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Chemical constituents, biological functions and pharmacological effects for comprehensive utilization of *Eucommia ulmoides* Oliver

Yi-Fan Xing[a,1], Dong He[a,1], Yi Wang[a], Wen Zeng[a], Chong Zhang[a,b], Yuan Lu[a], Nan Su[a,b], Yan-Hua Kong[c], Xin-Hui Xing[a,b,*]

[a] *Key Laboratory for Industrial Biocatalysis, Ministry of Education, Institute of Biochemical Engineering, Department of Chemical Engineering, Room 601, Yingshi Building, Beijing 100084, China*
[b] *Centre for Synthetic and Systems Biology, Tsinghua University, Beijing 100084, China*
[c] *Animal Disease Control and Prevention Centre, South Section of Hangu Road, Lingbao City, Henan 472500, China*

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ABSTRACT

Eucommia ulmoides Oliver is a native plant and valuable tonic Chinese medicine in China with a long history, great economic value and comprehensive development potential. Traditionally, the comprehensive utilization rate of *E. ulmoides* Oliv. is still very low, only bark has been used as medicine and other parts of *Eucommia ulmoides* Oliv. cannot be fully utilized, even the leaves have been well utilized in food products in Japan in the past decades. In order to improve the comprehensive utilization efficiency of *E. ulmoides* Oliv., in this review, we summarized the varieties and contents of main active compounds, biological functions and pharmacological effects in different parts of *E. ulmoides* Oliv. The findings suggest that other parts of *E. ulmoides* Oliv. could replace the bark of *E. ulmoides* Oliv. to some extent besides of their respective applications. The unique and extensive physiological functions between different parts of *E. ulmoides* Oliv. indicate that the comprehensive utilization of *E. ulmoides* Oliv. has a wide space to develop, which is also an effective way to protect *E. ulmoides* Oliv. resources and improve its the utilization rate.

1. Introduction

Eucommia ulmoides Oliver, also known as Du-Zhong, Guttapercha tree, Sixian, Sizhong, and Sijinshu, are ancient tree species left over from the Tertiary glacial movement and Chinese second-class rare and protected plants in nature [1]. It is a hi-light tree species that grows well under strong light conditions, and is suitable for growing in sandy and containing more humus soils with a pH of 4.5–8.0. It grows on altitudes between 300 and 2500 m and annual rainfall around 1000 mm. *E. ulmoides* Oliv. can stand high temperatures of 44 °C and low temperatures of −40 °C [2]. *E. ulmoides* Oliv. is native to the mountainous areas of southwestern China, and the planting area in China is about 33 million are, accounting for more than 99% of the total resources of *E. ulmoides* Oliv. in the world. *E. ulmoides* Oliv. cultivation in China has a wide geographical distribution. Its natural distribution includes Sichuan, Guizhou, Hubei, Hunan, Shaanxi, Gansu, Henan, Anhui, Jiangxi provinces. Jiangsu, Zhejiang, Guangxi, Yunnan, Shanxi, Shandong, Hebei, Beijing, Xinjiang and other provinces and regions have also been introduced successfully [3]. It is also found that *E. ulmoides* Oliv. in different places has a little difference on bark, leaves and seeds morphology. Therefore, it is a multi-species medicinal material of "different species" (Fig. 1).

According to ancient medical records, *E. ulmoides* Oliv. has been recognized and utilized for at least 2000 years. The earliest record of *E. ulmoides* Oliv. can be found in Shennong Herbal Classic. The Compendium of Materia Medica summarized the knowledge of *E. ulmoides* Oliv. comprehensively and systematically. In 1955, the first international symposium on pharmacology of *E. ulmoides* Oliv. was held in Leningrad. At that academic conference, the research results of *E. ulmoides* Oliv. on lowering blood pressure were officially announced. Since then, medical scientists and phytochemistry experts at home and abroad have carried out a large number of scientific research and clinical trials on *E. ulmoides* Oliv., making it popular all over the world [3]. *E. ulmoides* Oliv. has great economic value and comprehensive

* Corresponding author.
E-mail address: xhxing@mail.tsinghua.edu.cn (X.-H. Xing).
[1] The authors contributed equally to this work.
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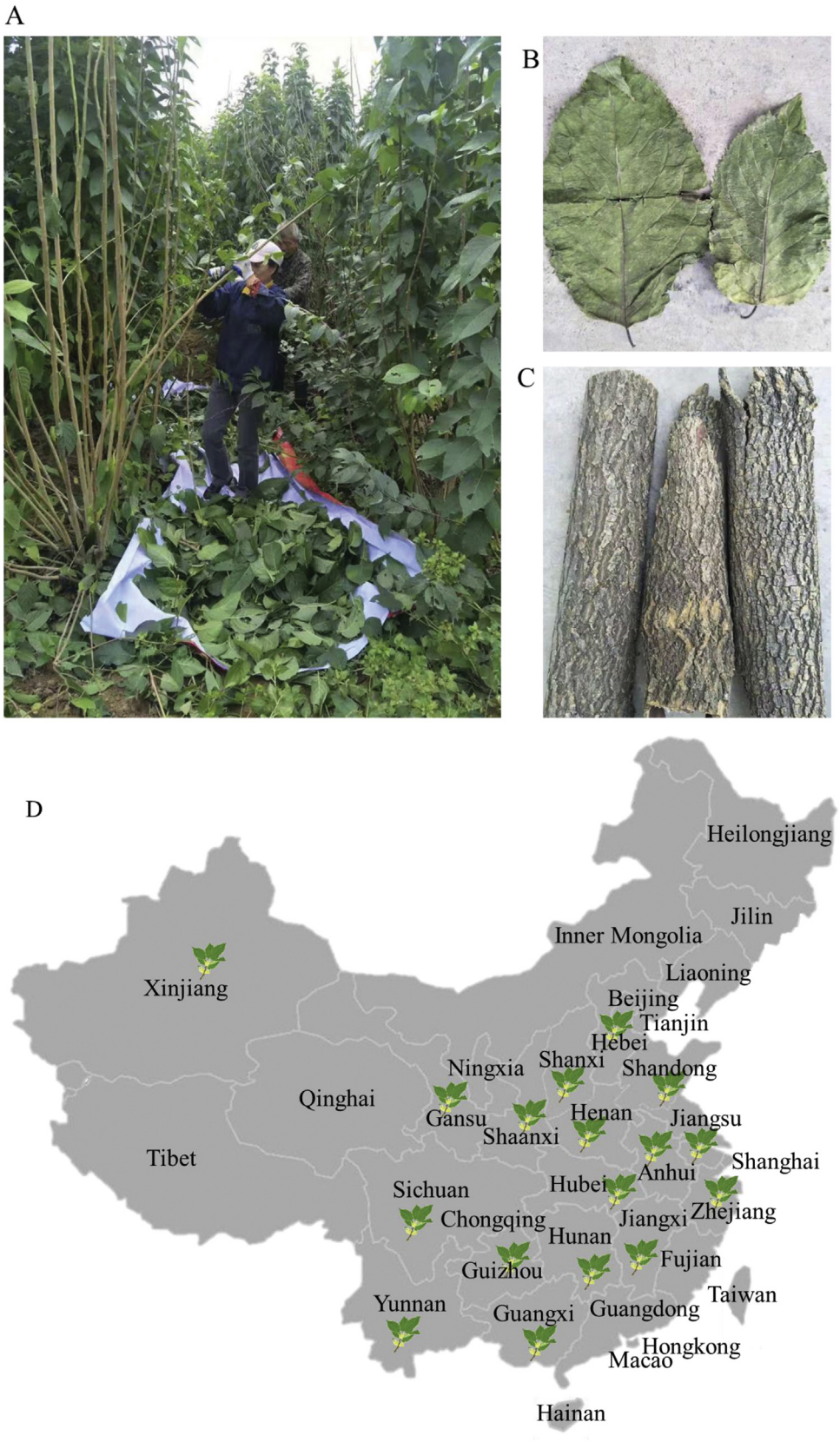

