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Review article

A review of "plant gold" *Eucommia ulmoides* Oliv.: A medicinal and food homologous plant with economic value and prospect

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A R T I C L E I N F O

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A B S T R A C T

Eucommia ulmoides Oliv. is an ancient and precious plant that has been used as medicine in China for more than 2000 years. Because its bark, leaves, seeds, and male flowers can be used in medicine, it plays an important role in medicine, food, chemical industry, and other fields, so it is also called "plant gold". 246 compounds have been isolated from E. ulmoides, which endow E. ulmoides with many unique pharmacological effects and make it wide to study in the fields of osteoporosis, hypertension, liver protection, and so on. Besides, E. ulmoides also has significant medicinal effects on anti-inflammatory, antioxidant, immunomodulation, and neuroprotection, and is often used in clinical compound medicines of traditional Chinese medicine. In addition to updating its ethnobotany, phytochemistry, pharmacology, and toxicology information, the economic botany of leaves, seeds, and male flowers was also introduced. It hopes hoping to fully understand this economically important Chinese medicine and provide a scientific basis for further development and utilization of E. ulmoides.

1. Introduction

Eucommia ulmoides Oliv. (EU) is a deciduous tree of the genus *Eucommia* in the family Eucommiaceae, also known as Mumian, Sizhong, Silk Cotton Skin, and Silk Pulled Skin. EU is an ancient tree species that existed more than 2 million years ago and is considered a living fossil in the plant kingdom. Due to the invasion of glaciers, many EU plants in Europe, Asia, and North America have become extinct one after another. Only a small amount of EU was preserved in central and western China due to the complex terrain of glaciers, and it became a unique tree species in China. EU was introduced to Europe in 1896, to Japan in 1899, to Russia in 1906, and then to France, the United States, South Korea, North Korea, Germany, Hungary, India, and Canada [1]. EU can withstand cold and drought, has strong vitality, and is suitable for growing in a wide area. It is distributed in Guizhou, Shaanxi, Gansu, Sichuan, Henan, Hubei, and other places in China and is now widely planted throughout the country [2]. As of June 2019, the planting area of EU has reached 400,000 hm^2 [3], accounting for about 95 % of the total EU resources in the world. This is a valuable Chinese herb unique to China.

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The dried bark of EU is used in traditional Chinese medicine (TCM) to nourish the liver and kidneys, strengthen the muscles and bones, and prevent miscarriage, and it is classified as a top-class product [4]. Phytochemical studies have found that EU is rich in iridoids, lignans, flavonoids, phenylpropanoids, polysaccharides, and other active ingredients, which have significant effects in preventing osteoporosis, lowering blood pressure, regulating glucose and lipid metabolism, antioxidation, immunomodulation, etc. It is widely used in clinical prescriptions of TCM and various Chinese patent medicines and can be further processed into tablets, granules, oral liquids, and other Chinese patent medicines for anti-osteoporosis effects, improving immunity, and reducing triglycerides. It can be used for anti-osteoporosis, improving immunity, lowering cholesterol, tonifying the kidneys and protecting the liver, beautifying and losing weight, etc. The application of EU has been extended from clinical medicine to daily chemical, food, feed, rubber, materials, and other fields [5].

Although there are many reviews that have comprehensively summarized the ethnopharmacology, phytochemistry, and pharmacological effects of EU, fewer reviews have systematically compiled the various compounds extracted from the leaves, male flowers, and other parts of EU and their related botanical uses. In order to update the research information on EU in time, this review summarizes the achievements of EU in ethnobotany, phytochemistry, processing technology, pharmacological action, toxicology, and applications in recent years, it explains the economic value of EU, increases the contents about its leaves, male flowers, and fruits, analyzes the limitations of current research, and puts forward its own. We hope to fully understand the current research progress and provide a rich reference base and innovation for further research on EU.

Fig. 1. Bark (A), leaves (B), samaras (C), male flowers (D) of *E. ulmoides*.

2. Botany

EU is a deciduous tree, up to 20 m tall. The bark is gray-brown, with a rough surface and rubber inside. When the bark breaks and is pulled apart, there will be many tiny filaments. The thin leathery leaves are elliptic, ovate, or rectangular, with rounded or broad cuneate bases, acuminate apexes, dark green above, serrate margins, young leaves with brown pilose, soon becoming bald and net, mature leaves slightly wrinkled, abaxially light green, with brown hairs only on the veins. The fracture surfaces of the leaf and petioles are also connected by elastic silvery white dense glue wires [6]. Unisexual flowers, born at the base of annual branches, with obovate bracts. The male flowers are clustered, and the female flowers are axillary. Samara is flat and oblong, with 1 or 2 seeds inside, and there is *Eucommia ulmoides* rubber with important application value in the shell. The flowering period is April to May, and the fruiting period is September [7]. The morphology of the bark (A), leaves (B), samaras (C), and male flowers (D) of EU is depicted in Fig. 1.

3. Economic botany

EU is an important strategic resource in China, showing great application value and development prospects in landscaping, furniture, food development, new feed, the rubber industry, and pharmaceutical engineering [8].

Eucommia trees have straight trunks, beautiful shapes, and tall crowns, which have high ornamental value and can be used for landscaping and urban greening [9]. EU is a kind of solid material with a fine texture that is not easy to crack or worm and is often used as a furniture material. In addition, because of its strong drought and wind resistance, EU can plant in arid areas to play a better role in wind and sand fixation, improving the ecological environment and adjusting the urban climate. It also has strong carbon sequestration capacity, which is conducive to achieving the goal of carbon neutrality. It is a multifunctional tree species with great potential. With the deepening of research, EU has gradually developed from a single bark to an all-round development of leaves, flowers, and fruits. It not only improved the utilization rate of resources but also developed a variety of new green products, which promoted the diversification and modernization of the Chinese medicine industry.

Eucommia ulmoides leaves (EUL) can be harvested in summer and autumn each year. With abundant resources, the annual production of EUL can reach ten million tons, which is a renewable medicinal resource of good quality and low price. With an in-depth study, we found that the chemical composition and pharmacological effects of EUL are similar to those of EU. The feasibility of replacing EU with EUL has been proven clinically and pharmacologically, which is not only low in price but also less destructive to trees. In addition, the chlorogenic acid content of EUL can reach 1 %–5.5 %, and it is cheap and easily available, so it can be used as a high-quality raw material for extracting and separating chlorogenic acid [10]. Compared with antibiotics, it is natural, green, safe, environment-friendly, and non-dependent. It is often added to animal feed as a natural additive to improve immunity and meat quality [11]. In addition to being used as a traditional medicine, EUL also has important edible value. In 2017, EUL was listed on the homologous list of medicines and foods. In the Song Dynasty, it was recorded in the Ben Cao Tu Jing that EU is edible when the first leaves are tender. EUL is rich in nutrients such as VE, VB_1, β-carotene and free amino acids. The crude protein content is higher than that of corn, cereals, sorghum, and potatoes, and the amino acid content is higher than that of wheat. It can be made into a superfine powder as a new baking raw material, which expands the use of EUL [12]. Li et al. [13] developed a unique flavor with rich nutrition. EUL steamed bread, which not only increased amino acids, vitamins, dietary fiber, and other nutrients necessary for the human body but also improved the hardness of steamed bread. Besides being processed into food, it has also been developed into EU tea and other health products. Japanese scholars believe that *Eucommia* tea not only has no toxic side effects when consumed for a long time but is also the tea beverage with the most healthful ingredients [14]. In recent years, Chinese researchers have developed EU black tea, EU green tea, EU oolong tea, EU compound health beverages, EU yogurt, and other products and applied for more than 50 related patents.

EU is dioecious, with male flowers clustered at the base of the branches of the same year, which bloom in early spring, with a short flowering period of only about one week, a high yield, and easy collection [15]. The male flowers of EU contain similar chemical components to the bark and leaves of EU, but the content of flavonoids is higher than that of EUL and bark, and the contents of calcium and zinc are 1.8 times and 5.2 times that of EUL, respectively. Compared with EUL, which is also easily available in large quantities, EU male flowers contain high and comprehensive active ingredients [16]. EU male flower is also rich in nutrients, which have been included in the National List of New Food Raw Materials and have been developed into health products such as EU male flower tea, EU male flower wine, EU male flower functional beverages, and other health products. In 2011, the chemical constituents and pharmacological effects of EU tea were studied. It was found that EU tea contains 8 essential amino acids and rich mineral elements needed by the human body. It has pharmacological effects such as reducing blood lipids, relieving fatigue, and enhancing immunity, and it is an ideal natural nutritional health care product [17].

EU seeds are rich in oil and protein. EU seed oil, which is extracted at low temperatures by leaching after peeling, is a new edible vegetable oil resource in China. EU seed oil is rich in unsaturated fatty acids, of which the content of α-linolenic acid is more than 60 %, which is the highest content of plants found so far [18]. EU seed oil has pharmacological actions such as decreasing blood pressure, controlling blood lipids, being anti-inflammatory, anti-tumor, and boosting memory. Based on this, a variety of functional health products have been developed, enriching EU resources.

Eucommia bark, leaves, seeds and peels contain a kind of white colloidal substance, which is called *Eucommia ulmoides* rubber (EUR). It is a natural polymer resource, and its molecular structure is *trans* −1,4- polyisoprene [19]. It is an isomer with natural rubber, and it is considered as an ideal candidate to replace natural rubber. It is commonly known as gutta-percha internationally. The content distribution of EUR is strongly dependent on different growth periods, growth conditions and some parts of EU. Some studies show that the rubber content of EUL is 1 %–3 %, the rubber content of EU bark and root is 6 %–10 %, and the rubber content of EU fruit is 13 %–17 % [20]. The annual output of leaves is large, and it can be renewed every year. Recycling fallen leaves can not only turn waste into treasure, but also improve the shortage of natural rubber in China. The rubber content in leaves is the most abundant in November, which is the main raw material for extracting gutta-percha at present [21].

In recent years, because of its unique and excellent duality of rubber and plastic [22], researchers have successfully extracted, purified, and modified EUR to further optimize its performance and application scope. By controlling the critical crosslinking degree, EUR is made into three series of products: thermoplastic, thermal elastomer, and high elastomer [23]. It has no toxic side effects or catalyst residue and can be used to make dental filling materials, splints, prosthetic sleeves, and other medical materials. In addition, EUR has the advantages of elasticity, fatigue resistance, adhesion, and physical and mechanical properties similar to traditional rubber, which makes EUR have broad application prospects in the fields of green tires, medical devices, and submarine cable [24]. EUR has great development potential in preparing functional biomaterials due to its excellent properties [25]. Peng's group [26–30] has developed a series of non-plasticizing gutta-percha film material with good moisture barrier, light shielding, oil-water separation, photothermal conversion, and bacteriostasis, which has potential application prospects in food packaging, agricultural water conservation, agricultural planting, water pollution, oil enrichment and separation, and new plant protection materials. To sum up, EUR, as a high-quality natural rubber resource, has shown good development potential. The current research and development work provides a solid foundation for its future application. Looking forward to the future, EUR will have broad development prospects under the requirements of sustainable development and environmental protection.

4. Ethnobotany

Since ancient times, traditional Chinese medicine (TCM) has played an important role in improving the quality of life, prolonging life, preventing diseases, and making great contributions to the prosperity of the Chinese nation. Since the beginning of history, EU has been known and used for more than 2000 years. The medicinal properties of EU have been explored for a long time through rich clinical practice by successive generations of pharmacists and the usage, and specific effects of EU have been recorded in many ancient books.

EU was firstly published in Shen Nong Ben Cao Jing, in which it was recorded that EU has a pungent taste and is mainly used for treating lumbar and spinal pain, tonifying the spleen and stomach, strengthening tendons and bones, enhancing memory, removing itching and wetness under the vagina, improving post-urine leaching, and fighting fatigue [31], which clearly defined the medicinal properties, odor, and main therapeutic functions and it was subsequently proved to be reliable by modern scientific research and clinical practice. Later modern scientific research and clinical practice proved that these contents are very reliable, indicating that the understanding of EU was more profound and scientific at that time. With the emergence of new drug varieties and the continuous improvement of pharmacological levels, the understanding of EU is also deepening. Ming Yi Bie Lu records: "EU tastes sweet, has mild medicinal properties, and is nontoxic. It is mainly used to treat sore feet and people who can't walk. EU, also known as Sizhong and Kapok, grows in Shangyu Valley, Shangdang, and Hanzhong. Bark is collected in February, May, June, and September each year" [32]. Not only does it add new understanding of the medicinal properties of EU, new functions and synonyms, specific places of origin, and

Table 1
The traditional application of *E. ulmoides* recorded by ethnic minorities in China.

Ethnic	Ethnic medicine names	Medicinal parts	Main diseases	Literature Sourcesg
Tibetan	Dabusan	Bark	Treat stomach heat, eye diseases, red eyes, swelling, and pain; Treat bone injuries, fractures, sores after making ghee.	Tibetan herbal medicine
Miao	Nduizhoux sod	Stem	Elderly low back pain and restless fetal movement	Miao medicine
	Det dent Det uab udfab	Bark	Kidney deficiency and lumbago, weakness of the waist and knees, fetal movement restlessness, threatened abortion, hypertension	Xianglankao
Lisu	Sigongzi	Bark	Lumbago, rheumatism, dizziness, hypertension, restless fetal movement, and traumatic injury	Nujiang medicine
Wa	Luo Kao yang yi	Bark	Chronic kidney disease and hypertension	
Mao Nan	Meiduzhong	Bark	Low back pain caused by kidney deficiency	Gui Yao bian
Yi	Eucommiae Cortex	Stem	Kidney deficiency and low back pain, muscle weakness, rheumatic bone pain, aching all over, restless fetal movement, and erectile dysfunction	Ailao herbal medicine
Shui	Bimei Dulcimer	Stem	Hypotensive, nephritis, edema	Shui medicine
Jingpo	Sikjicq		Hypertension, dizziness, frequent urination due to kidney deficiency, and restless fetal movement	Dehong medicine record
De'ang		Bark	Cutting injury, soreness of the waist and knees, restless fetal movement, hypertension	Yunnan provincial chronicles
Hani	Qida	Stem/Leaves	Fracture	Yunnan medicine record
		Bark	External application of a wound	Yunnan provincial chronicles
Dai	Yage Gao	Bark	External application of a wound	Yunnan provincial chronicles
Dong	Meix sabt enl Sangp meix sabt enl	Bark	Men have difficulty with urination and defecation, and their urine is turbid.	Dong medicine

Table 2
Chemical constituents of *E. ulmoides*.

Category	No.	Compound	Formula	Molecular weight	Part	Reference
Lignans	1	(−)-olivil	$C_{20}H_{24}O_7$	376.1522	barks, leaves	[36]
	2	(−)-olivil-4′-*O*-*β*-D-glucopyranoside	$C_{26}H_{34}O_{12}$	538.2050	barks	[37]
	3	(−)-olivil-4″-*O*-*β*-D-glucopyranoside	$C_{26}H_{34}O_{12}$	538.2050	barks	[37]
	4	olivil-di-O-*β*-*D*-glucopyranoside	$C_{32}H_{44}O_{17}$	700.2578	barks	[38]
	5	lariciresinol	$C_{22}H_{28}O_6$	388.1886	barks	[39]
	6	8′-methoxy-olivil	$C_{21}H_{26}O_7$	390.1679	barks	[40]
	7	(+)-medioresinol-di-*O*-*β*-D-glucopyranoside	$C_{33}H_{44}O_{17}$	712.2578	barks	[41]
	8	eucommin A	$C_{27}H_{34}O_{12}$	550.2050	barks	[38]
	9	medioresinol	$C_{21}H_{24}O_7$	388.1522	barks	[42]
	10	(+)-pinoresinol-di-*O*-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	682.2473	barks, leaves	[41]
	11	(+)-pinoresinol-4′-*O*-*β*-D-glucopyranoside	$C_{26}H_{32}O_{11}$	520.1945	barks	[41]
	12	pinoresinol	$C_{20}H_{22}O_6$	358.1416	barks	[42]
	13	(+)-pinoresinol-4-*O*-*β*-D-glucopyranosyl (1→6)-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	682.2473	barks	[37]
	14	(+)-syringaresinol-4′-*O*-*β*-D-glucopyranoside	$C_{28}H_{36}O_{13}$	580.2156	barks	[38]
	15	liriodendrin	$C_{34}H_{46}O_{18}$	742.2684	barks	[41]
	16	(+)-syringaresinol	$C_{22}H_{26}O_8$	418.1628	barks	[42]
	17	1-hydroxypinoresinol-di-*O*-*β*-D-glucopranoside	$C_{32}H_{42}O_{17}$	698.2422	barks	[38]
	18	1-hydroxypinoresinol-4-*O*-*β*-D-glucopranoside	$C_{26}H_{32}O_{12}$	536.1894	barks	[36]
	19	(+)-1-hydroxypinoresinol-4′-*O*-*β*-D-glucopyranoside	$C_{26}H_{32}O_{12}$	536.1894	barks	[36]
	20	1-hydroxypinoresinol	$C_{20}H_{22}O_7$	374.1366	barks	[42]
	21	epipinoresinol	$C_{20}H_{22}O_6$	356.1416	barks	[42]
	22	erythro-guaiacylglycerol-*β*-coniferyl aldehyde ether	$C_{20}H_{22}O_7$	374.1366	barks	[42]
	23	threo-guaiacylglycerol-*β*-coniferyl aldehyde ether	$C_{20}H_{22}O_7$	374.1366	barks	[42]
	24	citrusin B	$C_{27}H_{36}O_{13}$	568.2156	barks	[43]
	25	hedyotol-C-4′, 4″-di-*O*-*β*-D-glucopyranoside	$C_{35}H_{40}O_{15}$	700.2367	barks	[43]
	26	syringylgylycerol-*β*-syringaresinol ether-4′, 4″-*O*-*β*-D-glucopyranoside	$C_{37}H_{44}O_{17}$	760.2578	barks	[43]
	27	guaiacylgylglycerol-*β*-syringaresinol ether-4′, 4″-di-*O*-*β*-D-glucopyranoside	$C_{36}H_{42}O_{16}$	730.2473	barks	[44]
	28	dihydrodehydrodiconiferyl alcohol	$C_{20}H_{24}O_6$	360.1573	barks	[42]
	29	erythro-dihydroxydehydro-di-coniferyl alcohol	$C_{20}H_{24}O_8$	392.1471	barks	[42]
	30	threo-dihydroxydehydro-di-coniferyl alcohol	$C_{20}H_{24}O_8$	392.1471	barks	[42]
	31	dehydro-di-coniferyl alcohol 4, *γ*′-di-*O*-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	682.2473	barks	[43]
	32	dehydro-di-coniferylalcohol-*γ*′-*O*-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	416.1471	barks	[45]
	33	(+)-cyclo-olivil	$C_{20}H_{24}O_7$	376.1522	barks, leaves	[36]
	34	vladinol D	$C_{20}H_{22}O_7$	374.1366	barks	[46]
	35	8-hydroxy pinoresinol	$C_{20}H_{22}O_7$	374.1366	barks	[45]
	36	9*α*-hydroxy pinoresinol	$C_{20}H_{22}O_7$	374.1366	barks	[46]
	37	8-methoxy-medioresinol	$C_{22}H_{26}O_8$	418.1628	leaves	[47]
	38	8-hydroxy-medioresinol	$C_{21}H_{24}O_8$	404.1471	leaves	[47]
	39	hedytol C	$C_{31}H_{36}O_{11}$	584.2258	barks	[46]
	40	hedytol D	$C_{31}H_{36}O_{11}$	584.2258	barks	[46]
	41	guaiacylglycerol-8-*O*-4’- (sinapyl aldehyde) ether	$C_{21}H_{24}O_8$	404.1471	barks	[46]
	42	guaiacylglycerol-8-*O*-4’- (sinapyl alcohol) ether	$C_{21}H_{26}O_7$	390.1679	barks	[46]
	43	guaiacylglycerol-8-*O*-4′-coniferyl aldehyde ether	$C_{20}H_{22}O_7$	374.1366	barks	[46]
	44	pinoresinol vanillic acid ether-di-glucopyranoside	$C_{35}H_{40}O_{15}$	700.2367	barks	[44]
	45	syringaresinol vanillic acid ether-di-gucopyranoside	$C_{37}H_{44}O_{17}$	760.2578	barks	[44]
	46	(7*S*, 8*S*, 8′*S*)-4, 9, 4′, 8′-tetrahydroxy-3, 3′-dimethoxy-7, 9′-monoepoxy	$C_{20}H_{24}O_7$	376.1522	barks	[48]
	47	(8*S*, 7′*S*, 8′R) -vladinol D-4, 4′-O-β-D-diglucopyranoside	$C_{26}H_{32}O_{12}$	536.5326	leaves	[49]
	48	(+)-neoolivil	$C_{20}H_{24}O_7$	376.4004	leaves	[49]
	49	8′-hydroxyl-lariciresinol-4′-O-β-D-glucopyranoside	$C_{26}H_{34}O_{12}$	538.5418	leaves	[49]
	50	forsythialanside E	$C_{26}H_{32}O_{12}$	535.1816	leaves	[49]
	51	Arctiinoside B	$C_{32}H_{42}O_{17}$	698.6749	leaves	[49]
	52	dehydro-di-coniferylalcohol-4-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{11}$	520.5302	leaves	[49]
	53	massoniresinol-3α-*O*-β-D-glucopyranoside	$C_{26}H_{34}O_{13}$	554.5476	leaves	[49]
	54	(+)-8-hydroxy-pinoresinol-4′-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{12}$	536.5314	leaves	[49]
	55	(+)-8-hydroxyl-pinoresinol-4, 4′-*O*-β-D-diglucopyranoside	$C_{32}H_{42}O_{17}$	698.6728	leaves	[49]
	56	(+)-medioresinol-4, 4′-*O*-β-D-diglucopyranoside	$C_{33}H_{44}O_{17}$	712.6963	leaves	[49]
	57	prinsepiol-4-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{13}$	552.5245	leaves	[49]
	58	balanophonin	$C_{20}H_{20}O_6$	356.1260	barks	[45]
	59	(+)-epicycloolivil	$C_{20}H_{24}O_7$	399.1420	barks	[50]
	60	noreucol A	$C_{19}H_{20}O_6Na$	367.1158	barks	[50]
	61	Arctiin	$C_{27}H_{34}O_{11}$	534.5558	leaves	[51]
Iridoids	62	asperulosidic acid	$C_{18}H_{24}O_{12}$	432.1268	leaves	[52]
	63	deacetyl asperuloside acid	$C_{15}H_{22}O_9$	346.1264	leaves	[52]

