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Review article

Eudesmane-type sesquiterpenoids: Structural diversity and biological activity

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ABSTRACT

Sesquiterpenoids are integral constituents of terpenoid-bearing plants, comprising a diverse and abundant class of natural compounds, among which eudesmane-type sesquiterpenoids have bicyclic structures that feature the fusion of two six-membered carbon rings, thereby attracting considerable attention. They are widespread in nature, with multifaceted biological activities such as anti-inflammatory, anticancer, antimicrobial, antimalarial, and insecticidal activities, thus gaining focus in life science research. The discovery and identification of these active compounds have laid a foundation for unraveling their potential medicinal value. In this review, we comprehensively explore the natural eudesmane-type sesquiterpenoids isolated (totaling 391 compounds) between 2016 and 2022, elucidating their chemical structures, plant distribution patterns, and pertinent biological properties. Accordingly, the study serves not only as a framework for researchers to thoroughly comprehend these compounds but also as a robust reference for future endeavors aimed at exploring the pharmaceutical potential and prospective applications of these molecules.

EC_{50}	Concentration for 50 % of maximal effective
IC_{50}	Half-maximal inhibitory concentration
CC_{50}	50 % Cytotoxic Concentration
NO	Nitric oxide
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
RAW 264.7	Mouse monocyte macrophages
TNF-*α*	Tumor necrosis factor-*α*
IL-6	Interleukin-6

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(*continued*)

IL-12	Interleukin-12
IFN-γ	Interferon-γ
NF-κB	Nuclear factor kappa B
L-NMMA	N^G-Monomethyl-L-arginine
Dex	Dexamethasone
LNCaP	Lymph Node Carcinoma of the Prostate
AD	Alzheimer's disease
Aβ	amyloid β-protein
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
STAT3	Signal Transducer and Activator of Transcription 3
SAR	Structure-activity relationships

1. Introduction

Sesquiterpenoids, which are a class of natural compounds composed of three isoprene-derived units, exhibit an extensive distribution across plants, marine organisms, and microbes, being most diverse among terpenoids in terms of structural variations. The fundamental framework of sesquiterpenoids encompasses acyclic, monocyclic, bicyclic, tricyclic, and multicyclic forms, often manifested as derivatives containing oxygen, alcohols, ketones, and lactones [1]. Imparting a wide range of biological activities, sesquiterpenoids manifest anti-inflammatory, cytotoxic, antibacterial, insecticidal, and vasorelaxant properties [2], and in particular, the discovery of artemisinin has revolutionized the development of antimalarial drugs, making it and its derivatives one of the most important treatments for malaria. Owing to their diverse chemical structures and noteworthy biological properties, sesquiterpenoids have piqued substantial interest among pharmacologists and chemists, continually yielding novel and potent discoveries [3–9].

Notably, eudesmane-type sesquiterpenoids form a distinctive subset of natural products with broad pharmaceutical utility, characterized by a fundamental structure comprised of two six-membered carbon rings. While most exist in monomeric form, a subset transforms into sesquiterpenoid dimers through Diels–Alder cycloaddition reactions or Michael addition reactions. The proposed biosynthetic pathway of eudesmane-type sesquiterpenoids involves the sesquiterpenoid precursor, farnesyl pyrophosphate (FPP), undergoing pyrophosphate group loss catalyzed by sesquiterpene synthase (STS) to form a farnesyl$^+$ carbocation. Then, cyclization occurs at C-10, yielding the gremacrene-11-yl$^+$ carbocation. Subsequent protonation of the double bond at C-6 followed by cyclization at C-7 generates the generalized eudesmane-type sesquiterpenoid structure (Fig. 1). Many of these compounds exhibit diverse biological or therapeutic activities, such as anti-inflammatory [9], cytotoxic [10], anti-bacterial [11], anti-malaria [7], insecticidal [12], hypoglycemic [13], and hypolipidemic [14] activities.

While numerous novel eudesmane-type sesquiterpenoids with significant structural variations and activities have been discovered over time, a comprehensive review and discourse concerning the structures and effects of these compounds remain absent. Only a few scholars have addressed eudesmane-type sesquiterpenoids and their derivatives from Asteraceae until 2014 [15and16]. Thus, this review summarized studies on eudesmane-type sesquiterpenoids in the last 7 years (2016–2022), with the primary objective of providing an indispensable reference to potentially stimulate and guide subsequent investigations and developments in this specialized field.

2. Methodology

To comprehensively review the research progress on the structural diversity and biological activity of natural eudesmane-type sesquiterpenoids, a total of 137 published articles from 2016 to December 2022 were referenced. These articles were sourced from reputable scientific databases, including the Web of Science, Science Direct, Google Scholar, PubMed, SciFinder, CNKI, ACS, and RSC. Search terms such as "Eudesmane", "Asteraceae", and "Eudesmane and biological activity" were employed to collect pertinent data. Additionally, the botanical Latin names of all plant species mentioned in the review were retrieved from the World Flora Online database (http://www.worldfloraonline.org/).

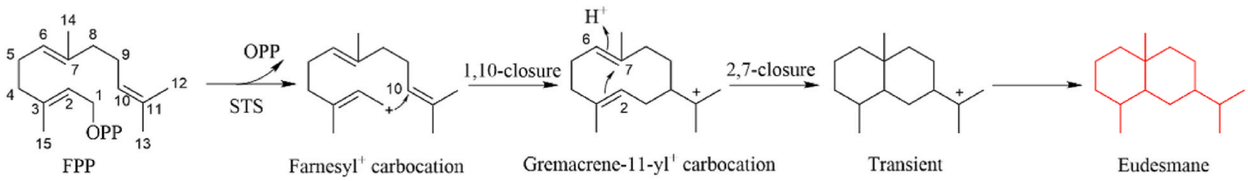

Fig. 1. Proposed biogenetic pathway of eudesmane-type sesquiterpenoids.

3. Distribution and chemical structures of eudesmane-type sesquiterpenoids

From 2016 to 2022, more than 391 eudesmane-type sesquiterpenoids have been identified and isolated, with the majority originating from species within the family Asteraceae. Subsequently, significant contributions have also been observed from the families Lamiaceae, Chloranthaceae, Solanaceae, Anacardiaceae, and Thymelaeaceae. Additionally, a limited number of eudesmane-type compounds can be sourced from bryophytes, microorganisms, and marine organisms (Fig. 2).

3.1. Eudesmane-type sesquiterpenoids from species in the family Asteraceae

We compiled the distribution of 182 natural eudesmane-type sesquiterpenoids from species in the family Asteraceae (Fig. 3). A statistical study found that sesquiterpenoids in the family Asteraceae are mainly distributed in species of genera *Artemisia*, *Atractylodes*, *Inula*, *Laggera*, *Asterothamnus*, *Dittrichia*, *Parasenecio*, *Centaurea*, *Pluchea*, *Sphagneticola*, *Anthemis*, *Saussurea*, *Kalimeris*, *Ainsliaea*, *Sonchus*, *Seriphidium*, *Echinops*, *Crepis*, *Pulicaria*, *Miyamayomena*, *Ambrosia*, *Dolomiaea*, and *Verbesina.*

3.1.1. Eudesmane-type sesquiterpenoids from species in the genus Artemisia

Previous studies have identified 75 eudesmane-type sesquiterpenoids from plants in the genus *Artemisia* (Fig. 4, Table 1), primarily from *A. hedinii*, *A. argyi*, *A. freyniana*, *A. leucophylla*, and *A. rupestris.* These compounds exhibit consistent characteristics. For instance, H-5 and H-7 consistently adopt α-orientations, whereas the methyl group at C-10 is predominantly positioned in the β-direction. Moreover, around 40 % of the sesquiterpenoids exhibit substitution at C-9, often involving acetoxyl and hydroxyl groups. Additionally, roughly one-third of the compounds feature a hydroxy group at C-1. Intriguingly, more than one-third of the compounds (**33**–**60**) manifest as sesquiterpene lactones, wherein the isopropyl branch forms an α,β-unsaturated-γ-lactone between C-6 and C-7.

The C-11 is prone to dehydrogenate and cause double bond formation. Further, C-13 is usually oxidized to a carboxyl group (**1**–**18**), or with a methyl/ethyl formate (**19**–**27**). Compounds **28**–**32**, however, have multiple hydroxyl substitutions. In particular, compounds **61**–**68** sourced from *A. hedinii* are classified as 12,13-bisnorsesquiterpenoids, with the C-11 oxidized to a carboxyl group. Additionally, compounds **69**–**70** can be categorized as 11,12,13-trinorsesquiterpenoids; compounds **22**–**27** originating from *A. argyi* exhibit an isopentenyl ester at C-8; compounds **71**–**73** are dimers formed by one eudesmane-type and one guaiane-type sesquiterpenoid through Diels–Alder [2 + 2] cycloaddition, while compounds **74**–**75** consist of one eudesmane-type and one guaiane-type sesquiterpenoid connected by ester bonds.

3.1.2. Eudesmane-type sesquiterpenoids from species in the genus Atractylodes

In total, 30 eudesmane-type sesquiterpenoids have been reported from the genera *Atractylodes* in the family Asteraceae (Fig. 5, Table 1), derived from *A. lancea, A. chinensis*, and *A. macrocephala.* Compounds **77** and **78** are a pair of enantiomers from *A. macrocephala*, and compounds **79**–**84** and **91** possess a hydroxy group at C-7. In addition, a substantial proportion of compounds from *A. macrocephala* (**80**–**90**) are characterized by one $\Delta^{4(14)}$ double bond. As exceptions, compounds **94**–**96** are eudesmanolactam hybrids consisting of an atractylenolactam moiety and a phenol unit, an ethyl unit, or an *n*-butyric acid unit linked via a C–N bond. Finally, compounds **98**–**105** from *A. lancea* and *A. macrocephala* are categorized as sesquiterpenoid glycosides, notable for having an α,β-unsaturated ketone located in either ring A or B.

3.1.3. Eudesmane-type sesquiterpenoids from species in the genus Inula

In the genus *Inula*, 14 compounds were isolated (Fig. 6, Table 1), primarily derived from *I. japonica* and *I. helenium*, among which compounds **106**–**110** are bicyclic sesquiterpenoids that feature two terminal double bonds. The remaining compounds (**111**–**119**) are

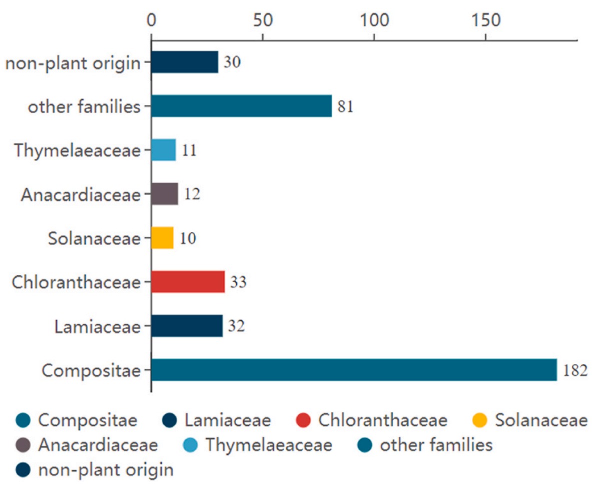

Fig. 2. Distribution of 391 eudesmane-type sesquiterpenoids.

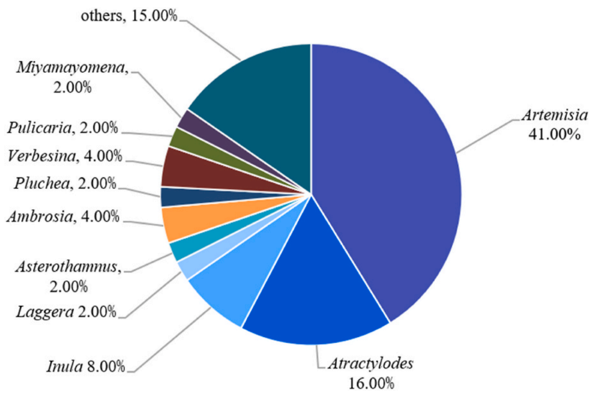

Fig. 3. Distribution of 182 eudesmane-type sesquiterpenoids from the family Asteraceae.

all sesquiterpene lactones generated by linking C-8 and C-12 via an ester bond.

3.1.4. Eudesmane-type sesquiterpenoids from species in other genera

In addition to the eudesmane-type sesquiterpenoids isolated from plants in the three genera above, 63 additional compounds have been reported from species in several other genera in the family Asteraceae (Fig. 7, Table 1). Notably, the C-11 of compounds **120**–**124** is readily dehydrogenated to double bonds and the C-13 is oxidized to carboxyl groups. A distinct trait of compounds **137**–**145** lies in the presence of a carbonyl group, either at the C-3 or C-8. Interestingly, compounds **141**–**144** are characterized by a 4,6-dien-3-one or a 1,4,6-trien-3-one conjugated system; meanwhile, compounds **137**–**139** exhibit the same basic eudesmane structure with a 2,3-epoxy-2-methylbutanoyloxy residue at C-3. These observations reveal that compounds **130**, **134**–**135**, and **145** all possess oxygen bridges between C-7 and C-8/11/6. Distinctively, each compound ranging from **146** to **153** incorporates a cinnamoyloxy group at C-6, all of which are in the β-orientation. In addition, a subset of compounds, specifically **154–160**, are categorized as sesquiterpene lactones, among which compound **154** stands out as an instance of a peroxide-substituted eudesmane-type sesquiterpenoid.

Of these compounds, over 25 % are sesquiterpenoide glycosides (**166–182**). Impressively, three sesquiterpene dimers (**163**–**165**) were isolated from *Dolomiaea souliei* and *Echinops grijsii.* Compounds **163** and **164** are a pair of isomers, presumably produced by the Diels–Alder [4 + 2] cycloaddition reaction of one eudesmane-type sesquiterpenoid and one germacrane-type sesquiterpene lactone. Compound **164**, with an exceptional 6/6/5/6/6 ring system and an oxygenated spiro ring structure, is speculated to form from two eudesmane-type sesquiterpenoids through a Michael addition reaction.

3.2. Eudesmane-type sesquiterpenoids from species in the family Lamiaceae

Previous studies have reported 32 eudesmane-type sesquiterpenoids in the family Lamiaceae (Fig. 8, Table 2), all derived from *Salvia plebeia*. Most compounds have an α,β-unsaturated-γ-lactone structure and are prone to carbonyl groups at C-2. Compound **209** is a sesquiterpene alkaloid with an 8,12-lactam structure and **214** is an eudesmane-type sesquiterpene dimer, formed via two copies of compound **135** through C-8. Intriguingly, nearly 50 % of the compounds in the family Lamiaceae had the α-orientation for the methyl group at C-10, which differs from Asteraceae.

