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Review

Advances in phytochemistry, ananlysis methods and pharmacology of *Eleutherococcus trifoliatus*: A promising medicinal and edible resource with development value

Maofang Lu [a,1], Bin Wang [a,1], Ling Dai [b], Jian Wu [c], Jiao Luo [a], Changsoo Yook [d], Xiangqian Liu [a,*]

[a] School of Pharmacy, Hunan University of Chinese Medicine, Changsha 410208, China
[b] School of Pharmacy, Hunan Vocational College of Science and Technology, Changsha 410200, China
[c] Instrumental Analysis Center, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China
[d] School of Pharmacy, Kyung Hee University, Seoul 130-701, South Korea

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ABSTRACT

Eleutherococcus trifoliatus (*Araliaceae*) is called Baile or Lecai in China. *E. trifoliatus* is a medicinal and edible plant widely used in folk traditions. As a TCM, the dried herb of this species can remove damp heat and detoxicity, cure rheumatism, remove blood stasis, relieve pain, and alleviate cough and asthma symptoms. Many chemical compounds have been reported including diterpenoids, triterpenoids, phenylpropanoids, flavonoids, lignans, caffeoyl quinic acids, steroids, essential oils, etc., in which flavonoids, saponins, and caffeoyl quinic acids are the most bioactive components. *In vitro* and *in vivo* pharmacological experiments demonstrated that *E. trifoliatus* has anti-inflammatory, hypoglycemic, anticancer, antioxidant, antibacterial, anti-hyperalgesic, anti-fatigue, analgesic, and hemostatic effects. Here we reviewed *E. trifoliatus* in phytochemistry, analysis methods, and pharmacology.

Contents

* Corresponding author.
E-mail address: lxq0001cn@163.com (X. Liu).
[1] These authors have contributed equally to this work.

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1. Introduction

There are more than 900 species in *Acanthopanax* Miq. over the world (Flora of China Editorial of Committee of Chinese Academy of Sciences, 1978), including *Eleutherococcus nodiflorus* (Dunn) S. Y. Hu and *Eleutherococcus senticosus* (Ruprecht & Maximowicz) Maximowicz that have been admitted in *the Chinese Pharmacopoeia* (2020 edition) (Chinese Pharmacopoeia Commission, 2020). *Acanthopanax* plants are often used to treat rheumatic arthralgia, weakness of waist and knees. Studies showed that *Acanthopanax* plants have many pharmacological activities, such as anti-inflammatory, anti-stress, anti-arrhythmia, anti-platelet aggregation, regulation of the immune system and so on (Zhang et al., 2019).

Eleutherococcus trifoliatus (Linnaeus) S. Y. Hu, is called Baile and Lecai in China. The roots, stems, and leaves have been used as medicines or food for a long history, upon which the edible standard (NO. DBS 44/009–2018) has been established by the Guangdong Provincial Health and Wellness Committee, China. *E. trifoliatus* is mainly used for treating symptoms such as cold, cough, rheumatism, and sciatica. Before the Liang Dynasty (AD 502−557), people believed that *E. trifoliatus* was as same as *E. nodiflorus* for medical and dietary purposes (Xiu et al., 2016). *E. trifoliatus* is mainly distributed in south-central China, India, Japan, Vietnam, and the Philippines. It grows in the bushes beside streams, at the foot of mountains, along roadsides, or in hilly areas with a warm climate, abundant rainfall, and significant variations in hydrothermal conditions. It prefers to live in moist, slightly acidic sandy soil (Fig. 1).

Up to now, a great deal of research has been conducted on *E. nodiflorus* and *E. senticosus* which have clear and definite pharmacological activities. Nevertheless, there is a significant need for thorough investigation and comprehension of *E. trifoliatus*. We believed that the extensive utilization of this resource is crucial not only for improving China's health industry but also for the sustainable use of environmental resources. Here we summarized the recent studies of *E. trifoliatus* in phytochemistry, ananlysis methods and pharmacology.

2. Chemical constituents

There are diterpenes, triterpenes, phenylpropanoids, flavonoids, lignans, caffeoyl quinic acids, steroids, and essential oils in *E. trifoliatus*, in which flavonoids, caffeoyl quinic acids, diterpenes, and triterpenes are the major components responsible for functions similar to ginseng (Table 1). Lupane triterpenoids and flavonoids were largely isolated from the leaves, while diterpenes, phenylpropanoids, lignans, caffeoyl quinic acids, and steroids from the stems (Table 1).

2.1. Diterpenoids

E. trifoliatus contains abundant secondary metabolites. Among them, the diterpenoids are the major ones. To date, 12 diterpenoid compounds have been isolated from stems and leaves of *E. trifoliatus* (Fig. 2). They include one new tetracyclic diterpene, ent-kauran-16,17-dihydroxy-19-oic acid 16-*O*-*β*-*D*-glucopyranosyl ether 19-*O*-*β*-*D*-glucopyranosyl ester (acantrifoside D) (**1**), which was isolated from stem bark of *E. trifoliatus*. The basic skeleton of these compounds can be divided into two types: tricyclic diterpene and tetracyclic diterpene. Of them, nine are tetracyclic diterpenes (**1–9**), and three are tricyclic diterpenes (**10–12**).

2.2. Triterpenoids

Triterpenoid is another large category of active components unveiled in *E. trifoliatus*. Up to now, 21 triterpenoids have been discovered from *E. trifoliatus*, such as acantrifoside A (**13**), 11α,23-dihydroxy-3-oxo-lup-20(29)-en-28-oic acid (**14**), acantrifoic acid A (**15**), acantrifoside C (**16**), 3α,11α-Dihydroxy-23-oxo-lup-20(29)-en-28-oic acid (**17**), impressic acid (**18**), 3α,11α-Dihydroxy-lup-20

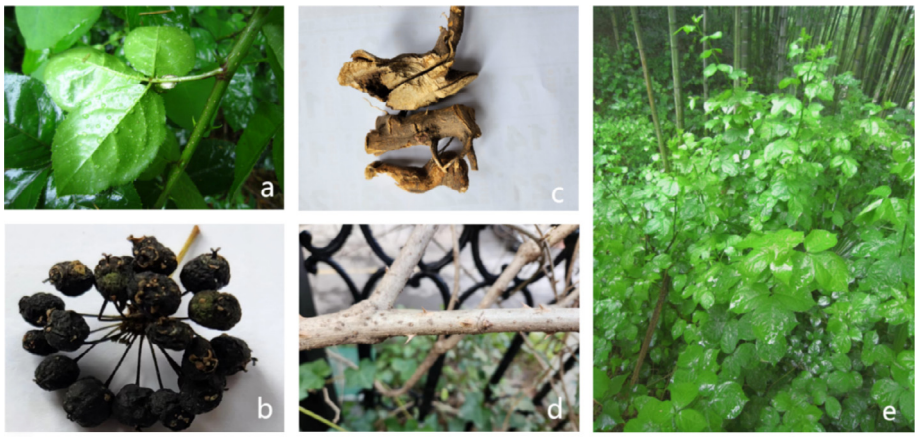


Fig. 1. *Eleutherococcus trifoliatus*. a: Leaves; b: Fruits; c: Roots; d: Stems; e: Herbs.