(continued on next page)

Table 2 (*continued*)

Category	No.	Compound	Formula	Molecular weight	Part	Reference
	64	asperulosidic acid ethyl ester	$C_{21}H_{30}O_{11}$	458.1788	flowers	[53]
	65	daphylloside	$C_{20}H_{28}O_{11}$	444.1632	flowers	[53]
	66	geniposide	$C_{17}H_{24}O_{10}$	388.1369	barks	[54]
	67	geniposidic acid	$C_{16}H_{22}O_{10}$	374.1213	barks, leaves, seeds	[52]
	68	genipin	$C_{11}H_{14}O_5$	226.0841	barks	[42]
	69	aucubin	$C_{15}H_{22}O_9$	346.1264	leaves, seeds	[55]
	70	ulmoidoside	$C_{15}H_{22}O_9$	346.1264	leaves	[56]
	71	scandoside-10-*O*-acetate	$C_{18}H_{24}O_{12}$	432.1268	leaves	[52]
	72	scandoside methyl ester	$C_{19}H_{26}O_{12}S$	478.1145	leaves	[57]
	73	deacetyl asperulosidic acid methyl ester	$C_{17}H_{24}O_{11}$	404.1319	leaves	[57]
	74	eucommiol	$C_9H_{16}O_4$	188.1049	barks, leaves	[55]
	75	eucommiol I	$C_{15}H_{26}O_9$	350.1977	barks, leaves, seeds	[58]
	76	eucommiol II	$C_{15}H_{26}O_9$	350.1977	barks, leaves	[58]
	77	1-deoxyeucommiol	$C_9H_{16}O_3$	172.1099	barks	[54]
	78	epieucommiol	$C_9H_{16}O_4$	188.1049	leaves	[44]
	79	ajugoside	$C_{17}H_{26}O_{10}$	390.1526	leaves	[55]
	80	harpagide acetate	$C_{17}H_{26}O_{11}$	406.1475	leaves	[55]
	81	reptoside	$C_{15}H_{24}O_9$	348.1420	leaves	[55]
	82	ulmoidoside A	$C_{48}H_{62}O_{28}$	1086.3428	seeds	[59]
	83	ulmoidoside B	$C_{50}H_{64}O_{29}$	1128.3533	seeds	[59]
	84	ulmoidoside C	$C_{64}H_{82}O_{37}$	1442.4535	seeds	[59]
	85	ulmoidoside D	$C_{66}H_{84}O_{38}$	1484.4641	seeds	[59]
	86	eucomosides A	$C_{18}H_{22}O_{11}$	414.1162	leaves	[60]
	87	eucomosides B	$C_{25}H_{31}NO_{11}$	417.1424	leaves	[60]
	88	eucomosides C	$C_{27}H_{32}N_2O_{11}$	560.2006	leaves	[60]
	89	asperuloside	$C_{18}H_{22}O_{11}$	414.1162	leaves	[52]
	90	4-dihydro-3-methoxypaederoside	$C_{19}H_{26}O_{12}S$	478.1145	flowers	[53]
	91	dihydrochalcone	$C_{15}H_{14}O$	210.1045	barks	[61]
	92	bartsioside	$C_{15}H_{22}O_8$	330.1315	seeds	[62]
	93	catalpol	$C_{15}H_{22}O_{10}$	362.1213	barks	[63]
	94	ulmoidol A	$C_{29}H_{38}O_5$	466.2719	seeds	[64]
	95	8-*epi*-loganin	$C_{17}H_{26}O_{10}$	390.1526	leaves	[57]
	96	loganin	$C_{17}H_{26}O_{10}$	390.1526	leaves	[57]
	97	7-*epi*-loganin	$C_{17}H_{26}O_{10}$	390.1526	leaves	[57]
	98	2-Phenylbutyric Acid-d5	$C_{10}H_7D_5O_2$	169.2318	leaves	[65]
	99	Cynaroside	$C_{21}H_{20}O_{11}$	448.3807	flowers	[66]
	100	3β-methoxyartselawnin C	$C_{10}H_{14}O_4$	221.0791	flowers	[67]
	101	6β-hydroxyl-1β,3β-dimethoxyartsclaenin III	$C_{11}H_{18}O_5$	253.1055	flowers	[67]
	102	3,4- dihydro-3β-ethoxyasperuloside	$C_{20}H_{28}O_{12}$	483.1481	flowers	[67]
	103	3,4-dihydro-3β-ethoxydesacetylasperuloside	$C_{18}H_{26}O_{11}$	441.1375	flowers	[67]
	104	Artselaenin C	$C_9H_{12}O_4$	184.1892	flowers	[67]
	105	Ulmoside C	$C_{19}H_{26}O_{11}$	430.4128	leaves	[68]
	106	Ulmoside D	$C_{25}H_{40}O_{13}$	548.5896	leaves	[68]
	107	Baltus glycoside	$C_{15}H_{22}O_8$	353.2017	seeds	[69]
	108	linaride	$C_{15}H_{22}O_8$	682.7403	seeds	[69]
	109	scyphiphin D	$C_{32}H_{42}O_{19}$	753.1964	seeds	[69]
	110	borreriagenin	$C_{10}H_{14}O_5$	214.0841	leaves	[39]
Phenolic acids	111	methyl chlorogenate	$C_{17}H_{20}O_9$	368.1107	barks, leaves	[42]
	112	chlorogenic acid	$C_{16}H_{18}O_9$	354.0951	barks, leaves, seeds	[52]
	113	3-*O*-feruloylquinic acid	$C_{17}H_{20}O_9$	368.1107	leaves	[44]
	114	vanillic acid	$C_8H_8O_4$	168.0423	barks	[70]
	115	ascorbic acid	$C_6H_8O_6$	176.0321	barks	[71]
	116	ascorbic acid	$C_9H_8O_4$	180.0423	barks, leaves, seeds	[42]
	117	caffeic acid ethyl ester	$C_{11}H_{12}O_4$	208.0736	leaves	[71]
	118	ferulic acid	$C_{10}H_{10}O_4$	194.0579	leaves	[72]
	119	p-coumaric acid	$C_9H_8O_3$	164.0473	leaves	[73]
	120	coniferol	$C_{10}H_{12}O_3$	180.0786	barks	[71]
	121	coniferin	$C_{16}H_{22}O_8$	342.1315	stems	[54]
	122	erythro-guaiacylglycerol	$C_{10}H_{14}O_5$	214.0841	barks	[36]
	123	threo-guaiacylglycerol	$C_{10}H_{14}O_5$	214.0841	barks	[36]
	124	eucophenoside	$C_{14}H_{16}O_8$	312.0845	barks	[58]
	125	catechin	$C_{15}H_{14}O_6$	290.0790	barks, leaves	[74]
	126	epicatechin	$C_{15}H_{14}O_6$	290.0790	barks	[74]

(*continued on next page*)

Table 2 (*continued*)

Category	No.	Compound	Formula	Molecular weight	Part	Reference
	127	protocatechuic acid methyl ester	$C_8H_8O_4$	168.0423	barks	[75]
	128	gallic acid	$C_7H_6O_5$	170.0215	leaves	[71]
	129	protocatechuic acid	$C_7H_6O_4$	154.0266	leaves	[73]
	130	isochlorogenic acid A	$C_{25}H_{24}O_{12}$	516.1268	leaves	[76]
	131	isochlorogenic acid C	$C_{25}H_{24}O_{12}$	516.1268	leaves	[76]
	132	3-(3，4-dihy-droxyphenyl) propionic acid	$C_9H_{10}O_4$	182.0579	leaves, seeds	[59]
	133	3-(3-hydroxyphenyl) propionic acid	$C_9H_{10}O_3$	166.0630	leaves	[77]
	134	pyrogallol	$C_6H_6O_3$	126.0317	leaves	[73]
	135	phthalic acid dibutyl ester	$C_{16}H_{22}O_4$	278.1518	seeds	[62]
	136	koaburaside	$C_{14}H_{20}O_9$	332.1107	stems	[54]
	137	phthalic acid bis-(7-ethy-2-hydroxyethyl decyl)-ester	$C_{36}H_{62}O_6$	590.4546	seeds	[62]
	138	phthalic acid bis-(2-ethy decyl)-ester	$C_{32}H_{54}O_4$	502.4022	seeds	[62]
	139	syringin	$C_{17}H_{24}O_9$	372.1420	stems	[54]
	140	*β*-hydroxypropiovanllone	$C_{10}H_{12}O_4$	196.0736	barks	[48]
	141	epigallocatechin	$C_{15}H_{14}O_7$	306.0740	roots	[78]
	142	*C*-veratroylglycol	$C_{10}H_{12}O_5$	212.0685	barks	[48]
	143	3-hydroxy-4-methoxycinnamaladehyde	$C_{10}H_{10}O_3$	178.0630	barks	[48]
	144	5-methoxy-guaiacylglycerol	$C_{11}H_{16}O_6$	244.0947	leaves	[40]
	145	5，9-dimethoxy-guaiacylglycerol	$C_{12}H_{18}O_7$	274.1053	leaves	[40]
	146	9-*n*-butyl-guaiacylglycerol	$C_{14}H_{22}O_5$	270.1467	leaves	[40]
	147	9-*n*-butyl-isoguaiacylglycerol	$C_{14}H_{22}O_5$	270.1467	leaves	[40]
	148	3-hydroxy-1-(3-merhoxy-4-hydroxyphenyl)-propan-1-one	$C_{10}H_{12}O_4$	196.0736	barks	[46]
	149	licochalcone A	$C_{21}H_{22}O_4$	338.1518	barks	[46]
	150	catechin-(7,8-b,c)-4*α*-(3,4-dihyxyphenyl)-2(3H)-pyranone	$C_{24}H_{20}O_9$	452.1107	barks	[44]
	151	catechin-(7,8-b,c)-4*β*-(3,4-dihyxyphenyl)-2(3H)-pyranone	$C_{24}H_{20}O_9$	452.1107	barks	[44]
	152	Guaiacylglycerol	$C_{10}H_{14}O_5$	214.2152	leaves	[40]
	153	caffeic acid	$C_9H_8O_4$	180.1574	barks, leaves, flowers, seeds	[79]
	154	catechol	$C_6H_6O_2$	110.1106	leaves	[73]
	155	Glucosyringic acid	$C_{15}H_{20}O_{10}$	360.3198	barks	[80]
	156	*O*-phthalic acid bis-(2-ethyl decyl)-ester	$C_{32}H_{54}O_4$	502.4005	seeds	[62]
	157	*O*-phthalic acid bis-(7 - ethyl-2-hydroxyethyl decyl)-ester	$C_{36}H_{62}O_6$	590.4517	seeds	[62]
Terpenoids and Steroids	158	3-oxo12-en-ursane-28-*O*-*α*-L-arabinofuranosyl(1→6)-*β*-D-glucopyranoside	$C_{41}H_{66}O_{11}$	734.4605	flowers	[81]
	159	2*α*, 3*β*-dihydroxyurs-12-en-28-oic-acid (28→1)-*β*-D-glucopyranosyl ester	$C_{36}H_{60}O_9$	636.4237	flowers	[81]
	160	3-*O*-acetylursolic acid acetate	$C_{32}H_{50}O_4$	498.3709	flowers	[81]
	161	*α*-amyrin	$C_{30}H_{50}O$	426.3862	flowers	[81]
	162	3-*O*-acetyl oleanolic acid	$C_{30}H_{48}O_3$	456.3603	flowers	[53]
	163	loliolide	$C_{11}H_{16}O_3$	193.1099	leaves	[82]
	164	ulmoidol	$C_{29}H_{42}O_5$	470.3032	leaves	[64]
	165	betulin	$C_{30}H_{50}O_2$	442.3811	barks, seeds	[70]
	166	betulic acid	$C_{30}H_{48}O_3$	456.3603	barks, seeds	[70]
	167	ursolic acid	$C_{30}H_{48}O_3$	456.3603	barks, seeds	[70]
	168	24-methylene cycloatronone	$C_{31}H_{50}O$	438.3862	barks	[45]
	169	cycloeucalenone	$C_{30}H_{48}O$	424.3705	barks	[45]
	170	*β*-sitosterol	$C_{29}H_{50}O$	414.3862	barks, leaves	[70]
	171	daucosterol	$C_{35}H_{60}O_6$	576.4390	barks, seeds	[62]
	172	rehmaglutin C	$C_9H_{12}O_5$	200.0685	barks	[83]
	173	cycloeucalenol	$C_{30}H_{50}O$	426.3862	barks	[45]
	174	gardendiol	$C_{10}H_{14}O_4$	198.0892	barks	[46]
	175	moridolide	$C_9H_{12}O_3$	168.0786	barks	[46]
	176	eucommienol	$C_{30}H_{50}O$	426.3862	barks, seeds	[71]
	177	1, 4a, 5, 7a-tetrahydro-7-hydroxymethylcyclopentyl ［ c ］ pyran-4-carboxylic acid methyl ester	$C_{11}H_{14}O_4$	210.0892	barks	[83]
	178	eucommidiol (6, 6a-dihydroxymethyl-3, 3a, 4, 6a-tetrahydro-2*H*-cyclopen- tane ［ b ］ furan-2-one)	$C_9H_{12}O_4$	184.0106	barks	[83]
Flavonoids	179	Naringenin	$C_{15}H_{12}O_5$	272.0685	flowers	[53]
	180	Prunin	$C_{21}H_{22}O_{10}$	434.1213	flowers	[53]
	181	4-methyl-7-hydroxycoumarin	$C_{10}H_8O_3$	176.0473	roots	[78]
	182	procyanidin B2	$C_{30}H_{26}O_{12}$	578.1424	roots	[78]
	183	wogonside	$C_{22}H_{20}O_{11}$	460.1006	barks	[58]
	184	isoliquiritigenin	$C_{15}H_{12}O_4$	256.0736	barks	[58]
	185	quercetin	$C_{15}H_{10}O_7$	302.0427	barks, flowers	[73]
	186	isoquercitrin (quercetin-3-*O*-glucoside)	$C_{21}H_{20}O_{12}$	464.0955	barks, leaves, flowers	[52]
	187	quercetin-3-*O*-*α*-L-glucopyranosyl (1→2)-*β*-D-glucopyranoside	$C_{26}H_{28}O_{16}$	596.1377	barks, leaves, flowers	[84]

(*continued on next page*)

Table 2 (*continued*)