Fig. 1. *E. ulmoides* Oliv. (A) Whole *E. ulmoides* Oliv. (B) Leaves, (C) Bark. (D) Planting distribution, *E. ulmoides* Oliv. is native to the mountainous areas of southwestern China. *E. ulmoides* Oliv. cultivation in China has a wide geographical distribution. Its natural distribution includes Sichuan, Guizhou, Hubei, Hunan, Shaanxi, Gansu, Henan, Anhui, Jiangxi provinces. Jiangsu, Zhejiang, Guangxi, Yunnan, Shanxi, Shandong, Hebei, Beijing, Xinjiang and other provinces and regions have also been introduced successfully.

development potential. According to its structure, the chemical constituents extracted from *E. ulmoides* Oliv. can be divided into iridoids, phenols, flavonoids, lignans, sterols, gutta-percha and so on. Therefore, it has the functions of tonifying liver and kidney, strengthening muscles and bones, fixing meridians and relieving pregnancy in the records of traditional Chinese medicine [4]. Furthermore, *E. ulmoides* Oliv. has been reported to have antihypertensive, hypolipidemic, antidiabetic, antioxidative, anti-inflammatory, neuroprotective, bone metabolism, hepatoprotective, kidney protective, anti-fatigue, anti-aging, sedative and hypnotic, antidepressant, enhancement of cognition, immune regulation, uterine smooth muscle relaxation, erectile function improvement effects.

However, so far the comprehensive utilization efficiency of *E. ulmoides* Oliv. resources is still very low. For a long time, only the bark has been used as medicine. Due to the long growth cycle, *E. ulmoides* Oliv. resources become scarce in the face of increasing demand for medicinal use. Moreover, the traditional peeling method will cause damage to *E. ulmoides* Oliv. and waste resources to a certain extent [5]. Therefore, the comprehensive utilization of *E. ulmoides* Oliv. resources will be an effective way to reduce the shortage of *E. ulmoides* Oliv. resources and improve the economic benefits of related industries. Recent research results have shown that the main active compounds in the leaves and roots of *E. ulmoides* Oliv. are almost the same as in the bark of *E. ulmoides* Oliv., so they can replace the bark to some extent for medicinal use [6,7]. *E. ulmoides* Oliv. bark, leaves and roots can not only be used as medicine, but also be refined into various health products, such as *E. ulmoides* Oliv. beverage series [8]. Gutta-percha of *E. ulmoides* Oliv. is a new polymer material, which is a transitioner between plastic and rubber, and has potential applications in special industries such as national defense, military industry, submarine cable, etc. [9]. Fruit of *E. ulmoides* Oliv. contains quantities of oil, which can be exploited and utilized as high-grade edible oil, and it is expected to become a new health-care resource in China [10].

In this review, the chemical compounds, biological functions and pharmacological effects of *E. ulmoides* Oliv. are introduced from the perspective of comprehensive or integrated utilization, which will provide a basis for the pharmacological research and comprehensive development and utilization of the active compounds of *E. ulmoides* Oliv., especially as Chinese medicinal homologous food (Fig. 2).

2. Chemical compounds

In recent years, reseachers have done lots of study on the chemical compounds of *E. ulmoides* Oliv. As many as 132 chemical compounds have been obtained from the bark, leaves, flowers and seeds of *E. ulmoides* Oliv. According to their structures, they can be divided into iridoids, phenols, flavonoids, lignans, sterols, terpenoids, gutta-percha, polysaccharides, amino acids, unsaturated fatty acids and mineral elements. Some compounds display important biological activities in vivo or in vitro.

2.1. Iridoids

Iridoids are cyclic monoterpenoids derived from formicaldehyde in plants and is abundant in content in *E. ulmoides* Oliv. [11]. At present, 27 kinds of iridoids have been isolated and identified from the bark, leaves, flowers and seeds of *E. ulmoides* Oliv., as listed in Table 1. Geniposidic acid, geniposide, aucubin are the most studied. The active double bond property of cycloene ether and the instability of hydroxyfuran ring are the main reasons for the blackening of *E. ulmoides* Oliv. during picking and natural drying [12]. In addition, *E. ulmoides* Oliv. also contains eucommiol and its derivatives.

Table 1
The Iridoids isolated from *E. ulmoides* Oliv.

No.	Compounds	Resources
1	Ajugoside [14]	Leaves
2	Asperuloside [15,16]	Leaves, flowers
3	Asperuloside acid [16,17]	Leaves, flowers
4	Aucubin [14,18,19]	Bark, leaves, flowers, seeds
5	Catalpol [20]	Bark
6	Deacetyl asperuloside acid [17,19]	Leaves, flowers
7	1-Deoxyeucommiol [21]	Leaves
8	Epieucommiol [21]	Leaves
9	Eucommiol [14,16,22]	Bark, leaves, flowers
10	Eucommiol I [14,22]	Bark, leaves
11	Eucommiol II [4]	Bark
12	Eucommiside [16,23]	Leaves, flowers
13	Eucommiside I [4]	Bark
14	Eucomosides A [15,19]	Leaves, fowers
15	Eucomosides B [15]	Leaves
16	Eucomosides C [15]	Leaves
17	Genipin [18]	Bark
18	Geniposide [4,18,19]	Bark, leaves, flowers, seeds
19	Geniposidic acid [17–19]	Bark, leaves, flowers, seeds
20	Harpagide acetate [14]	Leaves
21	Loliolide [3]	Leaves
22	Reptoside [14]	Leaves
23	Scandoside 10-O-acetate [15]	Leaves
24	Ulmoidoside A [24]	Seeds
25	Ulmoidoside B [24]	Seeds
26	Ulmoidoside C [24]	Seeds
27	Ulmoidoside D [24]	Seeds

Eucommiol is a cleavage iridoids compound, which only exists in *E. ulmoides* Oliv. It has not been reported from other sources and is probably a specific component in *E. ulmoides* Oliv. [13].

2.2. Phenylpropanoids (phenols)

Phenylpropanoids, a class of compounds with C6–C3 structure, are precursors of lignans and flavonoids, most of which have phenolic properties. Phenylpropanoid derivatives can also bind to sugar or polyols and exist in plants in the form of glycosides or esters. These compounds often have strong physiological activities and are widely found in the green leaves, deciduous leaves, roots, stem and male flowers of *E. ulmoides* Oliv. [25]. So far, 26 phenols have been isolated from *E. ulmoides* Oliv. (Table 2). Among them, chlorogenic acid is the most important and most studied compound. The content of chlorogenic acid in *E. ulmoides* Oliv. leaves is rich, up to 1%–5.5% [26], followed by male flowers, higher than the bark and stem [27]. The content of chlorogenic acid in *E. ulmoides* Oliv. leaves is often used as an important basis for evaluating the quality of leaves.

2.3. Flavonoids

Flavonoids, also known as permeable vitamins, are derivatives of chromogenic ketones or chromogenic alkanes, which are the natural products with C6–C3–C6 structure as the basic mother nucleus [11]. The content of flavonoids is an important index for judging the quality of *E. ulmoides* Oliv. raw medicinal materials and their products [3]. The flavonoids are rich in leaves and male flowers of *E. ulmoides* Oliv. 16 flavonoids have been isolated and identified from *E. ulmoides* Oliv., as summarized in Table 3.