Table 1
Chemical components in *E. trifoliatus*.

Classification	No.	Chemical components	Formula	Parts of plants	References
Diterpenoids	**1**	Acantrifoside D	$C_{32}H_{52}O_{14}$	Stem bark	Kiem et al., 2003c Kiem, Cai, Minh, Lee, & Kim, 2004
	2	16α,17-Isovalerate- ent-kauran-19-oic acid	$C_{25}H_{40}O_4$	Stem bark	Kiem, Cai, Minh, Lee, & Kim, 2004
	3	Ent-kaur-15-en-17-al-19-oic acid	$C_{20}H_{25}O_3$	Stem and leaf	Li et al., 2016b
	4	17-Hydroxy-16α-ent-kauran-19-oic acid	$C_{20}H_{32}O_3$	Stem and leaf	Li et al., 2016b
	5	16α-Hydroxy-ent-kauran-19-oic acid	$C_{20}H_{32}O_3$	Stem and leaf	Li et al., 2016b
	6	Kaurenoic acid	$C_{20}H_{30}O_2$	Stem bark	Kiem, Cai, Minh, Lee, & Kim, 2004Li et al., 2016b Luo et al., 2020
	7	Ent-kaur-16-en-19-al	$C_{20}H_{30}O$	Stem and leaf	Li et al., 2016b
	8	18-Nor-ent-kaur-16-ene-4β-ol	$C_{19}H_{30}O$	Stem and leaf	Li et al., 2016b
	9	15α-Hydroxy-ent-kaur-16-en-19-oic acid	$C_{20}H_{28}O_3$	Root	Jiang, 2024
	10	Ent-pimara-8(14),15-dien-19-oic acid	$C_{20}H_{30}O_2$	Stem bark	Kiem, Cai, Minh, Lee, & Kim, 2004; Li et al., 2016b
	11	13-*Epi*-ent-manoyloxide-19-oic acid	$C_{20}H_{32}O_3$	Stem and leaf	Li et al., 2016b
	12	Ent-19-hydroxy-13-epi-manoyl oxide	$C_{20}H_{34}O_2$	Stem and leaf	Li et al., 2016b
Triterpenoids	**13**	Acantrifoside A	$C_{48}H_{78}0_{18}$	Leaf	Luo et al., 2020; Yook, Kim, Hahn, Nohara, & Chang, 1998
	14	11α,23-Dihydroxy-3-oxo-lup-20(29)-en-28-oic acid	$C_{30}H_{47}O_5$	Aerial part	Tam, Thien, & Le, 2013
	15	Acantrifoic acid A	$C_{32}H_{48}O_7$	Leaf	Van, Kiem, Minh, Lee, & Ho, 2003
	16	Acantrifoside C	$C_{50}H_{77}O_{21}$	Leaf	Van, Kiem, Minh, Lee, & Ho, 2003
	17	3α,11α-Dihydroxy-23-oxo-lup-20(29)-en-28-oic acid	$C_{30}H_{46}O_5$	Leaf	Luo et al., 2020; Ty et al., 1985
	18	Impressic acid	$C_{30}H_{48}O_4$	Stem and leaf	Li et al., 2016; Ty et al., 1985; Ty et al., 1984
	19	3α,11α-Dihydroxy-lup-20(29)-en-23-al-28-oic acid	$C_{30}H_{46}O_5$	Stem and leaf	Li et al., 2016b
	20	Acankoreanogenin	$C_{30}H_{46}O_5$	Stem and leaf	Li et al., 2016b
	21	3α,11α-Dihydroxy-lup-20(29)-en-23,28-dioic acid	$C_{30}H_{46}O_6$	Stem and leaf	Li et al., 2016b
	22	3α-Hydroxy-lup-20(29)-en-30-ol-23,28-dioic acid	$C_{30}H_{46}O_6$	Stem and leaf	Li et al., 2016b
	23	3α,l lα,23-Trihydroxylup-20(29)-en-28-oic acid	$C_{30}H_{48}O_5$	Leaf	Ty et al., 1984
	24	Acankoreoside A	$C_{48}H_{76}O_{19}$	Stem	Luo et al., 2020
	25	Acanthodiolglycoside	$C_{48}H_{78}O_{18}$	Leaf	Yook et al., 1999
	26	Acantrifoside B	$C_{47}H_{74}O_{18}$	Leaf	Kiem et al., 2003a
	27	24-Nor-11α-hydroxy-3-oxo-lup-20(29)-en-28-oic acid	$C_{29}H_{46}O_4$	Aerial part	Tam, Thien, & Le, 2013; Lischewski et al., 1985
	28	24-Nor-3α,11α-dihydroxy-lup-20(29)-en-28-oic acid	$C_{29}H_{44}O_4$	Aerial part	Tam, Thien, & Le, 2013; Lischewski et al., 1985; Kutschabsky, Pfeiffer, Lischewski, Ty, & Adam, 1986
	29	Acantrifoic acid C	$C_{30}H_{46}O_7$	Stem and leaf	Li et al., 2016b
	30	Acantrifoic acid D	$C_{30}H_{46}O_6$	Stem and leaf	Li et al., 2016b
	31	Acantrifoic acid	$C_{32}H_{48}O_8$	Leaf	Phan et al., 2004
	32	Taraxerol	$C_{30}H_{50}O$	Stem	Luo et al., 2020; Du & Gao, 1992
	33	Taraxeryl acetate	$C_{32}H_{52}O$	Stem	Luo et al., 2020; Du & Gao, 1992
Phenylpropanoids	**34**	Syringin	$C_{17}H_{24}O_9$	Stem	Luo et al., 2020;Kiem et al., 2003
	35	1-β-*D*-Glucopyranosyl-2,6-dimethoxy-4-propenylphenol	$C_{17}H_{24}O_8$	Stem bark	Kiem et al., 2003
	36	1-[β-*D*-Glucopyranosyl-(1 → 6)-β-*D*-glucopyranosyl]-2,6-dimethoxy-4- propenylphenol	$C_{23}H_{34}O_{13}$	Stem bark	(Kiem et al., 2003)
	37	(−)(2*R*,3*R*)-Secoisolariciresinol	$C_{20}H_{26}O_6$	Root	Jiang, 2024
	38	Icariside E4	$C_{26}H_{34}O_{10}$	Root	Jiang, 2024
Flavonoids	**39**	Quercitrin	$C_{17}H_{24}O_9$	Stem bark	Luo et al., 2020; Kiem et al., 2003
	40	Quercetin	$C_{15}H_{10}O_7$	Aerial part	Chen & Liu, 2008
	41	Isoquercetin	$C_{21}H_{20}O_{12}$	Stem bark	Sithisarn, Muensaen, & Jarikasem, 2011
	42	Rutin	$C_{27}H_{30}O_{16}$	Stem	Luo et al., 2020
	43	Hyperoside	$C_{21}H_{20}O_{12}$	Stem	Luo et al., 2020
	44	Lysionotin	$C_{18}H_{16}O_7$	Leaf	Du & Gao, 1992

(*continued on next page*)

Table 1 (*continued*)