Category	No.	Compound	Formula	Molecular weight	Part	Reference
	188	quercetin-3-*O*-xyloseglucoside (quercetin-3-*O*-sambubioside)	$C_{26}H_{28}O_{16}$	596.1377	barks, leaves	[76]
	189	rutin	$C_{27}H_{30}O_{16}$	610.1534	barks, leaves, flowers	[52]
	190	hyperin (quercetin-3-*O*-galactoside)	$C_{21}H_{20}O_{12}$	464.0955	barks，leaves	[85]
	191	quercetin 3-*O*-6″-acetyl-glucopyranoside	$C_{23}H_{22}O_{13}$	506.1060	leaves	[86]
	192	quercetin-3-*O*-*β*-D-glucopyranosyl (1→2)-*β*-D-glucopyranoside	$C_{27}H_{30}O_{17}$	626.1483	barks, flowers	[78]
	193	kaempferol-3-*O*-glucoside (astragalin)	$C_{21}H_{20}O_{11}$	448.1006	barks, leaves, flowers	[52]
	194	kaempferol	$C_{15}H_{10}O_6$	286.0477	leaves	[87]
	195	kaempherol 3-*O*-rutinoside (nicotifiorin)	$C_{27}H_{30}O_{15}$	594.1585	leaves	[86]
	196	kaempherol 3-*O*-sambubioside	$C_{26}H_{28}O_{15}$	580.1428	leaves	[85]
	197	kaempferol 3-*O*-6″-acetyl-glucopyranoside	$C_{23}H_{22}O_{12}$	490.1111	leaves, flowers	[73]
	198	isorhamnetin-3-*O*-*β*-D-glucopyranoside	$C_{22}H_{22}O_{12}$	478.1111	flowers	[53]
	199	oroxylin	$C_{16}H_{12}O_6$	284.0685	barks	[88]
	200	wogonin	$C_{16}H_{12}O_5$	284.0685	barks	[88]
	201	baicalein	$C_{15}H_{10}O_5$	270.0528	leaves	[88]
	202	luteolin	$C_{15}H_{10}O_6$	286.0477	leaves	[72]
	203	4′, 7-dihydroxyflavene	$C_{15}H_{12}O_3$	240.0786	roots	[78]
	204	hirsutin	$C_{21}H_{20}O_{12}$	464.3763	barks, leaves	[89]
	205	Licoflavones B	$C_{25}H_{26}O_4$	391.1931	barks	[90]
	206	3,5,4′-trihydroxy-7,3′-dimethoxy flavone	$C_{17}H_{14}O_7$	331.0773	barks	[90]
	207	Liquiritigenin	$C_{15}H_{12}O_4$	257.0800	barks	[90]
	208	formononetine	$C_{16}H_{12}O_4$	269.0808	barks	[90]
	209	4′-*O*-Methyl-glabridin	$C_{21}H_{22}O_4$	339.1608	barks	[90]
	210	Paratocarpin E	$C_{25}H_{28}O_4$	393.2021	barks	[90]
	211	Loureirin C	$C_{16}H_{16}O_4$	273.1079	barks	[90]
Other components	212	salicifoliol	$C_{13}H_{14}O_5$	250.0841	barks	[45]
	213	alternariol	$C_{14}H_{10}O_5$	258.0528	barks	[45]
	214	(*α*R)-*α*-*O*-*β*-D-glucopyranosyl-4, 2′, 4′-trihydroxydihydrochalcone	$C_{21}H_{24}O_{10}$	436.1369	barks	[58]
	215	(*α*R)-*α*, 4, 2′, 4′-tetrahydroxydihydrochalcone	$C_{15}H_{14}O_5$	274.0841	barks	[58]
	216					
	217	diisobutyl phthalate	$C_{16}H_{22}O_4$	278.1518	leaves	[39]
	218	phatynecine	$C_8H_{15}NO_3$	173.1052	seeds	[62]
	219	syringic acid glucosides	$C_{15}H_{20}O_{12}$	392.0955	barks	[91]
	220	vanillic acid glucosides	$C_{14}H_{18}O_9$	330.0951	barks	[91]
	221	(3*S*, 5*R*, 6*R*, 9*S*)-tetrahydroxy-7-ene-megastigmane	$C_{13}H_{24}O_4$	244.1675	leaves	[39]
	222	4-hydroxyphenylethanol-8-*O*-*β*-D-apiofuranosyl(1→6)-*β*-D-glucopyranoside	$C_{19}H_{28}O_{11}$	432.1632	leaves	[39]
	223	pervoside A	$C_{16}H_{20}O_8$	340.1158	barks	[91]
	224	(3*S*, 5*R*, 6*R*, 7*E*)-3, 5, 6-trihydroxy-7-megastigmen-9-one	$C_{13}H_{22}O_4$	242.1518	leaves	[92]
	225	(3*S*, 5*R*, 6*S*, 7*E*)-3, 5, 6-trihydroxy-7-megastigmen-9-one	$C_{13}H_{22}O_4$	242.1518	leaves	[92]
	226	(3*S*, 5*R*, 6*S*, 7*E*, 9*S*)-megastigmen-7-ene-3, 5, 6, 9-tetrol	$C_{13}H_{22}O_4$	242.1518	leaves	[92]
	227	(3*S*, 5*R*, 6*S*, 7*E*, 9*R*)-megastigmen-7-ene-3, 5, 6, 9-tetrol	$C_{13}H_{22}O_4$	242.1518	leaves	[92]
	228	saussureol B	$C_{13}H_{20}O_3$	224.1412	leaves	[92]
	229	(6*R*, 9*S*)-9, 10-dihydroxy-4-megastigmen-3-one	$C_{13}H_{22}O_3$	226.1569	leaves	[92]
	230	cucumegastigmane I	$C_{13}H_{20}O_4$	240.1362	leaves	[92]
	231	3, 9-dihydroxy-megastigmen-5-ene	$C_{13}H_{24}O_2$	212.1776	leaves	[92]
	232	(3*R*)-3-hydroxy-8-ionone	$C_{13}H_{20}O_2$	208.1463	leaves	[92]
	233	(2*E*, 4*E*, 1′*S*, 2′*R*, 6*R*)-phaseic acid	$C_{15}H_{20}O_5$	280.1311	leaves	[92]
	234	(2*Z*, 4*E*, 1′*S*, 2′*R*, 6*R*)-phaseic acid	$C_{15}H_{20}O_5$	280.1311	leaves	[92]
	235	Ｒei-5-(3*S*, 8*S*-dihydroxy-1*R*, 5*S*-dimethyl-7-oxa-6-oxa-6-oxobicyclo [3, 2, 1] -oct-8-yl)-3-methyl-2*Z*, 4*E*-pentadienoic acid	$C_{15}H_{20}O_7$	312.1209	leaves	[92]
	236	grasshopper ketone	$C_{13}H_{20}O_3$	224.1412	leaves	[92]
	237	ethyl-glucopyranoside	$C_8H_{16}O_6$	208.0943	leaves	[87]
	238	(+)-D-sucrose	$C_{12}H_{22}O_{11}$	342.1162	leaves	[54]
	239	*α*-D-glucopyranosyl (1→1′)-3′-amino-3′-deoxy-*β*-D-glucopyranoside	$C_{12}H_{23}NO_{10}$	341.1322	leaves	[39]
	240	5-hydroxy-2-furfural	$C_5H_4O_3$	112.0160	leaves	[54]
	241	*n*-butyl-*O*-*β*-D-fructopyranoside	$C_{10}H_{20}O_6$	236.1260	leaves	[39]
	242	*β*-D-fructose	$C_6H_{12}O_6$	180.0634	leaves	[39]
	243	5-hydroxy-9-isopropyl-guaiacylglycerol	$C_{13}H_{20}O_6$	272.1260	leaves	[39]
	244	*β*-D-furanofructosyl-*α*-D-galactopyranoside	$C_{12}H_{22}O_{11}$	342.1162	leaves	[39]
	245	*n*-oetaeosanoic acid	$C_{28}H_{56}O_2$	424.4280	barks	[74]
	246	tetradecanoic acid glyceride	$C_{26}H_{54}O_3$	414.4073	barks	[74]

harvesting times, but it also clearly records for the first time that EU is used as medicine by its bark. The Song Dynasty's "Ben Cao Tu Jing" has a more profound and comprehensive record of medicine, adding a lot of new content to the description of the medicinal botany of EU, such as the origin, form, and new names of EU in the Song Dynasty, and also adding the use of EU leaves, flowers, fruits, and materials: "the young leaves that have just grown of EUL can be collected and eaten, called Mian Ya, mainly treating wind poison, athlete's foot, indigestion, and hemorrhoids. The flowers and fruits of EU have a bitter taste and can also be used in medicine. EU wood can be used to make clogs, and it is also the main useful rubber" [33].

Li Shizhen has systematically summarized the knowledge of EU accumulated for more than a thousand years in the Compendium of Materia Medica and put forward profound opinions on the medicinal properties of EU with his rich clinical experience. He explained the reasons why EU was well used with wine in ancient prescription and further expounded on the pharmacology of EU. EU is purplish red in color, moist in texture, sweet and slightly spicy in taste, and mild in medicinal properties. EU's warm medicine nourishes the body, so it can enter the liver meridian to tonify the kidneys and prevent miscarriage [34].

The ancients discovered that EUL could be used as a substitute for EU several years ago, and developed a variety of health products by using its medicinal and edible characteristics. It can be seen that the classic ancient books contain rich theories and experiences in disease prevention and treatment and are important carriers for the transmission of TCM culture inheritance. In the future, we need to strengthen the modernization and analysis of ancient documents and promote modern research in TCM.

China has a vast territory, and different geographical environments and customs have influenced medical theories and treatment methods, thus resulting in distinctive ethnobotany and promoting the development of ethnomedicine. TCM is developed on the basis of the traditional medical theories and disease prevention experiences of representative ethnic minorities such as Han, Tibetan, Mongolian, Wei, Dai, Yi, Miao, and other representative minority groups in China. Jia et al. [35] systematically summarized the Latin names, Chinese names, ethnic names, different medicinal parts, main diseases treated, and literature sources of EU (Table 1). The table shows that several ethnic groups use *Eucommia* in medicine, and the application of using *Eucommia* to treat hypertension, nourish the liver and kidneys, and strengthen the muscles and bones is consistent with the record in the Chinese Pharmacopoeia.

5. Phytochemistry

Chemical composition is the bridge between the theory of TCM and the research of modern chemical drugs. Modern research shows that different parts of EU (bark, leaves, flowers, seeds) contain various chemical components, including lignans, iridoids, phenylpropanoids, flavonoids, terpenoids, steroids, polysaccharides, etc. So far, 246 compounds have been isolated from EU. Table 2 provides a comprehensive list of the chemical components present in EU, and Fig. 4 depicts the particular chemical structures of these constituents.

5.1. Lignans

Lignans are a kind of natural product formed by oxidative polymerization of two molecules of phenylpropanoid derivatives (C_6–C_3 monomers) [93]. Most lignans exist in Eucommiae cortex in the form of β-D- glucopyranoside compounds [94]. Studies have shown that lignans and their derivatives are the most studied compounds in EU, with the clearest structure and the most definite components. According to their basic carbon skeleton and condensation conditions, they can be divided into monoepoxy lignans, diepoxy lignans, cyclolignans, neolignans, and sesquilignans [3]. Up to now, 61 lignans (E) have been isolated from all parts of EU, most of which are glycosides [95]. Among them, pinoresin diglucoside has the function of two-way blood pressure regulation and is considered a high-quality natural antihypertensive drug. Syringin diglucoside has the functions of being anti-fatigue, anti-cancer, enhancing memory, and strongly inhibiting cMAP phosphodiesterase [96].

5.2. Iridoids

Natural iridoid is a kind of monoterpene compound with the basic skeleton of a cyclopentadienyl pyran ring, which mainly exists in the form of a glycoside [97]. Because its glycosides are easily hydrolyzed by enzymes and acids [98], the hydroxyl furan ring is extremely unstable. The content of iridoid compounds in EU fluctuates with the changes in producing area, harvest time, and post-harvest treatment, and it is higher in fresh EU tissues, mainly in EU bark and leaves [69]. At present, there are 49 kinds of iridoid compounds (F) reported in EU, mainly including geniposide, geniposide, aucubin, and ajugaside. Among these compounds, geniposide, aucubin, and clover glycoside have been proven to have various pharmacological activities in vitro and in vivo. For example, aucubin can be used to protect vascular endothelial cells from damage caused by lipopolysaccharide [99]. Geniposide and geniposide have been studied a lot and they can be used as important components of anti-aging and osteoporosis, lowering blood pressure, and improving the body's anti-tumor ability [95].

5.3. Phenolic acids

Phenolic acid compounds are a kind of aromatic secondary metabolites containing phenolic hydroxyl and carboxyl groups [100], which are widely distributed in nature and exist widely in EU bark and leaves. At present, 47 phenolic compounds (G) have been isolated and identified from EU, including chlorogenic acid, caffeic acid, guaiacol, coniferyl, and syringin, and the research on phenylpropanoids in EU mainly focuses on chlorogenic acid. EU contains chlorogenic acid, with the highest content of chlorogenic acid in EUL [101]. It has a wide range of pharmacological effects, such as being antibacterial, antiviral, antioxidant, antihypertensive, exciting central nervous system, significantly increasing gastrointestinal peristalsis, and promoting gastric juice secretion [102]. It is an important raw material for health care products, foods, medicines, and cosmetics [71].

5.4. Terpenoids and steroids

Terpenoids are compounds derived from pentanedioic acid, and their derivatives take isoprene (C_5) as the basic structural unit. These oxygen-containing derivatives can be alcohols, aldehydes, ketones, carboxylic acids, esters, etc [69]. Steroids have the basic skeleton structure of cyclopentane and phenanthrene and are converted from pentene dicarboxylic acid [103]. At present, there are 21 terpenoids and steroids (H) isolated and identified in EU.

5.5. Flavonoids

Flavonoids are usually composed of two benzene rings (the A ring and the B ring) connected by three intermediate carbon atoms (the C ring), which have a C_6–C_3–C_6 structure. These compounds are generally used as secondary metabolites in Chinese herbal medicine, and most of them combine with sugars to form glycosides, which exist stably in Chinese herbal medicine [104]. Flavonoids usually contain some common chemical groups, such as phenolic hydroxyl, methoxy or glycosyl. It is reported that the substituted hydroxyl groups of flavonoids play an important role that is closely related to their pharmacological activities. The hydroxyl groups of the B ring are important sites for antioxidant activity [105]. Flavonoids are abundant in the leaves and male flowers of EU, but less so in bark and fruits [106]. Up to now, 33 compounds (I) have been isolated, including kaempferol, astragaloside IV, hyperoside, and so on. Flavonoids are also one of the important active components of EU. Its content is an important index to judge the quality of EU, and its

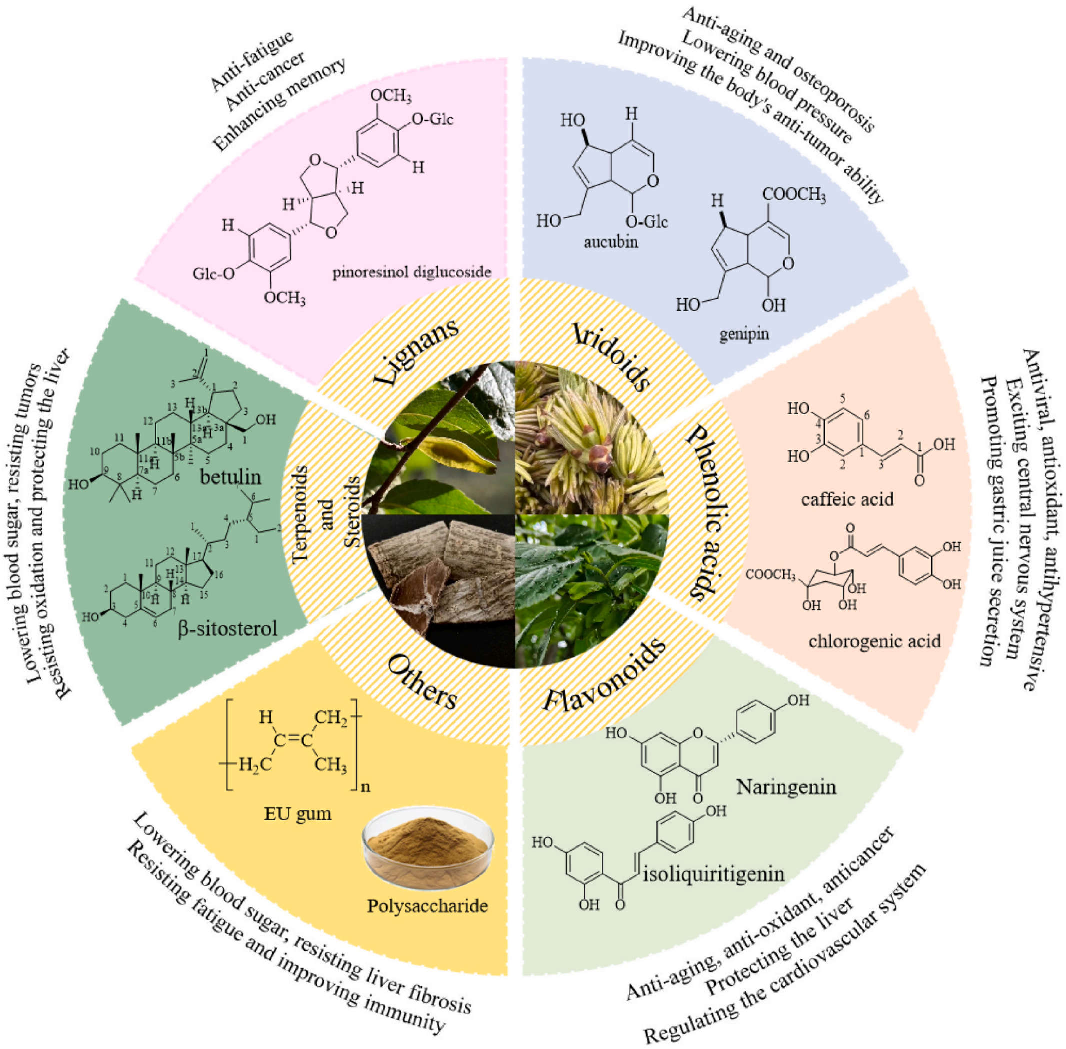

Fig. 2. A brief introduction of the chemical constituents of *E. ulmoides*.

products have many functions, such as protecting the liver, being antibacterial, anti-aging, anti-oxidant, anticancer, and regulating the cardiovascular system [95]. It is a kind of material with great development value.

5.6. Polysaccharide

Eucommia ulmoides polysaccharide (EUPS) is a water-soluble sugar component extracted from EU bark, and it is another active component of EU discovered in recent years. EUPS mainly consists of glucose, fructose, mannose, fucose, galactose and arabinose [107]. Existing studies have proved that polysaccharides extracted from EU have biological activities such as lowering blood sugar, resisting liver fibrosis, resisting fatigue, resisting toxic and side effects, and improving immunity [108], but their mechanism of action and safety in use are still unclear, and they are all in the stage of animal experiments, which limits their wide application in medical and food health care fields.

5.7. Amino acids, vitamins and trace elements

Essential amino acids are abundant in all parts of EU. It is found that there are few free amino acids in EU, which mainly exist in the form of protein. EU contains 17 kinds of free amino acids and 15 kinds of trace elements, including zinc, copper, magnesium, iron, calcium, phosphorus, and potassium [109]. EU pollen is rich in nutrition and has a high utilization value. Du et al. [110] analyzed the nutritional components of EU male flower tea. The results showed that the content of crude protein in EU male flower tea was 32.9 %, and the content of amino acids was 21.41 %. It contained all eight essential amino acids needed by the human body, was rich in mineral elements, had typical characteristics of high potassium and low sodium, and had high nutritional value and medical and health care functions. EUL is rich in protein, dietary fiber, vitamin C, and vitamin B_2, and has a high proportion of unsaturated fatty acids. Among them, α -linolenic acid is rich in content, accounting for 55.5 % of fat and complete amino acids, and its proportion reaches the standard of high-quality protein. EUL is also rich in potassium, calcium, magnesium, iron, and a variety of trace elements beneficial to the human body, which have broad application prospects as new food resources.

5.8. Gutta percha

EU rubber, also known as gutta percha, is a component with a high content in EU that exists in the leaves, barks, and roots of EU. Its main chemical composition is *trans*-polyisoprene, which has the characteristics of strong insulation, moisture resistance, acid and alkali resistance, good thermoplasticity, and shape memory. It is an important chemical raw material and can also be used as a new medical functional material [72].

The chemical composition of EU is complicated and diverse. In this review, the chemical components of EU are classified according to the structure and functional groups of the mother nucleus, which reflect the skeleton characteristics of compounds and the connection mode of substituents, laying the foundation for the further study of EU. However, at present, the research on EU mainly focuses on the pharmacological activities of several chemical components or a single component, which is similar to the research methods of chemical drugs, while ignoring the integrity of TCM. Fig. 2 illustrates that the focus on EU chemical composition is mostly on non-specific chemicals such as chlorogenic acid, pinoresinol diglucoside, and kaempferol glycosides, with less emphasis on unique distinguishing components. Therefore, how to make effective use of the medicinal parts of EU and how to rationally develop its functions in different fields are the future research directions.

