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Food applications and health benefits of bioactive constituents in *Eucommia ulmoides*: a review

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ABSTRACT

Eucommia ulmoides is an important economic forest tree species in China, of which the different tissues and organs are widely used in traditional medicine for their abundant bioactive ingredients. Previous studies always focused on the *Eucommia* gum, a potential alternative to natural rubber because of its "rubber plastic duality". In recent years, *Eucommia* has increasingly attracted more attention and interest for its excellent nutritional and economic value, with the deepening of research and the development of products involving in the application of bioactive ingredients. However, the dietary health effects and future application prospects of the bioactive components of *E. ulmoides* have not been systematically summarized. Therefore, we firstly reviewed the main bioactive ingredients category, structural characteristics, extraction methods and nutritive value. Furthermore, we also summarized the wide application of bioactive ingredients in food and medicine fields. Finally, this review provides a comprehensive overview of the safety and future development of products derived from *E. ulmoides*, as well as exploring potential applications for its bioactive constituents, aiming to facilitate further extensive investigation into its utilization.

1. Introduction

Eucommia ulmoides, native to China, is a perennial woody plant of Eucommiaceae with a long cultivation history. Nowadays, *Eucommia* has been introduced to Japan, South Korea, America and many countries in Europe[1]. *Eucommia* thrives in sunny and humid environments, exhibits cold tolerance, and has minimal soil requirements for cultivation. The species has a broad distribution across central and southern regions, albeit in limited quantities within northwest China[2]. *Eucommia* is a veritable treasure trove, with its leaves (EUL), bark (EUB), seeds (EUS) and male flowers (EUMF) all having been utilized throughout the history of traditional medicine[3]. In particular, EUB is an important medicinal material for nourishing liver and kidney, strengthening tendons and bones, and soothing fetus[4]. EUL and EUMF also have edible and medicinal value, in which liriodendrin, aucubin and geniposidic acid extracts have been proved to have the effect of regulating blood pressure by inhibiting nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase[5]. It has been found that the therapeutic components of treatment are various bioactive ingredients contained in different tissues of *E. ulmoides*[6], and an increasing number of them have been successfully extracted from various parts of *E. ulmoides* with the continuous improvement of extraction and analytical technology. As the details of the structure and properties of these diverse components become increasingly clear, their application scope continues to expand[7].

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The modern development of effective components of *E. ulmoides* has made it a new resource for food industry and has promoted its application in food development[8]. For instance, *Eucommia* tea, which includes EUL tea and EUMF tea, has become a popular product as a traditional beverage due to its unique flavor and has obtained marketing approval[9]. However, up to now, the nutritional health and comprehensive utilization of *E. ulmoides* have not been reviewed in detail in the fields of food and health[10-12]. Therefore, we here comprehensively summarized the bioactive ingredients, extraction technology, food application, and improvement of *E. ulmoides*, and will continuously promote the health benefits of this plant.

2. Types of bioactive ingredients of *E. ulmoides*

For the past 50 years, *E. ulmoides* has been utilized for medicinal purposes without a clear understanding of its mechanisms. However, with the advent of metabolomics, researchers have conducted extensive investigations into the chemical constituents of *E. ulmoides* and have successfully isolated various bioactive substances from different organs and tissues. These compounds can be broadly categorized based on their chemical structures as lignans, iridoids, flavonoids, phenolics, and polysaccharides[13] (Table 1).

Table 1
Bioactive ingredients isolated from the barks, leaves, male flowers and seeds of *E. ulmoides.*

Source	Lignans[108-111]	Iridoids[108-109,112-115]	Flavonoids[113-119]	Phenolics[108,113,116-117,120-121]
Bark	Monoepoxylignans	Geniposide	Isoquercetin	(±)-Erythro-guaiacylglycerol
	(–)-Olivil	Geniposidic acid	Rutin	(–)-Epicatechin
	(–)-Olivil 4''-*O*-*β*-*D*-glucopyranoside	Genipin	Astragalin	(±)-Threo-guaiacylglycerol
	(–)-Olivil 4'-*O*-*β*-*D*-glucopyranoside	Aueubin	Quercetin	3-Hydroxy-4-methoxycinnamaladehyde
	(–)-Olivil 4',4''-*O*-*β*-*D*-glucopyranoside	Eucommiol	Quercitrin	Alternariol
	8-Hydroxypinoresinol	Eucommiol-I	Quercetin-3-*O*-*β*-*D*-sambubioside	Caffeic acid
	(+)-Cyclo-Olivil	Eucommioside-II	Quercetin-3-*O*-*α*-arabinosyl (1→2)-*β*-glucoside	Catechin
	Balanophonin	1-Deoxyeucommiol	Quercetin-3-*O*-galactoside(hyperin)	Chlorogenic acid
	Vladinol D	Epieucommiol	Kaempferol	Coniferol
	Bisepoxylignans	Deacetyl asperulosidic acid	Wogonoside	Cryptochlorogenic acid
	(+)-Medioresinol di-*O*-*β*-*D*-glucopyranoside	Asperulosidic acid	Wogonin	C-veratroylglycol
	Eucommin A	Eucomoside B	Luteolin	Erythro-guaiacylglycerol-*β*-coniferyl aldehyde ethe
	(+)-Pinoresinol	Harpagide	Avicularin	Eucophenoside
	(+)-Pinoresinol di-*O*-*β*-*D*-glucopyranoside	Catalpol	Oroxylin A	Ferulic acid
	(+)-Pinoresinol-*O*-*β*-*D*-glucopyranoside	Asperuloside	Baicalein	Isochlorogenic acid A
	Liriodendrin		(–)-Epicatechin	Isochlorogenic acid C
	(+)-Syringaresinol-*O*-*β*-*D*-glucopyranoside		Catechin	Licochalcone A
	(+)-Syringaresinol		(*αR*)-*α*,4,2',4'-tetrahydroxydihydrochalcone	Methyl chlorogenate
	(+)-1-Hydroxypinoresinol-4',4''di-*O*-*β*-*D*-glucopyranoside		(*αR*)-*α*-*O*-*β*-*D*-glucopyranoside-4,2',4'-trihydroxydihydrochalcone	Neochlorogenic acid
	(+)-1-Hydroxypinoresinol-4''-*O*-*β*-*D*-glucopyranoside		Isoliquiritigenin	*p*-Coumaric acid
	(+)-1-Hydroxypinoresinol-4'-*O*-*β*-*D*-glucopyranoside			Protocatechuic acid methyl ester
	(+)-Epipinoresinol			Salicifoliol
	(+)-l-Hydroxypinoresinol			Threo-guaiacylglycerol-*β*-coniferyl aldehyde ethe
	(+)-Medioresinol			Vanillic acid
	(+)-Pinoresinol-4-*O*-*β*-*D*-glucopyranosyl (1 → 6)-*β*-*D*-glucopyranoside			*β*-Hydroxypropiovanllone
	Neolignan			Chlorgenic acid methyl ester
	Dehydrodiconiferyl alcohol 4, *γ*'-di-*O*-*β*-*D*-glucopyranoside			Catechin-(7,8-b,c)-4*α*-(3,4-dihyxyphenyl)-2(3*H*)-pyranone
	Dehydrodiconiferyl alcohol *γ*'-di-*O*-*β*-*D*-glucopyranoside			Catechin-(7,8-b,c)-4*β*-(3,4-dihyxyphenyl)-2(3*H*)-pyranone
	Dihydroxydehy-drodiconiferyl alcohol			

Table 1 (*Continued*)

Source	Lignans[108-111]	Iridoids[108-109,112-115]	Flavonoids[113-119]	Phenolics[108,113,116-117,120-121]
	Threo-dihydroxydehy-drodiconiferyl alcohol barks			
	Erythro-dihydroxydehy-drodiconiferyl alcohol			
	Erythro-guaiacylglycerol-*β*-coniferyl aldehyde ether			
	Threo-guaiacylglycerol-*β*-coniferyl aldehyde ether			
	Citrusin B			
	Sesquilignan			
	(–)-Hedyotol C 4',4"-di-*O*-*β*-*D*-glucopyranoside			
	Syringylgylycerol-*β*-syringaresinol ether 4",4"'-*O*-*β*-*D*-glucopyranoside			
	Guaiacylglycerol-*β*-syringaresinol ether 4",4"'-di-*O*-*β*-*D*-glucopyranoside			
	(+)-Pinoresinol vanillic acid ether digluco-pyranoside			
	(+)-Syringaresinol vanillic acid ether diglu-copyranoside			
	Hedyotol C			
	Monoepoxylignans	Geniposide	Isoquercetin	3-(3,4-Dihydroxyphenyl) propionic acid
	Lariciresinol	Geniposidic acid	Rutin	3-(3-Hydroxyphenyl) propionic acid
	Bisepoxylignans	Aueubin	Astragalin	3,4-Dihydroxy benzoic acid
	(+)-Medioresinol di-*O*-*β*-*D*-glucopyranoside	Bartsioside	Quercetin	3-*O*-Feruloylquinic acid
	(+)-Pinoresinol di-*O*-*β*-*D*-glucopyranoside	Scandoside 10-*O*-acetate	Quercitrin	5,9-Dimethoxy-guaiacylglycerol
	8-Hydroxy-medioresinol	Ulmoidoside	Quercetin-3-*O*-*β*-*D*-sambubioside	5-Hydroxy-9-isopropylether-guaiacylglycerol
	8-Methoxy-medioresinol	Reptoside	Quercetin-3-*O*-*β*-*D*-xylopyranosyl	5-Methoxy-guaiacylglycerol
	(–)-Syringaresinol-4-*O*-*β*-*D*-glucopyranosidev	Ajugoside	Quercetin-3-*O*-*β*-*D*-xylopyranosyl (1→2)-*β*-*D*-glucopyranoside	7-Hydroxy-coumarin
	(+)-Syringaresinol	Harpagide acetate	Quercetin 3-*O*-galactoside(hyperin)	8'-Methoxy-olivil
	(+)-1-Hydroxy-6-epipinoresinol	Eucommiol	Kaempferol	9-*n*-Butyl-guaiacylglycerol
	(–)-7-Epi-pinoresinol mr1	Eucommiol-I	Kaempferide-3-*O*-*β*-*D*-glucopyranoside	9-*n*-Butyl-isoguaiacylglycerol
	(+)-Medioresinol	Eucommioside-II	Kaempferol-3-*O*-(6"-acetyl)-*β*-*D*-glucopyr-anoside	Caffeic acid
	(–)-Medioresinol	1-Deoxyeucommiol	Kaempferol-3-*O*-*α*-*L*-rhamnopyranosyl(1→6)-*β*-*D*-glucopyranoside	Caffeic acid ethyl ester
Leaves	(+)-Diapinoresinol	Epieucommiol	Kaemphferol-3-*O*-*β*-*D*-rutinoside (nicotiflorin)	Catechin
	(+)-Pinoresinol	Deacetyl asperulosidic acid	Luteolin	Catechol
	(+)-de4',4"-*O*-Dimethylepimagnolin A	Asperulosidic acid	Baicalein	Chlorgenic acid methyl ester
	Neolignan	Daphylloside	(2*S*,3*S*)-Taxifolin-3-*O*-*β*-*D*-glucopyranoside	Chlorogenic acid
	Threo-guaiacylglycerol-8-*O*-4'-sinapyl alcohol ether	Scandoside methyl ester	Catechin-(7,8-b,c)-4*α*-(3,4-dihydroxyphenyl)-2(3*H*)-pyranone	
	Sesquilignan	Loganin	Catechin-(7,8-b,c)-4*β*-(3,4-dihydroxyphenyl)-2(3*H*)-pyranone	Ferulic acid
	Cinchonain Ib	7-Epi-loganin	Thunberginol C	Gallic acid
	Firmianols B	8-Epi-loganin	Naringenin	Guaiacylglycerol
	Hedyotol C	Asperuloside		Isochlorogenic acid A
	Hedyotol D	Eucomoside A		Isochlorogenic acid C
		Eucomoside B		Methyl chlorogenate
		Eucomoside C		*p*-Coumaric acid
		Deacetyl asperulosidic acid methyl ester		Protocatechuic acid

Table 1 (*Continued*)

