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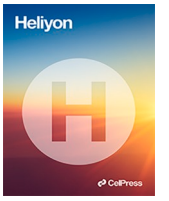

Review article

Traditional use, phytochemistry and pharmacology of Viticis Fructus

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A R T I C L E I N F O

Keywords:
Viticis fructus
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Anti-allergic
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A B S T R A C T

Ethnopharmacological relevance: Viticis Fructus (called Manjingzi in China) is the dried ripe fruits of the plant species *Vitex trifolia* subsp. *litoralis* Steenis and *Vitex trifolia* L. in the family Lamiaceae. Viticis Fructus has been used as a traditional Chinese medicine for thousands of years to treat illness such as colds, headache, vertigo, anesthesia, and hyperkinesias. More chemical constituents and medicinal effects have been discovered in Viticis Fructus with the development of modern technology.

The aim of the review: This review aims to analyze the research progress of Viticis Fructus from the aspects of botany, ethnopharmacology, phytochemistry, and pharmacological activity, as well as to provide an outlook on the research and use prospects of Viticis Fructus.

Material and methods: A comprehensive literature search using online databases such Science Direct, CNKI, Wiley online library, Spring Link, Web of Science, PubMed, Wanfang Data and SCI-Finder. In addition, information was obtained from local and foreign books on ethnobotany and ethnomedicine.

Results: The application of Viticis Fructus as a medicine can be traced back to around 480 AD. So far, more than 190 compounds have been isolated from Viticis Fructus, including flavonoids, sterols, cyclic enol ether terpenoids, and diterpenoids. Modern pharmacological studies have shown that the extracts of Viticis Fructus have various pharmacological effects, such as anti-allergic, antioxidant, anti-inflammatory, anti-cancer, and anti-bacterial effects.

Conclusion: As a widely used traditional medicine, Viticis Fructus is rich in chemical compositions and has an obvious biological activity. However, the application and pharmacological activity of Viticis Fructus have not been scientifically evaluated or convincing due to poor methodology, unclear results and lack of clinical data. Systematic and comprehensive research evaluations are needed to verify its pharmaceutical activity, clinical therapeutic efficacy and safety. As an important herbal medicine, it should be further explored to facilitate the development of new medicines and treatments for a variety of diseases.

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1. Introduction

Viticis Fructus is the dried fruits of two perennial plants *Vitex. trifolia subsp. litoralis* Steenis and *Vitex. trifolia* L. (Lamiaceae), native to China on the coast. These species are also distributed in Korea, Japan, Australia, etc [1,2] (Fig. 1(a–c)). Viticis Fructus is known as "Manjingzi" in China, "Man Hyung Ja" in Korea, "Man keishi" in Japan which is predominantly regarded as a folk remedy. It is used to treat anemopyretic cold, headache, swelling and pain of eyes, tinnitus and deafness, in traditional Chinese medicine (TCM). In the traditional Indian medical system, tribal and local doctors use Viticis Fructus to treat a variety of ailments, including liver disease, tumors, rheumatic pain, inflammation, sprains, fever, and tuberculosis. In Korea, Viticis Fructus was used to treat several allergic diseases and upper respiratory tract infections [3].

Because these plants have long been used to treat various diseases, a series of studies have been conducted on them, and more than 190 chemical components have been isolated from them, including flavonoids, triterpenoids, diterpenoids, iridois, phenolis, and ligans. Among them, flavonoids are considered to be the main bioactive components, most likely responsible for most of the activity of

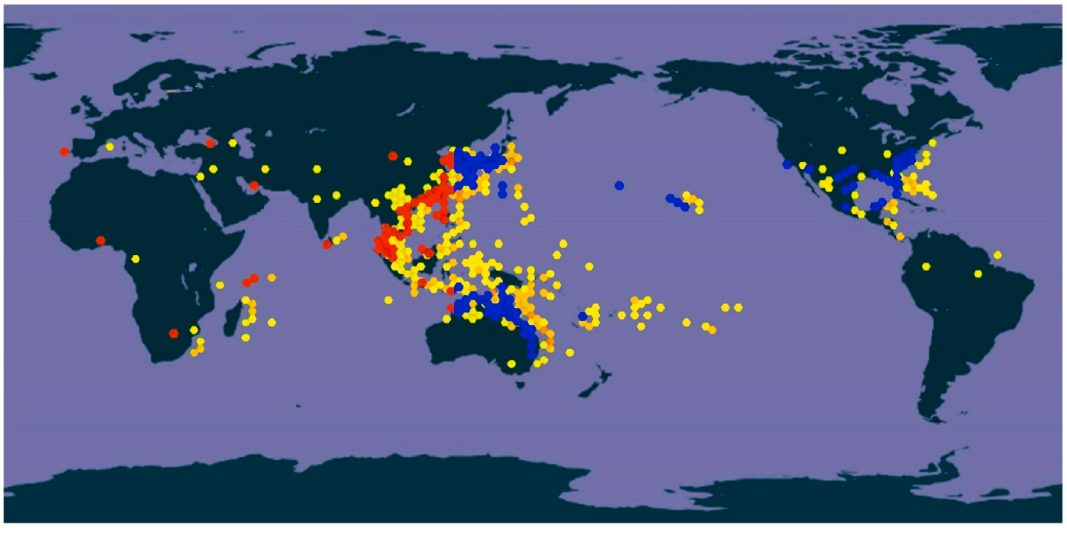

Fig. 1. The picture of Viticis Fructus (a: Viticis Fructus; b: *V. trifolia* subsp. *litoralis*; c: *V. trifolia*;d: the worldwide distribution of Viticis Fructus, red represents *V. trifolia* subsp. *litoralis*, blue represents *V. trifolia*, and yellow indicates the presence of both).

both plants. In addition, in vivo or in vitro experiments have shown that Viticis Fructus extracts have a wide range of pharmacological properties, including the following activities: anti-oxidative activities [4–6], anti-inflammatory activities [7,8], anticancer activities [9], Larvicidal activity [10], hepatoprotective activity [11,12], analgesic activity [13], antibacterial activity [14], antifungal activity [15], anti-feeding activity [15] and so on.

Due to the assorted medical specialty properties and complicated chemical composition of Viticis Fructus, a scientific and

Table 1
Traditional prescriptions containing Viticis Fructus.

Compound Preparation name	Main TCM	Traditional clinical use	References
Qi Wei Ke Teng Zi Wan	*Entada phaseoloides*(L.) Merr.; *Croton tiglium* L.; *Ferula sinkiangensis* K. M. Shen; *Piper nigrum* L.; Viticis Fructus; *V. trifolia*; *Nigella glandulifera* Freyn et Sint.; *Eclipta prostrata* (L.) L.	Dispelling summer heat, harmonizing the middle, relieving spasm and pain. Used for vomiting and diarrhea, abdominal pain, chest tightness, dysthymia, headache and fever.	[2]
Xiong Ju Shang Qing Wan	*Ligusticum sinense 'Chuanxiong'*; *Chrysanthemum morifolium* Ramat.; *Scutellaria baicalensis* Georgi; *Gardenia jasminoides* J. Ellis; Viticis Fructus; *Coptis chinensis* Franch.; *Mentha canadensis* L.; *Forsythia suspensa* (Thunb.) Vahl; *Nepeta cataria* L.; *Hansenia weberbaueriana* (Fedde ex H. Wolff) Pimenov & Kljuykov; *Conioselinum anthriscoides* (H. Boissieu) Pimenov & Kljuykov; *Platycodon grandiflorus* (Jacq.) A. DC.; *Saposhnikovia divaricata* (Turcz.) Schischk.; *Glycyrrhiza uralensis* Fisch.; *Angelica dahurica* (Fisch. ex Hoffm.) Benth. & Hook. f. ex Franch. & Sav.	Clearing heat and relieving symptoms, dispersing wind and relieving pain. Used for the symptoms of external wind, such as bad wind and body heat, migraine headache, runny nose, toothache and sore throat.	[2]
Fu Ke Yang Kun Wan	*Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. & C. A. Mey.; *Glycyrrhiza uralensis* Fisch.; *Ligusticum sinense 'Chuanxiong'*; *Angelica sinensis* (Oliv.) Diels; *Corydalis yanhusuo* (Y. H. Chou & C. C. Hsu) W. T. Wang ex Z. Y. Su & C. Y. Wu; *Scutellaria baicalensis* Georgi; *Curcuma aromatica* Salisb.; *Dolomiaea souliei* (Franch.) C. Shih; *Eucommia ulmoides* Oliv.; *Cyperus rotundus* L.; *Paeonia lactiflora* Pall.; Viticis Fructus; *Amomum villosum* Lour.	Diversifying the liver and Qi, nourishing the blood and invigorating it. Used for irregular menses, amenorrhoea, dysmenorrhea and period headache due to blood weakness and depression of the liver.	[2]
Bo Yun Tui Yi Wan	*Buddleja officinalis* Maxim.; *Tribulus terrestris* L.; *Chrysanthemum morifolium* Ramat.; *Equisetum hyemale* L.; Snake slough; Cicada slough; *Nepeta cataria* L.; Viticis Fructus; *Mentha canadensis* L.; *Angelica sinensis* (Oliv.) Diels; *Ligusticum sinense 'Chuanxiong'*; *Coptis chinensis* Franch.; *Lycium chinense* Mill.; *Zanthoxylum bungeanum* Maxim.; *Broussonetia papyrifera* (L.) L'Hér. ex Vent.; *Trichosanthes kirilowii* Maxim.; *Glycyrrhiza uralensis* Fisch.	Dispersing wind and clearing heat, reducing opacity and brightening the eyes. Used for external obstruction of the eyes due to wind-heat upheaval, blurred vision, hidden pain and tears.	[2]
Huang Lian Shang Qing Pian	*Coptis chinensis* Franch.; *Gardenia jasminoides* J. Ellis; *Forsythia suspensa* (Thunb.) Vahl; Viticis Fructus; *Saposhnikovia divaricata* (Turcz.) Schischk.; *Nepeta cataria* L.; *Angelica dahurica* (Fisch. ex Hoffm.) Benth. & Hook. f. ex Franch. & Sav.; *Scutellaria baicalensis* Georgi; *Chrysanthemum morifolium* Ramat.; *Mentha canadensis* L.; *Rheum palmatum* L.; *Phellodendron chinense* C. K. Schneid.; *Platycodon grandiflorus* (Jacq.) A. DC.; *Ligusticum sinense 'Chuanxiong'*; gypsum; *Inula japonica* Thunb.; *Glycyrrhiza uralensis* Fisch.	Dispersing wind and clearing heat, relieving fire and pain. Used for dizziness and dizziness, violent fire eyes, tooth pain, sore mouth and tongue, sore throat, earache and tinnitus, constipation, short urine and red urine caused by wind-heat attack and heat in the lung and stomach.	[2]
Yi Qi Cong Ming Wan	*Actaea cimicifuga* L.; *Pueraria montana* (Lour.) Merr.; *Phellodendron chinense* C. K. Schneid.; *Paeonia lactiflora* Pall.; Viticis Fructus; *Codonopsis pilosula* (Franch.) Nannf.; *Astragalus membranaceus* var. *mongholicus* (Bunge) P. K. Hsiao; *Glycyrrhiza uralensis* Fisch.	Benefiting Qi, raising Yang, clearing the ears and brightening the eyes. For dimming of vision, deafness and tinnitus.	[2]
Ya Jiao Ha Dun San	*Asparagus officinalis* L.; *Streptocaulon juventas* (Lour.) Merr.; *Benincasa hispida* (Thunb.) Cogn.; *Tacca chantrieri* André; *Duhaldea cappa* (Buch.-Ham. ex DC.) Anderb.; Viticis Fructus	Clearing heat and removing toxins, relieving pain and stopping bleeding. Used for cold and fever, laryngitis, pain in the chest and abdomen, palpitations of false labor, menstrual disorders, postpartum bleeding.	[2]
Zhang Yan Ming Pian	*Acorus calamus* L.; *Senna tora* (L.) Roxb.; *Cistanche deserticola* Ma; *Pueraria montana* var. *lobata* (Ohwi) Maesen & S. M. Almeida; *Celosia argentea* L.; *Codonopsis pilosula* (Franch.) Nannf.; Viticis Fructus; *Lycium chinense* Mill.; *Plantago asiatica* L.; *Paeonia lactiflora* Pall.; *Cornus officinalis* Sieb. & Zucc.; *Glycyrrhiza uralensis* Fisch.; *Cuscuta chinensis* Lam.; *Actaea cimicifuga* L.; *Prinsepia uniflora* Batalin; *Chrysanthemum morifolium* Ramat.; *Buddleja officinalis* Maxim.; *Ligusticum sinense 'Chuanxiong'*; *Polygonatum sibiricum* Redouté; *Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. & C. A. Mey.; *Phellodendron chinense* C. K. Schneid.; *Astragalus membranaceus* var. *mongholicus* (Bunge) P. K. Hsiao	Tonifying the liver and kidney, lightning cataracts and brightening the eyes. For dryness and discomfort, double vision in one eye, lumbar and knee weakness or mild loss of vision caused by deficiency of liver and kidney; for the above symptoms of cataract in early and middle age.	[2]