6. Processing

Processing is a core technology of TCM that uses water, fire, or water-fire processing methods to achieve the purpose of increasing effectiveness, and reducing toxicity, and correcting taste and odor. It is a treasure in China's culture. EU the efficacy of warming the liver and kidneys, anti-osteoporosis, the fetus, and lowering blood pressure. However, because the dissolution of active ingredients is affected by EUR contained in EU raw products, the pharmacological activity is enhanced by processing EUR to destroy it in the clinic.

6.1. Modern processing methods

6.1.1. Net selection, processing, and cutting of slices

EU is harvested from April to June, usually from EU trees that have been planted for more than 10 years, and the older ones with thick bark are the best. EU is now classified as a protected medicinal herb, so it is often obtained by the partial peeling or ring peeling method. The inner bark of the collected tree is placed on a flat surface with overlapping layers, pressed with heavy objects, and surrounded by straw to make it sweat, and after 5–7 days, when the inner surface of the bark is purple-black, it is taken out and dried in the sun, which is the medicinal material of EU [111].

The crude bark of EU is mainly composed of decadent dead cells, which not only has a lower content of active ingredients but also contains a higher heavy metal content in EU with crude bark than that with the crude bark removed [112]. Therefore, in addition to removing impurities and lichen spots attached to the surface of the herb by washing and brushing with water before cutting, the residual coarse bark is also scraped off. After purification, EU was cut into wide shreds, dried naturally, sieved to remove debris, and stored in a ventilated place [111].

6.1.2. Processing operation

The quality of EU is closely related to the concoction method, which has been emphasized for generations. Since the Song Dynasty, at least 60 kinds of medical documents have recorded the concoction information of EU. Stir-frying, charcoal-frying, and stir-frying with auxiliary ingredients are some of the modern common processing methods for EU. Table 3 details the specific operation steps and processing concepts.

The term frying refers to the process of frying raw EU without any auxiliary materials until the filaments are broken and removed. In addition, the smoke generated during the frying process is not good for health, so this method is rarely used now. In recent years, with the improvement of frying equipment, intelligent processing has gradually moved from the traditional manual concoction. In recent years, the microwave heating method has been derived from the principle of using the unique penetrating characteristics of microwaves to penetrate into the interior of the herbs. The method has the advantages of strong penetration, short heating time, intact appearance, and no coking paste [113]. Although the appearance and properties of the concoction products made by the microwave concoction method are more in line with the standard, the effect of the microwave concoction method on the chemical composition and efficacy of EU needs to be further studied, and whether the clinical efficacy is the same as that of traditional concoction products is also an area that needs to be focused on in future studies.

The method of frying charcoal is to take EU block and fry it in a pot until it is black and broken, then spray it with salt water and take it out to dry. Alternatively, take EU tablets, mix them with salt water, suck them dry, then put them in a pot and fry them until they are black, spray water to extinguish the sparks, and take them out to dry. EU charcoal can enhance the effects of nourishing the liver and kidneys, lowering blood pressure, and stopping bleeding.

Table 3
The processing method of *E. ulmoides*.

Processing method			Specific operation	Processing effect
Traditional processing method	Stir-fry method		Take raw EU and put it in a wok. Stir-fry with a strong fire, then stir-fry with a slow fire until the edge begins to smoke, the appearance is dark brown, and the inside is yellowish brown. Then take it out after the filaments break.	After the processing of EU, the EU rubber is destroyed, and the active ingredients are easily dissolved.
	Charcoal Frying method		Stir-fry raw products in a pot over high heat until they are black and broken, spray with salt water, and take them out to dry. Or mixing EU blocks with salt water first, then frying them in a pot with a strong fire until they are black, spraying sparks with water, and taking them out to dry.	Enhance the effects of EU on nourishing the liver and kidneys, lowering blood pressure, and stopping bleeding.
	Adding auxiliary materials frying method	Wine frying	Take EU blocks, mix them with yellow wine, smother them thoroughly, heat them in a pot over a slow fire, fry them until they break, and take them out and let them cool. Add 20 kg of yellow wine to every 100 kg of medicinal materials.	The product has the effects of eliminating cold and dampness in the body, accelerating blood circulation, and warming the spleen and stomach.
		Honey frying	50g of refined honey is diluted with an appropriate amount of boiling water, then 200g of EU blocks are added to mix well, smothered thoroughly, put in a pot and heated on a slow fire, stir-fried until the filaments are broken, and then taken out and cooled.	Enhancing the curative effect of nourishing the liver and kidneys.
		Ginger frying	Mash the washed ginger into ginger juice, mix well with EU blocks, smother thoroughly, put it in a pot and heat it on a slow fire, fry until it is broken, take it out, and let it cool.	Treating waist and knee pain.
		Salt roasting method	Take EU blocks, mix them with salt water, smother them thoroughly, put them in a pot and heat them on a slow fire, fry them until they break, and take them out and let them cool. 2 kg of salt are added to every 100 kg of medicinal materials. Or wetting EU blocks with salt water, standing overnight, steaming for 1 h, taking them out, and drying. Salt content is 0.9 kg per 100 kg.	Salt-baked EU can enter the kidney meridian and has the effects of nourishing the liver and kidneys, strengthening tendons and bones, and preventing miscarriage. It is mainly used for treating backaches caused by kidney deficiency.
Modern processing methods	Microwave Heating method		Heat in the microwave oven over medium heat for 6 min.	The strong penetration and short heating time can make the appearance of the mixture complete-not carbonized, not paste.
	Baking method		Bake EU dipped in salt water in the oven.	The operation is simple, and the salt can fully penetrate into the medicinal materials so as to ensure efficacy.
	Sand ironing method		Heat clean fine sand in a pot, stir-fry until it is smooth, pour EU blocks soaked in salt water into the pot, stir-fry quickly until the surface is dark brown, take out the fine sand, and spread it out to dry for later use.	Using the uniform heat transfer characteristics of sand, the local focus of medicinal materials can be avoided.

The purpose of the auxiliary material frying method is to break the filaments of EU fried with auxiliary materials so as to facilitate the presentation of effective components in the crushing and decocting process of medicinal materials and at the same time to give better play to the efficacy with the help of auxiliary materials. The first record of frying EU with excipients and the types, proportions, and dosages of excipients are stipulated in the "Lei Gong Gun and Sizzling Theory" [113]. The modern auxiliary material frying method is based on wine frying, honey frying, ginger frying, salt frying, and their derivatives. The baking method and sand scalding method are further improvements on the traditional salt roasting method.

6.2. Modern processing effect study

6.2.1. Changes in chemical composition after processing

The chemical composition of herbs is the material basis for their medicinal effects, so the analysis of the changes in chemical composition before and after the processing of herbs is the key to revealing the mechanism of processing in depth.

The choice of excipients had a significant effect on the chemical composition and content of EU processing products. Zhang et al. [114] compared the content differences between salt-baked EU, purified EU, and raw products using pinoresinol diglucoside as an index component and concluded that salt-baked EU contained more pinoresinol diglucoside. The content of amino acids and polysaccharides increased significantly after EU processing, total flavonoids decreased [115], chlorogenic acid increased significantly [116], and the content of chlorogenic acid was generally higher in salted EU than in fried and raw products, among which the salt steaming method was the most desirable [117]. Liu et al. [118] also compared the indicator components of chlorogenic acid, geniposide, aucubin, terpineol diglucoside, and geniposidic acid in EU concoction products and found that aucubin and geniposidic acid were the highest in raw herbs, geniposide and pinoresinol diglucoside were the highest in salt-baked EU, and chlorogenic acid was the highest in the sand blanching method.

Different processing methods and excipients can also affect the heavy metal content in EU. By using chemical pattern recognition methods such as HCA, PCA, and OPLS-DA, Wu et al. [119] can clearly classify EU raw products and salt-baked products into two categories, OPLS-DA, and screen out seven components, including geniposide, Catechol, geniposide, and hyperoside, which may be the different characteristic components of the EU before and after salt-baking. Zhang [120] used atomic absorption spectrophotometry to investigate the effect of processing on the content of heavy metals and harmful non-metallic elements such as arsenic in raw, salt-baked, fried, and roasted EU and their fugitive forms. The comparison of the heavy metal contents of EU concocted products with those of raw products revealed that the heavy metal contents of salt-baked EU products increased and those of fried and roasted products decreased; the analysis of the heavy metal fugitive forms showed that there was no significant difference between the raw and concocted products. In addition to the excipients chosen, temperature and time have a great influence on the chemical composition, but the temperature of the processing has been a highly controversial issue. If the temperature of the processing is low, the processing time will be prolonged, while if the temperature is too high, although it can destroy EU rubber, it will carbonize EU quickly. At present, we found that a temperature of 140°C–180°C can achieve "broken filament", and when the temperature exceeds 140°C, the chemical composition of raw and concocted products will be significantly different [121]. Cao et al. [122] extracted and separated the chemical components of the processing, identified the structures, and found that they were all cyclic enol ether terpenes, which were analyzed to be related to their special structure of being prone to oxidation or polymerization when exposed to heat. In addition, they suggested that geniposide, the main active component of EU, which is sensitive to temperature, could be selected as an indicator component for the quality control of the processing. Chen et al. [123] also concluded that the content of pinoresinol diglucoside, the main antihypertensive component in EU, gradually decreased with the increase in temperature and time of the processing. Although the effect of rubber removal could be achieved by increasing the temperature, the longer the processing time, the more serious the loss of active ingredients. Zhang et al. [124] described the effect of processing on the target components from the perspective of in vivo exposure and concluded that it is more reasonable to control the processing time of EU at 2 h. The traditional roasting process in EU has disadvantages such as fire that is not easily controlled, high losses, uneven wire breakage, and uneven heating of the processing products. The baking method can control the temperature by using a thermometer; the sand frying method can make the raw EU not directly contact with the bottom of the pot and control the temperature of the processing very well. Both methods can make the herbs heated evenly, no matter storage, preparation, or decoction of active ingredients. Both methods are better than the traditional method, which can reduce the loss rate of herbs, improve the utilization rate, and ensure the decoction of the active ingredient content of the processing for the rational development and full utilization of Chinese herbal medicine. It is an ideal decoction method to solve the increasing scarcity of EU resources, which is of great significance. Different processing methods have their own advantages and disadvantages, and a single index cannot fully measure the goodness of various processing methods. At present, most of the scores have been combined by weighting coefficients, which solves the problem of inconvenient comparison of multiple indicators at the same time and reflects the quality of each processing in a more comprehensive manner, which helps to compare the processings in a comprehensive manner. However, in the analysis of chemical content changes of processing products, the research on the transformation of ingredients in different processing methods and times is not deep enough, but only in the content changes of several ingredients before and after processing, and the research on the mutual transformation of ingredients is less, and the mechanism of processing is not deep enough.

6.2.2. The effect of processing on the pharmacological effect

After processing, TCM can change its efficacy and improve its curative effect. Different processing methods can change the chemical composition and content of TCM, leading to different clinical curative effects. Understanding the changes in pharmacological properties after processing is helpful in developing the processing technology of TCM.

Osteoporosis (OP) is a systemic disease with progressive bone loss, and Chinese medicine considers kidney deficiency the main cause of OP. Salt roasting can enhance the effect of the drug on the "kidney meridian". Dong et al. [125] evaluated EU's ability to scavenge free radicals. The results showed that the same dose of EU was superior to the raw herb in scavenging free radicals, which indicated that the salt processing improved the anti-oxidative stress ability of Europium in repairing renal tissue injury and also explained the scientific processing theory of "salt entering the kidney". Deng et al. [115] analyzed that the principle of salt preparation of EU nobilis to enhance the efficacy of kidney tonic may be due to changing the structure of most chemical components in EU, increasing their lipophilicity, thus promoting their absorption into the blood and improving their bioavailability in vivo.

EU is considered a natural antihypertensive herb with high quality and no side effects. It contains terpineol diglucoside, dehydroterpineol diglucoside, pine single glucoside, citrulline B, caffeic acid, ferulic acid, chlorogenic acid, kynurenin, quercetin and rutin, all of which have antihypertensive activity [72]. Raw EU, salted EU, EU charcoal, and sand scalded EU can obviously reduce the blood pressure of rabbits and dogs. The strength of EU charcoal and sand-scalded EU is basically the same, both of which are stronger than that of raw EU, and the decoction of alcohol-extracted residue still has the effect of lowering blood pressure. He et al. [126] studied and analyzed the antihypertensive activity and characteristics of EU. It was found that both raw EU and EU processing had significant antihypertensive activity, and the antihypertensive activity of EU processing was slightly better than that of raw EU, but there was no significant difference between them. EU processing also has a significant effect on lowering the heart rate.

EU is traditionally used for habitual abortion caused by fetal movement, bleeding during pregnancy, and liver and kidney deficiency. Raw EU, EU charcoal, and sand scalding products can all slow down the spontaneous activity of isolated rat uteri, and the effect of EU charcoal and sand scalding products on the uterus is stronger than that of raw products [127]. According to the theory of TCM, fetal movement is closely related to kidney function. Wang et al. [128] found that EU enhanced the inhibitory effect on spontaneous contraction of the isolated uterus of mice in the second trimester and antagonized the effect of uterine contractile agents. Some scholars have investigated the effects of EU extracts with different processing degrees and different parts of EU processed with salt on isolated uterine smooth muscle in non-pregnant rats. *In vitro* studies show that EU can significantly inhibit the contraction of rat uterine smooth muscle, and the inhibitory effect is enhanced after salt boiling [129].

Some scholars have compared the polyphenol content, reducing power, and free radical scavenging abilities of raw EU, EU charcoal, and salt-baked EU to evaluate their antioxidant effects. It was found that EU processing showed effective ABTS free radical scavenging activity, and its strong antioxidant effect was positively correlated with polyphenol content, which also proved that more polyphenols were extracted from processed EU. In addition, the anti-cancer characteristics of raw EU and EU processing were examined by evaluating the proliferation of cancer cells, cell cycle analysis, and cancer cell migration. The results showed that raw EU and EU processing have a concentration-dependent effect on the activity of PANC-1 pancreatic cancer cells, while EU processing showed a stronger inhibitory effect on the migration of cancer cells [130].

The above pharmacological experiments have proved that processing is not only a common pretreatment for the preparation of TCM but also a pharmaceutical technology to enhance the efficacy of TCM. Although some achievements have been made in the study of the efficacy and corresponding material basis of EU, the material basis and mechanism of the difference in efficacy after processing are still unclear and need further study.

6.3. Prospects of processing

The processing of TCM has a long history, and it is a treasure of Chinese pharmaceutical technology. Physicians in past dynasties have accumulated rich experience in processing TCM, which is an important basis for studying the processing mechanism. Research on the processing mechanism of TCM is an important part of revealing the mystery of TCM. Only when the principle is clear can we improve the processing technology and establish a unified standard. EU, as a unique medicinal material in China, is rich in active components and pharmacological effects. However, there is a big gap in processing technology, and the quality evaluation standard for processed products has not been unified. The cutting shape, direction, and specifications of EU all affect the frying rate. In addition, the temperature of the processed products and the quality of the finished products are mainly judged by experience, which is extremely difficult to grasp and easy to burn, resulting in unstable quality. In recent years, the processing technology has been improved, and the microwave heating method has been developed, which is more convenient for operation and quality control. However, due to the different brands, models, and powers of microwave ovens on the market, it is difficult to grasp the specific temperature of microwave high fire, which is easy to cause the phenomenon of too much or too little processing. Great changes have taken place in the chemical composition and pharmacological effects of processed cuttlefish bone, but the processing principle and clinical material basis are still unclear. At present, the research mostly adopts the indexes of chemical composition and pharmacology. Although it provides some basis, on the whole, it cannot explain the mechanism of processing too little, which needs a lot of clinical research to verify. In addition, we also pay attention to multidisciplinary cross-cooperation, combine modern science and technology to analyze and integrate the changes in material basis and mechanism of action before and after processing, and comprehensively carry out research on processing theory.

The research on the processing of TCM should be innovated on the basis of inheritance, and the processing ingredients and mechanisms should be further explored by using new modern analytical techniques. The research on the processing of TCM should be raised to a new level by fully drawing lessons from new theories and methods of other disciplines. I believe that after a long period of hard work, the pharmaceutical technology processed by TCM will definitely go global and make new contributions to the protection of human health.

Table 4
The pharmacological effects of *E. ulmoides*.

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Time period of application	Dose range	Result	References
Anti-osteoporosis	Ethanol extracts	senescence-accelerated mice	Mice	12 weeks	1.5/ 3.0 g/ kg	Improved OP based on the results of bone mineral density (BMD), a dual-energy X-ray bone scan, and HE staining of the distal femur.	[141]
	Ethanol extracts	OVX + vehicle	rat	2 months	4 g/kg	There was a good fit between the mathematical model evolved and the data on extract yield. The extract significantly increased the Ca, P, and Cr levels in the OVX + EUOE group compared to those in the OVX control. Moreover, the extract significantly increased macro-mechanical indices of trabecular bone in the OVX + EUOE group relative to those in the OVX control.	[142]
	Ethanol extracts	Rats model of osteoarthritis	rat	8 weeks	50/ 200 mg/kg	The low and high dosage groups of EU ethanol extract significantly improved the cartilage injury in rats and reduced the degree of surface calcification. It may play a protective role in the articular cartilage of osteoarthritis rats by inhibiting the JAK1/STAT3 pathway, promoting SOCS3 protein expression, and alleviating inflammatory reactions.	[143]
	EU flavonoids	Osteoporosis model caused by estrogen deficiency	rat	12 weeks	50/ 100/ 200 mg/kg	Compared with the model group, the amino-terminal peptide concentration, bone density, bone mineral content, and collagen area ratio of type I procollagen in the middle and high doses of TFE total flavonoids were significantly higher. The effect of TFE was positively related to dose.	[133]
Antioxidation	EU flavonoids	Mice model of lead poisoning	Mice	14 days	50/ 200 mg/kg	The content of MDA in immune organs of lead poisoning mice decreased significantly, while the activities of SOD, GSH-Px, and T-AOC increased obviously, which improved the activity of peroxidase in immune organs of lead poisoning mice, enhanced the antioxidant capacity of the body, and partially alleviated the lead-induced oxidative stress.	[144]
	EUL flavonoids	H_2O_2-induced oxidative damage model of IEC-6 cells	IEC-6 cell	24h	25/ 50/	Compared with H_2O_2 treatment, the total flavonoids of EUL can	[145]

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Table 4 (*continued*)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Time period of application	Dose range	Result	References
					100 μg/mL	improve the survival rate of cells, reduce the infiltration of LDH into culture medium and the content of MDA in cells, and increase the activity of SOD in cells. The total flavonoids of EUL have an obvious protective effect on the oxidative damage of IEC-6 cells induced by H_2O_2.	
	EUL extracts		Ira rabbit	28 days	100/ 200/ 300 mg/kg	Adding 100–300 mg/kg of EUL extract to the diet can improve the average daily gain, average daily feed intake, total protein, and albumin content in the serum of meat rabbits.	[146]
Anti-inflammatory	Water extracts of EU charcoal	Xylene-induced inflammatory swelling model of mice ear shell	Mice	3h	20/ 10/2 mg/g	EU charcoal extract has an anti-inflammatory effect, which is related to its concentration. With the increase in concentration of the extract, its anti-inflammatory effect gradually enhanced. Through ultraviolet identification and analysis, it was found that the extract contained chlorogenic acid.	[147]
	Total glucosides of EU seeds	Xylene-induced ear swelling model in mice/ carrageenan foot swelling model in rats	Mice/rat	7 days	55/ 110/ 220 mg/kg	110/220 mg/kg of EU seed total glycoside can obviously reduce the ear swelling volume of mice caused by xylene, and 55/ 110/220 mg/kg of EU seed total glycoside can obviously reduce the swelling rate of carrageenan foot in rats about 4 h after administration.	[148]
Regulate blood glucose and blood lipid metabolism	Ethanol extracts of EU flavonoids	T2DM mice model	Mice	60 days	80/ 160 mg/kg	The fasting blood glucose of mice decreased, the pathological morphology of the pancreas improved, the content of serum C-peptide increased, the contents of ROS, IL-6, TNF-α, Fas, Fasl, and the expression of Bax decreased, and the expression of Bcl-2 increased.	[149]
	Water extracts of EU	Diabetic mice model	Mice	14 days	500/ 250/ 125 mg/kg	EU polysaccharide can reduce blood glucose and blood fat, and its mechanism may be related to improving the antioxidant capacity of diabetic mice, reducing the content of inflammatory factors in serum, and reducing the content of TLR4 and NF-κ B protein in the pancreas.	[150]

