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Review article

A review of Viticis Fructus: botany, historical records, phytochemistry, pharmacology, toxicity, quality control, pharmacokinetics and comprehensive applications

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ABSTRACT

Background: Viticis Fructus (also known as Manjingzi) has been used in China for more than 2000 years. It is one of the most famous traditional Chinese medicines with the main effect of dispelling wind-heat. In Asian countries, it is used in the treatment of common cold with wind-heat syndrome, swollen gums, migraines, dizziness, *etc*.
The aim of the review: The paper emphasizes on the botany, historical records, phytochemistry, pharmacology, toxicity, quality control, pharmacokinetics and comprehensive applications of Viticis Fructus to furnish with a scientific theoretical reference for its exploration and applications.
Materials and methods: Correlative data on Viticis Fructus were obtained from PubMed, ScienceDirect, Web of science, Embase, Scopus, Google Scholar, CNKI, WeiPu, Chinese ancient books and DuXiu academic search. The data collection ended in May 2024.
Results: The results showed 324 compounds, including terpenoids, flavonoids, lignans and others, which were isolated and identified from Viticis Fructus. In addition to treating headaches and eye pain, Viticis Fructus also had anti-inflammatory, antiplatelet activation, analgesia, antitumor and antihypertensive effects. In addition, this review summarized the botany, toxicity, counterfeit identification, pharmacokinetics and patent information

Abbreviations: AUC $_{(0\text{-}t)}$, Area under the plasma concentration–time curve; Bax, Bcl-2 associated X protein; Bcl-2, B cell lymphoma-2 protein; Bcl-xL, B-cell lymphoma extra-large; Bim, Bcl-2 interacting mediator of cell death; Caspase-3, Cysteinyl aspartate specific proteinase-3; CD, Circular dichroism; ChP, Pharmacopoeia of the People's Republic of China; C_{max}, Maximum drug concentration in plasma; CNKI, China National Knowledge Infrastructure; COSY, Correlation spectroscopy; CRC, Colorectal cancer; CYR61, Cysteine-rich61; DR5, Death receptor 5; ERK, Extracellular regulated protein kinases; FOXM1, Forkhead box protein M1; FOXO3a, Forkhead box O3; GABA, γ-amino butyric acid; GC×GC–MS, Comprehensive two-dimensional gas chromatography hyphenated with mass spectrometry; HCC, Hepatocellular carcinoma; HDL, High-density lipoprotein; HRESIMS, High-resolution electrospray ionization mass spectroscopy; HRFABMS, High-resolution fast atom bombardment mass spectrum; KOA, Knee osteoarthritis; LC/MS, Liquid chromatography/mass spectrometry; LCSLCs, Lung cancer stem-like cells; LDL, Low density lipoprotein; LD_{50}, median lethal dose; MAPK, Mitogen-activated protein kinase; MMP-1, Matrix metalloproteinase-1; MMP-2, Matrix metalloproteinase-2; MMP-9, Matrix metalloproteinase-9; NF-κB, Nuclear factor kappa-B; NIR, Near Infrared; NLRP3, Nucleotide oligomerization domain-like receptor protein 3; NMR, Nuclear magnetic resonance; NO, Nitric Oxide; NOESY, Nuclear overhauser effect spectroscopy; NPC, Nasopharyngeal carcinoma; PI3K/AKT, Phosphatidylinositol 3-kinase/protein kinase B; PKR, Protein kinase R; PMS, Premenstrual syndrome; PPY, Pyranopyran-1,8-dione; ROS, Reactive oxygen species; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IR, Infrared ray; SCTF, Shrub Chaste Tree Fruits; TCMs, Traditional Chinese medicines; T_{max}, The time to reach maximum drug concentration; TNF-α, Tumor necrosis factor-α; UC, Ulcerative colitis; HPLC-DAD, High-performance liquid chromatography coupled with a diode array detector; ISSR, Inter simple sequence repeat; ITS2, Internal transcribed spacer 2; JNK, c-Jun N-terminal kinase; K2P, Kimura 2-Parameter; UHPLC-Q-Orbitrap HRMS, Ultra-high-performance-liquid chromatography-quadrupole-Orbitrap high resolution mass spectrometry; UHPLC-MS, Ultra-High performance liquid chromatography-mass spectrometry; UV, Ultraviolet..

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of Viticis Fructus in detail. The shortcomings and feasible suggestions are put forward, which provide a basis for further research and utilization of Viticis Fructus.

Conclusion: Viticis Fructus has been used to remedy common cold with wind-heat syndrome, cephalalgia, ophthalmodynia, dizziness, *etc*. The pharmacological activities of the main components have been clarified and backed up the traditional applications. However, the botany, processing, pharmacological mechanism, quality control and toxicological studies of Viticis Fructus need to be further improved.

1. Introduction

Viticis Fructus (also known as Manjingzi in China) is the dry ripe fruit of *Vitex rotundifolia* L. (synonyms of *Vitex trifolia* var. *simplicifolia* Cham.) and *Vitex trifolia* L. of the Lamiaceae family. It has been used as traditional Chinese medicine in China for more than 2000 years. It is also called "Manjingshi", "Jingzi", "Wanjingzi", "Baibeifeng" and so on. Viticis Fructus is initially mentioned in *Shennong Bencao Jing* as "Manjingshi", which is listed among the top grade (Zhang et al., 2018). It is recorded in ancient books for treating colds, headaches, gingivitis, dizziness, ophthalmalgia and so on.

Viticis Fructus mainly contains terpenoids, flavonoids, phenolic acids and other chemical components. It is classified as the genus Vitex. Many plants in the genus Vitex have been widely studied and have multifarious pharmacological activities (Auniq et al., 2019; Hobbs, 1991; Jangwan et al., 2013). Viticis Fructus has antipyretic, analgesic, antioxidant, anti-inflammatory, antitumor, blood pressure lowering and other activities. It is not only used for the treatment of headaches, swelling and aching of gum, but also for the prevention and treatment of trigeminal neuralgia (Wen et al., 2020), atherosclerosis (Kim et al., 2020), tumors (Liu et al., 2019), premenstrual syndrome (PMS) (Ye, 2010), inflammation (Fang et al., 2019) and other diseases. Therefore, the extracts and compounds of Viticis Fructus have far-reaching medicinal value and deserve further research and development.

The research hotspots of Viticis Fructus can be explored through the frequency analysis and visual display of keywords. "*V. rotundifolia*", "apoptosis", "casticin" and "Viticis Fructus" are keywords with high frequency and the average publication year of Viticis Fructus keywords is shown in Fig. 1 (the redder the color, the higher the popularity). In botany, *Vitex rotundifolia* (*V. rotundifolia*) fruits are more frequently studied as Viticis Fructus. The family of Viticis Fructus has been controversial in recent years from Verbenaceae to Lamiaceae family. In phytochemistry, the main research focus on the flavonoids, terpenoids and iridoids of Viticis Fructus. Casticin is the most studied compound. In pharmacological effects, the main research direction of Viticis Fructus focuses on exploring pharmacological mechanisms by "apoptosis", "proliferation", "cells", "*in vitro*" and other hot keywords. The pharmacological activity mainly focuses on anti-tumor research. The most of the current pharmacological experiments remain at the *in vitro* cell level *via* "cells" and "*in-vitro*". In addition to the above points of view, many studies researched the leaves of *V. rotundifolia* or *Vitex trifolia* (*V. trifolia*). Viticis Fructus has been listed as the third level of Chinese wild traditional Chinese medicine species for crucial protection. The comprehensive development and utilization of non-medicinal parts can avoid resource waste and is conducive to the sustainable development of traditional Chinese medicines (TCMs).

The traditional pharmacological actions of Viticis Fructus have been supported by some modern pharmacology with the deepening of the research on Viticis Fructus, whose research direction is also gradually enriched. The plant morphology, phytochemistry and pharmacological effects have been preliminarily reviewed (Meng et al., 2023; Yan et al., 2023). However, the current summary of the chemical constituents is not comprehensive and the relevant pharmacological mechanisms are not clear enough. Thus, this review generalizes the advances on variation of the origin plant of Viticis Fructus, isolation and identification approaches of chemical constituents, counterfeit identification, toxicity studies, pharmacokinetics, patent information, clinical applications, different processing methods, changes in constituents after processing, the indications scope of various processed products and so on. In addition, the repetitive modules such as traditional applications, phytochemistry, pharmacology and so on were refined and supplemented in more detail. The corresponding chemical composition structure, pharmacological mechanism and hotspot map of Viticis Fructus research were drawn to further utilization of Viticis Fructus. A well-rounded understanding will set the basis for further studies and the development of Viticis Fructus.

2. Method

Relevant information was obtained from PubMed, ScienceDirect, Web of science, Embase, Scopus, Google Scholar, China National Knowledge Infrastructure (CNKI), WeiPu, Chinese ancient books and DuXiu academic search. The selected literature was screened by publication date (from the years 1935——2024) and language (Chinese and English). The database was searched based on some synonyms (from https://powo.science.kew.org), such as "Viticis Fructus", "seed of *Vitex trifolia* L.", "the fruits of *Vitex trifolia* L.", "the fruits of *Vitex trifolia* L. var. *simplicifolia* Cham.", "Shrub chaste tree fruits" and "the fruits of *Vitex rotundifolia*". Additionally, some data were collected from Pharmacopoeia of the People's Republic of China (ChP), Chinese classic books and official websites. The characteristics of the plant were collected from botanical database (https://www.kew.org/science, https://powo.scienc

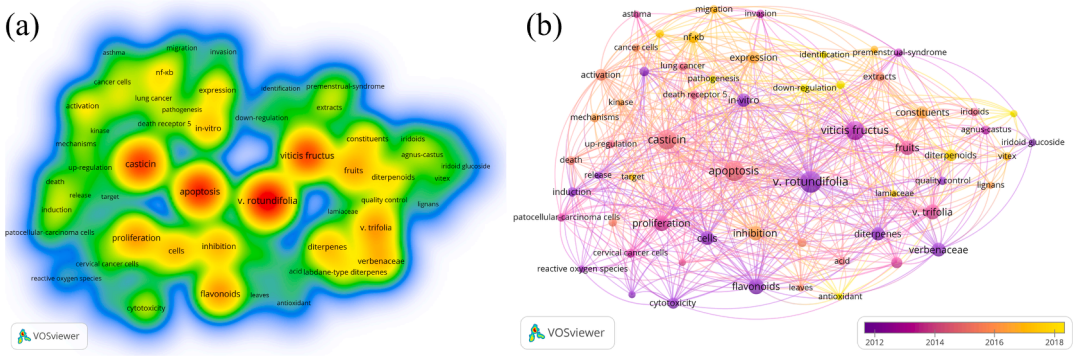

Fig. 1. The hot word density view and average publication year of Viticis Fructus keywords.

e.kew.org, https://www.iplant.cn/foc). The traditional prescription of Viticis Fructus came from Yaozhiwang (https://www.yaozh.com). Its patent information came from CNKI, Yaozhiwang (https://www.yaozh.com) and Baiteng (https://www.baiten.cn/). CAS SciFinder (https://scifinder-n.cas.org/), PubChem (https://pubchem.ncbi.nlm.nih.gov/) and ChemSpider (https://www.chemspider.com/) were used to check the structure of the compounds in the literature. Some images were from freepik (https://www.freepik.com/).

3. Botany

3.1. Botanical origin

Viticis Fructus is considered to have two origins, namely *V. rotundifolia* and *V. trifolia*. It was found that the fruits of *Vitex negundo* var. *cannabifolia* were misused as Viticis Fructus by consulting relevant data (Zhou and Jin, 2001). The origin of Viticis Fructus has also been changing (Table S1). *V. trifolia* and *V. negundo* var. *cannabifolia* were not distinguished before the Northern and Southern Dynasties. It was written in *Guangzhi* and *Guangya* as "*V. negundo* var. *cannabifolia* was *V. trifolia*". *V. trifolia* and *V. negundo* var. *cannabifolia* were distinguished by Tao Hongjing for the first time in the *Bencao Jingji zhu* after the Northern and Southern Dynasties (Tao, 1994). He recorded that the fruits of *V. negundo* var. *cannabifolia* were larger than Viticis Fructus. However, the statement was contrary to the present findings. In the Tang and Song Dynasties, there were two main changes. (1) In *Xinxiu Bencao*, the plant morphology was described in detail. It was consistent with the current statement that Viticis Fructus were larger than the fruits of *V. negundo* var. *cannabifolia* (Su, 1981). (2) In the Song Dynasty, the main difference between *V. trifolia* and *V. negundo* var. *cannabifolia* was whether it was a trailing plant, which was recorded in *Bencao Yanyi* (Kou, 1985). In the Ming Dynasty, it was listed and recorded in *Bencao Gangmu*: "Its branches were small and weak as *V. trifolia*, so it was called manjing (trailing plant)". It could be found from the picture attached to the book that it was ternate compound leaves, which was in line with the characteristics of *V. trifolia* (Li, 2011). The mainstream view has been that *V. rotundifolia* and *V. trifolia* were the origin plants of Viticis Fructus since 1961 (Zhang et al., 2019).

Nowadays, the family and variety of Viticis Fructus are widely discussed. Viticis Fructus is stipulated as Verbenaceae family by the ChP (Chinese Pharmacopoeia, 2020) and Flora of China (https://www.iplant.cn/foc) according to relevant information. However, it is classified as Lamiaceae family by some botanical-related websites, such as Plants of the World Online database (https://powo.science.kew.org). The family of Viticis Fructus is uneven in the literature. In addition, the investigation on whether *V. rotundifolia* belongs to one of the varieties of *V. trifolia* also needs to be further conducted. Now *V. rotundifolia* is considered to be one of the varieties of *V. trifolia* in some standardized works of taxonomy and pharmacy in China, such as ChP and Flora of China. The Flora of China (English edition), Flora of Australia and Royal Botanic Gardens of the United Kingdom have listed *V. rotundifolia* as an independent species of Vitex (Sun, 2018).

3.2. Botanical taxonomy

Viticis Fructus belongs to the Lamiaceae family, mainly grown in Borneo, China, Thailand and Western Australia (https://powo.science.kew.org/). According to the Flora of China (English edition), there are three varieties of *V. trifolia*, namely *Vitex trifolia* var. *taihangensis*, *Vitex trifolia* var. *trifolia* and *Vitex trifolia* var. *subtrisecta* (**Table S2**). However, *V. rotundifolia* was also considered to be one of the varieties of *V. trifolia* in the ChP, called *Vitex trifolia* var. *simplicifolia* Cham.

3.3. Botanical description

The two origin plants of Viticis Fructus are clearly distinguished in the plant morphology. The leaves of *V. trifolia* are simple leaves and the leaves of *V. rotundifolia* are ternate compound leaves, but their fruits are very similar in morphology (Yang et al., 2023). It is spherical with a diameter of 4–6 mm and has four chambers each with one seed. The surface is gray-black or black-brown with gray powder cream-like fuzziness and has 4 longitudinal shallow ditches. Its base has gray-white calyx and short fruit stalk.

3.4. Botanical distribution

V. Rotundifolia grows in open sandy areas, usually near the sea. *V. Rotundifolia* is distributed in the north-central and southeast of China, such as Jiangxi and Shandong province. Besides, *V. Rotundifolia* is widely cultivated in Borneo, India, Japan, Korea, Vanuatu, Vietnam, Western Australia and other places. *V. Rotundifolia* is different from *V. trifolia*, which grows in plains, river beaches, sparse forests and villages. Furthermore, *V. Trifolia* spreads over the north-central, south-central and southeast of China. *V. Trifolia* is widely cultivated in Afghanistan, Algeria, Assam, Bangladesh, Bismarck Archipelago and so on (https://powo.science.kew.org/). They are all shrubs or trees that grow mainly in moist tropical communities

The origin plants of Viticis Fructus are currently unified as *V. rotundifolia* and *V. trifolia*. But the family of Viticis Fructus and varieties of *V. trifolia* should be unified. In addition, although the plant morphology of the two origin plants is easy to distinguish, their fruits are very similar in morphology.

4. Historical records

4.1. Traditional medicinal applications

Viticis Fructus is pungent, bitter taste with a cold character, which enters the bladder, liver and stomach meridian (Chinese Pharmacopoeia, 2020). It was used for treating colds, headaches, gingivitis, dizziness, ophthalmalgia, *etc*. Recent studies have discovered that Viticis Fructus exerted preventive and therapeutic effects on various diseases, including trigeminal neuralgia (Wen et al., 2020), senile cataracts (Sun and Yang, 2010), arthritis (Chu et al., 2020) and inflammation (Fang et al., 2019). These pharmacological activities were matched with headaches, dizziness, blurred vision, rheumatism and anti-inflammation. In addition, Viticis Fructus had an effect on relieving or treating diseases, such as supraorbital neuralgia (Li, 1998) and neurovascular headache (Hu and Yang, 2016) in clinical.

Viticis Fructus has been employed in clinical practice for more than 2000 years as TCM. The main traditional effects recorded in different books were to dispel wind-heat (treating fever, chills, cough, thirst and other wind-heat syndromes), treat rheumatism, headache and promote hair growth and so forth (**Table S3**). In the Qin-Han Dynasties, Viticis Fructus was first recorded in *Shennong Bencao Jing* and listed as one of the top grades. It was employed to treat rheumatism, tapeworm parasites and had healthy effects of improving eyesight, firming teeth and anti-aging (Zhang et al., 2018). In the Southern and Northern Dynasties, it was applied to treat headaches, intracranial tinnitus and benefit qi (benefiting vital energy) as recorded in *Mingyi Bielu* (Tao, 1986). During the Five Dynasties and Ten States period, it had therapeutic effects on eye swelling, itching and ulcerous eyelid margin and promoted hair growth. In the Tang Dynasty, its efficacy had been clarified to relieve the symptoms of headaches and promote hair growth (Sun, 1982; Zhen, 1983). In the Song Dynasty, the usage of Viticis Fructus in the treatments of head and face wind (symptoms of head and face sweating, headaches, dizziness, *etc*) was more frequent (Wang, 1958b). The treatment of intermittent headaches by Viticis Fructus was introduced in *Danxi Xinfa* in the Yuan Dynasty. The description of its efficacy in *Shennong Bencao Jing* was reaffirmed in *Bencao Gangmu* (Li, 2011). In the Qing Dynasty, the functions of Viticis Fructus were emphasized by many Chinese ancient books, such as dispelling cold-dampness syndrome (treating

rheumatism), removing headaches and improving visual acuity. Viticis Fructus was recorded in *Depei Bencao,* which could dispel cold-dampness, cure headaches, relieve eye pain and treat damp arthralgia, intracranial tinnitus and toothaches. Additionally, it was devoted to dispelling wind, treating solar wind headaches (migraine), vertigo and eye pain according to *Bencao Shugou Yuan* (Yang, 1958).

Furthermore, Viticis Fructus was also used in conjunction with other herbs to exert curative effects (**Table S4**). There are two classic prescriptions for Viticis Fructus, which are Qiang-Huo-Sheng-Shi Decoction and Qing-Shang-Juan-Tong Decoction. Qiang-Huo-Sheng-Shi Decoction derived from *Neiwai Shangbian Huolun* of Li DongYuan. It was combined with *Notopterygii Rhizoma et Radix*, *Chuanxiong Rhizoma* and so on (Li, 1959; Yan et al., 2022). Its effect was to dispel wind, eliminate dampness and relieve pain (Hu et al., 2022). It was commonly used to treat rheumatoid arthritis, bone hyperplasia, ankylosing spondylitis, *etc*. *Notopterygii Rhizoma et Radix* and *Angelicae Pubescentis Radix* in the prescription could dispel wind-dampness and dredge joints. Their combination had favorable effects in treating rheumatism around the body and relieving arthralgia, which were sovereign drugs (playing a major role in the treatment of main syndromes or main symptoms in prescriptions). *Saposhnikoviae Radix* cured pain and *Chuanxiong Rhizoma* could not only evacuate the wind evil around the body, but also could promote blood and qi circulation to alleviate body pain. They were used to minister drugs (assisting the sovereign drugs to cure the main symptoms) and helped the sovereign drugs to disperse evil and relieve pain. *Ligustici Rhizoma et Radix* evacuated wind-dampness and relieved headaches, which was the assistant drug (assisting the sovereign and minister drugs to treat concurrent syndromes and secondary symptoms). *Glycyrrhizae Radix et Rhizoma* mitigated the nature of various herbs and reconciled medicines as assistant drugs. The compatibility of multiple herbs could dispel wind-dampness and relieve pain (Zhang et al., 2023). Viticis Fructus was an assistant drug in the prescription and mainly played the role of dispelling wind and relieving pain. Pharmacological research has supported its therapeutic roles (Chu et al., 2020; Li et al., 2020b). The other is the Qing-Shang-Juan-Tong Decoction recorded in *Shoushi Baoyuan* of Gong TingXian. The prescription included *Radix Angelicae Sinensis*, *Radix Angelicae Dahuricae*, Viticis Fructus, *etc* (Gong, 1999). It was mainly used to treat intractable pain and trigeminal neuralgia. This effect had also been supported by pharmacological studies (Wen et al., 2020; Yu et al., 2021).

