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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.1 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.2 In recent years, terpenoids derived from T. wilfordii have garnered significant attention due to their diverse biological activities, including antitumor, antiinflammatory, 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

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.⁵ In this section, we provide a comprehensive summary

features and biological activities. The α,β-unsaturated lactone ring of diterpenoids, such as triptolide, is considered a key pharmacophore for their antitumor activity.3 The quinone structure of triterpenoids, such as celastrol, is directly associated with antioxidant and anti-inflammatory effects.4 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.5 These compounds include sesquiterpenoids, diterpenoids, triterpenoids, flavonoids, lignans, steroids, and others, each contributing to the plant's medicinal properties.4 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).

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Review

Anti-angiogenesis

Cardioprotection

Sesquiterpenoid

Tripterygium wilfordii Hook. f. Neuroprotection

Neuroprotection

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

Immunosuppressive

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**). The structural types of diterpenoids encompass abietane-type, kaurane-type, and other subtypes (compounds **103–150**, **151–185**). Triterpenoids, based on their carbon skeleton and substituents, predominantly belong to the friedelane type, oleanane type, ursane type, and related groups (compounds **186–217**). 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, broadspectrum antitumor effects and diverse sensitizing properties.³⁵ In recent years, an array of investigations have confirmed triptolide's substantial antitumor activity and therapeutic potential in various cancers, including breast cancer,³ lung cancer,³⁵ liver cancer,³⁵ colon cancer,³⁶ thyroid cancer, and pancreatic

cancer.^{3,36} 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. 35,36 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 CaMKKβ-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 chloroguine resulted in significant tumor growth suppression compared to monotherapy groups.37 In subsequent in vivo studies, administration of triptolide at 1 mg kg⁻¹ significantly reduced metastatic nodules of SKOV3 xenograft tumors in mice, without causing remarkable systemic toxicity during treatment.3 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-κB, vascular endothelial growth factor, and programmed cell death ligand 1.36,38,39 New dihydroagarofuran sesquiterpene polyol esters, including tripterdine A (80), tripterdine C (12), and tripterdine G (83), have exhibited inhibitory effects on the growth of human tumor cell lines (Huh7, MCF-7, and HCT-116).15 Cangoring K (76), dimacroregeline C (77), dimacroregeline D (78), and hypoglaunine A (8) have demonstrated potent cytotoxicity against SMMC7721 cells, with 20 h IC50 values ranging from 0.26 to 9.67 μM. This effect was achieved by disrupting the mitochondrial membrane potential.40 These four constituents, along with hypoterpene D, also showed similar inhibitory effects on LN-229 cells, with IC50 values ranging from 0.50 to 7.38 μM.14 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

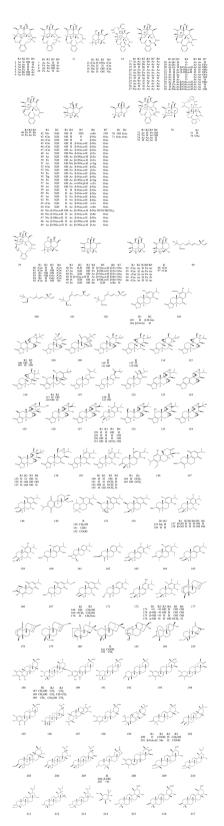


Fig. 1 The chemical structures of diterpenoids derived from *T. wilfordii*.