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Table 4 (*continued*)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Time period of application	Dose range	Result	References
	Water extracts of EUL	Diabetic rat model	rat	30 days	2.5/ 5.0 g/ kg	The levels of FBG, TG, TC, LDL-C, and MDA in EUL water extract group decreased, while the levels of HDL-C and SOD increased, which had a certain regulatory effect on blood glucose and blood lipids in diabetic rats. It is speculated that lowering the level of oxidative stress is one of its mechanisms.	[151]
The protection of liver and kidney	EU flavonoids	Damage model of CCl_4	Mice	7 days	200/ 50 mg/kg	Total flavonoids of EU can reduce the activities of ALT and AST in serum and MDA in liver tissue of mice with acute liver injury and increase the activities of SOD and GSH in liver tissue, thus enhancing the antioxidant capacity of the body and achieving the role of protecting the liver.	[152]
	EU polysaccharide	70 % liver I/R model	rat	10 days	320/ 160/ 80 mg/kg	EUP can reduce liver damage by decreasing ROS levels and inhibiting TLR-4-NF-κB pathway activation and may be a promising drug in liver surgery to prevent HIRI.	[153]
Hypotensive effect	EU salt solution	Spontaneous hypertension rat model	rat	14 days	6 g/ml	Both raw and concocted products of EU showed significant inhibitory activity on the increase of basal blood pressure and heart rate in SHR-SP rats. In addition, the concocted products from EU showed significant heart rate-lowering activity.	[126]
	Ethanol extract of chlorogenic acid from EUL	Spontaneous hypertension rat model	rat	8 weeks	20/5 mg/kg	The high-dose group of chlorogenic acid extract from EUL has a good and stable antihypertensive effect on spontaneously hypertensive rats.	[154]
Prevent miscarriage	Water extract of EU		Empty pregnant rabbit		10 g/ ml	The water decoction of EU, at a concentration of 10 g/ ml and a dosage of 1 ml, can enhance the tension of isolated uterine smooth muscle in pregnant rabbits to different degrees.	[153]
	EUL granule	Incomplete abortion model of pregnant mice caused by posterior pituitary gland	Mice	7 days	3/6g	EUL granules can obviously resist the strong contraction of uterine smooth muscle caused by the posterior pituitary gland. It can significantly reduce the number of aborted animals caused by the posterior pituitary gland and increase the number of litters.	[155]
Immunoregulation	The polysaccharide water extract of EUL	Immunosuppression mouse model induced by cyclophosphamide	Mice	14 days	300/ 200/	EUPS can improve the clearance ability, phagocytosis speed, and	[156]

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Table 4 (*continued*)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Time period of application	Dose range	Result	References
					100 mg/kg	serum hemolysin content of peritoneal macrophages in mice, improve the coefficients of the thymus and spleen, and improve the immune ability of mice.	
	EUPS	Mice injected with FMDV vaccine	Mice	14 days	0.5 mg	Compared with inoculation with FMDV vaccine alone, EUPS significantly promoted the production of FMDV-specific antibodies in immunized mice, and it can be used as an adjuvant to induce a significantly higher level of T cell proliferation.	[157]
	Water extract of EU	Con A or LPS-treated Mouse spleen cells	Mice	10 days	500/ 200/ 100 mg/kg	The water extract of EU can inhibit the proliferation of primary spleen cells induced by Concanavalin A and lipopolysaccharide (LPS). In addition, genipin treatment of primary spleen cells and mice can reduce the proliferation of spleen cells induced by Con A and LPS. These results show that EU and its component, genipin, have inhibitory effects on cellular and humoral adaptive immunity.	[158]
	EUL extract	Immunosuppression mouse model induced by cyclophosphamide	Mice	28 days	1.6 g/ kg	EUL extract can promote the proliferation and phagocytosis of peritoneal macrophages, increase the immune organ index and phagocytosis index, increase the number of peripheral blood leukocytes and lymphocytes, and enhance the auricle swelling of delayed hypersensitivity (DTH).	[159]
Anti-tumor and anticancer	EUL dichloromethane extract	MDA-MB-231 cells, Hela and T47D cells	MDA-MB-231 cells, Hela and T47D cells	48 h	40 μmol/ L	The growth inhibition rate of Hela, MDA-MB-231, and T47D cells increased with the increase in compound concentration. It can effectively induce apoptosis in HeLa cells. It significantly inhibited the production of lysosomes and induced mitochondrion breakage.	[160]
	Ethanol extract of EU flavonoids	H22 liver cancer transplanted tumor mice model	Mice	12 days	200/ 100/ 50 mg/kg	EU flavonoids can significantly reduce the quality of transplanted tumors, significantly increase the spleen index of tumor-bearing mice, increase the levels of serum IL-2 and TAOC, and decrease the levels of TNF-α and MDA. Its mechanism may be related to its	[161]

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Table 4 (*continued*)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Time period of application	Dose range	Result	References
						regulating the secretion of cytokines such as IL-2 and TNF-α, enhancing the immune function, and improving the antioxidant capacity of tumor-bearing mice.	
Neuroprotection	EU extract	Establishment of PD model in vivo by MPTP injection	Mice			EU significantly reduced the behavioral disorder and dopaminergic neuron degeneration in PD mice, and inhibited the expression of proinflammatory cytokines.	[162]
	Geniposidic acid extract	Transgenic mice model	Mice	90 days		Geniposidic acid significantly improved the spatial learning and memory abilities of APP/ PS1 mice, decreased the deposition of amyloid β in the brain, inhibited the activation of astrocytes and microglia, and down-regulated the expression of proinflammatory cytokines and iNOS.	[163]
	Ethanol extract	Parkinson's disease model induced by 6-hydroxydopamine (6-OHDA)	rat	7 days	1 mL/ kg	It can effectively improve the motor function of Parkinson's rats induced by 6-OHDA, which may be achieved by increasing the relative expression of TH protein and DA level in the substantia nigra of rats, increasing the levels of SOD, GSH-Px, and NOS, and reducing the level of MDA, so as to play an antioxidant role and protect dopaminergic neurons.	[164]
	EU extract	Model of paraquat poisoning in mice	Mice	92 days	50 mg/kg	Paraquat is toxic to dopaminergic neurons in the substantia nigra of mice, and the number of CHAT + cells and the expression of TH, TPH 2, and other proteins in the striatum of mice decreased significantly. After the treatment with EU water extract, the number of dopaminergic neurons increased significantly, and the number of CHAT + cells and the expression levels of TH, TPH 2, and other proteins began to show a clear recovery trend.	[165]

7. Pharmacology

7.1. Anti-osteoporosis

Osteoporosis (OP) is a kind of systemic bone disease characterized by a decrease in bone loss and bone microstructure changes, which lead to increased bone fragility and are prone to fracture. In western medicine, parathyroid hormone analogues (PTHa) are often used to promote bone formation, then anti-bone absorption therapy is carried out by taking osteoclast inhibitors (bisphosphonates, calcitonin, estrogen, and selective estrogen receptor modulator SERMs), and finally supplements (calcium and vitamin D) to improve bone health are used as adjuvant therapy. The pathogenesis of OP is complicated. Single-target drug therapy not only can't fundamentally prevent OP but is also expensive and its safety is unknown. According to its clinical manifestations, Chinese medicine believes that the lesion is in the bone and the root of the disease is the kidney. Some scholars have found that patients with kidney deficiency syndrome may affect calcium and phosphorus metabolism due to the decrease of pituitary function, growth hormone secretion, or estrogen and androgen secretion, thus causing bone mineral density to decrease [131]. EU is the top grade of TCM, which has the effects of strengthening tendons and bones and nourishing the liver and kidneys. It has been proven that EU has therapeutic effects on osteoporosis caused by postmenopausal hypoestrogenism, osteoporosis caused by aging, osteoporosis, and diseases caused by lead affecting bone composition. The anti-OP pathways involved in EU extract mainly include the OPG/RANKL/RANK signaling pathway for regulating osteoclasts, the Wnt/β-catenin signaling pathway for promoting the differentiation of bone marrow mesenchymal stem cells into osteoblasts, and the BMP/Smad signaling pathway for promoting bone formation and inducing osteoblast differentiation [132].

Flavonoids and iridoid glycosides in EU are effective components for preventing and treating osteoporosis. The deficiency of estrogen in postmenopausal women leads to the decrease of bone mass, the change of bone tissue structure, the increase of bone brittleness and the easy fracture. At the same time, various complications caused by fractures have seriously affected their health and quality of life. At present, most clinical treatments are supplemented with exogenous estrogen, which may not only have a curative effect but also stimulate endometrial hyperplasia, increase the incidence of endometrial cancer, and increase the risk of thrombosis, breast cancer, and stroke. Total flavonoids of *Eucommia ulmoides* Oliv. (TFE) can increase the concentrations of procollagen amino-terminal peptide (PINP) and β-type collagen cross-linked carboxyl-terminal peptide (β-CTX) in the serum of ovariectomized SD rats, which not only inhibit bone resorption but also promote bone formation, thus protecting the bone tissue of estrogen-deficient SD rats [133]. The iridoid glycosides in EU also play an important role in bone resorption and bone remodeling. Aucubin and Geniposide are typical anti-op active components. Aucubin can inhibit the maturation of pre-osteoclasts, improve the secretion of PDGF-BB, and promote H-type angiogenesis with the functions of blocking bone resorption and promoting bone formation by inducing MAPK/NF-κB signal, thus increasing the osteogenic ability [134]. Geniposide (GEN) targets miR-214 through the activation of Wnt/β-catenin, thus inducing the proliferation and differentiation of MC3T3-E1 and ATDC5 cells [135]. These results indicate that iridoid glycosides mainly affect the differentiation and survival of osteoclasts and osteoblasts through the PI3K-Akt signaling pathway, MAPK signaling

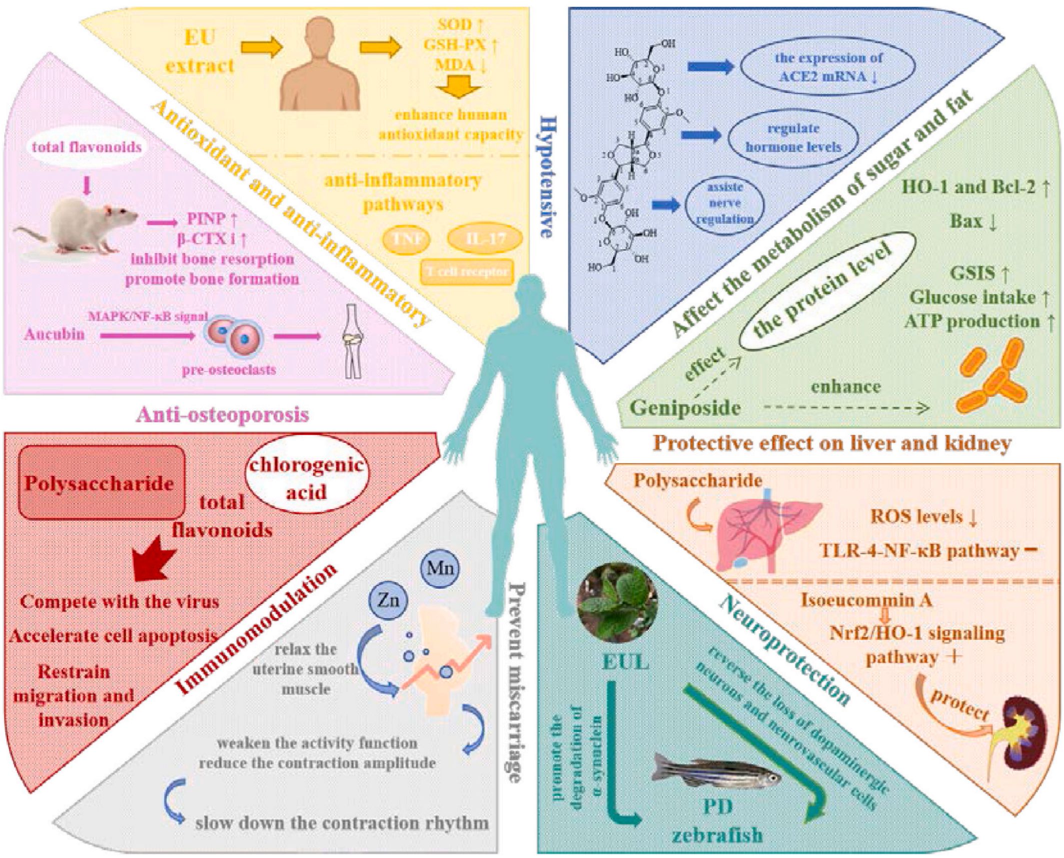
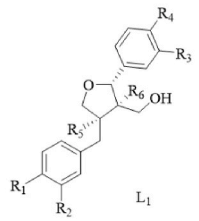
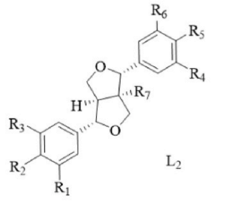


Fig. 3. Pharmacological mechanism diagram of *E. ulmoides*.

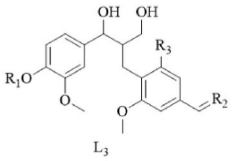
E



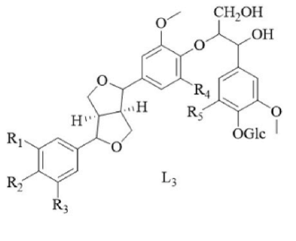
	R1	R2	R3	R4	R5	R6
1	OH	OCH_3	OCH_3	OH	OH	H
2	OH	OCH_3	OCH_3	O-Glc	OH	H
3	O-Glc	OCH_3	OCH_3	OH	OH	H
4	O-Glc	OCH_3	OCH_3	O-Glc	OH	H
5	OH	OCH_3	OCH_3	OH	CH_3	CH_3
6	OH	OCH_3	OCH_3	OH	OCH_3	H



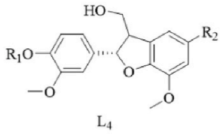
	R1	R2	R3	R4	R5	R6	R7
7	OCH_3	O-Glc	OCH_3	H	O-Glc	OCH_3	H
8	H	OH	OCH_3	OCH_3	O-Glc	OCH_3	H
9	H	OH	OCH_3	OCH_3	OH	OCH_3	H
10	OCH_3	O-Glc	H	H	O-Glc	OCH_3	H
11	OCH_3	O-Glc	H	H	OH	OCH_3	H
12	H	OH	OCH_3	OCH_3	OH	H	H
13	H	OH	OCH_3	OCH_3	O-Glc-6Glc	H	H
14	OCH_3	OH	OCH_3	OCH_3	O-Glc	OCH_3	H
15	OCH_3	O-Glc	OCH_3	OCH_3	O-Glc	OCH_3	H
16	OCH_3	OH	OCH_3	OCH_3	OH	OCH_3	H
17	H	O-Glc	OCH_3	OCH_3	O-Glc	H	OH
18	H	OH	OCH_3	OCH_3	O-Glc	H	OH
19	H	O-Glc	OCH_3	OCH_3	OH	H	OH
20	H	OH	OCH_3	OCH_3	OH	H	OH
21	H	OH	OCH_3	OCH_3	OH	H	H



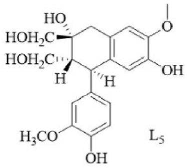
	R1	R2	R3
22	H	CHO	H
23	H	CHO	H
24	Glc	CH_2OH	OCH_3



	R1	R2	R3	R4	R5
25	H	O-Glc	OCH_3	OCH_3	H
26	OCH_3	O-Glc	OCH_3	OCH_3	OCH_3
27	OCH_3	O-Glc	OCH_3	OCH_3	H



	R1	R2
28	H	$CH_2CH_2CH_2OH$
29	H	CH(OH)CH(OH)CH_2OH
30	H	CH(OH)CH(OH)CH_2OH
31	Glc	$CHCHCH_2O$-Glc
32	H	$CH=CHCH_2O$-Glc



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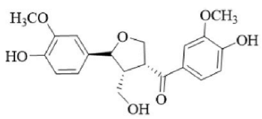

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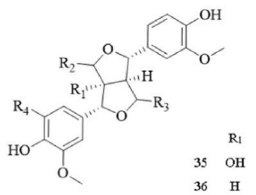
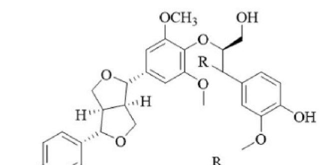
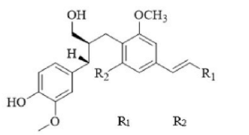


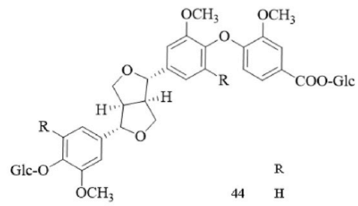
	R1	R2	R3	R4
35	OH	H	H	H
36	H	α-OH	H	H
37	H	H	OCH_3	OCH_3
38	H	H	OH	OCH_3



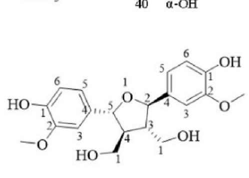
	R
39	β-OH
40	α-OH



	R1	R2
41	CHO	OCH_3
42	CH_2OH	CH_3
43	CHO	O



	R
44	H
45	OCH_3



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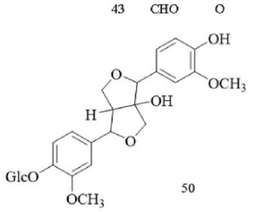

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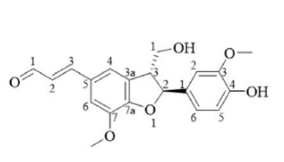

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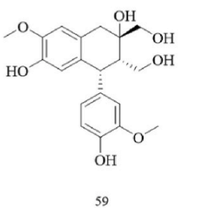

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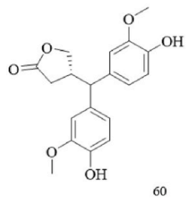

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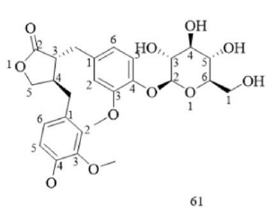

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Fig. 4. Lignans (E), Iridoids (F), Phenolic acids (G), Terpenoids and Steroids (H), Flavonoids (I) in *E. ulmoides*.