Classification	No.	Chemical components	Formula	Parts of plants	References
	45	(±)-Epicatechin	$C_{15}H_{14}O_6$	Leaf	Chen & Liu, 2008
	46	Naringin	$C_{27}H_{32}O_{14}$	Root	Jiang, 2024
Lignans	**47**	Eleutheroside E	$C_{34}H_{46}O_{18}$	Stem bark	Kiem et al., 2003
	48	(2*R*,3*R*)-2,3-Di-(3,4-methylenedioxy-benzyl)-butyrolactone	$C_{23}H_{34}O_{13}$	Stem bark	Kiem et al., 2003
	49	(+)-Sesamin	$C_{20}H_{18}O_6$	Root	Jiang, 2024
	50	(±)-Pinoresinol	$C_{20}H_{22}O_6$	Root	Jiang, 2024
	51	Piperitol	$C_{20}H_{20}O_6$	Root	Jiang, 2024
Caffeoyl quinic acids	**52**	Chlorogenic acid	$C_{16}H_{18}O_9$	Stem bark	Guo et al., 2021; Sithisarn, Muensaen, & Jarikasem, 2011
	53	Neochlorogenic acid	$C_{16}H_{18}O_9$	Stem bark	Guo et al., 2021
	54	3,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	Stem bark	Guo et al., 2021
	55	Isochlorogenic acid B	$C_{25}H_{24}O_{12}$	Stem bark	Guo et al., 2021; Sithisarn, Muensaen, & Jarikasem, 2011
	56	4,5-Di-*O*-caffeoylquinic acid	$C_{25}H_{26}O_{13}$	Stem bark	Guo et al., 2021; Sithisarn, Muensaen, & Jarikasem, 2011
Organic acids (Esters)	**57**	Phthalic acid	$C_8H_6O_4$	Stem	Luo et al., 2020
	58	Benzoic acid	$C_7H_6O_2$	Aerial part	Chen & Liu, 2008
	59	2,5-Dihydroxybenzoic acid	$C_7H_6O_4$	Aerial part	Chen & Liu, 2008
	60	Syringic acid	$C_9H_{10}O_5$	Aerial part	Chen & Liu, 2008
	61	Salicylic acid	$C_7H_6O_3$	Aerial part	Chen & Liu, 2008
	62	Gallic acid	$C_7H_6O_5$	Aerial part	Chen & Liu, 2008
	63	Protocatechuic acid	$C_7H_6O_4$	Root	Jiang, 2024
	64	Protocatechuic acid methyl ester	$C_8H_8O_4$	Root	Jiang, 2024
	65	Caffeic acid	$C_9H_8O_4$	Root	Jiang, 2024
Steroids	**66**	Stigmasterol	$C_{29}H_{48}O$	Stem	Luo et al., 2020
	67	*β*-Sitosterol	$C_{29}H_{48}O$	Stem	Luo et al., 2020
	68	Daucosterol	$C_{35}H_{60}O_6$	Stem	Luo et al., 2020
	69	Stigmasterolglucoside	$C_{35}H_{58}O_6$	Stem	Luo et al., 2020
Other compounds	**70**	Resveratrol	$C_{14}H_{12}O_3$	Aerial part	Chen & Liu, 2008
	71	*n*-Butyl-*β*-*D*-fructopyranoside	$C_{10}H_{20}O_6$	Stem	Luo et al., 2020
	72	*p*-Hydroxybenzaldehyde	C_7H_6O	stem	Luo et al., 2020
	73	Pubinernoid A	$C_{11}H_{16}O_3$	stem	Luo et al., 2020
	74	Benzyl-*O*-*β*-*D*-glucopyranoside	$C_{13}H_{18}O_6$	root	Jiang, 2024

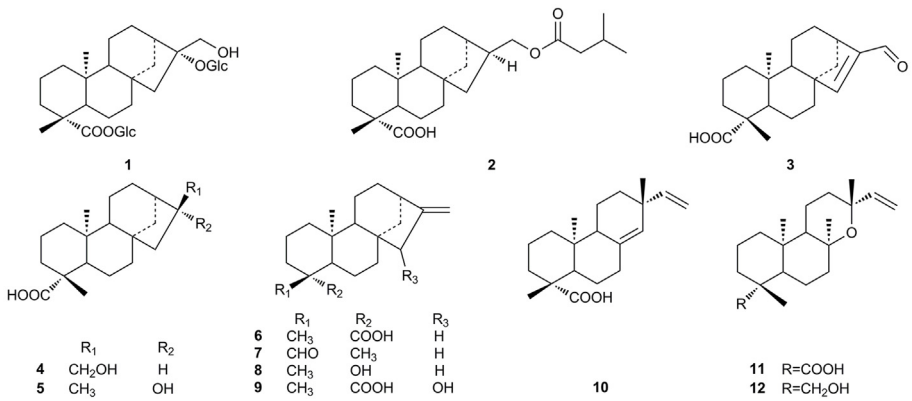


Fig. 2. Chemical structures of deterpenoids (**1**–**12**) in *E. trifoliatus*.

(29)-en-23-al-28-oic acid (**19**), 3α-hydroxy-lup-20(29)-en-23,28-dioic acid (20), 3α,11α-Dihydroxy-lup-20(29)-en-23,28-dioic acid (**21**), 3α-Hydroxy- lup-20(29)-en-30-ol-23,28-dioic acid (**22**), 3α,11α,23-Trihydroxylup-20(29)-en-28-oic acid (**23**), acankoreoside A (**24**), acanthodiolglycoside (**25**), acantrifoside B (**26**), 24-nor-11α-hydroxy-3-oxo-lup-20(29)-en-28-oic acid (**27**), 24-Nor-3α,11α-dihydroxy-lup-20(29)-en-28-oic acid (**28**), acantrifoic acid C (**29**), acantrifoic acid D (**30**), acantrifoic acid (**31**), taraxerol (**32**), and tarax-

eryl acetate (**33**) (Table 1, Fig. 3**)**. The basic skeleton of these triterpenoids can be divided into two types: lupane-type and ursane-type. Among the 21 compounds, the sugar groups are generally located at C-28.

2.3. Phenylpropanoids

Five phenylpropanoids have been isolated and purified from *E. trifoliatus* (Table 1, Fig. 4**)**. They are syringin (**34**), 1-*β*-*D*-glucopyranosyl-2,6-dimethoxy-4-propenylphenol (**35**), 1-[*β*-*D*-glucopyranosyl-(1 → 6)-*β*-*D*-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol (**36**) and (−)(2*R*,3*R*)-secoisolariciresinol (**37**), and icariside E4 (**38**). Among them, Compound 35 and Compound 36 are recently isolated and identified from *E. trifoliatus*.

2.4. Flavonoids

Up to now, there are eight flavonoids detected from this plant (Table 1, Fig. 5). Quercitrin (**39**), quercetin (**40**), isoquercetin (**41**), rutin (**42**), hyperoside (**43**), lysionotin (**44**), (±)-epicatechin (**45**), and naringin (**46**), have been obtained from leave and stem barks of *E. trifoliatus*.