breast cancer cells MCF-7.²⁹ 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.4 The anticancer effects of celastrol are primarily achieved through multiple pathways, including inducing apoptosis,41 causing cell cycle arrest,41 inhibiting cell proliferation,42 targeting tumor-promoting inflammation, 43 suppressing angiogenesis, 44 and restraining cell invasion and metastasis. 4,45 The antitumor effects of celastrol are associated with the up-regulation of caspase-3/7/9, Ecadherin, VEGF, bax, IkB, 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. 4,41,42,45 In vitro studies showed celastrol (193) significantly suppressed proliferation of ovarian cancer A2780 and SKOV3 cells with an 72 h IC50 of around 2 µM, triggering G2/M phase arrest and apoptosis via ROS elevation.42 In vitro studies demonstrated that triptonide (127) effectively suppressed proliferation of PaTu8988 and Panc-1 pancreatic cancer cells with an IC50 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⁻¹ triptonide significantly inhibited tumor growth in PaTu8988 xenograft models without inducing observable systemic toxicity.37 In addition, tripterdine C (12) inhibited the proliferation of HCT-116 colon cancer cells, with an IC50 value of 5.8 µM. The underlying mechanism was the suppression of the JAK/STAT3 pathway. 15 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.46 Wilforine (3) has been detected to re-sensitize MDR cancer cells with 72 h IC50 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 47 Tripchlorolide (135) was demonstrated to effectively inhibit proliferation of A549 and cisplatinresistant 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.48 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.13 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	Туре	Subtype	Ref.
L	Tripfordine A	Sesquiterpenoid	Nitrogen-containing	9
	Tripfordine B	Sesquiterpenoid	Nitrogen-containing	9
	Wilforine	Sesquiterpenoid	Nitrogen-containing	9 and 10
	Wilforgine	Sesquiterpenoid	Nitrogen-containing	9 and 10
	Wilfordine	Sesquiterpenoid	Nitrogen-containing	11 and 1
	Wilfortrine	Sesquiterpenoid	Nitrogen-containing	11 and 1
	Tripfordine C	Sesquiterpenoid	Nitrogen-containing	9
	Hypoglaunine A	Sesquiterpenoid	Nitrogen-containing	13 and 1
0	Hypoglaunine B Hypoglaunine D	Sesquiterpenoid Sesquiterpenoid	Nitrogen-containing Nitrogen-containing	9 and 13 9 and 13
0 1	Euonymine	Sesquiterpenoid	Nitrogen-containing	9 and 13
2	Tripterdine C	Sesquiterpenoid	Nitrogen-containing Nitrogen-containing	15
3	Tripterdine D	Sesquiterpenoid	Nitrogen-containing	15
4	Tripterdine E	Sesquiterpenoid	Nitrogen-containing	15
5	Tripterdine J	Sesquiterpenoid	Nitrogen-containing	15
6	Tripterygiumine A	Sesquiterpenoid	Nitrogen-containing	5 and 16
7	Tripterygiumine B	Sesquiterpenoid	Nitrogen-containing	5
8	Tripterygiumine C	Sesquiterpenoid	Nitrogen-containing	5
9	Tripterygiumine D	Sesquiterpenoid	Nitrogen-containing	5
0	Tripterygiumine E	Sesquiterpenoid	Nitrogen-containing	5
1	Tripterygiumine F	Sesquiterpenoid	Nitrogen-containing	5
2	Tripterygiumine G	Sesquiterpenoid	Nitrogen-containing	5
3	Tripterygiumine H	Sesquiterpenoid	Nitrogen-containing	5
4	Tripterygiumine I	Sesquiterpenoid	Nitrogen-containing	5
5	Tripterygiumine J	Sesquiterpenoid	Nitrogen-containing	5
6	Tripterygiumine K	Sesquiterpenoid	Nitrogen-containing	5
7	Tripterygiumine L	Sesquiterpenoid	Nitrogen-containing	5
8	Tripterygiumine M	Sesquiterpenoid	Nitrogen-containing	5
9	Tripterygiumine N	Sesquiterpenoid	Nitrogen-containing	5
0	Tripterygiumine O	Sesquiterpenoid	Nitrogen-containing	5
1	Tripterygiumine P	Sesquiterpenoid	Nitrogen-containing	5
2	Tripterygiumine Q	Sesquiterpenoid	Nitrogen-containing	5
3	Tripterygiumine S	Sesquiterpenoid	Nitrogen-containing	5
4	Tripterygiumine T	Sesquiterpenoid	Nitrogen-containing	5
5	Tripterygiumine U	Sesquiterpenoid	Nitrogen-containing	5
6 7	Tripterygiumine V 1-Desacetylwilforgine	Sesquiterpenoid	Nitrogen-containing	5 17
7 8	1-Desacetylwillorgine 1-Desacetylwillforine	Sesquiterpenoid Sesquiterpenoid	Nitrogen-containing Nitrogen-containing	17 17
9	9'-Hydroxy-2-nicotinoylwilforine	Sesquiterpenoid	Nitrogen-containing Nitrogen-containing	17
0	Tripterygiumine W	Sesquiterpenoid	Nitrogen-containing	18
0 1	Wilfornine H	Sesquiterpenoid	Nitrogen-containing	18
2	Tripterygiumine R	Sesquiterpenoid	Nitrogen-containing	18
3	Triptersinine A	Sesquiterpenoid	Nitrogen-containing	19
4	Triptersinine B	Sesquiterpenoid	Nitrogen-containing	19
5	Triptersinine C	Sesquiterpenoid	Nitrogen-containing	19
6	Triptersinine D	Sesquiterpenoid	Nitrogen-containing	19
7	Triptersinine E	Sesquiterpenoid	Nitrogen-containing	19
8	Triptersinine F	Sesquiterpenoid	Nitrogen-containing	19
9	Triptersinine G	Sesquiterpenoid	Nitrogen-containing	19
0	Triptersinine H	Sesquiterpenoid	Nitrogen-containing	19
l	Triptersinine L	Sesquiterpenoid	Nitrogen-containing	19
2	Triptersinine M	Sesquiterpenoid	Nitrogen-containing	19
3	Triptersinine N	Sesquiterpenoid	Nitrogen-containing	19
Į.	Triptersinine O	Sesquiterpenoid	Nitrogen-containing	19
5	Triptersinine P	Sesquiterpenoid	Nitrogen-containing	19
5	Triptersinine Q	Sesquiterpenoid	Nitrogen-containing	19
7	Triptersinine R	Sesquiterpenoid	Nitrogen-containing	19
3	Triptersinine S	Sesquiterpenoid	Nitrogen-containing	19
9	Triptersinine T	Sesquiterpenoid	Nitrogen-containing	19
0	Triptersinine Z4	Sesquiterpenoid	Nitrogen-containing	5 and 1
1	Triptersinine Z5	Sesquiterpenoid	Nitrogen-containing	5 and 1
2	Triptersinine Z6	Sesquiterpenoid	Nitrogen-containing	5 and 1