Source	Lignans[108-111]	Iridoids[108-109,112-115]	Flavonoids[113-119]	Phenolics[108,113,116-117,120-121]
		Ulmoside A		Pyrogallol
		Ulmoside B		Isochlorogenic acid B
		Ulmoside C		Protocatechuic acid methyl ester
		Ulmoside D		Methyl chlorogenate
		Asperuloside		
		Geniposide	Isoquercetin	Isochlorogenic acid A
		Geniposidic acid	Isorhamnetin-3-*O*-*β*-*D*-glucopyranoside	Isochlorogenic acid B
		Aueubin	Rutin	Isochlorogenic acid C
		Asperulosidic acid ethyl ester	Astragalin	Protocatechuic acid methyl ester
		Daphylloside	Quercetin	3-*O*-feruloylquinic acid
		3,4-Dihydro-3*β*-ethoxyasperuloside	Quercetin-3-*O*-*α*-arabinosyl (1→2)-*β*-glucoside	Caffeic acid
		3,4-Dihydro-3*β*-ethoxydesacetylasperuloside	Quercetin-3-*O*-*β*-*D*-glucopyranosyl (1→2)-*β*-*D*-glucopyranoside	Chlorgenic acid methyl ester
		3*β*-Methoxyartselawnin C	Kaempferol-3-*O*-(6"-acetyl)-*β*-*D*-glucopyranoside	Chlorogenic acid
Male Flowers		Artselaenin C	Naringenin	Ferulic acid
		Eucomoside A	Prunin	Methyl chlorogenate
		Eucomoside C	Kaempferol	
		Deacetyl asperulosidic acid methyl ester		
		6*β*-Hydroxyl-1*β*,3*β*-dimethoxyartsclaenin III		
		Eucomoside B		
		Eucommiol		
		Epieucommiol		
		Deacetylasperulosidic acid		
		Asperuloside		
		Geniposidic acid	Astragalin	Koaburaside
		Aueubin	Catechin	3-(3,4-Dihydroxyphenyl) propionic acid
		Ulmoidoside A	Isoquercitrin	Caffeic acid
		Ulmoidoside B	Rutin	Chlorogenic acid
		Ulmoidoside C	Procyanidin B2	Coniferin
		Ulmoidoside D	7,4'-Dihydroxyflavone	Epigallocatechin
		Scyphiphin D (SD)		Protocatechuic acid methyl ester
Seeds	(+)-Pinoresinol di-*O*-*β*-*D*-glucopyranoside	Eucommiol		Syringin
		Epieucommiol		Isochlorogenic acid A
		Deacetylasperulosidic acid		Isochlorogenic acid B
		Asperuloside		Isochlorogenic acid C
		Bartsioside		Chlorgenic acid methyl ester
				Ferulic acid
				O-Phthalic acid bis-(7-ethy-2-hydroxyethyl decyl)-ester
				O-Phthalic acid bis-(2-ethy decyl)-ester

2.1 Lignans

Lignin is a natural compound composed of 2 *β*,*β*'(8,8')-C linked phenyl-propanoid molecules (C3–C6 monomers)[12]. Most lignins is known to exist in *E. ulmoides* as *β*-*D*-glucopyranoside, which were mainly concentrated in EUB[7]. As the most widely studied and comprehensive compound class in *E. ulmoides*, a total of 49 types of lignin have been isolated, which can be divided into bisepoxylignans, monoepoxylignans, neolignans, sesquilignans according to their chemical structure[10,14] (Fig. 1). The pinoresinol diglucoside in lignin is an important index for quality control of cortex *Eucommiae*.

The lignin synthesis process can be divided into 3 stages: the first stage is the metabolic pathway of phenylpropyl, phenylalanine ammonia-lyase, which catalyzed the deamination of phenylalanine, and cinnamic acid 4-hydroxylase and 4-coumarate CoA ligase catalyzed the formation of *p*-coumarin acyl-CoA. The second stage involves the specific synthesis of *p*-coumarin acyl-CoA by shikimate/quinate hydroxy cinnamoyl transferase. This process is followed by the continuous catalysis of 3-hydroxylase, which leads to the formation of coniferyl alcohol. Additionally, cinnamoyl-CoA is also converted into cinnamyl alcohol by cinnamyl alcohol dehydrogenase. The third stage is the polymerization of monomers. Coniferyl alcohol forms lignin polymers through oxidation polymerization of peroxidases (POD)[15]. There are 10 key enzymes for lignan biosynthesis: phenylalanine ammonia-lyase, cinnamic acid 4-hydroxylase, 4-coumarate CoA ligase, cinnamoyl-CoA reductase, phenylalanine ammonia-lyase, cinnamic acid 4-hydroxylase, 4-coumarate coa ligase, cinnamoyl-CoA reductase, cinnamyl alcohol dehydrogenase, *p*-hydroxycinnamoyl-CoA, *p*-coumarate 3-hydroxylase, POD, dirigent, caffeoyl-CoA 3-*O*-methyltransferas[16]. Class III POD is involved in the lignification, disease resistance of plants, and the synthesis of lignin[17]. When the host plant is infected by pests and diseases, the POD expression will increase significantly to mediate regional and stereoselectivity during lignan synthesis[18].

2.2 Iridoids

Iridoids are monoterpene derivatives containing a cycloalkene ether bond and cyclopentane with a glucose moiety attached to C_1 in the pyran ring, the majority of which are concentrated in the EUL and EUB[13]. The synthesis of iridoids involves a series of chemical reactions initiated by citral, encompassing cyclization, double bond displacement, hydration, and oxidation to generate iridodial. Subsequent enolization and molecule condensation result in the formation of cycloalkene-derived iridoid alcohols that ultimately yield iridoids. As the second largest bioactive metabolite category, a total of 36 iridoids, including eucommiol, asperuloside, geniposidic acid, aucubin have been identified in *E. ulmoides*[19] (Fig. 2). The darkening of EUB during harvesting and drying is attributed to the inherent instability of hydroxy-furan rings and active double bonds[7]. The higher concentration of cyclic ether terpenes in fresh *E. ulmoides* compared to that after drying can be primarily attributed to their susceptibility to hydrolysis[12]. Moreover, eucommiol is a special component solely discovered in *E. ulmoides*, characterized by a highly specific schizocyclic iridoid terpenoid structure with an open ring and the absence of cycloalkene ether bond present in related compounds. The structure of eucommiol exhibits four hydroxyl groups, while its high polarity enables ease of solubility in water, methanol, and ethanol solvents.

2.3 Flavonoids

Flavonoids, significant bioactive compounds primarily distributed in EUMF and EUL, are known to accumulate as a response to external environmental stresses such as temperature fluctuations and ultraviolet radiation[20]. The content of flavonoids varies significantly among different organs and tissues of *E. ulmoides*, with the highest concentration being found in leaves, particularly mature leaves, where it can reach up to 6.05%[19]. Flavonoids consist of 2 benzene rings connected by 3 intermediate carbon atoms with a phenolic hydroxyl group. The majority of flavonoids are derivatives of chromone or chroman, featuring a core structure consisting of 2 benzene rings connected by 3 intervening carbon atoms and possessing a phenolic hydroxyl group. Substituted hydroxyl groups on flavonoids exhibit pharmacological effects, while the B-ring hydroxyl groups have antioxidant effects and glycosyl-substituted flavonoids show better anti-inflammatory effects than phenolic hydroxyl-substituted ones. A total of 7 subclasses of flavonoids, namely flavone, flavonol, flavanone, flavanonol, anthocyanidin, flavanol and isoflavone have been isolated. These subclasses contain approximately 43 metabolites with the primary components being quercetin, kaempferol, astragalus and rutin[21] (Fig. 3). Chalcone and flavonol synthases play crucial roles in the biosynthesis of flavonoids. In the case of quercetin, phenylalanine is converted to caffeoyl-CoA through the catalytic action of phenylalanine ammonia-lyase and coumarate-CoA ligase. The condensation reaction between one molecule of caffeoyl-CoA and three molecules of malonyl-CoA catalyzed by chalcone synthase leads to the formation of chalcone, which is subsequently transformed into naringenin by chalcone isomerase and further converted into dihydrokaempferol by flavonol 3-hydroxylase. Dihydrokaempferol undergoes conversion to dihydroquercetin *via* flavonoid 3-hydroxylase before finally being converted to quercetin by flavonol synthase. Moreover, flavonoids also serve as a critical indicator for evaluating the quality of EUB.

2.4 Phenolics

Phenolics are aromatic compounds in which the hydrogen of the benzene ring is substituted by a hydroxyl group[22]. The antioxidant activity of phenolics is determined by the position and quantity of phenolic hydroxyl groups, with ortho-hydroxyl groups exhibiting stronger antioxidant activity compared to intersite and parapace hydroxyl groups. Furthermore, modifications such as methylation and glycosylation of phenolic hydroxyl groups can alter their molecular structure and affect antioxidant activity. Currently, 46 phenolic compounds belonging to the class of phenylpropanoids have been identified in *E. ulmoides* (Fig. 4). Some of these compounds act as precursors for lignans and flavonoids, primarily found in the root bark, stem bark, and leaves of *E. ulmoides*[7]. These derivatives can form glycosides or esters through combination with sugars or polyols within plants. Among them, chlorogenic acid has been extensively studied due to its strong physiological activities, including neuroprotective effects[23]. It is predominantly present in EUL at a concentration ranging 1%−5.5% and often serves as a standard marker for evaluating the quality of EUL and medicinal

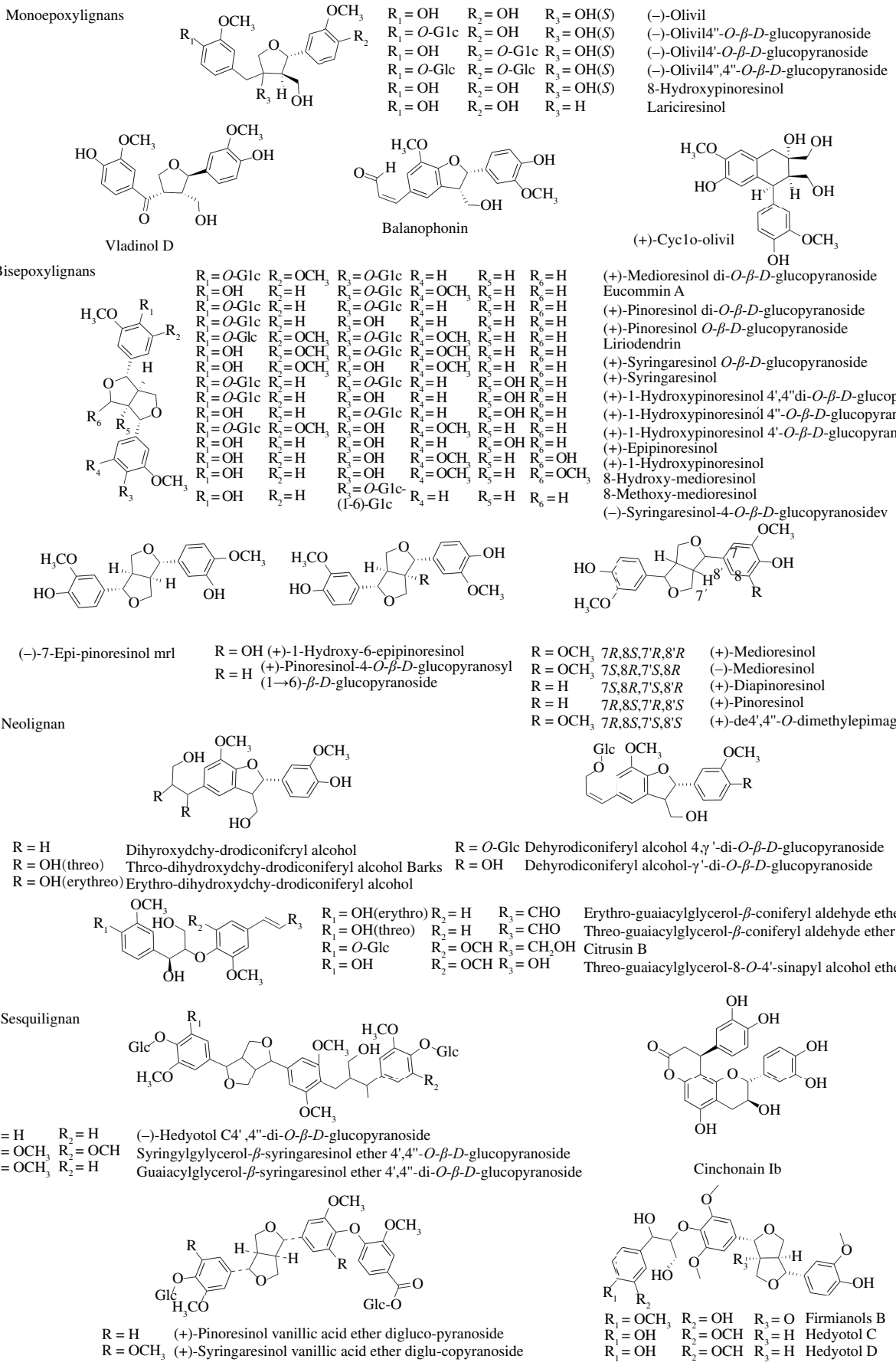
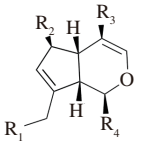
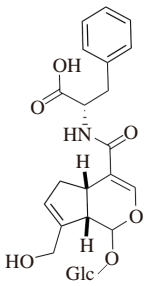