2.5. Lignans

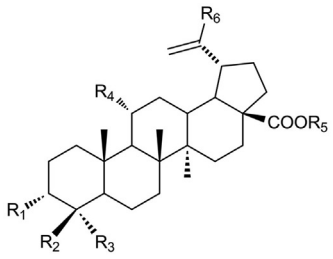
To date, researchers have also isolated five lignans from *E. trifoliatus* stems, leaves and roots (Fig. 6, Table 1). They are eleutheroside E (**47**), (2R,3R)-2,3-di-(3,4-methylenedioxy-benzyl)-butyrolactone (**48**), (+)-sesamin (**49**), (±)-pinoresinol (**50**), and piperitol (**51**). Eleutheroside E has been obtained from other *Acanthopanax* plants as well.

2.6. Caffeoyl quinic acids

E. trifoliatus also contains caffeoyl quinic acid derivatives (Table 1, Fig. 7). Using the method of HPLC, five caffeoyl quinic acids have been isolated and identified from *E. trifoliatus*. A stable and reliable method (Quantitative analysis of multi-component with single-marker) was used to determine these five caffeoyl quinic acids. It has been shown that two of them are caffeoyl monosubstituted compounds (**52**–**53**), and the other three are caffeoyl disubstitutes compounds (**54**–**56**).

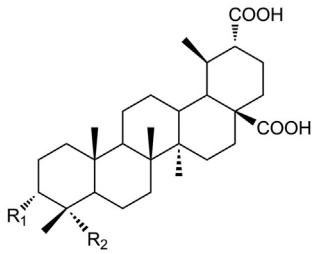
2.7. Organic acids (Esters)

A comprehensive analysis has identified nine organic acids (esters) in *E. trifoliatus*. They are phthalic (**57**), benzoic acid (**58**),



Lupane-type triterpenoid

	R_1	R_2	R_3	R_4	R_5	R_6
13	OH	CH_3	CH_3	OH	Glc-6-Glc-4-Rha-	CH_3
14	OH	CH_3	CH_3	OH	H	CH_3
15	CH_3CO O	CH_3	COOH	H	H	CH_2OH
16	CH_3CO O	CH_3	COOH	H	Glc-6-Glc-4-Rha-	CH_2OH
17	OH	CH_3	CHO	OH	H	CH_3
18	OH	CH_3	CH_3	OH	H	CH_3
19	OH	CH_3	CHO	OH	H	CH_3
20	OH	CH_3	COOH	H	H	CH_3
21	OH	CH_3	COOH	OH	H	CH_3
22	OH	CH_3	COOH	H	H	CH_2OH
23	OH	CH_3	CH_2OH	OH	H	CH_3
24	OH	CH_3	COOH	H	Rha-4-Glc-6-Glc-	CH_3
25	OH	CH_3	CH_3	OH	Rha-4-Glc-6-Glc-	CH_3
26	=O	H	CH_3	OH	Glc-6-Glc-4-Rha-	CH_3
27	OH	H	CH_3	OH	H	CH_3
28	=O	H	CH_3	OH	H	CH_3



Ursane-type triterpenoid

	R_1	R_2
29	OH	COOH
30	OH	CHO
31	CH_3COO	COOH
32	OH	CH_3
33	CH_3COO	CH_3

Fig. 3. Chemical structures of triterpenoids (**13**–**33**) in *E. trifoliatus*.

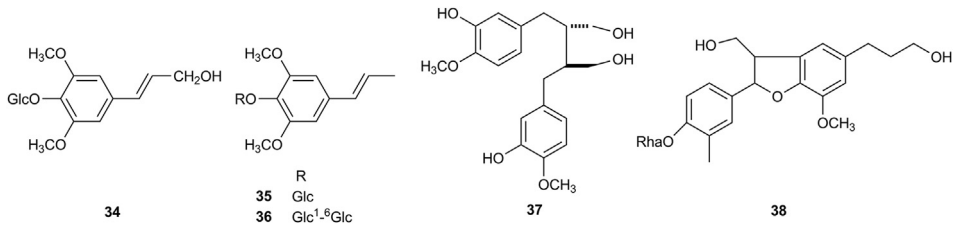


Fig. 4. Chemical structures of phenylpropanoids (**34**–**38**) in *E. trifoliatus*.

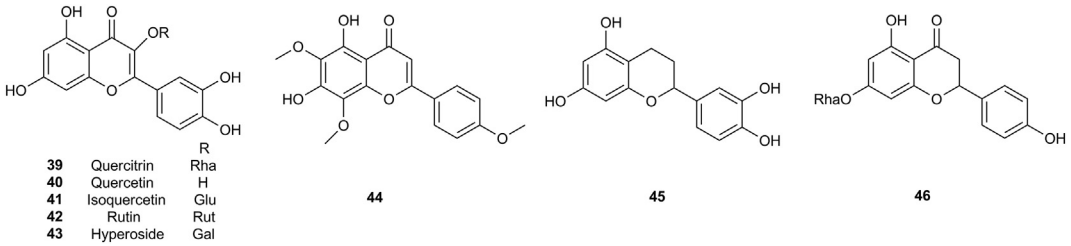


Fig. 5. Chemical structures of flavonoids (**39**–**46**) from *E. trifoliatus*.

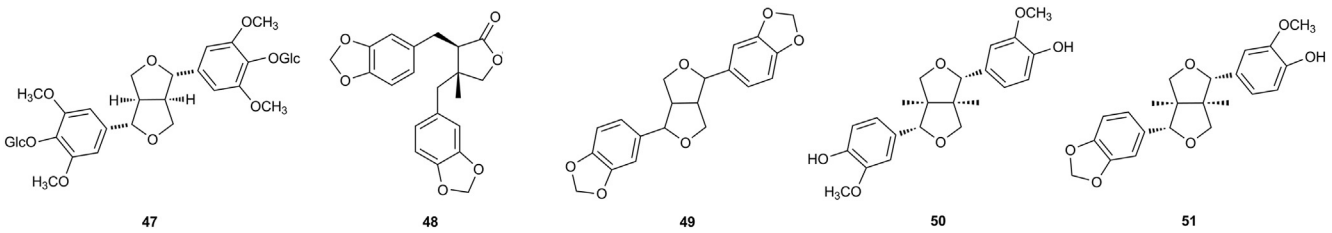


Fig. 6. Chemical structures of lignans (**47**–**51**) in *E. trifoliatus*.

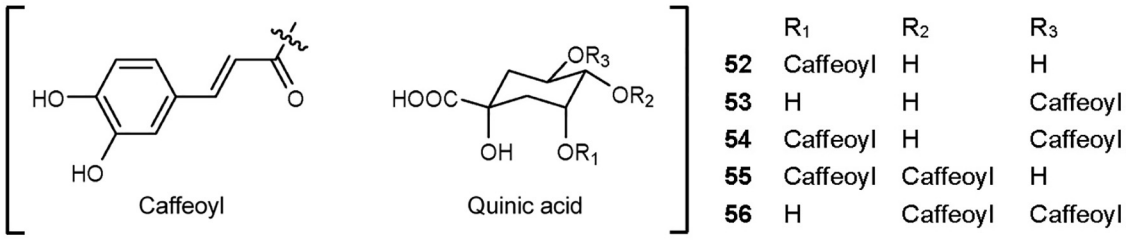


Fig. 7. Chemical structures of caffeoyl and quinic acids (**52**–**56**) in *E. trifoliatus*.