Viticis Fructus could cure colds, headaches, migraines and neuralgia in Korea (Kim, et al., 2012). In India, it could be employed to improve symptoms of amenorrhoea, liver disease, rheumatic pain and other disorders (Meng et al., 2023). In Japan, it had therapeutic effects on colds, headaches, migraine and eye pain (Yan et al., 2023). Furthermore, many countries not only used the fruits of *V. trifolia* and *V. rotundifolia* to treat diseases, but also their other parts could be utilized for various illnesses. For example, Samoans had applied *V. trifolia* to relieve sprains and rheumatic pain. In Tonga, its efficacy had been clarified to cure oral infections and inflammation. In Papua New Guinea and New Caledonia, its stems and leaves could remedy dysentery (Kamal et al., 2022). In India, the flowers and leaves of *V. trifolia* were employed for fever and alopecia, respectively (Yan et al., 2023). In European herbal medicine, *V. rotundifolia* was used to relieve various diseases associated with women (Azizul et al. 2022). It is listed as a protected plant in China and Japan, so the development and utilization of multiple parts can avoid waste of resources and is conducive to sustainable development.

4.2. Processing

There are mainly two specifications for clinical use according to the 2020 edition of ChP, namely crude and stir-fry processed Viticis Fructus. The processing not only could remove non-medicinal parts, but also could moderate the nature of Viticis Fructus (Wang et al., 2010). Various processing methods were recorded in ancient books, such as crude, stir-frying (micro-fried, stir-frying coke, stir-frying char, stir-frying liquor) and steaming with liquor (**Fig. S1**, **Table S5**). The crude Viticis Fructus was first recorded with "the persistent sepal removal" both in *ShengJi ZongLu* and *Taiping Huimin Heji Jufang* in Song Dynasty (Hejiju, 1985; Zhao, 1982). Viticis Fructus had been emphasized to the removal of non-medicinal parts and crushed before use in many works. Its stir-fry processed products had micro-fried, stir-frying char and so forth. The two methods of Viticis Fructus recorded in *Boji Fang* were "washed Viticis Fructus, baked with mild fire then crushed" (Wang, 1958a). The other was "washed and then fried". According to the records of *Danxi Xingfa*, it was requested that should be "fried to black" (Zhu, 1956). "It was crushed, washed with liquor, fried and decocted" in *Yizong Cuiyan* (Luo, 1982). *Bencao Tongxuan* recorded that "the persistent calyx removal, fried with liquor and crushed" (Li, 2015). Micro-fried Viticis Fructus was the most widely used among them. Furthermore, Viticis Fructus also had a liquor steaming processing method. Traditional Chinese medicine believed that the quality of Viticis Fructus was light and the smell was mild. It moved upward to treat head and face wind. The liquor stir-frying method had contributed to treating headaches by Viticis Fructus (Yin et al., 2019). Liquor steaming was first recorded in *Leigong Paozhi Lun* (Lei, 1986). Viticis Fructus should be removed the persistent calyx and pedicle. After soaking in liquor for ten days, it was steamed for several hours and dried in the sun. Besides, it could also be prepared by boiling method, the steaming and frying method. It was recorded in *Taiping Shenghui Fang* that the ratio of medicine to liquor is 1:5. It was boiled in the liquor and dried in the sun (Wang, 1958b). However, the boiling method and the steaming and frying method were less used.

Viticis Fructus and its stir-fried products are commonly used in clinics. Their chemical constituents also changed during processing. First, whether the crude and fried products are crushed is particularly critical. The content of extract significantly increased after crushing compared with uncrushed Viticis Fructus (Wang et al., 2017a). It was explained that the scientific nature of the use after crushing was emphasized in ancient books. Secondly, the volatile oil and flavonoids in Viticis Fructus changed differently during processing. For example, the total volatile oil content in Viticis Fructus decreased after thermal processing (Wang et al., 2017b). However, the flavonoids with high melting points were not easily destroyed (Wang et al., 2010). Other studies had also displayed that the content of total flavonoids was stir-frying coke > stir-frying charcoal > slightly stir-frying = crude product (Guo et al., 2005; Zhang et al., 2003). Furthermore, the casticin content of each processed product was determined, crude Viticis Fructus < stir-frying Viticis Fructus < stir-frying Viticis Fructus with liquor < baking Viticis Fructus with liquor (Xu et al., 2020).

The pharmacological effects of processed products showed specific differences. Crude Viticis Fructus was often used for treating wind-heat headaches, red eyes, swelling and pains, while stir-fried Viticis Fructus was chiefly used for the treatment of deafness, rheumatic arthralgia and migraine (Wang et al., 2017b). The crushed crude product was suitable for the evacuation of wind-heat. The mixed frying of 10 % yellow rice liquor and Viticis Fructus was applied for analgesia (Jin et al., 2000). It was advisable to use stir-fried carbon or stir-frying Viticis Fructus with liquor to reduce blood pressure (Diao (2018)). However, there were some bifurcations in analgesic research. Some scholars regarded the analgesic effect of fried products were more potent than that of crude products. The intensity of the analgesic effect was as follows: stir-frying coke > micro-fried products > stir-frying char > crude products (Sun et al., 1997). Other scholars believed that the liquor products were more effective than the crude products, because liquor and Viticis Fructus had compatible medicinal properties (Jin et al., 2000). It had been advocated that the crude products analgesic effect was more vital than fried products (Liu, 2005). Another point of view was that the analgesic effect of crude Viticis Fructus is strong. Its analgesic effect was reduced after stir-frying and processing with liquor does not improve its analgesic effect. Crude Viticis Fructus should be used for analgesic (Gong and Wang, 2012).

Viticis Fructus has a long history as TCM application. It can cure

headaches, eye diseases, head and face wind, rheumatism, intracranial tinnitus and promote hair growth according to ancient books. Furthermore, the processing products of Viticis Fructus are mainly divided into crude, stir-frying and liquor products according to the records of ancient books. However, the primary clinical applications at present are crude Viticis Fructus and micro-fried Viticis Fructus, and more attention should be paid to other processed products. Because the types and contents of flavonoids, volatile oils and other components have been altered during the processing process, diverse processed products are appropriate for different ailments. Therefore, it is paramount to select the best processed products for disease treatment.

5. Phytochemistry

The chemical composition database of Viticis Fructus was systematically and comprehensively established and 324 compounds were isolated and identified (Table 1). It contains terpenoids, flavonoids, phenolic acids and others, of which terpenoids and flavonoids as the main compounds accounting for 57.7 % and 13.8 % (Fig. S2**a**), respectively. In addition, there were some differences in the 324 compounds isolated and identified in the two origin plants, of which 155 compounds could be isolated and identified in both origin plants (Fig. S2b).

5.1. Terpenoids

Terpenoids account for the largest proportion, mainly diterpenoids and iridoids (1–143) (Fig. 2, Fig. 3 and Fig. 4). Labdane-type diterpenoids vitexilactone (**3**), rotundifuran (**4**) and halimane-type diterpene vitetrifolin D (**7**) were isolated and purified from the ethyl acetate fraction of Viticis Fructus (Fang et al., 2019). Iridoids are also a class of special monoterpenoids composed of five-membered carbon rings and six-membered oxygen heterocycles. They mainly exist in the form of glycosides in Viticis Fructus. Two iridoids were isolated and identified from 80 % ethanol extract: 10-*O*-vanilloylaucubin (**104**) and agnuside (**150**) (Bao et al., 2018).

5.2. Flavonoids

Flavonoids are typical compounds in Viticis Fructus (**144–177**) (Fig. 5). Casticin is the only index component of Viticis Fructus in ChP, which is used to measure and evaluate the quality of Viticis Fructus. The flavonoids in Viticis Fructus are mainly divided into flavonoids, isoflavones, dihydroflavones and anthocyanins, among which flavonoids are the main compounds. Luteolin (**152**) was identified from cold soak of 95 % ethanol. Three flavonoids were isolated from chloroform fraction of Viticis Fructus: luteolin-4′-*O*-glucoside (**156**), casticin (**162**) and apigenin (**173**) (Chen et al., 2018). In addition, flavonoids in Viticis Fructus were recognized by ultra-high-performance-liquid chromatography-quadrupole-Orbitrap high-resolution mass spectrometry (UHPLC-Q-Orbitrap HRMS), including taxifolin (**149**), genistein (**151**), quercetin (**153**) (Zhang et al., 2021).

5.3. Phenolic acids

Viticis Fructus also includes phenolic acids (**178–211**) (Fig. 5), such as protocatechuic acid (**183**), neochlorogenic acid (**184**), chlorogenic acid (**185**), hydroxybenzoic acid (**186**), vanillic acid (**189**), ferulic acid (**201**) and so on (Yoshioka et al., 2004; Zhang et al., 2021). *V. trifolia* fruits were extracted with ethanol to obtain a crude extract and then further extracted with ethyl acetate. The ethyl acetate fraction was eluted with a mixture of petroleum ether and acetone, and the compounds (**179–181**) were successfully isolated and identified in the fraction (Djimabi et al., 2021).

5.4. Lignans

Thirteen lignan compounds were isolated from Viticis Fructus, which were divided into diepoxy lignans, neolignans and other types (**212–224**) (Fig. 6). Viticis Fructus extract was carried out repeatedly by column chromatography using silica gel, RP-18 and MCI gel to obtain viterolignan A (**213**), viterolignan B (**214**), ficusal (**215**) and so on (Lee et al., 2013).

5.5. Volatile oil

Fresh Viticis Fructus contains massive volatile oil. The crude and processed products of Viticis Fructus were extracted by continuous reflux in soxhlet extractors and then identified by GC–MS. A total of 56 compounds (**225–280**) were identified, such as hentriacontane (**276**), hexatriacontane (**277**), tetracontane (**278**) (Wang et al., 2017b). In another study, the volatile oil was extracted by steam distillation for 6 h and 9 compounds (**281–288**, **299**) were identified by GC–MS (Chen et al., 2007).

5.6. Other compounds

In addition to the above compounds, steroids, anthraquinones, sugars, fatty acids and alkaloids were also isolated from Viticis Fructus (Fig. 6). Three compounds (**305–307**) were identified by nuclear magnetic resonance (NMR) from Viticis Fructus extracted with 95 % ethanol (Djimabi et al., 2021). Five compounds such as karakoline (**310**) were identified from the extract of Viticis Fructus by UHPLC-Q-Orbitrap HRMS (Zhang et al., 2021). It may still contain other compounds in Viticis Fructus, which gives a direction for further research.

Various compounds had been isolated and identified from Viticis Fructus, most of which were from the fruits of *V. rotundifolia*. The main chemical constituents were terpenoids and flavonoids. Terpenoids had anti-tumor activity and most of terpenoids were diterpenes and iridoids in structure. Their structure–activity relationship should be further elucidated. Casticin had good activity in tumors, inflammation, oxidative damage and other ailments. Some studies revealed a difference in the casticin content of *V. rotundifolia* and *V. trifolia* fruits, which was possible to use as quality markers. Therefore, the extraction process optimization and batch preparation of casticin should be focused on. Moreover, the information on many compounds is not complete, such as CAS number. It is necessary to further improve the compound information to avoid the misuse of synonyms.

6. Pharmacological activities

Viticis Fructus was mainly used for treating colds, headaches, eye pain, swelling, aching of gum and dizziness according to ancient records. With the progress and development of pharmacology, it could also be used to prevent cervical cancer (Zeng et al., 2012), prostate cancer (Meng et al., 2012) and other cancers, as well as anti-inflammatory (Fang et al., 2019), antioxidant (Le et al., 2022), PMS (Ye, 2010) (Table 2). Additionally, *V. rotundifolia* fruits were more widely used in the treatment of various diseases than *V. trifolia* fruits.

6.1. Antitumor

The extract and its main compounds of Viticis Fructus had different degrees of inhibitory and preventive effects on cervical cancer, nasopharyngeal carcinoma, lung cancer, breast cancer and other cancers (Fig. 7**,** Fig. 8 and Fig. 9). Helianane diterpenoids from Viticis Fructus slowed down cell division in human chronic myeloid leukemia K562 cells and mouse breast cancer tsFT210 cells, resulting in apoptosis of cancer cells (Li et al. 2005b). The flavonoids of Viticis Fructus, such as persicogenin, artemetin and luteolin, restrained G2/M of cell cycle progression and induced mammalian cancer cell death (Li et al., 2005a).

Table 1
Isolation and identification of compounds from Viticis Fructus.

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
Terpenoids							
1	viterotulin C	$C_{24}H_{38}O_6$	422.27	N/A	*V. rotundifolia*/ *V. trifolia*	NMR	(Fang et al., 2019)
2	vitexilactone D	$C_{22}H_{34}O_5$	378.24	N/A	*V. rotundifolia*	NMR	(Fang et al., 2019)
3	vitexilactone	$C_{22}H_{34}O_5$	378.24	61263–49-8	*V. rotundifolia*/ *V. trifolia*	NMR	(Fang et al., 2019)
4	rotundifuran	$C_{22}H_{34}O_4$	362.50	50656–65-0	*V. rotundifolia*/ *V. trifolia*	NMR	(Fang et al., 2019)
5	vitetrifolin B	$C_{22}H_{34}O_4$	362.50	329763–47-5	*V. rotundifolia*/ *V. trifolia*	NMR	(Fang et al., 2019)
6	viterotulin B	$C_{22}H_{34}O_5$	378.24	1469986–05-7	*V. rotundifolia*	NMR	(Fang et al., 2019)
7	vitetrifolin D	$C_{24}H_{38}O_5$	406.60	351427–18-4	*V. rotundifolia*/ *V. trifolia*	NMR	(Fang et al., 2019)
8	(rel 5*S*,6*R*,8*R*,9*R*,10*S*)-6-acetoxy-9-hydroxy-13 (14)-labden-16,15-olide	$C_{22}H_{34}O_5$	378.24	N/A	*V. rotundifolia*/ *V. trifolia*	UV, NMR, CD, MS	(Li et al., 2005b)
9	viteagnusin I	$C_{22}H_{34}O_6$	394.50	1345994–66-2	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
10	vitetrifolin E	$C_{22}H_{36}O_4$	364.50	372967–06-1	*V. rotundifolia*/ *V. trifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
11	vitetrifolin F	$C_{22}H_{36}O_4$	364.50	372967–07-2	*V. rotundifolia*/ *V. trifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
12	vitetrifolin H	$C_{22}H_{34}O_4$	362.25	1202522–21-1	*V. rotundifolia*/ *V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
13	vitetrifolin G	$C_{20}H_{32}O_2$	304.50	372967–08-3	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
14	9,13-epoxy-16-nor-labda-13E-en-15-al	$C_{19}H_{30}O_2$	290.22	180628–06-2	*V. rotundifolia*/ *V. trifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
15	13-epi-2-oxokolavelool	$C_{20}H_{32}O_2$	304.24	221466–41-7	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
16	isolophanthin A	$C_{20}H_{30}O_2$	302.50	1370511–54-8	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
17	vitedoin B	$C_{19}H_{30}O_4$	322.40	819861–42-2	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
18	viteagnusin F	$C_{23}H_{38}O_7$	426.50	1206489–93-1	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
19	viteagnusin G	$C_{23}H_{38}O_7$	426.50	1206489–94-2	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
20	viterotulin A	$C_{20}H_{32}O_3$	320.24	1423125–18-1	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
21	(rel 3*S*,5*S*,8*R*,9*R*,10*S*)-3,9-dihydroxy-13(14)-labden-16,15-olide	$C_{20}H_{32}O_4$	336.23	1467744–96-2	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
22	viterotulin D	$C_{24}H_{38}O_6$	422.27	N/A	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
23	15,16-epoxy-9-hydroxylabda-13(16),14-diene	$C_{20}H_{32}O_2$	304.24	N/A	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
24	prevetexilactone	$C_{22}H_{34}O_5$	378.24	2730961–28-9	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
25	trisnor-γ-lactone	$C_{19}H_{30}O_4$	322.21	N/A	*V. rotundifolia*/ *V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
26	vitexifolin D	$C_{19}H_{30}O_4$	322.40	351427–21-9	*V. rotundifolia*/ *V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
27	13-hydroxy-5(10),14-halimadien-6-one	$C_{20}H_{32}O_2$	304.24	N/A	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
28	abietatrien-3β-ol	$C_{20}H_{30}O$	286.23	N/A	*V. rotundifolia*/ *V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
29	3β-acetoxyabieta-8,11,13-trien-12-ol	$C_{22}H_{32}O_3$	344.24	N/A	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
30	helipterol	$C_{20}H_{34}O$	290.26	120852–66-6	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
31	vitetrifolin I	$C_{20}H_{34}O_3$	322.25	1202522–22-2	*V. trifolia*	MS, NMR, IR	(Wu et al., 2009)
32	6-acetoxy-9-hydroxy-13(14)-labdane-16,15-olide	$C_{22}H_{34}O_5$	378.24	329976–53-6	*V. trifolia*	MS, NMR, IR	(Wu et al., 2009)
33	previtexilactone	$C_{22}H_{34}O_5$	378.50	106894–28-4	*V. trifolia*	MS, NMR, IR	(Wu et al., 2009)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
34	6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane	$C_{23}H_{38}O_5$	394.27	248925–24-8	*V. trifolia*	MS, NMR, IR	(Wu et al., 2009)
35	vitetrifolin A	$C_{20}H_{32}O_3$	320.24	329763–38-4	*V. trifolia*	X-ray crystallographic analysis, NMR, MS	(Ono et al., 2000)
36	vitetrifolin C	$C_{22}H_{32}O_4$	360.23	329763–48-6	*V. trifolia*	NMR, MS	(Ono et al., 2000)
37	dihydrosolidagenone	$C_{20}H_{30}O_3$	318.22	N/A	*V. trifolia*	NMR, MS	(Ono et al., 2000)
38	vitrifolin B	$C_{22}H_{36}O_5$	380.26	1681015–93-9	*V. trifolia*	HRESIMS, IR, NMR	(Wang et al., 2014)
39	vitexlactam A	$C_{22}H_{35}NO_4$	377.26	459167–05-6	*V. trifolia*	HRESIMS, IR, NMR	(Wang et al., 2014)
40	vitextrifolin A	$C_{24}H_{40}O_6$	424.28	1418297–87-6	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
41	vitextrifolin B	$C_{24}H_{40}O_6$	424.28	1418297–88-7	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
42	vitextrifolin C	$C_{22}H_{32}O_4$	360.23	1418297–89-8	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
43	vitextrifolin D	$C_{20}H_{30}O_3$	318.22	1418297–90-1	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
44	vitextrifolin E	$C_{20}H_{30}O_3$	318.22	1418297–91-2	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
45	vitextrifolin F	$C_{20}H_{32}O_4$	336.23	1418297–92-3	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
46	vitextrifolin G	$C_{20}H_{30}O_3$	318.22	1418297–93-4	*V. trifolia*	COSY-NMR, HRESIMS, IR, NOESY-NMR	(Zheng et al., 2013)
47	isoambreinolide	$C_{17}H_{28}O_2$	264.21	18676–08-9	*V. trifolia*	HRFABMS, IR, UV, NMR	(Kiuchi et al., 2004)
48	(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	$C_{26}H_{42}O_{10}$	514.31	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
49	viteagnuside A	$C_{26}H_{42}O_9$	498.60	1401711–97-4	*V. rotundifolia*/ *V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
50	vitrifolin A	$C_{19}H_{28}O_5$	336.42	1469746–48-2	*V. rotundifolia*	HRESIMS, IR, NMR	(Zhang et al., 2013)
51	ent-2-oxo-15,16,19-trihydroxy-pimar-8 (14)-ene	$C_{20}H_{32}O_4$	336.50	N/A	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
52	leucasin A	$C_{28}H_{46}O_{11}$	558.30	1423779–98-9	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
53	leucasin B	$C_{28}H_{46}O_{11}$	558.30	1423779–99-0	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
54	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*R*,15*R*)-6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane	$C_{23}H_{38}O_5$	394.27	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
55	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*R*,15*S*)-6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane	$C_{23}H_{38}O_5$	394.27	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
56	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*S*)-6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane	$C_{23}H_{38}O_5$	394.27	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
57	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*R*)-6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane	$C_{23}H_{38}O_5$	394.27	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
58	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*S*,16*R*)-6-acetoxy-9,13;15–16-diepoxy-15,16-methoxylabdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
59	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*R*,16*R*)-6-acetoxy-9,13;15–16-diepoxy-15,16-dimethoxylabdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
60	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*S*,16*S*)-6-acetoxy-9,13;15–16-diepoxy-15,16-dimethoxylabdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
61	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,15*R*,16*S*)-6-acetoxy-9,13;15–16-diepoxy-15,16-dimethoxylabdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
62	ferruginol	$C_{20}H_{30}O$	286.50	514–62-5	*V. rotundifolia*	NMR, X-ray crystallographic analysis	(Ono et al., 1999)
63	vitexifolin A	$C_{20}H_{34}O$	290.50	351427–17-3	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)