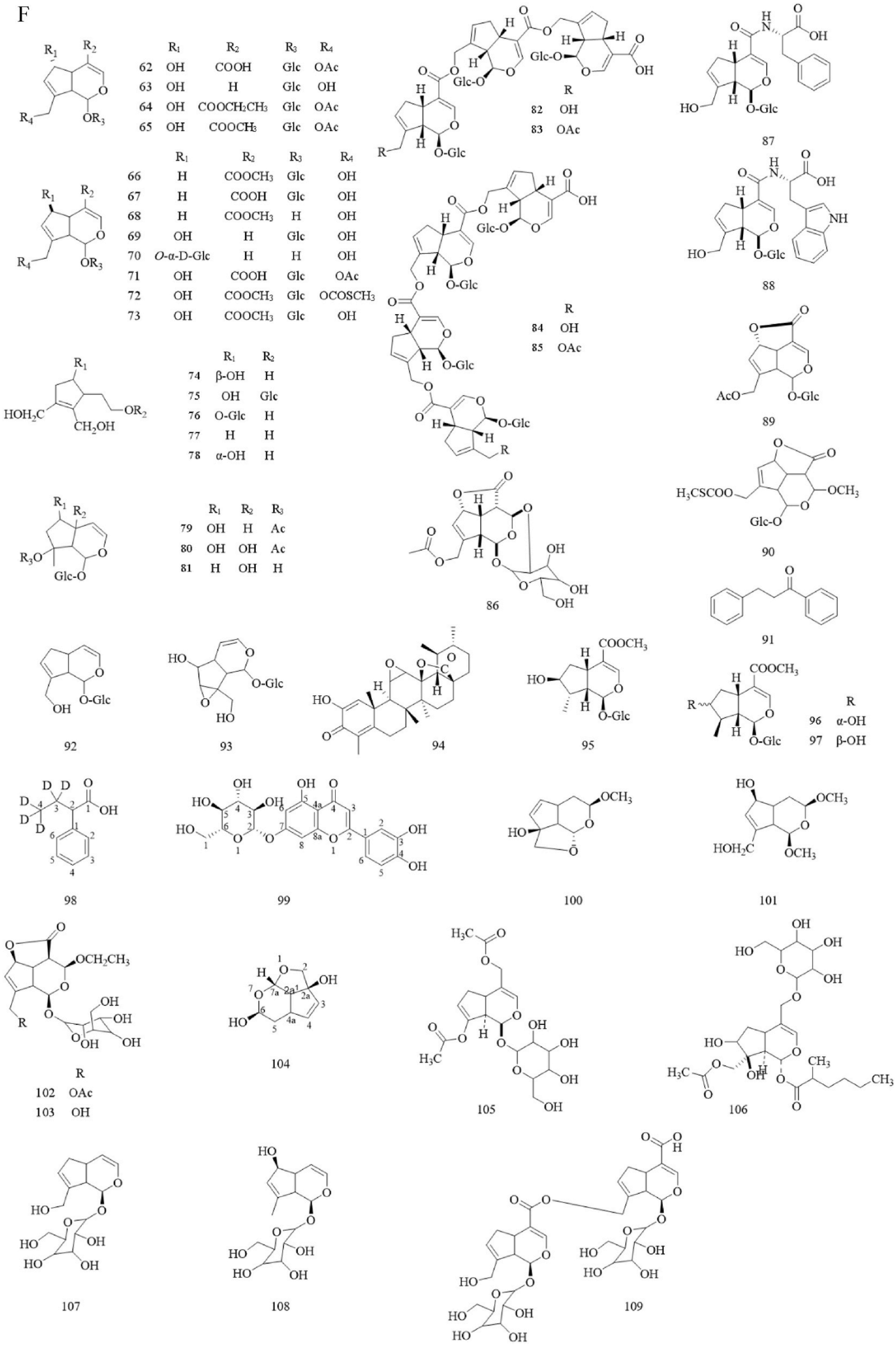

Fig. 4. (*continued*).

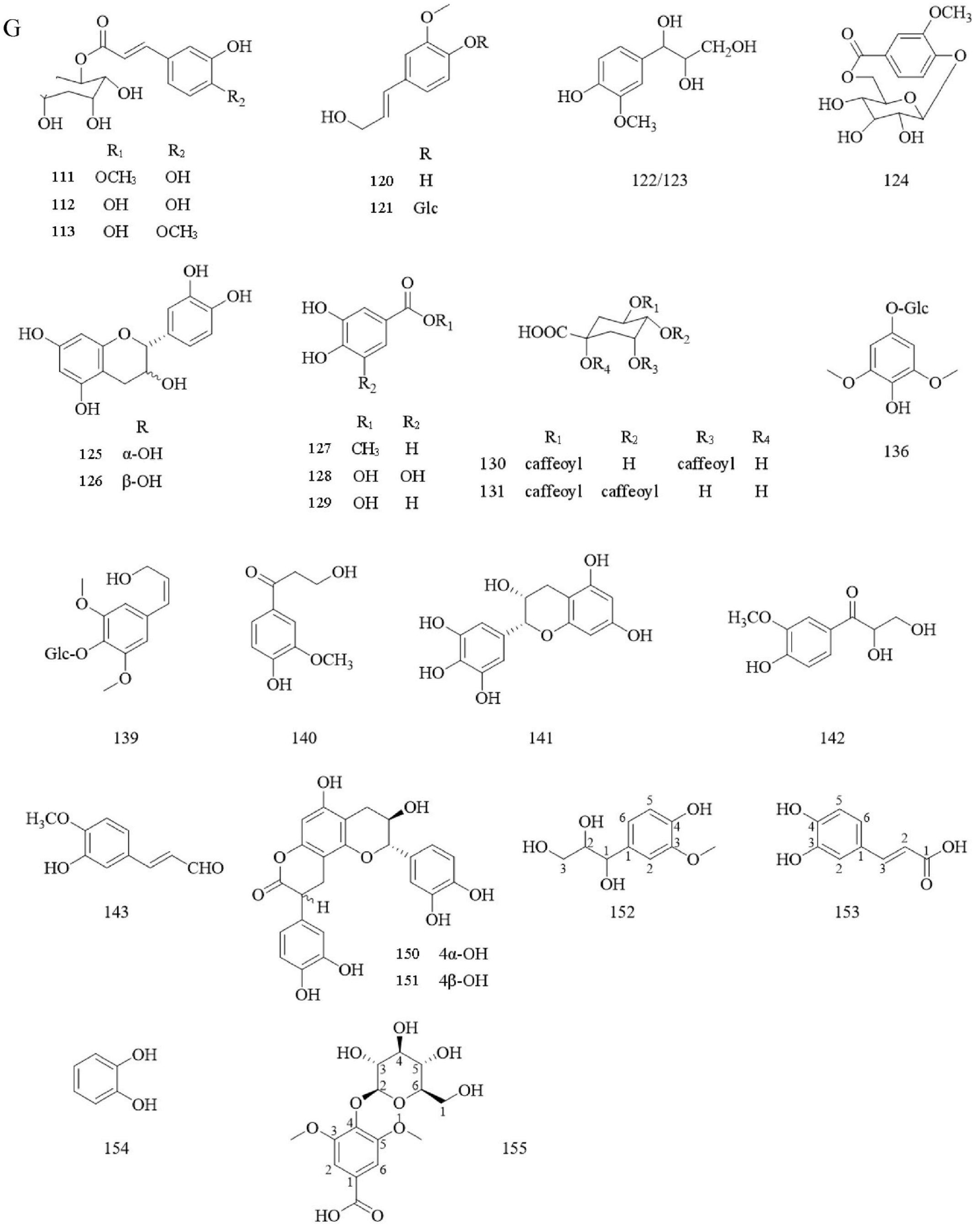

Fig. 4. (*continued*).

pathway, and estrogen signaling pathway, regulate the balance between bone absorption and osteogenesis, and achieve the purpose of treating OP [136]. It is worth noting that all components of EU participate in the activities of osteoblasts or osteoclasts, which may be more effective than single components in curative effects [137].

Commonly used drugs to treat OP not only affect the absorption and formation of bone matrix by directly acting on osteoclasts and osteoblasts, but also stimulate the osteogenic differentiation of bone marrow mesenchymal stem cells. The changes in intestinal flora are also related to the changes in bone mass and microstructure, which may become a new therapeutic target for treating osteoporosis and preventing fractures. TCM improves bone metabolism by improving the composition of intestinal flora and protecting intestinal barriers [138]. EuOCP3 is an acidic polysaccharide isolated from EU that can alleviate the symptoms of OP mice induced by dexamethasone (Dex), restore the thickness of cortical bone, increase the area of mineralized bone, and increase the number of osteoblasts, showing a significant anti-OP effect. Song et al. [139] explored its mechanism in vivo, it was found that EuOCP3 not only activates the

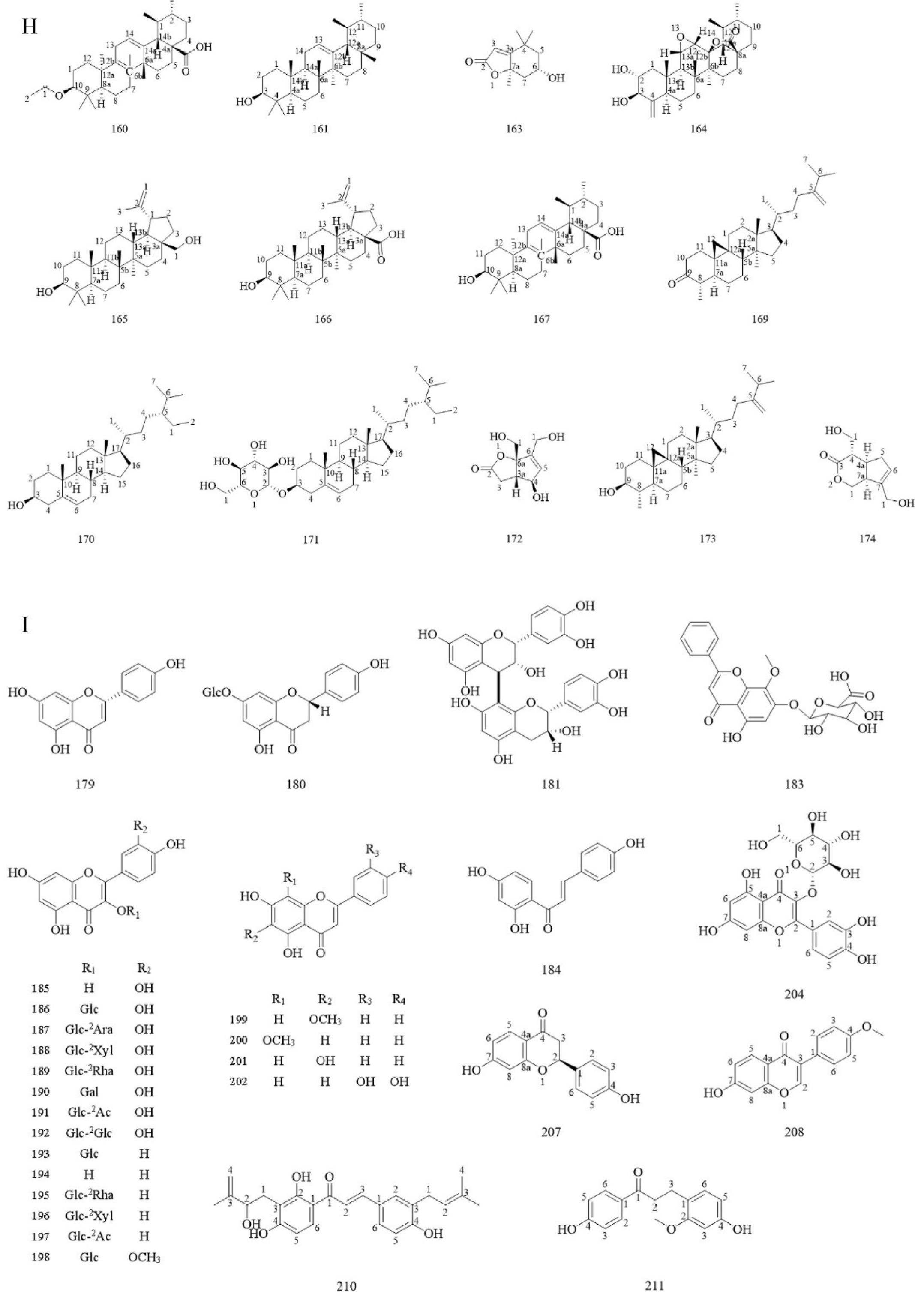

Fig. 4. (*continued*).

expression of the Nrf2 pathway and downstream factor, enhances the osteogenic function, and restores bone metabolism, but also regulates the types of intestinal flora, promotes the growth of probiotics, inhibits the proliferation of harmful organisms, and reduces the level of oxidative stress, thus improving the health of the host and providing a new direction for anti-OP therapy. The chemical composition of EUL is similar to that of EU, which is easy to obtain in large quantities, but it is not effectively used, resulting in a waste of resources. Some scholars evaluated the effects of EUL water extract on intestinal microflora (GM), short-chain fatty acids (SCFAs), and osteoporosis (OP) and found that it increased the bacterial diversity in the intestine, increased the concentration of SCFAs in feces and serum, and significantly decreased the activity of tartrate-resistant acid phosphatase (trap) in a dose-dependent manner. Inhibiting the formation of osteoclasts in vitro, significantly reducing the sunken area of bone lacunae, and improving OP, which provides ideas for fully developing resources [140].

Table 4 details the pharmacological activity, modeling methodologies, and active parts of EU, whereas Fig. 3 depicts the corresponding mechanism. Based on the current research results, it is shown that the active components, key targets, and signal pathways of the EU for the treatment of OP are mostly screened by combining network pharmacology with molecular docking. EU and its extracts can regulate the osteogenic differentiation of human bone marrow mesenchymal stem cells, promote the proliferation of osteoblast formation, effectively reduce bone resorption, improve bone metabolism, and promote bone reconstruction, which are effective in the treatment of osteoporosis, and lay the foundation for the development of drugs against osteoporosis. Although great progress has been made in the preliminary simulation of its possible molecular mechanism, due to the limitations of the technology, its prediction results need to be further verified in large-scale clinical trials. In addition, the active components or compounds of anti-osteoporosis drugs in EU have not been clarified, and their pharmacokinetics and pharmacokinetics in animals are also lacking. Therefore, how to combine the overall concept of TCM in treating osteoporosis with the operability of mechanism research and large-scale clinical control research is the future development direction.

7.2. Antioxidant effect

Free radicals produced by normal human metabolism are indispensable reactive substances in the body and can participate in the immune and signaling processes of the body. However, with the aging or degradation of the body, the oxidation and antioxidant effects in the body are unbalanced, and the excess free radicals cannot be removed in time, thus accumulating and attacking cells in large quantities, interfering with the normal physiology and biochemistry of the body, leading to inflammatory infiltration of neutrophils, increased secretion of protease, and a large number of oxidation intermediates, which is considered to be an important factor leading to aging and disease. It has been reported that EU has antioxidant effects, and EU extract can enhance human antioxidant capacity by increasing SOD activity, GSH-PX activity and decreasing MDA content. EU has also increased the levels of other antioxidant enzymes in the blood to neutralize free radicals. Zhang et al. [145] found that total flavonoids of EU can improve the survival rate of cells, reduce the infiltration of LDH into culture medium and the content of MDA in cells, and increase the activity of SOD in cells, which has an obvious protective effect on the oxidative damage of IEC-6 cells induced by H_2O_2.

In recent years, people have done a lot of antioxidant research on leaves, flowers, and fruits of EU, among which leaves and flowers have shown strong antioxidant activity. EUL resources are abundant and easily available, have a low price, and can be harvested for a long time. EUL and EU male flowers are easy to collect and can be the first choice to develop related antioxidant active components. Zhong et al. [166] compared the contents of total flavonoids in different parts of EU and found that the contents of total flavonoids in leaves and male flowers of EU and their antioxidant activity in vitro were higher than those of EU. At present, the related functional substances, antioxidant activity mechanism, and evaluation methods of EUL are very mature. It is found that the total flavonoids and polyphenols in EUL are the main active substances that play an antioxidant role [167]. Xu and Liu [168] extracted total flavonoids from EUL and studied their antioxidant activity in vitro. It was found that the scavenging ability of DPPH and hydroxyl radicals was stronger than that of VC, which showed a good antioxidant effect and could be used as a new natural antioxidant. Dong et al. [169] found that the polarity of phenols in EUL was greater than that of flavonoids, which showed more obvious antioxidant effects in vivo. Lin et al. [170] studied the inhibitory effect of the ethanol extract of EUL on H_2O_2-induced apoptosis of rat osteoblasts MC3T3-E1 and its internal mechanism. It was found that it may inhibit the oxidative damage of cells by inhibiting the activation of caspases 3, 6, and 9, and improve the survival rate of cells in a dose-dependent manner. The results showed that EUL may have a protective effect on many kinds of cells and is an effective antioxidant. At present, EUL extracts have been developed as natural additives and added to animal feed. They have many functions, such as improving immunity, antioxidation, antibacterial and anti-inflammatory properties, meat quality, and so on. Functional components in EUL, such as chlorogenic acid and flavonoids, have specific antioxidant effects. In addition, the effects of key factors (including planting and processing methods) on the content of effective components and the effects of different extraction methods on the extraction rate were analyzed, which provided a theoretical basis for the research and development of EUL antioxidant functional foods. Zhang et al. [171] found that the antioxidant capacity and the content of related active components were related to the month, which showed that flavonoids played an important role in inhibiting linoleic acid oxidation; Polyphenol content affects the activity of DPPH free radicals; May and August are the best months for harvesting industrialized EUL.

In addition, ultraviolet (UV) b radiation will produce reactive oxygen species (ROS) in the skin, which will cause oxidative damage to cell components, lead to skin aging. and easily cause cancer. Developing anti-photoaging products has become a hot research topic in the field of daily chemicals. According to reports, EU has the function of anti-photoaging. Chen et al. [172] found that the protective effects of EU extract on UVB mainly focused on oxidative stress, DNA damage repair, anti-apoptosis, and cell proliferation through functional analysis of differentially expressed genes. Jimbo et al. [173] studied the effects of daily intake of EUL and Korean ginseng herbal extracts on skin damage caused by repeated ultraviolet radiation in hairless mice. It was found that geniposidic acid in EUL and ginsenoside Rg1 in Korean ginseng decreased transepidermal water loss (TEWL) in hairless mice and increased the water content of skin damaged by ultraviolet rays, respectively, but the mechanism of action was not clear, which needed to be proved by fibroblasts or epidermal cells in the later stage.

It has been proven that antioxidants can scavenge reactive oxygen species (ROS), inhibit free radical reactions, and repair damaged cells. At present, antioxidants are divided into two types: synthetic antioxidants and natural antioxidants. The former has potential toxicities and side effects, and most of them are devoted to the screening and development of natural antioxidants. Flavonoids and polyphenols in EU are the main active substances with an antioxidant effect, but their monomer compounds are still unclear, and the antioxidant cellular mechanism of EU has not been fully studied. However, most pharmacological activities are carried out on compound extracts, and because compounds are not available, it may be impossible to clearly understand each function of these components.