3.3. Eudesmane-type sesquiterpenoids from species in the family Chloranthaceae

Currently, 33 eudesmane-type sesquiterpenoids with an α,β-unsaturated-γ-lactone ring or a furan ring have been reported from the family Chloranthaceae (Fig. 9, Table 3). Compounds **215**–**216, 217**–**218,** and **219**–**220** from *Chloranthus serratus* are three pairs of enantiomers, and according to the compiled literature, all the eudesmane-type sesquiterpenoids extracted from this plant are enantiomers. It is worth noting that sesquiterpene dimers are predominant in this family. Researchers have isolated 12 sesquiterpene dimers from *C. fortune, Hedyosmum orientale,* and *C. henryi* var. *hupehensis*. Compounds **236–237** from *C. fortune* are produced by Diels–Alder cycloaddition of one eudesmane-type and one lindenane-type sesquiterpenoid. Compound **238** is an eudesmane-guaiane heterodimeric sesquiterpenoid possessing a unique bridged 2,10-dioxabicyclo[6.2.1] undecane moiety with a strained anti-Bredt bridgehead double bond. Four unique enantiomeric pairs of eudesmane-type sesquiterpenoid dimers with two new carbon skeletons were isolated from *C. henryi* var. *hupehensis* (**240**–**247**). Compounds **240**–**243** possess a 6/6/5/6/6 pentacyclic carbon skeleton with a new dimerization pattern of two eudesmane-type sesquiterpenoids. Compounds **244**–**247**, which are fused with two eudesmane-type sesquiterpenoids via an unprecedented five-membered *O*-heterocyclic ring—represent a new 6/6/5/5/6/6/5 heptacyclic ring system.

3.4. Eudesmane-type sesquiterpenoids from species in the family Solanaceae

Presently, 10 eudesmane-type sesquiterpenoids (Fig. 10, Table 4) have been reported from species in the family Solanaceae. Compounds **248**–**252**, derived from *Datura metel*, have a propane-1,2-diol fragment on the isopropyl branched chain.

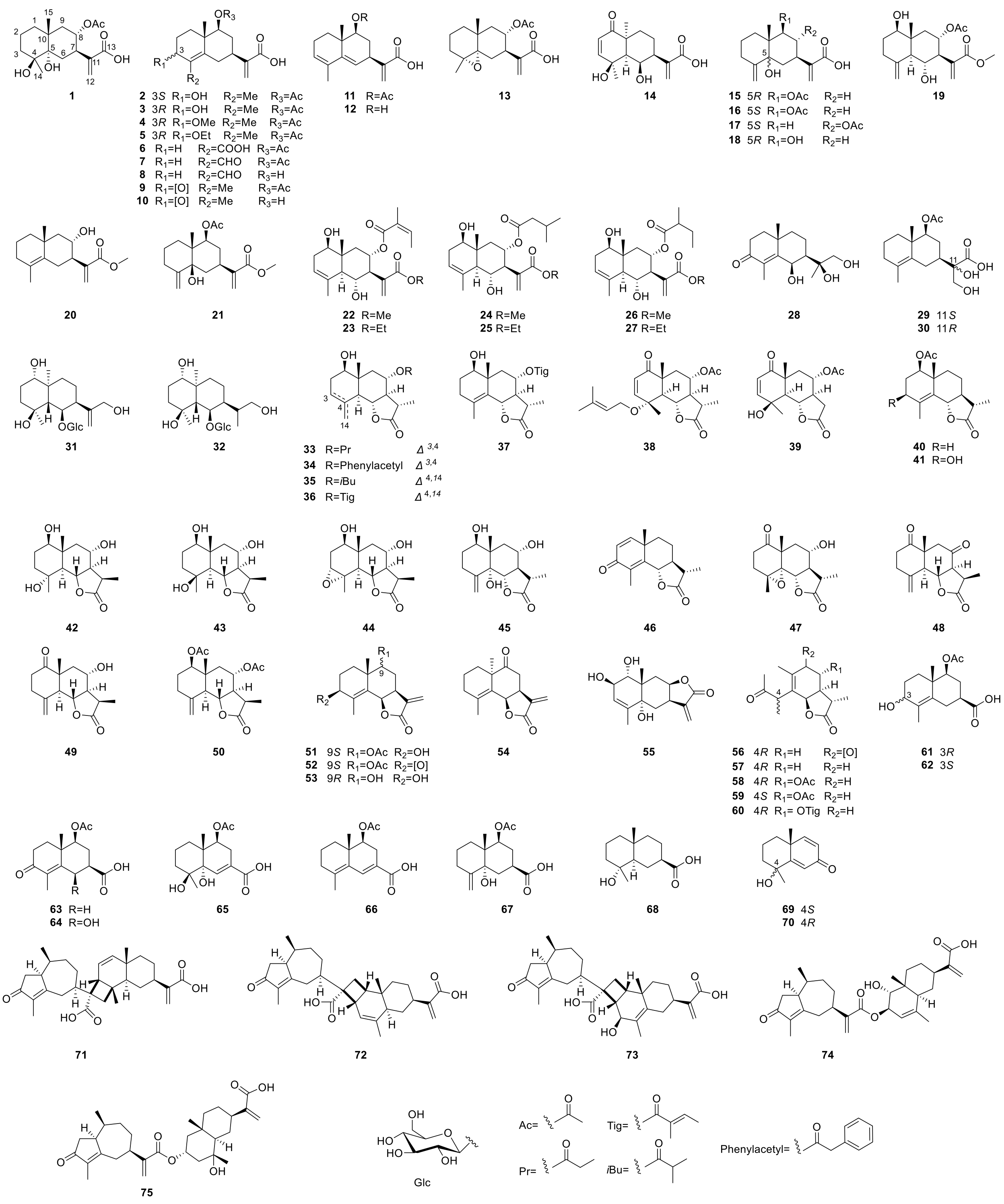

Fig. 4. Structures of eudesmane-type sesquiterpenoids from species in the genus *Artemisia*.

3.5. Eudesmane-type sesquiterpenoids from species in the family Anacardiaceae

Twelve eudesmane-type sesquiterpenoids (Fig. 11, Table 5) have been isolated from plants in the family Anacardiaceae, all of which were derived from *Dobinea delavayi.* Except for compound **258**, most eudesmane-type sesquiterpenoids have a cyclic structure in their isopropyl chain. In addition, five eudesmane-type sesquiterpene dimers were isolated from this plant.

Table 1
Eudesmane-type sesquiterpenoids (compounds **1**–**182**) from plants in the family Asteraceae.

No.	Name	Sources	Reference
Artemisia			
1	Artefreynic acid H	*Artemisia freyniana* (Pamp.) Krasch.	[17]
2	Artemihedinic acid A	*Artemisia hedinii* Ostenf.	[18]
3	(3*R*,7*S*,9*S*,10*S*)-3-Hydroxy-9-acetoxyeudesm-4,11(13)-dien-12-oic acid	*A. hedinii*	[18]
4	Artemihedinic acid B	*A. hedinii*	[18]
5	Artemihedinic acid C	*A. hedinii*	[18]
6	Artemihedinic acid K	*A. hedinii*	[18]
7	Artemihedinic acid L	*A. hedinii*	[18]
8	Artemihedinic acid M	*A. hedinii*	[18]
9	Artemihedinic acid G	*A. hedinii*	[18]
10	Artemihedinic acid H	*A. hedinii*	[18]
11	Artemihedinic acid I	*A. hedinii*	[18]
12	Artemihedinic acid J	*A. hedinii*	[18]
13	Artefreynic acid I	*A. freyniana*	[17]
14	Artanoic acid	*Artemisia vulgaris* L.	[19]
15	Artemihedinic acid D	*A. hedinii*	[18]
16	9*β*-Acetoxy-5*β*-hydroxy-eudesma-4(15),11(13)-dien-7*αH*-12-oic acid	*A. hedinii*	[18]
17	Artefreynic acid J	*A. freyniana*	[17]
18	Artetourneforin acid	*Artemisia tournefortiana* Rchb.	[20]
19	Austroyunnane H	*Artemisia austro-yunnanensis* Ling et Y. R. Ling	[21]
20	(7*R*,8*S*,10*R*)-8-Hydroxyeudesma-4,11(13)-dien-12-oate	*A. freyniana*	[17]
21	Artetourneforin D	*A. tournefortiana*	[20]
22	Artemargyinin A	*Artemisia argyi* H.Lév. & Vaniot	[22]
23	Artemargyinin B	*A. argyi*	[22]
24	Artemargyinin C	*A. argyi*	[22]
25	Artemargyinin D	*A. argyi*	[22]
26	Artemargyinin E	*A. argyi*	[22]
27	Artemargyinin F	*A. argyi*	[22]
28	Artemihedinin A	*A. hedinii*	[18]
29	Artemihedinic acid E	*A. hedinii*	[18]
30	Artemihedinic acid F	*A. hedinii*	[18]
31	Vulgaroside A	*A. vulgaris*	[23]
32	Vulgaroside B	*A. vulgaris*	[23]
33	Artemleucolide F	*Artemisia leucophylla* C.B.Clarke	[24]
34	Artemleucolide G	*A.leucophylla*	[24]
35	Artemleucolide H	*A.leucophylla*	[24]
36	Artemleucolide I	*A.leucophylla*	[24]
37	Artemleucolide J	*A.leucophylla*	[24]
38	Artemleucolide K	*A.leucophylla*	[24]
39	Artemleucolide L	*A.leucophylla*	[24]
40	Arhalin	*A. halophila* Krasch.	[25]
41	3*β*-Hydroxyarhalin	*A. halophila* Krasch.	[25]
42	Persianolide A	*Artemisia kopetdaghensis* Krasch., Popov & Lincz. ex Poljakov	[26]
43	4-*epi*-Persianolide A	*A. kopetdaghensis*	[26]
44	3*α*,4-Epoxypersianolide A	*A. kopetdaghensis*	[26]
45	8*α*-Hydroxyartemin	*Artemisia ferganensis* Krasch. ex Poljakov	[27]
46	*α*-Santonin	*A. ferganensis*	[27]
47	8*α*-Hydroxy-4*α*,5*α*-epoxytaurin	*A. ferganensis*	[27]
48	1*α*,13-Dihydroeudesma-12,6*α*-olide-1,8-dione	*A. Kopetdaghensis*	[26]
49	*β*-Hy-droxy-11*α*,13-dihydroeudesma-12,6*α*-olide-1-one	*A. kopetdaghensis*	[26]
50	1,8-*O*-Diacetyl-11*α*,13- dihydroeudesma-12,6*α*-olide	*A. kopetdaghensis*	[26]
51	Artetourneforin A	*A. tournefortiana*	[20]
52	Artetourneforin B	*A. tournefortiana*	[20]
53	Artetourneforin C	*A. tournefortiana*	[20]
54	Artetourneforin E	*A. tournefortiana*	[20]
55	Artemisargin A	*A. argyi*	[28]
56	Artemleucolide A	*A.leucophylla*	[24]
57	Artemleucolide B	*A.leucophylla*	[24]
58	Artemleucolide C	*A.leucophylla*	[24]
59	Artemleucolide D	*A.leucophylla*	[24]
60	Artemleucolide E	*A.leucophylla*	[24]
61	(3*R*,7*S*,9*S*,10*S*)-3-Hydroxy-9-acetoxy-dinor-eudesm-4-en-11-oic	*A. hedinii*	[29]
62	(3*S*,7*S*,9*S*,10*S*)-3-Hydroxy-9-acetoxy-dinor-eudesm-4-en-11-oic	*A. hedinii*	[29]
63	(7*S*,9*S*,10*S*)-3-Oxo-9-acetoxy-dinor-eudesm-4-en-11-oic	*A. hedinii*	[29]
64	(6*R*,7*R*,9*S*,10*S*)-3-Oxo-6-hydroxy-9-acetoxy-dinor-eudesm-4-en-11-oic	*A. hedinii*	[29]
65	(4*S*,5*S*,9*S*,10*R*)-4,5-Dihydroxy-9-acetoxy-dinor-eudesm-6-en-11-oic	*A. hedinii*	[29]
66	(9*S*,10*S*)-9-Acetoxy-dinor-eudesm-4,6-dien-11-oic	*A. hedinii*	[29]

(*continued on next page*)

Table 1 (*continued*)

