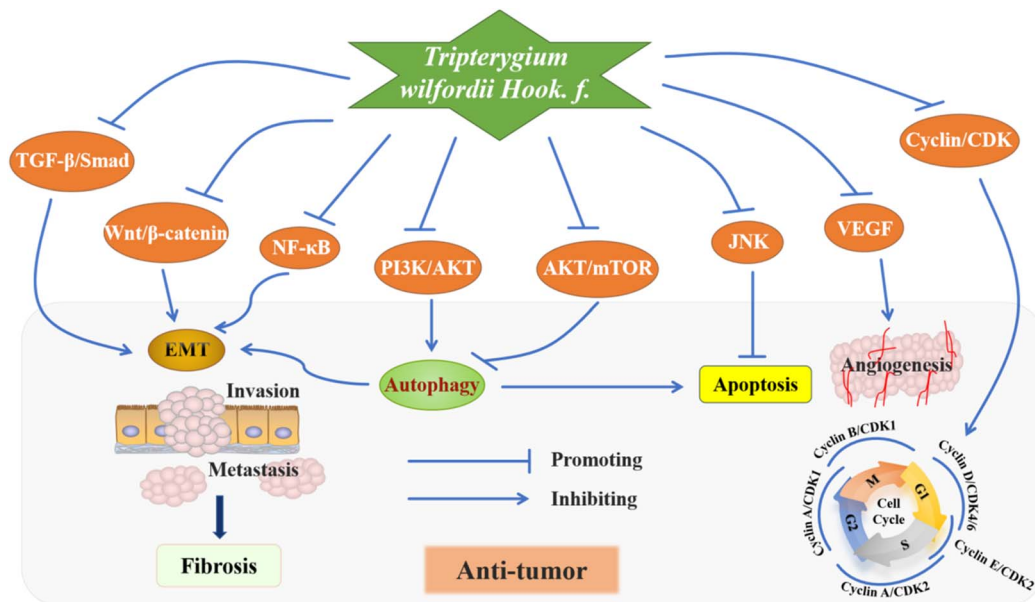


Fig. 2 Schematic of the molecular targets of *T. wilfordii* in the treatment of tumor.

shown to act on rheumatoid arthritis-related pathways through eight targets, including MCL1, JUN, TNF, STAT1, RELA, IL23A, CASP3, and CDKN1A.<sup>52</sup> A triptolide-phospholipid complex (TPCX) was engineered to enable transdermal rheumatoid arthritis therapy. Compared with free triptolide, TPCX demonstrated significantly improved aqueous solubility and *in vitro* skin permeation capacity. In arthritis models, TPCX topical formulation improved pharmacokinetics, reduced paw edema, and downregulated TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 while protecting articular tissue. Transdermal delivery minimized systemic exposure, potentially reducing hepatorenal toxicity.<sup>53</sup> Intraperitoneal celastrol (193) (1 mg per kg per day), administered as a 7-day pretreatment in endotoxemia or 1 day post-treatment in CLP-induced sepsis models, covalently targeted PKM2 and HMGB1, validated by ABPP, SPR, and molecular docking. This dual-binding inhibited Warburg metabolism and proinflammatory cytokine secretion (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), improving survival ( $P < 0.05$ ) and alleviating organ injury. Despite multi-target anti-inflammatory efficacy, low oral bioavailability and dose-dependent ALT/AST elevations with potential hepatorenal toxicity necessitate cautious translational optimization.<sup>54</sup> Intra-articular celastrol-loaded chitosan-capped hollow mesoporous silica nanoparticles (CSL@HMSNs-Cs) enhanced the solubility of celastrol, while surface conjugation with chitosan conferred pH-responsive drug release, thereby improving CSL bioavailability. At 200  $\mu\text{g mL}^{-1}$ , they suppressed IL-1 $\beta$ /TNF- $\alpha$ /IL-6 and MMPs *via* NF- $\kappa$ B inhibition *in vitro*. In MIA-induced OA rats, treatment improved cartilage integrity, reduced effusion, and alleviated pain.<sup>55</sup> Additional studies have confirmed celastrol's potent effects in treating rheumatoid arthritis, dementia, diabetic nephropathy, angiogenesis, and ulcerative colitis, with biological activity against various cell types including fibroblast-like synoviocytes, astrocytes, podocytes, human umbilical vein endothelial cells, and colonic epithelial cells.<sup>56</sup> The anti-inflammatory activity of celastrol is associated with the