(*continued on next page*)

Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
64	vitexifolin B	$C_{20}H_{36}O_3$	324.50	2730967–87-8	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
65	vitexifolin C	$C_{20}H_{28}O$	284.40	351427–23-1	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
66	vitexifolin E	$C_{20}H_{32}O_4$	336.50	351427–22-0	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
67	manool	$C_{20}H_{34}O$	290.50	596–85-0	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
68	vitexfolin A	$C_{25}H_{28}O_{11}$	504.50	N/A	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)
69	vitexfolin C	$C_{23}H_{26}O_{10}$	462.40	N/A	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
70	(rel 5*S*,6*R*,8*R*,9*R*,10*S*)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide	$C_{22}H_{34}O_5$	378.24	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
71	(rel 5*S*,6*S*,8*R*,9*R*,10*S*)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide	$C_{22}H_{34}O_5$	378.24	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
72	(rel 5*S*,6*R*,8*R*,9*R*,10*S*)-6-acetoxy-9-hydroxy-15-methoxy-13(14)-labden-16,15-olide	$C_{23}H_{36}O_6$	408.25	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
73	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*,16*S*)-6-acetoxy-9,13-epoxy-16-methoxy-labdan-15,16-olide	$C_{23}H_{36}O_6$	408.25	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
74	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*R*,16*S*)-6-acetoxy-9,13-epoxy-16-methoxy-labdan-15,16-olide	$C_{23}H_{36}O_6$	408.25	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
75	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*S*)-6-acetoxy-9,13-epoxy-15-methoxy-labdan-16,15-olide	$C_{23}H_{36}O_6$	408.25	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
76	(rel 5*S*,6*R*,8*R*,9*R*,10*S*,13*R*)-6-acetoxy-9,13-epoxy-15-methoxy-labdan-16,15-olide	$C_{23}H_{36}O_6$	408.25	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
77	(rel 5*S*,8*R*,9*R*,10*S*,13*S*,15*S*,16*R*)-9,13;15,16-Diepoxy-15,16-dimethoxy-labdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
78	(rel 5*S*,8*R*,9*R*,10*S*,13*S*,15*R*,16*S*)-9,13;15,16-Diepoxy-15,16-dimethoxy-labdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
79	(rel 5*S*,8*R*,9*R*,10*S*,13*S*,15*R*,16*R*)-9,13;15,16-Diepoxy-15,16-dimethoxylabdane	$C_{24}H_{40}O_6$	424.28	N/A	*V. rotundifolia*	MS, NMR	(Ono et al., 2001)
80	negundol	$C_{22}H_{34}O_6$	394.24	1421609–79-1	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
81	deacetyl vitexilactone	$C_{20}H_{32}O_4$	336.23	885069–79-4	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
82	6β-acetoxyl-9α,16-dihydroxy-13(14)-labden-15,16-olide	$C_{22}H_{34}O_6$	394.24	1345994–66-2	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
83	vitexilactone B	$C_{22}H_{34}O_5$	378.24	1276541–12-8	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
84	viterofolin A	$C_{20}H_{34}O_3$	322.25	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
85	viterofolin B	$C_{20}H_{34}O_3$	322.25	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Oh et al., 2024)
86	viterofolin C	$C_{20}H_{32}O_2$	304.24	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
87	viterofolin D	$C_{20}H_{34}O_2$	306.26	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
88	viterofolin E	$C_{20}H_{34}O_2$	306.26	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
89	viterofolin F	$C_{21}H_{34}O_2$	318.26	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
90	viterofolin G	$C_{21}H_{34}O_2$	318.26	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
91	viterofolin H	$C_{20}H_{34}O_2$	306.26	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
92	viterofolin I	$C_{24}H_{38}O_6$	422.27	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
93	viterofolin J	$C_{20}H_{32}O_3$	320.24	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
94	viterofolin K	$C_{20}H_{32}O_2$	304.24	N/A	*V. rotundifolia*	NMR, IR, HRESIMS	(Yin, 2015)
95	sclareol	$C_{20}H_{36}O_2$	308.50	515–03-7	*V. rotundifolia*/ *V. trifolia*	MS, NMR	(Gu, 2007)
96	vitexoid	$C_{10}H_{16}O_3$	184.11	1202522–23-3	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
97	(1*R*,2*R*,4*S*)-2-*endo*-hydroxy-1,8-cineole-β-*D*-glucopyranoside	$C_{16}H_{28}O_7$	332.18	155836–26-3	*V. rotundifolia*	NMR, MS	(Wu et al., 2010)

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Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
98	pedicularis-lactone	$C_9H_{12}O_4$	184.07	N/A	*V. rotundifolia*/ *V. trifolia*	NMR	(Yu et al., 2021)
99	viteoid I	$C_9H_{12}O_4$	184.07	193969–04-9	*V. rotundifolia*/ *V. trifolia*	NMR	(Yu et al., 2021)
100	viteoid II	$C_9H_{12}O_4$	184.07	193969–06-1	*V. rotundifolia*/ *V. trifolia*	NMR	(Yu et al., 2021)
101	iridolactone	$C_9H_{12}O_4$	184.07	138913–55-0	*V. rotundifolia*/ *V. trifolia*	NMR	(Yu et al., 2021)
102	eucommiol	$C_9H_{16}O_4$	188.10	55930–44-4	*V. trifolia*	HRESIMS, IR, UV, NMR	(Gu et al., 2008)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
103	(1*S*,5*S*,6*R*,9*R*)-10-*O*-p-hydroxybenzoyl-5,6*β*-dihydroxyiridoid 1-*O*-*β*-*D*-glucopyranoside	$C_{22}H_{26}O_{12}$	482.14	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
104	10-*O*-vanilloylaucubin	$C_{23}H_{28}O_{12}$	496.50	193969–08-3	*V. rotundifolia*/ *V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
105	agnuside	$C_{22}H_{26}O_{11}$	466.40	11027–63-7	*V. rotundifolia*/ *V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
106	nishindaside	$C_{23}H_{30}O_{12}$	498.17	88204–92-6	*V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
107	3-normal-butyl-nishindaside	$C_{26}H_{36}O_{12}$	540.22	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
108	3-normal-butyl-isonishindaside	$C_{26}H_{36}O_{12}$	540.22	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Bao et al., 2018)
109	1-oxo-eucommiol	$C_9H_{14}O_5$	202.08	N/A	*V. trifolia*	NMR, HRFABMS, IR,	(Ono et al., 1997)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
110	(7*R*,8*S*)-dihydrodehydrodiconiferyl alcohol 9-*O*-*β*-*D*-glucopyranoside	$C_{26}H_{34}O_{11}$	522.50	N/A	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
111	6′,10-di-*O*-(4-hydroxybenzoyl) aucubin	$C_{29}H_{30}O_{13}$	586.17	N/A	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
112	4,10-aromadendranediol	$C_{15}H_{26}O_2$	238.37	70051–38-6	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
113	spathulenol	$C_{15}H_{24}O$	220.35	6750–60-3	*V. trifolia*	MS, NMR	(Gu, 2007)
114	ent-4*α*,10*β*-dihydroxyaromadendrane	$C_{15}H_{26}O_2$	238.19	N/A	*V. rotundifolia*/ *V. trifolia*	NMR, IR, HRESIMS	(Yin, 2015)
115	3*β*-hydroxy-30-al-urs-12-en-28-oic acid	$C_{30}H_{46}O_4$	470.68	N/A	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
116	ursolic acid	$C_{30}H_{48}O_3$	456.70	77–52-1	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
117	taraxerol	$C_{30}H_{50}O$	426.72	127–22-0	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
118	taraxerone	$C_{30}H_{48}O$	424.70	514–07-8	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
119	*α*-amyrin	$C_{30}H_{50}O$	426.72	638–95-9	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
120	*β*-amyrin	$C_{30}H_{50}O$	426.72	559–70-6	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
121	lupeol	$C_{30}H_{50}O$	426.70	545–47-1	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
122	betulinic acid	$C_{30}H_{48}O_3$	456.70	472–15-1	*V. rotundifolia*	IR, NMR, MS	(Huang et al., 2016)
123	tormentic acid	$C_{30}H_{48}O_5$	488.70	13850–16-3	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
124	2*α*,3*β*,23-trihydroxyolean-12-en-28-oic acid	$C_{30}H_{48}O_5$	488.70	102519–34-6	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
125	dammarenediol-I 3*S*-*O*-*β*-glucopyranoside	$C_{36}H_{62}O_7$	606.45	N/A	*V. rotundifolia*	FAB-MS, NMR	(Ono et al., 1998a)
126	arjunglucoside	$C_{36}H_{58}O_{11}$	666.80	62319–70-4	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
127	nigaichigoside F1	$C_{36}H_{58}O_{11}$	666.80	95262–48-9	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
128	3-oxotaraxer-14-en-30-al	$C_{30}H_{46}O_2$	438.35	1527520–76-8	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
129	3-epiursolic acid	$C_{30}H_{48}O_3$	456.70	989–30-0	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
130	2*α*,3*β*-dihydroxyurs-12-en-28-oic acid	$C_{30}H_{48}O_4$	472.36	4547–24-4	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
131	*β*-daucosterol	$C_{35}H_{60}O_6$	576.85	474–58-8	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
132	oleanolic acid	$C_{30}H_{48}O_3$	456.70	508–02-1	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
133	maslinic acid	$C_{30}H_{48}O_4$	472.70	4373–41-5	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
134	betulinaldehyde	$C_{30}H_{48}O_2$	440.70	13159–28-9	*V. trifolia*	MS, NMR	(Gu, 2007)
135	8-hydroxycolumbin	$C_{20}H_{22}O7$	374.39	104513–87-3	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
136	atractylenolide II	$C_{15}H_{20}O_2$	232.32	73069–14-4	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)

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Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
137	neoandrographolide	$C_{26}H_{40}O_8$	480.59	27215–14-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
138	atractylenolide I	$C_{15}H_{18}O_2$	230.30	73069–13-3	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
139	2α,19α-dihydroxyur-3-oxo-urs-12-en-28-oic acid	$C_{30}H_{46}O_5$	486.68	176983–21-4	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
140	euscaphic acid	$C_{30}H_{48}O_5$	488.70	53155–25-2	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
141	enoxolone	$C_{30}H_{46}O_4$	470.68	471–53-4	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
142	2α-hydroxyursolic acid	$C_{30}H_{48}O_4$	472.70	52213–27-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
143	viteoside A	$C_{28}H_{44}O_{11}$	556.60	209899–63-8	*V. rotundifolia*	MS, NMR	(Ono et al., 1998b)
Flavonoids							
144	schaftoside	$C_{26}H_{28}O_{14}$	564.50	51938–32-0	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
145	kaempferil-3-*β*-*D*-glucopyranoside	$C_{21}H_{20}O_{11}$	448.09	N/A	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
146	cyanidin-3-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.11	N/A	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
147	vitexin	$C_{21}H_{20}O_{10}$	432.38	3681–93-4	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
148	cynaroside	$C_{21}H_{20}O_{11}$	448.38	5373–11-5	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
149	taxifolin	$C_{15}H_{12}O_7$	304.25	480–18-2	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
150	5,3′-dihydroxy-6,7,4′-trimethoxy-flavanone	$C_{18}H_{18}O_7$	346.11	N/A	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
151	genistein	$C_{15}H_{10}O_5$	270.24	446–72-0	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
152	luteolin	$C_{15}H_{10}O_6$	286.24	491–70-3	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
153	quercetin	$C_{15}H_{10}O_7$	302.23	117–39-5	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
154	5,3′-dihydroxy-6,7,5′-trimethoxyflavanone	$C_{18}H_{16}O_7$	344.09	N/A	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
155	penduletin	$C_{18}H_{16}O_7$	344.32	569–80-2	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
156	luteolin-4′-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.38	6920–38-3	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
157	hypolaetin-7-*O*-*β*-*D*-glucopyranoside	$C_{21}H_{20}O_{12}$	464.40	32455–43-9	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
158	swertisin	$C_{22}H_{22}O_{11}$	462.40	6991–10-2	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
159	agestricin D	$C_{18}H_{18}O_7$	346.30	85563–76-4	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
160	eupatorin	$C_{18}H_{16}O_7$	344.32	855–96-9	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
161	casticin-3′-*O*-*β*-*D*-glucopyranoside	$C_{25}H_{28}O_{13}$	536.15	N/A	*V. rotundifolia*	HRESIMS, IR, UV, NMR	(Zhao et al., 2017)
162	casticin/vitexicarpin	$C_{19}H_{18}O_8$	374.30	479–91-4	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
163	artemetin	$C_{20}H_{20}O_8$	388.37	479–90-3	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
164	centaureidin	$C_{18}H_{16}O_8$	360.30	17313–52-9	*V. rotundifolia*	HRFABMS, NMR	(Ono et al., 2002)
165	5,5′-dihydroxy-4′,6,7-trimethoxyflavanone	$C_{18}H_{18}O_6$	330.11	N/A	*V. rotundifolia*	IR, NMR	(Yoshioka et al., 2004)
166	kaempferol	$C_{15}H_{10}O_6$	286.24	520–18-3	*V. rotundifolia*	NMR, MS	(Wu et al., 2010)
167	chrysospleol D	$C_{18}H_{16}O_8$	360.32	14965–20-9	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
168	persicogenin	$C_{17}H_{16}O_6$	316.30	28590–40-1	*V. trifolia*	UV, NMR, MS	(Li et al., 2005a)
169	luteolin 7-methyl ether	$C_{16}H_{12}O_6$	300.26	20243–59-8	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
170	3′,4′,5-trihydroxy-3,7-dimethoxy-flavone	$C_{17}H_{14}O_7$	330.29	2068–02-2	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
171	acacetin	$C_{16}H_{12}O_5$	284.26	480–44-4	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
172	3′,4′,7-trimethoxy-5-hydroxy-flavanone	$C_{18}H_{16}O_6$	328.32	29080–58-8	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
173	apigenin	$C_{15}H_{10}O_5$	270.24	520–36-5	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
174	4′,5-dihydroxy-3, 6,7-trimethoxy-flavone	$C_{17}H_{14}O_6$	314.08	41365–32-6	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
175	7,3′-dihydroxy-5′-methoxy-isoflavone	$C_{16}H_{12}O_5$	284.26	947611–61-2	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
176	isoorientin	$C_{21}H_{20}O_{11}$	448.38	4261–42-1	*V. rotundifolia*	HRESIMS, IR, NMR	(Zhang et al., 2013)
177	oroxylin A	$C_{16}H_{12}O_5$	284.26	480–11-5	*V. rotundifolia*/ *V. trifolia*	IR, MS, NMR	(Xin, 2005)
Phenols							
178	p-hydroxybenzoic acid ethyl ester	$C_9H_{10}O_3$	166.17	120–47-8	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
179	p-hydroxyacetophenone	$C_8H_8O_2$	136.15	99–93-4	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
180	vanillin	$C_8H_8O_3$	152.15	121–33-5	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
181	coniferaldehyde	$C_{10}H_{10}O_3$	178.18	458–36-6	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)

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Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
182	9,12,15-octadecatrienoic acid	$C_{18}H_{30}O_2$	278.40	28290–79-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
183	protocatechuic acid	$C_7H_6O_4$	154.12	99–50-3	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
184	neochlorogeinic acid	$C_{16}H_{18}O_9$	354.31	906–33-2	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
185	chlorogenic acid	$C_{16}H_{18}O_9$	354.31	327–97-9	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
186	hydroxybenzoic acid	$C_7H_6O_3$	138.12	99–96-7	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
187	salicylic acid	$C_7H_6O_3$	138.12	69–72-7	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
188	ω-hydroxypropioguaiacone	$C_{10}H_{12}O_4$	196.20	2196–18-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
189	vanillic acid	$C_8H_8O_4$	168.15	121–34-6	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
190	4-p-coumaroylquinic acid	$C_{16}H_{18}O_8$	338.31	93451–44-6	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
191	apocynin	$C_9H_{10}O_3$	166.17	498–02-2	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
192	cryptochlorogenic acid	$C_{16}H_{18}O_9$	354.31	905–99-7	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
193	coniferyl aldehyde	$C_{10}H_{10}O_3$	178.19	20649–42-7	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
194	3,4-Di-*O*-caffeoylquinic acid methyl ester	$C_{26}H_{26}O_{12}$	530.48	114637–83-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
195	pyrogallol	$C_6H_6O_3$	126.11	87–66-1	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
196	*erythro*-guaiacylglycerol	$C_{10}H_{14}O_5$	214.21	38916–91-5	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)
197	*threo*-guaiacylglycerol	$C_{10}H_{14}O_5$	214.08	N/A	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)
198	4-hydroxybenzoic acid methyl ester	$C_8H_8O_3$	152.05	99–76-3	*V. rotundifolia*	IR, NMR	(Yoshioka et al., 2004)
199	vanillic acid methyl ester	$C_9H_{10}O_4$	182.17	3943–74-6	*V. rotundifolia*	IR, NMR	(Yoshioka et al., 2004)
200	4-hydroxy benzaldehyde	$C_7H_6O_2$	122.12	123–08-0	*V. rotundifolia*	IR, NMR	(Yoshioka et al., 2004)
201	ferulic acid	$C_{10}H_{10}O_4$	194.18	1135–24-6	*V. rotundifolia*	IR, NMR	(Yoshioka et al., 2004)
202	docosanoic acid	$C_{22}H_{44}O_2$	340.58	112–85-6	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
203	tetracosanoic acid	$C_{24}H_{48}O_2$	368.64	557–59-5	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
204	cerotic acid	$C_{26}H_{52}O_2$	396.69	506–46-7	*V. rotundifolia*	NMR, IR, HRESIMS	(Huang et al., 2013)
205	4-ethoxyphenol	$C_8H_{10}O_2$	138.16	622–62-8	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
206	1-ethoxy-4-methoxybenzene	$C_9H_{12}O_2$	152.19	5076–72-2	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
207	p-cresol	C_7H_8O	108.14	106–44-5	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
208	3-p-tolylpropanoic acid	$C_{10}H_{12}O_2$	164.20	1505–50-6	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
209	raspberry ketone	$C_{10}H_{12}O_2$	164.20	5471–51-2	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
210	α-hydroxy acetovanillone	$C_9H_{10}O_4$	182.06	N/A	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
211	phenyl β-*D*-glucopyranoside	$C_{12}H_{16}O_6$	256.25	1464–44-4	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
Lignan							
212	(7*S*,8*R*)-dihydrodehydrodiconiferyl alcohol	$C_{20}H_{24}O_6$	360.16	28199–69-1	*V. rotundifolia*/*V. trifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
213	viterolignan A	$C_{21}H_{24}O_7$	388.15	1469986–06-8	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
214	viterolignan B	$C_{22}H_{26}O_7$	402.17	1469986–07-9	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
215	ficusal	$C_{18}H_{18}O_6$	330.30	321991–55-3	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
216	(+)-lariciresinol	$C_{20}H_{24}O_6$	360.40	27003–73-2	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
217	ficusesquilignan A	$C_{31}H_{36}O_{11}$	584.23	321991–56-4	*V. rotundifolia*	UV, NMR, CD, MS	(Lee et al., 2013)
218	vitrifol A	$C_{30}H_{34}O_9$	538.22	1111080–82-0	*V. trifolia*	IR, UV, NMR, HRESIMS	(Gu et al., 2008)
219	dihydrodehydrodiconiferyl alcohol	$C_{20}H_{24}O_6$	360.40	28199–69-1	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
220	salicifoliol	$C_{13}H_{14}O_5$	250.25	125564–65-0	*V. rotundifolia*	MS, NMR	(Chen et al., 2018)
221	(+)-sesamin	$C_{20}H_{18}O_6$	354.40	607–80-7	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
222	4-hydroxysesamin	$C_{20}H_{18}O_7$	370.40	63427–86-1	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
223	(+)-paulownin	$C_{20}H_{18}O_7$	370.35	13040–46-5	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
224	4, 8-dihydroxysesamin	$C_{20}H_{18}O_7$	370.11	63398–39-0	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)