No.	Name	Sources	Reference
67	(5*R*,7*R*,9*S*,10*R*)-5-Hydroxy-9-acetoxy-dinor-eudesm-4(13)-en-11-oic	*A. hedinii*	[29]
68	(4*R*,5*R*,7*R*,10*R*)-4-Hydroxy-dinor-eudesm-11-oic	*A. hedinii*	[29]
69	(4*S*,10*R*)-4-Hydroxy-11,12,13-trinor-eudesm-5,8-dien-7-one	*A. hedinii*	[29]
70	(4*R*,10*R*)-4-Hydroxy-11,12,13-trinor-eudesm-5,8-dien-7-one	*A. hedinii*	[29]
71	Artepestrin A	*Artemisia rupestris* L.	[30]
72	Artepestrin B	*A. rupestris*	[30]
73	Ardeparin C	*A. rupestris*	[30]
74	Rupestrinate A	*A. rupestris*	[30]
75	Rupestrinate B	*A. rupestris*	[30]
Atractylodes			
76	Eudesmane-4*α*,11,15-triol	*Atractylodes chinensis* (DC.) Koidz.	[31]
77	(+)-Atramacronoids F	*Atractylodes macrocephala* Koidz.	[32]
78	(−)-Atramacronoids F	*A. macrocephala*	[32]
79	Atramacronoid L	*A. macrocephala*	[32]
80	Atramacronoid G	*A. macrocephala*	[32]
81	Atramacronoid H	*A. macrocephala*	[32]
82	Atramacronoid O	*A. macrocephala*	[32]
83	Atramacronoid P	*A. macrocephala*	[32]
84	Atractylmacrol A	*A.macrocephala*	[33]
85	Atramacronoid M	*A. macrocephala*	[32]
86	Atramacronoid N	*A. macrocephala*	[32]
87	Atractylmacrol C	*A. macrocephala*	[33]
88	Atramacronoid J	*A. macrocephala*	[32]
89	Atractylmacrol B	*A. macrocephala*	[33]
90	Atractylmacrol D	*A. macrocephala*	[33]
91	Atramacronoid R	*A. macrocephala*	[32]
92	Atramacronoid K	*A. macrocephala*	[32]
93	Atrchiterpene B	*A. chinensis*	[31]
94	Atrchiterpene A	*A. chinensis*	[31]
95	Atramacronoid E	*A. macrocephala*	[32]
96	Atramacronoid D	*A. macrocephala*	[32]
97	Atrchiterpene C	*A. chinensis*	[31]
98	(2*S*,7*R*,10*S*)-3-Hydroxylcarissone-11-*O*-*β*-*D*-glucopyranoside	*Atractylodes lancea* (Thunb.) DC.	[34]
99	(2*R*,7*R*,10*S*)-3-Hydroxylcarissone-11-*O*-*β*-*D*-glucopyranoside	*A. lancea*	[34]
100	(5*R*,7*R*,10*S*)-Isopterocarpolone-11-*O*-*β*-*D*-apiofuranosyl-(1 → 6)-*β*-*D*-glucopyranoside	*A. lancea*	[34]
101	(5*R*,7*R*,10*S*)-6’’-*O*-Acetylatractyloside I	*A. lancea*	[34]
102	(5*R*,7*R*,10*S*)-6’-*O*-Acetylatractyloside I	*A. lancea*	[34]
103	(5*R*,7*R*,10*S*)-3-Hydroxylisopterocarpolone-3-*O*-*β*-*D*-glucopyranoside	*A. lancea*	[34]
104	(5*R*,7*R*,10*S*)-14-Hydroxyisopterocarpolone-11-*O*-*β*-*D*-glucopyranoside	*A. lancea*	[35]
105	Atramacronoid I	*A. macrocephala*	[32]
Inula			
106	Inujaponin A	*Inula japonica* Thunb.	[36]
107	Inujaponin B	*I. japonica*	[36]
108	Inujaponin C	*I. japonica*	[36]
109	8*β*-Hydroxycostic acid methyl ester	*Inula helenium* L.	[37]
110	12-Acetoxy-1*β*,2*α*-dihydroxyeudesma-4(15),11(13)-diene	*I. japonica*	[38]
111	Inujaponin D	*I. japonica*	[36]
112	Inujaponin E	*I. japonica*	[36]
113	Inujaponin F	*I. japonica*	[36]
114	Inujaponin G	*I. japonica*	[36]
115	11*β*-Hydroxy-13-chloro-eudesm-5-en-12,8-olide	*I. helenium*	[39]
116	2*α*,7*α*-Dihydroxy-11,13-dihydroalantolactone	*I. helenium*	[37]
117	2*α*-Formyloxy-11,13-dihydroalantolactone	*I. helenium*	[37]
118	2*α*-Formyloxy-11,13-dihydroisoalantolactone	*I. helenium*	[37]
119	11(13)*β*-Epoxyalantolactone	*I. helenium*	[37]
Other genera			
120	(6*S*,7*S*,10*R*)-3-Oxo-6*α*-hydroxy-*γ*-costic acid	*Crepis sancta* (L.) Bornm.	[40]
121	Costic acid	*Dittrichia viscosa* (L.) Greuter	[12]
122	1*β*-Angeloyl-5*β*-hydroxycostic acid	*Anthemis orientalis* (L.) Degen	[41]
123	1*β*-*O*-Angeloyl-*β*-isocostic acid	*Anthemis orientalis*	[41]
124	Lappaterpene E	*Saussurea lappa* (Decne.) C.B Clarke	[42]
125	1*β*,6*α*,8*α*-Trihydroxy-15-oxo-eudesm-11(13)-en-12-oate	*Centaurea polyclada* DC.	[43]
126	Lappaterpene C	*Saussurea lappa*	[42]
127	Lappaterpene D	*Saussurea lappa*	[42]
128	Kalshinoid H	*Kalimeris shimadae* (Kitam.) Kitam	[44]
129	Lappaterpene B	*Saussurea lappa*	[42]
130	Echingriol B	*Echinops grijsii* Hance	[45]
131	Ainslide B	*Ainsliaea pertyoides* Franch.	[46]
132	Echingriol A	*Echinops grijsii*	[45]

(*continued on next page*)

Table 1 (*continued*)

No.	Name	Sources	Reference
133	6,11-Diacetoxy-1,4-dihydroxyeudesmane	*Ainsliaea bonatii* Beauverd	[47]
134	7*β*,11*β*-Epoxy-eudesman-4*α*-ol	*Laggera pterodonta* (DC.) Sch. Bip. ex Oliv.	[48]
135	7*α*,11*α*-Epoxy-eudesman-4*α*-ol	*Laggera pterodonta*	[48]
136	Pterodondiol	*Laggera pterodonta*	[49]
137	(3*S**,4*R**,5*S**,10*S**,2'*R**,3'*R**)-3-(2',3'-Epoxy-2'-methylbutyryloxy)-4,7-dihydroxy-eudesm-11-en-8-one	*Pluchea odorata* (L.) Cass.	[50]
138	(3*S**,4*R**,5*S**,10*S**,2'*R**,3'*R**)-3-(2',3'-Epoxy-2'-methylbutyryloxy)-4-acetyloxy-7-hydroxy-eudesm-11-en-8-one	*Pluchea odorata*	[50]
139	(3*S**,4*R**,5*S**,10*S**,2'*R**,3'*R**)-3-(2',3'-Epoxy-2'-methylbutyryloxy)-4-acetyloxy-6-methoxy-11-hydroxy-eudesm-6-en-8-one	*Pluchea odorata*	[50]
140	(3*S**,4*R**,5*S**,10*S**)-3-(2',3'-Dhydroxy-2'-methylbutyryloxy)4-acetyloxy-11-hydroperoxy-eudesm-6-en-8-one	*Pluchea odorata*	[50]
141	Asterothamnone A	*Asterothamnus centrali-asiaticus* Novopokr.	[51]
142	Asterothamnone B	*Asterothamnus centrali-asiaticus*	[51]
143	Asterothamnone C	*Asterothamnus centrali-asiaticus*	[51]
144	Asterothamnone D	*Asterothamnus centrali-asiaticus*	[51]
145	Parasenin	*Parasenecio roborowskii* (Maxim.) Y.L.Chen	[52]
146	6*β*-Cinnamoyloxy-1*β*,3*α*-dihydroxyeudesm-4(15)-ene	*Plasmopara viticola* (Berk. & M. A. Curtis) Berl. & de Toni	[3]
147	6*β*-Cinnamoyloxy-1*β*,2*α*-dihydroxyeudesm-4(15)-ene	*Verbesina lanata* B.L.Rob. & Greenm.	[3]
148	6*β*-Cinnamoyloxy-1*β*-hydroxyeudesm-4-ene	*Verbesina lanata*	[3]
149	6*β*-Cinnamoyloxy-1*β*,3*α*-dihydroxyeudesm-4-ene	*Verbesina lanata*	[3]
150	6*β*-Cinnamoyloxy-1*β*,15-dihydroxyeudesm-4-en-3-one	*Verbesina lanata*	[3]
151	6*β*-Cinnamoyloxy-1*β*,15-dihydroxyeudesm-3-ene	*Verbesina lanata*	[3]
152	6*β*-Cinnamoyloxy-4*β*,9*β*,15-trihydroxyeudesmane	*Verbesina lanata*	[3]
153	15-Cinnamoyloxy-1*β*,4*β*,6*β*-trihydroxyeudesmane	*Verbesina lanata*	[3]
154	Sonarvenolide A	*Sonchus arvensis* L.	[53]
155	Sonarvenolide B	*Sonchus arvensis*	[53]
156	1*β*,3*α*,8*α*-Trihydroxy-11*β*,13-dihydroeudesma-4(15)-en-12,6*α*-olide	*Seriphidium khorassanicum* (syn. *Artemisia khorassanica*)	[54]
157	1*β*,4*α*,8*α*-Trihydroxy-11*β*,13-dihydroeudesma-12,6*α*-olide	*Seriphidium khorassanicum*	[54]
158	Arbusculin A	*Saussurea lappa*	[42]
159	Wedetrilide B	*Wedelia trilobata* (L.) Hitchc.	[55]
160	Wedetrilide C	*Wedelia trilobata*	[55]
161	Norpterodonol A	*Laggera pterodonta* (DC.) Benth	[56]
162	(6*S*,7*S*,10*R*)-3-Oxo-di-*nor*-eudesm-4-en-6*α*-hydroxy-11-oic acid	*Crepis sancta* (L.) Bornm.	[40]
163	Vlasoulone A	*Vladimiria souliei* (Franch.) Ling	[57]
164	Vlasoulone B	*Vladimiria souliei*	[57]
165	Echingridimer A	*Echinops grijsii*	[45]
166	Pulisignoside D	*Pulicaria insignis* J.R.Drumm. ex Dunn	[58]
167	Pulisignoside A	*Pulicaria insignis*	[58]
168	Pulisignoside B	*Pulicaria insignis*	[58]
169	(1*R*,5*S*,6*R*,7*S*,9*S*,10*R*)-9-*O*-(*Z*-*p*-Coumaroyl)-1,6,9-Trihydroxy-eudesm-3-ene-6-*O*-*β*-*D*-glucopyranoside	*Aster koraiensis* Nakai	[59]
170	(1*R*,5*S*,6*R*,7*S*,9*S*,10*R*)-9-*O*-(*E*-Feruloyl)-1,6,9-Trihydroxy-eudesm-3-ene-6-*O*-*β*-*D*-glucopyranoside	*Aster koraiensis*	[59]
171	1*α*,6*β*,9*β*-Trihydroxy-5,10-bis-*epi*-eudesm-3-ene-9-*O*-[(*S*)-3″-hydroxy-3″-methylglutaryl]-6-*O*-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia* L.	[60]
172	1*α*,6*β*,9*β*-Trihydroxy-5,10-bis-*epi*-eudesm-3-ene-1-*O*-[(*S*)-3″-hydroxy-3″-methylglutaryl]-6-*O*-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
173	1*β*,6*α*-Dihydroxy-7-*epi*-eudesm-3-ene-1-*O*-[(*S*)-3″-hydroxy-3″-methylglutaryl]-6-*O*-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
174	1*α*,6*β*,9*β*-Trihydroxy-5,10-bis-*epi*-eudesm-3-ene-9-*O*-[(*S*)-3″-hydroxy-3″-methylglutaryl]-6-*O*-(6′-*O*-acetyl)-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
175	1*α*,6*β*,9*β*-Trihydroxy-5,10-bis-*epi*-eudesm-3-ene-1-*O*-*α*-*L*-arabinopyranosyl-6-*O*-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
176	1*α*,6*β*,9*β*-Trihydroxy-5,10-bis-*epi*-eudesm-3-ene-6-*O*-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
177	1*β*,6*α*-Dihydroxy-7-*epi*-eudesm-3-ene-6-*O*-*β*-*D*-apiofuranosyl(1 → 6)-*β*-*D*-glucopyranoside	*Ambrosia artemisiifolia*	[60]
178	(1*R*,5*S*,6*R*,7*S*,9*S*,10*S*)-1,6,9-Trihydroxy-eudesm3-ene-1,6-di-*O*-*β*-*D*-glucopyranoside	*Aster koraiensis*	[59]
179	(1*R*,5*S*,6*S*,7*R*,9*S*,10*S*)-1,6,9,11-Tetrahydroxy-eudesm-3-ene-1,6-di-*O*-*β*-*D*-glucopyranoside	*Aster koraiensis*	[59]
180	Pulisignoside C	*Pulicaria insignis*	[58]
181	4(15)-en-Eudesma-6,12-olide-15-*O*-*β*-*D*-glucopyranoside	*Ainsliaea bonatii* Beauverd	[47]
182	3(4)-en-Eudesma-6,12-olide-15-*O*-*β*-*D*-glucopyranoside	*Ainsliaea bonatii*	[47]

3.6. Eudesmane-type sesquiterpenoids from species in the family Thymelaeaceae

Previous studies have isolated and characterized 11 eudesmane-type sesquiterpenoids from *Aquilaria agallocha* of family Thymelaeaceae (Fig. 12, Table 6), the compounds of which often have double bonds at C-3(4), C-4(5), or C-4(15). Furthermore, compounds **270**–**274** all possess an aldehyde group at C-4.

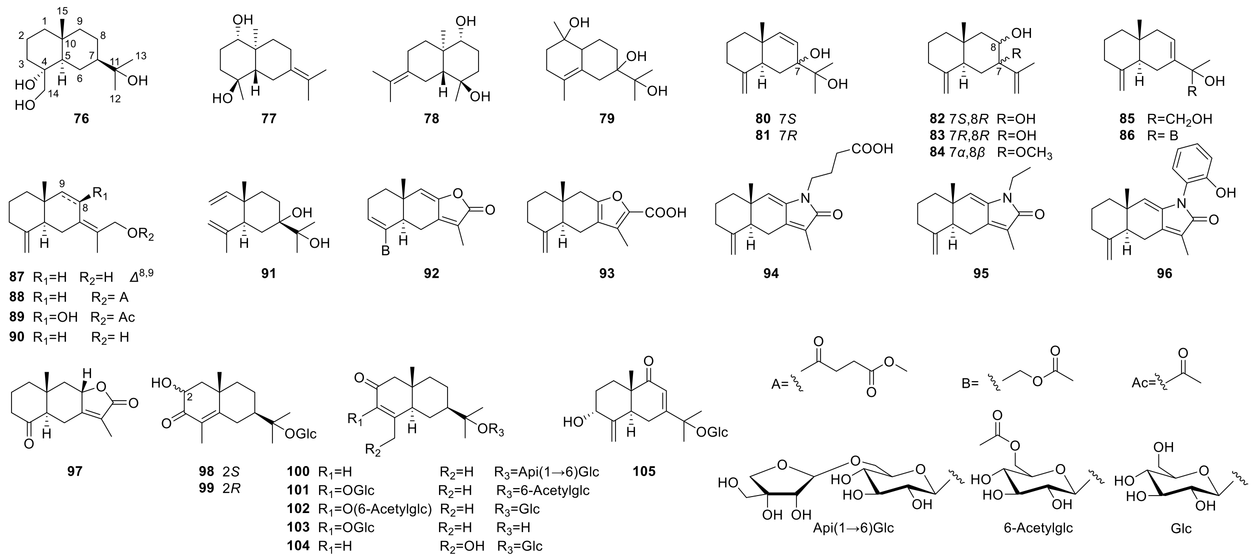

Fig. 5. Structures of eudesmane-type sesquiterpenoids from species in the genus *Atractylodes*.