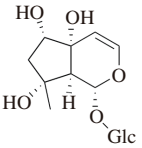
Fig. 1 Chemical structure of lignans in *E. ulmoides.*



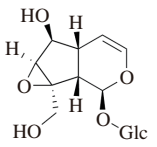
R_1 = OH	R_2 = H	R_3 = $COOCH_3$	R_4 = *O*-Glc	Geniposide
R_1 = OH	R_2 = H	R_3 = COOH	R_4 = *O*-Glc	Geniposidic acid
R_1 = OH	R_2 = H	R_3 = $COOCH_3$	R_4 = OH	Genipin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = *O*-Glc	Aueubin
R_1 = OH	R_2 = H	R_3 = H	R_4 = *O*-Glc	Bartsioside
R_1 = $OOCCH_3$	R_2 = OH	R_3 = COOH	R_4 = *O*-Glc	Scandoside-10-*O*-acetate
R_1 = OH	R_2 = *O*-*α*-*D*-Glc	R_3 = H	R_4 = OH	Ulmoidoside



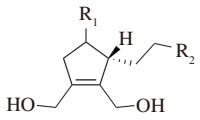
Eucomoside B



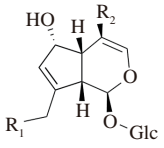
Harpagide



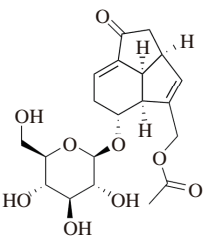
Cartalpol



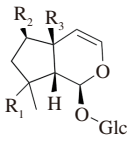
R_1 = OH(R	R_2 = OH	Eucommiol
R_1 = OH	R_2 = *O*-Glc	Eucommiol-I
R_1 = *O*-Glc	R_2 = OH	Eucommioside-II
R_1 = H	R_2 = OH	1-Deoxyeucommiol
R_1 = OH(*S*)	R_2 = OH	Epieucommiol



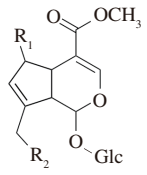
R_1 = OH	R_2 = COOH	Deacety1 asperulosidic acid
R_1 = $OOCCH_3$	R_2 = COOH	Asperulosidic acid
R_1 = $OOCCH_3$	R_2 = $COOCH_2CH_3$	Asperulosidic acid ethy1 ester



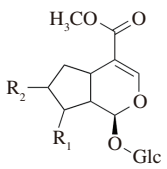
Asperuloside



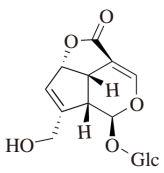
R_1 = OH	R_2 = OH	R_3 = H	Reptoside
R_1 = OH	R_2 = OH	R_3 = H	Ajugoside
R_1 = $OOCCH_3$	R_2 = OH	R_3 = OH	Harpagide acetate



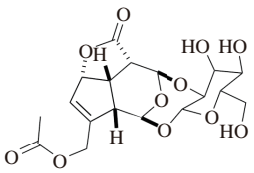
R_1 = OH(*S*)	R_2 = $OOCCH_3$	Daphylloside
R_1 = OH(*R*)	R_2 = OH	Scandoside methyl ester



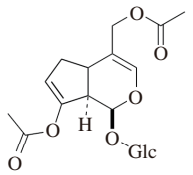
R_1 = CH_3(*R*)	R_2 = OH(*R*)	Loganin
R_1 = CH_3(*R*)	R_2 = OH(*S*)	7-Epi-loganin
R_1 = CH_3(*S*)	R_2 = OH(*R*)	8-Epi-loganin



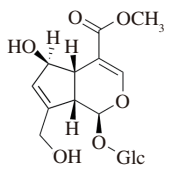
Asperuloside



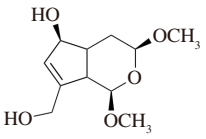
Eucomoside A



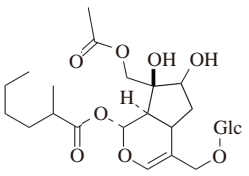
Ulmoside C



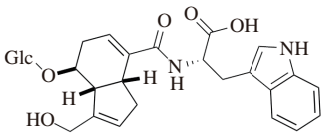
Deacetyl asperulosidec acid methyl ester



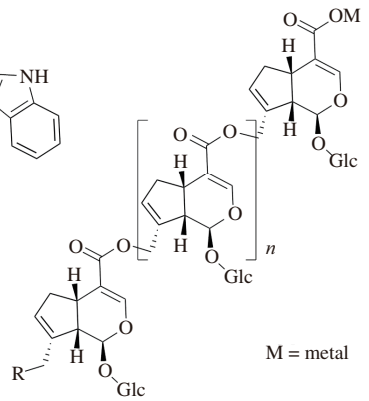
6*β*-Hydroxyl-l*β*,3*β*-dimethoxyartsclaenin III



Ulmoside D

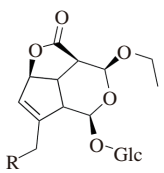


Eucomoside B

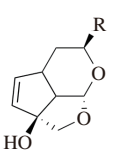


M = metal

n = 1	R = OH	Ulmoidoside A
n = 1	R = $OOCCH_3$	Ulmoidoside B
n = 2	R = OH	Ulmoidoside C
n = 2	R = $OOCCH_3$	Ulmoidoside D

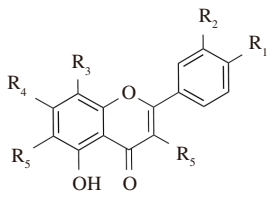


R = $OOCCH_3$	3,4-Dihydro-3*β*-ethoxyasperuloside
R = OH	3,4-Dihydro-3*β*-ethoxyesacetylasperuloside

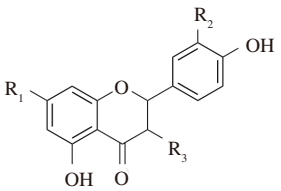


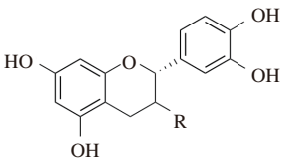
R = OCH_3	3*β*-Methoxyartselawnin C
R = OH	Artselaenin C

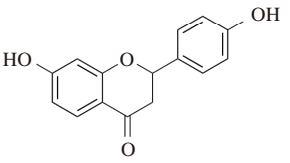
Fig. 2 Chemical structure of iridoids in *E. ulmoides.*



R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc	Isoquercetin
R_1 = OH	R_2 = OCH_3	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc	Isorhamnetin-3-*O*-*β*-*D*-glucopyranoside
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Rut	Rutin
R_1 = OH	R_2 = H	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc	Astragalin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = OH	Quercetin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Man	Quercitrin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Sam	Quercetin 3-*O*-*β*-*D*-sambubioside
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Xyl	Quercetin 3-*O*-*β*-*D*-xylopyranosyl
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc(1→2)-Ara	Quercetin 3-*O*-*α*-arabinosy1(1→2)-*β*-glucoside
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Xyl(1→2)-Glc	Quercetin-3-*O*-*β*-*D*-xylopyranosyl (1→2)-*β*-*D*-glucopyranoside
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc(1→2)-Glc	Quercetin-3-*O*-*β*-*D*-glucopyranosyl (1→2)-*β*-*D*-glucopyranoside
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Gal	Hyperin
R_1 = OH	R_2 = H	R_3 = H	R_4 = OH	R_5 = H	R_6 = OH	Kaempferol
R_1 = OCH_3	R_2 = H	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Glc	Kaempferide-3-*O*-*β*-*D*-glucopyranoside
R_1 = OH	R_2 = H	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-6"-acetyl-Glc	Kaempferol-3-*O*-(6"-acetyl)-*β*-*D*-glucopyr-anoside
R_1 = OH	R_2 = H	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Rha(1→6)-Glc	Kaempferol-3-*O*-*α*-*L*-rhamnopyranosy1 (1→6)-*β*-*D*-glucopyranoside
R_1 = OH	R_2 = H	R_3 = H	R_4 = H	R_5 = H	R_6 = *O*-Rha(1→6)-Glc	Nicotiflorin
R_1 = H	R_2 = H	R_3 = OCH_3	R_4 = *O*-Glc	R_5 = H	R_6 = H	Wogonoside
R_1 = H	R_2 = H	R_3 = OCH_3	R_4 = OH	R_5 = H	R_6 = H	Wogonin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = H	Luteolin
R_1 = OH	R_2 = OH	R_3 = H	R_4 = OH	R_5 = H	R_6 = *O*-Ara	Avicularin
R_1 = H	R_2 = H	R_3 = H	R_4 = OH	R_5 = OCH_3	R_6 = H	Oroxylin A
R_1 = H	R_2 = H	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	Baicalein



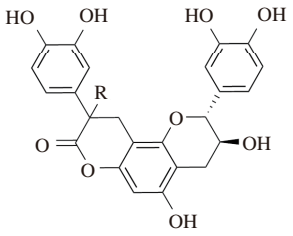


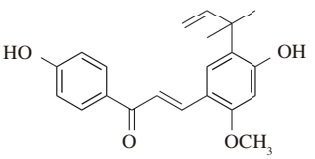


7,4'-Dihydroxyflavon

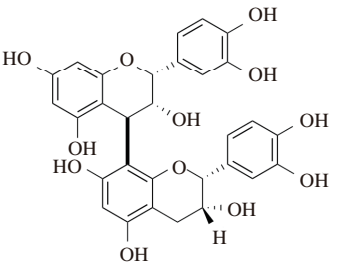
R = OH(*S*) (−)-Epicatechin
R = OH(*S*) Catechin

R_1 = OH	R_2 = H	R_3 = H	(2*S*,3*S*)-Taxifolin-3-*O*-*β*-*D*-glucopyranoside
R_1 = *O*-Glc	R_2 = H	R_3 = H	Naringenin
R_1 = OH	R_2 = OH	R_3 = *O*-Glc	Prunin



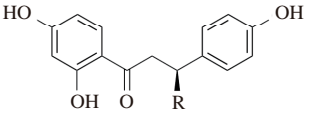


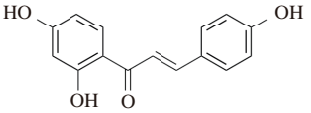
Thunberginol C



Procyanidin B2

R = H(*S*) Catechin-(7,8-b,c)-4*α*-(3,4-dihydroxyphenyl)-2(3*H*)-pyranone
R = H(*S*) Catechin-(7,8-b,c)-4*β*-(3,4-dihydroxyphenyl)-2(3*H*)-pyranone

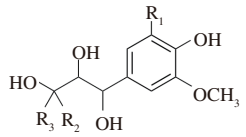




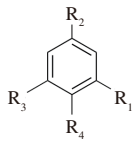
Isoliquiritigenin

R = OH (*αR*)-*α*,4,2',4'-Tetrahydroxydihydrochalcone
R = *O*-Glc (*αR*)-*α*-*O*-*β*-*D*-Glucopyranoside-4,2',4'-trihydroxydihydrochalcone

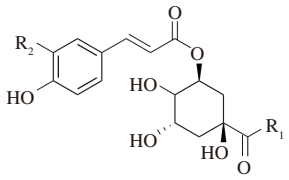
Fig. 3 Chemical structure of flavonoids *in E. ulmoides.*