2.4. Lignans

Lignans are one of the most widely studied chemical compounds of *E. ulmoides* Oliv. with the clearest structure and composition [11]. They are a kind of compound which are polymerized by bimolecular phenylpropanoid derivatives in vivo. At present, there

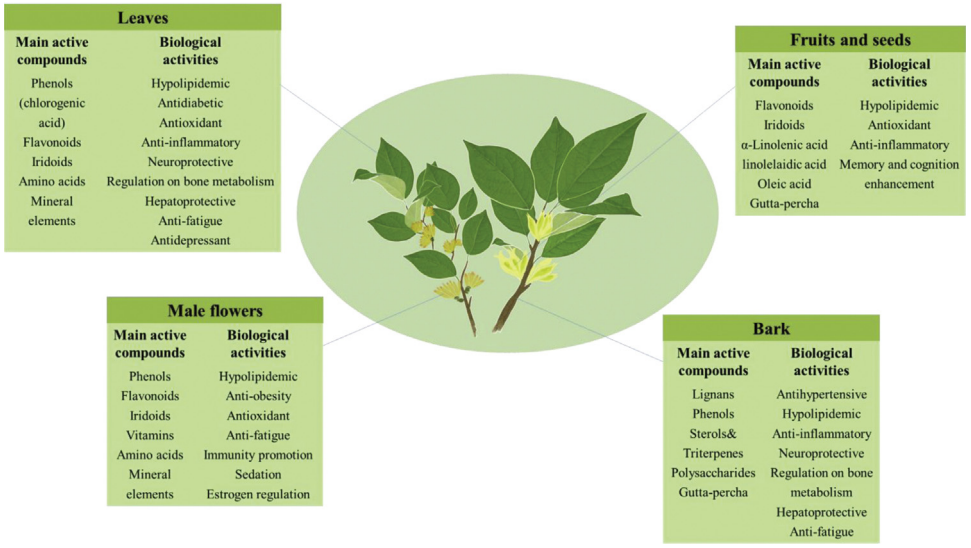

Fig. 2. Summary of chemical compounds and biological activities of different parts of *E. ulmoides* Oliv. for comprehensive utilization.

Table 2
The phenols isolated from *E. ulmoides* Oliv.

No.	Compounds	Resources
1	Caffeic acid [4,16,28]	Bark, leaves, flowers
2	Caffeic acid ethyl ester [29]	Leaves
3	Dihydrocaffeic acid [3,18,24]	Bark, leaves, seeds
4	Catechol [21]	Leaves
5	Catechin [21]	Bark, leaves
6	Catechin-(7,8-bc)-4α-(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone [22]	Leaves
7	Catechin-(5,6-bc)-4α,β-(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone [22]	Leaves
8	2,5-Dimethoxy-3-glucopyranosyl cinnamic alcohol [22]	Leaves
9	Epicatechin [4,16]	Bark, flowers
10	Chlorogenic acid [18,24,29,30]	Bark, leaves, flowers, seeds
11	Isochlorogenic acid A [16,31]	Bark, flowers
12	Isochlorogenic acid C [16,31]	Bark, flowers
13	Methyl chlorogenate [4,32]	Bark, leaves
14	Coniferin [29,33]	Leaves, stem
15	Coniferol [28]	Bark
16	p-Coumaric acid [29,34]	Leaves, roots
17	Eucophenoside [35]	Bark
18	Ferulic acid [34]	Roots
19	Guaiacylglycerol [16,32]	Leaves, flowers
20	Koaburaside [16,33]	Flowers, stem
21	3-(3-Hydroxyphenyl) propionic acid [21]	Leaves
22	Protocatechuic acid [18,21]	Bark, leaves
23	Protocatechuic methyl-ester [4]	Bark, leaves
24	Pyrogallol [4,21]	Leaves
25	Syringin [32]	Leaves, stem
26	Vanillin acid [18]	Bark

Table 3
The flavonoids isolated from *E. ulmoides* Oliv.

No.	Compounds	Resources
1	Astragalin [21,30,34,36]	Leaves, flowers, roots, seeds
2	Kaempferol [16,21,34,36]	Leaves, flowers, roots
3	Kaempferol-3-O-rutinoside [17,21]	Leaves
4	Kaempferol-3-O-6″-acetyl-glucopyranoside [21]	Leaves
5	Hirsutin (quercetin 3-O-β-D-glucopyranoside) [30,34,36]	Leaves, flowers, roots
6	Hyperin (quercetin 3-O-galactoside) [37]	Bark
7	Nicotiflorin [3,16]	Leaves, flowers
8	Oroxylin A [38]	Bark
9	Quercetin [21,30,34,36]	Leaves, flowers, roots
10	Isoquercitrin [16,18,31]	Bark, flowers, seeds
11	Quercetin 3-O-sambubioside [17,18]	Leaves, bark
12	Quercetin 3-O-glucopyranoside [21]	Leaves
13	Quercetin 3-O-xylopyranosyl-(1 → 2)–glucopyranoside [21,30,37]	Bark, leaves, flowers
14	Quercetin 3-O-α-L-arabinopyranosyl-(1 → 2)-β-D-glucopyranoside [30,39,40]	Bark, leaves, flowers
15	Rutin [16,18,34,36]	Bark, leaves, flowers, roots
16	Wogonside [35]	Bark

are 30 kinds of lignans isolated from *E. ulmoides* Oliv., as listed in Table 4. According to structural characteristics, they can be divided into bisepoxylignans, monoepoxylignans, neolignans and sesquilignans. Most of them are glycosides with glycosyl group of beta-D-glucose [4]. Studies on lignans in *E. ulmoides* Oliv. are mostly concentrated in the bark, and less on leaves and male flowers. Pinoresinol di-O-β-D-glucopyranoside is an important index for material control of *E. ulmoides* Oliv. [41]. Feng et al. [42] firstly used HSCCC method to isolate and prepare pinoresinol di-O-β-D-glucopyranoside from *E. ulmoides* Oliv. leaves. *E. ulmoides* Oliv. male flowers has rich content of pinoresinol di-O-β-D-glucopyranoside with good hypotensive effect, followed by syringaresinol, which has the effects of anti-cancer, anti-amnesia and enhancing exercise endurance [43].

2.5. Sterols and triterpenes

Sterols and triterpenoids are ubiquitous in nature. There are a few of them found in the bark, leaves and male flowers of *E. ulmoides* Oliv. At present, there are 10 kinds of sterols and triterpenoids isolated and identified from *E. ulmoides* Oliv. (Table 5).

2.6. Gutta-percha

Gutta-percha exists in plant tissues and is a white filamentous substance. Its chemical composition is trans-1,4-polyisoprene [9], which has rubber-plastic duality. Gutta-percha distributes in leaves, bark, fruit, stem, roots and shell of *E. ulmoides* Oliv. with 2%–3%, 10%–12%, 10%–18%, 6%–12%, 10%–12%, 12%–18% [27], respectively. The data showed that *E. ulmoides* Oliv. and its bark

Table 4
The lignans isolated from *E. ulmoides* Oliv.