2,5-Dihydroxybenzoic acid (**59**), syringic acid (**60**), salicylic acid (**61**), gallic acid (**62**), protocatechuic acid (**63**), protocatechuic acid methyl ester (**64**), and caffeic acid (**65**), respectively (Table 1, Fig. 8**)**. As an important secondary metabolite in plants, the content of organic acids in different parts, different producing areas and different harvest periods is usually different, so the quality evaluation and control can be carried out through the content of organic acids.

2.8. Steroids

Stigmasterol (**66**), *β*-sitosterol (**67**), daucosterol (**68**), and stigmasterolglucoside (**69**), four steroids were isolated from different parts of *E. trifoliatus*. More details were available in Fig. 9 and Table 1.

2.9. Essential oils and other compounds

A limited amount of work has been carried out on volatile components of *E. trifoliatus*. A combined methodology of capillary GC, GC–MS, and C-13 NMR spectroscopy, with fractionation by column chromatography proceeded, was employed to investigate the essential oil from *E. trifoliatus*. More than 60 compounds, representing 97.4% of the total volatile oil were identified from *E. trifoliatus* stems and leaves. The main components, α-pinene and sabinene, were 23.9% and 14.9% of the total volatile oils, respectively. Other components identified in the essential oil in high amounts (> 5%) included terpinen-4-ol, *β*-pinene, and *p*-cymene (Muselli et al., 1999). The volatile oil from the leaves of *E. trifoliatus* was analyzed by GC–MS, and their relative contents were determined by area normalization via Na. Among the 108 GC peaks, 81 compounds were identified, accounting for 96.50% of the volatile oil. Terpenes and their oxo-derivatives were the major chemical constituents in the volatile oil (Na, 2005). Liu et al. also used GC–MS to analyze the components of the volatile oil extracted from the leaves of *E. Trifoliatus* (Liu, Yan, & Fang, 2009). Among 38 isolated components, 17 compounds were identified, accounting for 69.402% of the total volatile oil. Additionally, 12 of these components are more than 2%. The volatile components mentioned above, such as α-pinene, *β*-phellandrene, and *β*-pinene, have high content and exhibit significant antitussive, expectorant, antifungal, anti-inflammatory, and analgesic effects.

In addition, following compounds were isolated from different parts of *E. trifoliatus*: resveratrol (**70**), *n*-butyl-*β*-*D*-fructopyranoside (**71**), *p*-hydroxybenzaldehyde (**72**), pubinernoid A (**73**), and benzyl-*O*-*β*-*D*-glucopyranoside (**74**) (Table 1, Fig. 10).

3. Purification and analysis methods

Phenylpropanoids, flavonoids, lignans, and caffeoyl quinic acids are main active compounds in *E. trifoliatus*. Therefore, they are often chosen as index components for qualitative and quantitative analyses. These compounds have the same functional groups belonging to the class of polyphenols, thus they exhibit similar chemical properties. Studies have focused on the detection, extraction, and purification technology of polyphenols in *E. trifoliatus*.

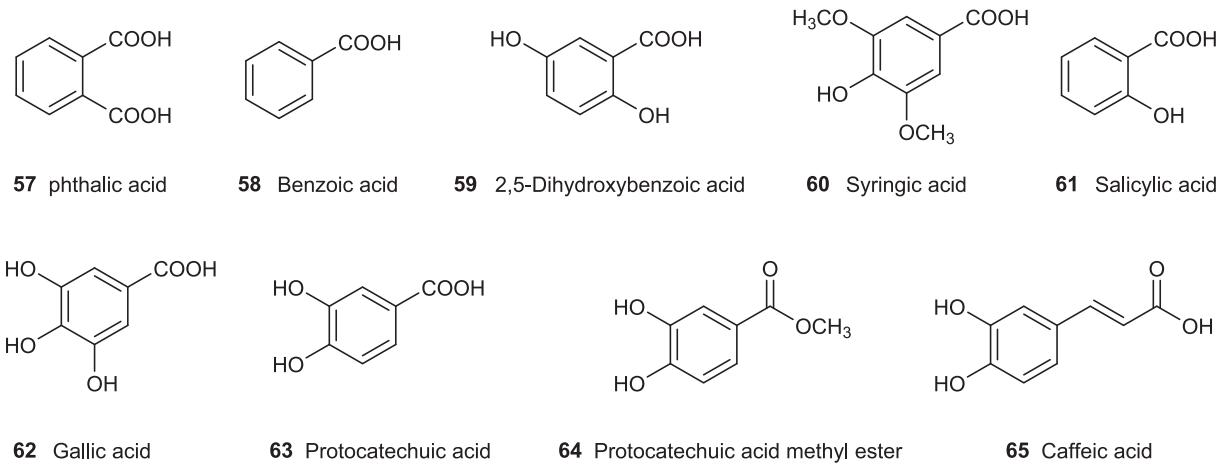


Fig. 8. Chemical structures of organic acids (Esters) (**57**–**65**) from *E. trifoliatus*.

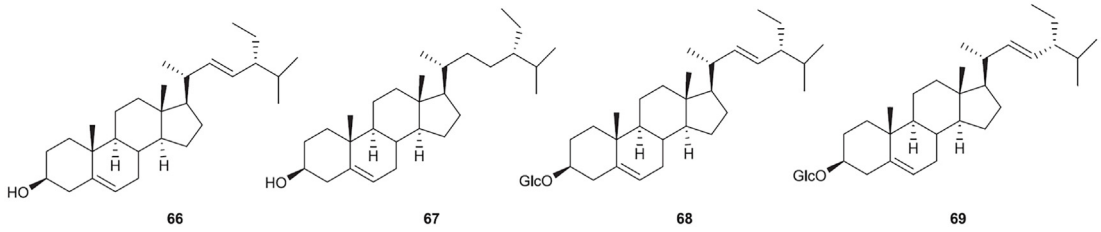


Fig. 9. Chemical structures of steroids (**66**–**69**) in *E. trifoliatus*.

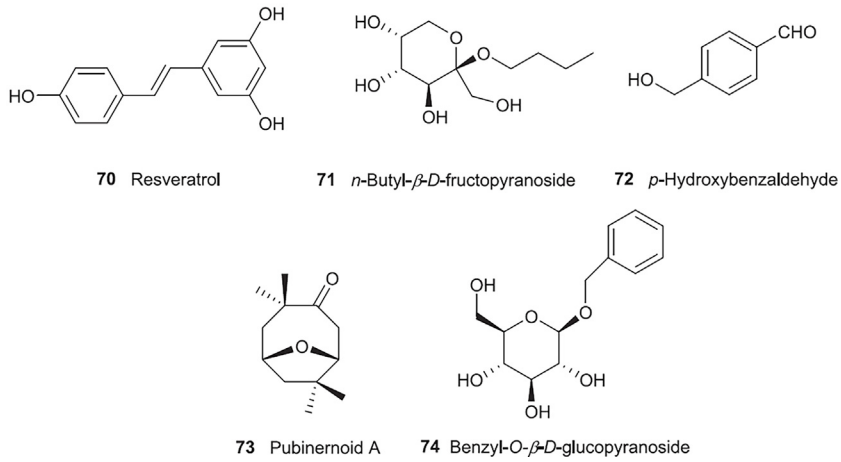


Fig. 10. Chemical structures of other compounds (**70**–**74**) from *E. trifoliatus*.