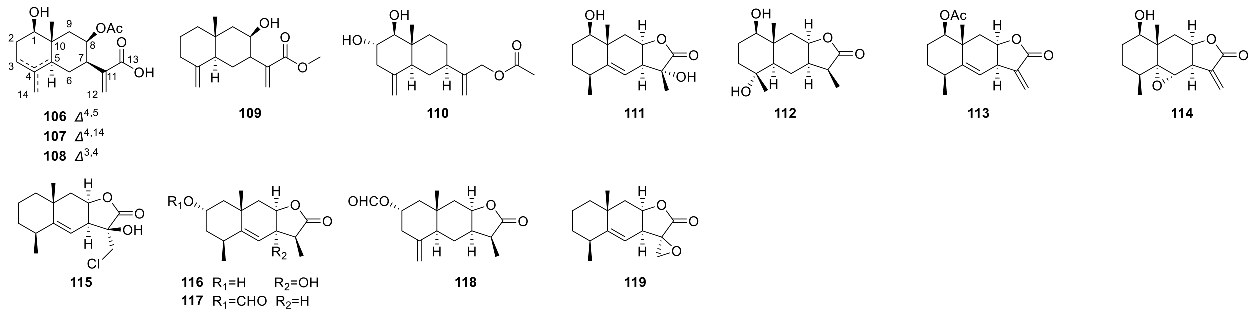

Fig. 6. Structures of eudesmane-type sesquiterpenoids from species in the genus *Inula*.

3.7. *Eudesmane-type sesquiterpenoids isolated from species in other families*

In addition to 280 eudesmane-type sesquiterpenoids isolated from species belonging to the families Asteraceae, Lamiaceae, Chloranthaceae, Solanaceae, Anacardiaceae, and Thymelaeaceae, previous studies have isolated and characterized 81 eudesmane-type sesquiterpenoids from species in 17 other families (Fig. 13, Table 7). These eudesmane-type sesquiterpenoids are vulnerable to substitution at C-6, while hydroxy substitution is easily achieved at C-1. In combination, these compounds are analogous to those of the above families whose C-1 and C-2 are susceptible to being oxidized to carbonyl groups. Moreover, a proportion of these compounds often contain $\Delta^{3(4)/4(5)/4(15)}$ double bonds, and some compounds have an oxygen-bridged structures. It is worth noting that compounds (**318**–**339**) tend to form five-membered rings through their isopropyl branch chains. Specifically, compounds **318**–**320** predominantly yield furan rings, while compounds **321**–**339** predominantly yield lactone rings. Some compounds contain a C_5–OH group, of which compounds **323**–**326** are the first examples of eudesmane sesquiterpene lactones containing C_5–OH groups. These compounds are also representative of the eudesmane-type sesquiterpenoids found in the genus *Croton*. In particular, compound **314**, from *Ammoides atlantica*, contains an acetyl moiety at C-6, and compounds **301**–**302** are peroxide-substituted eudesmane-type sesquiterpenoids. Moreover, compound **342** was also characterized as a sesquiterpenoid dimer with a hybrid framework of eudesmane and germacrene from the family Meliaceae.

3.8. *Eudesmane-type sesquiterpenoids of non-plant origin*

In addition to the aforementioned plants, eudesmane-type sesquiterpenoids can also be synthesized from marine organisms and microbes (Fig. 14, Table 8). A summary reveals that these compounds are readily substituted with hydroxy groups at C-1, C-2, or C-11. Compounds **373**–**375**, isolated from *Laurencia pinnata*, are examples of brominated eudesmane-type sesquiterpenoids featuring bromine at C-1. Compound **389** from *Flammulina velutipes* contains a C-3–O–C-9 oxygen bridge, while compounds **380**–**383** from *Axinyssa variabilis* are nitrogen-containing eudesmane-type sesquiterpenoids. Additionally, compound **391** possesses a benzoic acid

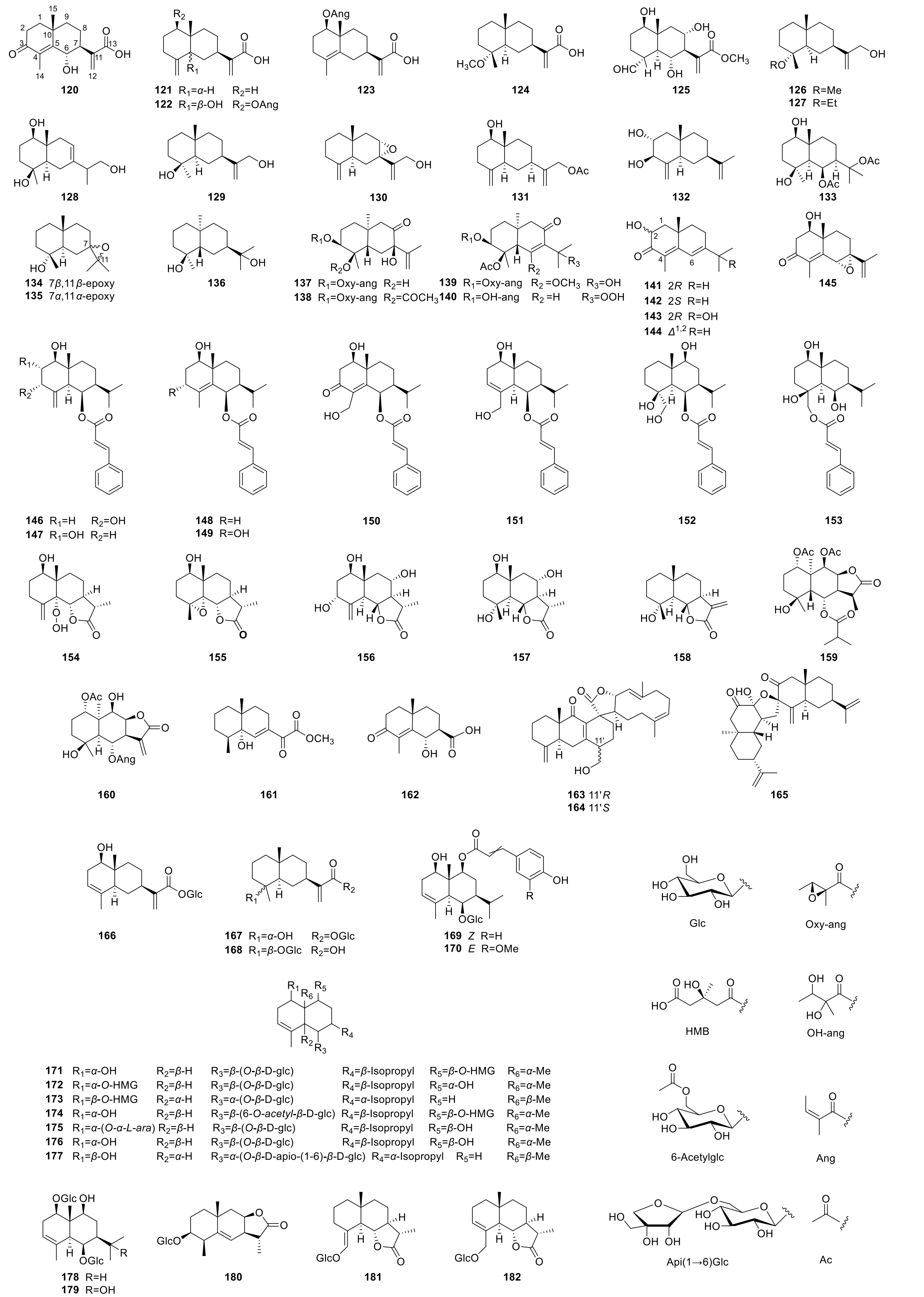

Fig. 7. Structures of eudesmane-type sesquiterpenoids from species in other genera.

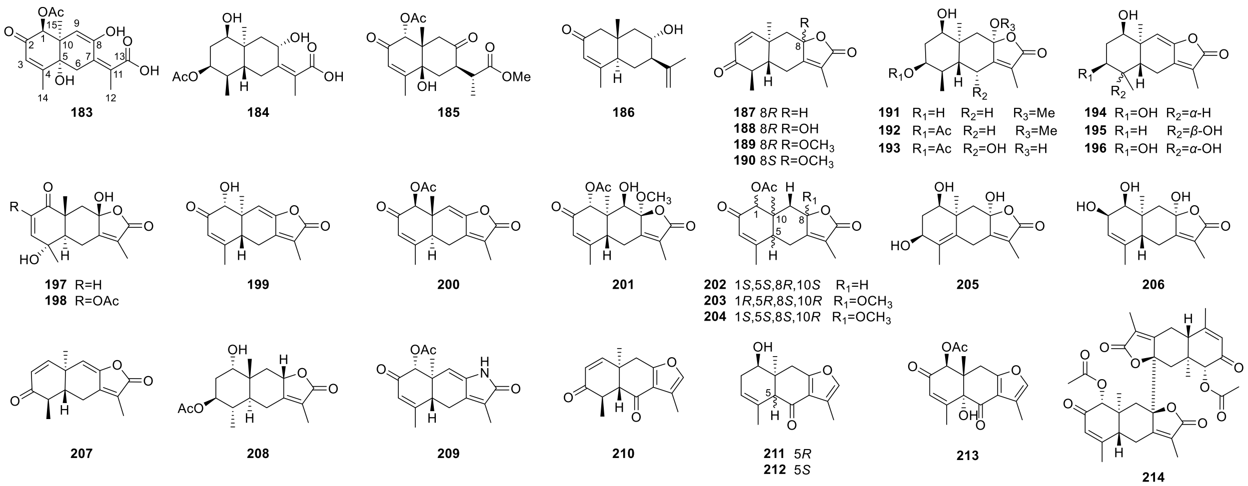

Fig. 8. Structures of eudesmane-type sesquiterpenoids from plants in the family Lamiaceae.

Table 2
Eudesmane-type sesquiterpenoids (compounds **183–214**) from plants in the family Lamiaceae.

No.	Name	Sources	Reference
183	Plebeic acid C	*Salvia plebeia* R.Br.	[61]
184	Plebeic acid B	*S. plebeia*	[61]
185	Methyl plebeiate A	*S. plebeia*	[61]
186	Sapleudesone	*S. plebeia*	[62]
187	Eudebeiolide A	*S. plebeia*	[63]
188	Eudebeiolide B	*S. plebeia*	[63]
189	Eudebeiolide C	*S. plebeia*	[63]
190	8-*epi*-Eudebeiolide C	*S. plebeia*	[64]
191	8-Methoxy-plebeiolide B	*S. plebeia*	[63]
192	Eudebeiolide E	*S. plebeia*	[63]
193	6-Hydroxyplebeiolide A	*S. plebeia*	[64]
194	Eudebeiolide F	*S. plebeia*	[63]
195	1-*epi*-Phaeusmane G	*S. plebeia*	[64]
196	Eudebeiolide K	*S. plebeia*	[64]
197	Eudebeiolide G	*S. plebeia*	[64]
198	Eudebeiolide H	*S. plebeia*	[64]
199	Salplebeone D	*S. plebeia*	[65]
200	Salviplenoid E	*S. plebeia*	[66]
201	Salplebeone E	*S. plebeia*	[65]
202	(1*S*,5*S*,8*R*,10*R*)-1-Acetoxy-2-oxoeudesman-3,7(11)-dien-8,12olide	*S. plebeia*	[61]
203	(1*R*,5*R*,8*S*,10*S*)-1-Acetoxy-8-methoxy-2-oxoeudesman-3,7(11)-dien-8,12-olide	*S. plebeia*	[61]
204	(1*S*,5*S*,8*S*,10*R*)-1-Acetoxy-8-methoxy-2-oxoeudesman-3,7(11)-dien-8,12-olide	*S. plebeia*	[64]
205	Eudebeiolide I	*S. plebeia*	[64]
206	Eudebeiolide J	*S. plebeia*	[64]
207	Eudebeiolide D	*S. plebeia*	[63]
208	(1*S*,3*S*,4*S*,5*S*,8*S*,10*R*)-3-Acetoxy-1-hydroxyeudesman-7(11)-en-8,12-olide	*S. plebeia*	[61]
209	Salplebeone F	*S. plebeia*	[65]
210	Salviplenoid A	*S. plebeia*	[66]
211	Salviplenoid B	*S. plebeia*	[66]
212	Salviplenoid C	*S. plebeia*	[66]
213	Salviplenoid D	*S. plebeia*	[66]
214	Salplebeone G	*S. plebeia*	[65]

linked to the eudesmane-type sesquiterpenoid via a C–N bond.

4. Biological activity of eudesmane-type sesquiterpenoids

Numerous experimental data have shown that eudesmane-type sesquiterpenoids possess a wide range of biological activities, including anti-inflammatory, cytotoxic, anti-bacterial, anti-malaria, insecticidal, and neuroprotective activities. In general, the biological activities of compounds are strongly influenced by their molecular structures, particularly the types, positions, quantities, and electronic effects of substituent groups. This phenomenon arises because structural modifications can significantly affect the stability

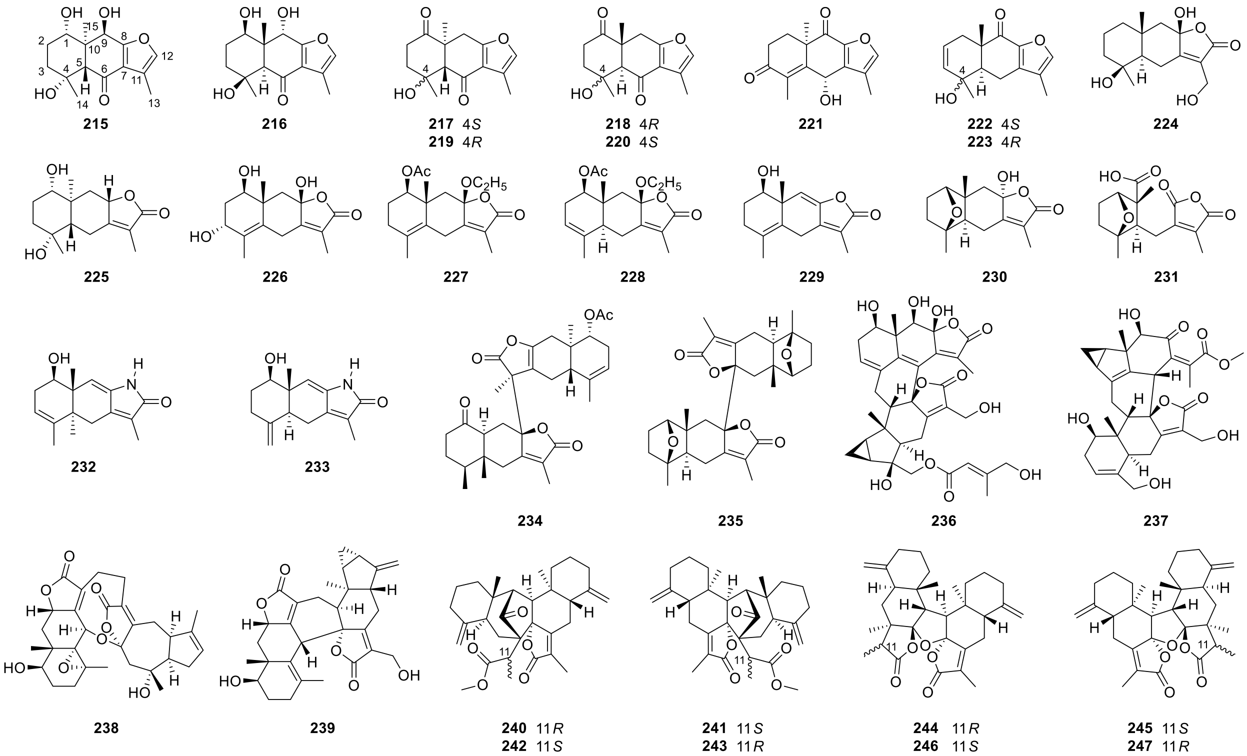

Fig. 9. Structures of eudesmane-type sesquiterpenoids from species in the family Chloranthaceae.

and the stereo configuration of a compound, as well as the mode of interaction with the target molecule. Prior investigations have indicated that the inclusion of alkenes or hydroxy groups in eudesmane-type sesquiterpenoids often leads to enhanced activity. In addition, numerous other factors can potentially influence their activity. For example, the size and type of the fused ring (e.g., a five-, six- or seven-ring), the presence of heteroatoms like nitrogen or sulfur, the polarity of the molecule, and the availability of hydrogen bond donor and acceptor sites, can all affect their biological activity. Here we present a summary of the different activities of eudesmane-type sesquiterpenoids reported from 2016 to 2022.