Table 1 (Contd.)

No	Compounds	Туре	Subtype	Ref.
54	Triptersinine Z8	Sesquiterpenoid	Nitrogen-containing	5 and 19
5	Wilforsinine C	Sesquiterpenoid	Nitrogen-containing	5 and 20
6	Wilforsinine D	Sesquiterpenoid	Nitrogen-containing	5 and 20
7	Wilforsinine E	Sesquiterpenoid	Nitrogen-containing	5 and 20
8	Wilforsinine G	Sesquiterpenoid	Nitrogen-containing	5 and 20
9	Wilforsinine H	Sesquiterpenoid	Nitrogen-containing	5 and 20
0	Wilforsinine A	Sesquiterpenoid	Nitrogen-containing	21
1	Wilforsinine B	Sesquiterpenoid	Nitrogen-containing	21
2	Hypoglaunine E	Sesquiterpenoid	Nitrogen-containing	13
3	Hypoglaunine F	Sesquiterpenoid	Nitrogen-containing	13
4	Peritassine A	Sesquiterpenoid	Nitrogen-containing	13 and 2
5	Wilfordinine A	Sesquiterpenoid	Nitrogen-containing	13
6	Cangorin K	Sesquiterpenoid	Nitrogen-containing	14
7	Dimacroregeline C	Sesquiterpenoid	Nitrogen-containing	14
8	Dimacroregeline D	Sesquiterpenoid	Nitrogen-containing	14
9	Euonine	Sesquiterpenoid	Nitrogen-containing	13 and 2
0	Tripterdine A	Sesquiterpenoids	Nitrogen-free	15
1	Tripterdine B	Sesquiterpenoids	Nitrogen-free	15
2	Tripterdine F	Sesquiterpenoids	Nitrogen-free	15
3	Tripterdine G	Sesquiterpenoids	Nitrogen-free	15
4	Tripterdine H	Sesquiterpenoids	Nitrogen-free	15
5	Tripterdine I	Sesquiterpenoids	Nitrogen-free	15
6	Triptersinine I	Sesquiterpenoids	Nitrogen-free	22 and
7	Triptersinine J	Sesquiterpenoids	Nitrogen-free	22 and
8	Triptersinine K	Sesquiterpenoids	Nitrogen-free	22 and
9	Wilforsinine F	Sesquiterpenoids	Nitrogen-free	5 and 2
0	Triptregelol A	Sesquiterpenoids	Nitrogen-free	22 and
1	Triptregelol B	Sesquiterpenoids	Nitrogen-free	22 and
2	Triptersinine V	Sesquiterpenoids	Nitrogen-free	5
3	Triptersinine W	Sesquiterpenoids	Nitrogen-free	5
4	Triptersinine X	Sesquiterpenoids	Nitrogen-free	5
5	Triptersinine Y	Sesquiterpenoids	Nitrogen-free	5
6	Triptersinine Z1	Sesquiterpenoids	Nitrogen-free	5
7	Triptersinine Z2	Sesquiterpenoids	Nitrogen-free	5
8	Triptersinine Z3	Sesquiterpenoids	Nitrogen-free	5
9	Triptergosidol A	Sesquiterpenoids	Nitrogen-free	6
00	Triptergosidol B	Sesquiterpenoids	Nitrogen-free	6
01	Triptergosidol C	Sesquiterpenoids	Nitrogen-free	6
02	Triptergosidol D	Sesquiterpenoids	Nitrogen-free	6
03	Tripterycoside A	Diterpenoids	Abietane	24
04	Tripterycoside B	Diterpenoids	Abietane	24
05	Tripterycoside C	Diterpenoids	Abietane	24
06	2α-Hydroxytriptonide	Diterpenoids	Abietane	24
07	15-Hydroxytriptonide	Diterpenoids	Abietane	24
08	Triptergulide A	Diterpenoids	Abietane	25 and
09	Triptergulide B	Diterpenoids	Abietane	25 and
10	Triptergulide C	Diterpenoids	Abietane	25 and
11	Triptergulide D	Diterpenoids	Abietane	25 and
12	Triptergulide E	Diterpenoids	Abietane	25 and
13	Triptergulide F	Diterpenoids	Abietane	25 and
14	Triptergulide G	Diterpenoids	Abietane	25 and
15	Triptergulide H	Diterpenoids	Abietane	25 and
16	Triptergulide I	Diterpenoids	Abietane	25 and
17	Triptergulide J	Diterpenoids	Abietane	25 and
18	Triptergulide K	Diterpenoids	Abietane	25 and
19	Tripterlide A	Diterpenoids	Abietane	27
20	Tripterlide B	Diterpenoids	Abietane	27
21	Tripterlide C	Diterpenoids	Abietane	27
22	Tripterlide O	Diterpenoids	Abietane	27
22 23	Tripterlide E	Diterpenoids	Abietane	27
23 24	Tripterlide E Tripterlide F	Diterpenoids	Abietane	27
2 4 25	16-Hydroxytriptolide	Diterpenoids	Abietane	28
49	Triptolide Triptolide	Diterpenoids	ADICIAIIC	40