Table 2
Compounds isolated from Viticis Fructus.

Type	NO.	Chemical component	References
Diterpenes and diterpen glycosides	1	dihydrosolidagenone	[24]
	2	vitetrifolin B	[24]
	3	rotundifuran	[24]
	4	abietatriene 3 b-ol	[24]
	5	ferruginol	[4]
	6	vitetrifolin A	[24]
	7	vitetrifolin C	[24]
	8	previtexilactone	[25]
	9	6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide	[26]
	10	vitexilactone	[26]
	11	viteagnusin I	[27]
	12	vitexifolin E	[28,26]
	13	vitrifolin A	[26]
	14	vitexifolin A	[28]
	15	vitexifolin B	[28]
	16	vitexifolin C	[28]
	17	vitexifolin D	[28]
	18	trisnor-γ-lactone	[28]
	19	isoambreinolide	[28]
	20	13-hydroxy-5(10),14-halimadien-6-one	[6]
	21	vitetrifolin D	[29]
	22	vitetrifolin E	[29]
	23	vitetrifolin F	[29]
	24	vitetrifolinH	[29]
	25	vitetrifolin G	[29]
	26	monoacetate	[29]
	27	9,13-epoxy-16-nor- labda-13E-en-15-al	[27]
	28	13-*epi*-2-oxokolavelool	[27]
	29	isolophanthin A	[27]
	30	vitedoin B	[27]
	31	viteagnusin F	[27]
	32	viteagnusin G	[27]
	33	viterotulin A	[27]
	34	(rel 3S,5S,8R,9R,10S)-3,9-dihydroxy-13(14)- labden-16,15-olide	[27]
	35	viterotulin B	[27]
	36	vitexilactone B	[30]
	37	6α,7α-diacetoxy-13-hydroxy-8(9),14-labdadien	[6]
	38	9-hydroxy-13(14)-labden-16,15-olide	[6]
	39	deacetylvitexilactone	[30]
	40	viteoside A	[4]
	41	(rel 5S,6R,8R,9R,10S,13R,15R)-6-acetoxy-9,13; 15,16-diepoxy- 15-methoxylabdane.	[4]
	42	(rel 5S,6R,8R,9R,10S,13R,15S)-6-acetoxy-9,13; 15,16- diepoxy-15-methoxylabdane	[4]
	43	(rel 5S,6R,8R,9R,10S,13S,15S)-6-acetoxy-9,13; 15,16- diepoxy-15-methoxylabdane	[4]
	44	(rel 5S,6R,8R,9R,10S,13S,15R)-6-acetoxy-9,13; 15,16- diepoxy-15-methoxylabdane	[4]
	45	(rel 5S,6R,8R,9R,10S,13S,15S,16R)-6-acetoxy-9,13; 15,16-diepoxy-15,16-dimethoxylabdane	[4]
	46	(rel 5S,6R,8R,9R,10S,13S,15R,16R)-6-acetoxy-9,13; 15,16-diepoxy-15,16-dimethoxylabdane	[4]
	47	(rel 5S,6R,8R,9R,10S,13S,15S,16S)-6-acetoxy-9,13; 15,16-diepoxy-15,16-dimethoxylabdane	[4]
	48	(rel 5S,6R,8R,9R,10S,13S,15R,16S)-6-acetoxy-9,13; 15,16-diepoxy-15,16-dimethoxylabdane	[4]
	49	(rel 5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)-labden-16,14-olide	[29]
	50	(rel 5S,6S,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide	[29]
	51	(rel 5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-15- methoxy-13(14)-labdan-16,15-olide	[29]
	52	(rel 5S,6R,8R,9R,10S,13R,16S)-6-acetoxy-9,13-epoxy-16-methoxy-labdan-15,16-olide	[29]
	53	(rel 5S,6R,8R,9R,10S,13R)-6-acetoxy-9,13-epoxy-15-methoxy-labdan- 16,15-olide	[29]
	54	(rel 5S,6R,8R,9R,10S,13S,16S)-6-acetoxy-9,13-epoxy-16-methoxy-labdan-15,16-olide	[29]
	55	(rel 5S,6R,8R,9R,10S,13S)-6-acetoxy-9,13-epoxy-15-methoxy-labdan- 16,15-olide	[29]
	56	(rel 5S,8R,9R,10S,13S,15S,16R)-9,13; 15,16-diepoxy-15,16-dimethoxy-labdane	[29]
	57	(rel 5S,8R,9R,10S,13S,15R,16S)-9,13; 15,16-diepoxy-15,16- dimethoxylabdane	[29]
	58	(rel 5S,8R,9R,10S,13S,15R,16R)-9,13; 15,16-diepoxy-15,16- dimethoxylabdane	[29]
	59	(rel 5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)- labden-16,15-olide	[31]
	60	vitetrifolin I	[32]
	61	vitextrifolin A	[30]
	62	vitextrifolin B	[30]
	63	vitextrifolin C	[30]
	64	vitextrifolin D	[30]
	65	vitextrifolin E	[30]
	66	vitextrifolin F	[30]
	67	vitextrifolin G	[30]
	68	negundol	[30]

(*continued on next page*)

Table 2 (*continued*)