expression of heme oxygenase-1, PI3K/Akt/mTOR, ROS/Akt/p70S6K, and Fc $\epsilon$ RI signaling pathways.<sup>5,56</sup> The results of a growing number of studies suggested that inflammation was involved in regulating different stages of the tumorigenesis process. The role of inflammation in tumorigenesis was well-established, with Cyclooxygenase-2 (COX-2) playing a pivotal role in the inflammatory process and cancer development. The initiation of COX-2 transcription on account of binding of activated NF- $\kappa$ B and COX-2 promoter region.<sup>46,57</sup> Triptolidenol (134) was demonstrated to suppress NF- $\kappa$ B/COX-2 signaling by targeting IKK $\beta$ 's ATP-binding domain in ccRCC, reducing IL-1 $\beta$ , TNF- $\alpha$ , and COX-2 while inducing caspase-dependent apoptosis under 48-h treatment. This dual anti-inflammatory/antitumor profile suggests Triptolidenol's potential for COX-2-mediated ccRCC therapy with optimized dosing.<sup>46</sup> Tripteridine C (12), tripteridine E (14), and tripteridine J (15) have exhibited potent anti-inflammatory effects by inhibiting the secretion levels of TNF- $\alpha$  and IL-6.<sup>15</sup> Wilforine (3), wilfortrine (6), wilforine (4), and wilfordine (5) have also shown inhibitory effects on cancer cells, with wilforine demonstrating anti-inflammatory effects in adjuvant arthritis rat models.<sup>11,12</sup> Triptonide (127) administration significantly alleviated CFA-induced inflammatory pain in murine models by inhibiting AKT phosphorylation and suppressing TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 expression, while *in vitro* experiments demonstrated its inhibitory effects on pro-inflammatory cytokine production in ND7/23 cells. Intravenous delivery (0.1, 0.5, 2.0 mg kg<sup>-1</sup>) attenuated paw edema and nociceptive hypersensitivity in arthritic mice through AKT pathway modulation and cytokine downregulation, indicating its potential as a therapeutic agent for chronic inflammatory disorders.<sup>58,59</sup> Nine nitrogen-containing sesquiterpenoids, triptersinines A-L (43–51), have exhibited moderate inhibitory effects on NO nitric oxide (NO) production in lipopolysaccharide (LPS)-induced macrophages, along with neotripterifordin.<sup>12</sup> These findings underscore the complex molecular interaction

Table 3 Summary of the anti-inflammatory activities of terpenoids

Compound	Type	Model	Dose	Key targets	Ref.
Triptolide (126)	Diterpenoid	IgAN mesangial cells Wistar rats model of RA	50 nM in vitro 0.5 mg kg <sup>-1</sup> transdermal administration	p-JUN signaling TNF- $\alpha$ , IL-1b, IL-6	35 and 51 53
Celastrol (193)	Triterpenoid	Chondrocytes <i>in vitro</i>	200 $\mu$ g mL <sup>-1</sup>	IL-1 $\beta$ , TNF- $\alpha$ , IL-6, MMP-3 and MMP-13 and NF- $\kappa$ B signaling pathway	55
		Male BALB/c mice sepsis induced by cecal ligation puncture Male BALB/c mice LPS-induced endotoxemia	1 mg kg <sup>-1</sup> intraperitoneal injection	PKM2, HMGB1, TNF- $\alpha$ , IL-1 $\beta$ , IL-6	54
Triptolidenol (134)	Diterpenoid	HK-2 ccRCC cells Caki-1 ACHN 786-O	>1000 nM in vitro 245 nM in vitro 140 nM in vitro 87 nM in vitro	IKK $\beta$ /NF- $\kappa$ B, COX-2	46 and 57
Wilforine (3)	Sesquiterpenoid	Adjuvant arthritis rat ( <i>in vivo</i> )	10 mg kg <sup>-1</sup> intragastric administration	IL-6, IL-8	12 and 11
Wilforgine (4)	Sesquiterpenoid	Adjuvant arthritis rat ( <i>in vivo</i> )	10 mg kg <sup>-1</sup> intragastric administration	IL-6, IL-8	12 and 11
Triptonide (127)	Diterpenoid	Rat DRG neuron hybrid ND7/23 cells Mouse injection of CFA	1 $\mu$ g mL <sup>-1</sup> in vitro  0.1, 0.5, 2.0 mg kg <sup>-1</sup> Intravenous Administration	AKT, TNF- $\alpha$ IL-1 $\beta$ , IL-6	58 and 59