No.	Compounds	Resources
Bisepoxylignans		
1	(+)-Epipinoresinol [28]	Bark
2	(+)-l-Hydroxypinoresinol [28]	Bark
3	(+)-1-Hydroxypinoresinol 4′-O-β-D-glucopyranoside [44]	Bark
4	(+)-1-Hydroxypinoresinol 4″-O-β-D-glucopyranoside [44]	Bark
5	(+)-1-Hydroxypinoresinol 4′,4″-di-O-β-D-glucopyranoside [45]	Bark
6	(+)-Medioresinol [28]	Bark
7	EucomminA ((+)-medioresinol 4′-β-D-glucopyranoside) [45]	Bark, leaves
8	(+)-Medioresinol di-O-β-D-glucopyranoside [46]	Bark
9	(+)-Pinoresinol [28]	Bark, leaves
10	(+)-Pinoresinol 4-O-β-D-glucopyranosyl (1-6)-β-D-glucopyranoside [47]	Bark
11	(+)-Pinoresinol 4′-O-β-D-glucopyranoside [16,46]	Bark, flowers
12	(+)-Pinoresinol 4′,4″-di-O-β-D-glucopyranoside [4,16]	Bark, leaves, flowers
13	(+)-Syringaresinol [28]	Bark, leaves
14	(+)-Syringaresinol O-β-D-glucopyranoside [45]	Bark, leaves
15	Liriodendrin ((+)-syringaresinol di-O-β-D-glucopyranoside) [46,48]	Bark, leaves, flowers
Monoepoxylignans		
16	(+)-Olivil [44]	Bark, leaves
17	(+)-Cyclo-olivil [44,48]	Bark, leaves
18	(+)-Olivil 4′-O-β-D-glucopyranoside [44,49]	Bark, leaves
19	(+)-Olivil 4″-O-β-D-glucopyranoside [44]	Bark
20	(−)-Olivil 4′,4″-di-O-β-D-glucopyranoside [45]	Bark
Neolignans		
21	CitrusinB [50]	Bark
22	Dihydroxydehy-drodiconiferyl alcohol [28]	Bark, leaves
23	Erythro-dihydroxydehy-drodiconiferyl alcohol [28]	Bark
24	Threo-dihydroxydehy-drodiconiferyl alcohol [28]	Bark
25	Dehydrodiconiferyl alcohol 4,γ′-di-O-β-D-glucopyranoside [50]	Bark
Sesquilignans		
26	(−)-Hedyotol C 4′,4‴-di-O-β-D-glucopyranoside [44]	Bark
27	Guaiacylglycerol-β-syringaresinol ether 4″-4‴-di-O-β-D-glucopyranoside [21]	Bark
28	Syringylglylycerol-β-syringaresinol ether 4″-4‴-di-O-β-D-glucopyranoside [50]	Bark
29	(+)-Pinoresinol vanillic acid ether diglucopyranoside [21]	Bark
30	(+)-Syringaresinol vanillic acid ether diglucopyranoside [21]	Bark

Table 5
The sterols and triterpenes isolated from *E. ulmoides* Oliv.

No.	Compounds	Resources
1	Betalin [51,52]	Bark, flowers
2	Betulic acid [51,52]	Bark, flowers
3	Daucosterol [53]	Bark
4	Eucommidiol [54]	Bark
5	Rehmaglutin C [54]	Bark
6	β-Sitosterol [52]	Bark
7	1,4α,5,7α-Tetrahydro-7-hydroxymethyl-cyclopenta (c) pyran-4-carboxylicmethylester [54]	Bark
8	Ulmoprenol [55]	Bark
9	Ulmoidol [56]	Leaves
10	Ursolic acid [29,51,52]	Bark, leaves, flowers

were the main sources of gutta-percha. In the 1980s, Yan et al. [57] developed a method for preparing trans-polyisoprene vulcanized rubber, which marked a new era for the research and development of gutta-percha. It can be used as a series of new functional materials in rubber industry, aerospace, national defense, ship, chemical industry, medical and other areas of national economy through rubber extraction, vulcanization modification and deep processing [58].

2.7. Polysaccharides

Polysaccharides of *E. ulmoides* Oliv. are active constituents found in recent years. Japanese researchers have isolated two kinds of polysaccharides with immunopotentiating activity from the bark of *E. ulmoides* Oliv. Gonda [59] has isolated an acid polysaccharide from *E. ulmoides* Oliv., eucomman A, which was composed of *L*-arabinose, *D*-galactose, *D*-glucose, *L*-rhamnose and *D*-galacturonic acid in molar ratio of 8:6:4:5:8. It was proved that it could activate the reticuloendothelial system and enhance the non-specific immune function of the body. Then another acidic polysaccharide, eucomman B was found, which was composed of *L*-arabinose, *D*-galactose, *L*-rhamnose and *D*-galacturonic acid in molar ratio of 10:5:24:24 [60].

2.8. Unsaturated fatty acids

Recently, Zhang et al. [61] analyzed the constituents of fatty acids from the seed oil of *E. ulmoides* Oliv. using the fraction chain length and mass spectrometry. The main components of polyunsaturated fatty acids are α-linolenic acid and linolelaidic acid, and oleic acid is the main monounsaturated fatty acid.

2.9. Other compounds

E. ulmoides Oliv. contains nutrients such as amino acids and mineral elements beneficial to human body. *E. ulmoides* Oliv. contains 16 kinds of amino acids [62], among which human essential amino acids are abundant and high in content, accounting for 34–40% of total amino acids. The highest content of the essential amino acids in *E. ulmoides* Oliv. is leucine, followed by valine [12]. In addition, *E. ulmoides* Oliv. leaves contain tyrosine, a semiessential amino acid deficient in milk and eggs, and histidine necessary for infant growth and development. 13 trace elements, including iron, zinc, copper, manganese, potassium, sodium, calcium, magnesium, chromium, cobalt, phosphorus, selenium and boron, are detected in *E. ulmoides* Oliv. leaves and male flowers [63]. They were also rich in VE, beta-carotenoids and trace amounts of VB_1 and VB_2 [4].

To sum up, the lignans of *E. ulmoides* Oliv. bark are more abundant than leaves, while the contents of iridoids, phenols and flavonoids in leaves are more abundant, which have the hypolipidemic, antidiabetic and antioxidant effects. At present, it has been found that the active compounds of leaves are basically the same as those of bark, which has a certain degree of substitution. *E. ulmoides* Oliv. male flower tea is a popular health product on the market. It has rich flavonoids and magical antioxidant effect. There are few studies on the constituents of *E. ulmoides* Oliv. roots and seeds, but several important chemical constituents have been found in them. *E. ulmoides* Oliv. roots has a good antihypertensive effect,

Table 6
Contents of main active compounds in different parts of *E. ulmoides* Oliv. (%) [64].

	Aucubin	Chlorogenic acid	Flavonoids	Total
Bark	1.14	0.41	0.36	1.91
Leaves	1.34	1.75	1.67	4.76
Male flowers	1.13	1.11	1.82	4.06

and the seeds are rich in unsaturated fatty acids. The main active compounds of *E. ulmoides* Oliv. are geniposidic acid, geniposide, aucubin, asperuloside, chlorogenic acid, syringin, quercetin, isoquercetin, astragalin, rutin, pinoresinol di-O-β-D-glucopyranoside, etc. The contents of main active compounds in different parts of *E. ulmoides* Oliv. are summarized in Table 6.

3. Biological activities

3.1. Antihypertensive effects

Hypertension is the most common chronic disease and the most important risk factor for cardiovascular diseases characterized by increased systemic arterial blood pressure (systolic and/or diastolic blood pressure), which may be associated with functional or organic damage of organs such as the heart, brain, and kidney. *E. ulmoides* Oliv. is considered to be a high quality natural antihypertensive drug without side effect from ancient times to the present. In recent years, in vivo and in vitro experiments have shown that different extracts from different parts of *E. ulmoides* Oliv. have antihypertensive effects. Among them, lignans are the main active compounds, which can be used as a new vasodilator for vascular remodeling in humans. Chlorogenic acid, geniposidic acid, asperuloside and aucubin also have antihypertensive effects [22,65].