Type	NO.	Chemical component	References
	69	chastol	[33]
	70	epichastol	[33]
	71	vitextrifloxide A	[34]
	72	vitextrifloxide B	[34]
	73	prevetexilactone	[34]
	74	vitextrifloxide C	[34]
	75	vitextrifloxide D	[34]
	76	vitextrifloxide E	[34]
	77	vitextrifloxide F	[34]
	78	vitextrifloxide G	[34]
	79	vitextrifloxide H	[34]
	80	vitexfolin B	[34]
	81	vitextrifloxide I	[34]
	82	viterofolin A	[35]
	83	viterofolin B	[35]
	84	viterofolin C	[35]
	85	viterofolin D	[35]
	86	viterofolin E	[35]
	87	viterofolin F	[35]
	88	viterofolin G	[35]
	89	viterofolin H	[35]
	90	(3*S*,5*S*,6*S*,8*R*,9*R*,10*S*)-3,6,9-trihydroxy-13(14)-labdean-16,15-olide 3-*O*-β-D-glucopyranoside	[36]
	91	viteagnuside A	[29,36]
	92	viterotulin C	[37]
	93	vitexilactone D	[37]
	94	vitetrolins A	[38]
	95	vitetrolins B	[38]
	96	vitetrolins C	[38]
	97	vitetrolins D	[38]
	98	abietane 9 (11):12 (13) -di-a-epoxide	[24]
	99	(4aS,4bR,5aR,6S,7R,8aS,10aS)-7-isopropyl-6-methoxy-1,1,4a-trimethyldodecahydro-1H-phenanthro [4,4a-b]oxiren-7-ol	[24]
	100	ent-2R,15,16,19-tetrahydroxypimar-8(14)-ene	[24]
	101	abieta-9 (11),12-diene	[24]
	102	(E)-2-((2R,2′R,4a′S,8a′S)-2′,5′,5′,8a′-tetramethyldecahydro-2′H,5H-spiro[furan-2,1′-naphthalen]-5 ylidene)acetaldehyde	[26]
	103	(Z)-2-hydroxy-2-((2R,2′R,4a′S,8a′S)-2′,5′,5′,8a′-tetramethyldecahydro-2′H,5H-spiro[furan-2,1′-naphthalen]-5-ylidene)acetic acid	[26]
	104	(2R,2′R,4′R,4a′S,8a′S,E)-2′,5′,5′,8a′-tetramethyl-5-(2-oxoethylidene)decahydro-2′H,3H-spiro[furan-2,1′-naphthalen]-4′-yl acetate	[26]
Triterpenes	105	α-amyrin	[6]
	106	uvaol	[39]
	107	3-*epi*-ursolic acid	[39]
	108	2α,3β,24-trihydroxyolean-12-en-28-oic acid	[39]
	109	2α,3α,24-trihydroxyurs-12-en-28-oic acid	[39]
	110	2α,3α,24-trihydroxyolean-12-en-28-oic acid	[39]
	111	2α,3α,24-trihydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranosyl ester	[39]
	112	ursolic acid	[6]
	113	3β-acetyloxy-12-en-28-ursolic acid	[40]
	114	oleanolic acid	[41]
	115	3*β*-hydroxy-30-al-urs-12-en-28-oic acid	[42]
Flavones and flavone glycosides	116	vitexin	[6]
	117	persicogenin	[31]
	118	luteolin	[43]
	119	vitexicarpin	[43]
	120	artemetin	[28]
	121	casticin	[28]
	122	centaureidin	[28]
	123	chrysosplenol-D	[31]
	124	2′,3′,5-trihydroxy-3,6,7-trimethoxyflavone	[9]
	125	penduletin	[31]
	126	taxifolin	[4]
	127	emodin	[41]
	128	chrysophanol	[41]
	129	physcion	[41]
	130	5,5′-dihydroxy-4′,6,7-trimethoxyflavanone	[43]
	131	agestricin D	[44]
	132	oroxylin A	[45]
	133	kaempferol	[46]
	134	quercetin	[46]

(*continued on next page*)

Table 2 (*continued*)

Type	NO.	Chemical component	References
Iridoids	135	rotundial	[47]
	136	negundoside	[48]
	137	agnuside	[48]
	138	6′-ρ-hydroxy benzoyl mussaenosidic acid	[48]
	139	viteoids I	[4]
	140	viteoids II	[4]
	141	eucommiol	[4]
	142	iridolactone	[4]
	143	pedicularislactone	[4]
	144	vr-i	[4]
	145	1-oxo-eucommiol	[4]
	146	mussaenosidic acid	[6]
	147	(1S, 5S,6R,9R)-10-*O*-p-hydroxybenzoyl-5,6β-dihydroxy iridoid 1-*O*-β-D-glucopyranoside	[36]
	148	nishindaside	[36]
	149	3-normal-butyl-nishindaside	[36]
	150	3-normal-butyl-isonishindaside	[36]
Lignans and lignan glycosides	151	detet rahydroconidendrin	[41]
	152	vitedoamine A	[41]
	153	vitrofolal A	[49]
	154	vitrofolal B	[49]
	155	vitrofolal C	[49]
	156	vitrofolal D	[49]
	157	vitrofolal E	[49]
	158	vitrofolal F	[49]
	159	4-(3,4-dimethoxyphenyl)-6-hydroxy-5-methoxynaphtho [2,3-c]furan-1(3H)-one	[49]
	160	4-(3,4-dimethoxyphenyl)-6-hydroxy-7-methoxynaphtho [2,3-c]furan-1(3H)-one	[49]
	161	6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-7-methoxynaphtho [2,3-c]furan-1(3H)-one	[49]
	162	vitrifol A	[50]
	163	(+)-lariciresinol	[27]
	164	fiscusesquilignan A	[27]
	165	viterolignan A	[27]
	166	viterolignan B	[27]
Phenolics and phenolic glycosides	167	vanillic acid	[4]
	168	*threo*-guaiacyl glycerol	[4]
	169	*erythro*-guaiacyl glycerol	[4]
	170	dihydrodehydrodiconiferyl alcohol	[4]
	171	dihydrodehydrodiconiferyl alcohol-9- O-ρ-D-glucoside	[4]
	172	dihydrodehydrodiconiferyl alcohol-(4–8)-*erythro*-guaiacyl glycerol ether	[4]
	173	4-hydroxybenzoic acid methyl ester	[43]
	174	vanillic acid methyl ester	[43]
	175	4-hydroxy benzaldehyde	[43]
	176	4-hydroxy benzoic acid	[43]
	177	ferulic acid	[43]
	178	vitexfolin A	[13]
	179	vitexfolin B	[13]
	180	ρ-methoxy benzoic acid	[6]
	181	2-hydroxy,3- methoxy benzoic acid	[6]
	182	2,3-dihydroxy benzoic acid	[6]
	183	3,4-dihydroxybenzoic acid	[41]
	184	4-hydroxy-3-methoxybenzoic acid	[41]
	185	caffeic acid	[41]
	186	protocatechuic acid	[46]
	187	coniferylaldehyde	[46]
	188	ficusa	[27]
Steroids and glycosides	189	β-rosaterol palmitate	[39]
	190	β-sitosterol	[39]
	191	β-daucosterol	[39]

significant analysis of future analysis directions during this field and its applications is critical for Viticis Fructus. Therefore, the manuscript is concentrated on finding out the standard medical uses of Viticis Fructus, exploring its basal plant species, and summarizing its bioactive components as well as its pharmacological effects.

The present review aims to provide a critical and updated review of Viticis Fructus with regard to its traditional use, phytochemistry and pharmacology means to support the further research and therapeutic potential of this folk medicine.

2. Botanical description

V. *trifolia* subsp. *litoralis* is perennial shrubs, prostrate to creeping, rooting at nodes; branchlets silky tomentose when young. Leaves mostly 1 (−3)-foliolate, sessile or short petiolate; blade obovate-spatulate, ovate-elliptic, broadly oblong-elliptic, or circular, 2.5–5

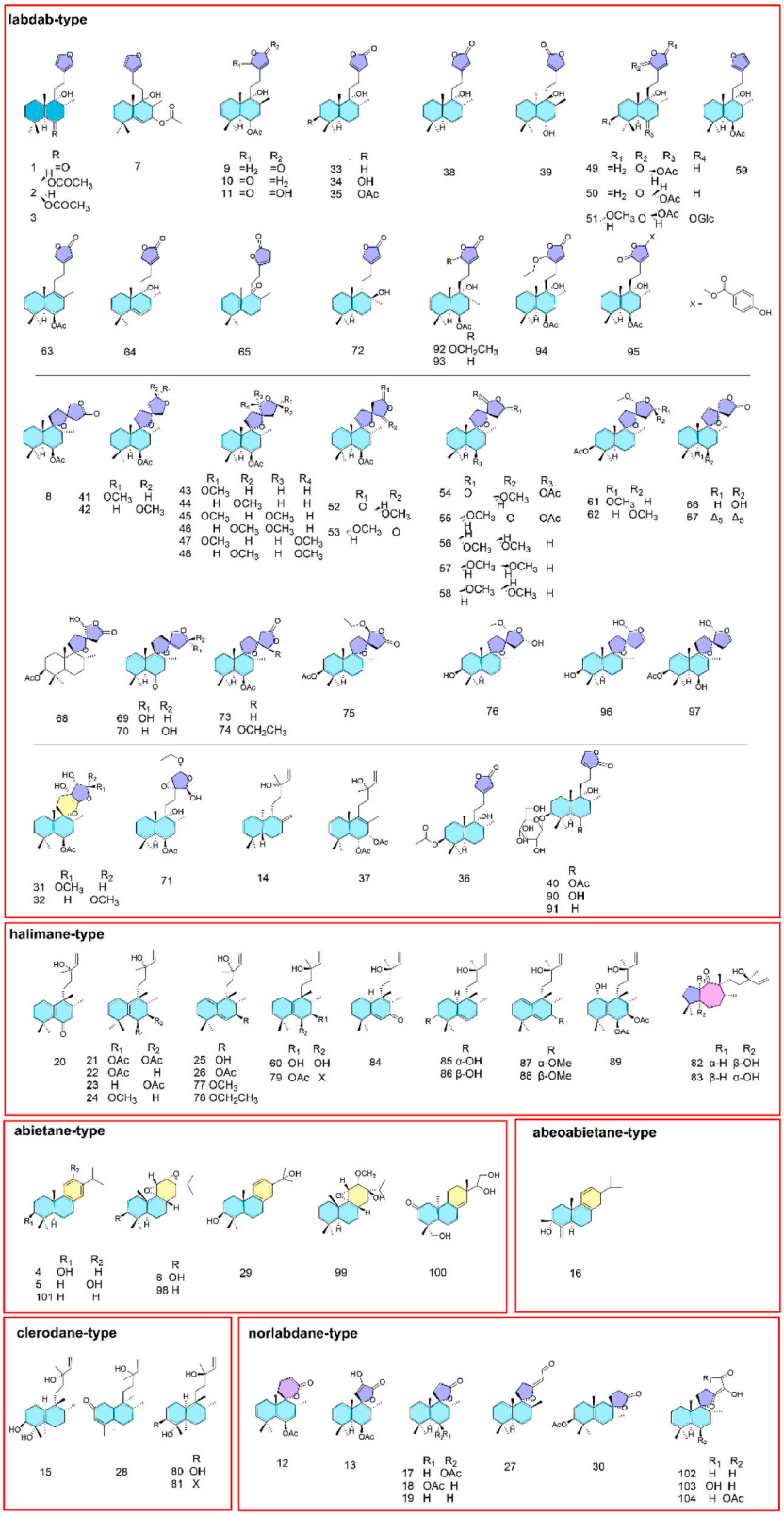

Fig.2 Diterpenes produced by Viticis Fructus

(caption on next page)

Fig. 2. Diterpenes produced by Viticis Fructus.