effects and reveal the potential pharmacological and molecular mechanisms of *T. wilfordii* in the treatment of inflammatory diseases. The studies summarized in Table 3 and Fig. 3, along with the current investigations and researches, highlight the diverse anti-inflammatory effects of *T. wilfordii*'s constituents.<sup>34</sup>

### Immunosuppressive activity

The immunosuppressive effects of terpenoids from *T. wilfordii* are related to their ability to modulate the immune response by suppressing the activation and proliferation of immune cells.<sup>60</sup>

Celastrol (193) has been shown to reduce the rate of IL-17 producing CD4<sup>+</sup> and CD8<sup>+</sup> T cells to T<sub>reg</sub>, demonstrating its potential effects to inhibit the expansion of antigen-reactive T cells and the migration of inflammatory cells into an arthritic joint.<sup>61</sup> Celastrol also markedly suppresses the expression of TRAP, osteoclastic genes (Trap, MMP-9, CTR, Ctsk), and transcriptional factors (c-Jun, c-Fos, and NFATc1).<sup>5,62</sup> Celastrol at concentrations from 0.03–30  $\mu$ M showed significant immunomodulatory effects. It inhibited cytoplasmic DNA- and RNA-mediated IFN production *in vitro* and *in vivo* by targeting IRF3 and NF- $\kappa$ B pathways. In Trex1<sup>-/-</sup> mice, celastrol (0.2–5 mg kg<sup>-1</sup>)

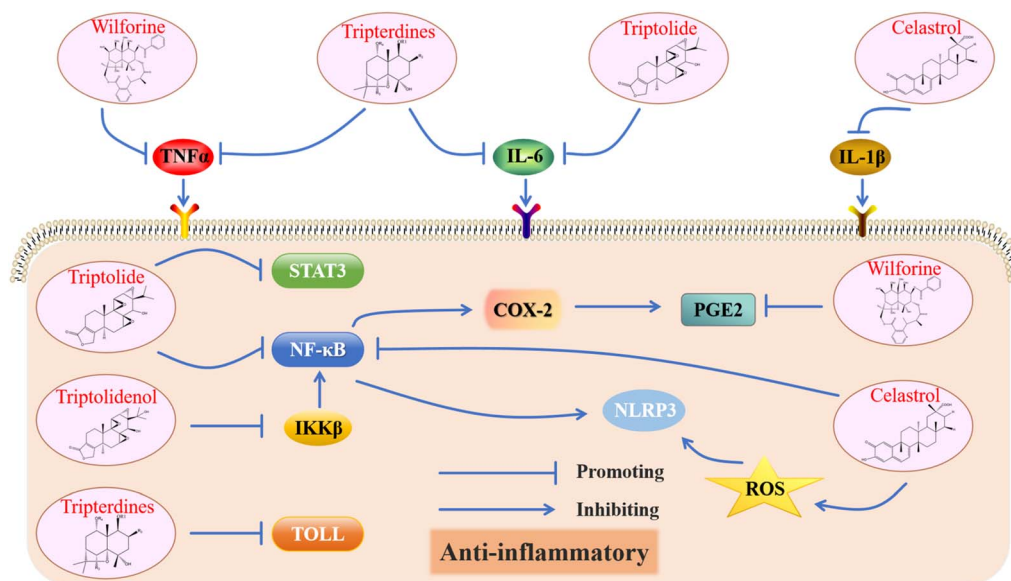


Fig. 3 Mechanisms of *T. wilfordii* and active compounds on anti-inflammatory activity.