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Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
Volatile oil							
225	1-vinyl-1-methyl-4-methylene-2-(2-methyl-1-propen-1-yl) cycloheptane	$C_{15}H_{24}$	204.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
226	1,3,3-trimethyl-2-(1-methylbutene-1-ene-3-carbonyl) cyclohexene	$C_{14}H_{22}O$	206.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
227	(7α-isopropenyl-4,5-dimethyl-octahydro-inden-4-yl) methanol	$C_{15}H_{26}O$	222.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
228	caryophyllene oxide	$C_{15}H_{24}O$	220.35	1139–30-6	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
229	2,6-dimethyl-3-citronellylpyrazine	$C_{16}H_{26}N_2$	246.39	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
230	4-(2,7,7-trimethylcyclo [3.2.0] hept-2-en-1-yl)-3-en-2-one	$C_{14}H_{20}O$	204.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
231	7-isopropyl-1,1,4α-trimethyl-1,2,3,4,4α, 9,10,10α-octahydrophenanthrene	$C_{20}H_{30}$	270.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
232	2,4α, 8, 8-tetramethyl-decahydrocyclopropane [d]-nai	$C_{15}H_{26}$	206.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
233	methyl abietate	$C_{21}H_{32}O_2$	316.50	127–25-3	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
234	9,19-cycloergost-24(28)-en-3-ol,4,14-dimethyl-acetate (3α,4α,5α)	$C_{32}H_{52}O_2$	468.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
235	cedranone	$C_{15}H_{24}O$	220.35	68891–95-2	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
236	3α, 9β-dihydroxy-3,5α, 8-trimethyl-tricyclo [6.3.1.0 (1,5)] dodecane	$C_{15}H_{26}O_2$	238.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
237	13-heptadecen-1-ol	$C_{17}H_{32}O$	252.00	56554–77-9	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
238	α-bisabolene	$C_{15}H_{24}$	204.00	17627–44-0	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
239	(−)-globulol	$C_{15}H_{26}O$	222.36	489–41-8	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
240	sclareol oxide	$C_{18}H_{30}O$	262.00	5153–92-4	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
241	(1*S*,2*E*,4*S*,5*R*,7*E*,11*E*)-2,7,11-cembratriene	$C_{20}H_{34}O_2$	306.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
242	3,7-dimethyl-1-acetoxy-6,11-undecene	$C_{16}H_{28}O_2$	252.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
243	3,3α-epoxydicyclopenta [a, d] cyclooctan-4β-ol,9,10α-dimethyl-6-methylene-3β-isopropyl	$C_{20}H_{32}O_2$	304.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
244	1-(2,8,8-trimethyl-5,6,7,8-tetrahydro-4H-cycloheptatrieno [b] furan-5-yl) ethanone	$C_{14}H_{20}O_2$	220.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
245	4-(2,6,6-trimethyl-cyclohexen-1-yl)-butane-2-ol	$C_{13}H_{24}O$	196.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
246	2,5,5,8α-Tetramethyloctahydro-2H-benzopyran	$C_{13}H_{24}O$	196.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
247	acetic acid,1- [2-(2,2,6-trimethyl-bicyclo [4.1.0] hept-1-yl)-ethyl]-vinyl ester	$C_{16}H_{26}O_2$	250.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
248	di (2-ethyl hexyl) adipate (deha)	$C_{22}H_{42}O_4$	370.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
249	9,11-dedihydrotestosterone, acetate	$C_{21}H_{28}O_3$	328.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
250	(−)-epicedrol	$C_{15}H_{26}O$	222.37	19903–73-2	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
251	17-hydroxyandrostane-3,11-dione	$C_{19}H_{28}O_3$	304.00	1010823–99-0	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
252	cedrol	$C_{15}H_{26}O$	222.37	77–53-2	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
253	2,2,4-trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl)-cyclohexanol	$C_{30}H_{52}O$	428.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
254	cyclodecacyclotetradecene,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20-eicosahydro	$C_{22}H_{40}$	304.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)

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Table 1 (*continued*)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
255	1,4-methanoazulen-9-one, decahydro-1,5,5,8α-tetramethyl-[1*R*-(lα-3$\alpha\beta$,4α,8$\alpha\beta$)]	$C_{15}H_{24}O$	220.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
256	oxalic acid,2-ethylhexyl octadecyl ester	$C_{28}H_{54}O_4$	454.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
257	8-propoxy cedrane	$C_{18}H_{32}O$	264.40	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
258	trumpet alcohol	$C_{15}H_{26}O$	222.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
259	4-(2,2,6-trimethyl-bicyclo [4.1.0] hept-1-yl)-butan-2-one	$C_{14}H_{24}O$	208.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
260	*cis*-2,3,4,4α, 5,6,7,8-octahydro-1,1,4α, 7-tetramethyl-1H-benzocycloheptene-7-ol	$C_{15}H_{26}O$	222.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
261	*N*-(*N*-methylformamidyl)-semithiocarbazide	$C_3H_8N_4OS$	148.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
262	iron, tetracarbonyl [(6,7-eta.)-3-oxabicyclo [3.2.0] hept-6-ene-2,4-dione]	$C_{10}H_4FeO_7$	292.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
263	spiro [2.5] octane,5,5-dimethyl-4-(3-oxobutyl)	$C_{14}H_{24}O$	208.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
264	1β,4α-epoxy-2H-cyclopenta [3,4] cyclopropa [8,9] cycloundec[1,2-b] oxiren-5(6H)-one,7-(acetyloxy) decahydro-2,9,10-trihydroxy-3,6,8,8,10a-pentamethyl	$C_{22}H_{32}O_8$	424.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
265	valeric acid,2,6-dimethylnon-1-en-3-yn-5-yl ester	$C_{16}H_{26}O_2$	250.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
266	thunbergol	$C_{20}H_{34}O$	290.00	25269–17-4	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
267	4,8,13-doufatriene-1,3-diol	$C_{20}H_{34}O_2$	306.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
268	cholestan-3,5-diol-6-one,3-acetate	$C_{29}H_{48}O_4$	460.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
269	D-homo-24-nor-17-oxachola-20,22-diene-3,7,16-trione,14,15:21,23-diepoxy-4,4,8-trimethyl-(5α,13α,14β,15β,17α)	$C_{26}H_{32}O_6$	440.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
270	8-n-Hexylpentadecane	$C_{21}H_{44}$	296.57	13475–75-7	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
271	squalene	$C_{30}H_{50}$	410.71	7683–64-9	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
272	heneicosane	$C_{21}H_{44}$	296.57	629–94-7	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
273	3-keto-*N*-acetyl-dihydro-pseudotomatidine	$C_{29}H_{47}NO_3$	457.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
274	pentacosane	$C_{25}H_{52}$	352.68	629–99-2	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
275	tetrahy droactinidiolide	$C_{11}H_{18}O_2$	182.26	16778–27-1	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
276	hentriacontane	$C_{31}H_{64}$	436.84	630–04-6	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
277	hexatriacontane	$C_{36}H_{74}$	506.00	630–06-8	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
278	tetracontane	$C_{40}H_{82}$	563.08	4181–95-7	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
279	(1*S*,2*E*,4*S*,6*R*,7*E*)-2,7,11-cembratriene	$C_{20}H_{34}O_2$	306.00	N/A	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
280	n-tetratetracontane	$C_{44}H_{90}$	619.19	7098–22-8	*V. rotundifolia*	GC–MS	(Wang et al., 2017b)
281	α-thujene	$C_{10}H_{16}$	136.00	470–82-6	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
282	Δ^3-carene	$C_{10}H_{16}$	136.00	13466–78-9	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
283	camphene	$C_{10}H_{16}$	136.234	79–92-5	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
284	β-phellandrene	$C_{10}H_{16}$	136.00	555–10-2	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
285	sabinene	$C_{10}H_{16}$	136.234	3387–41-5	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
286	β-pinene	$C_{10}H_{16}$	136.00	127–91-3	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
287	m-cymene	$C_{10}H_{14}$	134.22	535–77-3	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
288	1, 8-cineole	$C_{10}H_{18}O$	154.00	N/A	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
289	eucalyptone	$C_{28}H_{38}O_7$	486.597	172617–99-1	*V. rotundifolia*	GC–MS	(Luo et al., 2015)
290	β-terpineol	$C_{10}H_{18}O$	154.249	138–87-4	*V. rotundifolia*	GC–MS	(Luo et al., 2015)
291	(5β,9β,10α)-kaur-16-ene	$C_{20}H_{32}$	272.468	20070–61-5	*V. rotundifolia*	GC–MS	(Luo et al., 2015)
292	estrone	$C_{18}H_{22}O_2$	270.366	53–16-7	*V. rotundifolia*	GC–MS	(Luo et al., 2015)
293	4-carene	$C_{10}H_{16}$	136.234	29050–33-7	*V. rotundifolia*	GC–MS	(Luo et al., 2015)
294	*cis*-vaccenic acid	$C_{18}H_{34}O_2$	282.461	506–17-2	*V. rotundifolia*	GC–MS	(Zhang et al., 2011)
295	octadeca-9,17-dienoic acid	$C_{18}H_{32}O_2$	280.445	17351–35-8	*V. rotundifolia*	GC–MS	(Zhang et al., 2011)
296	aromadendrene	$C_{15}H_{24}$	204.35	489–39-4	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
297	caryophyllene oxide	$C_{15}H_{24}O$	220.35	1139–30-6	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
298	agarospirol	$C_{15}H_{26}O$	222.366	23811–08-7	*V. rotundifolia*	GC–MS	(Chen et al., 2015)

Number	Compounds	Molecular formula	Molecular weight	CAS No.	Plant	Identification method	References
299	α-muurolene	$C_{15}H_{24}$	204.00	10208–80-7	*V. rotundifolia*	GC–MS	(Chen et al., 2007)
300	hexadecyne	$C_{16}H_{30}$	222.41	451500–33-7	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
301	α-caryophyllene	$C_{15}H_{24}$	204.35	6753–98-6	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
302	eudesmol	$C_{15}H_{28}O$	224.38	51317–08-9	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
303	limonene oxide	$C_{10}H_{16}O$	152.23	203719–54-4	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
304	3,5-di-*tert*-butylphenol	$C_{14}H_{22}O$	206.32	1138–52-9	*V. rotundifolia*	GC–MS	(Chen et al., 2015)
Other compounds							
305	stigmast-4-ene-3,6-dione	$C_{29}H_{46}O_2$	426.70	23670–94-2	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
306	6β-hydroxystigmast-4-en-3-one	$C_{29}H_{48}O_2$	428.69	36450–02-9	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
307	β-sitosterol	$C_{29}H_{50}O$	414.71	83–46-5	*V. trifolia*	HRESIMS, NMR	(Djimabi et al., 2021)
308	stigmast-4-en-6b-ol-3-one	$C_{29}H_{48}O_2$	428.00	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Gu et al., 2008)
309	7-oxositosterol	$C_{29}H_{48}O_2$	428.37	2034–74-4	*V. trifolia*	MS, NMR, IR, UV	(Zhu, 2013)
310	karakoline	$C_{22}H_{35}NO_4$	377.52	39089–30-0	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
311	panaxydol	$C_{17}H_{24}O_2$	260.37	72800–72-7	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
312	coronaric acid	$C_{18}H_{32}O_3$	296.40	6814–52-4	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
313	ricinolic acid	$C_{18}H_{34}O_3$	298.50	141–22-0	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
314	sucrose	$C_{12}H_{22}O_{11}$	342.12	57–50-1	*V. rotundifolia*	MS, NMR, IR, UV	(Zhu, 2013)
315	physcion	$C_{16}H_{12}O_5$	284.26	521–61-9	*V. rotundifolia*	HPLC, ESIMS, NMR	(Guan et al., 2010)
316	stearic acid	$C_{18}H_{36}O_2$	284.48	57–11-4	*V. rotundifolia*	GC–MS	(Hu et al., 2007)
317	pyranopyran-1,8-dione	$C_8H_4O_4$	164.01	N/A	*V. trifolia*	HRESIMS, IR, UV, NMR	(Lee et al., 2017)
318	thymylisobutyrate	$C_{14}H_{20}O_2$	220.31	5451–67-2	*V. rotundifolia*	UHPLC-Q-Orbitrap HRMS	(Zhang et al., 2021)
319	dihydrodehydrodiconiferylalcohol-β-*D*-(2′-*O*-p-hydroxybenzoyl) glucoside	$C_{33}H_{38}O_{13}$	642.23	N/A	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)
320	vanilloyl-β-*D*-(2′-*O*-p-hydroxybenzoyl) glucoside	$C_{21}H_{22}O_{11}$	450.12	N/A	*V. rotundifolia*	MS, NMR, UV	(Okuyama and Yamazaki, 1998)
321	(*E*)-3,3′-dimethoxy-4,4′-dihydroxystilbene	$C_{16}H_{16}O_4$	272.10	7329–69-3	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
322	(8*R*)-evofolin B	$C_{17}H_{18}O_6$	318.32	N/A	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
323	l-picein	$C_{14}H_{18}O_7$	298.29	530–14-3	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)
324	4-(4′-hydroxyphenyl)-2-butanone-4′-*O*-β-*D*-glucopyranoside	$C_{17}H_{24}O_7$	340.15	N/A	*V. rotundifolia*	MS, NMR	(Xu et al., 2019)

However, the anti-tumor effect of Viticis Fructus was mostly *in vitro* tests and was rarely reported *in vivo* tests. The effect should be further evaluated in combination with clinical research.

6.1.1. Breast cancer

Breast cancer cell multiplication in rats was successfully halted by the acetic acid extract of Viticis Fructus. The acetic acid extract of Viticis Fructus had a good inhibitory effect on the proliferation of breast cancer cells in rats (Guan, 2011). Casticin was of great significance for the development of breast cancer treatment drugs (Li et al., 2005a). There were three main conclusions about the therapeutic effect of casticin on breast cancer. (1) Casticin could act directly on cyclin A. Finally, the down-regulation of the anti-apoptotic protein B cell lymphoma-2 protein (Bcl-2) led to apoptosis (Haïdara et al., 2006). (2) Forkhead box O3 (FOXO3a) was a crucial mediator for casticin inducing apoptosis of breast cancer cells (Liu, 2014). (3) It inhibited the expression of matrix metalloproteinase-9 (MMP-9) *via* curbing phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, preventing breast cancer cells from migration and invasion (Fan et al., 2018). Therefore, Viticis Fructus could prevent and treat breast cancer by blocking G2/M cell growth, acting on FOXO3a target and PI3K/AKT pathways.

6.1.2. Cervical cancer

The PI3K/AKT pathway is a key pathway for the treatment of cervical cancer by Viticis Fructus. The hot water extract of Viticis Fructus exhibited inhibition on the cervical cancer cells (Jiangsu New Medical College, 1977). Rotundifuran and casticin had been proven effective in treating cervical cancer (Chen et al., 2011). It was found that rotundifuran dramatically repressed the propagation and invoked apoptosis of cervical cancer cells. The mechanism was that it bound to cysteine-rich61 (CYR61) protein to promote the expression of CYR61, inhibited PI3K/AKT and extracellular regulated protein kinases (ERK) pathways, activated the c-Jun N-terminal kinase (JNK) pathway, up-regulated Bcl-2 interacting mediator of cell death (Bim) and Bcl-2 Associated X Protein (Bax), down-regulated Bcl-2 and B-cell lymphoma extra-large (Bcl-xL), thereby enabled activation of the mitochondrial apoptosis pathway and causing cell death (Shen, 2020). Rotundifuran inhibition of cervical cancer cell proliferation was related to mitochondrial apoptosis. Reactive oxygen species (ROS) invoked mitochondrial-dependent apoptosis *via* mitogen-activated protein kinase (MAPK) and PI3K/AKT (Gong et al., 2021). ROS and JNK could be regulated by casticin in human cervical cancer cell lines, thereby increasing intracellular ROS, promoting the expression of C-Jun protein and phosphorylated JNK to induce apoptosis (Zeng et al., 2012).

6.1.3. Lung cancer

It has been found that reducing the phosphorylation level of AKT is the main way for Viticis Fructus to alleviate lung cancer by numerous studies. The lung cancer stem-like cells (LCSLCs) of the NCI-H446 cell line could be restrained in terms of their function and characteristics by the total flavonoids of Viticis Fructus. The mechanism of action involved the reduction of AKT phosphorylation level in LCSLCs, thereby

inhibiting stem cell markers (CD133, CD44 and ALDH 1), self-renewal transcription factors (Bmil, Nanog and Oct4), invasion-related factors (Twist 1 and Snail 1) and protein expression (Cao et al., 2014). Another experiment also showed that down-regulation of p-AKT inhibited the invasion and self-renewal of LCSLCs in A549 cells, which had a certain delaying effect on lung cancer cells (Liu et al., 2014a).

6.1.4. *Liver cancer*

The extract of Viticis Fructus (the fruits of *V. rotundifolia*) had some preventive action on liver cancer cell H22. The mice tumor weight in the group receiving high-dose treatment markedly showed less than that of the control group (normal saline treatment) (Yan et al., 2023). Moreover, Viticis Fructus induced apoptosis by reducing glutathione content in human hepatocellular carcinoma (HCC) cells, up-regulating death receptor 5 (DR5) and then activating cysteinyl aspartate specific proteinase-3, -8 and -9 (caspase-3, -8 and-9) (Yang et al., 2011). It could cause forkhead box protein M1 (FOXM1) inactivation in HCC cells by inhibiting FOXO3a phosphorylation to induce growth repression and cell cycle stagnation (He et al., 2013). With the deepening of research, it had been found that casticin could effectively eradicate liver cancer stem

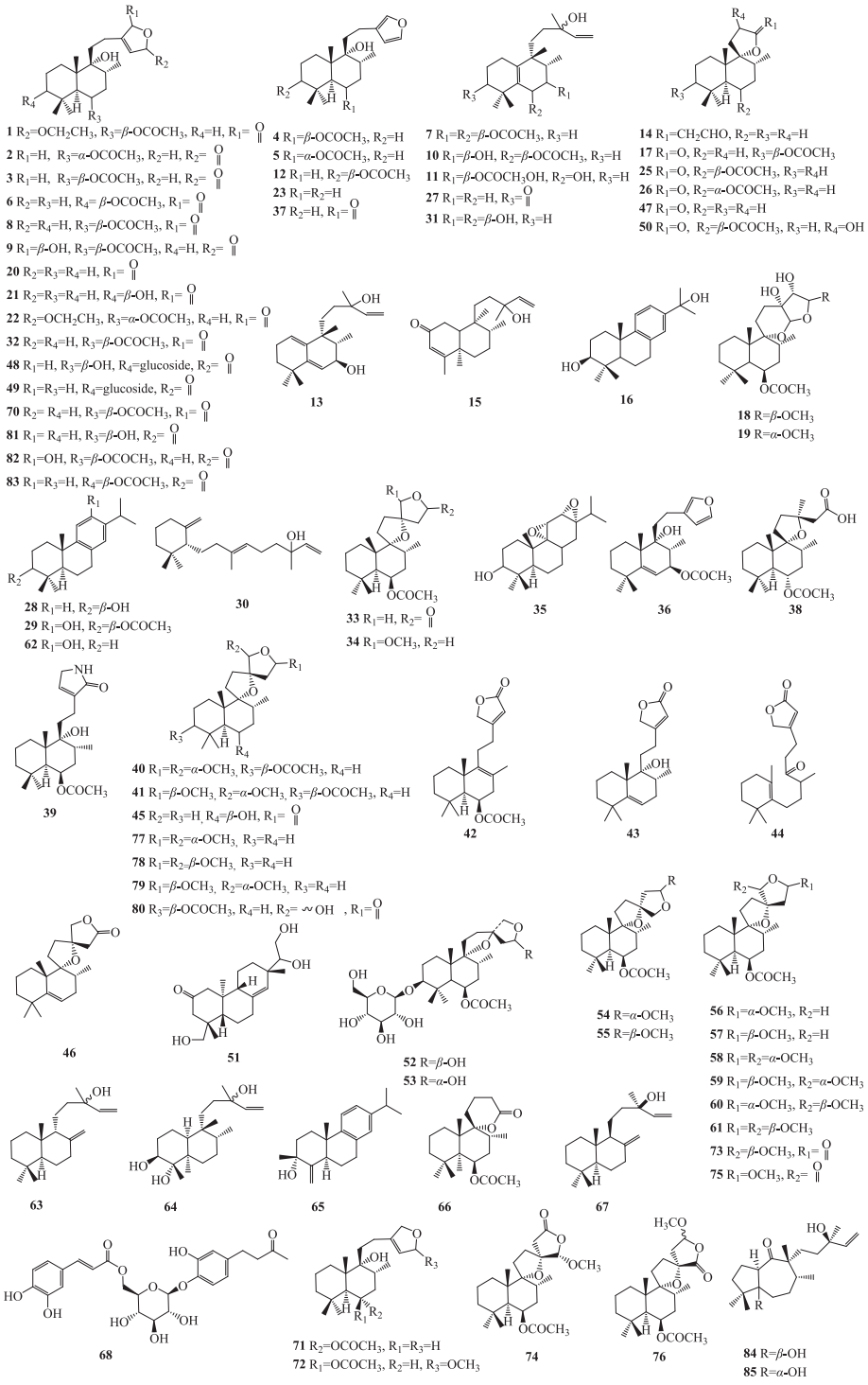

Fig. 2. Structures of terpenoids (1–85).