The commonly used methods for determining polyphenols include HPLC and UV–Vis. The contents of caffeoyl quinic acid and flavonoid glycosides in *E. trifoliatus* were determined using HPLC by Sithisarn et al (2011). The results showed that the highest levels of flavonoid glycosides (calculated as rutin) were observed in most extracts, with amounts ranging from 0.22 to 2.49% (Sithisarn, Muensaen, & Jarikasem, 2011). Zhou et al. (2021) established an HPLC method to simultaneously determine five phenolic acids. This method was used to predict that the Q-marker of *E. trifoliatus* roots is polyphenols. Some researchers used UV–Vis spectroscopy to determine the flavonoid content in the fruits and leaves of *E. trifoliatus*. The results showed that the flavonoid content in the fruits of *E. trifoliatus* was 76.93 mg/g, and that of ethyl acetate fraction in leaves was as high as 282.39 mg/g (Sen et al., 2013; Cheng et al., 2017).

The methods for purifying flavonoids and polyphenols, as well as extracting polysaccharides, involved the use of polyamide resin, HPD-600 resin, and macroporous resin. The purification technology for total flavonoids from *E. trifoliatus* leaves was studied using polyamide resin and macroporous resin. Their mass fraction of fla-

vonoids after purification was found to be 60% and 21.3%, respectively (Cai, Li, Shi, Gao, & Chen, 2011; Xiao, Li, Cai, & Gao, 2010). The purification process of total polyphenols from *E. trifoliatus* leaves was also proceeded using macroporous resin. The polyphenol sample from *E. trifoliatus* leaves was purified using HPD100 resin, resulting in an increase in purity from 11.7% to 49.7%. The purification effect was 4.25 times greater than before (Cen et al., 2019). The extraction process of total polyphenols was optimized using the response surface methodology. The total polyphenol yield was 62.71 ± 1.48 mg/g with the optimal process parameter, which were 55% ethanol concentration, extraction temperature of 75 °C, extraction time of 113 min, and ratio value of liquid to solid 25 (mL/g) (Zhang et al., 2015). Some researchers used the ultrasonic cell disruption method to extract polysaccharide components. Their results showed that the extraction rate was 6.85% (Guo, Zhao, Hu, Yang, & Wang, 2020).

According to our previous studies (Xiao et al., 2020; Xiao et al., 2020), we have established HPLC methods for the simultaneous determination of 14 phenylpropanoids (syringin, chlorogenic acid, caffeic acid, *p*-coumaric acid, ferulic acid, ethylsyringin, ethylconiferin, (+)-fraxinol, (±)-rosin, (±)-syringin, taiwanin C, savinin, helioxanthin, and (−)-sesamin) and 10 flavonoids (apigenin-6,8-C-*di*-*β*-*D*-glucopyranoside, rutin, hypericin, naringin, apigenin-7-*O*-neohesperidin, daboside, quercetin, apigenin, kaempferol, and isorhamnetin) in 16 species and 33 batches of *Acanthopanax*, respectively. These 33 batches of *Acanthopanax* included six batches of *E. trifoliatus*. These results indicated that our methods are effective, accurate, reproducible, and stable, providing a reference for further studies on plants in *Acanthopanax*.

Some key components of *E. trifoliatus,* such as terpenoids and total saponins, were also determined in amount. A reasonably and efficient method was established for the determination of kaurenoid acid (**6**, KA) in *E. trifoliatus*. KA was extracted using ultrasound-assisted extraction and further purified by solid phase extraction (SPE). It was then quantified and isolated with UHPLC-MS/MS method. This method has been successfully applied for the determination of KA in *E. trifoliatus* leaves (Peng, Chen, Duan, & Wang, 2020). The total saponins from *E. trifoliatus* leaves were purified by macroporous resin. Under optimal conditions, we increased the content of saponin in the crude extract increased to 71.50% after collecting the 70% ethanol eluent, concentrating, vacuum drying and purifying (Gao et al., 2009).

4. Pharmacology research

The traditional functions of *E. trifoliatus* include clearing away heat and toxic materials, curing rheumatism, removing blood stasis, relieving pain, and alleviating cough and asthma symptoms. *E. trifoliatus* is mainly used for treating symptoms such as colds, coughs, rheumatism, and sciatica. Based on its traditional efficacy, researchers have conducted a series of studies and found that the plant also has anti-inflammatory, antibacterial, anticancer, antioxidant, and other functionalities. The main active ingredients responsible for these functions are flavonoids, and caffeoyl quinic acids, lignans, and triterpenoid saponins.

4.1. Anti-inflammatory

Some studies have reported that the leaves and stems of *E. trifoliatus* had a significant anti-inflammatory effect. For instance, Chien et al. (Chien et al., 2015) examined the anti-inflammatory effects of the ethyl acetate fraction of *E. trifoliatus* (EAET). Their results showed that EAET attenuated the production of LPS-induced nitric oxide (NO), tumor necrosis factor-alpha, interleukin-1β, and IL-6 induced by LPS *in vitro* and *in vivo*. EAET significantly reduced LPS-induced histological alterations in lung tissues. Furthermore, EAET significantly reduced the total cells count and protein concentration levels in the bronchoalveolar lavage fluid. Western blotting test results revealed that EAET blocked the protein expression of inducible NO synthase, cyclooxygenase-2, phosphorylation of nuclear factor-kappa-B Inhibitor alpha (NF-κB-α) protein, and mitogen-activated protein kinases in LPS-stimulated RAW264.7 cells, as well as LPS-induced lung injury.

The TPA-induced ear swelling model was utilized to investigate the anti-inflammatory activity. *In vitro* experiments were also conducted to evaluate the effect of the ethanol extract from *E. trifoliatus* stems and leaves and chlorogenic acid on TPA-induced ear swelling. The results indicated that the ethanol extract exhibited greater activity in inhibiting TPA-induced ear swelling compared to chlorogenic acid (Wang et al., 2015). These results are consistent with the above experimental ones. Another study showed that the inhibition rate of the chloroform layer from *E. trifoliatus* stems and leaves was as high as 99.99% at the concentration of 50 mg/kg. The ELISA study showed that all the extracts of *E. trifoliatus* could reduce the level of IL-1β in TPA-induced mouse ears (Chen et al., 2021).

The anti-inflammatory activity was investigated by using carrageenan to induce rat foot swelling models. The results showed that the methanol fraction of *E. trifoliatus* leaves exhibited strong anti-inflammatory activity, with an inhibition rate of 77.24% at the highest dose of 500 mg/kg. The effect may be due to polar compounds, such as flavonoids and polyphenols (Hamid, Kee, & Othman, 2013). Another work reported that the inhibition rate of *E. trifoliatus* stem polysaccharide on the swelling of rat toes caused by carrageenan was 62%, 69%, and 92% in low, medium, and high dose groups, respectively, at 12 h (Yang, Zhang, Chen, & Pan, 2015). Furthermore, a study indicated that the inhibition rates of flavonoids from *E. trifoliatus* leaves was 52%, 65%, and 82%, respectively, in the low, medium, and high dose groups at 6 h (Yang, Zhang, Liang, & Pan, 2014). Although these studies have demonstrated the significant anti-inflammatory activities of the stems and leaves of *E. trifoliatus,* there is still a lack of in-depth research on the mechanism of action and the activity of monomeric compounds.