× 1.5–3 cm, abaxially velvety to minutely silky tomentose, adaxially usually pale dull green and pubescent, base attenuate to rounded, margin entire, apex abruptly subacuminate to rounded. Inflorescences terminal thyrses, 3–10 × 1–2.5 cm. Calyx cup-shaped, 4–5 mm, slightly 2-lipped, 5-denticulate, outside minutely silky tomentose and glandular, inside glabrous. Corolla purplish mauve to lilac blue, salverform, outside minutely silky tomentose and glandular, villous in tube and inside on lower half of large anterior lobe of lower lip. Stamens and style exserted. Ovary globose, glabrous, densely glandular. The plants flowers in month of July to September, and it produces the fruits in the month of September to November. The herb grows on the open sandy areas, usually distributed along the Chinese coastline from high latitude to low latitude, as well as in Japan, SE Asia, Pacific Islands [1].

V. *trifolia* is shrubs or small trees, 1.5–5 m tall, erect. Branchlets densely pubescent. Leaves 1–3(-5)-foliolate; petiole 1–3 cm; leaflets sessile, oblong, lanceolate, or obovate, abaxially densely gray tomentose, adaxially green and glabrous or subglabrous, base cuneate, margin entire, apex obtuse, veins circa 8 pairs and slightly prominent on both surfaces; central or single leaflet 2.5–9 × 1.7–3 cm. Panicles 3–15 cm; peduncle densely gray tomentose. Calyx slightly 5-dentate, outside gray pubescent, inside glabrous. Corolla purplish to bluish purple, 6–10 mm, outside scaly white, pubescent at filament bases and on inside of lower lobe. Stamens exserted. Ovary glabrous, with or without glands. Style glabrous. The plant flowers in the month of April to August, and it produces the fruits in the month of August to November [1].

The herb grows in Fujian, Guangdong, Hainan, Yunnan, Guangxi, etc., and also grows in S and SE Asia, Australia, Pacific Islands. The distribution of these two plants is very similar, as shown in Fig. 1(d) [16]. However, the classification of two plant sources of Vitex Fructus has always been controversial. In the 2020 edition of the Pharmacopoeia of the People's Republic of China, *V. trifolia*

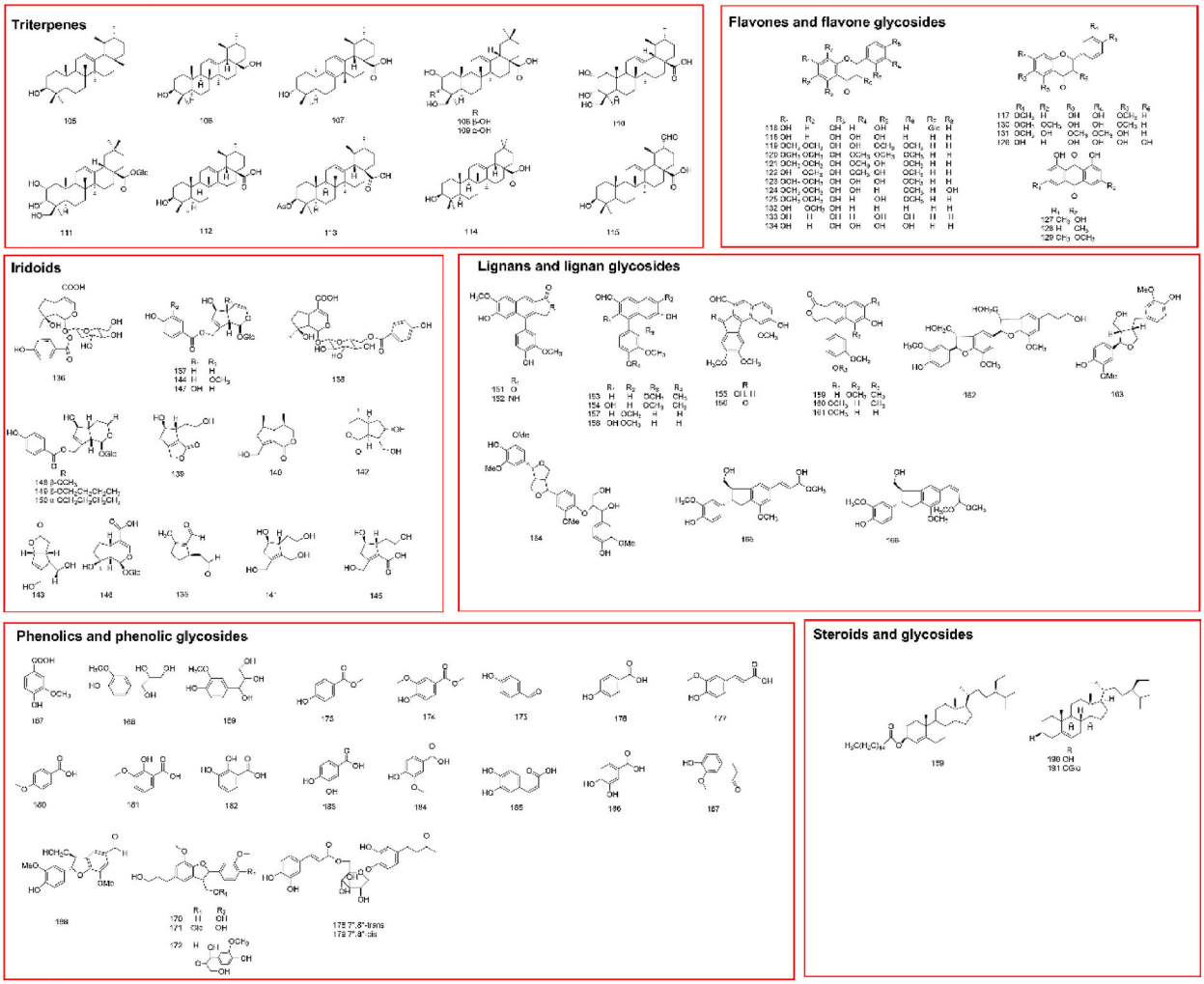

Fig. 3. Triterpenes, flavones, iridoids, lignans, phenolics and sterodis produced by Viticis Fructus.

Table 3
Pharmacological activities of natural products from Viticis Fructus.

pharmacological activity	extracts/compounds	types	model	dose range	Activity concentration	effect	Reference
Anti-allergic activity	Aqueous extract	in vivo	The original stock of male Wistar rats	0.001–1.0 g/kg	1.0 g/kg	Inhibited sysivitytemic allergic reaction	[3]
	Aqueous extract	in vitro	TNF-α	0.01–10 mg/ml	0.01 mg/ml	Inhibited TNF-α production	[3]
	Alcoholic extracts	in vitro	RBL-2H3 cells	0.5 mg/ml		Inhibited histamine release	[51]
Anti-angiogeneic activity	5,3′-Dihydroxy-6,7,5′-trimethoxyflavanon	in vitro	Human umbilical vascular endothelial cells	0.5,2Mm		Inhibited tube formation and endothelial cells migration	[25]
	Vitexicarpin	in vitro	Human umbilical vascular endothelial cells	0.1,1,2.5,5 μM	5 μM	Inhibited endothelial cell proliferation and migration	[54]
Antibacterial activity	Petroleum ether and Ethanol extracts	in vitro	Gram-positive and Gram-negative bacteria	500 μg/disc 400 μg/disc		Inhibited both gram-positive and gram-negative bacteria	[14]
	VitrofolalB, VitrofolalD, Detetrahydroconidendrin	in vitro	Methicillin-resistant *Staphylococcus aureus* methicillin-sensitive *S. aureus*	64 μg/ml		Inhibited eight out of 18 strains of MRSA inactive against MSSA	[49]
	Methanol extracts	in vitro	Five strains of Gram-positive and seven strains of Gram-negative human pathogenic bacterial strains	8000.0, 4000.0, 2000.0, 1000.0, 500.0, 250.0and 62.5 μg/ml	125.0 μg/ml	Inhibited both gram-positive and gram-negative bacteria	[52]
	Hexanic extract	in vitro	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, Shigella sonei, Proteusmirabilis, *Salmonella typhi*, and Candida albicans	10, 5,2.5, and 1.25 mg/ml	10 mg/ml	Inhibited the growth of Gram-positive and Gram-negative bacteria	[15]
	Petroleum ether, Chloroform, Methanol and Hot Water extracts	in vitro	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, Streptococcus pyogenes and *Klebsiella pneumoniae*	100 mg/ml, 50 mg/ml, 25 mg/ml		Inhibited the tested pathogenic bacteria	[53]
Anticancer activity	Vitexicarpin	in vitro	K562 cells	1.0 μg/ml	1.0 μg/ml	Induced apoptosis on human myeloid leukemia K562 cells	[89]
	Vitexilactone,(rel 5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)- Labden-16,15-olide,rotundifuran, Vitetrifolin D, Vitetrifolin E	in vitro	tsFT210 cells	100 μg/ml		Induced apoptosis of the tsFT210 cells	[89]
	Vitexicarpin	in vitro	Human prostate cancer PC-3 cells	0–200 μM	200 μM	Inhibited proliferation of the PC-3 cells	[55]
	Total flavonoids	in vitro	NCI–H446 cells	0.5、1.0、2.0 μg/ml		Significantly reduce the volume of a sphere of lung cancer	[56]
	Flavone extract	in vivo	The mice of Kunming species	400 mg/kg、200 mg/kg、100 mg/kg	400 mg/kg	Inhibited both Sarcoma 180 and Hepatoma 22	[57]
	2′,3′,5-trihydroxy-3,6,7-trimethoxyflavone Vitexicarpin Artemetin	in vitro	HL-60 cells			Inhibited the proliferation of HL-60 cells	[9]
	Ethanol extract	in vitro	HCT 116 and A549 cells	20, 40, 60 and 80 μg/ml		Reducedtheproliferation of the HCT 116 and A549 cancer cell lines	[58]
	Casticin	in vitro	HT-29, HCT-116, SW480 and Caco-2 cells	0,5,10,20 μmol/l	10 μmol/l	Inhibited the proliferation colon cancer cell	[59]
	5,3′-Dihydroxy-6,7,4′-trimethoxyflavanon	in vitro	H522, H23, H226 human lung cancer cells and IMR-90 cells	0.1,0.5,1,2 μM	1 μM	Inhibited the viability of lung cancer cells	[25]