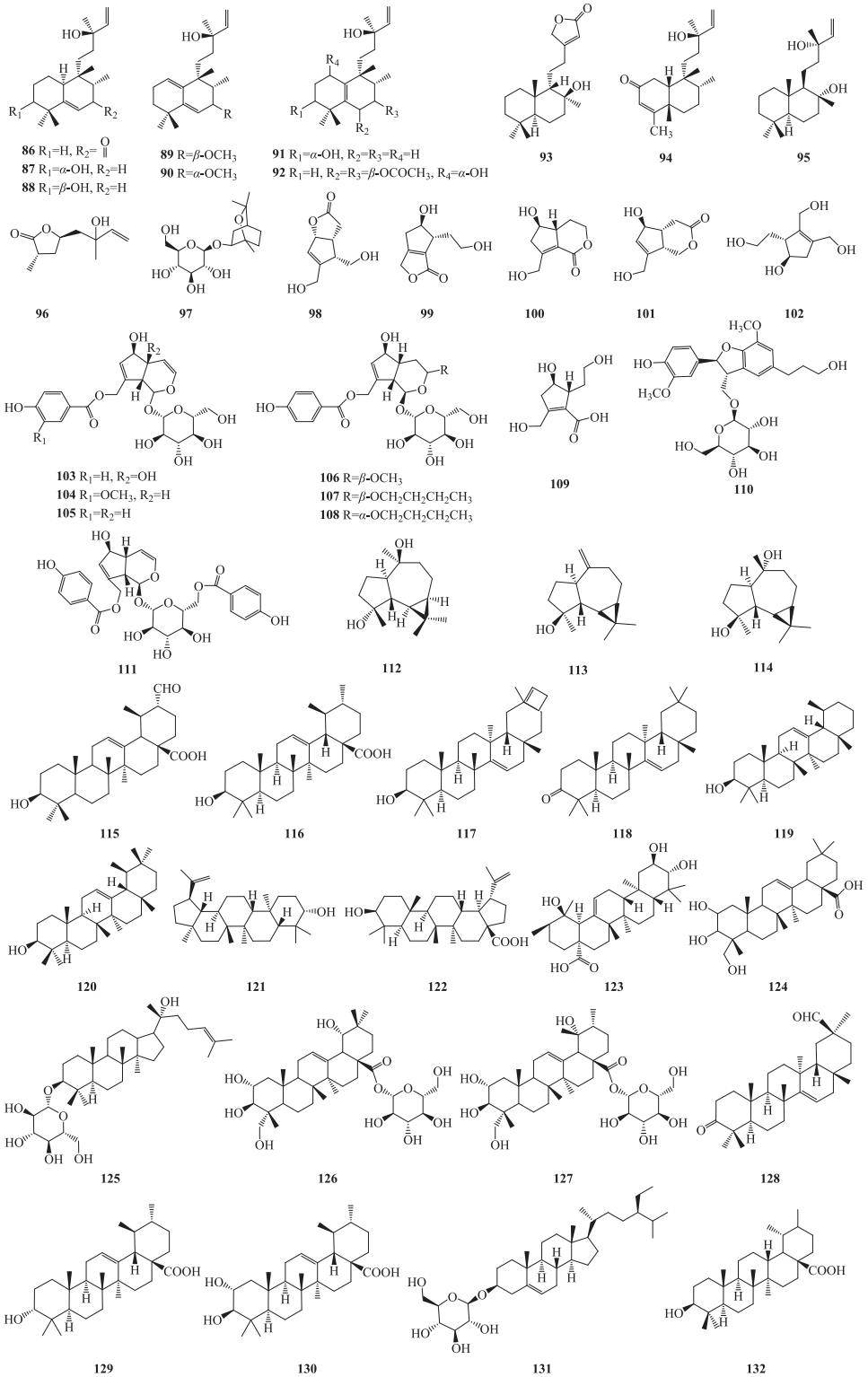

Fig. 3. Structures of terpenoids (86–132).

cells through the *β*-catenin target (He et al., 2014). It could additionally suppress the stemness characteristics of HCC cells *via* interfering with the mutual negative adjustment between miR-148a-3p and DNA methyltransferase 1 (Li et al., 2020a).

6.1.5. *Colorectal cancer*

Viticis Fructus could potentially become a candidate herb for developing chemoprevention or therapeutic drugs for human colorectal cancer (CRC). The ethanol extracts of *V. rotundifolia* fruits inhibited the proliferation of human CRC cells through down-regulating Cyclin D1 and cyclin-dependent kinases-4 (CDK4) (Yan et al., 2023). Casticin had significant proliferation inhibitory activity on HCT116 (human CRC cells) (Ono et al., 2002). It could enhance TRAIL-induced apoptosis in human CRC cells. On the one hand, it could down-regulate cell survival proteins, including X-chromosome-linked Inhibitor of apoptosis (IAP), cellular IAP1 and so forth. Furthermore, it could also up-regulate the

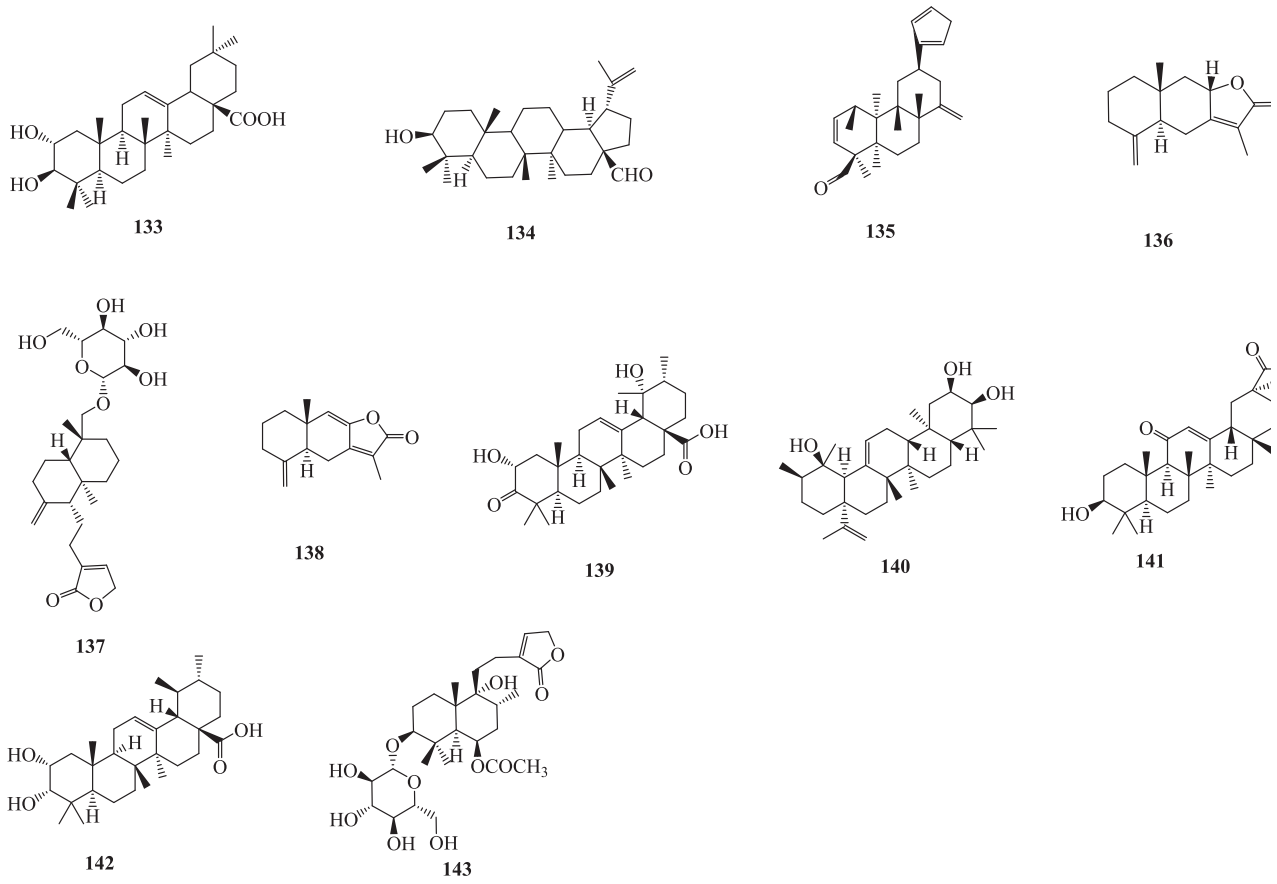

Fig. 4. Structures of terpenoids (133–143).

expression of Bax and induce DR5 (Tang et al., 2013). It could also induce apoptosis in human Colo 205 (CRC cells) by activating caspase and/or mitochondrial-dependent signaling cascades, ROS accumulation and altering the expression of related genes (Shang et al., 2017).

6.1.6. *Nasopharyngeal carcinoma*

Viticis Fructus decoction could be used to treat nasopharyngeal carcinoma (Li, 2003). Casticin suppressed the expansion of nasopharyngeal carcinoma (NPC) (Jiang et al., 2020). It inhibited the growth of NPC by targeting phosphoinositide 3-kinase (Liu et al., 2019). Inhibition of 5-8F cell (human NPC cell lines) proliferation *via* triggering cell cycle stagnation and pyroptosis, protein kinase R (PKR) /JNK axis was pivotal in caspase-1 inflammasome and the release of inflammatory cytokines (Jiang et al., 2020).

6.1.7. *Other cancers*

It was also confirmed that Viticis Fructus had the potential to treat pancreatic cancer, glioma, gastric cancer, prostate carcinoma, melanoma, leukemia, *etc*. Viticis Fructus had significant inhibitory activity on PC-12 proliferation (human lung cancer cells) (Ono et al., 2002). It greatly repressed the proliferation of PANC-1 (pancreatic carcinoma cells), mainly by arresting G2/M of the cell cycle, regulating the proportion of Bax/Bcl-2 and triggering apoptosis by activating caspase-3 (Ding et al., 2012; Huang et al., 2013). Casticin in Viticis Fructus suppressed U251 (human glioma cells) in a dose-dependent manner, which could control the polymerization of tubulin in U251 cells, block cells in G2/M phase and had a p53 and Caspase-3-dependent effect on apoptosis (Liu et al., 2013). Casticin could enhance the apoptosis of gastric cancer cell lines through endoplasmic reticulum stress. The mechanism involved the down-regulation of cell survival protein and the up-regulation of the DR5 (Zhou et al., 2013). Another study confirmed that the active compounds in Viticis Fructus were a potential leading drug in the therapy of prostate carcinoma. Casticin induced apoptosis of PC-3 (prostate cancer cells). The mechanism involved blocking G2/M phase, increasing intracellular ROS, decreasing membrane potential of mitochondria, freeing cytochrome *C*, initiating Caspase-3, up-regulating pro-apoptotic protein Bax, down-regulating anti-apoptotic protein Bcl-2 and intracellular cyclins Cyclin B1 and CDK1 (Meng et al., 2012). Rotundifuran, 2′, 3′, 5-trihydroxy-3, 6, 7-trimethoxyflavone, casticin and artemetin could inhibit the multiplication of HL-60 cells (human myeloid leukemia) (Ko et al., 2000; Ko et al., 2001). Furthermore, casticin has been proven *in vivo* experiments that could promote the immune response in leukemia mice, thereby increasing the survival rate of leukemia mice (Lai et al., 2019). In B16F10 cancer cells (mouse skin melanoma cells), casticin arrested the expression of the p-EGFR, AKT and Nuclear factor kappa-B (NF-κB) pathways, which led to the suppression of MMP-9, MMP-2 and MMP-1(Shih et al., 2017).

6.2. *Anti-inflammation*

The anti-inflammatory activity of Viticis Fructus mainly involves NF-κB, MAPK and AKT signaling pathways (Fig. 8). There was a certain gap in the anti-inflammatory activity of different extraction parts of Viticis Fructus, among which the n-butanol fraction had better activity. It was speculated that terpenoids and flavonoids, such as Viteagnusin I, Vitetrifolin D and others, inhibited the production of nitric oxide (NO) (Yan et al., 2023). Viterotulin C, Vitexilactone and Rotundifuran had anti-inflammatory activity and suppressed tumor necrosis factor-α (TNF-α)-induced NF-κB activation. The inhibition rate was 42.52 % – 68.86 % at a concentration of 50 μM (Fang et al., 2019). Casticin could repress the chemotaxis of cultured human neutrophils and produce anti-inflammatory effects (Ahmad et al., 2010). It attenuated the

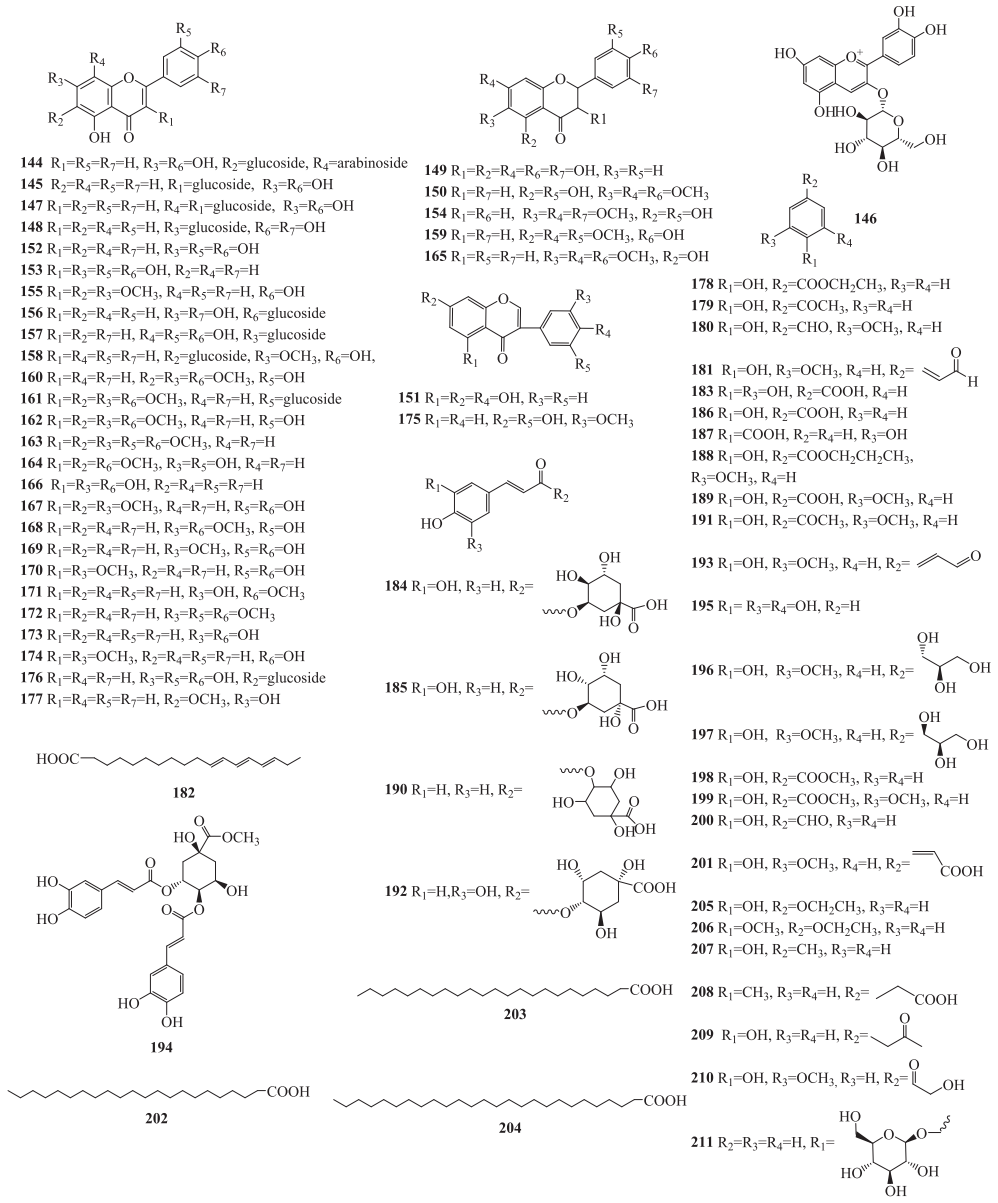

Fig. 5. Structures of flavonoids (144–177) and phenolic acids (178–211).

generation of pro-inflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6) and TNF-α by blocking NF-κB, AKT and MAPK signaling pathways, thereby inhibiting NO and Prostaglandin E2 levels and exerting anti-inflammatory activity (Liou et al., 2014).

Viticis Fructus played a therapeutic role in many diseases through anti-inflammation, such as systemic anaphylaxis reaction, allergic asthma, ulcerative colitis (UC), knee osteoarthritis (KOA), vascular inflammation, *etc*. Its extract and monomer components had been proven to have certain anti-inflammatory activities. The water extract (the fruits of *V. rotundifolia*) and pyranopyran-1,8-dione (PPY) had protective effects on systemic anaphylaxis reaction, pulmonary inflammation and asthma. They restrained secretion of inflammatory factors by declining the activation of ERK1/2 and NF-κB signaling pathways, such as TNF-α and IL-6 (Yan et al., 2023). Another study found that casticin was a prominent immunomodulator that improved the pathology by inhibiting the expression of T-helper two-cell cytokines in asthmatic mice (Liou et al., 2018). Casticin was also a potential remedy for KOA, particularly for fibrosis of synovial membrane. It reduced the release of inflammatory mediators and the elevation of fibrosis markers induced by monoiodoacetic acid/lipopolysaccharide through suppressing the stimulation of nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome (Chu et al., 2020). In addition, casticin was able to repress ROS-mediated NF-κB pathway to achieve marked relief of cartilage degeneration associated with experimental osteoarthritis (Chu et al., 2020). The protective effect of casticin on dextran sulfate sodium-induced UC was achieved by increasing the expression of antioxidant enzymes peroxiredoxin three and Mn-containing superoxide dismutase, and reducing the generation of proinflammatory cytokines *via* inhibiting AKT pathway (Ma et al., 2018). Casticin could markedly decrease vascular inflammation by inhibiting the NF-κB pathway of vascular endothelium cells (Lee et al., 2012).