Table 1 (Contd.)

No	Compounds	Туре	Subtype	Ref.
127	Triptonide	Diterpenoids	Abietane	2
28	Hinokione	Diterpenoids	Abietane	21
29	Triptonoterpene	Diterpenoids	Abietane	28
30	Triptobenzene A	Diterpenoids	Abietane	20
31	Wilforol F	Diterpenoids	Abietane	7
32	Tripdiolide	Diterpenoids	Abietane	28
33	Tripterolide	Diterpenoids	Abietane	28
34	Triptolidenol	Diterpenoids	Abietane	28
35	Tripchlorolide	Diterpenoids	Abietane	28
36	Isotriptetraolide	Diterpenoids	Abietane	28
37	Triptriolide	Diterpenoids	Abietane	28
.38	Tripdioltonide	Diterpenoids	Abietane	28
39	Triptonolide	Diterpenoids	Abietane	28
40	Triptophenolide	Diterpenoids	Abietane	2
41	Triptophenolide methyl ether	Diterpenoids	Abietane	28
42	Neotriptophenolide	Diterpenoids	Abietane	28
43	Isoneotriptophenolide	Diterpenoids	Abietane	28
44	Triptonoterpene methyl ether	Diterpenoids	Abietane	28
45	Neotriptonoterpene	Diterpenoids	Abietane	7
46	Triptonoterpenol	Diterpenoids	Abietane	28
47	Triptoquinone A	Diterpenoids	Abietane	7 and
48	Triptoquinone B	Diterpenoids	Abietane	21
49	Triptoquinone C	Diterpenoids	Abietane	28
50	Triptoquinone D	Diterpenoids	Abietane	7 and
51	Triptoquinone E	Diterpenoids	Abietane	29
.52	Triptoquinone F	Diterpenoids	Abietane	7 and
.53	Triptoquinone G	Diterpenoids	Abietane	28
54	Triptoquinone H	Diterpenoids	Abietane	21
.55	Triptinin A	Diterpenoids	Abietane	20
.56	Triptinin B	Diterpenoids	Abietane	20
.57	Triptobenzene B	Diterpenoids	Abietane	7
158	Triptobenzene J	Diterpenoids	Abietane	29
.59	Triptobenzene M	Diterpenoids	Abietane	7
160	Triptobenzene H	Diterpenoids	Abietane	20
61	Triptobenzene I	Diterpenoids	Abietane	30
.62	Triptobenzene Q	Diterpenoids	Abietane	31
163	Triptobenzene R	Diterpenoids	Abietane	31
.64	Triptobenzene S	Diterpenoids	Abietane	31
.65	Triptobenzene Y	Diterpenoids	Abietane	31
66	Triregelin A	Diterpenoids	Abietane	7
.67	Triregelin B	Diterpenoids	Abietane	7
.68	Triregelin C	Diterpenoids	Abietane	7
.69	Triregelin D	Diterpenoids	Abietane	7
70	Triregelin E	Diterpenoids	Abietane	7
71	Triregelin F	Diterpenoids	Abietane	7
.72	Triregelin G	Diterpenoids	Abietane	7
.73	Triregelin H	Diterpenoids	Abietane	7
.74	Triregelin I	Diterpenoids	Abietane	7
.75	Triregelin J	Diterpenoids	Abietane	7
76	Triregelin K	Diterpenoids	Abietane	7
77 77	Doianoterpene A	Diterpenoids	Kaurane	32
78	Doianoterpene B	Diterpenoids	Kaurane	32
79	Doianoterpene C	Diterpenoids	Kaurane	32
80	Neotripterifordin	Diterpenoids	Kaurane	32
81	Doianoterpene D	Diterpenoids	Kaurane	32
82	Ent-kauranol	Diterpenoids	Kaurane	32
	Tripterifordin	Diterpenoids		28
83			Kaurane	
84 e=	Tripterinin	Diterpenoids	Kaurane	28
.85	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
.87	nor-D: A-friedooleana-29-olcacid 2α,3α,23-Trihydroxyurs-12-en-28-olcacid	Triterpenoids	Friedelane	-
0/	۷۵.۵۵.۷۵-11111VU10XVU1S-12-CII-28-01CaClQ	LITTEEDEHOIGS	rucaeiane	5