Kwan et al. [66] evaluated the antihypertensive activity of aqueous extracts of *E. ulmoides* Oliv. leaves and bark using isolated rat aortic and dog carotid rings. Both aqueous extracts isolated from leaves and bark concentration dependently caused endothelium-dependent relaxation in vessels precontracted with 1 AM phenylephrine. This vasorelaxant action is involved with the nitric oxide (NO) synthase pathway. Later, Lang et al. [67] through experiments verified the safety and efficacy of *E. ulmoides* Oliv. extracts in the treatment of hypertension. The maximum tolerated dose of *E. ulmoides* Oliv. extracts was 1200 mg/kg. And when spontaneous hypertensive rats (SHRs) were administered *E. ulmoides* Oliv. extracts daily with 200 mg/kg, 600 mg/kg or 1200 mg/kg doses, the mid or high dosages lowered systolic blood pressure (SBP) in male rats at a rate of approximately 10 mmHg per hour. Luo et al. [68] through in vivo study found that *E. ulmoides* Oliv. lignans (EUL) could lower blood pressures of both Sprague–Dawley(SD) rats and SHRs dose-dependently by either intravenous or intragastric administration, but *E. ulmoides* Oliv. Iridoids (EUI) and their combination failed. The plasma NO level in SHRs treated with EUL 300 mg/kg twice a day was markedly increased. Both plasma renin activity (RA) and angiotensin II (Ang II) level were decreased with long-term oral treatment of EUL 150 and 300 mg/kg twice a day. In perfusion experiment, EUL relaxed mesenteric artery quickly and dose-dependently. Gu et al. [69] also found that lignans decreased mean arterial blood pressure in SHRs. Besides, lignans can inhibit aldose reductase and reversed hypertensive vascular remodeling, to alleviate cardiovascular disease. Hosoo et al. [70] examined the effects of chronic *E. ulmoides* Oliv. leaves extract (ELE) administration on artery function and morphology in SHRs. ELE significantly improved acetylcholine(ACh)-induced aortic endothelium-dependent relaxation in the SHRs. Plasma NO levels and media thickness were significantly increased and decreased, respectively. Therefore, long-term ELE administration may effectively improve vascular function by preventing vascular hypertrophy in the SHRs aorta. Later, this group found when rats received both ELE and the high-fat diet (HFD), they could significantly lower blood pressure and thinner aortic media than the control rats receiving the HFD only. Antihypertensive effects may be caused by the geniposidic acid and/or asperuloside present in ELE. These were the other active ingredients found to have hypotensive effect besides lignans. These findings suggested long-term administration of ELE might inhibit the development of arteriosclerosis [71].

The hypotensive effect of *E. ulmoides* Oliv. may be related to (1) the regulatory effects against endothelial nitric oxide synthase uncoupling which promoted NO release [22]; (2) the inhibition of renin–angiotensin system and cyclic adenosine phosphate; (3) the regulation of EDHF-mediated response involves the activation of potassium-channels and gap junctions.

3.2. Hypolipidemic effects

Hyperlipidemia refers to high blood lipid levels and causes serious complications, such as atherosclerosis, coronary disease, and so on. Researchers have found that the high-content active compounds in *E. ulmoides* Oliv., especially in leaves, such as asperuloside, geniposidic acid, quercetin, chlorogenic acid, aucubin have magical hypolipidemic effects [72–74].

The *E. ulmoides* Oliv. leaves water extract was given to C57BL/KsJ-db/db mice as a dietary supplement (0.187 g/100 g standard diet). In this study, the plasma and hepatic triglyceride (TG), total cholesterol (TC) concentrations were significantly lowered as a result of lower HMG-CoA reductase and ACAT activities, along with a simultaneous increase in the high density lipoprotein (HDL)-cholesterol and skeletal muscle lipoprotein lipase (LPL) activity and low level of hepatic FAS activity [75]. Besides, free fatty acid (a marker of lipolysis) was significantly lowered due to the lower hepatic fatty acid synthase and HMG-CoA reductase activities, whereas apolipoprotein A–I levels was elevated [76]. Horii et al. [77] found that intraduodenal injection of ELE elevated epididymal white adipose tissue sympathetic nerve activity (WAT-SNA) and interscapular brown adipose tissue sympathetic nerve activity (BAT-SNA) in urethane-anesthetized rats, and the body temperature (BT) (a marker of thermogenesis) in conscious rats. Furthermore, it was observed that ELE given as food reduced food intake, body and abdominal adipose tissue weights. Lee et al. [72] examined the potential regulatory effects of *E. ulmoides* Oliv. extracts on hepatic dyslipidemia. *E. ulmoides* Oliv. extracts and its two active constituents, aucubin and geniposide, inhibited palmitate-induced endoplasmic reticulum (ER) stress, reducing hepatic lipid accumulation through secretion of apolipoprotein B and associated triglycerides and cholesterol in human HepG2 hepatocytes. Lysosomal enzyme activities including V-ATPase were significantly increased by *E. ulmoides* Oliv. extracts as well as aucubin and geniposide in HepG2 cells. These findings further indicated that geniposide and aucubin may be therapeutic candidates for non-alcoholic fatty liver disease [78]. Hao et al. [79] investigated the lipid-lowering effects of chlorogenic acid (CGA)-enriched extract from *E. ulmoides* Oliv. (CAEF) in human hepatoma HepG2 cells. The results suggested that CAEF and CGA increased mRNA expression of ABCA1, CYP7A1, and AMPKa2, while it decreased SREBP2. Importantly, all drugs significantly inhibited protein expression of HMGCR at mRNA and protein levels. *E. ulmoides* Oliv. bark and male flower also have hypolipidemic effects. Jin et al. [80] examined protective effects of *E. ulmoides* Oliv. cortex extracts (EUCE) on the carbon tetrachloride (CCl_4)-induced hepatic lipid accumulation. Rats were orally treated with EUCE in different doses prior to an intraperitoneal injection of 1 mg/kg CCl_4. The pretreatment with EUCE significantly improved these deleterious effects of CCl_4. Lou et al. [81] explored the prevention and health protection of *E. ulmoides* Oliv. male flower on hyperlipemia. The results showed that that TC, TG, LDL-C decreased greatly in high dose group, while HDL-C increased compared with that of model group. Thus, *E. ulmoides* Oliv. male flower tea had a certain prevention action on mice' blood-fat caused by high fat emul.

Based on observations of effects of *E. ulmoides* Oliv. on lipid metabolism, the underlying mechanisms may include the following

points: (1) up-regulation of genes involved in hepatic α-, β- and ω-oxidation, mainly related to the peroxisome proliferator-activated receptor α and δ signaling pathway [74]; (2) regulation of lipid metabolism-related enzymes activities, such as the hepatic fatty acid synthase, HMG-CoA reductase, ACAT and LPL activities [75]; (3) stimulating lipolysis through elevations in sympathetic nerve activity [77]; (4) enhancement of lysosomal activity, resulting in the regulation of lysosomal BAX activation [72,78]; (5) improvement of lipid metabolism by activating adenylate-activated protein kinase (AMPK), inhibiting cholesterol synthesis genes, and increasing activities of membrane proteins to increase cholesterol efflux and bile acid transport, synthesis and excretion [79].

3.3. Antidiabetic effects

Due to the lack of insulin, blood glucose levels increases, leading to polyuria, polyphagia, weight loss and other symptoms. *E. ulmoides* Oliv. is regarded to have great potential in the field of diabetes treatment. The main hypoglycemic compounds includes quercetin, astragaloside, isoquercitrin, rutin, quercetin 3-O-α-L-arabinopyranosyl-(1→2)-β-D-glucopyranoside and other flavonoids [45].