6.3. Antioxidation

Viticis Fructus was discovered good antioxidant activity and individual compounds were even better than vitamin C in antioxidant activity. The compounds (such as vanillic acid and taxifolin) in the methanol extract of *V. rotundifolia* fruits showed more potent antioxidant action over 3-*tert*-butyl-4-hydroxyanisole (Ono et al., 1998b). The

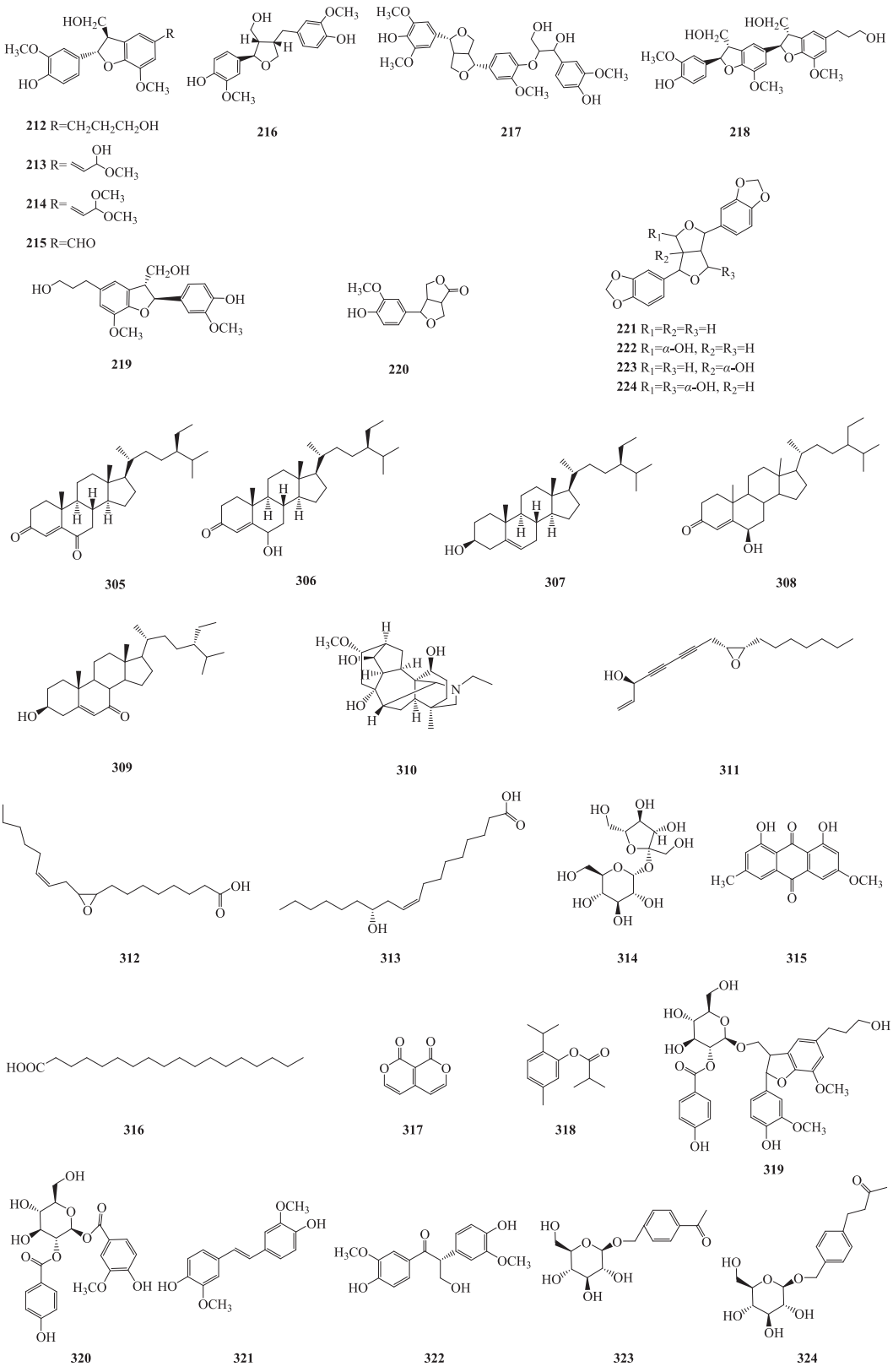

Fig. 6. Structures of lignan (212–224) and others (305–324).

scavenging ability of alkaloids, total flavonoids and volatile oil on hydroxyl radicals and superoxide radicals displayed a significant dose–effect relationship with their concentrations (Yan et al., 2023). Ferruginol and vitrifolin A had certain antioxidant activity (Ono et al., 1999; Zhang et al., 2013). The superoxide quenching activity of orientin and 3, 4-di-*O*-caffeoylquinic acid was more powerful than that of vitamin C (Kim, 2009). In addition, it was found that 3,4-dihydroxybenzaldehyde, chlorogenic acid and orientin showed strong DPPH free radical scavenging ability (Le et al., 2022).

Table 2
Pharmacological activities of Viticis Fructus.

Activity	Compounds or extracts	Dose	Model/ Animal/Cell lines	Result/Mechanism	Reference
Antitumor-breast cancer effects	vitexilactone, (rel 5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide, rotundifuran, vitetrifolin D and vitetrifolin E	100 μg/mL	mouse breast cancer thermosensitive stFTZ10 cell line	Inhibited the proliferation of tsFT210 cells through arresting the cell cycle at the G2/M phase and inducing apoptosis.	(Li et al., 2005a)
Antitumor-breast cancer effects	casticin	0.5 μM	MDA-MB-231 and MCF-7 cell lines	FOXO3a was a fatal mediator of casticin inhibiting breast cancer cell apoptosis.	(Liu et al., 2014b)
Antitumor-breast cancer effects	casticin	0.25 and 0.5 μM	human breast cancer cell line MDA-MB-231 and mouse breast cancer cell line 4 T1	Inhibited the migration and invasion of breast cancer cells.	(Fan et al., 2018)
Antitumor-breast cancer effects	casticin	0.5–2 μM	MCF-7 sub-lines MN1 and MDD2	Led to apoptosis.	(Haïdara et al., 2006)
Antitumor-cervical cancer effects	casticin	0.5, 1, 2 and 4 μM	human cervical cancer cell lines HeLa, CasKi, and SiHa	Inhibit cell apoptosis.	(Zeng et al., 2012)
Antitumor-cervical cancer effects	RTF	8 and 16 μM. 10 and 40 mg/kg/day	HeLa, SiHa cells and BALB/C nude mice	It is related to ROS-induced mitochondrial-dependent apoptosis.	(Gong et al., 2021)
Antitumor-cervical cancer effects	casticin	2 and 4 μM	human cervical cancer cell lines	Induced apoptosis of cervical cancer cells by ROS-mediated mitochondrial pathway	(Chen et al., 2011)
Antitumor-cervical cancer effects	rotundifuran	8 and 16 μM	HeLa and SiHa cells	Inhibited the proliferation and induce apoptosis of cervical cancer cells.	(Shen, 2020)
Antitumor-lung cancer effects	total flavonoids of Viticis Fructus	0.5, 1 and 2 μg/mL	lung cancer NCI-H446 cell line	Inhibited the characteristics of LCSLCs.	(Cao et al., 2014)
Antitumor-lung cancer effects	casticin	1, 5 and 10 μM	human lung cancer A549 cell line, were injected subcutaneously into the back of BALB/C-nude mice.	Inhibited the self-renewal and invasion of lung cancer stem-like cells.	(Liu et al., 2014a)
Antitumor-liver cancer effects	casticin	0.1, 0.3, 1, 3 and 10μM	MHCC97 cell line	Arrested self-renewal of MHCC97 liver cancer stem cells.	(He et al., 2014)
Antitumor-liver cancer effects	casticin	1, 3, 10, 30 and 100 μM	MHCC97H, SK-Hep-1, L02 cell Lines and male BALB/c-nude mice.	Suppressed the stemness of HCC cells.	(Li et al., 2020a)
Antitumor-liver cancer effects	casticin	2.5, 5 and 10 μM	Hep G2 (p53 wild-type) and PLC/PRF/5 (p53 mutant) cells.	Induced growth inhibition and cell cycle arrest.	(He et al., 2013)
Antitumor-liver cancer effects	casticin	3, 10 and 30μM	PLC/PRF/5 (p53 mutant) and Hep G2 (p53 wild type) human HCC cells.	Glutathione depletion and DR5 upregulation.	(Yang et al., 2011)
Antitumor-colorectal cancer effects	casticin	40 μM	colo 205 human colon cancer cells	Induced apoptosis in human CRC cells.	(Shang et al., 2017)
Antitumor-colorectal cancer effects	casticin	1 and 3μM	human colon cancer HT-29, HCT-116 and SW480 cell lines.	Caused apoptosis via regulating anti-apoptotic proteins and DR5 from colon cancer cells.	(Tang et al., 2013)
Antitumor-glioma effects	casticin	10, 20 μM	human glioma cells U251, U87 and U373	Prevented the growth of human glioma cells by mitosis arrest.	(Liu et al., 2013)
Antitumor-gastric cancer effects	casticin	1μM	human gastric cancer cells BGC-823, SGC-7901 and MGC-803	Enhanced trail-induced apoptosis via down-regulating cell survival protein and up-regulating DR5 receptor.	(Zhou et al., 2013)
Antitumor-prostate carcinoma effects	casticin	10, 30 and 50 μM	human prostate cancer PC-3 cell line	Induced apoptosis of human prostate cancer cells by arresting G2/M phase.	(Meng et al., 2012)
Antitumor-leukaemia effects	rotundifuran	25 and 50 μM	human myeloid leukaemia HL-60 cells	Killed HL-60 cells by the activation of the apoptosis mechanism.	(Ko et al., 2001)
Antitumor-leukemia effects	casticin	0.1, 0.2 and 0.4 mg/kg	male BALB/c mice were peritoneally injected with WEHI-3 leukemia cells	Potentiated immune response.	(Lai et al., 2019)
Antitumor-melanoma effects	casticin	0.25–5 μM	B16F10 cell line	Attenuated the proliferation, migration and invasion of cells.	(Shih et al., 2017)
Antitumor-leukemia effects	2′,3′,5-trihydroxy-3,6,7-trimethoxyflavone, vitexicarpin and artemetin	N/A	HL-60 cells	Suppressed the proliferation of human myeloid leukemia cells by inducing apoptosis.	(Ko et al., 2000)
Antitumor effects	persicogenin, artemetin, luteolin, penduletin, vitexicarpin	100, 50, 25, 6.25 and 1 μg/mL	tsFT210 and K562 cells	Inhibited cell cycle progression of G2/M and induced apoptosis in mammalian cancer cells.	(Li et al., 2005a)
Antitumor effects	vitetrifolin H, vitetrifolin I and vitexoid	25–50 μM	tsFT210 cells	Inhibited the proliferation of tsFT210 cells.	(Wu et al., 2009)
Anti-inflammatory effects	casticin	N/A	human neutrophils	Inhibited the chemotaxis of human neutrophils.	(Ahmad et al., 2010)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
An-inflammation effects	casticin	0.3, 1, 3 and 10 μM	lipopolysaccharide-stimulated RAW264.7 cells	The anti-inflammatory activity suppressed the expression of COX-2 and iNOS by blocking NF-κB, MAPK and Akt pathways.	(Liou et al., 2014)
An-inflammation effects	casticin	5–100 nM	human umbilical vein endothelial cells	Alleviated vascular inflammation.	(Lee et al., 2012)
Anti-inflammation effects	viterotulin C, vitexilactone D, vitexilactone, rotundifuran, vitetrifolin B, viterotulin B, vitetrifolin D	50 μM	HEK293 cells	Activation of NF-κB	(Fang et al., 2019)
An-inflammation-asthma effects	casticin	5 and 10 mg/kg	ovalbumin −induced asthma in female BALB/c mice	Improved pathological changes by inhibiting the expression of T helper 2 cell cytokines in asthmatic mice.	(Liou et al., 2018)
Anti-inflammation-UC effects	casticin	5, 10 and 20 mg/kg	RAW264.7 cell line and dextran sulfate sodium-induced colitis in C57BL/6 mice	Prevented UC in mice by suppressing NF-κB and ROS signaling pathways.	(Ma et al., 2018)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
Anti-inflammation-KOA effects	casticin	0.2 mg/kg/day	monoiodoacetic acid-induced knee osteoarthritis in mice and an inflammatory model in primary synovial fibroblasts induced by lipopolysaccharide	Treated KOA via suppressing HIF-1α/NLRP3 inflammasome signaling.	(Li et al., 2020b)
Anti-inflammation effects	casticin	animal experiment:10 mg/kg. cell experiment:10, 20 and 30 μM	surgery destabilizing the medial meniscus was performed on the right knees of mice and IL-1β-induced inflammation in mice	Ameliorated osteoarthritis-related cartilage degeneration.	(Chu et al., 2020)
Antioxidation effects	orientin and 3,4-di-O-caffeoylquinic acid	0.1–100 μg/mL	DPPH	Significant antioxidant activity.	(Kim, 2009)
Antioxidation effects	vitrifolin A	1, 5, 10, 20, 40 and 60 μM	lipopolysaccharide-activated mouse macrophages	Vitrifolin A had a moderate inhibitory activity on lipopolysaccharide-activated rat macrophages.	(Zhang et al., 2013)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
Antioxidation effects	ferruginol	N/A	N/A	Compared with the standard antioxidant, ferruginol showed more potent antioxidant activity.	(Ono et al., 1999)
Antioxidation effects	methanol extract	N/A	ferric thiocyanate method	They could exhibit stronger antioxidative activity than 3-*tert*-butyl-4hhydroxyanisole.	(Ono et al., 1998b)
Antioxidation effects	Viticis Fructus extract	300, 150 and 75 mg/kg	mice neck hypodermic injection D-galactose	The ethanol extract of Viticis Fructus had good anti-aging and antioxidant effects.	(Yin et al., 2016)
PMS effects	rotundifuran and casticin	rotundifuran and casticin:40 mg/kg/d, 10 mg/kg/d.	diethylstilbestrol induction female SD rats	Improved the related pathological changes of PMS.	(Ye, 2010)
Cardiovascular Disease-hyperlipidemia effects	viterofolin H, (5S, 6R, 8R, 9R, 10S)-6-acetoxy-9-hydroxy-13 (14)-labden-16,15-olide and previtexilactone	N/A	HepG2 cells	Viterofolin H, previtexilactone and (5S, 6R,8R, 9R, 1 0S)-6-acetoxy-9-hydroxy-13 (14)-labden-16,15-olide had moderate activity to promote LDL uptake.	(Wang et al., 2018)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
Cardiovascular Disease-antiplatelet activation effects	casticin	1 and 2μM	blood of healthy volunteers aged 18–26 years	Inhibited platelet activation.	(Xiong et al., 2022)
Cardiovascular Disease-decrease blood pressure effects	alcohol extract of Viticis Fructus	N/A	cat	The alcohol extract of Viticis Fructus had noticeable antihypertensive effect and maintained for a long time.	(Guan, 2011)
Cardiovascular disease-antiatherosclerosis effects	ethanol extract of *V. rotundifolia*, casticin and luteolin	extract:10 and 100 μg/mL casticin and luteolin: 10, 20 and 40 μM.	young and healthy male volunteers	Inhibited LDL and HDL oxidation.	(Kim et al., 2020)
Other-analgesia effects	Viticis Fructus methanolic extract	1.75 and 7 g/kg	nitroglycerin-induced migraine in mice	Suppressed hyperalgesia of the trigeminovascular system.	(Wen et al., 2020)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
Other-analgesia effects	pedicularis-lactone, viteoid I and viteoid II	15 mg/kg	paclitaxel-induced mechanical allodynia in C57BL/6NCr mice and LY-PPB6 cell line	Inhibited paclitaxel-induced heterologous pain in mice.	(Yu et al., 2021)
Other-analgesia effects	vitexfolin A, agnuside, 10-*O*-vanilloylaucubin, dihydrodehydrodiconiferylalcohol-β-*D*-(2′-O-p-hydroxybenzoyl) glucoside	15, 50, 25 and 50 mg/kg	acetic acid-induced writhing method in mice	Alleviated the writhing symptoms.	(Okuyama and Yamazaki, 1998)

(*continued on next page*)

Table 2 (*continued*)

Activity	Compounds or extracts	Dose	Model/Diseases	Result/Mechanism	Reference
Other-analgesia effects	Viticis Fructus extract	1.17 g/kg	0.6% acetic acid-induced pain in mice	Total flavonoids and volatile oil were analgesic active ingredients.	(Sun et al., 1997)
Other-aldose reductase activity effects	ether extract	N/A	enzyme reactions	Inhibited the enzyme activity.	(Shin et al., 1994)
Other-antiasthmatic effects	the water decoction and petroleum ether extract of Viticis Fructus	N/A	isolated tracheal volume measurement method	The water decoction and petroleum ether extract of Viticis Fructus had anti-asthmatic effect.	(Liu, 2002)
Other-promote sleep effects	Viticis Fructus water extract	8 g/kg	rat	The effect of *V. rotundifolia* fruit on promoting sleep was stronger than that of *V. trifolia* fruit.	(Zhong et al., 1996)
Other-pulmonary fibrosis effects	Viticis Fructus formula granules	0.025 g/mL	pulmonary fibrosis induced by bleomycin in rat	Viticis Fructus could intervene pulmonary fibrosis.	(Tian, 2017)
Other-osteoporosis effects	casticin	0.125, 0.25 and 0.5 μM	RAW 264.7 cell	Inhibited the differentiation of RAW 264.7 cells into osteoclasts.	(Huang, 2022)

6.4. Premenstrual syndrome

The pathogenesis of PMS was generally believed to be the result of a combination of psychosocial factors and endocrine regulation, such as prolactin, ovarian hormones and brain neurotransmitter imbalance (Ye, 2010). Pharmacological studies had found that ethanol extract of *V. rotundifolia* fruits was used to alleviate PMS regulating prolactin levels, estrogen and progesterone levels (Hu, 2007). First, directly reduced the excessive estrogen content in the body so that the estradiol/progesterone ratio decreased. Casticin could reduce the content of estradiol in serum. At the same time, rotundifuran could increase serum progesterone content. Second, Decreased the content of β-endorphin in the hypothalamus. Third, Casticin could significantly reduce the content of prolactin (Ye, 2010).