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Table 3 (*continued*)

pharmacological activity	extracts/compounds	types	model	dose range	Activity concentration	effect	Reference
Anti-feeding activity	Hexane and DCM extract	in vitro	Spodoptera frugiperda	10, 100and 1000 μg/ml	1000 μg/ml	Larvae of S. frugiperda were weighed loss	[15]
	Ether extract	in vitro	Spodoptera *litura* F.	10, 5, 2.5, and 1% concentrations		Against Spodoptera *litura* F.	[66]
Anti-hyperprolactinemia activity	Ethanol extract	in vivo	Female ICR mice	25 mg/kg 50 mg/kg	50 mg/kg	Decreased the serum prolactin level	[67]
	Casticin	in vitro	Primary pituitary cells were	0.1, 1, and 10 μmol/l		Inhibited prolactin release from E2-stimulated pituitary cells	[68]
	Casticin	in vivo	Female Sprague Dawley (SD) rats	10, 20, and 40 mg/kg		Pituitary cell proliferation	[68]
Anti-inflammatory activity	Aqueous extract	in vitro	RAW 264.7 cells	0, 25, 250, 2500 and 5000 μg/ml	2500 μg/ml	Reduced the LPS-dependant induction of IL-1β, IL-6 and iNOS mRNA	[7]
	Vitex trifolia subsp. litoralis extract	in vitro	A549 cells	0.1, 1, or 10 μg/ml	1 μg/ml	Inhibited Eosinophil Migration	[90]
	Casticin	in vitro	A549 cells	0.001, 0.01, 0.1, 1, and 10 μg/ml		Ihhibited the eosinophil migration	[8]
	Vitexicarpin	in vitro	Human umbilical vein endothelial cells (HUVEC)	1–1000 nM		Inhibited the ROS–NF-κB pathway	[91]
	Aqueous extract	in vitro	RAW 264.7 cells	250,2500,5000 mg/ml	5000 mg/ml	Inhibited the expression of various LPS-induced inflammatory genes in RAW 264.7 cells	[69]
	VR-extract/aqueous extract	in vivo	Male BALB/c mice	100 mg kg–1		Inhibited eosinophilia	[92]
	Viteagnusin I , Vitetrifolin D , Viteagnusin F , Casticin , VitetrifolinH , Viterotulin A , Viterolignan A	in vitro	RAW264.7 cells	11.3–24.5 μM		Inhibited nitric oxide production in RAW264.7 cells	[27]
	Casticin	in vivo	Female C57BL/6 mice	1,2, and10 mg/kg		Decreased numbers of total and inflammatory cells	[73]
	Casticin	in vitro	RAW264.7 cells	0.3–10 μM		Inhibit the inflammatory response	[75]
	Casticin	in vivo	Male ICR mice	5,10,20 mg/kg		Inhibited the acetic acid-induced increased vascular permeability	[70]
	Extract from leaves of V. trifolia L.	in vivo	CA-induced rat paw edema model	100–200 mg/kg		Inhibited the paw edema induced by CA ($p < 0.05$) and effectively reduced the inflammatory leukocyte infiltration	[93]
Antioxidant activity	Methanol extract	in vitro	DPPH radical	1 ml		Inhibited DPPH	[4]
	Aqueous extract	in vitro	DPPH radical	0.0025, 0.025, 0.25 and 2.5 g/l		Inhibited DPPH	[5]
	Negundoside, agnuside and 6′-p-hydroxy benzoyl mussaenosidic acid	in vitro	DPPH radical	9.96, 9.81 and 10.31 μg		Inhibited DPPH	[48]
	Methanol extract	in vitro	Ferric thiocyanate method	0.05 ml			[4]
	Ferruginol	in vitro	DPPH radical	1 ml		Inhibited DPPH	[24]
	Essential Oil	in vitro	DPPH radical	0.05–20 mg/ml		Inhibited DPPH	[94]

(*continued on next page*)

Table 3 (*continued*)

pharmacological activity	extracts/compounds	types	model	dose range	Activity concentration	effect	Reference
Anti-proliferative activity	Persicogenin, artemetin, luteolin, penduletin, vitexicarpin and chrysosplenol-D,	in vitro	tsFT210 cells	various concentrations		Inhibited the proliferation of tsFT210 cells	[31]
	vitetrifolin H vitetrifolin I and vitexoid	in vitro	Hela cells	4–28 μM		Inhibited the proliferation of Hela cells	[32]
	Vitexicarpin	in vitro	Spleens cell of male C57BL/6 mice			Inhibited activity on T-and B-cell proliferation	[64]
Larvicidal activity	Fatty acid methyl ester extracts	in vitro	*Culex quinquefasciatus*	50, 25, 12.5, 6.25 and 3.125 ppm		Increased the larval mortality of *C. quinquefasciatus*	[76]
	Methyl-p-hydroxybenzoate	in vitro	*Culex quinquefasciatus/Aedes aegypti*	20, 10, 5, 2.5 and 1.25 ppm	20 ppm	Against *C. quinquefasciatus* and *Ae. aegypti.*	[77]
	Acetone and methanol extracts	in vitro	*Anopheles gambiae* Giles	25, 50, 100, 250 and 500 ppm		Led to retardation and 100% mortality	[10]
	Essential oils were extracted by steam distillation	in vitro	*Aedes aegypti*	50, 75, 100, and 125 ppm		LC50 and LC90 For V. trifolia against *Ae. aegypti* and *C. quinquefasciatus* were 57.7 + 0.4, 77.9 + 0.9 ppm and 55.17 + 3.14, 78.28 + 2.23 ppm	[78]
Hepatoprotective activity	Aqueous and ethanol extracts	in vivo	Male Wistar rats	20 and 30 mg/kg/day		Increase in the levels of total bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase	[79]
	Ethanol extract	in vivo	Male Wister rats	200 mg/kg/day	200 mg/kg	Reduced the elevated levels of SGPT, SGOT, ALP, bilirubin and GGTP	[11]
Estrogenic activity	Volatile	in vitro	MCF-7 cells	5 mg/l to 500 mg/l	50 mg/l	Stimulation of MCF-7 cell proliferation	[67]
	Ethanol extract	in vitro	MCF-7 cells	200 mg ml−1	200 mg ml−1	Stimulate the proliferation of MCF-7 cells	[67]
Cytotoxic activity	Hexane and DCM extract	in vitro	Carcinoma(SQC-1 UISO), ovarian cancer(OVCAR-5), colon carcinoma (HCT-15 COLADCAR), humannasopharyngeal carcinoma (KB)cells	1, 10, 100 μg/ml		Hexanic and DCM extracts have shown interesting ED50 values	[15]
	Ethanol extract	in vitro	HepG2 cells	50、25、12.5、6.25、3.125 μmol/l		Inhibited the HepG2 cells	[56]
Cell cycle inhibitory activitie	Persicogenin, artemetin, luteolin, penduletin, vitexicarpin	in vitro	tsFT210 cells	100, 25, 6.25, 50, and 1.0 μg/ml		Accumulated at theG2/Mphase decreased	[89]
	Vitetrifolin I	in vitro	Hela cells	5, 10, 25, and 50 μM		Accumulatied the cells in the G0/G1 phase	[32]
Other activities							
Aldose reductase activity	Ether extract	in vitro	Enzyme reactions	100 μl		Inhibited the enzyme activity	[81]
Analgesic activity	Vitexfolin A,agnuside,10-*O*-vanilloylaucubin, dihydrodehydrodiconiferylalcohol-β-D (2′-O-P-hydroxybenzoyl) glucoside	in vivo	Acetic acid-induced writhing method in mice	15,50,25 and 50 mg/kg	15,50,25 and 50 mg/kg	Inhibited the writhing symptoms	[13]
antiamnesic activity	Aqueous extract	in vivo	Wistar albino rats	10 mg/kg, 20 mg/kg	20 mg/kg	Improved in memory retention	[82]

(*continued on next page*)

Table 3 (*continued*)

pharmacological activity	extracts/compounds	types	model	dose range	Activity concentration	effect	Reference
antiasthmatic activity	1H,8H-Pyrano [3,4-c]pyran-1,8-dione (PPY)	in vitro	A549 cells	0.1,1,10 μg/ml	10 μg/ml	Decreased eotaxin secretion and suppression of eosinophil migration	[83]
Antifungal activity	Hexane and DCM extract	in vitro	Penicillium sp., Aspergillus flavus, A. parasiticus, Trichoderma sp. and Fusarium sp.			Inhibited the growth of *Fusarium* sp.	[15]
Anti-mitotic activity	Casticin	in vitro	KB cells, A431 cells	0.6 mM		Inhibited the growth of KB cells	[84]
Anti-nociceptive activity	Ethanol extract	in vivo	Female ICR mice	25 mg/kg 50 mg/kg	50 mg/kg	Inhibited the writhing symptoms	[67]
HIV-1 reverse transcriptase inhibition activity	80% ethanol extracts/aqueous extract	in vitro	HIV-1 reverse transcriptase	200 μg/ml	200 μg/ml	Inhibited HIV-1 reverse transcriptase	[85]
Insect growth regulatory activity	Essential oils	in vitro	*Spilosoma obliqua*	0.5, 1.0, 1.5, 2.0 and 2.5 μl	2.5 μl	Increase the larval mortality and larval duration of *S. obliqua*	[86]
Mosquito repelling activity	CHCI3 extract	in vitro	*Aedes aegypti*				[47]
NO inhibition activity	Aqueous extract	in vitro	RAW 264.7 cells	0.0025, 0.025, 0.25 and 2.5 g/l	2.5 g/l	Inhibited NO production	[5]
Plant growth activity	4-hydroxybenzoic acid, ferulic acid, vanillic acid	in vitro	Lettuce seedlings	10^{-3} M		Inhibited the root growth	[43]
Tracheospasmolytic activity	ViteosinA, vitexcarpin	in vivo	Sensitized male guinea pigs	1.3×10^{-4} M	1.3×10^{-4} M	Inhibited the tracheal contraction	[87]
Wound healing activity	Ethanol extract	in vivo	Swiss Wistar strain rats	20 mg/ml		Promoted the epithelialization of the wound area/increased the skin breaking strength	[79]

subsp. *litoralis* is considered as a variant of *V. trifolia*. In the newly published Flora of China, *V. trifolia* subsp. *litoralis* is identified as *V. rotundifolia* L. f., which is an independent species of Vitex, because it can be identified by its usually simple leaves.