Table 4 Immunosuppressive activities of terpenoids from *T. wilfordii*

Compound	Type	Model	Dose/IC50	Key targets	Ref.
Celastrol (193)	Triterpenoid	RAW264.7 HEK293T BJ cells	0.03–30 $\mu\text{M}$ in vitro	Cytoplasmic DNA- and RNA-mediated IFN production	58
Triptolide (126)	Diterpenoid	Trex1 <sup>-/-</sup> mice on C57BL/6	0.2–5 mg kg <sup>-1</sup> intraperitoneal injection	T Cell activation IRF3 activation	63
		UCMSCs	0.01 $\mu\text{M}$ in vitro	IL-10 PD-L1 PD-L2	64
		Systemic lupus erythematosus mice	100 $\mu\text{g/kg}$	IL-6, TNF- $\alpha$ , IFN- $\gamma$ , IL-10, CD4+CD25+Foxp3+T cell positivity	58
Triphlorolide (135)	Diterpenoid	Female C57BL/6 mice	40 $\mu\text{g kg}^{-1}$ intraperitoneal injection	ERK1/2-NF- $\kappa$ B, JAK/STAT	65
Demethylzeylasteral (190)	Triterpenoid	CDT8 <sup>+</sup> cell	4.54 $\mu\text{M}$ in vitro	STAT1-CXCL9/10 signaling, JAK2	66
		C57BL/6 mice with B16F10 cells	5 mg kg <sup>-1</sup> 2.5 mg kg <sup>-1</sup> intraperitoneal injection		
Triphlorolide (135)	Diterpenoids	EAE C57BL/6 mice model	40 $\mu\text{g kg}^{-1}$ intraperitoneal injection	ERK1/2-NF- $\kappa$ B, JAK/STAT	65
Wilfordine (5)	Sesquiterpenoid	H9 lymphocytes	20 $\mu\text{g mL}^{-1}$	Anti-HIV activity	9
Wilfortrine (6)	Sesquiterpenoid	H9 lymphocytes	>100 $\mu\text{g mL}^{-1}$	Anti-HIV activity	9
Hypoglaunine B (9)	Sesquiterpenoid	H9 lymphocytes	>100 $\mu\text{g mL}^{-1}$	Anti-HIV activity	9
Euonymine (11)	Sesquiterpenoid	H9 lymphocytes	>100 $\mu\text{g mL}^{-1}$	Anti-HIV activity	9
Hypoglaunine A (8)	Sesquiterpenoid	H9 lymphocytes	>100 $\mu\text{g mL}^{-1}$	Anti-HIV activity	9
Tripfordine	Sesquiterpenoid	H9 lymphocytes	1 $\mu\text{g mL}^{-1}$ in vitro	Anti-HIV activity	28
Triptoquinone	Diterpenoid	Peripheral blood mononuclear cells	10 $\mu\text{g mL}^{-1}$ in vitro	IL-1 $\alpha$ IL-1 $\beta$	28
Euonine (79)	Sesquiterpenoid	DNCB-induced DTH reaction on mouse skin	80 mg kg <sup>-1</sup> intraperitoneal injection	Hemolysin reaction	28