6.5. Cardiovascular protection

Viticis Fructus had certain therapeutic effects on some cardiovascular diseases, such as hypertension, hyperlipidemia and coagulopathy. Viticis Fructus had an antihypertensive effect. The blood pressure of cats decreased significantly after administration of Viticis Fructus decoction and Viticis Fructus ethanol extract (Guan, 2011). Its extract could significantly prolong the time of bovine thrombin condensing human fibrinogen *in vitro*, indicating that it had a strong anticoagulant effect (Ou et al., 1987). Casticin could inhibit platelet aggregation, release, adhesion and plaque retraction, which was achieved by inhibiting PI3K/Akt signaling pathway (Xiong et al., 2022). Furthermore, *V. rotundifolia* fruits extract had strong activities toward the oxidation of low-density-lipoprotein (LDL) and high-density lipoprotein (HDL) (Kim et al., 2020). Viterofolin H, previtexilactone and other compounds indicated moderate activities in facilitating LDL uptake. These compounds showed

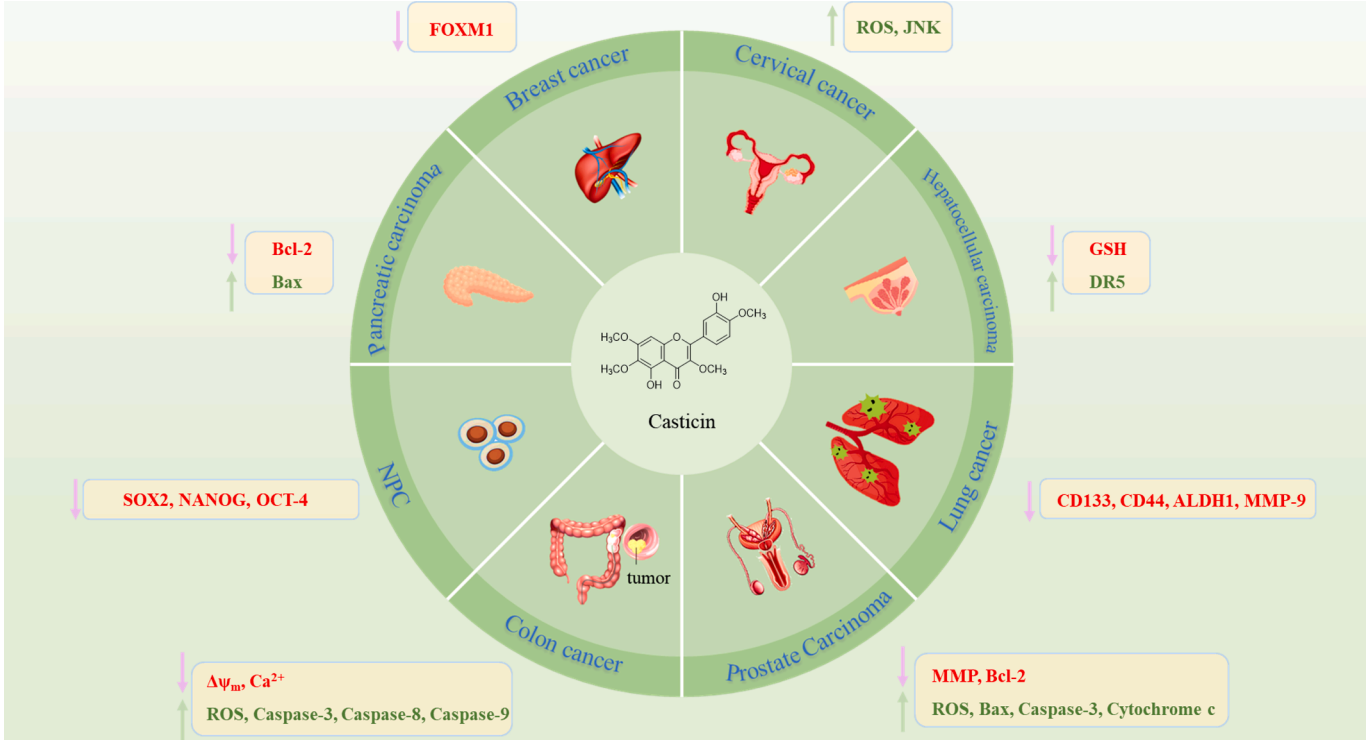

Fig. 7. Antitumor activity of casticin.

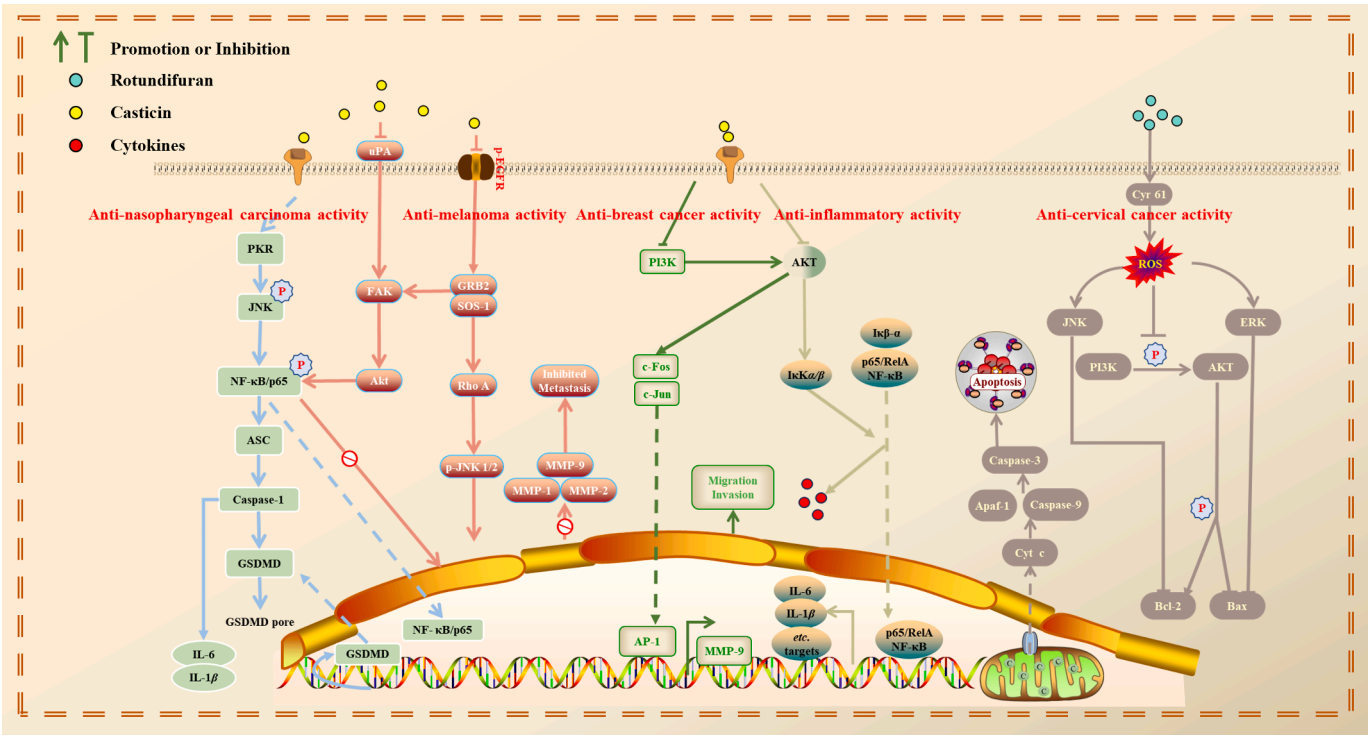

Fig. 8. The molecular mechanism of the active components of Viticis Fructus on anti-nasopharyngeal cancer, anti-cervical cancer, anti-breast cancer and anti-inflammatory.

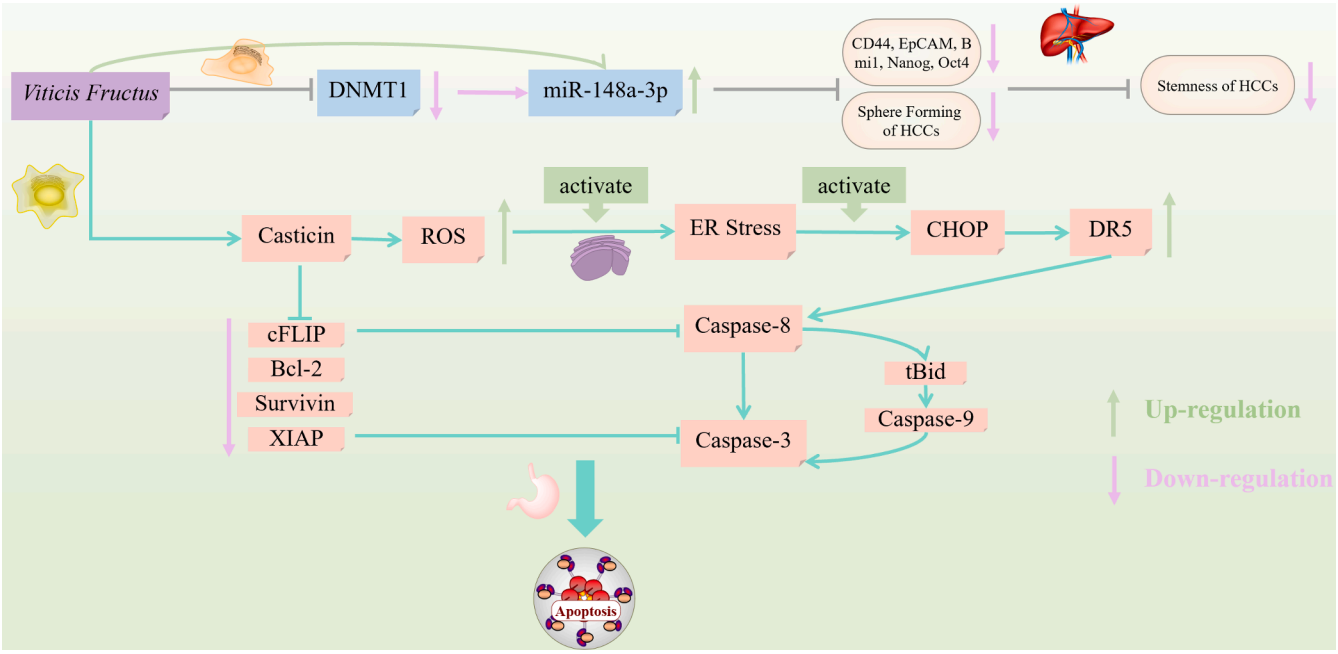

Fig. 9. Changes of biological indexes of anti-hepatocarcinoma and anti-gastric cancer of Viticis Fructus.

certain anti-hyperlipidemic activity (Wang et al., 2019a).

6.6. Other activities

In addition to the above effects, Viticis Fructus can also be used for analgesic, antipyretic, expectorant, asthma, whitening, antibacterial, anti-fatigue, *etc*. It is a TCM with an analgesic effect. The methanol extract of *V. trifolia* fruits could effectively relieve migraines, among which the flavonoid fraction has a good analgesic response inhibition rate. Pedicularis-lactone, viteoid I and viteoid II significantly suppressed paclitaxel-induced mechanical allodynia. This is related to the levels of 5-hydroxytryptamine and γ-aminobutyric acid (GABA) increased, and the decrease of plasma calcitonin gene-related peptide and substance P levels (Yan et al., 2023). Crude and processed *V. rotundifolia* fruits products had an apparent antipyretic effect (Yan et al., 2023). It had expectorant and antiasthmatic effects. An obvious expectorant effect could be observed by phenol red excretion method in mice after oral administration of water decoction and alcohol extract of Viticis Fructus.

The water decoction and petroleum ether extract of Viticis Fructus could relax the isolated guinea pig tracheal specimens. It could slow histamine-induced tracheal contraction (Liu, 2002). This was mutually supportive with its traditional efficacy in treating wind-heat colds (upper respiratory tract infections). Aldolase role of the rat lens was strongly inhibited by ether extract of *V. rotundifolia* fruits (Shin et al., 1994). Viticis Fructus water extract could also promote sleep in mice (Zhong et al., 1996). Viticis Fructus showed an effect against tyrosinase, indicating that it was able to inhibit the formation of melanin (Wang, 2003). Viticis Fructus water decoction had a moderate antibacterial effect on staphylococcus epidermidis *in vitro* and had moderate antibacterial effect on bacillus subtilis (Guan, 2011). Viticis Fructus could also interfere with pulmonary fibrosis by inhibiting apoptosis and improving excessive angiogenesis (Tian, 2017). Viticis Fructus could be used as a potential anti-menopausal osteoporosis drug. Within the safe range of casticin, it could inhibit the differentiation of RAW 264.7 cells into osteoclasts through the NF-κB/BCL-2 signaling pathway (Huang, 2022).

Viticis Fructus can trigger the apoptosis of various tumors and cancer cells to prevent and treat cancer with respect to antitumor activity. Many studies have manifested that Viticis Fructus induced apoptosis by regulating JNK, NF-κB, PI3K/AKT, ERK and other pathways. The hot water extract, ethanol extract, terpenoids and flavonoids of Viticis Fructus are the main components of its function. Among them, casticin can modulate key targets and pathways of breast cancer, cervical cancer, nasopharyngeal carcinoma and other cancers. It needs further research and may be used as a potential new drug to inhibit cancer cells. The anti-inflammatory properties of various Viticis Fructus fractions varied to some extent in terms of anti-inflammatory effects. The optimal extraction solvent should be selected to ensure better anti-inflammatory activity of Viticis Fructus. It could prevent the formation of anti-inflammatory proteins by modulating the NF-κB, AKT and MAPK signaling pathways, thereby reducing inflammation and curing various illnesses. However, the mechanism of many diseases was still unclear, such as systemic allergic reactions. In addition, the anti-rheumatic effect of Viticis Fructus was mentioned in many books such as *Bencao Gangmu* and *Shennong Bencao Jing*, which was mutually corroborated with pharmacological research, but the specific action mechanism should be further studied. Flavonoids and terpenoids in Viticis Fructus manifested favorable antioxidant activity *in vitro*. Oxidative-related diseases should be validated at the cellular and animal levels for better clinical application of Viticis Fructus. In the area of female diseases, Viticis Fructus had a good preventive and therapeutic effect on female illness by regulating hormone levels such as prolactin, estrogen and progesterone. In addition to improving the symptoms of PMS, it could also be used to relieve hyperprolactinemia and menopausal symptoms (Yan et al., 2023). The mechanism of Viticis Fructus in cardiovascular disease is still unclear. Further experiments *in vivo* are needed to prove its efficacy and clarify the corresponding mechanism of action. This can expand its use scope and provide a new direction for the treatment of cardiovascular.

7. Toxicity

Adverse reactions and toxins of TCM are issues that need constant attention to ensure the safety of TCM. Toxicological experiments were performed on manjing oral liquid with Viticis Fructus as the primary raw material, including median lethal dose (LD_{50}), mutagenicity test (mouse bone marrow micronucleus test, ames test and mouse sperm deformity test). It emerged that the LD_{50} exceeded 20 g/kg, demonstrating non-toxicity. Negative results of three mutagenicity tests demonstrated the absence of mutagenic effects (Zhang et al., 2000). Continuous administration of aqueous extracts of Viticis Fructus and *Scrophulariae Radix* (50 or 100 mg/kg) had no systemic toxicity in normal mice (Kim and Ma, 2019). The mice survived after administration of the ethanol extract and aqueous extract of Viticis Fructus with exceeding the clinical dose, which implied a low level of toxicity (Wang et al., 2008). The impact of varying Viticis Fructus volatile oil concentrations on the survival rate of HaCaT cells (Human immortalized keratinocytes) was approximately concentration-dependent. Viticis Fructus essential oil (285.10 μg/mL) had a half-inhibitory concentration that was above that of azone (17.08 μg/mL), a positive penetration enhancer. It showed that Viticis Fructus volatile oil has low irritation to the skin. Only excessive use can damage skin cells. 0.5 %, 1 % and 2 % Viticis Fructus essential oil had no irritation symptoms such as erythema and edema on the intact skin of guinea pigs after repeated administration (Liang, 2019).

Viticis Fructus has a low degree of toxicity and it rarely causes harm to the body unless improperly used. However, although studies have indicated that Viticis Fructus has a low toxic level, its toxicological research is relatively weak. Toxicological studies on mice only are one-sided. Toxicological research should be carried out on different animals and different doses should be explored to ascertain the toxic range. In addition, the toxic reactions and toxicity mechanism of Viticis Fructus have not been elucidated.

8. Quality control

Quality control is the basis for ensuring the stability and safety applications of TCM. Therefore, different scientific and technological means were applied to evaluate and control the quality of TCM. The quality control of Viticis Fructus covered the authentication of TCM, physical and chemical identification, microscopic identification, impurities, moisture, total ash, extract and content determination. Presently, the main methods for evaluating the quality of Viticis Fructus were ultraviolet–visible (UV) spectrometry, inter simple sequence repeat (ISSR), Near Infrared (NIR), Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) analysis, UPLC-Orbitrap-MS, comprehensive two-dimensional gas chromatography hyphenated with mass spectrometry (GC × GC–MS), liquid chromatography/mass spectrometry (LC/MS) analysis and high-performance liquid chromatography coupled with a diode array detector (HPLC-DAD). However, the research on the quality control of Viticis Fructus is relatively simple, mostly for content determination and counterfeit identification. There is an urgent need to improve the relevant contents of quality control for Viticis Fructus and then comprehensively evaluate the quality Viticis Fructus.

The quality control of different origin plants, processed products and batches of Viticis Fructus was carried out by content determination. Viticis Fructus chemical constituents before and after processing were distinguished by NIR, HPLC and UPLC-MS analysis. Forty-two of the detected compounds underwent considerable alteration during processing and sixteen chemical constituents were picked as distinctive markers. Crude and processed Viticis Fructus could be successfully identified using these techniques (Diao, 2018). The contents of casticin and agnuside were evidently varied in the two origin plants by establishing the HPLC fingerprint of Viticis Fructus. The content of casticin in *V. rotundifolia* fruits was higher, while the content of agnuside in *V. trifolia* fruits was higher. There was no significant difference in the content of isoorientin and p-hydroxybenzoic acid (Yang et al., 2023). The comparative study of Viticis Fructus and the fruits of *Vitex negundo* was carried out by UPLC characteristics chromatogram combined with multi-index content determination. Compared with the fruits of *Vitex negundo*, orientin and isovitexin were not detected in Viticis Fructus (Li et al., 2023). It is worth mentioning that the significant polarity differences among the chemical constituents of Viticis Fructus make simultaneous extraction challenging. Using the Beta/ZSM-22 Zeolites-Based-Mixed Matrix Solid-Phase Dispersion approach, eight chemicals (agnuside, DHTMF, vanillin, *etc*) from Viticis Fructus were extracted and measured concurrently. Compared to the conventional approaches, achieving the highest extraction rate is simple (He et al., 2019).

The adulteration of Viticis Fructus often appeared in the market, which in the market circulation are the fruits of *Vitex negundo*, *Euphorbiae Semen*, *Litseae Fructus* and so on. Their appearance traits are very similar and difficult to distinguish (Zhou and Jin, 2001). Based on the

differences in the maximum intraspecific Kimura 2-Parameter (K2P) genetic distance of Viticis Fructus and its adulterants, the Internal Transcribed Spacer 2 (ITS2) sequence method was used to successfully distinguish the adulteration. The maximum intraspecific K2P genetic distance of Viticis Fructus based on ITS2 sequence was less than the minimum interspecific K2P genetic distance with adulterants (Zhang et al., 2014). Shrub Chaste Tree Fruits (SCTF, synonyms of Viticis Fructus)-specific marker compounds (3-*O*-*trans*-feruloyl tormentic acid) were identified by LC/MS metabolic analysis, then accurately identified their origin plant and clearly distinguished between SCTF and Agnus Castus fruit (Yahagi et al., 2016). In addition, the stereoscope and scanning electron microscope were adopted to compare the microscopic and ultramicroscopic characteristics of the peel surface of Viticis Fructus and its adulterants. It was found that the surface ultrastructure of Viticis Fructus and its adulterants were significantly different, which could be used as a basis for identification. Its surface was reticular, while the surface of the counterfeit showed other traits (Cai et al., 2017). UPLC-Orbitrap-MS and GC × GC–MS were used to select betulinic acid, myricetin and volatile 4-(2,2,6-trimethyl-bicyclo [4.1.0] hept-1-yl)-butane-2-one as specific markers to successfully distinguish Viticis Fructus and its adulterants (*Vitex cannabifolia* fruits, *Vitex negundo* fruits, *Piper cubeba* fruits, *Euphorbia lathyris* seeds and *Vaccinium bracteatum* fruits) (Li et al., 2020c). Moreover, the HPLC fingerprinting and ISSR molecular markers methods were built to study the relationship between the intraspecific variation and the chemical composition diversity of *Vitex negundo* var. *heterophylla*. It was found that the influence of different genetic backgrounds cannot be ignored. Combined with chemical and genetic diversity, chemical type selection could be carried out for different efficacies of Viticis Fructus to achieve quality control (Hu et al., 2010).

The quality control of Viticis Fructus primarily centered on content determination and counterfeit identification. There are few studies on the identification of the two origin plants of Viticis Fructus, but the fruits of *V. rotundifolia* are more used than the fruits of *V. trifolia*. There is a big gap between the two origin plants in the content of compounds such as casticin, agnuside and other compounds. In addition, there are many counterfeits and a simpler method for identifying counterfeits should be developed.

9. Pharmacokinetics

The active ingredients of TCM are in a dynamic process of change after intake into the human body (Ma et al., 2023). Studying the process of drug concentration in the blood over time is indispensable for interpreting the scientific connotation of TCM. Pharmacokinetics is a powerful tool for promoting the scientific development of TCM. The pharmacokinetic studies of Viticis Fructus in various aspects are also constantly enriched, providing the scientific basis for the development and utilization of Viticis Fructus.