3. Traditional use in TCM

Viticis Fructus has an ancient history as a medicine in Asian countries, particularly in China, and is universally used as herbal medicine in the herbal books of ancient times and in the Pharmacopoeia of the People's Republic of China [2]. According to the theory of TCM, it can drain the wind heat and clear the leader. According to the application of classical prescription *XiangSuS*an , Viticis Fructus has been used to treat cold, invigorating qi for strengthening superficies, and right evil spirits by ingesting it orally [17]. In the TCM theory, Viticis Fructus is also used to treat dizziness, headaches, swelling and pain of eye and tinnitus and deafness. Many studies support the use of headache, migraine and vertigo. In the clinic practice of TCM, it is reported to treat senile cataract, gastritis, acute mastitis and habitual constipation [18]. Traditionally, the treatments of various kinds of pain with headache as the main treatment of the Viticis Fructus. The clinical treatment is usually used Viticis Fructus to treat nasitis, supra-orbital neuralgia [19], vascular headache [20] , migraine, douloureux tic [21], sciatica [22], nerve root type cervical vertigo, brain disease [23].

Viticis Fructus is commonly used in herbal formulations in TCM. There are many prescriptions containing Viticis Fructus with a wide range of pharmacological effects, and these have good therapeutic effects. We have collected traditional prescriptions for the application of Viticis Fructus, which are shown in Table 1.

4. Phytochemisty

In addition to the Viticis Fructus, the chemical constituents of *V. trifolia* subsp. *litoralis* and *V. trifolia* have been investigated in this review. Up to date, more than 190 compounds including diterpenes (104), triterpenes (11), flavonoids (19), iridoids (16), lignans (16), phenolics (22), steroids (3) etc. representing a wide spectrum of secondary metabolite classes, have been isolated and identified from *V. trifolia* subsp. *litoralis* and *V. trifolia*. The phytochemical investigations of both species showed that terpenes and flavonoids are their main metabolites. Table 2, Fig. 2 and Fig. 3 show the name and structures of the isolated compounds.

The *V. trifolia* subsp. *litoralis* and *V. trifolia* are rich in diterpenes, the types of diterpenes including Ladane-Type (**62**) [24,27–29], Halimane-Type (**19**) [6,29,27], Abietane-Type (**8**) [24], Norlabdane-Type (**10**) [28], Abeoabietane-Type (**1**) [28], Clerodane-Type (**4**) [28]. Besides the diterpenes, a range of terpenoids, steroides, lignans, flavonids, iridoids, phenolics and other type of compounds have been reported from these two species.

5. Pharmacological properties

5.1. Anti-allergic activity

To evaluate the antiallergic activity of the aqueous extract of Viticis Fructus, a model of anaphylaxis induced by compound 48/80 was used. The aqueous extract of *V. trifolia* subsp. *litoralis* fruit (VRFE) inhibited systemic allergic reactions induced by compound 48/80 at (10^{-4}-1.0 g/kg) doses. When VRFE was used in the whole-body allergic reaction test, histamine levels in plasma were reduced in a dose dependent way. VRFE ($5 \times 10^{-1}$and 1.0 g/kg) inhibited passive skin allergic reactions activated by anti-dinitrophenyl (DNP) IgE. VRFE (10^{-3}-1.0 mg/ml) also inhibited in a dose dependent manner compound 48/80 or anti-DNP IgE release of histamine from rat peritoneal mast cells (RPMC). In addition, VRFE (10^{-3} mg/ml) significantly inhibited the production of tumor necrosis factor-α from anti-DNP IgE-induced RPMC. These results indicate that VRFE may be useful in regulating an immediate type of allergic reactions [3].

Alcoholic extracts of *V. trifolia* leaves were shown to inhibit the IgE-dependent release of histamine from RBL-2H3 cells [51].

5.2. Antibacterial activity

Anti-bacterial activity of leaves of *V. trifolia* has been studied. Petrol extract (500 μg/disc) and EtOH extract (400 μg/disc) showed moderate activity against the majority of Gram-positive and Gram-negative bacteria tested [14]. Anti-bacterial activity was studied in vitro by using18 strains of methicillin-resistant *Staphylococcus aureus* (MRSA) andsix strains of methicillin-sensitive *S. aureus* (MSSA) with agar disk diffusion test, and the test showed that none of the compounds had effective activity against MSSA. However, in similar screening against MRSA, vitrofolal B, vitrofolal D and detetrahydroconidendrin showed anti-bacterial effect against eight out of 18 strains. The minimum inhibitory concentration (MIC) of these components was identified as less than 64 μg/ml [49]. Recent results have shown that methanolic extracts of the leaves of *V. trifolia* exhibit significant antibacterial activity against five Gram-positive strains and seven Gram-negative strains of human pathogenic bacteria [52]. In order to determine the fungicidal activity of the plant extracts, five fungi were tested: *Penicillium* sp., *Aspergillus flavus*, *A. parasiticus*, *Trichoderma* sp. and *Fusarium* sp. The results showed that hexanic leaf extract inhibited 100% of *Fusarium* sp. in 2 days of growth [15]. Different concentrations of crude extracts of *V. trifolia* (100 mg/ml, 50 mg/ml, 25 mg/ml) were used to test against selected bacterial pathogens namely *Pseudomonas aeruginosa*, *Staphylococcus aureus*, Streptococcus pyogenes and *Klebsiella pneumoniae*. In vitro antimicrobial studies showed significant areas of suppression against the pathogenic bacteria tested [53].

5.3. Anticancer activity

5.3.1. Anti-angiogeneic activity

5,3′-Dihydroxy-6,7,4′-trimethoxyflavanone (DHTMF) is one of the ingredients of *V. trifolia* subsp. *litoralis*. It inhibits vasculogenesis and induces apoptosis via the Akt/mTOR pathway, and may induce pharmacological effects beneficial for the therapy of lung cancer [25]. Vitexicarpin (VIT) was isolated from the fruits of *V. trifolia* subsp. *litoralis* showing anti-angiogenic effects, and the results validate that VIT can be used as a novel angiogenesis inhibitor [54].

5.3.2. Anti-proliferative activity

Viticis Fructus considered as active antitumor candidate to inhibit cancer cells growth, such asK562 cells [31], tsFT210 cells [31], Human prostate cancer PC-3 cells [55], NCI–H446 cells [56], HL-60 cells [9]. Correlations among the pharmacological properties of Viticis Fructus and the active components indicated that flavonoids were the main bioactive components. For instance, vitexicarpin isolated from Viticis Fructus can induce caspase-mediated cell death in tsFT210 and K562 cells [31], and also can inhibit proliferation of the human adenocarcinoma PC-3 and HL-60 cells [55], persicogenin, artemetin, luteolin, penduletin and chrysosplenol-D from *V. trifolia* effectively evoked caspase-mediated cell death in tsFT210 and K562 cells [31]. Vitexilactone, (rel 5S,6R,8R, 10S)-6-acetoxy-9-hydroxy-13(14)-Labden-16,15-olide, rotundifuran, vitetrifolin D, and vitetrifolin E, significantly induced apoptosis in tsFT210 and K562 cells at higher concentrations (100 μg/ml) [31]. The studies also found that flavone extract can significantly reduce the volume of lung cancer and inhibited the function of both Sarcoma 180 cells and Hepatoma 22 cells [57].

2′,3′,5-trihydroxy-3,6,7-trimethoxyflavone and artemetin of *V. trifolia* subsp. *litoralis* decreased the proliferative activities in a dose-dependent manner in HL-60 cells with IC_{50} of 4.03 μM and 30.98 μM, respectively [9]. Anti-carcinogenic potential of ethanolic extracts of *V. trifolia* has been studied. Rat liver microsome degranulation is a short-term technology that has been used to detect potential chemical carcinogens in vitro, and the results showed that *V. trifolia* protected liver microsomes from attack by degranulation of the carcinogen EB, showing a significant decrease in proliferation of HCT-116 and A549 cancer cell lines [58]. Casticin, extracted from Viticis Fructus, is one of the flavonoid components that has been found to exert inhibitory effects on tumor cell proliferation through multiple modes of action. In this study, the effects of casticin on human colon cancer and its underlying mechanisms were studied. The results showed that casticin can cause the accumulation of reactive oxygen species (ROS) and increase the protein levels of apoptosis signal-regulated kinase 1 (ASK1), c-Jun N-terminal kinase (JNK), and B-cell lymphoma 2-interacting cell death mediator (BIM) in HT-29 cells, which can greatly induce apoptosis in HT29, HCT116, SW480, and Caco-2 cells [59]. It has also been found that casticin selectively inhibited the proliferation of 5–8F cells in vitro by participating in the regulation of GSDMD-dependent tumor cell death process [60]. Casticin induced G2/GM arrest and apoptosis by upregulating Bax/BCL2 expression, which could significantly inhibit the proliferation of nasopharyngeal carcinoma [61]. In addition, it has been shown that casticin inhibits breast cancer cell migration and invasion by inhibiting the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [62]. DHTMF is one of the constituents of *V. trifolia* subsp. *litoralis*, it significantly inhibited the growth of lung cancer cells and induced apoptosis in a dose-dependent manner, as evidenced by decreased levels of Bcl-2 and increased levels of Bax and cleaved caspase-3 [25].