Table 1 (Contd.)

No	Compounds	Type	Subtype	Ref.
189	2α, 3α, 24-Trihydroxyurs-12-en-28-oicacid	Triterpenoids	Friedelane	5
190	Demethylzeylasteral	Triterpenoids	Friedelane	8
191	Orthophenic acid	Triterpenoids	Friedelane	8
192	Polpunonic 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-oicacid	Triterpenoids	Oleanane	13
201	3-acetoxy oleanolic acid	Triterpenoids	Oleanane	13
202	3-Epikatonic acid	Triterpenoids	Oleanane	8
203	3β-Acetyl-oleanolic acid	Triterpenoids	Oleanane	33
204	Triptotriterpenic acid A	Triterpenoids	Oleanane	16
205	Triptotriterpenic acid B	Triterpenoids	Oleanane	8
206	Wilforlide A	Triterpenoids	Oleanane	8
207	Wilforlide B	Triterpenoids	Oleanane	8
208	22β-Hydroxytingenone	Triterpenoids	Ursane	8
209	Demethylregelin	Triterpenoids	Ursane	8
210	Regelin	Triterpenoids	Ursane	8
211	Regelin C	Triterpenoids	Ursane	8 and 1
212	Regelin D	Triterpenoids	Ursane	8 and 1
213	Triptocallic acid A	Triterpenoids	Ursane	8
214	Dulcioic acid	Triterpenoids	Ursane	34 and
215	Regelindiol A	Triterpenoids	Ursane	10 and
216	Regelindiol B	Triterpenoids	Ursane	10 and
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.⁵⁰ Network pharmacology studies have identified key genes such as AKT1, TNF-α, 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.⁵¹ 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^{-1} 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 μM in vitro 2 mg kg ⁻¹ intraperitoneal injection	42
Triptonide (127)	Diterpenoid	PaTu8988 (pancreatic cancer) Female NOD/SCID mouse with PaTu8988 cell tumor	MAPKP pathway suppression	10 nM in vitro 5 mg kg ⁻¹ intraperitoneal injection	49
Triptoquinone E (151)	Diterpenoid	A549 (lung cancer)	Cytotoxicity	35 μM in vitro	29
Wilforine (3)	Sesquiterpenoid	MDR cancer cells	P-gp inhibition	40 μM in vitro	47
Hypoglaunine A (8)	Sesquiterpenoid	SMMC7721 (liver cancer)	Mitochondrial disruption	0.29 μM in vitro	40
Tripterdine C (12)	Sesquiterpenoid	HCT-116 (colon cancer)	Cytotoxicity	5.8 μM in vitro	15
Triptolidenol (134)	Diterpenoid	768- O (renal cancer)	IKKβ/COX-2 blockade	87 nM in vitro	46
Cangorin K (76)	Sesquiterpenoid	LN-229 (glioblastoma)	Cytotoxicity	0.5 μM in vitro	40
Triptoquinone F (152)	Diterpenoid	MCF-7 (breast cancer)	Cytotoxicity	4.5 μM in vitro	29
Tripchlorolide (135)	Diterpenoid	A549 and A549/DDP (lung cancer)	AEG-1 inhibition	200 nM in vitro	48