The main pharmacokinetics of Viticis Fructus include the comparison of water extract and alcohol extract of Viticis Fructus, the comparison of oral and intravenous injections of casticin, the comparison of different processed Viticis Fructus and the metabolic process of casticin in Viticis Fructus. UHPLC-MS/MS was used to analyze and determine agnuside, casticin, luteolin and 10-*O*-vanillyl eucommoside in rat plasma after oral administration. It was successfully used to evaluate the pharmacokinetic characteristics of four active compounds in water extract and ethanol extract of Viticis Fructus in rat plasma. Agnuside in the water and alcohol extracts showed a large difference and the water extract was absorbed faster. 10-*O*-vanilloylaucubin was not detected in rats after oral administration of alcohol extract. Its absorption in aqueous extract is faster, but the absorption concentration *in vivo* was still at a low level. The absorption of luteolin in the two extracts was poor. The maximum drug concentration in plasma (C_{max}), the time to reach maximum drug concentration (T_{max}) and area under the plasma concentration–time curve ($AUC_{(0\text{-}t)}$) of water extraction were 6.37 ± 3.61 ng/mL, 0.25 ± 0.13 h and 5.14 ± 1.85 ng/mL*h, respectively. The C_{max}, T_{max} and $AUC_{(0\text{-}t)}$ of alcohol extraction were 8.14 ± 5.45 ng/mL, 0.19 ± 0.17 h and 11.5 ± 3.76 ng/mL*h, respectively. The content of casticin in the two extracts was so low that the relevant parameters could not be calculated (Chen et al., 2021). LC-MS was used to quantify casticin content in rat plasma following oral and intravenous injections. The C_{max}, T_{max} and $AUC_{(0\text{-}t)}$ were 287.06 ± 40.68 ng/mL, 43.83 ± 1.47 min and 18,652.72 ± 4030.88 ng/mL*h, respectively; for taking orally casticin 400 mg/kg to rats. The C_{max}, T_{max} and $AUC_{(0\text{-}t)}$ were 12,737.82 ± 7243.88 ng/mL, 0 min and 41,225.92 ± 1403.37 ng/mL*h, respectively, for intravenous administration of 50 mg/kg of casticin. It was rapidly distributed and eliminated in rats because casticin is a polyhydroxy flavone that is easily hydroxylated in plasma resulting in a short half-life (Xu et al., 2012). In another study, the pharmacokinetic effects of casticin and isoorientin in rats before and after processing Viticis Fructus showed no clear distinction between the crude and processed Viticis Fructus after oral administration. The T_{max} and C_{max} of casticin were about 5 min and 20 μg/L, respectively. The T_{max} of isoorientin was 1.50 ± 0.39 h and 1.75 ± 0.39 h, respectively (Yu, 2019). In addition, the metabolic process of casticin *in vivo* was also studied. 25 metabolites and main metabolic pathways were speculated. One is demethylation process, the other is methylation, sulfation and glucuronidation process (Zhu, 2013).

The pharmacokinetic study of Viticis Fructus focused on healthy rats. Other animal models should be added, such as dogs, rabbits and even healthy volunteers. In addition, the disease models should be established to compare with the normal group, reflecting the changes of Viticis Fructus metabolism in the disease state and promoting the better application of Viticis Fructus in clinical practice. There had been some investigating on absorption and metabolism of Viticis Fructus, but little was known about its distribution or excretion. It is crucial to gaze at the distribution and excretion kinetics of Viticis Fructus *in vivo*.

10. Comprehensive applications

10.1. Clinical application

Viticis Fructus is a commonly used TCM in clinics. It is used for treating various diseases combined with other herbs, such as nervous system disorders, eye diseases, otolaryngology diseases, digestive system diseases and so on (Fig. 10).

In the nervous system disorders, it was recorded in the ancient book that all headaches could be treated with Viticis Fructus., regardless of the left and right sides (Gong, 1999; Tian and Shi, 2022). It combined with other TCM in the treatment of headaches and curative effect was favorable. For example, Viticis Fructus combined with *Bupleuri Radix*, *Chuanxiong Rhizome* and *Chrysanthemi Flos* to treat migraine, played a role in clearing heat and relieving pain (Zhao, 2018; Niu et al., 2005). Neurovascular headache, tension headache, hypertension-related headache, trigeminal migraine, migraines and cluster headache could be treated with *Chrysanthemi Flos*, *Notopterygii Rhizome et Radix*, *Scutellariae Radix*, *etc* (Hu and Yang, 2016). One hundred and twenty patients with migraine were cured with Viticis Fructus Tou-Feng Decoction (*Chrysanthemi Flos*, *Uncariae Ramulus Cum Uncis*, *Menthae Haplocalycis Herba*, *etc*) for 10 days (twice a day). Headache symptoms disappeared in 92 patients. The degree of headache attack in 26 patients was significantly anesis and the frequency decreased. The total effective rate was 98.3 %. The difference was significant compared with the total effective rate of 88.3 % in the control group (intravenous ligustrozine hydrochloride injection, 60 volunteers). In addition, the recurrence rate was lower in the treatment group (10.87 %) than in the control group (32.43 %). Compared with the two groups, the treatment group was significantly better than the control group. Viticis Fructus mainly played an analgesic role in the prescription (Xu, 2007). Clinically, Viticis Fructus could be used alone to treat sciatica (Wang, 2001) and trigeminal neuralgia (Li, 1998). Fifty-six patients with sciatica were treated

with Viticis Fructus juice twice a day for 21 days. The total effective rate was 98.2 %. Primary sciatica was mostly related to rheumatism, cold and other reasons. Viticis Fructus combined with liquor had a fine effect of expelling wind, removing dampness and cold-dispelling effect, so the effect is obvious (Wang, 2001).

In Otorhinolaryngological diseases, 110 patients with chronic suppurative otitis media were treated with Viticis Fructus Decoction (*Cimicifugae Rhizoma*, *Peucedani Radix*, *Mori Cortex*, *etc*) and Hong-Mian powder. Thirty-eight cases were treated with Western medicine (antibiotics and steroid hormones). The curative effect of TCM group was significantly better than that of the Western medicine group. The cure rate was better in the Chinese medicine group (89.1 %) compared with the Western medicine group (86.8 %). And the recurrence rate of the Chinese medicine group (1.8 %) was significantly lower than that of the Chinese medicine group (31.6 %) (Guo and Wang, 2003). Viticis Fructus, *Eupatorii Herba*, *Angelicae Dahuricae Radix* and *Xanthii Fructus* were applied clinically for the treatment of rhinitis, sinusitis, ethmoid sinusitis and maxillary sinusitis (Guo, 2006). It was worth mentioning that Viticis Fructus also had a good therapeutic effect on gastritis. Four groups were set up, namely superficial gastritis with Weishu No.1 (*Angelicae sinensis radix*, *Paeoniae radix alba* and so on) plus Viticis Fructus 20–30 g, atrophic gastritis with Weishu No.2 (*Lilii bulbus*, *Codonopsis radix*) plus Viticis Fructus 20–30 g and the control groups without the addition of Viticis Fructus. Patients were monitored and had a repeat gastroscopy after 2–3 sessions (2–3 months). The heartburn, distension and pain disappeared on average 14.3 days in the treatment group and the control group 26.1 days on average. Gastroscopy results in patients with gastritis displayed an efficacy rate of 91.7 % in the treatment group and the control group was 74 %. Viticis Fructus played an analgesic and anti-inflammatory role in the prescription (Huang and Wen, 2000). Combined external application of Viticis Fructus powder and yellow wine had a good therapeutic effect on 19 patients with acute mastitis. The clinical symptoms of 17 patients disappeared and the total number of white blood cells and neutrophils in blood tests were normal. The symptoms and signs of two patients were significantly reduced. The total number of white blood cells and neutrophils was close to normal (Xiang, 1999). In addition, it could also treat eye diseases and rheumatism. Viticis Fructus prescription could cure herpes simplex keratitis, bacterial keratitis and papillary closed keratitis. It plays the role of heat dissipation, dispelling wind and relieving pain (Jin, 2018). Qiang-Huo-Sheng-Shi Decoction containing Viticis Fructus could improve symptoms of knee osteoarthritis (Wang, 2021), ankylosing spondylitis (Yang et al., 2021) and lower back pain (Lin, 2019) in clinical practice. It helped to relieve pain of patients.

10.2. Other applications

Viticis Fructus is used in cosmetics, healthcare products and daily necessities (**Table S6**). For example, Viticis Fructus could be made into medicine pillows, health tea, health liquor, beverages and other health care products. It can be applied to lowering blood pressure, lowering blood lipid, lowering blood sugar, improving menopausal syndrome, hair growth, benefits qi and so on (Gao et al., 2022; Park, 1999; Shi, 2016). In cosmetics and daily necessities, casticin, as a sunscreen ingredient in cosmetics, could reduce the use of current chemical sunscreens and play a beneficial role in synergistic sunscreen effects (Wang et al., 2019b). *Longanae Arillus* and Viticis Fructus extract had excellent effects on promoting skin elasticity, relieving wrinkles, skin moisturizing and relieving skin problems (Kim et al., 2018). In addition, toothpaste containing Viticis Fructus had significant antibacterial, anti-inflammatory and analgesic effects, which could fundamentally reduce oral problems such as swelling, aching and bleeding of gum (Mu and Liu, 2017). There were two kinds of head care products containing Viticis Fructus. One kind of hair shampoo had an antipruritic effect and the other kind of plant hair dye enhanced the dyeing effect without any toxic or side effects (Yin, 2019; Jiang, 2016). The volatile oil of Viticis Fructus has a strong aroma and could be used as material for blending flavors. The combination of Viticis Fructus and camphor is an efficient aromatic repellent (Xin et al., 2004).

The clinical effect of Viticis Fructus is worthy of recognition, which can be applied to treat migraine, neurovascular headache, tension headache, gastritis, acute mastitis and so on, and achieve splendid therapeutic effects. However, the detection techniques currently in use are gastroscopy and blood sample detection, which is not enough. It should be combined with more advanced medical instruments and technologies to evaluate the indicators of Viticis Fructus in the treatment of various diseases and to reflect the therapeutic effect more comprehensively and accurately. Currently, Viticis Fructus is utilized finitely. We ought to focus on its application in different domains to broaden the use of Viticis Fructus and maybe discover novel approaches to treating intricate illnesses.

10.3. Patent information

Patents could reflect the development status of hot frontier technology and developmental trend of a field to a certain extent. It was

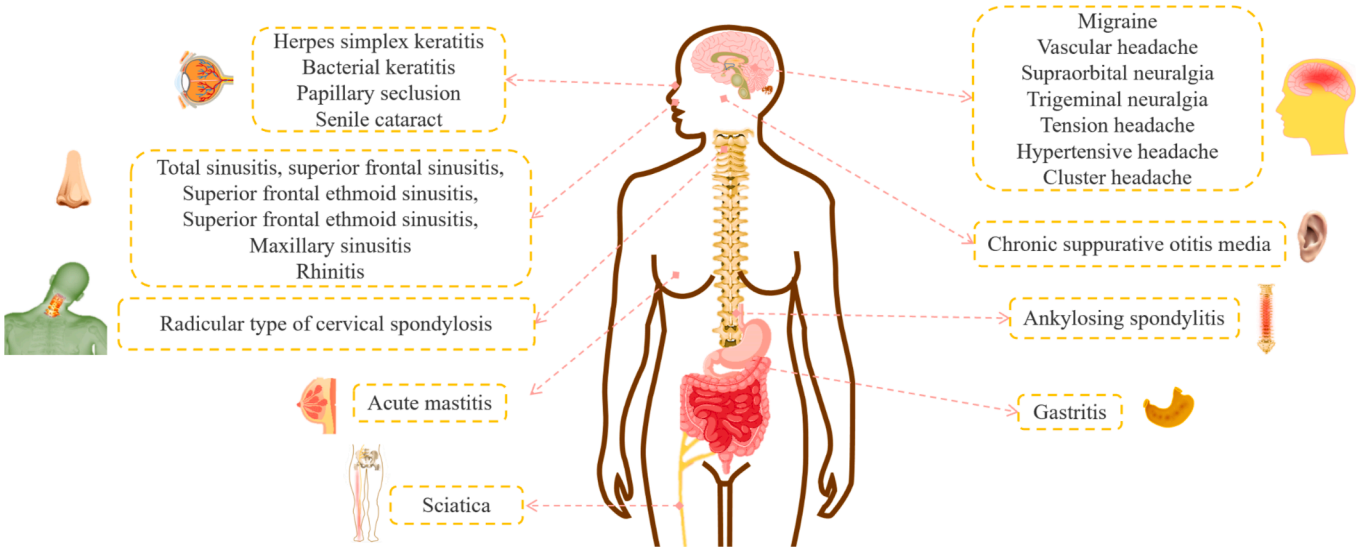

Fig. 10. The application of prescriptions containing Viticis Fructus in clinical diseases.

closely related to all aspects of product production and was the carrier of scientific research achievements transformation (Chen et al., 2023). More than 2,000 results were obtained by searching on the Baiten Patent Search Platform, Yaozhi Network and CNKI. Baiten patent retrieval platform analyzed the patent-related situation of Viticis Fructus. The main technical field of Viticis Fructus patent was necessary for human life, chemistry, metallurgy, operations, transport, physical, textile and papermaking. The necessities for human life account for the largest proportion among them. Viticis Fructus was most widely studied from 2014 to 2018, among which the application and publication peak in 2015 were 445 and 415 respectively (**Fig. S3**). The main areas of patent applications for Viticis Fructus were in China and a few other countries were distributed. In China, the patent applications of Viticis Fructus were concentrated in Shandong Province, Anhui Province, Jiangsu Province and Guangxi Province. Patent applications include cosmetics, daily products, health products, medical use and technical methods (**Table S6**). Cosmetics, daily products and health products are discussed in application in other fields above. It can also be used for antibacterial, antidepressant, treatment of depression and so on in terms of medical use. Patent applications for technical methods focus on quality control and extraction separation, such as component quantification, fingerprint establishment, extraction and separation of total flavonoids.

The patent applications of Viticis Fructus are concentrated in the fields of necessary for human life, chemistry, metallurgy, operations, transport, physical, textile and papermaking in terms of patents. Viticis Fructus is listed as the top grade in the *Shennong Bencao Jing* and is considered to have favorable tonic, health care and therapeutic properties. In addition, it can be used as food in some countries. Its edible value can be studied more to promote the better use of Viticis Fructus.

11. Conclusion and future perspectives

Viticis Fructus was a commonly used Chinese herbal medicine with a large market demand (Gong, 2016). It has apparent curative effect, low toxins and its plants could be used for coastal sand control afforestation (Liu, 2015). This paper summarizes the botany, traditional use, phytochemistry, pharmacological activity, quality control, pharmacokinetics, comprehensive application and toxicity of Viticis Fructus. In phytochemistry, the established database of chemical constituents of Viticis Fructus contains 324 compounds, among which terpenoids and flavonoids serve as their main representative compounds. Pharmacology has proven that Viticis Fructus could prevent and treat cancer, inflammation, PMS, hyperlipidemia, oxidative damage, fever, swollen gums, *etc*. In terms of quality control, the current research focused on the content determination of Viticis Fructus and the identification of adulterants. The 2020 edition of ChP recorded that the content of casticin was not less than 0.030 %. Nevertheless, there are still some gaps in the study of Viticis Fructus and further research is required to comprehend and utilize Viticis Fructus more effectively.

First, whether Viticis Fructus to Verbenaceae and whether the origin plant of *V. rotundifolia* belongs to an independent species needs further study and improvement. Secondly, *V. rotundifolia* and *V. trifolia* fruits are very similar in appearance and it is difficult to distinguish them effectively at present. It can be found that the applications of *V. rotundifolia* fruits are more extensive from Fig. 1 and the actual situation. Therefore, it is indispensable to distinguish *V. rotundifolia* and *V. trifolia* fruits. Thirdly, the research on processing methods is relatively weak. On the one hand, the processing research of Viticis Fructus focuses on the total components and individual pharmacological effects. There are few studies on the changes of specific active compounds before and after processing. The effects mainly involve the comparison of individual pharmacological effects, such as analgesic and cold before and after processing. There are differences in analgesia as previously discussed and further research is needed. On the other hand, the processing of Viticis Fructus is still mainly the stir-frying. However, the frying process of Viticis Fructus has no objective frying process parameters and the quality is difficult to guarantee. Fourthly, most of the studies on the antitumor activity of Viticis Fructus are limited to *in vitro* and the efficacy *in vivo* remains to be confirmed. Fifthly, the toxicology of Viticis Fructus is relatively weak. Its toxic reaction and toxic mechanism have not been elucidated. Sixthly, the pharmacokinetic study of Viticis Fructus is not comprehensive. The tissue distribution and excretion kinetics of Viticis Fructus are still vacant. Seventhly, ChP only stipulates casticin as the quality evaluation index of Viticis Fructus. However, the content of a single component does not fully represent the overall quality. Eighthly, Modern pharmacology mainly concentrates on the study of casticin. There are many compounds isolated and identified from Viticis Fructus, but only fewer compounds have been studied, such as rotundifuran, vitetrifolin H, artemetin, *etc*. Their pharmacological activity, active site and action mechanism need to be elucidated. Lastly, Viticis Fructus can be devoted to treat blurred vision, rheumatism, headache, toothache and other diseases according to ancient books. In the *Shennong Bencao Jing* and *Bencao Gangmu*, it has been repeatedly emphasized that Viticis Fructus can dispel rheumatism. It is also used in the classic prescription Qiang-Huo-Sheng-Shi Decoction. However, the action mechanism of arthritis is still unclear. In addition, rheumatism is divided into many types and the current experiment is limited to KOA model.

According to the above deficiencies raised, the following views are put forward. The family of Viticis Fructus and varieties of *V. trifolia* should be unified to promote the mutual development and utilization in varieties and families. The genetic variation patterns and evolutionary history of *V. rotundifolia* and *V. trifolia* were revealed by using modern technologies such as nuclear gene sequencing and chloroplast gene sequencing, which laid a foundation for solving the problems of taxonomy and genetic relationship between the two species. Accurate, stable and reliable analytical methods should be established to discriminate these two origin plants and ensure the medication quality. The difference in composition and curative effect of different processed products needs to be further studied *in vivo* and *in vitro*. Reliable and stable quality markers should be found to distinguish different processed products *via* metabolomics, cluster analysis and other technical means. The analgesic effect was accurately and reliably evaluated by establishing several analgesic models, such as acetic acid writhing test, hot plate test and formalin test. Moreover, there are numerous records of liquor-processed Viticis Fructus in ancient processing. Therefore, more attention can be paid to liquor-processed Viticis Fructus. The fried products of Viticis Fructus need the provision for uniform frying standards, such as frying time, frying fire and other related parameters. Anti-tumor animal models should be established *in vivo*. The targets, pathways and related mechanisms are explained from multiple levels of genes and proteins through advanced technologies such as transcriptomics, proteomics, *etc*. Different doses of Viticis Fructus can be injected or intragastrical administered to explore its toxic mechanism. Quality markers should be explored and multiple components together reflect the overall quality of Viticis Fructus. It should conduct a systematic, in-depth study of the therapeutic material basis and complement the mechanism of action, pathway and target, in order to better exploit Viticis Fructus. A variety of rheumatism models such as rheumatoid arthritis, ankylosing spondylitis and osteoarthritis should be established to determine the type of rheumatism best treated by Viticis Fructus and to study its action mechanism.

Consequently, this article makes a comprehensive review from botany, historical records, phytochemistry, pharmacology, toxicity, quality control, pharmacokinetics and comprehensive applications of Viticis Fructus. At present, the application of Viticis Fructus still has certain limitations. Further research and discovery are needed to explore the scientific connotation of Viticis Fructus.

CRediT authorship contribution statement

Xue Meng: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal

analysis, Data curation, Conceptualization. **Yang Liu:** Writing – review & editing, Visualization, Software, Methodology, Data curation, Conceptualization. **Suyi Liu:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Qianqian Zhang:** Visualization, Project administration, Formal analysis, Conceptualization. **Kunze Du:** Writing – review & editing, Formal analysis, Data curation. **Omachi Daniel Ogaji:** Resources, Investigation, Formal analysis. **Lirong Wang:** Resources, Investigation, Data curation. **Xingyue Jin:** Resources, Formal analysis, Conceptualization. **Jin Li:** Investigation, Data curation, Conceptualization. **Yanxu Chang:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

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