Lee et al. [82] investigated the antidiabetic efficacy of *E. ulmoides* Oliv. leaves on the hyperglycemia in streptozotocin (STZ)-induced diabetic rats. The blood glucose levels were significantly lowered in the diabetic rats groups supplemented with ELE, whereas the plasma insulin and C-peptide levels were significantly increased. *E. ulmoides* Oliv. leaves supplement seemed to be helpful to preserve the normal histological appearance of pancreatic islets as well as to preserve insulin-positive β-cells. Jin et al. [83] found long-term administration of ELE ameliorates pre-diabetic state of insulin resistance and abnormal perivascular innervation in the hyperinsulinemic state. A 4-week treatment with ELE (500 and 1000 mg/kg, p.o.) significantly decreased plasma levels of insulin and HOMA-IR without affecting blood glucose levels and significantly lowered SBP in fructose-drinking rats (FDRs). ELE treatment in FDRs resulted in significant increase in calcitonin gene-related peptide-immunoreactivity nerve fiber density and decrease in tyrosine hydroxylase-like immunoreactivity nerve fiber density in mesenteric arteries of FDRs. *E. ulmoides* Oliv. not only has hypoglycemic effect, but it can relieve the diabetic complications. Cheng et al. [84] investigated the effects of *E. ulmoides* Oliv. bark on renal dysfunction in type 1-like diabetic rats. Oral administration of *E. ulmoides* Oliv. bark extracts (1 g/kg/day) to STZ-diabetic rats not only decreased the plasma levels of blood urea nitrogen and creatinine but also improved renal fibrosis. The higher expressions of protein levels of transforming growth factor-beta (TGF-β) and connective tissue growth factor in diabetic rats were markedly attenuated, as well as the increased phosphorylation of Smad2/3. Kim et al. [39] discovered the flavonol glycosides from *E. ulmoides* Oliv. leaves could inhibit advanced glycation end-products (AGEs) formation, which was one of main molecular mechanisms implicated in diabetic complications, and attributed to the anti-diabetic action. Moon et al. [85] evaluated the effects of *E. ulmoides* Oliv. on AGEs-induced renal disease. The treated group showed a significant increase in the protein expression and activity of glyoxalase 1 (Glo1), which detoxifies the AGEs precursor, methylglyoxal. It up-regulated nuclear factor erythroid 2-related factor 2 (Nrf2) expression but downregulated that of receptor for AGE (RAGE). *E. ulmoides* Oliv. ameliorated the renal damage in diabetic mice by inhibiting AGEs formation and RAGE expression, and reducing oxidative stress, through the Glo1 and Nrf2 pathways.

The mechanism of antidiabetic effects may be related to (1) the inhibition of glycosylation and formation of AGEs [39]; (2) the enhancement of the function of pancreatic β-cells, prevention in insulin resistance development and amelioration of abnormal perivascular innervation [82,83]; (3) the increase in glycolysis and suppression in gluconeogenesis by significantly lowering glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities [75]; (4) the antioxidant activity of *E. ulmoides* Oliv. extract which is potentially beneficial for the prevention and management of complications of type 2 diabetes [86]; (5) the inhibition the activity of disaccharidases and glucose transporters [87].

3.4. Antioxidative effects

The human body counteracts the harmful effects of free radicals and other oxidants every day, and it is very important to consume some antioxidants to keep health. *E. ulmoides* Oliv., especially leaves has strong antioxidant activity, which can reduce the oxidative stress to the body. It is mainly due to the high-content phenols and flavonoids. The main antioxidant compounds are chlorogenic acid, caffeic acid, protocatechuic acid, ferulic acid, rutin and other flavonoids, and aucubin [88–90].

Hsieh and Yen [91] investigated the antioxidant effects of water extracts of *E. ulmoides* Oliv. including leaves, raw cortex, and roasted cortex on oxidative damage in biomolecules. All of them inhibited the oxidation of deoxyribose and 2′-dG to 8-OH-2′-dG induced by Fe3′-EDTA/H_2O_2/ascorbic acid in a concentration dependent manner. The extract of leaves inhibited the strand-breaking of DNA induced by the Fenton reaction. Among them, the leaves extract had a marked inhibitory effect on oxidative damage in biomolecules, followed by the extract of roasted cortex and raw cortex. Later, they investigated biologically active compounds and free radical-/or reactive oxygen species (ROS)-/scavenging effect of *E. ulmoides* Oliv. water extract. The results showed that the scavenging activity on ROS was correlated to its protocatechuic acid content. The order is leaves (17.17 mg/g) > roasted cortex (2.99 mg/g) > raw cortex (1.16 mg/g) [89]. Jin et al. [90] discovered aucubin might play an important role in the cellular defense mechanism against UV radiation-induced photoaging. Pretreatment with aucubin significantly inhibited the production of matrix metalloproteinases-1 and the senescence-associated β-galactosidase activity. The inhibited ROS formation and malondialdehyde (MDA) levels, and the increased cell viability and glutathione (GSH) level were observed with aucubin under UVB irradiation. Additional, *E. ulmoides* Oliv. extract supplementation resulted in higher activities of erythrocyte superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), and lower levels of hydrogen peroxide and lipid peroxide in erythrocytes, liver, and kidney [86]. Lin et al. [92] investigated inhibitory effects of *E. ulmoides* Oliv. leaves ethanol extracts on H_2O_2-induced apoptosis in rat osteoblastic MC3T3-E1 cells. *E. ulmoides* Oliv. remarkably restrained cell oxidative damage and increased cell survival rate in a dose-dependent manner with the half-effective concentration being around 25 μg/ml. Results showed that the expressions of caspases 3, 6, 7, and 9 were significantly decreased. It indicated that *E. ulmoides* Oliv. was a potent antioxidant, which might contribute to its many cellular protective functions.

In recent years, the antioxidant activities of male flowers and seeds have been gradually discovered, and could be used as raw material for further production of health products. Du et al. [93] found that male flower tea could significantly increase SOD and GSH-Px activities in serum and liver tissues of mice, and reduce MDA content. It enhanced the scavenging effect, reduced the production of oxygen free radicals in vivo, and improved oxidative stress injury caused by D-galactose, thus playing an antioxidant role. Qiu et al. [94] found that male flowers contained a large number of phenolic compounds, positively correlated with the antioxidant activity ($R_2 > 0.9$), and had a dose-effect relationship with the mass concentration. The seed oil of *E. ulmoides* Oliv. also had strong reducing power so that it could remarkably eliminate

superoxide anion free radicals and hydroxyl free radicals. In addition, the oil could also inhibit the MDA generation, H_2O_2-mediated oxidation hemolysis of erythrocytes and spontaneous lipid peroxidation of mouse liver tissue. The oil at the concentration of 9 mg/mL revealed the strongest effect [95].

The underlying mechanisms may include the following points: (1) oxygen free radicals and reactive oxygen species scavenging effect [89]; (2) regulation of antioxidant-related enzyme activities, such as SOD, CAT, and GSH-Px [86]; (3) inhibition expressions of caspases 3, 6, 7, and 9, and antagonization H_2O_2-induced cell apoptosis [92].

3.5. Anti-inflammatory effects

Inflammation is the pathological response of the human body to various stimuli, accompanied by swelling, pain, dysfunction and so on. *E. ulmoides* Oliv. can inhibit the release of inflammatory factors through regulating pathways, thus having anti-inflammatory effects. *E. ulmoides* Oliv. bark, leaves and seeds all have anti-inflammatory activities. Flavonoids such as quercetin, isoquercitrin, kaempferol, iridoids such as aucubin, genipin, geniposidic acid, asperuloside, chlorogenic acid, and polysaccharides are the main anti-inflammatory components of *E. ulmoides* Oliv. [48,96].