for 3 days reduced autoantibody production, and suppresses T cell activation. It also downregulated IFN-stimulated genes and protects against interferonopathy-related autoimmune diseases. These findings highlight celastrol's potential as an effective immunomodulatory agent for treating autoimmune disorders.<sup>58,63</sup> Triptolide (126) has been detected in the treatment of rheumatoid arthritis, osteoarthritis, and skin allograft recipients, with findings indicating that its role in these diseases may contribute to the inhibition of the migration and invasion of rheumatoid fibroblast-like synoviocytes and suppression of IL-2, NLRP3, JNK, caspase-1, and other pro-inflammatory cytokines.<sup>34</sup> Preconditioning with 0.1  $\mu\text{M}$  triptolide enhanced umbilical cord mesenchymal stem cells' immunomodulatory capacity, significantly suppressed CD4<sup>+</sup>/CD8<sup>+</sup> T-cell proliferation, elevated IL-10 secretion, and upregulated PD-L1/PD-L2 expression. This optimized protocol demonstrated improved therapeutic potential for T-cell-mediated immune dysregulation.<sup>64</sup> Triptolide at 100  $\mu\text{g kg}^{-1}$  suppressed JAK/STAT signaling, reduced IL-6, TNF- $\alpha$ , IFN- $\gamma$ , and IL-10 expression, and increased CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T cells in systemic lupus erythematosus mice, suggesting its therapeutic potential for SLE treatment.<sup>58</sup> In experimental autoimmune encephalomyelitis models, Triphchlorolide (135), administered intraperitoneally at a dose of 40  $\mu\text{g kg}^{-1}$ , was found to reduce IL-17 and IFN- $\gamma$  levels by inhibiting the ERK1/2-NF- $\kappa$ B signaling pathway and did not induce side effects on serum biochemical and blood counts.<sup>65</sup> Meanwhile, demethylzeylasteral (190) alleviated vitiligo progression in C57BL/6 mice by suppressing the JAK2-STAT1 pathway and downregulating CXCL9/10 expression and mitigated lupus nephritis by suppressing CD8<sup>+</sup>-T-cell migration through the IFN- $\gamma$ -JAK-STAT1-CXCL10 axis, with an *in vitro* concentration of 4.54  $\mu\text{M}$ .<sup>66</sup> Tripfordine exhibited anti-HIV activity at 1  $\mu\text{g mL}^{-1}$  in H9 lymphocytes, while triptoquinone reduced IL-1 $\alpha$ / $\beta$  levels at 10  $\mu\text{g mL}^{-1}$  in PBMCs, and euonine suppressed DTH and hemolysin responses at 80 mg kg<sup>-1</sup> in DNCB-induced mice.<sup>28</sup> A new study showed the potential of *T. wilfordii* as a treatment for paraquat-induced lung injury and fibrosis, as indicated by the regulation of ferroptosis through promoting the release of antioxidant enzymes superoxide dismutase (SOD) and reducing the expression of MDA and GSH *via* the activation of Nrf2/HO-1 signaling pathway.<sup>67</sup> Ten sesquiterpenoids, including tripfordine A (1), tripfordine B (2), tripfordine C (7), wilforine (3), wilfortrine (4), wilfordine (5), wilfortrine (6), hypoglaunine A (8), hypoglaunine B (9), and euonymine (11), were tested for cytotoxicities against H9 lymphocytes, with wilfordine, wilfortrine, hypoglaunine A, and hypoglaunine B showing anti-HIV activity with EC50 values under 2.54  $\mu\text{g mL}^{-1}$ .<sup>9</sup> The role of these compounds in the treatment of autoimmune diseases remains a research focus, and these studies are summarized in Table 4 and Fig. 4.

### Other activities

Various studies have indicated that triptolide (126) and celastrol (193) possess potential as anti-angiogenesis drugs due to their ability to downregulate the expression of angiogenic activators, including the canonical gene VEGF and VEGFR, as well as