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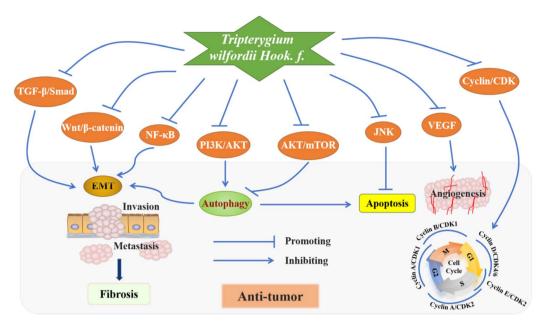


Fig. 2 Schematic of the molecular targets of *T. wilfordii* in the treatment of tumor.

shown to act on rheumatoid arthritis-related pathways through eight targets, including MCL1, JUN, TNF, STAT1, RELA, IL23A, CASP3, and CDKN1A.52 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-α, IL-1β, and IL-6 while protecting articular tissue. Transdermal delivery minimized systemic exposure, potentially reducing hepatorenal toxicity.⁵³ Intraperitoneal celastrol (193) (1 mg per kg per day), administered as a 7day 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-α, IL-1β, IL-6), improving survival (P < 0.05) and alleviating organ injury. Despite multitarget anti-inflammatory efficacy, low oral bioavailability and dose-dependent ALT/AST elevations with potential hepatorenal toxicity necessitate cautious translational optimization.54 Intraarticular 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 $\mu g \text{ mL}^{-1}$, they suppressed IL-1 β /TNF- α /IL-6 and MMPs via NF-κB inhibition in vitro. In MIA-induced OA rats, treatment improved cartilage integrity, reduced effusion, and alleviated pain.55 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 fibroblastlike synoviocytes, astrocytes, podocytes, human umbilical vein endothelial cells, and colonic epithelial cells.⁵⁶ The antiinflammatory activity of celastrol is associated with the

expression of heme oxygenase-1, PI3K/Akt/mTOR, ROS/Akt/ p70S6K, and FceRI signaling pathways. 5,56 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 wellestablished, 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-κB and COX-2 promoter region.46,57 Triptolidenol (134) was demonstrated to suppressed NF-κB/COX-2 signaling by targeting IKKβ's ATP-binding domainin ccRCC, reducing IL-1β, TNF-α, and COX-2 while inducing caspase-dependent apoptosis under 48-h treatment. This dual anti-inflammatory/ antitumor profile suggests Triptolidenol's potential for COX-2mediated ccRCC therapy with optimized dosing.46 Tripterdine C (12), tripterdine E (14), and tripterdine J (15) have exhibited potent anti-inflammatory effects by inhibiting the secretion levels of TNF-α and IL-6.15 Wilforine (3), wilfortrine (6), wilforgine (4), and wilfordine (5) have also shown inhibitory effects on cancer cells, with wilforine demonstrating anti-inflammatory effects in adjuvant arthritis rat models 11,12 Triptonide (127) administration significantly alleviated CFA-induced inflammatory pain in murine models by inhibiting AKT phosphorylation and suppressing TNF-α, IL-1β, and IL-6 expression, while in vitro experiments demonstrated its inhibitory effects on proinflammatory cytokine production in ND7/23 cells. Intravenous delivery $(0.1, 0.5, 2.0 \text{ mg kg}^{-1})$ 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.58,59 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.12 These findings underscore the complex molecular interaction

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Table 3 Summary of the anti-inflammatory activities of terpenoids

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

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.³⁴

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.⁶⁰

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

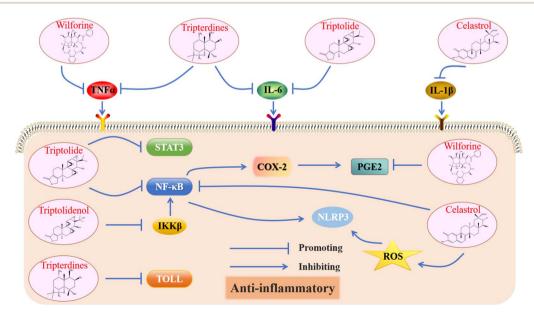


Fig. 3 Mechanisms of *T. wilfordii* and active compounds on anti-inflammatory activity.