For bark, Jiang et al. [97] verified the crude polysaccharides (EUPs) isolated from the stem bark of *E. ulmoides* Oliv. had beneficial effects on lupus-like syndrome in mice. Treatment with EUPs protected kidney from glomerular injury by reducing immunoglobulin deposition, lowering proteinuria, and inhibiting the production of serum autoantibodies and total immunoglobulin G. Li et al. [98] discovered a polysaccharide EUP1 stimulated Raw 264.7 cells to express mCD206 and a key anti-inflammatory cytokine IL-10. In the murine model of sepsis induced by lipopolysaccharide (LPS), administration of EUP1 effectively suppressed the expression of major inflammatory cytokines, alleviated lung injury and increased survival rate, which indicated EUP1 may become a valuable candidate for further development. Koh et al. [99] evaluated the effect of Cortex Eucommiae (CE) on the toll-like receptor (TLR)-4 pathway in LPS-stimulated RAW 264.7 murine macrophages. The results showed CE inhibited NO production without significant cytotoxicity, down-regulated both LPS-induced mRNA and protein expression of inducible nitric oxide synthase, COX-2, tumor necrosis factor-α, and interleukin-1β in a dose-dependent manner. CE suppressed LPS-induced activation of nuclear factor-κB (NF-κB) and the mitogen-activated protein kinase (MAPK) pathways, which together comprise the Myd88-dependent TLR-4 pathway. The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway was also down-regulated by CE. Moreover, CE suppressed LPS-induced activation of interferon-β and signal transducer and activator of transcription pathway, which was associated with the Myd88-independent TLR-4 pathway. Additional, Wang et al. [100] found *E. ulmoides* Oliv. cortex significantly decreased the number of Th17-positive cells in the spleen and IL-17, these results indicated the anti-inflammatory effect of *E. ulmoides* Oliv. cortex. For Leaves, the studies showed that *E. ulmoides* Oliv. leaves extracts inhibited LPS-stimulated NO and TNF-α production. Genipin exerted its anti-inflammatory effects through PI3K/Akt signaling pathway, whereas 4-(1,2-dimethoxyethyl) benzene-1,2-diol inhibited phosphorylation of p38 MAPK [96]. Hiramoto et al. [101] found consecutive oral administration of ELE, chlorogenic acid, or geniposidic acid significantly reduced UVB-induced suppression of the contact hypersensitivity response. The treatment with chlorogenic acid or geniposidic acid decreased the serum IL-10 levels in the sensitized mice after UVB irradiation. For seeds, Yang et al. [102] found that prophylactic oral administration of aucubin from seeds of *E. ulmoides* Oliv. significantly decreased TNF-α and IL-6. The findings demonstrated that aucubin shows protective effect against ethanol-induced acute gastric mucosal injury through its anti-inflammatory effects.

The underlying mechanisms mainly due to the regulatory effects of *E. ulmoides* Oliv. on production of interleukin, such as IL-1β, IL-6, IL-10 and serum IL-17 [100,103], pro-inflammatory cytokines, mediators, ROS, kinases such as p38 MAPKs, GSK-3β, signaling pathways, such as PI3K/Akt and TLR-4 pathways, and their downstream transcription factor, nuclear factor-κB [104].

3.6. Neuroprotective effects

Oxidative stress-mediated cellular injury, mitochondrial dysfunction and immune inflammation are the main causes of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). In recent years, more and more studies have shown the neuroprotective effects of *E. ulmoides* Oliv. in several experimental models. It could be potential drugs for treating neurodegenerative diseases. The main active compounds are chlorogenic acid, betulin, wogonin, oroxylin A, geniposidic acid, aucubin, ligand, and so on.

In 2011, Jang's group [105] made mice received a single intracerebroventricular injection of amyloid beta25–35 (Aβ25–35) as the critical factor in AD. Supplementation with aqueous extract of *E. ulmoides* Oliv. bark (EUE) significantly improved the Aβ25–35-induced memory deficit, and decreased the escape latencies with Aβ25–35-induced cognitive impairments. In the probe trial session, EUE increased time spent in the target quadrant. Importantly, EUE was found to inhibit acetylcholinesterase (AChE) activity in the in vivo and in vitro study. These results demonstrate that EUE possesses potent neuroprotective effects. Then, the studies showed EUE inhibited H_2O_2-induced up-or-down-regulation of cleaved poly-ADP-ribose polymerase (PARP), cleaved caspase-3, Bcl-2, Bcl-xL, and the release of cytochrome c from mitochondria to the cytosol, and significantly suppressed the phosphorylation of c-Jun N-terminal kinase (JNK), p38 MAPK, extracellular signal-regulated kinase1/2 (ERK1/2), and PI3K/Akt [106]. Later, they found EUE protects neuronal cells from apoptosis induced by PD-related neurotoxin, 6-hydroxydopamine (6-OHDA). The results showed that in addition to the above effects, EUE as well as chlorogenic acid blocked 6-OHDA-induced NF-κB nuclear translocation in SH-SY5Ycells [107]. *E. ulmoides* Oliv. can relieve neurodegenerative diseases by reducing oxidative stress, inhibiting mitochondrial dysfunction and immune inflammation. Hu et al. [108] found that the treatment of pheochromocytoma (PC12) cells with macranthoin G from *E. ulmoides* Oliv., prior to H_2O_2 exposure effectively increased the cell viability, and stabilized the mitochondria membrane potential. Furthermore, it enhanced the antioxidant enzyme activities, decreased MDA content, intracellular ROS, caspase-3 activation, cell apoptosis, and activated phosphorylation of the extracellular signal-regulated kinase (ERK). Additional, *E. ulmoides* Oliv. antagonized the loss of striatal neurotransmitters and relieved the associated anomaly in ambulatory locomotor activity in PD mice. Its compounds attenuated 1-methyl-4-phenylpyridinium-induced dysfunction of protease activity and reduced MG132-induced cytotoxicity [38]. Glaucoma is also a neurodegenerative disease. Lignans treatment could improve oxidative stress response in RGCs and retinas of glaucomatous rats via the activation of AMPK signaling. Lignans might be an alternative for the prevention and treatment of glaucomatous neurodegeneration [109]. Wang et al. [110] found that pretreatment with aucubin significantly changed the number of neurons in DG, Hilus, CA1 and CA3 hippocampal regions post status epilepticus. Meanwhile, it significantly inhibited necroptosis proteins (MLKL and RIP-1) and enhanced autophagy protein (Beclin-1 and LC3BII/LC3BI) prevalence in the hippocampus.

The mechanisms are mainly related to the effects of inhibition of oxidative stress, mitochondrial dysfunction and immune inflammation, as summarized as follows: (1) attenuation of oxidative stress through up- and down-regulation of pathways and the antioxidant enzyme activities [108], thereby protecting cells from neuronal cell death; (2) ameliorating the ubiquitin–proteasome system [38]; (3) reducing the number of apoptotic neurons and increasing the number of survival neurons by inducing autophagy and inhibiting necroptosis [110].

3.7. Effect on bone metabolism

Bone metabolic disorders can affect bone absorption and growth, leading to bone diseases. *E. ulmoides* Oliv. is one of the commonly used tonic drugs in the treatment of bone diseases such as fracture, which has the effects of regulating bone metabolism and anti-osteoporosis. Biological studies now support these traditional uses, of which *E. ulmoides* Oliv. extracts and total glycosides have mild anti-osteoporotic effects.