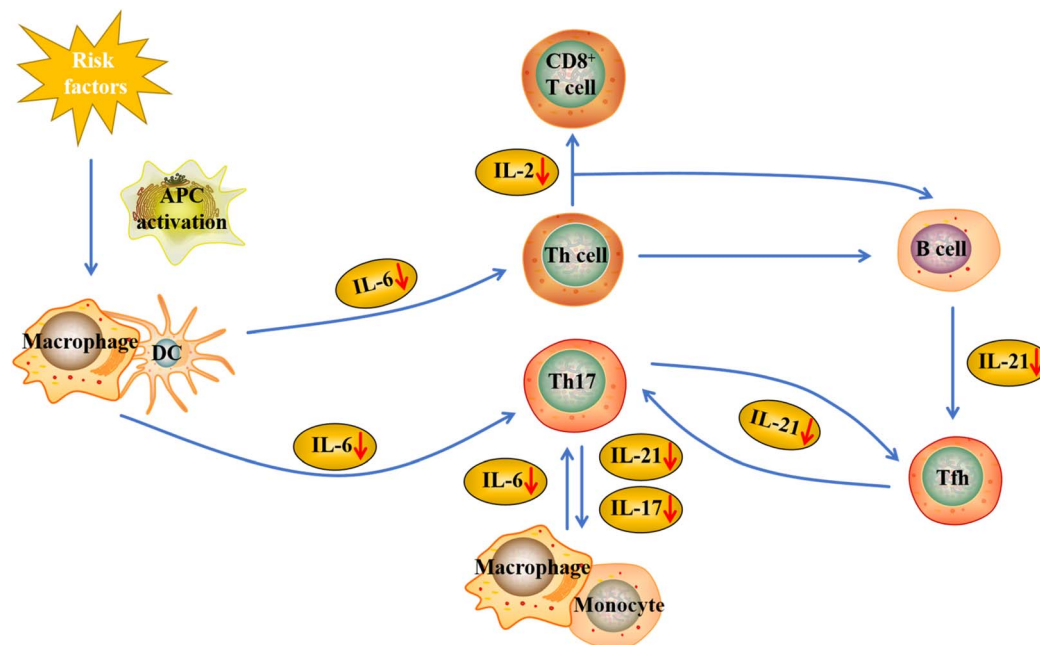


Fig. 4 The therapeutic mechanism of *T. wilfordii* in immunosuppressive activity.

TNF- $\alpha$ , IL-17, Ang-1, Ang-2, ERK, p38, and other cytokines.<sup>68</sup> These compounds have also demonstrated potent pharmacological cardioprotective effects through the nuclear accumulation of Nrf2 and the upregulation of its downstream target HO-1 in ischemic myocardial tissues. A network pharmacology study predicted the mechanism of *T. wilfordii* in treating myocardial fibrosis, suggesting that triptolide (126) is likely one of the principal active components, exerting its effects through the regulation of AGE-RAGE, PI3K-Akt, and MAPK pathways.<sup>69</sup> Triptchlorolide (135) has emerged as a promising agent for modulating A $\beta$ -related pathology in Alzheimer's disease (AD) at a concentration of 1  $\mu$ M, potentially improving learning and memory function by crossing the blood-brain barrier, with its molecular mechanism possibly involving the regulation of NMDAR1, PSD-95, CaMKII, and BDNF.<sup>5</sup> Triptonide (127) has been shown to lead to reversible male contraceptive effects in both mice and monkeys, targeting junction plakoglobin and disrupting its interactions with SPEM1 during spermiogenesis, indicating its potential as a promising male contraceptive agent.<sup>69</sup>

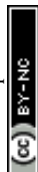
### Structure and activity relationship

The structure-activity relationship of terpenoids from *T. wilfordii* reveals the interaction between specific functional groups in these compounds and biological targets, thereby producing therapeutic effects. For example, triptolide (126), an abietane-type diterpenoid, has a lactone ring and a ketone group at C-3. The lactone ring is vital for its antitumor activity as it can bind to and inhibit the NF- $\kappa$ B pathway, which is often over-activated in cancer cells. This inhibition suppresses the expression of pro-inflammatory and pro-survival genes, thus inducing apoptosis in tumor cells. The ketone group at C-3 also significantly contributes by interacting with the Akt/mTOR

signaling pathway, further strengthening its anticancer effects.<sup>70–72</sup> In liver cancer cells, the presence of a hydroxyl group at C-16 in triptolide has been shown to enhance its cytotoxicity by improving its ability to bind to and inhibit key cellular targets related to cell proliferation and survival.<sup>71</sup> In the case of tripterifordin (183), a kaurane-type diterpenoid, the hydroxyl groups at C-3 and C-20 are critical for its anti-inflammatory activity. These hydroxyl groups allow the compound to interact with the NF- $\kappa$ B pathway, inhibiting the production of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6. This interaction reduces inflammation and tissue damage in diseases like rheumatoid arthritis.<sup>73</sup> Celastrol (193) contains a ketone group at C-3 and a hydroxyl group at C-28. The ketone group at C-3 is essential for its anticancer activity as it can bind to and inhibit the PI3K/Akt/mTOR signaling pathway, which is frequently dysregulated in cancer cells. This inhibition suppresses cell proliferation and triggers apoptosis. The hydroxyl group at C-28 further boosts its capacity to interact with cellular targets involved in cancer cell survival and growth.<sup>74</sup> Wilforine (3) has a pyridine ring and a hydroxyl group. The pyridine ring is crucial for its anti-inflammatory activity as it can bind to and inhibit the NF- $\kappa$ B pathway, decreasing the production of pro-inflammatory cytokines. The hydroxyl group enhances its ability to interact with cellular targets associated with inflammation and immune response.<sup>11,47</sup> Consequently, the presence and arrangement of these functional groups greatly influence the compounds' ability to bind to and modulate key cellular pathways, thus determining their biological activities and therapeutic potential.