Persicogenin, artemetin, luteolin, penduletin, vitexicarpin and chrysosplenol-D, which have been isolated as new cell cycle inhibitors from *V. trifolia*. The inhibitory effects of these six flavonoids on the multiplication of mammalian cancer cells have been assessed by the sulforaphane B (SRB) method, and their effects on cell cycle and apoptosis were examined by flow cytometry and morphological observation under light microscopy and agarose gel electrophoresis for inter-ribosomal DNA fragments. These six compounds can mainly inhibit the proliferation of mouse tsFT210 cancer cells [31]. Vitetrifolin H, vitetrifolin I and vitexoid isolated from *V. trifolia* fruits were identified by an extensive spectroscopic approach and all these compounds demonstrated suppression of HeLa cell proliferation with IC50 values ranging from 4 to 28 μM [32]. Rotundifuran, a natural product isolated from *V. trifolia* L. inhibits HeLa cell proliferation by inducing mitochondria-dependent apoptosis through reactive oxygen species (ROS) action on MAPK and PI3K/Akt signaling pathways [63]. In vitro lymphocyte proliferation inhibitory activity of vitexicarpin was examined. Vitexicarpin revealed an inhibitory activity of >0.1 pM against Con A or LPS-induced lymphocyte proliferation [64].

5.3.3. Cytotoxic activity

The extracts of hexane and dichloromethane (DCM) from the stems and leaves of *V. trifolia* have been shown to be highly toxic to several cancer cell lines in culture (SQC-1 UISO, OVCAR-5, HCT-15 COLADCAR and KB) [15]. The cytotoxic activity of ethanol extract isolated from *V. trifolia* subsp. *litoralis* was analyzed by MTT method, the ethanol extract can inhibit the proliferation of human liver cancer cell line HepG2 in vitro showing that the ethanol extract has a certain cytotoxic activity [56]. Casticin is a polymethyl flavonoid from Fructus viticis, sub-cytotoxic concentrations of it could inhibit the stemness characteristics in hepatocellular carcinoma cells, as demonstrated by the expression of stemness biomarkers (CD44, EpCAM, Bmi1, Nanog, and Oct4). Casticin could inhibit stemness characteristics in hepatocellular carcinoma cells by interruption of the reciprocal negative regulation between DNA methyltransferase 1 and miR-148a-3p [65].

5.4. Anti-feeding activity

The anti-feeding activities have been studies in the early 1974s. The survey of ether extract of *V. trifolia* against the larvae of *Spodoptera litura* F. was examined. The tests have showed that *V. trifolia* can against *S. litura* F. at the concentration of 10, 5, 2.5, and 1% [66].

Hexane and DCM extracts of *V. trifolia* are tried to equally have anti-feeding activities. The hexanic extract of the leaves utterly

inhibited the expansion of the phytopathogenic fungi *Fusarium* sp. throughout the primary a pair of days of the experiment [15].

5.5. Anti-hyperprolactinemia activity

The ethanol extract Viticis Fructus (the fruit of *V. trifolia* subsp. *litoralis*) have been studied. The test using acetic-acid-induced writhing and metodopramide-dihydrochloride induced in mice. In vivo experiment proved that the optimum concentration at the dose of 50 mg/kg [67]. The anti-hyperprolactinemia activity of casticin which is isolated from *V. trifolia* subsp. *litoralis* have been reported. In vivo, hyperprolactinemia (HP) was evoked by administering metoclopramide hydrochloride (50 mg/kg, tid, ip, for 10 days) to SD rats. Serum prolactin levels were 2.1-fold higher in the hyperprolactin model group than in the untreated control group ($P < 0.01$). Casticin (10, 20 and 40 mg/kg, ip, for 7 days) decreased serum levels of prolactin by 33.9%, 54.3% and 64.7%, respectively ($P < 0.01$). In vitro experiments further demonstrated that casticin suppressed E2-stimulated prolactin release from pituitary cells [68].

5.6. Anti-inflammatory activity

The anti-inflammatory activity of aqueous extract of *V. trifolia* subsp. *litoralis* and *V. trifolia* were tested. The aqueous extract reduced the induction of IL-1β, IL-6 and iNOS mRNA by LPS and inhibited the expression of various LPS-induced inflammatory genes in RAW 264.7 cells [7,69]. The effect of *V. trifolia* subsp. *litoralis* extracts on stimulated A549 cells was then assessed by analyzing Eotaxin secretion and eosinophil migration, showing that *V. trifolia* subsp. *litoralis* -treated A549 cells significantly inhibited Eotaxin secretion and eosinophil migration in a dose-dependent way. Casticin, an active compound isolated from *V. trifolia* subsp. *litoralis* has been found to show anti-inflammatory properties in vivo and vitro. In vivo, casticin significantly inhibited xylene-induced edema in mice, egg albumen-induced paw edema in rats, and acetic acid-induced vascular permeability in mice [70,71]. Casticin alleviated dextran sulfate sodium-induced ulcerative colitis by increasing the expression of the antioxidant enzymes peroxidase 3 and MnSOD and by reducing the production of pro-inflammatory chemokines through inhibition of AKT signaling [72]. In addition, casticin had a significant effect on cigarette smoke-induced lung inflammation in a mouse model [73]. The anti-inflammatory activity of casticin was studied in vitro in A549 human type II epithelial lung cells using an eotaxin inhibition assay, which showed that casticin can inhibit eosinophil migration and the activity of chemokines and adherence molecules participating in the process of asthma inflammation by inhibiting the NF-κB pathway [8]. Casticin alleviated monoiodoacetic acid-induced knee osteoarthritis by inhibiting of HIF-1α/NLRP3 inflammasome activation [74]. In addition, in LPS-induced inflammation, casticin significantly inhibited the NF-κB subunit p65 protein in the nucleus and reduced the activation of Akt and MAPK [75].

5.7. Antioxidant activity

Themethanol extract of Viticis Fructus and ferruginol isolated from *V. trifolia* subsp. *litoralis* showed a stronger antioxidant activity by using DPPH radical and ferric thiocyanate methods [4]. Negundoside (NS), agnuside (AS) and 6′-p-hydroxy benzoyl mussaenosidic acid (HMA) are known bioactive metabolites in *V. trifolia* and this study demonstrated a significantly active in DPPH and NO radical removal assays [48]. The aqueous extract of *V. trifolia* has also been found antioxidant activity by using DPPH assay [5].

5.8. Larvicidal activity

The larvicidal efficacy of *V. altissima, V. negundo* and *V. trifolia* fatty acid methyl ester (FAME) extracts against early fourth-instar *Culex quinquefasciatus* larvae was investigated. With an LC50 value of 9.25 ppm, the *V. trifolia* FAME extract had the highest larvicidal activity, followed by the *V. altissima* (14.82 ppm), and the *V. negundo* (18.64 ppm) [76]. The extracted substance methyl-p-hydroxybenzoate was tested for its larvicidal efficacy against early 4th instar larvae of *Culex quinquefasciatus* and *Aedes aegypti*. At a concentration of 20 ppm, the substance completely killed both mosquito larvae, with LC_{50} values of 5.77 and 4.74 ppm against *C. quinquefasciatus* and *A. aegypti*, respectively [77]. *Anopheles gambiae* Giless. s. larvae (Diptera: Culicidae) were tested for their ability to be controlled by methanol extract of *V. trifolia* leaves; it can result in 100% death at 100 ppm in 72 h [10]. Essential oil from *V. trifolia* revealed potential larvicidal properties, LC_{50} and LC_{90} for *V. trifolia* essential oils against *Ae. aegypti* and *C. quinquefasciatus* were 57.7 ± 0.4, 77.9 ± 0.9 ppm and 55.17 ± 3.14, respectively [78].

5.9. Hepatoprotective activity

The protective activity of aqueous and ethanolic extracts of *V. trifolia* leaves against carbon tetrachloride-induced liver damage was studied. The results of serum biochemical evaluation showed a significant decrease in total bilirubin and serum marker enzymes and an increase in total protein in animals treated with ethanol and aqueous extracts [79]. The protective effect of ethanolic extract of *V. trifolia* flowers on CCI4-induced liver damage in albino rats was investigated. The plant extract showed significant hepatoprotective activity at a dose of 200 mg/kg [11]. Casticin is one of the flavonoids extracted from Viticis Fructus, which can reduce the expression of matrix metalloproteinase (MMP)-2, MMP-9, tissue inhibitor of metalloproteinases (TIMP)-1 and TIMP-2 resulting from blocking TGF-β1/Smad signaling, as well as increased the apoptosis of hepatic stellate cells. The results suggest that casticin has potential benefits in the attenuation and treatment of liver fibrosis [80].

5.10. Estrogenic activity

The estrogen-like biological activity of the volatile components of the essential oil isolated from the fruit of *V. trifolia* subsp. *litoralis* was investigated in human breast cancer cells, and their experimental results showed that it was significantly inhibited by ICI 182,780, a specific estrogen receptor antagonist [67]. The ethanolic extract of *V. trifolia* subsp. *litoralis* fruit was tested for estrogen-like activity, as well as estrogen receptor (ERa), estrogen receptor-regulated progesterone receptor and pS2 mRNA expression in MCF-7 cells using a modified cell proliferation assay (E-SCREEN evaluation system). The results showed that VRE has estrogen-like activity [67].