4.1. Anti-inflammatory activity

The inhibition of inflammatory responses is one of the most important biological activities of eudesmane-type sesquiterpenoids. In recent years, many researchers have reported that eudesmane-type sesquiterpenoids can significantly inhibit the release of NO (Table 9), which plays an important role in the inflammatory response [133,139]. Taking LPS-induced RAW 264.7 cells as an inflammatory cell model. Specifically, the position of the substituent group has a significant effect on the anti-inflammatory activity of eudesmane-type sesquiterpenoids. Noteworthy substituent positions include C-8, C-11, and C-13, wherein substitutions can introduce new chemical properties that modify the activity. To elaborate, within the scope of compounds exhibiting anti-inflammatory activity (Table 9), compounds **1**–**21**, along with compound **109**, have substitutions at these three pivotal positions. This is manifested by the oxidation of C-11 to an alkene, the substitution of C-13 with a carboxylic acid or a methyl/ethyl formate group, and C-8 being incorporated into a group containing oxygen. Further analysis of compounds **22**–**27**, underlining their anti-inflammatory activities, reveals that substituent variations at C-8 considerably influence their activities. Meanwhile, the impact is less significant when there is a substitution with either methyl formate or ethyl formate at C-1. Supplementing this, the anti-inflammatory properties of eudesmane-type sesquiterpenoids are also influenced by the number of substituents, not merely their positions. It can be discerned from compounds **248**–**253** that the anti-inflammatory activity is augmented when both C-11 and C-13 are adorned with hydroxy substituents. This signifies that an increase in the number of hydroxy substituents often corresponds to an enhancement in the anti-inflammatory activity. Moreover, the evaluation of compounds **61**–**65** and **67**–**70** suggests that noreudesmane-type sesquiterpenoids might be responsible for the anti-inflammatory effects, among which compounds **61**–**63** and **67** strongly inhibit the aforementioned expression; meanwhile, compounds **68**–**70** show much weaker effects, thereby indicating that an acetoxy group at C-9 may enhance the anti-inflammatory activity.

Furthermore, lipopolysaccharide (LPS)-induced M1-like macrophages had a typical pro-inflammatory phenotype, and the over-activation of M1-like macrophages results in the production of large amounts of pro-inflammatory cytokines, usually including TNF-α, IL-6, IL-12, and IFN-γ; this leads to a series of inflammatory responses. Importantly, compounds **9**, **12**, **15**, **28**, and **55** were found to significantly reduce the levels of TNF-α, IL-6, IL-12, and IFN-γ in LPS-induced M1-type macrophages, thus demonstrating good anti-

Table 3
Eudesmane-type sesquiterpenoids (compounds **215**–**247**) from plants in the family Chloranthaceae.

No.	Name	Sources	Reference
Chloranthus			
215	Chloraserratiol A	*Chloranthus serratus* (Thunb.) Roem. et Schult	[67]
216	Chloraserratiol B	*C. serratus*	[67]
217	Chloraserratiol C	*C. serratus*	[67]
218	Chloraserratiol D	*C. serratus*	[67]
219	Chloraserratiol E	*C. serratus*	[67]
220	Chloraserratiol F	*C. serratus*	[67]
221	Chlorajaponol B	*Chloranthus japonicus* Siebold	[68]
222	Chlojaponol A	*C. japonicus*	[69]
223	Chlojaponol B	*C. japonicus*	[69]
224	Chloraserratiol G	*C. serratus*	[67]
225	Chlorajaponol A	*C. japonicus*	[68]
226	Chlorajapotriol	*C. japonicus*	[70]
Sarcandra			
227	Sarglanoid D	*Sarcandra glabra* (Thunb.) Nakai	[71]
228	Sarglanoid E	*S. glabra*	[71]
229	Sarglanoid C	*S. glabra*	[71]
230	Sarglanoid D	*S. glabra*	[72]
231	Sarglanoid E	*S. glabra*	[72]
232	Sarglanoid A	*S. glabra*	[71]
233	Sarglanoid B	*S. glabra*	[71]
234	Sarglanoid A	*S. glabra*	[72]
235	Sarglanoid C	*S. glabra*	[72]
Chloranthus			
236	Fortunoid B	*Chloranthus fortunei* (A. Gray) Solms	[73]
237	Fortunoid C	*C. fortunei*	[73]
Hedyosmum			
238	Horienoid A	*Hedyosmum orientale* Merr. et Chun	[74]
239	Horienoid B	*H. orientale*	[74]
Chloranthus			
240	(+)-Chlorahupetene A	*Chloranthus henryi* var. *hupehensis* (Pamp.) K. F. Wu	[75]
241	(−)-Chlorahupetene A	*C. henryi* var. *hupehensis*	[75]
242	(+)-Chlorahupetene B	*C. henryi* var. *hupehensis*	[75]
243	(−)-Chlorahupetene B	*C. henryi* var. *hupehensis*	[75]
244	(+)-Chlorahupetene C	*C. henryi* var. *hupehensis*	[75]
245	(−)-Chlorahupetene C	*C. henryi* var. *hupehensis*	[75]
246	(+)-Chlorahupetene D	*C. henryi* var. *hupehensis*	[75]
247	(−)-Chlorahupetene D	*C. henryi* var. *hupehensis*	[75]

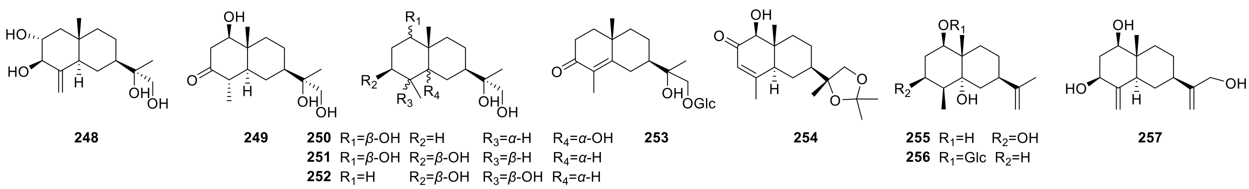

Fig. 10. Structures of eudesmane-type sesquiterpenoids from species in the family Solanaceae.

Table 4
Eudesmane-type sesquiterpenoids (compounds **248–257**) from plants in the family Solanaceae.

No.	Name	Sources	Reference
248	Dmetelin E	*Datura metel* L.	[76]
249	Dmetelin F	*D. metel*	[76]
250	Dmetelin B	*D. metel*	[76]
251	Dmetelin C	*D. metel*	[76]
252	Dmetelin D	*D. metel*	[76]
253	10*β*-Eudesm-4-en-3-one-11,12-diol-12-*O*-*β*-glucopyranoside	*Nicotiana tabacum* L.	[77]
254	Septemlobin E	*Solanum septemlobum* Bunge	[78]
255	Dmetelin G	*D. metel*	[76]
256	Dmetelin I	*D. metel*	[76]
257	Dmetelin H	*D. metel*	[76]

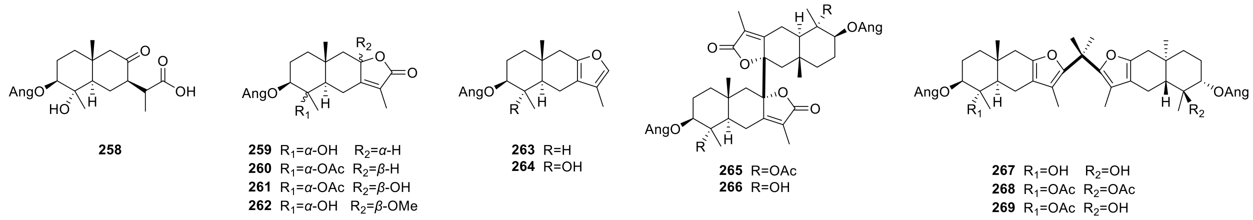

Fig. 11. Structures of eudesmane-type sesquiterpenoids from species in the family Anacardiaceae.

Table 5
Eudesmane-type sesquiterpenoids (compounds **258–269**) from plants in the family Anacardiaceae.

No.	Name	Sources	Reference
258	Dobinin J	*Dobinea delavayi* (Baill.) Baill.	[79]
259	Dobinin D	*D. delavayi*	[79]
260	Dobinin E	*D. delavayi*	[79]
261	Dobinin F	*D. delavayi*	[79]
262	Dobinin G	*D. delavayi*	[79]
263	Dobinin H	*D. delavayi*	[79]
264	Dobinin I	*D. delavayi*	[79]
265	Dodelate A	*D. delavayi*	[7]
266	Dodelate B	*D. delavayi*	[7]
267	Dodelate C	*D. delavayi*	[7]
268	Dodelate D	*D. delavayi*	[7]
269	Dodelate E	*D. delavayi*	[7]

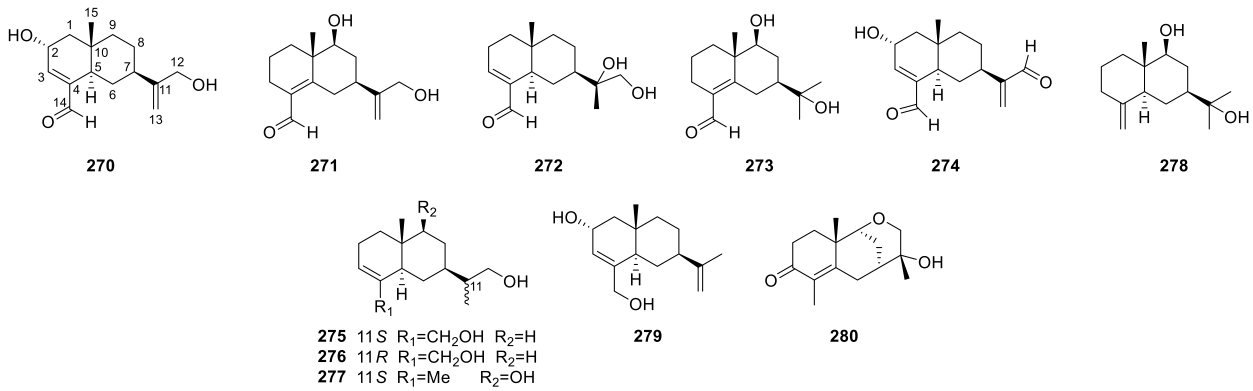

Fig. 12. Structures of eudesmane-type sesquiterpenoids from species in the family Thymelaeaceae.

Table 6
Eudesmane-type sesquiterpenoids (compounds **270–280**) from plants in the family Thymelaeaceae.

No.	Name	Sources	Reference
270	Agalleudesmanol A	*Aquilaria agallocha* Roxb.	[9]
271	Agalleudesmanol E	*A. agallocha*	[9]
272	Agalleudesmanol D	*A. agallocha*	[9]
273	Agalleudesmanol I	*A. agallocha*	[9]
274	Aquisinenoid C	*A. sinensis*	[80]
275	Agalleudesmanol B	*A. agallocha*	[9]
276	Agalleudesmanol F	*A. agallocha*	[9]
277	Agalleudesmanol G	*A. agallocha*	[9]
278	Agalleudesmanol H	*A. agallocha*	[9]
279	Agalleudesmanol C	*A. agallocha*	[9]
280	Aquisinenoid D	*Aquilaria sinensis* (Lour.) Spreng.	[80]

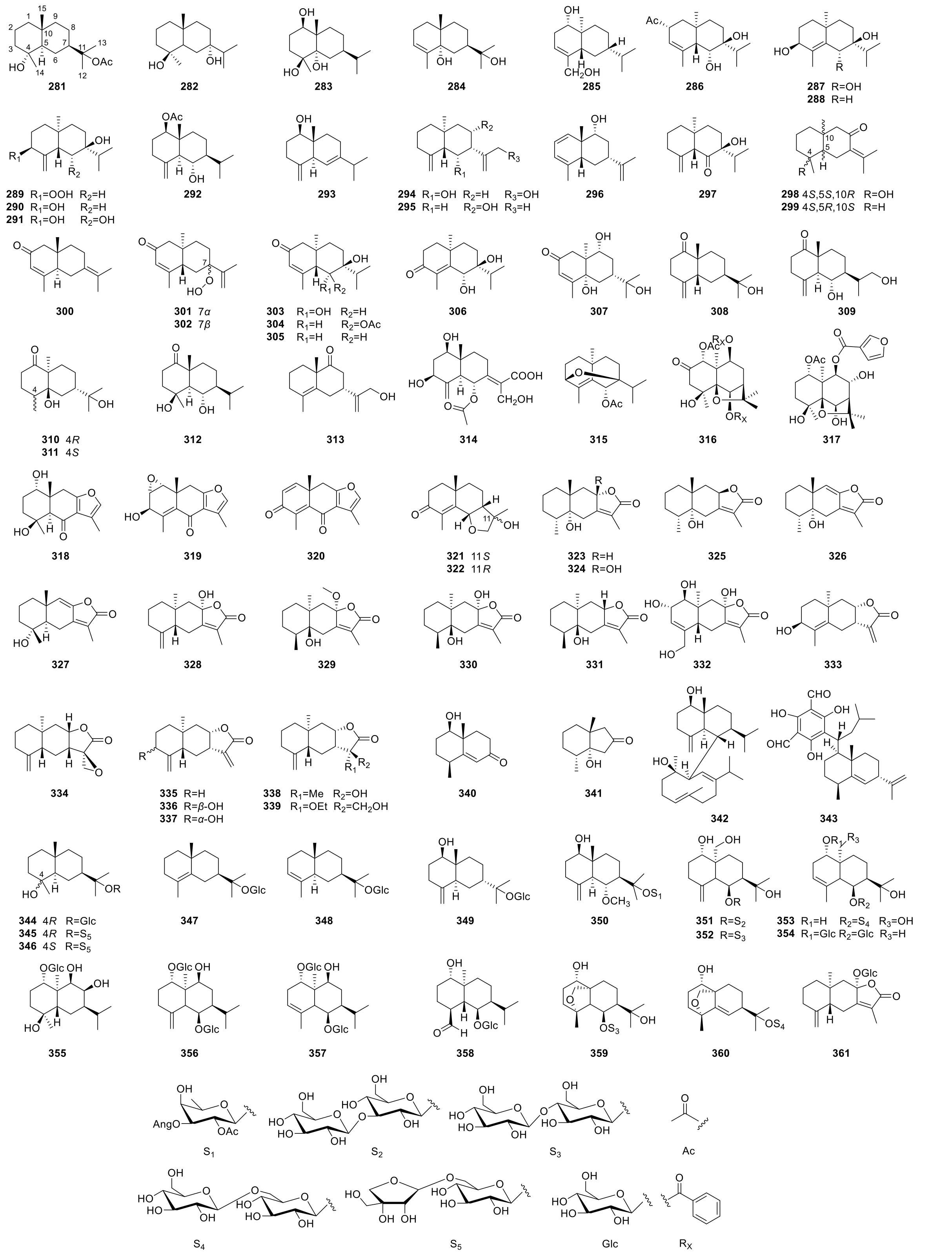

Fig. 13. Structures of eudesmane-type sesquiterpenoids from species in other families.