### Toxicity of *T. wilfordii*

*T. wilfordii*, a traditional Chinese herb used in treating rheumatoid arthritis (RA), has gained widespread clinical



applications due to the significant efficacy of its preparations, including Tripterygium Glycosides Tablets and Tripterygium Tablets. Over 30 clinical practice guidelines and consensus documents endorsed its use, with authoritative guidelines from American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and Chinese Society of Rheumatology (CSR) being widely adopted.<sup>12</sup> Studies indicated that terpenoids in *T. wilfordii* exerted therapeutic effects through anti-inflammatory and immunomodulatory activities. However, they posed multi-organ toxicity risks, including significant harm to the digestive, urinary, reproductive, cardiovascular, hematopoietic and bone marrow systems.<sup>60,75,76</sup>

### Hepatotoxicity

Meta-analyses revealed an overall adverse reaction rate of 11.7% for *T. wilfordii* preparations. Specific manifestations included alanine aminotransferase (ALT) elevation (8.6%), menstrual disorders in females (12.7%), cardiovascular events (4.9%), hematological abnormalities or mucosal damage (6.5–7.8%), as well as renal injury, alopecia, and weight loss.<sup>77,78</sup> The hepatotoxic mechanisms involved lipid peroxidation and oxidative stress triggered by metabolites, characterized by elevated ALT/aspartate aminotransferase (AST), abnormal bile acid/bilirubin levels, and hepatocyte necrosis.<sup>60</sup> Experimental studies demonstrated that Tripterygium Glycosides inhibited CYP27A1, CYP8B1, and SOD-1/GPX1 expression, reduced SOD and GPX activity, increased lipid peroxidation (LPO) levels, and disrupted mitochondrial function and antioxidant systems.<sup>79,80</sup> Triptolide induced hepatocyte apoptosis *via* ROS generation, while celastrol exacerbated hepatocyte damage by suppressing CYP450 activity.<sup>81</sup> These findings underscored that *T. wilfordii*-induced hepatotoxicity was closely linked to lipid peroxidation, oxidative stress, and inhibition of hepatic metabolic enzymes. Thus, clinical applications required vigilant monitoring of hepatotoxicity risks and exploration of interventions to mitigate adverse effects.

### Nephrotoxicity

*T. wilfordii* nephrotoxicity was primarily attributed to diterpenoids, triterpenoids, and alkaloid metabolites, which directly damaged renal tubular epithelial cells, leading to oliguria, edema, hematuria, hypotension, and hyperkalemia.<sup>82–84</sup> Animal studies confirmed that *T. wilfordii* extracts markedly increased serum creatinine, urea nitrogen, and uric acid levels in rats, accompanied by pathological changes such as glomerular atrophy and renal tubular liquefactive necrosis.<sup>85</sup> The mechanisms involved triptolide-mediated upregulation of the Fas/FasL death receptor pathway and angiotensin II receptor synthesis impairment, resulting in ROS accumulation and apoptosis in glomerular cells.<sup>86</sup>

### Cardiotoxicity

Blockade of the human ether-à-go-go-related gene (hERG) potassium channel was identified as a critical mechanism underlying drug-induced cardiotoxicity.<sup>87</sup> Studies showed that *T. wilfordii* aqueous extracts at concentrations of 0.05 mg mL<sup>-1</sup>

and 0.1 mg mL<sup>-1</sup> inhibited hERG current amplitudes by 21.4 ± 1.6% and 86.7 ± 5.7%, respectively. Celastrol directly bound to the hERG channel pore region, altering ion transport kinetics and reducing membrane potassium channel density without affecting activation/inactivation kinetics. This specific channel blockade was proposed as the key molecular mechanism of *T. wilfordii* cardiotoxicity.<sup>88</sup>