4.2. Hypoglycemic

The hypoglycemic mechanisms of traditional Chinese medicine (TCM) and its effective components include inhibiting α-glucosidase activity, inhibiting gluconeogenesis, and promoting glycogen synthesis. TCM has unique advantages in treating diabetes and other diseases because it regulates the body's function as a whole. Its mechanism and approach are multifaceted and multi-targeted.

Pan Yufang's team has conducted extensive research on the hypoglycemic activity and mechanism of polysaccharides derived from the stem of *E. trifoliatus* (Li et al., 2021) The team used a streptozotocin (STZ)-induced diabetic mouse model to study the hypoglycemic activity and mechanism of crude polysaccharide (ATP), decolorized polysaccharide (ATP1), and neutral homogeneous polysaccharide (ATP1-1) extracted from the stem of *E. trifoliatus*.

A series of results showed that ATP and ATP1 can effectively reduce the blood sugar levels in experimental diabetic mice, and there is a certain correlation between the dose and the effectiveness. The therapeutic effect of polysaccharide before and after decolorization in the middle and high dose groups on diabetic mice is very similar to that of metformin, a classic clinical hypoglycemic drug. After two weeks of administration, the inhibition rate of ATP and ATP1 in the high dose group was 32.02% and 43.04%, respectively. This suggests that ATP1 had a slightly enhanced hypo-

glycemic effect at the same dosage. ATP can significantly improve the glucose tolerance and glycogen content in the liver and muscle of diabetic mice (He et al., 2016; Zhang, 2016). HE staining observation showed that after the administration of ATP, the islet damage in mice from each group was recovered by varying degrees. Additionally, the administration of ATP enhanced the spleen immune function in mice (Yang et al., 2017). Another study also confirmed that the polysaccharide of *E. trifoliatus* can reduce blood sugar levels in diabetic mice by restoring the immune balance of the spleen (Li, Chen, Luo, Yang, & Pan, 2021).

ATP1-1 was obtained after separating and purifying the crude polysaccharide from *E. trifoliatus* stems. The results of the ATP1-1 hypoglycemic effect study showed that it can effectively increase the glycogen content in the livers of diabetic mice. This increase may be attributed to its ability to promote glucose transformation in the liver. Meanwhile, ATP1-1 can effectively reduce blood sugar levels, improve glucose tolerance, and repair impaired glucose metabolism in mice with type 1 diabetic. In addition, it can increase the expression of GLUT1 and GLUT2 to promote glycolysis and glycogen synthesis, while the expression of PEPCK and G6Pase expression to inhibit gluconeogenesis is reduced. These results may be applied to regulate to key enzymes and related transporters involved in glucose metabolism (Zhou et al., 2017; Zheng et al., 2018). The researchers conducted in-depth research and found that ATP1-1 can improve the integrity of the intestinal mucosal barrier, reduce intestinal inflammatory, and ultimately lower blood sugar level in diabetic mice. This is achieved by increasing the secretion of short-chain fatty acids (SCFAs) (Zhu et al., 2022). The research above mainly focuses on the hypoglycemic effect of *E. trifoliatus* in individuals with type 1 diabetes. In recent years, the research team has studied the regulatory effect of *E. trifoliatus* polysaccharide on type 2 diabetes. Their results showed that ATP1-1 could enhance the antioxidant effect of the liver and improve the disorder of glucose and lipid metabolism in type 2 diabetic mice (Li et al., 2022).

Another research team has utilized a screening model of enzyme inhibition with nitrobenzene-α-*D*-glucopyranoside (PNPG) as a substrate. They determined the inhibitory effect of the extract and its chemical components on α-glucosidase of *E. trifoliatus*. The experimental results showed that the ethyl acetate layer of leaves, stems, and roots exhibited the highest inhibitory activity. Among the nine terpenoids and six polyphenols in the ethyl acetate layer of *E. trifoliatus*, ent-kaur-15-en-17-al-19-oic acid (**3**) and 4,5-Di-*O*-caffeoylquinic acid (**55**) displayed the best α-glucosidase inhibitory activity. These compounds demonstrated greater activity than the control acarbose, suggesting that they may be the active components of the *E. trifoliatus* extract (Li et al., 2016a).

4.3. Anticancer

In recent years, an increasing number of researchers have dedicated themselves to studying the anti-cancer effect of TCM, and *E. trifoliatus* is one of the raw materials for their research. Their results showed that the anticancer activity of the ethyl acetate extract of *E. trifoliatus* was associated with the inhibition of nuclear factor-κB (NF-B) transcription activity, the increase in caspase-3 level, and the decrease in phosphorylated erk1/2 and phosphorylated akt level (Wang et al., 2014). Li et al. conducted a study on the anticancer activity of terpenoids in *E. trifoliatus*. Their results showed that three compounds, namely ent-kaur-15-en-17-al-19-oic acid (**3**), impressic acid (**18**), and acankoreanogenin (**20**) found in ethyl acetate fraction, exhibited inhibitory effects on the growth of PC-3 cells and induced cell apoptosis. The mechanism of action is that these terpenoids have a strong inhibitory effect on NF-κB, a signal sensor, and transcription activator 3 (STAT3). Moreover, these terpenoids also inhibited the expression of survivin in the downstream targets of NF-κB and STAT3. *In vivo* studies using xenotransplantation mouse models showed that acankoreanogenin (**20**) strongly inhibited the formation and growth of PC-3 tumors. In addition, treatments with acankoreanogenin (**20**) significantly reduced the expression of phosphorylated STAT3 and survivin in PC-3 tumors. The results show that acankoreanogenin (**20**) has a preventive effect on the occurrence and development of PC-3 xenograft tumors. This compound may be a potential candidate for the prevention of prostate cancer. With these, it becomes clear that terpenoids have great research values and prospects in their anticancer effects (Li et al., 2015; Li et al., 2016b).

4.4. Antioxidant

Though limited studies have been carried out on the antioxidant activity of *E. trifoliatus*, the obtained experimental results indicate that its antioxidant activity is associated with polyphenols and flavonoids. The research method of antioxidant activity of *E. trifoliatus* was mainly scavenging free radicals *in vitro*. Researchers used the TBARS method to detect the free radical scavenging activity and the inhibitory effect on lipid peroxidation of 11 types of *E. trifoliatus* leaf extracts. The results showed that their free radical scavenging activity and the inhibitory effect on lipid peroxidation were significant. This may be related to the rich polyphenols and flavonoids in the extracts (Sithisarn & Jarikasem, 2009; Sithisarn, Muensaen, Jarikasem, & Supatanakul, 2014). A free radical scavenging experiment was also conducted on the ATP1-1 in the stem of *E. trifoliatus*. The results showed its strong antioxidant activity and a positive dose–effect relationship (Cheng, Zhang, Yang, Zhang, & Pan, 2017). *E. trifoliatus* was made into herbal tea, and its antioxidant capacity for scavenging ABTS and DPPH free radicals was studied with total flavonoids. The results from this study exhibited that the antioxidant capacity for scavenging free radicals was excellent (Jiang et al., 2013).