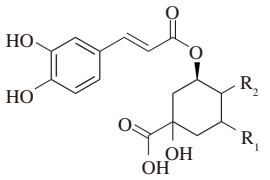
R_1 = H(erythro)	R_2 = H(erythro)	R_3 = H(erythro)	(±)-Erythro-guaiacylglycerol
R_1 = H(threo)	R_2 = H(threo)	R_3 = H(threo)	(±)-Thero-guaiacylglycerol
R_1 = OCH_3	R_2 = H	R_3 = H	5,9-Dimethoxy-guaiacylglycerol
R_1 = OH	R_2 = H	R_3 = $CH(CH_3)_2$	5-Hydroxy-9-isopropylether-guaiacylglycerol
R_1 = OCH_3	R_2 = H	R_3 = H	5-Methoxy-guaiacylglycerol
R_1 = H	R_2 = $C(CH_3)_3$	R_3 = H	9-M-butyl-guaiacylglycerol
R_1 = H	R_2 = H	R_3 = $C(CH_3)_3$	9-N-butyl-isoguaiacylglycerol



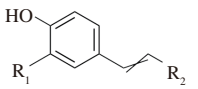
R_1 = OH	R_2 = CH_2CH_2COOH	R_3 = H	R_4 = OH	3-(3,4-Dihydroxyphenyl) propionic acid (dihy drocaffeic acid)
R_1 = OH	R_2 = CH_2CH_2COOH	R_3 = H	R_4 = H	3-(3-Hyroxyphenyl) propionic acid
R_1 = OH	R_2 = COOH	R_3 = H	R_4 = OH	3,4-Dihydroxy benzoic acid
R_1 = H	R_2 = CH=CHCHO	R_3 = OH	R_4 = OCH_3	3-Hyroxy-4-methoxycinnamaladehyde
R_1 = OH	R_2 = $CH=CHCOOCH_2CH_3$	R_3 = H	R_4 = OH	Caffeic acid ethyl ester
R_1 = H	R_2 = H	R_3 = OH	R_4 = OH	Catechol
R_1 = OCH_3	R_2 = $COCH(OH)CH_2OH$	R_3 = H	R_4 = OH	*C*-Veratroylglycol
R_1 = H	R_2 = CH=CHCOOH	R_3 = OCH_3	R_4 = OH	Ferulic acid
R_1 = H	R_2 = COOH	R_3 = OH	R_4 = OH	Protocatechuic acid
R_1 = H	R_2 = $COOCH_3$	R_3 = OH	R_4 = OH	Protocatechuic acid methyl ester
R_1 = OH	R_2 = COOH	R_3 = OH	R_4 = OH	Pyrogallol
R_1 = H	R_2 = COOH	R_3 = OCH_3	R_4 = OH	Vanillic acid
R_1 = H	R_2 = $COCH_2CH_2OH$	R_3 = OCH_3	R_4 = OH	*β*-Hydroxypropiovanllone



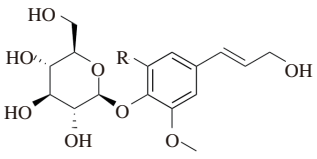
R_1 = OH	R_2 = OCH_3	3-*O*-feruloylquinic acid
R_1 = OH	R_2 = OH	Chlorogenic acid
R_1 = OCH_3	R_2 = OH	Chlorgenic acid methyl ester
R_1 = OCH_3	R_2 = OH	Methyl chlorogenate



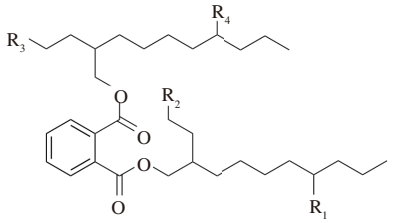
R_1 = H	R_2 = Caffeoyl	Isochlorogenic acid A
R_1 = Caffeoyl	R_2 = H	Isochlorogenic acid C
R_1 = OH	R_2 = OH	Neochlorogenic acid



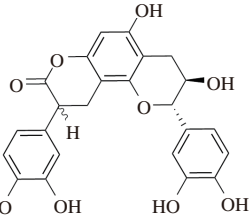
R_1=OH	R_2=COOH	Caffeic acid
R_1=OCH_3	R_2=CH_2OH	Coniferol
R_1=H	R_2=COOH	*p*-Counmaric



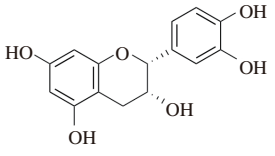
R = H	Coniferin
R = OCH_3	Syringin



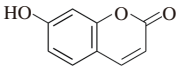
R_1 = H	R_2 = H	R_3 = H	R_4 = H	*O*-Phthalic acid bis-(2-ethy decyl)-ester
R_1 = CH_2CH_3	R_2=OH_2	R_3=OH	R_4=CH_2CH_3	*O*-Phthalic acid bis-(7-ethy-2-hydroxyethyl decyl)-ester



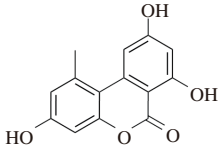
4*α*-*H* Catechin-(7,8-b,c)-4*α*-(3,4-dihyxyphenyl)-2(3*H*)-pyranone
4*β*-*H* Catechin-(7,8-b,c)-4*β*-(3,4-dihyxyphenyl)-2(3*H*)-pyranone



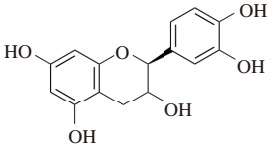
(–)Epicatechin



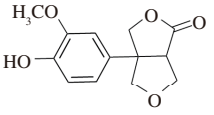
7-Hydroxy-coumarin



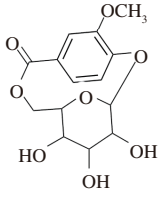
Alternariol



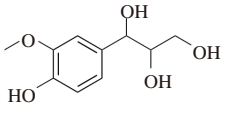
Catechin



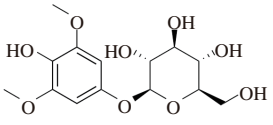
Cryptochlorogenic acid



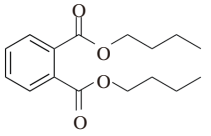
Eucophenoside



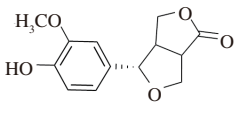
Guaiacylglycerol



Koaburaside



Phthalic acid dibutyl ester



Salicifoliol

Fig. 4 Chemical structure of phenolics in *E. ulmoides*.

extracts[3]. Phenylalanine dehydrogenase lyase (PAL) plays a pivotal role in the biosynthesis of chlorogenic acid. Remarkably high PAL polymorphism was observed in both fruit and leaf tissues of *E. ulmoides*, with at least 12 gene families identified. In the chlorogenic acid synthesis, pathway, shikimate hydroxycinnamoyl transferase (HCT) has been recognized as a rate-limiting enzyme with three *EuHCT* gene family members present in *E. ulmoides*.

2.5 Polysaccharides

Polysaccharides, such as cellulose, peptidoglycan, and starch, are biomacromolecules present in plant cells[24]. In *E. ulmoides*, the polysaccharides can be mainly classified into sucrose, eucomman A, and eucomman B. Eucomman A is an acidic polysaccharide composed of *L*-arabinose, *L*-rhamnose, *D*-galactose, *D*-glucose, galacturonic acid with small peptide moieties. Eucomman B is formed by the combination of *α*-1,2-*L*-rhamnose and *α*-1,4-*D*-galactose[12]. The polysaccharides extracted from EUL appear as a pale tasteless powder that dissolves in water but remains insoluble in highly concentrated organic solvents. The differences in chemical structure and metabolic processes account for the variation in monosaccharide composition between EUB and EUL polysaccharides. *E. ulmoides* polysaccharides primarily consist of complex carbohydrates with glucose units derived from xylan main chains along with other monosaccharide constituents[25]. Compared to EUL, the ratio of glucose to other monosacharides appears relatively lower within EUS due to its more intricate structure.

2.6 Eucommia ulmoides gum (EUG)

The main component of EUG, a natural polymer material, is *trans*-1,4-polyisoprene, which is also isomers of natural rubber molecules[26]. The macromolecules of EUG with a trans-structure have a tendency to stack and crystallize, resulting in distinct characteristics compared to natural rubber. The flexible long chain structure of EUG exhibits elastic properties at temperatures ranging from 40 to 50 ℃, with a softening point around 60 ℃ and viscosity at 100 ℃. EUG crystals exist in 2 primary forms: *α*-crystals with a melting point of 64 ℃ and *β*-crystals with a melting point of 57 ℃[27]. Transformation between the *α*- and *β*-crystal structures depends on specific conditions. During cold crystallization, the *β*-crystals condense below −50 ℃; however, they rapidly convert into *α*-crystals due to their instability[28]. Conversely, stretching can induce the transformation from *α*-crystals to *β*-crystals. Due to its abundant double bonds, flexible molecular chain structure, and symmetrical ordered crystal structure[29]. The EUG exhibits unique dual properties as both rubber-like elastic materials and thermoplastic polymers. It has been found in various tissues and organs, with the highest content observed in EUS and EUB at approximately 17%. Notably, the EUG possesses characteristics such as wear resistance, tear resistance, low-temperature plasticity along with shape memory capabilities[30].

3. Extraction of bioactive ingredients from *E. ulmoides*

The thorough investigation into a wide range of bioactive components greatly depends on the rapid progress of modern extraction technology. With the enhanced utilization rate of bioactive compounds derived from *E. ulmoides*, further advancements have been made in the extraction technology for these compounds. Currently, the commonly employed methods for extracting bioactive ingredients are as follows (Table S1).

3.1 Solvent extraction method

The process of solvent extraction can be classified into 2 main categories: leaching and reflux extraction, with leaching further divided into hot and cold methods. Hot leaching offers the advantages of shorter extraction time and higher yield compared to cold leaching, whereas high temperatures may lead to degradation of certain extracts. Reflux extraction is primarily employed for the recovery of organic extractants through high-temperature evaporation and refluxing; nevertheless, it is not suitable for extracting thermally labile substances.

The extraction techniques that employ water and organic solvents as extractants are commonly referred to as solvent extraction[31]. Water extraction is an early and widely utilized technique for extracting bioactive substances from *E. ulmoides* due to its advantages of simplicity, non-toxicity, and low cost. However, the simple water extraction method yields a low rate of substance extraction and fails to meet the requirements for partial extraction. Therefore, based on the principle that most substances in plant cells can be dissolved in organic solvents, some organic solvents such as ethanol, acetaldehyde and methanol have been found effective as extractors. Currently, flavonoids, chlorogenic acid and polysaccharides can be effectively extracted using an ethanol solution. For example, by implementing an enhanced extraction process with a water-to-raw material ratio of 1:3 repeated three times over an extraction time of 80 min a maximum yield of *E. ulmoides* polysaccharides polysaccharides reaching 23.9% was achieved[32]. Despite the potential high efficiency in substance extraction exhibited by organic solvent extracts, most organic solvents are challenging to recover and possess toxicity risks that can jeopardize human health. Consequently, auxiliary techniques such as ultrasonic, microwave, and supercritical extractions are frequently employed in conjunction with bioactive substance extractions.

3.2 Ultrasonic-assisted extraction

The ultrasonic-assisted extraction method employs ultrasonic mechanical vibration and cavitation effects to disrupt the structure of plant cells, facilitating solvent penetration and enhancing extraction efficiency. The aforementioned method is characterized by its efficiency, non-toxicity, time-saving nature, and ability to effectively extract terpenes, alkaloids, flavonoids, lipids, and other natural plant components at low temperatures while preserving the properties of heat-sensitive compounds. The addition of ultrasonic waves increased the extraction rate of total flavonoids of EUL from 0.75% to 3.8%[33], resulting in a maximum polysaccharide content of 164.95 mg/g[34], and the chlorogenic acid was 24.46 mg/g[35]. The antioxidant experiment showed that the extracted chlorogenic acid had good antioxidant activity.