7.3. Anti-inflammatory effect

With the aging of the population, the incidence and prevalence rate of osteoarthritis (OA) are increasing year by year. Epidemiological studies show that about 50 % of people over 50 years old in the world suffer from OA, while the prevalence rate of OA in people over 75 years old in China is as high as 80 %, and its disability rate can reach 53 % [174]. Inflammation is not only the initial factor of OA, but also its main pathological feature, which can activate the signal transduction process of various inflammatory reactions [175]. Studies have shown that EU plays an important role in the treatment of OA, and the compound preparation of TCM with EU as the monarch drug can improve the clinical symptoms and knee joint function of OA. The active components of EU for preventing and treating OA mainly include quercetin, *β*-sitosterol, kaempferol, eugenol, ephedrine, catechin, and resin alcohol. Its possible mechanism is not only directly involved in cell proliferation, differentiation, and apoptosis but also indirectly affects the microenvironment of bone and cartilage by regulating inflammation, immunity, and other systemic systems. It has the characteristics of being multi-channel, multi-component, and multi-target [176]. EU water extract may delay cartilage degeneration, reduce inflammatory cytokines, and prevent MMP-3 secretion by inhibiting the PI3K/Akt pathway, thus inhibiting OA [177].

Rheumatoid arthritis (RA) is a chronic autoimmune disease that can affect many organs and tissues all over the body. The typical clinical symptoms include joint pain, swelling, and morning stiffness [178]. The condition worsens and develops into joint deformity and poor mobility, and it can be disabled in severe cases [179]. The pathogenesis of rheumatoid arthritis is closely related to inflammatory factors. Tumor necrosis factor-α (TNF-α), IL-1, IL-17, and other pro-inflammatory cytokines can stimulate the inflammation and degradation of bone and cartilage, gradually leading to arthritis injury and deformity and eventually disability [180]. TCM believes that spleen and stomach weakness and liver and kidney deficiency are the fundamental causes of this disease, and EU is a commonly used drug for the treatment of rheumatoid arthritis [181]. Network pharmacology reveals that EU has therapeutic effects on RA through multiple components, multiple targets and multiple channels. In the above biological processes, several key pathways are involved, such as the TNF pathway, the IL-17 pathway, the T cell receptor pathway, the NOD-like receptor pathway, Toll-like receptor pathway, and so on [182]. Wang et al. [183] found that 70 % ethanol extract EU can relieve the symptoms of RA, enhance the anti-inflammatory effect of IL-10, inhibit the levels of key pro-inflammatory cytokines TNF-α and IL-1β in serum and tissue, and reduce the degradation of cartilage and bone, thus showing a good effect of inhibiting RA. Wei et al. [184] screened out 28 active components from EU through the database of systematic pharmacology of TCM. Among them, quercetin, kaempferol, and *β*-carotene can reduce the destruction of the subchondral matrix, inhibit synovial hyperplasia, and inhibit inflammation-related genes, which are the main effective components of anti-RA.

Chlorogenic acid compounds have biological characteristics such as being anti-inflammatory, anti-oxidant, anti-bacterial, hypolipidemic, hypoglycemic, and so on. They have a high content of EUL and are usually developed as substitutes for feed antibiotics to improve immunity and meat quality [185]. As iridoid compounds, aucubin in EUL has an obvious anti-inflammatory effect, which can effectively inhibit the release of inflammatory factors IL-6 and IL-10, moderately inhibit the release of NO, and inhibit the phosphorylation of interferonγ-γ (IFN-γ) to make IL-8, MCP-1 and IL-10. It can also be used as a specific inhibitor of nuclear factor kappa-B (NF-κ B), reducing the levels of inflammatory factors such as IL-6 and TNF-α, and playing an anti-inflammatory role [186]. According to the characteristics of rich anti-inflammatory active ingredients such as chlorogenic acid and aucubin and the homology of medicine and food, Zhang et al. [187] applied modern scientific extraction technology to toothpaste products and developed antibacterial and health toothpaste. The animal experiment of acute inflammation in mice's ears caused by xylene shows that EUL Health toothpaste has anti-inflammatory, antibacterial, and analgesic effects, and it has certain auxiliary effects on periodontitis, gingivitis, and gingival bleeding. The development of EUL products has broadened the direction.

After the inflammatory reaction is triggered, it will activate immune cells to remove foreign bodies and promote tissue healing. However, excessive inflammation will cause tissue damage. If inflammation persists for a long time, it will lead to its own chronic inflammatory diseases. In recent years, anti-inflammatory TCM has become an important research field. EU has shown good anti-inflammatory effects on some inflammatory diseases, such as osteoarthritis and rheumatoid arthritis, in clinical treatment and experimental research. In experiments, the expression level of cytokines is often used as an index to evaluate the anti-inflammatory activity of EU active substances, but research on the efficacy of active ingredients is still limited.

7.4. Affect the metabolism of sugar and fat

Diabetes mellitus (DM) is a comprehensive endocrine and metabolic disease characterized by disorders of glucose metabolism, hyperlipidemia, and hyperlipoproteinemia [188]. The body will produce excessive superoxide in the continuous high-sugar environment, which will lead to chronic complications of tissues and organs such as the eyes, kidneys, nerves, skin, blood vessels, and heart. In ancient China, people used EUL to soak in water to treat diabetes. In recent years, it has been found that EU polysaccharide is the main active component to play a hypoglycemic role, and its hypoglycemic mechanism is mainly through inhibiting the formation of peroxide, scavenging free radicals in vivo, reducing the level of oxidative stress, and promoting the repair of islets. Wang et al. [189]

found that EU polysaccharide can significantly reduce the serum blood glucose concentration and MDA level in diabetic model mice and significantly increase the serum SOD and GSH-Px levels. Su et al. [150] analyzed that the hypoglycemic mechanism of EU may be through reducing the protein content of Caspase-3 and Caspase-7 in pancreatic tissue, thus improving the damage to islet cells and affecting blood sugar. Lang et al. [190] confirmed that polysaccharide significantly inhibited α-glucosidase and decreased the expression of p38MAPK and TGF-β1 genes. In addition, iridoid compounds can reduce the blood glucose concentration of diabetic patients and improve the activity of antioxidant enzymes [191]. Geniposide is an iridoid compound isolated from EU, and it is also the main active component of EU, which significantly inhibits high glucose-induced INS1 cell damage. At the same time, it can increase the protein levels of apoptosis-related enzymes, including heme oxygenase-1 (HO-1) and Bcl-2, and decrease the protein level of Bax [192], which can significantly enhance the glucose-stimulated insulin secretariat (GSIS) in rat pancreatic INS-1 cells cultured in vitro [193]. EU is not only non-toxic to the liver and kidneys but can also obviously prevent diabetes complications. The increase in the formation of advanced glycation end-products (AGEs) is considered the fundamental cause of secondary complications caused by diabetes [194]. Advanced glycation end products (AGEs) can induce the generation of reactive oxygen species (ROS) in renal cells, which is harmful to the health of the kidney [195]. EU can reverse AGE-induced renal injury by activating the Nrf2-Glo pathway and improving the expression of RAGE, but further research is needed to determine the active components against glycotoxicity [196].

The research on the components of EU with hypolipidemic effects mainly focuses on flavonoids and chlorogenic acid. Because EUL is rich in flavonoids and chlorogenic acid, its lipid-lowering effect has always concerned scholars. Zhang et al. [197] found that the extract mainly regulates the blood lipids of rats by decreasing the contents of TC, LDL, and VLDL, increasing the content of HDL, and increasing the synthesis of hydroxyproline. Li et al. [198] studied the hypolipidemic mechanism of chlorogenic acid extract and speculated that it may be related to inhibiting the absorption and transformation of lipids, inhibiting the absorption of intestinal cholesterol, and reducing the synthesis of liver cholesterol. In addition, iridoid compounds in EU (genipin, geniposide, geniposidic acid, and aucubin) also have a good effect on regulating blood lipids. Chlorogenic acid and geniposide can significantly increase bile secretion and promote lipid metabolism in animals, and their regulation may be related to reducing the activity of 3-hydroxy-3-methylglutaric acid monoacyl-CoA reductase [199]. However, at present, the research on EUL on iridoid compounds mostly focuses on the extraction process and determination method, and the research on its function of regulating blood lipids is very limited, so related research can be carried out in the future. In addition to their strong hypolipidemic effect, Wen and Lou [200,201] reported that EU seed oil and EU male flower tea have a regulatory effect on hyperlipidemia induced by a high-fat diet in mice and have a significant protective effect on liver steatosis.

The anti-obesity study at EUL has also made progress. Hirata et al. [202] established a mouse model of metabolic syndrome by feeding high fat and found that geniposidic acid, asperuloside, and chlorogenic acid in EUL have anti-obesity effects. Fujikawa et al. [203] explored the potential anti-obesity mechanism of EUL extract by feeding a metabolic syndrome-like rat model induced by a 35 % high-fat diet (HFD), and found that the increase in body weight and visceral fat was minimized in a dose-dependent manner, and the plasma levels of TAG and NEFA and insulin resistance secondary to HFD were alleviated. By stimulating the metabolic function of multiple organs in rats, it is considered that the anti-obesity activity of EUL plays a role in improving insulin resistance or hyperlipidemia by secreting and regulating adipocytokines dependent on visceral fat accumulation.

To sum up, EU has anti-diabetic and hypolipidemic effects and can be used as a potential drug for treating diabetes and hyperlipidemia. However, although EU plays an anti-diabetic and hypolipidemic role, the monomer substance that can do this is still unknown. In the future, the screening of monomer drugs and the pharmacology, biochemistry, histology, and chemistry research of monomer drugs will need further research.

7.5. Protective effect on liver and kidney

The protective effect of EU on the liver is reflected in scavenging free radicals, protecting the plasma membrane of hepatocytes, and protecting the integrity of liver organs and tissues. Hepatic ischemia-reperfusion injury (HIRI) means that the structure and function of the ischemic liver are not recovered after blood perfusion but aggravated, which affects the prognosis and survival of patients [204]. EU is an endemic medicinal plant in China. Pharmacological research shows that EU bark has anti-inflammatory and antioxidant effects, and oxidative stress and inflammatory reactions are two important links in HIRI. *Eucommia ulmoides* Oliv. polysaccharide (EUP) has anti-inflammatory, anti-oxidation, and immunomodulatory effects that can alleviate liver injury by reducing ROS levels and inhibiting the activation of the TLR-4-NF-κB pathway. It may be a promising drug for preventing HIRI in liver surgery [153]. Gao et al. [205] found through HIRI rats that many kinds of EU extracts can improve HIRI, among which the alcohol extract of EUL has the most obvious effect, probably because the water extract of EUL contains more phenolic acids and flavonoids. EU chlorogenic acid protects HIRI in rats through anti-inflammatory and antioxidant effects, and its mechanism may be related to the release and expression of HMGB1. The specific molecular mechanism needs further study [206]. Jiang et al. [152] found that EU total flavonoids can significantly reduce the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in serum, reduce the content of malondialdehyde (MDA) in liver, and increase superoxide dismutase (SOD) and glutathione (GSH) in liver.

Diabetic nephropathy (DN) refers to the deterioration of renal function in patients with chronic type 1 and type 2 diabetes, which is one of the most common complications of diabetic patients and the most common cause of end-stage renal failure. It is of great clinical value to find drugs that can improve renal function in a high glucose environment [207]. Inflammation and oxidative stress are important factors in the development of DN. Inflammation promotes DN by causing renal tubular fibrosis and glomerulosclerosis, and the imbalance of reactive oxygen species and antioxidants is related to renal failure caused by diabetes [208,209]. Isoeucommin A is a lignin compound isolated from EU that can alleviate inflammation and oxidative stress in the DN model in vivo and in vitro, protect renal tubular epithelial cells stimulated by H_2O_2 from oxidative stress, activate the Nrf2/HO-1 signaling pathway in human glomerular mesangial cells stimulated by high glucose, and alleviate renal injury [210]. EU lignans can reduce the level of urinary protein in rats with renal injury, inhibit the proliferation of mesangial cells induced by angiotensin II, improve renal function, protect renal injury caused by hypertension, obviously inhibit the morphological changes of renal tubular epithelial cells induced by high glucose, and antagonize the transdifferentiation of renal tubular epithelial cells induced by high glucose, but the specific active components have not been determined [211]. Long-term excessive intake of foods rich in purines can also cause renal pathological changes. The main pathological change is renal interstitial fibrosis [212]. Li et al. [213] discussed the effect and protective mechanism of EU extract on kidney injury induced by a long-term high-purine diet in rats. After EU extract intervention, the structure and function of renal tubular epithelial cells can be enhanced by increasing the mRNA expression of E-cadherin. Extracellular matrix (ECM) is excessively deposited in renal tubules and interstitium, replacing normal renal tissue, and fibrous tissue is accumulated in renal interstitium, which leads to renal tubular atrophy and eventually leads to renal structural damage [214]. EU extract can regulate the ECM degrading enzyme (MMP/TIMP) system, reduce collagen deposition, promote renal tubular repair, and alleviate renal fibrosis.

7.6. *Hypotensive effect*

Hypertension is the most common cardiovascular disease, accompanied by damage to the heart, brain, kidneys and other target organs, resulting in a high mortality and disability rate that seriously threatens people's health. Simple western medicine treatments, such as diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, and other antihypertensive drugs, are widely used in clinics. Although it has improved, it still causes adverse reactions such as headaches, dry coughs and edema. With the modernization of TCM, people focus on extracting effective antihypertensive components from single Chinese medicine or compound Chinese medicine to study the antihypertensive mechanism so as to develop more Chinese medicine preparations to treat hypertension and improve the prognosis of patients with hypertension [215].

EU is a family plant endemic to China. Its leaves and bark are widely used to treat hypertension in China, either as a single drug or in combination with other drugs. In the 1950s, Russian scholars found that EU extract had the function of bidirectional blood pressure regulation, which could not be replaced by other chemical antihypertensive drugs [1]. With the deepening of research, it has been found that EU is a mild and non-toxic natural antihypertensive drug. The effective components with antihypertensive effects in EU mainly include lignans, phenylpropanoids, flavonoids, and iridoids. EU lignans are the most studied compounds in EU, and their components are also the most definite. They are the main effective parts of EU, and the effective component for lowering blood pressure is terpineol diglucoside [216]. The hypotensive mechanisms of EU mainly include regulating hormone levels, assisting nerve regulation, improving endothelial function, and regulating calcium channels [217].

However, because EU is a second-class protected plant in China, the annual output of EU bark is low, which greatly limits its application as a traditional tonic for treating hypertension. Different from EU bark, EU male flower has a relatively large yield and can be harvested every year. Ding et al. [218] studied the antihypertensive activity of male flower extract and found that it could induce the expression of ACE2 mRNA and protein in the kidneys of hypertensive rats, thus lowering blood pressure.

Most of the existing antihypertensive drugs are used to simply control blood pressure, ignoring the complications caused by persistent hypertension. EU can not only effectively control blood pressure but also improve the organic injury caused by hypertension. Li et al. [219] proved that EU lignin can not only reduce the arterial blood pressure of spontaneously hypertensive rats (SHR), but also inhibit the expression of aldose reductase (AR), reduce the expression of renal collagen III, and weaken the proliferation of interstitial cells, thus improving the structure and function of the kidney and alleviating the structural damage to the kidney caused by hypertension. In addition, after taking 6.68 g/kg of EU lignin (334 times the clinical dose), mice did not show obvious acute poisoning symptoms within 14 days. It can be concluded that EU lignin extracted from TCM is safe and may become an additional choice for treating hypertensive renal injury after clinical verification.

Compared with most antihypertensive drugs, EU is safe, effective, and has a good application prospect. In addition, China's EU resources have an absolute advantage in the world, which provides a resource guarantee for the development and utilization of EU. The hypotensive effect of EU has long been confirmed, but its mechanism and material basis have not been clear. At present, although a lot of research work has been carried out, it only focuses on the simple observation of antihypertensive effects, ignoring the study of antihypertensive mechanisms from the perspective of holistic TCM treatment, and there is no large-scale clinical trial. In addition, most of these studies focus on the crude extract of EU, which contains too many non-hypotensive substances, which interferes greatly with the research results. If the monomer is taken as the research object, the absolute content is too small to reflect the real antihypertensive effect of EU. Follow-up research can focus on the orthogonal combination of antihypertensive effective components or antihypertensive monomer components of EU, so as to study new antihypertensive drugs more effectively and contribute to the prevention and treatment of cardiovascular diseases by TCM.

7.7. *Prevent miscarriage*

The medical practice of EU recorded in TCM literature mainly focuses on nourishing the liver and kidneys and strengthening tendons and bones, but there is no monograph on the effect of preventing miscarriage, and there is no record that it can treat pregnancy bleeding. However, it has been used in the treatment of habitual abortion, indicating that EU can treat slippery fetus [220]. According to the theory of TCM, fetal movement is closely related to the kidney. When the kidney qi in the human body is insufficient, the uterus and ren meridian lose their support, and kidney deficiency cannot tie the fetus, which leads to abortion. EU plays a role in protecting the fetus by tonifying kidney qi and nourishing essence and blood. Generally speaking, EU mainly tones the kidneys and prevents miscarriage. Wang et al. [128] compared the inhibitory effects of EU and EU on the isolated uterus of pregnant mice. The results show that EU could weaken the contraction of the isolated uterus, enhance the inhibitory effect on the isolated uterus contraction, and antagonize the effect of uterine contractive agents, which verifies the scientific nature of "salt entering the kidney" and the efficacy of EU in preventing miscarriage.

Modern pharmacological studies show that its possible mechanisms include improving the function of vascular endothelial cells, maternal and fetal immune regulation, supplementing trace elements, enhancing the function of the adrenal cortex, and antioxidation [129]. Different processed products of EU and the decoction and ethanol extract of its leaves can resist the excitability of the isolated uterus of rats and rabbits caused by pituitrin or acetylcholine, relax the uterine smooth muscle, weaken the activity function, reduce the contraction amplitude, and slow down the contraction rhythm. Lv et al. [221] found that the water decoction of different parts of EU (1.0 g/mL) had different degrees of excitement on the isolated uterus of empty pregnant rabbits injected with diethylstilbestrol subcutaneously 24 h in advance, among which the root bark, branch bark and the enhancement of uterine contraction tension were the most obvious, and their effect on the uterus was weaker than those of root bark, branch bark, and root wood, similar to that of branch wood, but stronger than those of raw EU. Modern pharmacological studies have confirmed that Chinese medicine for tonifying the kidney has hormone-like effects and can regulate the human endocrine system. Kidney-tonifying herbs can significantly increase blocking antibodies through maternal-fetal immunomodulation, promote maternal immune protection to embryos, and inhibit maternal immune damage to embryos, thus playing a role in protecting embryos. TCM treatment is safe and reliable, without obvious side effects, and has no adverse effects on the development, intelligence, or heredity of offspring [222]. EU is rich in zinc, manganese, and other essential trace elements. Manganese is related to the synthesis of sex hormones, and zinc can restore the gonad function of patients with kidney deficiency. Modern pharmacological research has also found that trace elements such as zinc, manganese, and chlorogenic acid can excite the pituitary-adrenal cortex system and enhance adrenal cortex function.

At present, the pharmacological experiments with EU in an isolated uterus prove that EU has an anti-abortion effect, and the effect is stronger after processing, especially after salting. The active part of EU is the water extraction part, but it is still at the level of an in vitro experiment. The material basis of its efficacy has not been determined, and its therapeutic target and molecular mechanism still need further study. In the future, the effective components or parts of EU can be extracted and separated by using appropriate animal models and combining them with in vitro cell culture systems. In addition to the in vitro pharmacodynamic study combined with molecular biology, immunohistochemistry, and other techniques, the drug target and pharmacokinetics in vivo need further study. From the perspectives of trophoblast invasion, placental vascular recasting, and pregnancy immune tolerance mechanism, the mechanism of preventing miscarriage in EU is discussed, as is the scientific connotation of preventing miscarriage in EU. Because TCM has an obvious clinical effect, it is believed that it is safe to use TCM.