Table 7
Eudesmane-type sesquiterpenoids (compounds **281**–**361**) from plants in other families.

No.	Name	Sources	Reference
281	11-Acetoxyeudesman-4*β*-ol	*Cunninghamia konishii* Hayata	[81]
282	Eudesmane-4*β*,7*α*-diol	*Lawsonia inermis* Linn.	[82]
283	1*β*,4*β*,5*α*-Trihydroxyeudesmane	*Homalomena occulta* (Lour.) Schottt	[83]
284	5-Hydroxy-*α*-eudesmol	*Guatteria friesiana* (W. A. Rodrigues) Erkens & Maas	[84]
285	Commiphorane I	*Commiphora myrrha* (Nees) Engl.	[85]
286	(2*R*,5*S*,6*R*,7*S*,10*R*)-6,7-Dihydroxy-2-methoxy-eudesma-3*Z*-ene	*Chiloscyphus polyanthus* var. *rivularis* (Schrad.) Nees	[86]
287	(3*S*,6*R*,7*S*,10*S*)-3,6,7-Trihydroxyeudesma-4*E*-ene	*Chiloscyphus polyanthus*	[87]
288	(3*S*,7*R*,10*S*)-3,7-Dihydroxy-eudesma-4*Z*-ene	*Chiloscyphus polyanthus*	[87]
289	(3*S*,5*S*,7*R*,10*S*)-3-Hydroperoxy-7-hydroxy-eudesma-4(15)-ene	*Chiloscyphus polyanthus* var. *rivularis*	[86]
290	(3*S*,5*S*,7*R*,10*S*)-3,7-Dihydroxy-eudesma-4(15)-ene	*Chiloscyphus polyanthus* var. *rivularis*	[86]
291	(3*S*,5*S*,6*R*,7*S*,10*S*)-3,6,7-Trihydroxy-eudesma-4(15)-ene	*Chiloscyphus polyanthus* var. *rivularis*	[86]
292	Forkienin C	*Fokienia hodginsii* (Dunn) A. Henry & H. H. Thomas	[88]
293	Forkienin B	*Fokienia hodginsii*	[88]
294	*ent*-Eudesma-4(15),11(13)-dien-6*α*,12-diol	*Diplophyllum taxifolium* (Wahlenb.) Dumort.	[89]
295	(5*R*,7*S*,8*S*,9*S*)-*ent*-8-Hydroxy-4(15),11-eudesmadiene	*Tritomaria quinquedentata* (Huds.) H. Buch	[90]
296	Secamonol C	*Secamone lanceolata* Blume	[91]
297	*ent*-Chlorantene G	*Mastigophora diclados* (Bird.) Nees	[92]
298	Croargoid E	*Croton argyratus* Blume	[93]
299	Croargoid F	*Croton argyratus*	[93]
300	3,7(11)-Eudesmadien-2-one	*Prangos heyniae* H.Duman & M.F.Watson	[94]
301	7*α*-Hydroperoxy-eudesma-3,11-diene-2-one	*Alpinia oxyphylla* Miq.	[95]
302	7*β*-Hydroperoxy-eudesma-3,11-diene-2-one	*Alpinia oxyphylla*	[95]
303	(5*S*,6*R*,7*S*,10*R*)-6,7-Dihydroxy-2-oxo-eudesma-3*Z*-ene	*Chiloscyphus polyanthus* var. *rivularis rivularis*	[86]
304	(5*S*,6*R*,7*S*,10*R*)-7-Hydroxy-6-acetoxy-2-oxo-eudesma-3*Z*-ene	*Chiloscyphus polyanthus* var. *rivularis*	[86]
305	(5*S*,7*S*,10*R*)-7-Hydroxy-2-oxo-eudesma-3*Z*-ene	*Chiloscyphus polyanthus* var. *rivularis*	[86]
306	(6*R*,7*S*,10*R*)-6,7-Dihydroxy-3-oxo-eudesma-4*E*-ene	*Lepidozia reptans* (L.) Dumort.	[96]
307	Nelumbosesqui A	*Nelumbo nucifera* Gaertn.	[97]
308	Cynabungone	*Cynanchum bungei* Decne.	[98]
309	6*α*,12-Dihydroxy-4(15)-eudesmen-1-one	*Fissistigma maclurei* Merr.	[99]
310	Shiluone F	*Michelia shiluensis* Chun & Y. F. Wu	[100]
311	Shiluone G	*Magnolia shiluensis*	[100]
312	Homalomenin D	*Homalomena occulta* (Lour.) Schott	[101]
313	Sutchuenin J	*Thuja sutchuenensis* Franch.	[102]
314	1*β*,3*β*,13-Trihydroxy-6*α*-acetoxy-eudesma-4(15),7(11)-dien-12-oic acid	*Ammoides atlantica* (Coss. & Durieu) H. Wolff	[103]
315	(3*S*,6*R*,7*S*,10*S*)-3,7-Epoxy-6acetoxy-eudesma-4*E*-ene	*Chiloscyphus polyanthus*	[87]
316	Salaterpene E	*Salacia longipes* var. *camerunensis* Loes.	[104]
317	(1*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*R*,10*S*)-6-Acetoxy-4,9,10-trihydroxy-2,2,5*α*,9-tetramethyloctahydro-2*H*-3,9*α*-methanobenzo[*b*]oxepin-5-yl furan-3-carboxylate	*Maytenus boaria* Molina	[105]
318	Commiphorane E1	*Commiphora myrrha* (T.Nees) Engl.	[106]
319	Commiphorane E2	*Commiphora myrrha*	[106]
320	Commiphorane E3	*Commiphora myrrha*	[106]
321	Gracilistone A	*Acanthopanax gracilistylus* W.W.Sm.	[107]
322	Gracilistone B	*Acanthopanax gracilistylus*	[107]
323	Croargoid A	*Croton argyratus*	[93]
324	Croargoid C	*Croton argyratus*	[93]
325	Croargoid B	*Croton argyratus*	[93]
326	Croargoid D	*Croton argyratus*	[93]
327	Shizukolidol	*Magnolia vovidesii* A.Vázquez, Domínguez-Yescas & L.Carvajal	[108]
328	*ent*-Atractylenolide III	*Diplophyllum taxifolium*	[89]
329	Ermiasolide A	*Croton megalocarpus* Hutch.	[109]
330	Ermiasolide B	*Croton megalocarpus*	[109]
331	Ermiasolide C	*Croton megalocarpus*	[109]
332	Myrrhalindenane C	*Lindera myrrha* (Lour.) Merr.	[110]
333	*ent*-3*β*-Hydroxyeudesma-4,11-dien-12,8*α*-olide	*Diplophyllum taxifolium*	[89]
334	(5*R*,7*R*,8*S*,9*S*,11*R*)-*ent*-11,13-Epoxy-isoalantolactone	*Tritomaria quinquedentata*	[90]
335	*ent*-Isoalantolactone	*Diplophyllum taxifolium*	[89]
336	*ent*-Isotelekin	*Diplophyllum taxifolium*	[89]
337	*ent*-3-Epiisotelekin	*Diplophyllum taxifolium*	[89]
338	*ent*-11*β*-Hydroxydihydro-isoalantolactone	*Diplophyllum taxifolium*	[89]
339	(5*R*,7*R*,8*S*,9*S*,11*S*)-11-Ethoxy-13-hydroxy-*ent*-11,13-dihydroisoalantolactone	*Tritomaria quinquedentata*	[90]

(*continued on next page*)

Table 7 (*continued*)

No.	Name	Sources	Reference
340	Artahongkongol A	*Artabotrys hongkongensis* Hance	[10]
341	Croargoid G	*Croton argyratus*	[93]
342	Dysotican E	*Dysoxylum parasiticum* (Osbeck) Kosterm.	[111]
343	Eucarobustol D	*Eucalyptus robusta* Sm.	[112]
344	Sonneratioside A	*Sonneratia alba* Griff.	[113]
345	Sonneratioside B	*Sonneratia alba*	[113]
346	Sonneratioside C	*Sonneratia alba*	[113]
347	Sonneratioside E	*Sonneratia alba*	[113]
348	Sonneratioside D	*Sonneratia alba*	[113]
349	Epheganoside	*Ephedra sinica* Stapf	[114]
350	Pitqinlingoside M	*Pittosporum qinlingense* Y. Ren & X. Liu	[115]
351	Dictameudesmnoside A_1	*Dictamnus dasycarpus* Turcz.	[13]
352	Dictameudesmnoside A_2	*Dictamnus albus*	[13]
353	Dictameudesmnoside B	*Dictamnus albus*	[13]
354	Dictameudesmnoside C	*Dictamnus albus*	[13]
355	1α,4β,8β,9β-Eudesmane-tetrol-1-*O*-β-*D*-glucopyranoside	*Merremia yunnanensis* (Courchet & Gagnep.) R. C. Fang	[116]
356	1α,6β,9β-Trihydroxy-eudesm-4(15)-en-1,6-*O*-β-diglucopyranoside	*Lecokia cretica* (Lam.) DC	[117]
357	1α,6β,9β-Trihydroxy-eudesm-3-en-1,6-*O*-β-diglucopyranoside	*Lecokia cretica*	[117]
358	Liangwanoside A	*Metapanax delavayi* (Franch.) J. Wen & Frodin	[118]
359	Dictameudesmnoside D	*Dictamnus albus*	[13]
360	Dictameudesmnoside E	*Dictamnus albus*	[13]
361	Codonopsesquiloside C	*Codonopsis pilosula* (Franch.) Nannf.	[119]

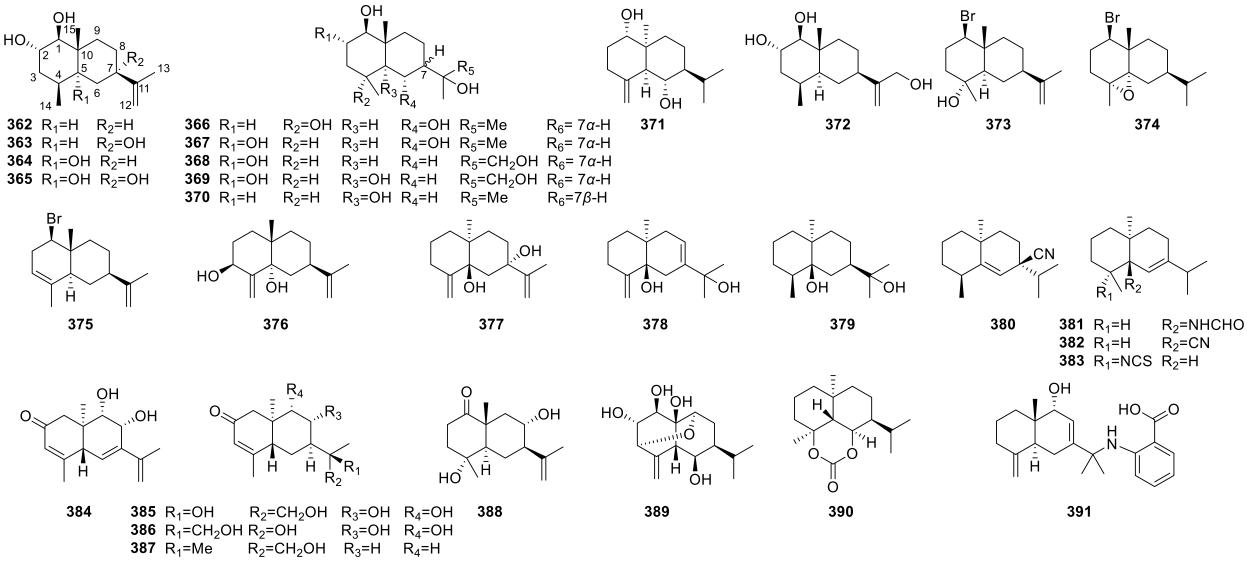

Fig. 14. Structures of eudesmane-type sesquiterpenoids from non-plant sources.

inflammatory activity [18].

Studies on the relevant pharmacological mechanisms suggested that compounds **190** and **210** had anti-inflammatory effects by intervening in the NF-κB signaling pathway. They specifically inhibited the phosphorylation of IκBα and prevented the nuclear translocation of p65, thereby suppressing NF-κB activation and the subsequent production of inflammatory mediators such as NO, TNF-α, IL-6, IL-1β, and IL-1α. Moreover, compound **210** further dampened inflammation by reducing the expression of iNOS and COX-2, as well as decreasing Erk1/2 phosphorylation. The discovery of these compounds holds promise as potential candidates for the development of innovative anti-inflammatory therapeutics [64,69].