3.3 Microwave-assisted extraction method

The microwave-assisted extraction method is based on the thermal characteristics of microwaves, which penetrate cell walls to disrupt cellular structures and facilitate solvent interaction with the extraction matrix, thereby enhancing extraction efficiency[36]. Due to high efficiency, non-toxic, and time-saving properties, this

method is suitable for extracting chlorogenic acid, geniposidic acid, polysaccharides, and flavonoids. However, it may not be suitable for industrial applications due to the requirement of high input in terms of extraction equipment and low processing capacity. The Plackett-Burman design was used to screen the 3 key factors of microwave-assisted extraction, and then Box-Behnken response surface method was employed to optimize the extraction process. As the result, the final polysaccharide yield was 4.02%[37]. The microwave induction technology optimized the extraction process of EUL polysaccharide effectively, and the maximum extraction yield reached 1.29%, which was 2.9 times that of traditional hot reflux extraction method[38].

3.4 Enzyme-assisted extraction

In the process of enzyme extraction, enzymes act as reaction catalysts that effectively enhance the rate of solvent extraction reactions. For example, cellulase can degrade hemicellulose, cellulose, and other substances present in plant cell walls to reduce resistance to reagent entry into cells and increase the extraction efficiency[39]. Enzyme-assisted extraction can be performed under mild conditions while effectively preserving the activity of the substance and offering ease of operation. The polysaccharide was extracted from EUL using ultrasound-assisted enzymatic extraction, resulting in a 4.79% yield of polysaccharide[40]. The contents of soluble phenols and flavonoids were increased by 103.1% and 81.7% respectively, and the bioactivities of quercetin and kaempferol were increased by 3.5 and 2.2 times, respectively[41].

3.5 Supercritical fluid extraction

Supercritical fluid extraction involves the utilization of liquid extractants under supercritical conditions to selectively extract specific components from solids or liquids[42]. The technique modifies the density of critical fluids by manipulating temperature and pressure, thereby disrupting cell walls and enhancing solvent extraction rates. It is particularly suitable for extracting rhinanthin, flavonoids, and EUS oil. CO_2 serves as an excellent supercritical fluid extractant due to its innocuousness, harmlessness, and moderate critical conditions[39]. The optimal extraction results for flavonoids from EUL were achieved using supercritical CO_2 as the extraction agent with the addition of 3.5 mL/g ethanol at an 80% concentration as an entrainer[43]. Despite its substantial energy consumption limiting its application, supercritical fluid extraction technology exhibits high efficiency in extraction of different metabolites.

4. Application of the bioactive ingredients of *E. ulmoides*

The *E. ulmoides* species is distinguished by its abundant bioactive constituents and exhibits one of the highest concentrations of phenolic compounds, including chlorogenic acid and flavonols, among all known metabolites[44]. With significant advancements in applied research and continuous product evolution, alongside the traditional utilization of EUB in Chinese medicine, its leaves, male flowers, and seeds have been developed and utilized. In recent years, the application of *E. ulmoides* has extended to include food production, animal feed supplementation as well as natural preservatives.

4.1 Medicines

The medicinal value of *E. ulmoides* has been documented as early as in the *Shennong Herbal Scripture and Compendium of Materia Medica.* In *Compendium of Materia Medica*, *E. ulmoides* is listed for its kidney-tonifying, tendons-strengthening bone-reinforcing, and miscarriage-preventing effects. According to modern medicine, EUB exhibits properties such as hypoglycemic, hypolipidemic, and antihypertensive effects along with anti-aging, anti-fatigue, anticancer, antioxidant, antibacterial and antiviral activities (Table 2). It also promotes bone tissue regeneration and improves memory function while inducing sedation and hypnosis[45]. The broad spectrum of bioactivity exhibited by *E. ulmoides* renders it a promising therapeutic agent that has found extensive application in clinical treatment (Fig. 5).

4.1.1 Regulating cardiovascular system

The main bioactive components of *E. ulmoides* extracts (EUE) include flavonoids, phenylpropane, lignans, iridoids, etc., which can effectively down-regulate the transformed proteins Ras homolog family member A (RhoA) and Rho-associated protein kinase (ROCK) to significantly reduce blood pressure and promote cardiovascular health[45] (Fig. 5A). Flavonoids such as quercetin, rutin and baicalin exhibit inhibitory properties against angiogenesis and vasoconstriction regulation. For example, quercetin mitigates vasoconstriction by activating the nitric oxide (NO)/soluble guanylyl cyclase (sGC)/cyclic guanosine monophosphate (cGMP) pathway, stimulating endothelial NO production and release, reducing the expression of endothelin-1 (ET-1), and modulating K^+ and Ca^{2+} channels to regulate vascular tone[46]. Rutin exhibits anti-thrombotic effects by inhibiting intravascular platelet aggregation and suppressing vascular endothelial growth factor, thereby contributing positively to the prevention of atherosclerosis. Baicalin possesses preventive properties against cardiovascular diseases through its ability to reduce blood pressure, stimulate the synthesis of vascular endothelial NO, and enhance vasodilation[47]. Phenylpropionic acids such as ferulic acid and caffeic acid can increase the activity of free radical enzymes and NO, and promote vasodilation. Ferulic acid effectively inhibits AngII-induced proliferation of vascular smooth muscle cells, reduces endothelial repair function and prevents an increase of blood pressure in case of vascular lumen stenosis[48]. Additonally, ferulic acid also enhances the activity of antioxidant enzymes such as superoxide dismutase (SOD), CAT and glutathione peroxidase (GSH-Px) to exert its antioxidant capacity, thereby reducing the formation of atherosclerotic plaque[49]. Caffeic acid effectively inhibits active oxide production and booststhe level of the antioxidant system. Consequently, it improves myocardial injury induced by isoproterenol and reduces cardiac lipid peroxide products. The antihypertensive activities of iridoids primarily manifest through their anti-inflammatory and antioxidant properties, exemplified by gardenioside acid, aucuboside, chlorogenic acid, and caffeic acid[50]. Additionally, genipin and geniposide exhibit the ability to attenuate thrombus formation by inhibiting endothelial exocytosis, reducing von Willebrand factor release, and impeding P-selectin translocation. Consequently, these compounds effectively diminish platelet adhesion and aggregation while mitigating thrombus formation. Lignins primarily reduce blood pressure by inhibiting the activity of aldose reductase, while pinoresinol diglucoside and eugenol diglucoside achieve

Table 2
Medicinal ingredients and effects of *E. ulmoides*.

Compounds	Class I	Part	Mechanism	Reference
Regulating cardiovascular system				
Rutin	Flavonoids	Bark, leaves	Inhibiting intravascular platelet aggregation	[45]
Quercetin	Flavonoids	Bark, leaves	Modulating vascular tone, mitigating vasoconstriction	[46]
Baicalin	Flavonoids	Bark, leaves	Facilitating NO synthesis in vascular endothelium	[47]
Ferulic acid	Phenolics	Bark, leaves	Attenuating atherosclerotic plaque formation	[48-49]
Caffeic acid	Phenolics	Bark, leaves	Ameliorating myocardial damage caused by isoproterenol	[50]
Genipin	Iridoid	Bark, leaves	Suppressing endothelial cell exocytosis	[51]
Eugenol diglucoside	Lignin	Bark	Adjusting plasma levels of endothelin and NO	[51]
Betulinic acid	Others	Bark, leaves	Augmenting NO concentration within endothelial cells.	[51]
Aucubin	Iridoid	Bark, leaves	Counteracting oxidative stress during cardiac remodeling	[125]
Anti-osteoporotic				
Rhodoerythrin	Iridoid	Leaves	Triggering AMPK signaling to counteract steroid-induced osteoblast apoptosis	[53]
Gardenioside	Iridoid	Bark	Fostering osteoblast differentiation	[54]
Quercetin	Flavonoid	Bark	Inhibiting iron overload-induced apoptosis	[58]
Polysaccharide	Others	Bark, leaves	Facilitating subchondral bone reconstruction	[59]
Anti-inflammatory activity				
Aucubin	Iridoid	Bark, leaves	Mitigating lipopolysaccharide-induced inflammation and apoptosis	[44]
Rutin	Flavonoid	Leaves	Exhibiting cytoprotective effects	[60]
Polyphenol	Others	Leaves	Reducing MDA content in serum and liver tissues	[67]
Remission of neurodegeneration				
Diepoxylignans	Lignin	Leaves	Activating the PI3K/Akt/GSK-3β/Nrf2 signaling pathway	[68]
Rhodoerythrin	Iridoid	Leaves	Protecting dopaminergic neurons while reducing inflammation	[69]
Ulmoidol	Others	Leaves	Activating PU.1 transcriptional signaling pathway	[70]
Aucubin	Iridoid	Bark, leaves	Inducing autophagy while inhibiting necrosis	[123-124]
Quercetin-3-*O*-sambubioside	Flavonoid	Male flowers	Regulating estrogen for its antidepressant effects.	[125]

antihypertensive effects by regulating plasma endothelin and NO levels[51]. Additionally, triterpenoids derived from *E. ulmoides*, such as ursolic acid and betulinic acid enhance the expression of endothelial NO synthase and increase NO concentration. They also inhibit the generation of reactive oxygen species (ROS), promote vasodilation, lower blood pressure, and thus exhibit antihypertensive properties[52].

4.1.2 Anti-osteoporotic

The primary etiology of osteoporosis is an imbalance in bone metabolism, characterized by reduced bone formation relative to bone resorption. The iridoid, lignans, and flavonoids in EUE have been proved to enhance the proliferation and differentiation of stem cells, as well as promote osteogenic cell proliferation and bone formation, making it a promising therapeutic agent for osteoporosis treatment. Iridoids such as aucubin, reptoside, geniposide and ajugoside are core anti-osteoporosis compounds with strong anti-osteoporosis activity, and play pivotal key role in bone resorption and bone remodeling through mitogen activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K)-Akt and estrogen signaling pathways to increase the differentiation of osteoblasts, promote the increase of bone thickness and bone density, and prevent the apoptosis of osteoclasts. Aucubin enhances autophagy by activating Adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling to counteract steroid-induced osteoblast apoptosis[53]. Notably, iridium glycosides and gardenioside have been demonstrated to enhance osteoblast differentiation while suppressing osteoclast activity, thereby effectively restraining bone resorption and promoting bone formation[54]. Moreover, the lignans found in EUB can effectively inhibit osteoclast formation by upregulating osteoprotegerin and downregulating nuclear factor κB (NF-κB) receptor activating factor ligand expression. It is worth noting that lignans exhibit divergent effects *in vitro* and *in vivo* experiments. *In vitro*, exposure to lignans (30−500 μg/mL) resulted in increased proliferation and differentiation of primary osteoblasts, while inhibiting the formation of osteoclasts. Conversely, *in vivo* administration of EUB lignans (20, 40, or 80 mg/kg) effectively prevented femur biomechanical mass loss and trabecular microstructure deterioration induced by obesity-induced ovariectomy in rats, thereby preserving their biological capacity[55]. Flavonoids in *E. ulmoides* can reduce cell damage and bone loss induced by oxidative stress, promote osteoblast differentiation and inhibit osteoclast formation[56-57]. Quercetin can resist oxidative stress damage by activating nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway, inhibit cell apoptosis induced by iron overload environment, preserve the osteogenic differentiation ability of mouse embryo osteoblast precursor (MC3T3-E1)

cells, mouse embryonic osteoblast precursor cells, and thus alleviate osteoporosis[58] (Fig. 5B). Additionally, *E. ulmoides* polysaccharides can be employed to mitigate the progression of osteoarthritis and facilitate the reconstruction of subchondral bone, as well as repair articular cartilage by regulating the functional status of macrophages[59].

4.1.3 *Anti-inflammatory activity*

EUL have emerged as a promising therapeutic candidate for the management of neuroinflammation, owing to the proven efficacy of its active component aucubin in alleviating neuroinflammation. Aucubin exhibits protective effects against lipopolysaccharide (LPS)-induced acute lung injury by modulating Nrf2 and AMPK pathways, while also inhibiting inflammation and apoptosis in LPS-induced cardiac dysfunction mice[44]. Flavonoids exert cellular protective effects during inflammation through the PI3K/NF-κB signaling pathway[60]. EUB extract effectively inhibits neuroinflammation induced by BV-2 microglia by inhibiting NF-κB activation and inducing Nrf2-dependent HO-1 activation[61] (Fig. 5C). In collagen-induced arthritis rats, the bioactive constituents in *E. ulmoides* demonstrates anti-inflammatory properties against rheumatoid arthritis and effectively suppresses synovial cell proliferation to prevent bone tissue damage[62]. Furthermore, bioactive constituents in *E. ulmoides* has been shown to protect renal health and enhance pathological kidney morphology. A prolonged study involving Sprague-Dawley rats fed with a high-purine diet revealed that the extract of EUB improved renal interstitial fibrosis in mice and may have contributed to the regulation of extracellular matrix degradation enzyme systems[63]. *E. ulmoides* is often used in Chinese medicine to treat male infertility. Studies have shown that EUE can prevent testicular injury by inhibiting cellular oxidative stress, reducing Sertoli cell apoptosis, reducing sperm morphological abnormalities and the destruction of blood-testicular barrier. Aucubin promotes the activation of the Nrf2 pathway, maintaining blood-testis barrier (BTB) integrity and normal levels of markers of oxidative stress and antioxidants by upregating the expression of a range of antioxidants and detoxification enzymes[64] (Fig. 5D).