The results of the DPPH and ORAC methods indicated that the total polyphenols of *E. trifoliatus* exhibited the same antioxidant activity as Trolox (Zhang, 2015). Another study elucidated that the total polyphenols found in *E. trifoliatus* leaves have a significant protective effect on PC12 cells. This can effectively alleviate the oxidative damage and aging in PC12 cells, providing a theoretical basis for the identifying and screening of natural drugs that can effectively prevent and treat Alzheimer's disease (Yu, Feng, Liu, Li, & Zhang, 2023).

4.5. Other activities

In addition to the aforementioned pharmacological activities, *E. trifoliatus* also demonstrated antibacterial, anti-hyperalgesic, anti-fatigue, analgesic, and hemostatic effects. Research results showed that the antibacterial effect is mainly related to the content of total flavonoids, and it has the strongest effect on *Escherichia coli* and *Staphylococcus aureus*. The petroleum ether layer extract was found to generate the strongest antibacterial effect, while the ethyl acetate layer extract yielded the highest content of active substances and exhibited strong hemostatic and analgesic activities (Chien et al., 2017). Sithisarn et al. (2013) investigated the effects of the aqueous extract of *E. trifoliatus* leaves on cognitive and emotional deficits using an olfactory bulbectomized mouse model (Sithisarn, Rojsanga, Jarikasem, Ken, & Kinzo, 2013). Their results demonstrated that the aqueous extract of *E. trifoliatus* leaves rendered an ameliorative effect on cognitive and emotional deficits. Li et al. (2021) investigated the hepatoprotective effects of various extracts of *E. trifoliatus*. Their results of hepatocyte microscopy suggested that all extracts were able to considerably reduce the extent of liver cell degeneration caused by alcohol.

5. Toxicity of *E. trifoliatus*

As a widely distributed plant in southern China, *E. trifoliatus* is a valuable medicinal and edible resource. Acute toxicity test was used to study the edible safety of *E. trifoliatus* (Lin, Lin, Tan, Li & Qiu, 2009). The results showed that the LD_{50} was more than 40 g/kg. After feeding for 30 d, the growth of SD rats and the blood biochemical indexes were not significantly affected. Pathological examination indicated that the three doses did not cause damage to spleen, liver, kidney and other organs in rats. In the maximum dose range, the results of bone marrow micronucleus test and mouse testicular chromosome aberration test were negative. Toxicological experiments show that *E. trifoliatus* is safe to eat. Hence, the products made with *E. trifoliatus* as raw materials have been researched and developed. Soaps developed from the raw material of *E. trifoliatus* demonstrated functions such as ridding rheumatism, diminishing inflammation, killing bacteria, and relieving itching. Similarly, toothpaste derived from *E. trifoliatus* has properties to be anti-inflammatory, detoxicating, clearing away heat and fire, and relieving pain (Liu, Huang, Zhong, Huang, & Zheng, 2007; Huang, Huang, Zhong, Liu, & Zheng, 2006). The anti-inflammatory spray of *E. trifoliatus* is a product with a potent anti-inflammatory effect. It is formulated using the abundant flavonoids found in *E. trifoliatus*, *Dendranthema indicum,* and *Plantago depressa* Willd. (Huang, Zheng, Huang, & Liu, 2008). The total flavonoids in *E. trifoliatus* and chlorogenic acid in *Lonicerae Japonicae Flos* were extracted by water, and prepared into Painstakingly Punctures Powder. This powder has the functions of clearing away heat and toxic materials (Huang, Huang, Zhong, Zheng, & Liu, 2007). The *E. trifoliatus* capsule demonstrated a good ability to scavenge ABTS free radicals and DPPH free radicals and exhibited a significant antioxidant capacity (Jiang, 2014). *E. trifoliatus* polysaccharide tablet, a kind of health-care medicine with hypoglycemic effects, was developed with polysaccharide of *E. trifoliatus* and appropriate auxiliary materials (Zhang, Yang, He, Cheng, & Pan, 2015). Based on the health effects of *E. trifoliatus*, Qing (2018) prepared three products: hard candies, granules, and green juice powder. These products were made using fresh *E. trifoliatus* as raw materials with modern processing techniques. These foods are easy to carry, safe, healthy, and have unique flavor. In addition, heath care products such as *E. trifoliatus* health wine and tea have been developed and are being sold.

6. Discussion

Although *E. trifoliatus* is a less studied species than others in *Acanthopanax*, the research progress of *E. trifoliatus* can be shown in the following aspects.

Firstly, *E. trifoliatus*, both used as medicine and food, have been the subject of research primarily focused on process purification processes, while research on fingerprints and quality markers are insufficient. People have been eating fresh vegetables of *E. trifoliatus* for hundreds of years. Therefore, much more attentions should be paid on main effective compounds to provide a basis for the deep development of its application products

Secondly, the studies on the pharmacological activities of *E. trifoliatus* were mostly focused on crude extracts *in vitro*. Most of these extracts have not been phytochemically analyzed. In other words, monomeric components are seldom studies in the bioactivities. Moreover, some pharmacological studies lack positive controls and *in vivo* investigations, especially for studies on antitumor and antioxidant effects. In addition, experiments should be performed on animal models rather than solely testing inflammatory cytokines or cytotoxicities *in vitro*. In a word, the action mechanism needs more invesitgation.

Thirdly, other species of *Acanthopanax* Miq., such as *E. nodiflorus* and *E. senticosus* in *the China Pharmacopoeia*, are used in roots, because the roots possess high medicinal values. However, most studies of *E. trifoliatus* were primarily focused on the shoots. For this reason, investigations into the chemical constituents and pharmacological activities of the underground parts of *E. trifoliatus* should be encouraged, which can expand its application scope and provide a basis for the effective utilization of TCM resources.

Finally, there are relatively little research on product development for medical and edible plants. As people's living standards continue to rise, advancing the development and utilization of medicinal materials that serve dual purposes as both medicine and food can effectively propel the modernization of Traditional Chinese Medicine (TCM). Furthermore, this endeavor significantly contributes to the advancement of the "Healthy China" initiative.

7. Conclusion

In this review, the status of current research on *E. trifoliatus* was summarized in order to provide a scientifically sound foundation and solid reference for future research for the Chinese endemic medicinal plant. This review presents a total of 74 chemical compounds from *E. trifoliatus*. These research findings indicated that the main chemical constituents of *E. trifoliatus* are diterpenes, triterpenes, phenylpropanoids, flavonoids, lignans, caffeoyl quinic acids, steroids, and essential oils. Phenylpropanoids, flavonoids, and caffeoyl quinic acids are known to exhibit excellent anti-inflammatory, hypoglycemic, anticancer, and antioxidant effects. More comprehensive studies on the effective ingredients, pharmacological mechanisms, overall research of the roots and product development are extremely important to further validate the clinical efficacy and safety of *E. trifoliatus*.

CRediT authorship contribution statement

Maofang Lu: Writing – original draft. **Bin Wang:** Writing – original draft. **Ling Dai:** Supervision. **Jian Wu:** Writing – review & editing. **Jiao Luo:** . **Changsoo Yook:** . **Xiangqian Liu:** Supervision.

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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