4.2. Cytotoxic activity

Cytotoxicity is another important biological activity of eudesmane-type sesquiterpenoids (Table 10). An initial study examining structure–activity relationships was conducted on compounds **42–44** and compounds **48–50**. A comparison of compounds **42** and **43** revealed that the inclusion of a β-oriented hydroxyl group at C-4 bolstered the cytotoxic activity of **43**, with the effect being especially

Table 8
Eudesmane-type sesquiterpenoids (compounds **362–391**) from non-plant sources.

No.	Name	Sources	Reference
362	Penicieudesmol A	*Penicillium* sp. J-54	[120]
363	Penicieudesmol B	*P.* sp. J-54	[120]
364	Penicieudesmol C	*P.* sp. J-54	[120]
365	Penicieudesmol D	*P.* sp. J-54	[120]
366	Ganodermanol I	the cultured mycelia of *Ganoderma capense*	[121]
367	Ganodermanol J	the cultured mycelia of *Ganoderma capense*	[121]
368	Penicieudesmol E	*P.* sp. J-54	[6]
369	Penicieudesmol F	*P.* sp. J-54	[6]
370	Ganodermanol K	the cultured mycelia of *Ganoderma capense*	[121]
371	(1*S*,5*S*,6*S*,7*S*,10*S*)-10α-Eudesm-4(15)-ene-1α,6α-diol	*Streptomyces* sp. *JMRC:ST027706.*	[122]
372	Penicieudesmol G	*P.* sp. J-54	[6]
373	1β-Bromoselin-11-en-4α-ol	*Laurencia pinnata* Yamada	[123]
374	1β-Bromo-4α,5α-epoxyselinane	*L. pinnata*	[123]
375	1β-Bromoselin-3,11-diene	*L. pinnata*	[123]
376	3β,5α-Dihydroxyeudesma-4(15),11-diene	Vietnamese soft coral *Sinularia erecta*	[124]
377	Eudesma-4(15),11-diene-5,7-diol	*Laurencia obtusa* Lamouroux	[125]
378	Eudesma-4(15),7-diene-5,11-diol	*L. obtusa*	[126]
379	(4*S*,5*S*,7*R*,10*S*)-4β,10α-Eudesmane-5β,11-diol	*Streptomyces* sp. JMRC:ST027706.	[122]
380	Axiriabiline D	Hainan Sponge *Axinyssa variabilis*	[127]
381	Axiriabiline A	Hainan Sponge *Axinyssa variabilis*	[127]
382	Axiriabiline B	Hainan Sponge *Axinyssa variabilis*	[127]
383	Axiriabiline C	Hainan Sponge *Axinyssa variabilis*	[127]
384	Stigolone	*Scytonema* sp. *(strain U-3-3)*	[128]
385	11*R*,12-Dihydroxystigolone	*Scytonema* sp. *(strain U-3-3)*	[128]
386	11*S*,12-Dihydroxystigolone	*Scytonema* sp. *(strain U-3-3)*	[128]
387	Thomimarine E	*Penicillium thomii KMM 4667*	[129]
388	4α,8α-Dihydroxyeudesman-11-en-1-one	*Aspergillus flavus*	[122]
389	1,2,6,10-Tetrahydroxy-3,9-epoxy-14-*nor*-5(15)-eudesmane	*Flammulina velutipes* (Fr)Sing.	[130]
390	Eudesmacarbonate	Marine Filamentous Cyanobacterial Mat (Oscillatoriales)	[131]
391	Eudesm-4(15),7-diene-9α-hydroxy-11-amino-benzoicacid	*Streptomyces* sp. A68	[132]

pronounced against the LNCaP cell line. In contrast, a decrease in cytotoxicity was evident in compound **48** compared to compound **49** due to the oxidation of the hydroxyl group at C-8 to a ketone. Furthermore, an analysis of cytotoxicity results from compounds **33**–**34** and **35**–**38** suggested that the presence of a phenylacetoxy group at C-8 could augment the cytotoxicity against three distinct human hepatocellular carcinoma cell lines. Overall, it was apparent that the majority of cytotoxic compounds predominantly originated from the family Asteraceae and were primarily sesquiterpene lactones.

4.3. Anti-microbial activity

Inhibition of fungal and bacterial growth is an important biological activity of eudesmane-type sesquiterpenoids (Table 11). Compounds **146**–**153** were eudesmane-type sesquiterpenes with cinnamoyloxy groups at C-6. Compounds **146**, **150**, **152**, and **153** all exhibited strong inhibitory activity against *Plasmopara viticola*. Notably, compound **378** isolated from *L. obtusa* showed significant growth inhibition activity against *Candida albicans*, *C. tropicals, Aspergillus flavus*, and *A. niger*, with better effects than the positive control Amphotericin B or comparable to its effect [126]. Compound **219** displayed a certain activity against *Botrytis cinerea* and *Sclerotinia sclerotiorum* with inhibition rates of 34.62 % and 13.04 %, respectively, at the concentration of 50 μg/mL [69]. The anti-protozoal activity of compounds **156**–**158** was evaluated against *Leishmania major* promastigotes, revealing dose- and time-dependent activity against *L. major* amastigotes with IC_{50} values in the range of 4.9–25.3 μM—which were favorably far below their toxicity against normal murine macrophages—and CC_{50} values ranging from 432.5 to 620.7 μM after 48 h of treatment. Compound **158** exhibited the strongest activity and the highest selectivity index (SI) with an IC_{50} of 4.9 ± 0.6 μM and an SI of 88.2. These are comparable to those of the standard drug, meglumine antimoniate (glucantime), with IC_{50} and SI values of 15.5 ± 2.1 μM and 40.0, respectively.

Compound **377** also showed a strong inhibitory effect on the growth of two fungi, *C. albicans* and *C. tropicals*, with half the effect of Amphotericin B [125]. In addition, researchers found that compound **379** was effective against bacteria (*Bacillus subtilis*, *Mycobacterium vaccae*, *Pseudomonas aeruginosa, Staphylococcus aureus*, methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus faecalis*, and *Escherichia coli*) and fungi (*Sporobolomyces salmonicolor, C. albicans*, and *P. notatum*) by an agar diffusion method. This suggests that compound **379** is a potential broad-spectrum antimicrobial agent [134]. The antimicrobial activities of compounds **377**–**379** are all significant, and it is hypothesized that the hydroxy group at C-5 may enhance the antimicrobial activity of the compounds.

Table 9
Anti-inflammatory of eudesmane-type sesquiterpenoids.

No.	Cells	Cytokines	IC_{50} (μM)	Positive control	IC_{50} (μM)	References
1	RAW 264.7	NO	15.0 ± 0.4	Dexamethasone	10.7 ± 0.3	[17]
19	RAW 264.7	NO	36.36 ± 1.86	L-NMMA	24.95 ± 11.46	[21]
20	RAW 264.7	NO	30.6 ± 0.7	Dexamethasone	10.7 ± 0.3	[17]
22	RAW 264.7	NO	61.19 ± 2.54	Quercetin	74.34 ± 1.39	[21]
23	RAW 264.7	NO	31.69 ± 1.93	Quercetin	74.34 ± 1.39	[22]
24	RAW 264.7	NO	8.08 ± 0.21	Quercetin	74.34 ± 1.39	[22]
25	RAW 264.7	NO	7.66 ± 0.53	Quercetin	74.34 ± 1.39	[22]
26	RAW 264.7	NO	26.90 ± 3.92	Quercetin	74.34 ± 1.39	[22]
27	RAW 264.7	NO	44.26 ± 1.74	Quercetin	74.34 ± 1.39	[22]
71	BV-2	NO	27.3 ± 0.7	Quercetin	8.7 ± 0.3	[30]
72	BV-2	NO	39.8 ± 2.7	Quercetin	8.7 ± 0.3	[30]
73	BV-2	NO	29.8 ± 1.4	Quercetin	8.7 ± 0.3	[30]
74	BV-2	NO	33.0 ± 1.3	Quercetin	8.7 ± 0.3	[30]
75	BV-2	NO	40.6 ± 0.9	Quercetin	8.7 ± 0.3	[30]
109	RAW 264.7	NO	4.78 ± 0.06	Indomethacin	57.21 ± 1.21	[37]
117	RAW 264.7	NO	34.24 ± 0.36	Indomethacin	57.21 ± 1.21	[37]
119	RAW 264.7	NO	46.79 ± 0.66	Indomethacin)	57.21 ± 1.21	[37]
190	RAW 264.7	NO	17.90 ± 1.0	Luteolin	5.6 ± 0.2	[64]
197	RAW 264.7	NO	57.00 ± 6.2	Luteolin	5.6 ± 0.2	[64]
200	RAW 264.7	NO	46.92	Quercetin	14.55	[66]
210	RAW 264.7	NO	5.1	Quercetin	14.55	[66]
221	RAW 264.7	NO	9.56 ± 0.71	Aminoguanidinea	8.5 ± 0.35	[67]
229	RAW 264.7	NO	20.00 ± 1.30	L-NMMA	41.40 ± 2.30	[71]
230	RAW 264.7	NO	25.7 ± 0.2	dexamethasone	9.3 ± 0.2	[72]
240	RAW 264.7	NO	12.91	Dex		[75]
241	RAW 264.7	NO	9.62	Dex		[75]
242	RAW 264.7	NO	12.31	Dex		[75]
243	RAW 264.7	NO	11.89	Dex		[75]
244	RAW 264.7	NO	10.07	Dex		[75]
245	RAW 264.7	NO	10.87	Dex		[75]
248	RAW 264.7	NO	10.50 ± 1.17	L-NMMA	15.33 ± 1.69	[76]
249	RAW 264.7	NO	15.44 ± 1.72	L-NMMA	15.33 ± 1.69	[76]
250	RAW 264.7	NO	16.32 ± 0.45	L-NMMA	15.33 ± 1.69	[76]
251	RAW 264.7	NO	18.97 ± 1.00	L-NMMA	15.33 ± 1.69	[76]
252	RAW 264.7	NO	16.54 ± 0.39	L-NMMA	15.33 ± 1.69	[76]
253	RAW 264.7	NO	29.30 ± 2.09	L-NMMA	15.33 ± 1.69	[77]
255	RAW 264.7	NO	28.12 ± 2.41	L-NMMA	15.33 ± 1.69	[76]
257	RAW 264.7	NO	29.73 ± 0.55	L-NMMA	15.33 ± 1.69	[76]
270	RAW 264.7	NO	5.46 ± 4.11	Aminoguanidine	20.33 ± 1.08	[9]
271	RAW 264.7	NO	45.59 ± 4.35	Aminoguanidine	20.33 ± 1.08	[9]
272	RAW 264.7	NO	14.07 ± 2.08	Aminoguanidine	20.33 ± 1.08	[9]
321	RAW 264.7	NO	1.95 ± 0.20	L-NMMA	12.89 ± 1.14	[107]
322	RAW 264.7	NO	1.21 ± 0.21	L-NMMA	12.89 ± 1.14	[107]

4.4. *Antimalarial activity*

Malaria is a parasitic disease caused by the *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium malariae*, which poses a serious health risk to humans. Currently, artemisinin derivatives, such as sodium artesunate, artemether or dihydroartemisinin, are widely used for the treatment of malaria. However, the recent emergence of *Plasmodium falciparum* parasites with reduced susceptibility to artemisinin-based drugs poses a significant challenge [135]. This resistance to traditional antimalarial drugs not only complicates treatment but also undermines malaria control efforts. To address this issue, it is critical to explore new antimalarial medications and implement rational drug use strategies. Therefore, it is crucial to search for new antimalarial drugs and adopt rational drug use strategies to address this issue. Compound **164** showed strong inhibition of the growth of the *Plasmodium falciparum* strain Dd2 (chloroquine resistant), with an IC_{50} value of 0.5 ± 0.01 μM, while the IC_{50} value for the positive drug (artemisinin) was 4.0 ± 4.2 nM [73]. Compounds **179**, **180**, **185**, and **187** derived from *D. delavayi* exhibited moderate antimalarial activity against *Plasmodium yoelii* BY265RFP with inhibition rates of 14.5 % (30 mg/kg/day), 18.5 % (30 mg/kg/day), 23.29 % (50 mg/kg/day), and 28.94 % (50 mg/kg/day), respectively.

4.5. *Insecticidal activity*

Certain eudesmane-type sesquiterpenoids from the family Asteraceae have good insecticidal activity; for example, compound **84** has a high internal insecticidal effect against *Varroa destructor*, a parasite of *Apis mellifera*, and can be used for the control of *Varroa destructor* in bee colonies with high efficiency and low toxicity [12]. The sesquiterpene dimer (**104**) showed significant inhibition of aphids *Lipaphis erysimi*, *Sitobion avenae*, *Rhopalosiphum padi*, and *Aphis craccivora* with LC_{50} values of 7.53 ± 0.33 μM, 35.80 ± 1.78 μM,

Table 10
Cytotoxic activity of eudesmane-type sesquiterpenoids.