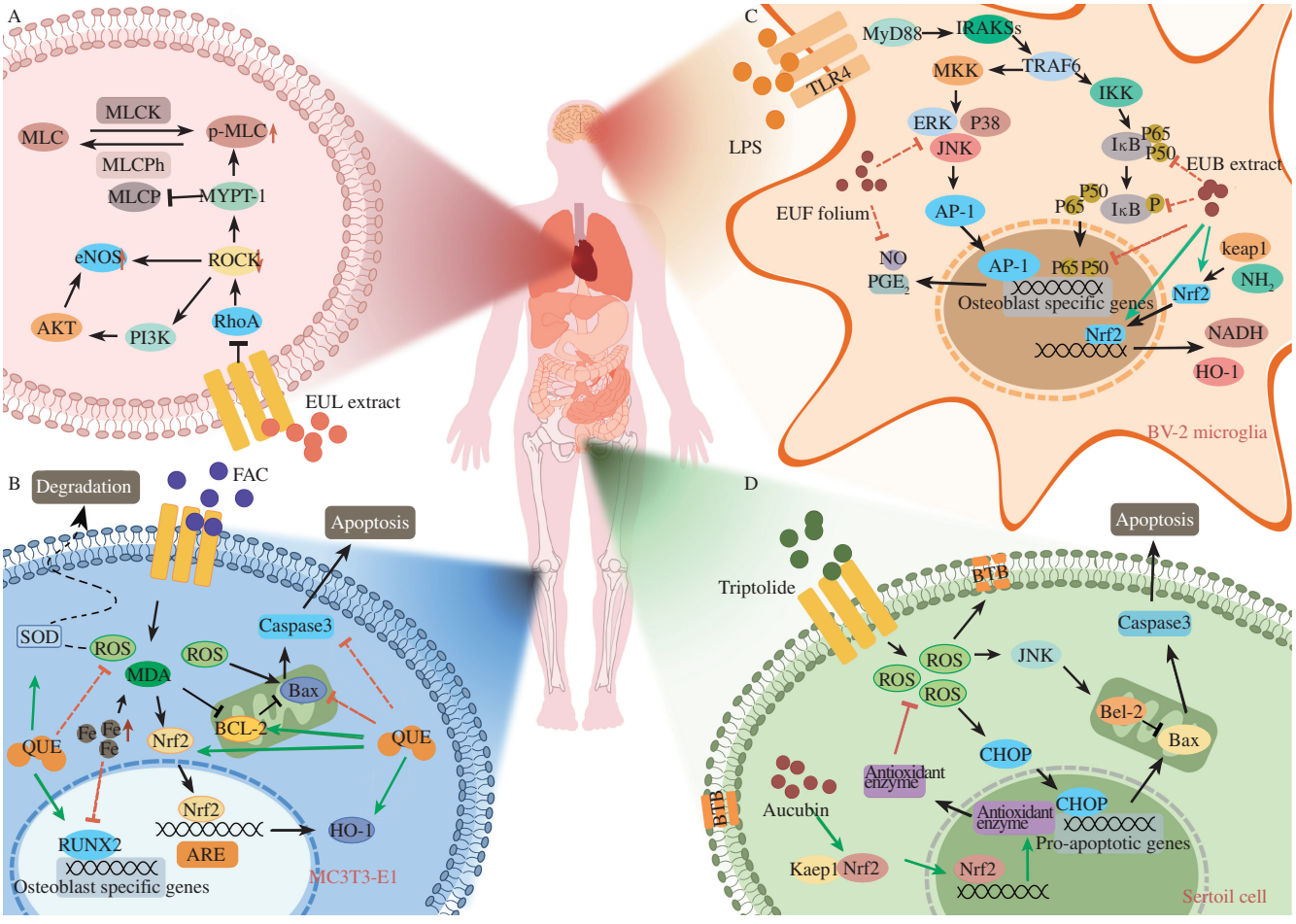


Fig. 5 Overview of health benefits of *E. ulmoides*. (A) Potential protective molecular mechanism of ELE against cardiovascular diseases; (B) Inhibitory molecular mechanism of quercetin on iron-overload osteoporosis; (C) Inhibitory molecular mechanism of EUB extract on the pro-inflammatory response of LPS-stimulated BV-2 microglia; (D) Molecular mechanism of aucubin against oxidative stress-induced testicular injury. 1-Arg: 1-arginine; AP-1: activated protein-1; ARE: antioxidant response element; Bax: BCL2-associated X; Bel-2: B-cell lymphoma-2; CHOP: C/EBP-homologous protein; eNOS: endothelial nitric oxide synthase; ERK: extracellular regulated protein kinases; IKK: inhibitor of kappaB kinase; IRAKs: interleukin-1 receptor-associated kinases; JNK: C-Jun N-terminal kinase; MC3T3-E1: mouse embryo osteoblast precursor cells; MKK: mitogen-activated protein kinase kinase; MLC: myosin light chain; MLCK:myosin light chain kinase; MLCP: myosin light chain phosphatase; MLCPh: myosin light chain phosphor; MyD88: myeloiddifferentiationfactor88; MYPT-1: myosin phosphatase target subunit 1; NADH: nicotinamide adenine dinucleotide; P: phosphorylation; PEG2: prostaglandin E2; PI3K-Akt: phosphatidylinositol-3-kinase-Akt; p-MLC: phospho-myosin light chain; RUNX2: runt-related transcription factor 2; TLR4: toll-like receptor 4; TRAF6: tumor necrosis factor receptor-associated factor 6.

4.1.4 Anti-oxidation activity

In biological studies, lignans, flavonoids, polysaccharides, and polyphenols derived from *E. ulmoides* have been identified as the bioactive constituent responsible for antioxidant activity. These compounds effectively mitigate oxidative stress-related conditions such as gastric mucosal damage, diabetes complications, chronic hepatotoxicity, and ischemia-reperfusion (I/R)-induced renal and hepatotoxicity[44]. Lignans exhibit the ability to activate the Nrf2/HO-1 signaling pathway to combat oxidative stress[65], while flavonoids are involved in regulating intestinal oxidative stress through interference with the Nrf2 signal. Additionally, *E. ulmoides* polysaccharides can exert pharmacological effects through multiple target and pathway. For example, a total of 105 cross-targets and identified 21 core target genes of *E. ulmoides* polysaccharides that act on immune disorders[54] (Figs. 6A and B). In the experimental model of liver I/R injury in rats, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and malondialdehyde (MDA) in the *E. ulmoides* polysaccharides pretreatment group were significantly lower than those in the control group, while the level of SOD was higher than that in the control group, indicating that *E. ulmoides* polysaccharides could improve the liver function of mice by alleviating oxidative stress damage[66] (Fig. 6C). Similarly, polyphenols have been found to decrease MDA content in serum and liver, while increasing SOD and GSH-Px levels in serum and GSH-Px levels in the liver[67]. Furthermore, geniposide and aucuboside may be key compounds involved in the antioxidant capacity of *E. ulmoides*, as they alleviate oxidative stress through regulation of the Nrf2/HO-1 pathway[44].

4.1.5 Mitigating neurodegeneration

Previous studies have demonstrated the potential of bioactive compounds derived from *E. ulmoides* in the treatment of neurodegenerative diseases. For instance, EUE contains lignin, gardenioside, chlorogenic acid, geniposide, botulinum toxin, and rhinanthin, which exhibit inhibitory effects on cell expression. Diepoxylignans play a neuroprotective role by activating the PI3K/Akt/glycogen synthase kinase-3 (GSK-3β)/Nrf2 signaling pathway[68]. Notably, aucubin has been shown to play a neuroprotective role in mice with Parkinson's disease by safeguarding dopaminergic neurons and reducing inflammation[69]. Additionally, ulmoidol acts as a triterpenoid that prevents neuroinflammation by targeting the *PU.1* transcriptional signaling pathway[70]. The positive effects of *E. ulmoides* on psychiatric disorders have been demonstrated, with diterpenes and iridoids effectively alleviating symptoms of depression[71]. Moreover, they also exhibit a physiological role in stimulating, interfering with, and bidirectionally regulating endocrine functions. Previous studies indicate that coniferaldehyde glucoside derived from EUE does not display cytotoxicity towards damaged L132 cells but significantly induces heat shock factor 1 (HSF1) activity, suggesting its potential as a cell protector and inducer of heat shock protein (HSP)[72].

4.1.6 Anti-oxidation activity

The thermogenic water-based shape memory polymer, EUG, exhibits excellent anti-leakage, anti-hydrolysis, and anti-corrosion properties, making it a promising material for intelligent medical devices in the field of biomedical engineering[73]. Its non-toxicity and good biocompatibility enable its wide application in self-healing elastomeric materials and various biomedical applications such as root bioengineering scaffolds, orthopedic fixation splint materials, and smart skin.

4.2 Foods

As an important traditional Chinese medicine, *Eucommia* has a long history of consumption in its main producing areas. Nowadays, it has received more attention due to its unique property of homology of medicine and food[74]. Its leaves, male flowers, and seeds all contain nutrients such as crude protein, crude fat, vitamins, and amino acids. These abundant bioactive ingredients offer immense potential for the development of functional foods. The studies showed that there were 114 kinds of health food in capsule form, accounting for 52.35% (Fig. 7A). The main raw material of health food is EUB, accounting for 61.69% (Fig. 7B).

4.2.1 Leaves

The distribution and composition of active constituents in various segments of *E. ulmoides* exhibited significant variations (Fig. 7C). The EUL is commonly marketed as a dietary supplement, primarily in the form of tea. EUL tea contains 5 iridoids (geniposidic acid, geniposide, deacetyl asperulosidic acid, asperulosidic acid, and asperuloside) and 3 phenols (protocatechuic acid, pyrogallol, and *p-trans*-coumaric acid)[5]. These bioactive compounds have been shown to contribute to the reduction of blood pressure and lipids while promoting metabolism. Furthermore, the leaves contain 4.32% chlorogenic acid and 4.08% aucubin which are responsible for the antioxidant activity (Fig. 7C)[3]. The anti-obesity effect of EUL tea can be attributed to its inhibition of pancreatic lipase activity through its iridoid compounds such as asperuloside[75].

Refined EUL powder, obtained through an ultrafine crushing process, is commonly incorporated into functional foods with anti-obesity properties. This process enhances the dissolution of total phenols and flavonoids, which play a crucial role in regulating lipid reduction by inducing autophagy[3,76]. By fermenting glutinous rice with ultrafine EUL powder, a novel *Eucommia* sweet rice wine can be produced that retains the flavor, aroma, and antioxidant properties of EUL while being rich in flavonoids and polyphenolic compounds. These ingredients not only maintain their flavor but also exhibit potent antioxidant activity and positive hypoglycemic effects[77]. Moreover, geniposide found in EUL can convert to genipin and promote bile secretion while demonstrating glucose-lowering and anti-inflammatory effects[5]. Consequently, EUL extract (ELE) holds potential for developing beverages targeted towards individuals with high blood sugar levels. The incorporation of reducing sugars, total phenols, and flavonoids has enhanced the nutritional value and distinct flavor profile of these products, thereby garnering popularity among health-conscious consumers. Owing to its high concentration of phenolic constituents such as phenolic acids and flavonoids, EUL exhibits potent antioxidant properties, rendering it a natural food antioxidant and antibacterial agent. Phenolics function by intercepting the oxidation of free radical chains to form stable end products that do not further oxidize lipids. The phenolic compounds present in EUL

effectively stabilize pork color by inhibiting lipid oxidation. Research has demonstrated that 0.1% ELE showcases antioxidant activity equivalent to 0.01% butylated hydroxytoluene (BHT) in raw pork patties[78]. Refined wood vinegar of *E. ulmoides* can proficiently serve as a biological preservative for extending the shelf life of berries. The findings illustrate that wood vinegar efficiently preserves the intrinsic quality of postharvest berries by suppressing respiration, delaying tissue softening, and reducing spoilage[79].