7.8. Immunomodulation

There are two types of human immunity: non-specific and specific immunity. Non-specific immunity, also known as innate immunity, can react quickly in the face of various invading pathogenic microorganisms and can help resist the invasion of external viruses, which is the most basic line of defense for human health and plays an important role in protecting human health.

In recent years, with continuous research on the development of natural immunomodulators, plant polysaccharides have been found to have unique biological activities in enhancing immunity by enhancing macrophage immunity and improving NK cell killing activity with relatively low toxicity, and therefore have received increasing attention from researchers [223]. EU is rich in a variety of natural active ingredients, and Eucommia polysaccharide (EUPS) also has the effect of enhancing immunity. Its mechanism is mainly through enhancing the phagocytic ability of macrophages, stimulating the spleen to strengthen its ability to respond to immunity, stimulating T cells and other secretions of more immune factors, and activating some dormant immune cells to achieve the effect of improving immunity. Feng et al. [157] confirmed that EUPS has immune-enhancing activity and is a potent immunostimulant through in vivo and in vitro experiments. In vitro experiments, EUPS induced the maturation of dendritic cells (DCs) and also significantly enhanced the proliferation of lymphocytes and significantly enhanced the production of cytokines (IL-4 and IFN-γ); in vivo experiments, relevant data showed that EUPS significantly enhanced Foot-and-mouth disease virus (FMDV)-specific IgG, IgG1, IgG2a, and IgG2b antibody titers and T cell proliferation in in vivo experiments, which could be followed by the development of novel polysaccharide immune boosters. Xu et al. [224] found that a high dose (200 mg/kg) of *Eucommia* polysaccharide treatment group could significantly increase the spleen index and serum levels of interleukin 2 (IL-2), interleukin 4 (IL-4), IgG and immunoglobulin M (Ig M) in mice. Ye et al. [156] established a mouse model of impaired immune function due to cyclophosphamide (CTX) and found that the phagocytic capacity of macrophages and serum levels of hemolysin in the peritoneal cavity of mice in the *Eucommia* polysaccharide-treated group were increased after 14 days of continuous administration, and the immunity of the mice was improved. *Eucommia* polysaccharide can be used as a potential adjuvant for vaccine design because of its low adverse effects. However, there is a lack of clinical data on the immune effects, and most of the experiments are still at the basic research stage. In addition, the research on the immunomodulatory mechanism of polysaccharides also needs to be deepened to find more precise targets.

In addition, chlorogenic acid can play an immunomodulatory role by promoting the metabolic activity, phagocytic activity, nitric oxide production, and pro-inflammatory cytokines of model macrophages and inhibiting the production of anti-inflammatory cytokines by macrophages, which also has a positive contribution to improving the immunity of animal organisms. Dai et al. [225] investigated the immunomodulatory effects of chlorogenic acid on macrophages in the normal resting state and the lipopolysaccharides (LPS) overactivation state and found that chlorogenic acid can improve metabolic activity, enhance phagocytosis, increase the secretion of NO, pro-inflammatory cytokines IL-1β and TNF-α, and reduce the secretion of anti-inflammatory cytokines IL-10 in both states, and the effect is good. The extract of EUL is often added to livestock feed as a substitute for antibiotics to improve the immunity of animals because it is rich in chlorogenic acids and does not remain like antibiotics. Cui et al. [159] found that the main compounds in EUL, such as kaempferol, quercetin, and chlorogenic acid, participate in the IL-17 and tumor necrosis factor signal pathways by regulating key targets such as tumor necrosis factor (TNF), interleukin-6 (IL-6), vascular endothelial growth factor A (VEGFA), and interleukin-1β (IL-1β).

Polysaccharides and chlorogenic acid in EU can enhance the nonspecific immune function of the human body, while Genipin not only retains the basic defense mechanism but also plays an immunosuppressive role. Immunosuppressants are the main treatment for patients with organ transplant rejection, and they are becoming more and more important in the treatment of autoimmune diseases. At present, immunosuppressants commonly used in clinics, such as Rapamycin, Cyclophosphamide, and prednisone, not only have nonspecific toxicity, but long-term immunosuppression will also increase the risk of infection and tumors. In order to find new immunosuppressants with fewer side effects, scholars look for clinically useful and safe substitutes from widely used traditional medicinal plants. Yang et al. [158] explored whether EU has immunosuppressive function by using in vitro and in vivo models and found that genipin in EU inhibited the proliferation of spleen lymphocytes to reduce the activation-specific immunity of cellular and humoral immunity, but did not inhibit the phagocytosis of macrophages and retained the basic host defense mechanism. These results prove that genipin may inhibit cellular immunity and humoral immune responses, and it is a candidate drug for developing better immunosuppressants.

7.9. Anti-tumor effects

A malignant tumor is a new organism formed by the abnormal proliferation of local tissues and cells under the action of many factors. Because of its biological characteristics, such as cell differentiation, abnormal proliferation, and metastasis, it has become a worldwide problem and seriously threatens human health. At present, targeted therapeutic drugs such as afatinib are widely used in clinics, but long-term use will produce obvious toxicities side effects, and drug resistance, so it is urgent for people to develop anti-tumor drugs with novel mechanisms, stronger effects and higher safety. In recent years, with the in-depth study of tumor biology and pharmacology, natural anti-tumor drugs have gradually attracted widespread attention in the medical field. EU is a precious medicinal material unique to China. It has pharmacological effects of enhancing immunity, being anti-tumor and anti-virus, and has been processed into single medicine or compound medicine, which is widely used in tumor prevention, orthopedics, cardiovascular diseases, and other disciplines, and has achieved good clinical results. At present, the anti-tumor effects of EU are mainly divided into two types: one is to directly inhibit the growth of tumor cells by promoting apoptosis; the other is to enhance host immunity, improve the pathological state of the body and restore the damaged immune function to normal, thus activating the immune response of tumor cells and playing an indirect anti-tumor role. According to the pharmacological effects of most pentacyclic triterpenoids, such as anti-tumor, anti-inflammatory, and anti-HIV, some scholars have isolated three compounds from the pentacyclic triterpenoids of EU. Through in vitro cell experiments, it was found that all three compounds could inhibit the production of lysosomes and promote the breakage of mitochondria, and all of them have good anti-tumor activities. It is inferred that the anti-tumor effect of these compounds may be related to lysosomal and mitochondrial dependence [160]. Xin et al. [226] took cyclophosphamide as a positive control drug and found that EU polysaccharide can inhibit the growth of S-180 tumor cells, increase the thymus index, spleen index, the number of white blood cells in peripheral blood, and the number of nucleated cells in bone marrow, which has a significant anti-tumor effect. Its mechanism is related to scavenging oxygen free radicals, enhancing the activities of antioxidant enzymes SOD and GSH, and improving the body's immunity. Zhang et al. [227] found that chlorogenic acid from EUL can significantly accelerate cell apoptosis and inhibit the growth of HCT116 cells. Studies have shown that a variety of polysaccharide components can compete with the virus for cell binding sites and play a role in inhibiting the virus. Inhibitory effect of total flavonoids from EU on proliferation, migration, and invasion of glioblastoma (GBMs). Because of the frequent recurrence of GBM, the effect of surgical treatment is limited. Radiation therapy is an important and widely used postoperative treatment method. The strong radiation resistance of GBM cells remains a serious problem in radiotherapy. In the process of radiotherapy, total flavonoids from EU can further induce apoptosis through endogenous apoptosis. In addition, it can significantly reduce the level of MDA after radiotherapy, indicating that it can inhibit tumor cells and protect normal neurons.

The anti-tumor effect of EU is accomplished by various compounds and signal pathways. At present, the analysis of its mechanism mainly focuses on network pharmacology. It has been proven that EU plays an anti-tumor role by inhibiting the proliferation of tumor cells, inducing autophagy and apoptosis, inhibiting the invasion and migration of tumor cells, regulating immune function, and inhibiting tumor angiogenesis. Although the "multi-component, multi-target, and multi-channel" research method of network pharmacology provides a solution to reveal the anti-tumor mechanism of EU, there are still the following problems: 1) the number of small molecular compounds and their target is limited; 2) the active ingredients retrieved can only be qualitative but not quantitative; 3) network pharmacology is a static study, which needs to study the dynamic body function and disease development process. Therefore, a comprehensive method that can grasp the overall characteristics of traditional Chinese medicine is really needed in the study.

7.10. Neuroprotection

Neuroinflammation refers to inflammation in brain tissue and is the main pathogenic factor in Neurodegenerative disease (NDD). Parkinson's disease (PD) is a common neurodegenerative disease with many pathogenic factors and clinical manifestations, such as bradykinesia, rigidity, silent tremor, and postural instability [228]. At present, there is no treatment that can slow down or prevent PD, and drug therapy is often used to alleviate its symptoms in clinics. Central cholinergic receptor blockers and dopamine-like drugs are the most commonly used drugs for the first-line treatment of Parkinson's disease. Although they can improve patients' daily function, they will have obvious side effects such as postural hypotension, depression, and dyskinesia after long-term use and can't bring lasting benefits [229]. Therefore, there is an urgent need to find effective anti-Parkinson drugs. EU may be a promising candidate drug for the treatment of neuroinflammation. Active components isolated from EU, such as Aucubin, have been fully proven to play a neuroprotective role by being anti-inflammatory and protecting dopaminergic neurons [230]. Geniposidic acid (GPA) is a substance extracted from EU. Some scholars have found that GPA can improve the histopathological changes in the brain. After GPA treatment, the activation of astrocytes and microglia was inhibited, the expressions of proinflammatory cytokines and iNOS were down-regulated, and the expressions of anti-inflammatory cytokines and Arg-1 were up-regulated. The reversal of the inflammatory state shows that GPA can be used as a multi-objective candidate for adjuvant therapy for Alzheimer's disease [231].

Li et al. [232] explored the therapeutic effects of different extracts of EU on PD mice and analyzed the spectrum-effect relationship by ultra-high performance liquid chromatography (UPLC). The results show that the ethanol extract of EU has an anti-Parkinson's disease effect, and the 75 % ethanol extract has the most remarkable effect. EU glycosides, Liriodendron, 5-hydroxymethylfurfural, and caffeic acid may be the main effective components of EU in treating PD. Chai et al. [233] systematically summarized the research progress of EU in treating PD from different links and different targets and found that the effective components of EU have mainly anti-inflammatory, antioxidant, and neuroprotective effects.

The etiology of nervous system diseases may also be the result of interactions between genes and the environment. In recent years, people's demand for crop yield and pest control has been increasing, but improper use of pesticides and herbicides will endanger the environmental ecosystem and people's lives and health. Through epidemiological investigation, frequent contact with agricultural pesticides will increase the risk of sporadic PD, and it is found that excessive use of paraquat pollutes groundwater sources, which leads to an increase in PD incidence [234,235].

It has been proven that the extract of EU bark has anti-PD activity, and similar components and clinical applications have been found between EU bark and EUL. Therefore, some scholars have studied whether the extract of EUL also has a therapeutic effect on PD. The chemical constituents of EUL were analyzed by HPLC-Q-TOF-MS, and its anti-PD effect was verified by the zebrafish PD model. The results showed that EUL significantly reversed the loss of dopaminergic neurons and neurovascular cells in the brain of zebrafish and reduced the number of apoptotic cells, thus alleviating the dyskinesia of PD zebrafish in the MPTP model. In addition, its potential mechanism was also studied, and it was found that EUL might promote the degradation of α-synuclein and alleviate PD-like symptoms by activating autophagy. The overall results show that EUL has an anti-PD effect, which provides the possibility for its use in PD treatment [236].

The prevalence of PD is increasing year by year, and the pathogenesis is complex. At present, the treatment effect's is poor. Traditional dopamine-like drugs are not ideal for PD. At present, the experimental studies provide phytochemical and pharmacological evidence to prove that EUL has anti-Parkinson's activity. Although its specific pharmacological mechanism has not been clarified, it is worth testing the potential anti-Parkinson's disease effect of EUL in future research. However, it is necessary to explore newer methods, such as using multi-group analysis (metabonomics and protein genomics), to promote the research progress of treating PD with TCM. Although the treatment of PD with TCM has a glorious history, experimental research has only begun in recent years, especially using the PD model. Because of the complexity of TCM and its active components, it is difficult to choose a suitable model to fully explore TCM. Therefore, we need to use a variety of models to make up for the shortcomings of a single model and better utilize and develop this treasure trove of Chinese herbal medicines.

8. Safety

In recent years, there have been many studies on the pharmacological effects of EU, and with the introduction of various pharmacological activities of EU, the development of health care products for EU also came into being. As a commonly used TCM, the safety evaluation of EU is mainly focused on the traditional toxicological evaluation methods, mainly focusing on the acute toxicity, chronic toxicity, genetic toxicity, and reproductive toxicity of EU [237].

Luo et al. [238] believes that EU extract has no genetic toxicity and will not cause acute toxicity. The maximum tolerated dose of EU extract is not less than 168 g/kg, which is 1260 times the clinical dose for adults. However, long-term (13 weeks) and high-dose administration can lead to partially reversible nephrotoxicity. Zeng et al. [239] compared the acute toxicity of water and alcohol extracts of EU in the Qinba area to mice. According to the modern toxicity classification of TCM, it is considered that the water extract of EU is safer than the alcohol extract, presumably because of the difference in the components extracted by different extraction solvents. Pang et al. [240] studied the genotoxicity of EU on mouse germ cells and proved that EU caused no genetic damage to mouse germ cells and was a safer TCM. Sui et al. [241] examined the acute toxicity test, cytotoxicity test, and genotoxicity test of EU and concluded that EU is non-toxic, showed some toxicity to both CHO and CHL cells at higher doses, and showed no genotoxicity of cell chromosome aberrations under the experimental conditions set. However, the genotoxicity of EU is controversial. Some scholars have found that the water extract of EU was negative in vivo and positive in vitro. Hu et al. [242] concluded that EU aqueous decoction could induce mutation at the tk locus of L5178Y cells and cause chromosome damage under±S9 conditions, tentatively suggesting potential genotoxicity, but the mutagenic ability was weakened after in vivo metabolic activation and there was no damage to mouse bone marrow cells chromosomes. However, the mutagenicity decreased after metabolic activation in vivo, and no chromosome damage was observed in mouse bone marrow cells. The reason for this difference is that the metabolites formed in vitro may not be formed in vivo, which is due to differences in biological systems and metabolic pathways tested in vivo and in vitro, or the active metabolites formed may be detoxified rapidly in vivo but not in vitro.

With the acceleration of the aging population and the vigorous development of the health service industry, people pay more and more attention to health care and health preservation. Under the influence of the thought of "homology of medicine and food" in TCM, people are devoting themselves to developing natural, safe, nutritious, and therapeutic TCM health care products. Based on the value of homology between medicine and food, product development in the EU has expanded from single medicine to EU health food, common food, Chinese veterinary medicine, and feed additives [8]. Attention should be paid to the safety evaluation of related products. At present, according to the procedure and method of food safety toxicology evaluation, EU leaf tea, EU seed oil, and EU male flower are all non-toxic and can be used as safe TCM health care products [243–245].

For EU products with the same origin as medicine and food, the research foundation for their safety is weak at present, and the safety evaluation model and method adopted are relatively simple. The research that has been carried out only focuses on the acute poisoning dose, but the poisoning mechanism is not clear. In the future, it is necessary to further study its absorption and degradation mechanisms in the human body in combination with clinical studies so as to fully understand its potential adverse reactions and safety problems and provide a more reliable basis for the rational use of EU and the protection of public health.

9. Conclusion and perspective

In the part on economic botany, the current development situation of EU bark, leaves, flowers, and seeds was sorted out. The EU product system continued to be rich, and the patent applications for related daily chemical products, tea, and beverages continued to grow, and the industry developed rapidly. Phytochemical studies showed that more than 200 compounds were separated from EU. Modern common processing methods in the EU include stir-frying, charcoal-frying, and adding auxiliary materials. With the continuous expansion of the clinical application field of EU, the focus of EU application has gradually expanded from the traditional field of the musculoskeletal system to the field of treating cardiovascular diseases and further expanded, with certain applications in nervous system diseases, metabolic diseases, skin diseases, and other fields. In a word, this review comprehensively summarizes the research results of EU in recent years, which not only provides important reference materials for the future research, development, and utilization of EU but also reveals its potential pharmacological effects and possible application value, laying a foundation for further promoting its application in the fields of medicine and health care products. Although the research content of the EU is extensive at present, there are still some problems that need further study and discussion.

The cluster analysis of EU-related core journals in the medical field shows that the research on EU is basically carried out in the mode of plant medicine, and less reflects the attributes of TCM. The research on EU in the field of medicine and health is very fragmented, focusing more on the clinical research and efficacy verification of TCM prescriptions than on their effective components and mechanisms of action. The research on chemical constituents mainly focuses on non-specific chemical constituents such as chlorogenic acid, geniposidic acid, and aucubin, while the specific identification constituents of EU are relatively less concerned. In addition, because EU lacks highly active components and parts, the development of high-value drugs is in trouble. The research of EU is not based on a relatively fixed product or formula and lacks a relatively clear material basis, which also makes the consistency and repeatability of the research relatively poor and the overall high-quality academic output less. EU has developed many health products with the same origin as medicine and food, but it lacks edible safety standards. EU is traditionally used as medicine by bark, but it is easy to cause the death of EU after peeling. In recent years, EU has made a series of breakthroughs in planting and harvesting technology in China, ensuring the sustainable development of EU resources. However, the uneven quality of EU medicines on the market has seriously affected the quality and efficacy of single pharmaceutical preparations and Chinese patent medicines compatible with EU medicines. After processing, the contents of effective components and extracts of EU have been affected to some extent, and the chemical components and pharmacological effects have changed greatly, but the processing principle and clinical material basis are still unclear.

In the next step, we should first strengthen the study of clinical mechanisms and deeply explore the active components of EU. Integrate and optimize from three dimensions of TCM theory, clinical practice, and basic research; carry out clinical evidence-based research; explore the intervention and regulation of effective components on the expression of target genes in related pathways; strengthen the original theoretical research of TCM, such as medicinal properties and curative effects, scientifically explain EU principles, and promote the modern development of EU. Secondly, the quality standard of EU products should be improved. We will build a quality control system for the whole process of planting, harvesting, processing, and production of EU, improve the level of product quality control, and improve and stabilize the quality of EU proprietary Chinese medicine. Strengthen the study of EU standards and formulate EU product standards as raw materials for medicine, veterinary drugs, food, and feed to meet a large number of different needs. While studying the safety of medicinal and edible TCM, we should study the correlation of their sources, edible parts, varieties, dosage, time, compatibility, taking methods, and contraindications, and establish inspection and evaluation standards that meet the requirements of the international market so as to promote Chinese medicinal and edible TCM to the world.

Data availability

There is no research related data stored in publicly available repositories, and the data will be made available on request.

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CRediT authorship contribution statement

Lei Bao: Writing – original draft. **Yinling Sun:** Conceptualization. **Jinming Wang:** Methodology. **Wanbao Li:** Data curation. **Jie Liu:** Software, Conceptualization. **Tianying Li:** Visualization, Conceptualization. **Zhenqiang Liu:** Funding acquisition.

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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