EUCE with graded doses has preventive effects on osteoporosis. Treatment at higher doses (300 or 500 mg/kg/day) was found to be able to significantly prevent ovariectomy (OVX) induced decrease in biomechanical quality of femur. The mechanical changes were associated with the prevention of a further bone mineral density (BMD) decrease or even with some improvements in microarchitecture. EUCE dose-dependently inhibited total BMD decrease in the femur caused by OVX, which was accompanied by a significant decrease in skeletal remodeling, as evidenced by the significantly decreased levels of the bone turnover markers osteocalcin (OC), alkaline phosphatase (ALP), deoxypyridinoline (DPD), urinary Ca and P excretions and receptor activator of nuclear factor-kappa B ligand (RANKL) were lower, and increased levels of serum osteoprotegerin (OPG) and OPG/RANKL ratio [111]. The highest doses (500 mg/kg/day) significantly prevents decrease in adipocyte volume/tissue volume (AV/TV), bone volume/tissue volume (BV/TV), connect density, trabecula number, bone marrow adipocyte number and trabecula thickness, which was also reported in the effects on bone density and bone strength of *E. ulmoides* Oliv. seeds. Besides, EUCE increased in trabecula separation and structure model index in OVX rats [112]. Pan et al. [113] also found EUCE could effectively prevent the bone loss and enhanced the biomechanical strength of bone and prevented the deterioration of trabecular bone microarchitecture. Additional, it significantly increased longitudinal bone growth rate and growth plate height in adolescent female rats, as well as BMP-2 and IGF-1 expressions in the proliferative and hypertrophic zones [114]. Lee et al. [115] confirmed the effects of *E. ulmoides* Oliv. on regulation of osteoclastic and osteoblastic differentiation. The expression of RANKL was significantly decreased, while that of OPG was significantly increased by *E. ulmoides* Oliv. treatment. In addition, runt-related transcription factor 2 and osterix expression were significantly increased. For leaves, Lin et al. [92] discovered the ethanol extracts of *E. ulmoides* Oliv. promoted the growth of MC3T3-E1 cells, and suppressed the H_2O_2-induced apoptosis in a rat MC3T3-E1 osteogenic cell model, likely due to the inhibition of caspases' activities. The results indicate that *E. ulmoides* Oliv. may contribute to the promotion of bone growth.

The underlying mechanisms may include the following points: (1) promoting effects on bone formation as well as inhibitory effects on bone resorption by stimulating the proliferation, differentiation and maturation of osteoblasts and inhibiting the growth of osteoclasts [115]; (2) improving bone biomechanical quality and strength through modifications of BMD, altering bone histomorphology and preventing the deterioration of trabecular bone microarchitecture [92,112,114].

3.8. Other effects

In addition to the above effects, *E. ulmoides* Oliv. also had hepatoprotective, kidney protective, anti-fatigue, anti-aging, sedative and hypnotic, antidepressant, cognition enhancement, immune regulation, uterine smooth muscle relaxation, erectile function improvement effects and so on. Many studies suggested the protective effects of *E. ulmoides* Oliv. and its active compound (such as protocatechuic acid) on liver damage in rats. It showed that treatment with *E. ulmoides* Oliv. extract could decrease the GOT, GPT, LDH, ALP, ALT and AST levels in serum. Administration of *E. ulmoides* Oliv. extract could significantly increase the activities of SOD, GSH, GPx, GRd and GST, and decrease the MDA content in liver. The biochemical biomarkers, total protein, albumin and total bilirubin were also restored forward normal level expression pattern of liver protein profile of rats. Moreover, P450 2E1 activation and ApoB accumulation were decreased and lysosomal enzymes activities was increased. Liver histopathology showed that it reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, cytoplasmic vacuolization, hepatic necrosis and fibrous connective tissue proliferated. These data suggested that oral administration with extract of *E. ulmoides* Oliv. for consecutive days can significantly relieve the chronic hepatotoxicity and decrease the hepatic damage induced by CCl_4, Bacille-Calmette-Guerin-lipopolysaccharide, thioacetamide and so on. It might be related to high phenolic content of *E. ulmoides* Oliv. extract which may have hepatoprotective effects in regulating liver proteins by scavenging free radicals [80,116–118]. Kidney injury is one of the most common complications of diabetes mellitus. Hyperglycemia can lead to severe nephropathy. Current studies have shown that the use of *E. ulmoides* Oliv. extract can reduce blood glucose, thereby effectively alleviating kidney damage [84,85]. *E. ulmoides* Oliv. bark, leaves, and male flower tea are found to have anti-fatigue effects. The findings showed that the extract of *E. ulmoides* Oliv. could significantly prolong weight-loaded swimming time, reduce blood lactic acid and blood ureanitrogen level, increase liver glycogen storage and enhance lactate dehydrogenase activity. Thus, *E. ulmoides* Oliv. can alleviate physical fatigue of mice. The anti-fatigue effects of *E. ulmoides* Oliv. is related to its anti-oxidative activity. There are many kinds of antioxidative components in *E. ulmoides* Oliv. leaves, such as flavones, polyphenols and so on [119–121]. The *E. ulmoides* Oliv. leaves extract has a marked anti-aging effects, followed by the bark extract. The granuloma formation and collagen synthesis were significantly increased by the administration of the extract of *E. ulmoides* Oliv. Besides, Nε-(carboxymethyl)lysine and Nω-(carboxymethyl)arginine formation were effectively inhibited during the incubation of gelatin with ribose to prevent age-related diseases. Geniposidic acid, aucubin, geniposide and isoquercetin were concluded to be the main effective components [122]. These results indicated that the oral intake of *E. ulmoides* Oliv. may inhibit the formation of AGEs, thereby representing a potential strategy to ameliorate age-related diseases [123]. Li et al. [124] discovered astragalin, a monomeric compound found in the leaves of *E. ulmoides* Oliv., showed significant effects on the central nervous system on mice, including reduced spontaneous activity, increased sleep ratio, shortened sleep latency and lengthened sleep time with a subthreshold or superthreshold dose of pentobarbital sodium. In addition, astragalin effectively reduced the convulsion rate and prolonged convulsion latency. These findings confirmed that astragalin had excellent sedative and hypnotic effects and has potential to be commercialized as a novel nutraceutical agent to promote calming and improve central nervous system-associated pathologies. Wu et al. [125] demonstrated that CGA was able to cross the blood-cerebrospinal fluid barrier to exhibit its neuron protection and promotion of serotonin release through enhancing synapsin I expression. More importantly, CGA on promoting 5-HT

release through enhancing synapsin I expression and CGA-enriched *E. ulmoides* Oliv. leaves extract has antidepressant-like effect in vivo. It may be developed as the natural drugs for the treatment of depression. *E. ulmoides* Oliv. extract significantly improved the impairment of short-term or working memory and reversed learning and memory deficits in mice. It significantly inhibited AChE and thiobarbituric acid reactive substance activities in the hippocampus and frontal cortex in a dose-dependent manner. Moreover, *E. ulmoides* Oliv. markedly increased brain-derived neurotrophic factor and phosphorylation of cAMP element binding protein in the hippocampus of scopolamine-induced mice [126]. These findings suggested that *E. ulmoides* Oliv. may be useful for the treatment of cognitive deficits by cholinergic signaling enhancement and/or protection.

4. Conclusion

In this review, we summarized the main active ingredients and pharmacological effects in different parts of *E. ulmoides* Oliv. for comprehensive utilization. The main active compounds of *E. ulmoides* Oliv. include geniposidic acid, geniposide, aucubin, asperuloside, chlorogenic acid, protocatechuic acid, syringin, quercetin, isoquercetin, astragalin, rutin, pinoresinol di-O-β-D-glucopyranoside and so on. Abundant active compounds make *E. ulmoides* Oliv. have various physiological activities and functions, including antihypertensive, hypolipidemic, antidiabetic, antioxidative, anti-inflammatory, neuroprotective, bone metabolism, hepatoprotective, kidney protective, anti-fatigue, anti-aging, sedative and hypnotic, antidepressant, enhancement of cognition, immune regulation, uterine smooth muscle relaxation, erectile function improvement effects. It has been indicated that other parts of *E. ulmoides* Oliv. have similar active compounds and pharmacological effects as the bark, suggesting they could replace the bark to some extent besides of their respective applications. We should make further use of advanced research methods to strengthen the chemical and interactive analysis of the active compounds of *E. ulmoides* Oliv., and elucidate the pharmaceutical mechanism, so as to make full use of the advantages of the unique resources and comprehensively promote the industrialization of authentic Chinese medicinal resources for production of health-care products.

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