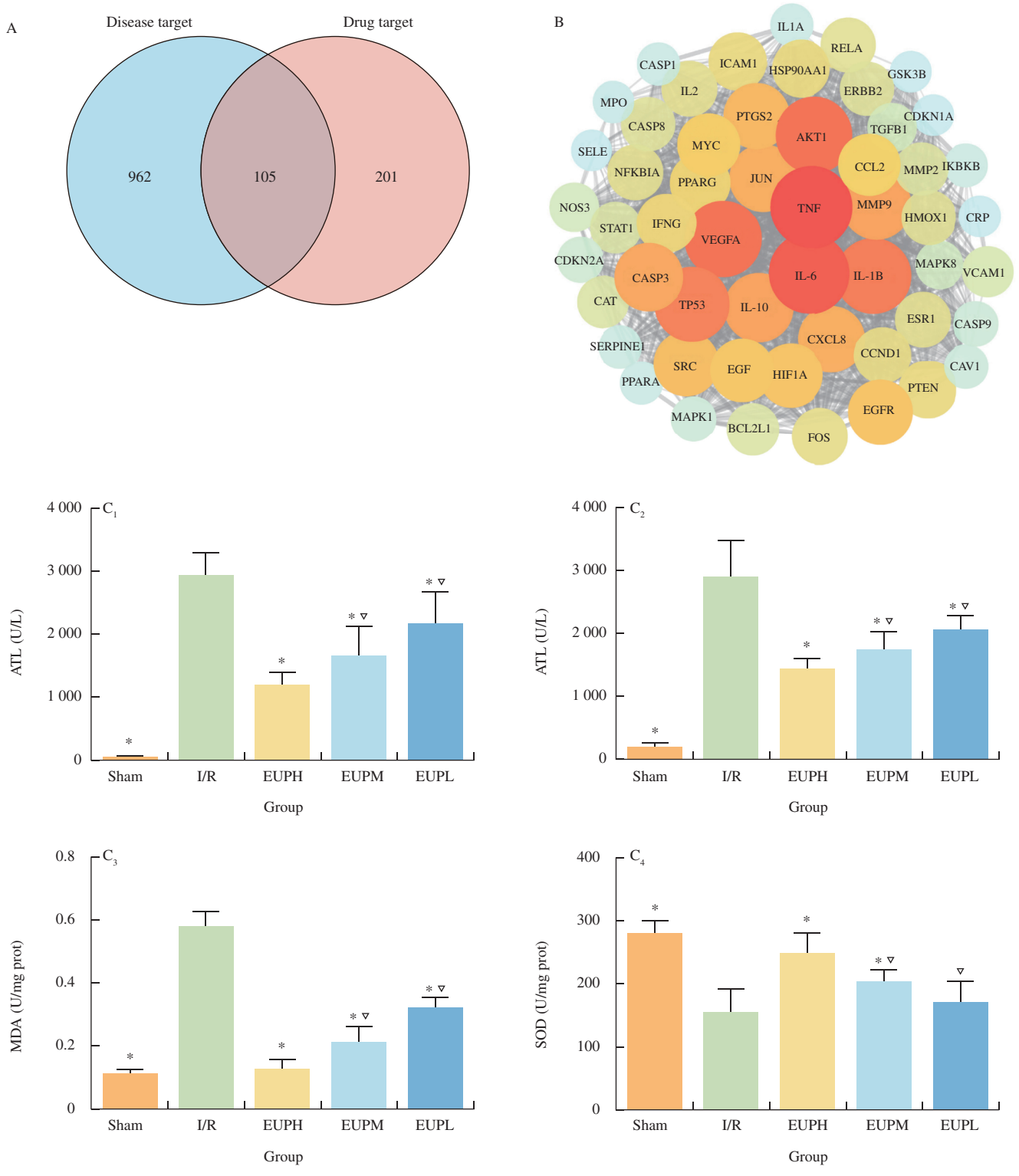


Fig. 6 Antioxidant activity of polysaccharides in *E. ulmoides*. (A) Intersection of polysaccharide targets with immune dysregulation targets[54]; (B) Polysaccharides act on 21 core targets of immune dysregulation[54]; (C) Polysaccharide improves representative index of liver function and oxidative stress injury[66]. Sham-operated group, Sham; EUPH, EUPM, and EUPL indicate the high-dose, medium-dose, low-dose polysaccharides in *E. ulmoides,* respectively. *Compared with the I/R group, $P < 0.05$; ▽ Compared with the EUPH group, $P < 0.05$.

4.2.2 Male flowers

The EUMF is rich in bioactive compounds, such as geniposidic acid,chlorogenic acid, rhimanthin and amino acids (Fig. 7C). Moreover, EUMF exhibits a high potassium-to-sodium ratio, and the ratio of essential to nonessential amino acids in EUMF health tea exceed 0.6, making it a valuable dietary source[80]. Additionally, the EUMF has been incorporated into natural dietary supplements as well as health tea products, while also finding applications in traditional Chinese medicine. Its active constituents, including aucubin, geniposide, and asperuloside, may exert their health-promoting effects through mechanisms associated with DAF-16 and mitochondrial function[81]. EUMF is incorporated as a beneficial ingredient in meal replacement products to effectively enhance their antioxidant and anti-aging properties. Fermentation of EUMF wine effectively preserves its bioactive components while enhancing mineral content and amino acid composition without compromising its flavor profile or specific health benefits. Additionally, EUMF extract exhibits notable antibacterial effects against *Staphylococcus aureus*, *Escherichia coli*, and *M. albus* by inducing cell membrane hyperpolarization, reducing bacterial DNA and protein content, increasing cell membrane permeability, and destroying cell membrane integrity and cell morphology, which endows it with the potential to serve as a food preservative[82].

4.2.3 Seeds

EUS is a valuable source of woody oil, possessing *in vitro* antioxidant properties and the ability to reduce blood lipids while maintaining cerebral nerve function. EUS oil is rich in unsaturated

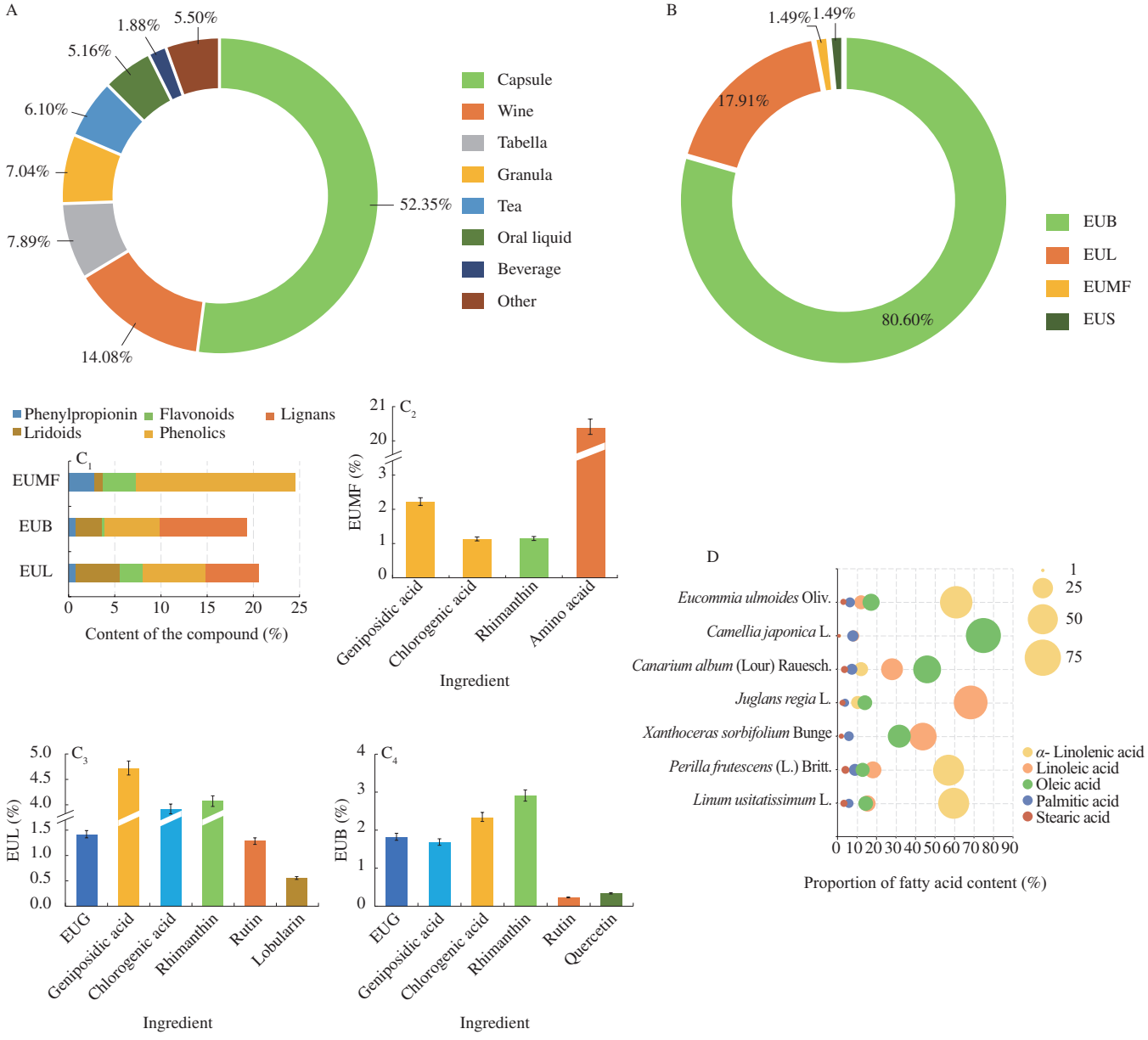


Fig. 7 Content of active ingredients in various organs and tissues of *E. ulmoides*. (A) The proportion of different health products of *E. ulmoides*; (B) The main raw material sources of *E. ulmoides* health products; (C) The content of active ingredients and representative substances in EUMF, EUB and EUL; (D) Comparison of fatty acid content in seeds between *E. ulmoides* and other oil plants.

fatty acids and diverse bioactive compounds, with an approximate oil content of 30%, rendering it highly nutritious[83]. Determined by gas chromatography mass spectrometry, content of α-linolenic acid in EUS oil was 56.51%, with 12.66% linoleic acid, 15.80% oleic acid, 9.82% palmitic acid, and 2.59% stearic acid[84]. The content of α-linolenic acid is significantly higher, which is 8−60 times that of tea seed oil, olive oil and walnut oil (Fig. 7D). The auxiliary hypolipidemic effect on mice has confirmed the effectiveness of EUS oil in reducing triglyceride and total cholesterol levels[85]. The presence of α-linolenic acid and linoleic acid in EUS oil inhibits fatty acid and triglyceride synthesis while promoting their oxidation, thereby exerting an antithrombotic function[86]. Due to its high content of unsaturated fatty acids, EUS oil is susceptible to oxidation and rancidity during food processing and storage, which can impact the chemical composition, sensory attributes, and nutritional properties of the oil. Consequently, EUS oils are primarily processed into cooking oil formulations or soft capsules to mitigate lipid peroxidation[87]. Moreover, EUS oils also possess a substantial protein content and phytosterols, particularly β-sitosterol, which can be utilized as a supplement such as microencapsulated powder[88].

4.3 Animal feeds

The EUL serves as the primary raw material for antibiotic-free cultivation, thus paving the way for a novel approach to the comprehensive utilization of medicinal plant resources. It is rich in various nutrients, which are essentially identical to those found in the EUB[89]. Moreover, it exhibits potential pharmacological effects including antioxidant, anti-inflammatory, and lipid-lowering properties. Additionally, due to its ease of collection, regeneration and processing capabilities, the ELE holds a wide range of potential applications as a valuable feed additive. Even after undergoing industrial oil extraction process, the meal derived from EUS remains rich in oil content along with protein minerals and diverse bioactive ingredients that can be crushed and processed economically to produce a feed additive.