 Table 4
 Immunosuppressive activities of terpenoids from T. wilfordii

Compound	Туре	Model	Dose/IC50	Key targets	Ref.
Celastrol (193)	Triterpenoid	RAW264.7 HEK293T BJ cells	0.03-30 µM in vitro	Cytoplasmic DNA- and RNA-mediated IFN production	28
Trintolide (126)	Diternenoid	Trext-/- mice on C57BL/6	0.2–5 mg kg ⁻¹ intraperitoneal injection	T Cell activation IRF3 activation	63
		Systemic lupus erythematosus mice	100 µg/kg	IL-6, TNF-a, IFN-y, IL- 10 CD4+CD25+Foxn3+T cell nositivity	28
Tripchlorolide (135)	Diterpenoid	Female C57BL/6 mice	40 ug kg ⁻¹ intraperitoneal injection	ERK1/2-NF-kB, IAK/STAT	65
Demethylzeylasteral (190)	Triterpenoid	CDT8 ⁺ cell C57Bl/6 mice with B16F10 cells	$4.54 \mu M$ in vitro $5 mg kg^{-1} 2.5 mg kg^{-1}$ intraperitoneal	STAT1-CXCL9/10 signaling, JAK2	99
			iniection		
Tripchlorolide (135) Wilfordine (5)	Diterpenoids Sesauiterpenoid	EAE C57BL/6 mice model H9 lymphocytes	$40 \mathrm{\mu g \ kg^{-1}}$ intraperitoneal injection $20 \mathrm{ug \ mL^{-1}}$	ERK1/2-NF-kB, JAK/STAT Anti-HIV activity	65
Wilfortrine (6)	Sesquiterpenoid	H9 lymphocytes	$>100 \mathrm{\mu g mL^{-1}}$	Anti-HIV activity	6
Hypoglaunine B (9)	Sesquiterpenoid	H9 lymphocytes	$>$ 100 $\mu g m L^{-1}$	Anti-HIV activity	6
Euonymine (11)	Sesquiterpenoid	H9 lymphocytes	$>$ 100 $\mu \mathrm{g} \ \mathrm{mL}^{-1}$	Anti-HIV activity	6
Hypoglaunine A (8)	Sesquiterpenoid	H9 lymphocytes	$^{>100}~\mathrm{\mu g~mL}^{-1}$	Anti-HIV activity	6
Tripfordine	Sesquiterpenoid	H9 lymphocytes	$1 \mathrm{\mu g mL^{-1}}$ in vitro	Anti-HIV activity	28
Triptoquinone	Diterpenoid	Peripheral blood mononuclear cells	$10~\mu \mathrm{g~mL}^{-1}$ in vitro	$\text{IL-}1\alpha \text{ IL-}1\beta$	28
Euonine (79)	Sesquiterpenoid	DNCB-induced DTH reaction on mouse skin	$80~{ m mg~kg}^{-1}$ intraperitoneal injection	Hemolysin reaction	28

for 3 days reduced autoantibody production, and suppresses T cell activation. It also downregulated IFN-stimulated genes and against interferonopathy-related autoimmune diseases. These findings highlight celastrol's potential as an effective immunomodulatory agent for treating autoimmune disorders.^{58,63} 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 proinflammatory cytokines.34 Preconditioning with 0.1 μM triptolide enhanced umbilical cord mesenchymal stem cells' immunomodulatory capacity, significantly suppressed CD4+/CD8+ Tcell 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.64 Triptolide at 100 μg kg⁻¹ suppressed JAK/STAT signaling, reduced IL-6, TNF-α, IFN-γ, and IL-10 expression, and increased CD4⁺CD25⁺Foxp3⁺ T cells in systemic lupus erythematosus mice, suggesting its therapeutic potential for SLE treatment.58 In experimental autoimmune encephalomyelitis models, Tripchlorolide (135), administered intraperitoneally at a dose of 40 μ g kg⁻¹, was found to reduce IL – 17 and IFN – γ levels by inhibiting the ERK1/2-NF-κB signaling pathway and did not induce side effects on serum biochemical and blood counts.65 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+T-cell migration through the IFN-γ-JAK-STAT1-CXCL10 axis, with an in vitro concentration of 4.54 µM.66 Tripfordine exhibited anti-HIV activity at 1 µg mL⁻¹ in H9 lymphocytes, while triptoquinone reduced IL- $1\alpha/\beta$ levels at 10 µg mL⁻¹ in PBMCs, and euonine suppressed DTH and hemolysin responses at 80 mg kg⁻¹ in DNCB-induced mice.28 A new study showed the potential of T. wilfordii as a treatment for paraguat-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.⁶⁷ Ten sesquiterpenoids, including tripfordine A (1), tripfordine B (2), tripfordine C (7), wilforine (3), wilforgine (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 µg mL⁻¹.9 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