### Reproductive toxicity

*T. wilfordii* disrupted reproductive function in both male and female animals through multiple pathways.<sup>12</sup> In males, active components (*e.g.*, triptolide, celastrol) induced caspase-3-dependent spermatocyte apoptosis *via* Bax/Bcl-2 and Fas/FasL pathways activation, impaired Tnp1/Tnp2 expression leading to sperm malformation, and dysregulated cholesterol synthesis and testosterone-producing enzymes, causing testicular injury and spermatogenic dysfunction in a concentration- and time-dependent manner.<sup>89</sup> In females, *T. wilfordii* inhibited granulosa cell proliferation, reduced antioxidant enzyme activity, and modulated Bax/Bcl-2 ratios, disrupting folliculogenesis and accelerating ovarian senescence.<sup>90</sup> Additionally, its reproductive toxicity involved germ cell apoptosis, autophagic damage, hormonal synthesis dysregulation, and endocrine dysfunction.<sup>91,92</sup>

### Drug delivery system

Despite *T. wilfordii*'s therapeutic potential in cancer and autoimmune diseases, its clinical utility has been limited by poor aqueous solubility, inadequate targeting, and systemic toxicity. Novel drug delivery systems (DDSs), such as nanoparticles, polymeric micelles, and functionalized bioconjugates, enhanced the bioavailability and safety of *T. wilfordii* terpenoids by optimizing distribution and delivery efficiency. To mitigate triptolide toxicity, researchers developed water-soluble derivatives, including PG490-88, which entered Phase I clinical trials in the U.S. for prostate cancer treatment.<sup>93</sup> Celastrol conjugated with polyethylene glycol (PEG) and EpCAM aptamer-modified dendrimers demonstrated improved solubility, potent antitumor activity in SW620 colon cancer cells, and reduced toxicity in AD293 cells, mice, and zebrafish.<sup>94,95</sup> Celastrol-loaded PEG-polycaprolactone (PCL) nanoparticles retained metabolic regulatory effects in obesity models while avoiding gastrointestinal injury.<sup>96</sup> A polydopamine@CEL-NS (PDA@CEL-NS) carrier system exhibited pH-responsive drug release and photothermal synergy, suppressing HepG2 cell proliferation, migration, and inducing apoptosis.<sup>97</sup> Celastrol self-assembled nanoparticles displayed enhanced cytotoxicity in breast and lung cancer cells with tumor-targeting capability and minimal histological alterations.<sup>98,99</sup> Celastrol-BSA-NPs prepared *via* high-pressure homogenization showed superior bioavailability and efficacy in diet-induced obesity.<sup>100</sup> Triptolide-ADIBO conjugates modified with hyaluronic acid (HA) demonstrated potent antitumor effects in breast and liver cancers.<sup>101</sup> These advancements highlight the role of modern DDSs in advancing *T. wilfordii* terpenoid applications. Therefore, developing



targeted delivery systems for terpenoids remains a pivotal direction for future clinical translation.

## Conclusions

In summary, terpenoids derived from *Tripterygium wilfordii* Hook. f. exhibit a diverse array of biological activities, including antitumor, anti-inflammatory, immunosuppressive, and other therapeutic effects. These compounds, characterized by their structural diversity and significant bioactivities, hold substantial promise for drug development. This review comprehensively summarizes the chemical structures and biological activities of 217 terpenoids from *T. wilfordii*, emphasizing their potential in pharmacological research and clinical applications. However, the clinical application of these terpenoids is constrained by their toxicity and poor bioavailability. Future research should prioritize the exploration of effective strategies to mitigate toxicity and enhance the drug delivery systems of these compounds. Furthermore, in-depth investigation into the structure–activity relationships and the identification of novel active constituents will facilitate the development of more efficacious and safer drugs. This review serves as a comprehensive reference for the discovery and development of novel drugs based on the natural active products of *T. wilfordii*, providing a solid foundation for future research and clinical translation.

## Data availability

The present review article does not contain any new experimental data. Therefore, there are no new data sets generated or analyzed during the study to be made available. The article is based on a comprehensive literature review and analysis of previously published studies, which are properly cited within the manuscript.

## Author contributions

Jiping li carried out the literature search and prepared a draft of the manuscript. Hong Liang, Likun Liu, Xiuli Gao, Yang Liu, Meng Zhang, Xiaolan Yuan, Shan Ren participated in a manuscript preparation and checked the literature. All authors have read and agreed to the published version of the manuscript. Wei Zhang conceptualized, organized, corrected and revised the manuscript.

## Conflicts of interest

The authors declare no competing interests.

## Acknowledgements

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