The inclusion of ELE in high-fat animal feed has been shown to enhance their constitution and increase egg production. In feeding experiments, a high dosage of ELE as an additive significantly improved the laying rate for hens compared to the basal diet, while also reducing lipid-related indexes and increasing immunoglobulin index[8]. Furthermore, the incorporation of ELE into animal diets has demonstrated significant reductions in lipid levels and improvements in immune function. When 1.0% ELE was incorporated into the diet of large juvenile yellow croaker larvae, it significantly improved their antioxidant capacity and immune function[8]. The inclusion of 0.04%−0.06% ELE in their diet led to an up-regulation of expression levels for Nrf2 pathway-associated antioxidant genes such as catalase (CAT) and SOD, as well as anti-inflammatory cytokines like TGF-β and IL-10. Moreover, it augmented the intestinal tract's antioxidant capacity in tilapia, bolstered immunity, and improved antibacterial activity against *Streptococcus agalactiae*[84,90]. In a diquat-induced oxidative stress piglet model, supplementation with *Eucommia* flavone nuclear Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) protein expression through feed resulted in improved antioxidant capacity among piglets[91].

Supplementation of *Eucommia* feed additives has been demonstrated to enhance the quality of animal meat. In a study involving growth-finishing pigs, inclusion of 0.01% ELE in their daily diet significantly elevated serum levels of adiponectin, insulin-like growth factor 1, hormone-sensitive lipase, and lipoprotein lipase, thereby improving carcass traits and contributing to lipid reduction[92]. Incorporation of ELE rich in chlorogenic acid effectively reduced stearic acid and saturated fatty acids levels while simultaneously enhancing average daily gain in heat-stressed broilers. Moreover, this intervention mitigated the adverse effects of heat stress on chickens by improving oxidative stability and fatty acid profile[93]. Incorporating ELE into broiler feed has been shown to decrease the levels of MDA, an oxidative stress indicator, in both liver and serum, as well as reduce the abdominal fat ratio[94]. Similarly, ELE has been utilized as a feed additive in high-fat diets for catfish, lamb fattening, pig fattening, weaned pigs, and laying ducks. In summary, ELE represents a highly promising novel feed additive that can serve as an antibiotic alternative without causing pollution or residue.

4.4 Others

Due to the antioxidant properties of *E. ulmoides*, EUE can be utilized in the production of cosmetics and daily necessities. The EUS oxidation degree is significantly low, while its saponification value is higher than that of soybean oil and comparable to linseed oil, making it suitable for industrial oil production. Silver nanoparticles synthesized from this extract have potential for enhancing skin health by inhibiting melanin production, making them a promising candidate for cosmetic applications[95–96].

5. Safety

According to the *Chinese Pharmacopoeia*, the recommended clinical dosage of EUE is 8 g/day. Furthermore, administration of EUE at a dose up to 1 200 mg/kg did not induce acute or subchronic toxicity in mice[97]. Some studies have suggested potential nephrotoxicity and genotoxicity associated with EUE. For instance, treatment of L5178Y cells with 20 mg/mL EUE resulted in mutations in the thymidine kinase gene and chromosome damage[98]. A toxicity experiment of EUE demonstrated the absence of genotoxicity within the dosage range of 22−88 g/kg body weight and 2−20 mg/mL. However, nephrotoxicity and drug dependence exhibited an increase after a duration of 13 weeks[99]. The mutagenic potential of EUE was evaluated using rat liver cells (S9) treated with 9 *Salmonella* strains. After 6 h, EUE showed no toxic effects in the presence or absence of S9. However after 24 h, doses of 8 and 20 mg/mL of EUE inhibited the growth of S9 (Figs. 8A and B). Further chromosomal aberration experiments revealed that the aberration rate (AB%) of c hinese hamster lung (CHL) cells exposed to a dose of 20 mg/mL of EUE did not exceed 10%, similar to that of the control group, indicating the absence of genetic toxicity to CHL[99] (Figs. 8C and D). In summary, EUE does not exhibit acute toxicity or genotoxicity, and yet prolonged exposure to high doses may result in partially reversible nephrotoxicity.

The safety and nutritional value of *Eucommia* tea has been confirmed. Safety evaluations conducted on mice revealed no signs of acute or chronic oral toxicity, and genetic toxicity test such as Ames,

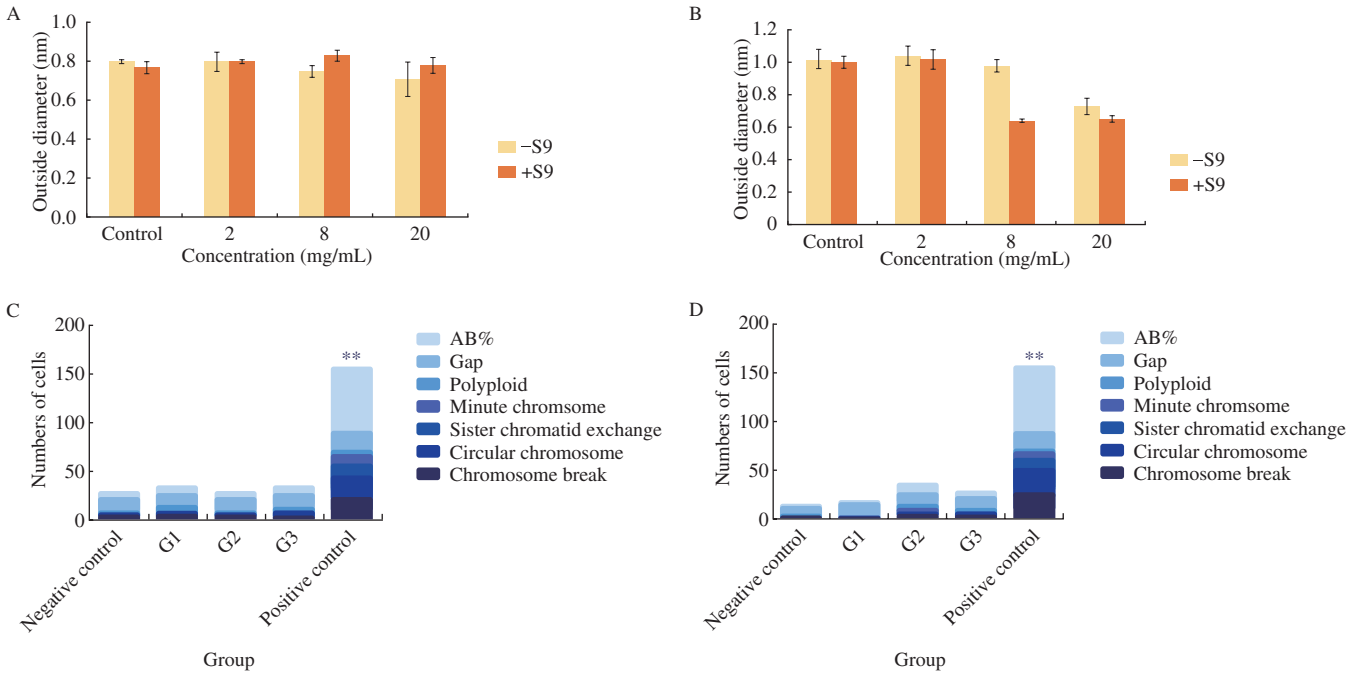


Fig. 8 Toxicity determination of *E. ulmoides* extract. Determination of toxicity to CHL cell lines after (A) 6 h and (B) 24 h; Chromosome aberration measurement (C) S9 metabolic activation and (D) no S9 metabolic activation)[99]. $^{**}P < 0.01$, relative to negative control.

bone marrow cell micronucleus, and sperm malformation indicated the absence of mutagenicity. Furthermore, a 30-day feeding trial showed no significant toxic reactions in any measured indices[100]. Toxicological safety experiments conducted on EUS oil demonstrated no significant adverse effects on growth and development, hematology, blood biochemistry, pathology or other indicators in rats fed with a dosage equivalent to 187 times the recommended human dosage (9.34 g/kg) for a period of 90 day. Additionally, there were no observed teratogenic effects in fetal rats. In conclusion, EUE, tea and EUS oil are non-toxic substances that can be safely consumed as part of a healthy diet[101].

6. Increase the yield of bioactive ingredients

To meet the ever-evolving demands, *Eucommia* was enhanced with high medicinal value, EUG content, abundant leaves, rapid growth rate and superior quality male flowers as breeding objectives through modern biotechnique such as meticulous variety selection, multi-variety hybridization, chromosome doubling techniques and molecular breeding. For example, interspecific selection was carried out during variety establishment to breed excellent varieties with objectives including α-linolenic acid content, male flower utilization and high EUG content. Through interspecific hybridization and directional selection, a series of clones with excellent phenotype have been successfully cultivated, including the “Huazhong” series varieties characterized by high growth rate and the “Qinzhong” series varieties known for their high biomass production. In addition to conventional breeding methods, chromosome doubling techniques have been applied to breed polyploid germplasm with desirable traits such as leaf hypertrophy, increased plant height, as well as target bioactive ingredients. Tetraploid *Eucommia* can be obtained by subjecting female buds to high temperatures, inducing chromosome doubling in the embryo sac[102]. In comparison to diploid plants, triploid *Eucommia* exhibited a 1.46 times increase in leaf area and leaf thickness compared to the diploid control, while secondary compounds such as chlorogenic acid and geniposide were found to be 1.10 and 2.18 times higher than those of the diploid plants[103]. These findings highlight the immense potential of triploid cultivation for the development and utilization of breeding programs of *E. ulmoides*. Molecular breeding techniques enable direct selection of species genotypes and targeted cultivation, significantly enhancing genetic improvement efficiency. Gene editing technology, in particular, enables precise modification of individual nucleotides within genes, which holds significant potential for genetic breeding of *E. ulmoides*. Currently, successful CRISPR/Cas9-mediated *PDS* gene knockout has been achieved in various woody plants such as poplar[104] and palm[105]. By utilizing CRISPR/Cas9 technology to knock out the immune defense gene *MdCNGC2* in apples, the resistance of apple fruits against *B. dothidea* is enhanced while reducing fruit lesions[106]. Meanwhile, active development of a gene editing system for *E. ulmoides* is underway with the successful achievement of gene editing in *E. ulmoides* cells targeting the *EuFLC* gene for the first time[107]. Furthermore, improved separation technology is essential for extracting target metabolites while minimizing material damage during the purification process, resulting in high-concentration bioactive substances.

7. Conclusion and perspectives

The benefits of *E. ulmoides* mainly rely on its abundant bioactive compounds and nutritional value. With the advancement of extraction technology, in-depth studies have found that while EUL, EUB, EUS, and EUMF contain different compounds, they can be broadly categorized into lignans, iridoids, flavonoids, phenolics, and polysaccharides. In addition to the current large-scale applications in Chinese medicine and wood industries, there is also a growing trend in the food industry for

the application of EUL, EUMF, and EUS. Based on the pharmaceutical effects that have been discovered, the current in-depth studies on various bioactive compounds of *E. ulmoides* mainly focus on clinical medicine. Many compounds exert regulatory effects by modulating anti-inflammatory, antioxidant, and other pathways. To cater to the diverse applications of *E. ulmoides*, breeding, hybridization, and chromosome doubling have been employed to develop various cultivars for leaf, seed, and medicinal purposes.

Although domestic scholars have made efforts in recent years to develop and utilize *E. ulmoides*, its potential should be further explored and its application scope pursued at a deeper level. Currently, there are still some issues in the application of *E. ulmoides*:

1) Standardization: the accumulation of various bioactive ingredients varies across different growth periods of *E. ulmoides* and can be influenced by the timing of harvesting and storage techniques employed, thus making standardization and uniformity essential for the development of the *Eucommia* industry.
2) Extraction and separation: advanced extraction and separation technology can ensure the effectiveness of bioactive ingredients of *E. ulmoides*, while a high level of quality bioactive ingredients can enhance its biological and medical applications.
3) Safety evaluation: the safety of products derived from *E. ulmoides* has been validated; however, the safety threshold values for various compounds have not yet been established, and the traditional products of *E. ulmoides* have a low level of safety assessment.
4) Product development: the increasing emphasis on healthcare presents an opportune time for the development of the *Eucommia* industry. We must delve deeper into high-value-added products, advance key technological research to upgrade the industry.

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Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://doi.org/10.26599/FSHW.2024.9250338.

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