5.11. Other activities

The ether extract of *V. trifolia* subsp. *litoralis* fruit exhibited effective inhibition of rat lens aldose reductase (RLAR) activity in vitro. It demonstrated an IC of 7.4×10^{-7} M against DL-glyceraldehyde as a substrate [81]. Extracts of Viticis Fructus appeared to have analgesic effects and activity-guided isolation was performed using acetic acid-induced peristalsis in mice. Vitexfolin A, agnuside, 10-*O*-vanilloylaucubin, revealed significant sprain inhibition after oral administration at doses of 15, 50, 25 and 50 mg/kg [13]. Cerebral protective and cognitive enhancing activities of aqueous extracts of *V. trifolia* leaves against scopolamine-induced amnesia and normal rats. In passive avoidance (PA) and T-maze (TM) models, higher doses (20 mg/kg) of the plant extract exhibited significant antiamnesic activity compared to controls ($P < 0.01$) [82]. A new natural compound, 1H,8H-Pyrano [3,4-c]Pyran-1,8-dione (PPY), was isolated from *V. trifolia* subsp. *litoralis*, and the mechanism of the anti-asthmatic response to PPY in vitro was elucidated. Stimulation of lung epithelial cells (A549 cells) with TNF-α, IL-4 and IL-1β. The expression of chemokines and adhesion molecules involved in eosinophil chemotaxis was induced. Eotaxin, IL-8, IL-16 and VCAM-1 mRNA expression were significantly reduced by PPY treatments [83]. Casticin, a flavonoid isolated from Viticis Fructus, significantly inhibited the growth of KB cells (IC50 ¼ 0.23 mM). On the contrary, there was no inhibition of proliferation of A431 cells by casticin, similar to normal cell lines, 3T3 Swiss Albino and TIG-103. Flow cytometric analysis showed that KB cells exposed to casticin resulted in a significant arrest at the G2-M phase. Casticin disrupted the mitotic spindle in immunostaining of KB cells. These results indicate that the blockade of G2-M by casticin may have anti mitogenic activity [84]. The flavone-enriched fraction of Viticis Fructus showed anti-nociceptive activity in a dose-dependent manner (10–50 mg/kg body wt., i. g.) [67]. The water extract of *V. trifolia* (aerial part) used in the treatment of AIDS was tested for HIV type 1 reverse transcriptase inhibitory activity, and the results revealed that the rate of HIV-1 RT inhibition (% IR) was higher than 90% at a concentration of 200 μg/ml [85]. The essential oil of *V. trifolia* was assessed on the spilosoma obliqua larvae and when topically applied to the dorsal side of the mesothoracic region, it had a regulating effect on the growth of the insects. It decreased the emergence of adults by increasing the mortality of larvae and the deformity of adults, and decreased the fertilization rate of females and the fertilization rate of eggs [86]. The isolation of a new natural mosquito repellent from the fresh leaves of *V. trifolia* subsp. *litoralis*. This compound exhibited potent repellent activity against *Aedes aegypti* [47]. The conventional treatments for Ciguatera fish poisoning (CFP) and the potential for application in the treatment of illnesses associated with excessive NO generation were both supported by the inhibitory action of the aqueous extract of *V. trifolia* [5]. 4-hydroxybenzoic acid, ferulic acid and vanillic acidwere isolated from fruits and leaves of *V. trifolia* subsp. *litoralis*. Using lettuce seedlings as a bioassay, these compounds' biological activities were investigated. The results of the investigation revealed that these compounds reduced the inhibitory action against root development [43]. Only vitexcarpin was active in a model utilizing sensitized guinea pig trachea activated by ovalbumin up to a minimum dosage of 1.3×10^{-5} M; Viteosin A and vitexcarpin isolated from *V. trifolia* may prevent spontaneous contraction of isolated male guinea pig trachea produced by histamine [87]. In excision, incision, and dead space wound models, the ability of ethanol leaf extracts of *V. trifolia* to promote wound healing was assessed. It was discovered to have considerable wound healing activity as demonstrated by a reduction in the time of epithelialization, an increase in the rate of wound contraction, skin breaking strength, granulation tissue dry weight, hydroxyproline content, and granulation tissue breaking strength [79].

6. Conclusion

We reviewed the existing traditional medical uses, phytochemical and pharmacological research on the Viticis Fructus, which is used in traditional Chinese medicine for the treatment of various diseases particularly colds, headaches, vertigo, and anesthesia with a long history. Currently, more than 190 compounds have been isolated, including the major ones such as diterpenes and flavones. These monomers compounds and crude extracts from *V. trifolia* subsp. *litoralis* and *V. trifolia* are screened for pharmacological activities in vivo and in vitro. Many experimental studies validated its traditional medicinal uses, and the chemical responsible.

By summarizing (Table 3), we can see that the research on the pharmacological effects of Viticis Fructus is not deep enough, such as antibacterial activity, larvicidal activity, anti-hyperprolactinemia activity, and other functions, but only at the level of pharmacological effects, without exploring the mechanism of action. Anticancer activity, anti-inflammatory activity is the popular direction for the study of Viticis Fructus, so the mechanism of action is also explored more deeply. For example, Casticin is one of the flavonoids extracted from Viticis Fructus, which is a structure with three phenyl rings, an ortho catechol moiety, an alkene group, two hydroxyl groups, and four methoxy groups. The C-30 and C-5 hydroxyl groups, as well as the C-3 and C-40 methoxy groups in the casticin molecule, consist of significant anti-proliferative activity, leading to unfavorable proliferation - a desirable feature of anti-cancer drugs [88]. Casticin induces mitochondria-dependent and ROS-mediated apoptosis, induces cell cycle arrest and inhibits invasive and migratory proliferation in breast, bladder, colon, lung, oral cavity and ovarian cancers. In addition, casticin affects multiple oncogenic pathways by regulating various proteins, such as MAPK, NF-κB and PI3K/Akt pathways; increases ROS production by enhancing Bax protein and decreasing Bcl protein, and induces cell cycle arrest by inhibiting the cell division cycle (cdc25c and cdc2) and cell cycle

proteins (B1). These signaling pathways are the key pathways through which Viticis Fructus exerts its antitumor effects.

Although studies have been made on some of *V. trifolia* subsp. *litoralis* and *V. trifolia*, there are issues still remaining to be resoved: 1. So far, no toxicological reports have been found on Viticis Fructus. More in-depth studies about the toxicity of Viticis Fructus should be carried out, which can provide a theoretical guidance for the application of Viticis Fructus. The number of in vivo studies conducted to date is small and the pharmacokinetic profile of Viticis Fructus (including dosing, bioavailability, distribution, etc.) is limited. the safety and efficacy of Viticis Fructus have not been reported, which poses a risk to the clinical evaluation of this drug. 2. In the 2020 edition of the Pharmacopoeia of the People's Republic of China, *V. trifolia* subsp. *litoralis* is seen as a variant of *V. trifolia* and the Latin name is *V. trifolia* L. var. simplicifolia Cham.(Committee, C·P., 2020). But in some monographs in the taxonomy, the *V. trifolia* subsp. *litoralis* has been regarded as an independent species of Vitex(Editorial Committee of the Flora of China, 2022). However, according to World Flora Online on the genus Vitex, *V. trifolia* subsp. *litoralis* is treated as a subspecies of *V. trifolia* [95]. So far, there is no consensus on this issue. Therefore, taxonomic studies should be strengthened. 3. In the Pharmacopoeia of the People's Republic of China, the base sources of Viticis Fructus are *V. trifolia* L var. *simplicifolia* Cham. and *V. trifolia*. But in the process of the chemical composition and pharmacological effects of the chemical composition and pharmacological effects of the two in the phytochemistry and pharmacological effects are very different some differences in morphological. Otherwise, it has been reported that *V. trifolia* subsp. *litoralis* and *V. trifolia* have some differences in antipyretic, analgesic, sedative and other aspects. It should be aimed at strengthening of *V. trifolia* subsp. *litoralis* and *V. trifolia* comparative study, for the quality control of frucuts viticis and clinical application provides sufficient basis.

In conclusion, this review summarizes the traditional applications, botany, phytochemistry, and pharmacology of Viticis Fructus, and points out some shortcomings of the current research, providing a basis for further research and new product development.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability

Data will be made available on request.

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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Abbreviations

iNOS	inducible Nitric Oxide Synthase
JNK	c-Jun N-terminal kinase
AIDS	Acquired Immune Deficiency Syndrome
ASK1	apoptosis signal-regulating kinase 1
LC_{50}	Lethal Concentration resulting in 50% mortality
AS	agnuside
LPS	Lipopolysaccharide
BIM	B-cell lymphoma 2 interacting mediator of cell death
CFP	Ciguatera fish poisoning
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *S. aureus*
DCM	dichloromethanic
NF-κB	nuclear factor kappa-B
DHTMF	5,3′-Dihydroxy-6,7,4′-trimethoxyflavanone
NS	Negundoside
PA	passive avoidance
DNP	dinitrophenyl
PPY	1H,8H-Pyrano[3,4-c]pyran-1,8-dione
DPPH	1,1-Diphenyl-2-picrylhydrazyl radical 2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl
ERa	estrogen receptor a
RLAR	rat lens aldose reductase

ROS	reactive oxygen species
RPMC	rat peritoneal mast cells
FAME	fatty acid methyl ester
SRB	sulforhodamine B
HMA	6′-p-hydroxy benzoyl mussaenosidic acid
TCM	traditional Chinese medicine
HP	Hyperprolactinemia
TM	T-maze
IC_{50}	concentration that causes 50% inhibition
TNF-α	tumor necrosis factor α
IL-1β	interleukin 1β
VCAM-1	vascular cell adhesion molecule-1
IL-6	interleukin 6
VIT	Vitexicarpin
VRFE	extract of *Vitex trifolia* subsp. *litoralis* Steenis fruits

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e19144.

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