No.	Cells	IC_{50} (μM)	Positive control	IC_{50} (μM)	References
34	HepG2	35.1 ± 2.9	Sorafenib	10.3 ± 1.0	[24]
	Huh 7	35.0 ± 2.0	Sorafenib	8.2 ± 2.4	
	SK-Hep-1	32.7 ± 4.0	Sorafenib	13.3 ± 2.2	
42	LNCaP	34.96 ± 8.5	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	26.30 ± 5.7	Doxorubicin	0.43 ± 0.09	
43	LNCaP	16.05 ± 6.1	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	18.40 ± 4.9	Doxorubicin	0.43 ± 0.09	
44	LNCaP	36.17 ± 11.5	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	38.70 ± 11.5	Doxorubicin	0.43 ± 0.09	
48	LNCaP	24.66 ± 7.7	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	18.10 ± 7.7	Doxorubicin	0.43 ± 0.09	
49	LNCaP	9.10 ± 4.5	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	17.77 ± 3.6	Doxorubicin	0.43 ± 0.09	
50	LNCaP	26.92 ± 3.1	Doxorubicin	0.45 ± 0.15	[26]
	DU-145	23.93 ± 10.6	Doxorubicin	0.43 ± 0.09	
55	BGC-823	49.87 ± 4.12	5-FU	75.05 ± 8.55	[28]
	HepG2	59.47 ± 5.81	5-FU	77.05 ± 6.36	
	A549	68.31 ± 4.40	5-FU	70.29 ± 6.50	
	MDA-MB231	71.07 ± 4.46	5-FU	86.01 ± 14.25	
	Kyse30	72.60 ± 10.22	5-FU	84.54 ± 14.64	
	HUVEC	205.3 ± 28.51	5-FU	117.3 ± 20.93	
76	HepG2	23.23 ± 1.35	DDP	4.75 ± 1.32	[31]
93	HepG2	21.50 ± 1.21	DDP	4.75 ± 1.32	[31]
94	HepG2	19.43 ± 0.93	DDP	4.75 ± 1.32	[31]
96	SGC-7901	31.78 ± 0.23	L-NAME		[32]
97	HepG2	42.40 ± 1.81	DDP	4.75 ± 1.32	[31]
139	HL-60	17.3	Etoposide	1 and 10	[50]
145	HeLa	106.2 ± 3.6	Cisplatin	11.9 ± 1.5	[52]
	K562	51.1 ± 3.7	Cisplatin	6.1 ± 0.1	
	MDA231	131.6 ± 5.0	Cisplatin	8.3 ± 0.9	
	B16	70.17 ± 3.9	Cisplatin	8.4 ± 0.7	
	NCI–H460	11.8 ± 0.2	Cisplatin	10.3 ± 0.7	
199	pfeiffer	17.06 ± 1.05	Cytarabine	17.20 ± 1.84	[65]
214	K562	7.92 ± 0.35	Cytarabine	25.10 ± 1.74	[65]
	THP-1	3.96 ± 0.48	Cytarabine	24.34 ± 0.57	
	pfeiffer	3.87 ± 0.51	Cytarabine	17.20 ± 1.84	
254	P-388	7.1 ± 0.4	Cisplatin	2.2 ± 0.3	[78]
	HONE-1	3.8 ± 0.5	Cisplatin	2.1 ± 0.5	
	HT-29	3.0 ± 0.3	Cisplatin	2.0 ± 0.3	
274	MCF-7	2.834 ± 1.121			[80]
	MDA-MB-231	1.545 ± 1.116			
	LO2	27.82 ± 1.093			
297	A549	27.7	Doxorubicin	2.4	[86]
340	HL-60	0.68 ± 0.07	Doxorubicin	0.36 ± 0.05	[10]
	SMMC-7721	2.46 ± 0.11	Doxorubicin	0.96 ± 0.07	
	A-549	1.49 ± 0.08	Doxorubicin	3.02 ± 0.10	
	MCF-7	3.92 ± 0.12	Doxorubicin	1.63 ± 0.08	
	SW480	0.57 ± 0.06	Doxorubicin	5.98 ± 0.13	
342	MCF-7	40.56 ± 0.24	Cisplatin	53.00 ± 0.02	[111]
363	K-562	90.1	Paclitaxel	9.5	[120]
366	HCT116	12.2			[121]
376	A549	14.79 ± 0.91	Camptothecin	11.42 ± 0.13	[124]
378	MCF-7	39.5 ± 0.04	Cisplatin	59 ± 0.045	[126]

17.09 ± 2.04 μM, and 20.17 ± 1.63 μM, respectively, which were better than the positive control pymetrozine with LC_{50} values of 28.57 ± 2.51 μM, 19.68 ± 0.31 μM, 61.89 ± 5.39 μM, and 133.96 ± 9.50 μM, respectively; this indicated that compound **104** could be used as a potential biocide [45]. Compound **119** had strong nematicidal activity against *Meloidogyne incognita* (IC_{50} = 25.42 ± 0.28 μM), which was better than albendazole (IC_{50} = 65.4 ± 0.33 μM) [58]. The above findings suggested that plants of the family Asteraceae could be an important resource for biopesticides.

4.6. Neuroprotective activity

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive decline, common in elderly patients [136–138]. Compounds **110**, **111**, **113**, and **115** isolated from *A. artemisiifolia* are protective against $A\beta_{1\text{-}42}$-induced HT22 cell damage, while compound **114** has comparable effects to the positive control andrographolide [60]. Further analysis by flow cytometry revealed that compounds **114** and **115** could reduce the fluorescence intensity in $A\beta_{1\text{-}42}$-transfected HT22 cells to some extent. The analysis

Table 11
Anti-microbial activity of eudesmane-type sesquiterpenoids.

No.	Strains	MIC	Positive control	MIC	References
146	*P. viticola*	7.9 μg/mL			[3]
150	*P. viticola*	9.9 μg/mL			[3]
152	*P. viticola*	50 μg/mL			[3]
153	*P. viticola*	39.7 μg/mL			[3]
291	*Candida albicans* DSY654	64 μg/mL			[90]
313	*B. cereus*	25 μg/mL	Vancomycin	0.62 μg/mL	[102]
	Staphylococcus epidermids	25 μg/mL	Vancomycin	0.62 μg/mL	
377	*C. albicans*	8.27 μM	Amphotericin B	4.63 μM	[125]
	C. tropicals	10.13 μM	Amphotericin B	5.27 μM	
378	*C. albicans*	2.92 μM	Amphotericin B	4.6 μM	[126]
	C. tropicals	2.10 μM	Amphotericin B	5.2 μM	
	A. flavus	2.92 μM	Amphotericin B	4.6 μM	
	A. niger	6.50 μM	Amphotericin B	5.4 μM	

demonstrated that the neuroprotective effect can be enhanced by the 5,10-bis-*epi*-eudesm-3-ene-6-*O*-*β*-*D*-glucopyranosyl structural unit. In another study, it has been observed that both compounds **158** and **161** can increase the viability of H_2O_2- damaged PC12 cells in neuroprotection assays.

4.7. Other biological activities

Eudesmane-type sesquiterpenoids exhibit a diverse array of other biological activities, thus becoming highly versatile in various aspects of health and disease. These compounds display anti-HIV, anti-hepatitis B (HBV), and anti-inflammatory properties, thereby displaying important potential in combating viral infections and modulating immune responses [13,34,50,98,112]. Additionally, the ability to inhibit triglyceride accumulation, suppress T lymphocyte proliferation, and interfere with enzyme activity has been demonstrated. Moreover, eudesmane-type sesquiterpenoids have shown promising effects in preserving cellular integrity and exerting hypoglycemic and hypolipidemic effects, indicating the potential thereof as therapeutic agents for managing lipid metabolism disorders and regulating glucose levels [6,130].

The inhibitory effects of select eudesmane-type sesquiterpenoids on IL6/STAT3 activation highlight their significance in modulating signaling pathways involved in cell growth and inflammation [63]. These findings underscore the remarkable range of the biological activities of eudesmane-type sesquiterpenoids, thereby emphasizing the potential thereof as valuable compounds for pharmacological and therapeutic applications.

5. Discussion

Given the unique skeletal structures, variations in functional groups, and diverse biological activities, natural sesquiterpenoids have been one of the popular research areas in natural product chemistry. Within the same genus, compounds originating from these plants may exhibit similarities in terms of their overall structural type or biological activity. This could be attributed to the fact that plants belonging to the same genus often possess comparable genomes, which leads to the possibility of similar synthetic and metabolic pathways in their chemical compositions.

Compounds isolated from the genus *Artemisia* in the family Asteraceae exhibit distinct characteristics, which are specifically characterized by the easy dehydrogenation of the C-11; this results in the formation of a double bond, while the C-13 is typically oxidized to a carboxyl group. Moreover, these compounds share the same stereo-configuration at C-5, C-7, and C-10, and are all in the *S*-configuration. Notably, within the genus *Artemisia*, a significant number of eudesmane-type sesquiterpenoids feature an *α*-methylene-*γ*-lactone moiety, located between C-6 and C-12, or between C-8 and C-12. Most of the compounds in plants from the genus *Atractylodes* are sesquiterpene glycosides with one carbonyl group at C-2 or C-3. In the plants of the genus *Inula*, sesquiterpene lactones are generated in most compounds by linking C-8 and C-12 through ester bonds, while compounds in other genera virtually do not form lactone rings. Moreover, the majority of the eudesmane-type sesquiterpenoids isolated from plants in the family Lamiaceae, Chloranthaceae, or Anacardiaceae normally have an *α*,*β*-unsaturated *γ*-lactone structure. In contrast, compounds from the family Thymelaeaceae often contain $\Delta^{3(4)/4(5)/4(14)}$ double bonds and lack lactone rings formed by isopropyl chains.

The bioactivities of eudesmane-type sesquiterpenoids vary across compounds due to their different substituents and different substitution positions. Nevertheless, the structure–activity relationships (SAR) of eudesmane-type sesquiterpenoids so far have not been studied systematically, but a few attempts can be made to discuss the effect of substitution on biological activity. For instance, the majority of compounds featuring an *α*-substituted acrylic acid or acrylate moiety exhibit an anti-inflammatory activity. The substituent at C-8 can also affect the efficacy of the anti-inflammatory activity. In addition, it is presumed that the number and positions of hydroxy groups in the structures of the compounds could affect their anti-inflammatory effects, and the terminal double bond between C-4 and C-15 could significantly enhance the anti-inflammatory activity of the compounds. Furthermore, a comparison of the anti-inflammatory effects of eudesmane-type sesquiterpenoids showed that the propane-1,2-diol moiety is likely the key active site. In addition, it was found that the neuroprotective effects of these compounds can be promoted by the 5,10-bis-*epi*-eudesm-3-ene-6-*O*-*β*-*D*-glucopyranosyl structural unit, and the *α*,*β*-unsaturated carbonyl at C-3 could be related to the enhanced inhibition of IL-6/STAT3 activation.

This review systematically explored the diversity of eudesmane-type sesquiterpenoids with a significant number isolated from plants in the families Asteraceae and Lamiaceae, which have a long-standing use in Traditional Chinese Medicine (TCM). For instance, compounds from the family Asteraceae are renowned for their anti-inflammatory and antimalarial properties, aligning with their use to treat fevers and infections. Similarly, species from the family Lamiaceae, such as *Salvia plebeia*, have analgesic and antipyretic effects, which are often attributed to the presence of bioactive sesquiterpenoids.

It has been found that some compounds can exert anti-inflammatory effects by interfering with the NF-κB signalling pathway. But, it is noteworthy that the majority studies only conducted preliminary efficacy at the cellular level, lacking in-depth exploration of the mechanism. As indicated in Table 9, with the exception of L-NMMA and aminoguanidine, the positive controls used in most studies (dexamethasone, quercetin, indomethacin, luteolin) are not specific inhibitors of NO synthesis. This highlights certain limitations in the current research on the anti-inflammatory efficacy of eudesmane-type sesquiterpenoids. Therefore, the anti-inflammatory mechanisms of these compounds require further investigation, including animal experiments. In the section on neuroprotection, it is important to note that the studies conducted so far have mainly been limited to simple cell models. The authors have not evaluated whether these compounds can effectively penetrate the blood-brain-barrier and exert their neuroprotective effects in brain tissue. Therefore, it is necessary to conduct further research using animal models to comprehensively evaluate the neuroprotective potential of these compounds. Such research will serve to address the current limitations in the research, enhance the scientific validity and reliability of the studies, and provide a more robust foundation for further advancements in this field. Moreover, a comprehensive exploration in absorption, distribution, metabolism, excretion, and toxicity of these compunds is pivotal for foreseeing the efficacy and safety of potential drug candidates, and ultimately enhancing their likelihood of success in clinical trials and beyond. Finally, the study on the mechanism of eudesmane-type sesquiterpenoids should be deepened, especially the definition of their targets. This is crucial for optimizing their pharmacological properties, crafting targeted therapies, and laying the groundwork for designing and synthesizing more potent, selective analogs with refined pharmacological profiles.

There are extensive and meticulous literature about eudesmane-type sesquiterpenoids but not any published research pertaining to the molecular targets of them. Subsequent studies should be directed towards the precise identification and rigorous validation of the prospective molecular targets of these bioactive compounds. Such endeavors will be instrumental in demystifying the modus operandi of their biological activity and could potentially unearth novel avenues for therapeutic intervention. Moreover, there were only a few studies on the synthesis and structural modification of eudesmane-type sesquiterpenoids, for example, compounds **48–50** were derived by acetylation or oxidation of the known compound,11-*epi*-artapshin [26]. Works in this area still need to be strengthened, and the incorporation of computational methods, including molecular docking and dynamics simulations, is particularly advantageous for forecasting their bioactivities and facilitating the rational design of more efficacious analogs.

6. Conclusion

The present review summarized the progress of research on the chemical structures and pharmacological activities of natural eudesmane-type sesquiterpenoids from 2016 to 2022. Notably, over 391 eudesmane-type sesquiterpenoids were reported in the published literature. These compounds were mainly found in the plants of the families Asteraceae, Lamiaceae, Chloranthaceae, Solanaceae, Anacardiaceae, and Thymelaeaceae; some compounds were from bryophytes, microorganisms, and marine organisms. Furthermore, about one third of all compounds were from the family Asteraceae, primarily from the genus *Artemisia*. Most of the eudesmane-type sesquiterpenoids isolated from the genera *Inula* and *S. plebeia* were sesquiterpene lactones with an α,β-unsaturated-γ-lactone ring. Multiple sesquiterpene dimers were available in plants of the families Asteraceae, Lamiaceae, Chloranthaceae, and Anacardiaceae. Pharmacological studies showed that eudesmane-type sesquiterpenoids had a variety of bioactivities. Among these, anti-inflammatory activity was preeminent, followed by cytotoxic, antibacterial, anti-malarial, insecticidal, and neuroprotective activities. Interestingly, the eudesmane-type sesquiterpenoids with anti-inflammatory effects were primarily isolated from species in the families Asteraceae and Solanaceae. Importantly, eudesmane-type sesquiterpenoids were found to widely exist in plants, microorganisms, and marine organisms, with a variety of remarkable bioactivities. As several eudesmane-type sesquiterpenoids with significant activity have been discovered, the in-vivo activity and mechanism of action should be studied in more depth. Simultaneously, the development and utilization of eudesmane-type sesquiterpenoids should also be proactively explored.

Data availability

The data referenced in this review are sourced from existing literature. As this study did not involve the generation of new data, there are no datasets to deposit in public repositories. Readers seeking detailed information are encouraged to refer to the cited works within our reference list, which thoroughly detail the methodologies, findings, and conclusions of the underlying research.

Ethical considerations

The present study is a comprehensive literature review and it does not encompass any primary data collection or experimental procedures, including those involving animal subjects. Therefore, the research was exempt from undergoing ethical review and did not require ethical clearance from an institutional review board.

CRediT authorship contribution statement

Guang-Xu Wu: Writing – original draft, Methodology, Investigation, Data curation. **Hao-Yu Zhao:** Methodology, Investigation, Data curation. **Cheng Peng:** Project administration, Conceptualization. **Fei Liu:** Writing – review & editing, Validation, Formal analysis. **Liang Xiong:** Validation, Project administration, Conceptualization.

Declaration of competing interest

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

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