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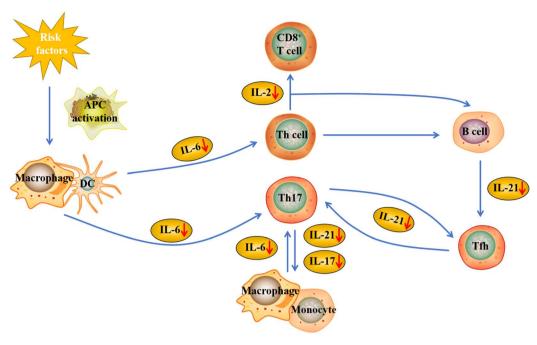


Fig. 4 The therapeutic mechanism of *T. wilfordii* in immunosuppressive activity

TNF-α, IL-17, Ang-1, Ang-2, ERK, p38, and other cytokines. 68 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.⁶⁹ Tripchlorolide (135) has emerged as a promising agent for modulating Aβ-related pathology in Alzheimer's disease (AD) at a concentration of 1 µM, 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.5 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.69

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-κB 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. 70-72 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.71 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-kB pathway, inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-6. This interaction reduces inflammation and tissue damage in diseases like rheumatoid arthritis.73 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.74 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-kB 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.11,47 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. 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. 60,75,76

Hepatotoxicity

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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.77,78 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. 60 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.^{79,80} Triptolide induced hepatocyte apoptosis via ROS generation, while celastrol exacerbated hepatocyte damage by suppressing CYP450 activity.81 These findings underscored that T. wilfordiiinduced 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. S2-84 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. 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. S6

Cardiotoxicity

Blockade of the human ether-à-go-go-related gene (hERG) potassium channel was identified as a critical mechanism underlying drug-induced cardiotoxicity. Studies showed that $T.\ wilfordii$ aqueous extracts at concentrations of 0.05 mg mL $^{-1}$

and 0.1 mg mL $^{-1}$ inhibited hERG current amplitudes by 21.4 \pm 1.6% and 86.7 \pm 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. 88

Reproductive toxicity

T. wilfordii disrupted reproductive function in both male and female animals through multiple pathways¹² In males, active components (e.g., triptolide, celastrol) induced caspase-3dependent 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 timedependent manner.89 In females, T. wilfordii inhibited granulosa cell proliferation, reduced antioxidant enzyme activity, and modulated Bax/Bcl-2 ratios, disrupting folliculogenesis and accelerating ovarian senescence. 90 Additionally, its reproductive toxicity involved germ cell apoptosis, autophagic damage, synthesis dysregulation, and endocrine hormonal dysfunction.91,92

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.93 Celastrol conjugated with polyethylene glycol (PEG) and EpCAM aptamer-modified demonstrated improved solubility, potent antitumor activity in SW620 colon cancer cells, and reduced toxicity in AD293 cells, mice, and zebrafish. 94,95 Celastrol-loaded PEG-polycaprolactone (PCL) nanoparticles retained metabolic regulatory effects in obesity models while avoiding gastrointestinal injury.96 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.97 Celastrol self-assembled nanoparticles displayed enhanced cytotoxicity in breast and lung cancer cells with tumor-targeting capability and minimal histological alterations.98,99 Celastrol-BSA-NPs prepared via high-pressure homogenization showed superior bioavailability and efficacy in diet-induced obesity.100 Triptolide-ADIBO conjugates modified with hyaluronic acid (HA) demonstrated potent antitumor effects in breast and liver cancers. 101 These advancements highlight the role of modern DDSs in advancing T. wilfordii terpenoid applications. Therefore, developing

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

Conclusions

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, Xiaoan 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.

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