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Advances in research on the bioactive compounds and genetic improvement of *Eucommia ulmoides*

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Abstract

Eucommia ulmoides, a tertiary relict plant species, remains the only extant representative of both the genus *Eucommia* and the family Eucommiaceae. With a history of more than two millennia of use in traditional Chinese medicine, its bark, leaves, and fruits harbor a diverse array of bioactive compounds, including flavonoids, iridoids, lignans, and phenylpropanoids. These compounds have various effects, such as regulating blood pressure, preventing osteoporosis, providing neuroprotection, modulating the immune system, and exhibiting antimicrobial and antiviral activities, as well as improving hypoxia tolerance and reducing lipid levels. In recent years, significant advancements have been made in the identification of bioactive components, pharmacological research, understanding the genetic basis of biosynthesis, breeding of new varieties, and the development of efficient cultivation techniques. These advancements have positioned *Eucommia* as a species with an extensive range of research interests. However, several challenges persist in the advanced development of *Eucommia*. These include insufficient research on pharmacological mechanisms, limited genetic diversity, and prolonged traditional cultivation cycles. To overcome these challenges, future research efforts should focus on breaking these bottlenecks by selecting high-yield, high-quality varieties through a combination of conventional and unconventional breeding methods. Additionally, integrating intensive cultivation techniques with comprehensive utilization strategies is crucial. Promoting the establishment of a green circular economy centered around the active ingredients of *Eucommia* can further enhance the economic benefits of the *Eucommia* industry.

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Introduction

Eucommia ulmoides (*E. ulmoides*), a tertiary relict species belonging to the family Eucommiaceae, is a monotypic genus with a chromosome count of 2n = 2X = 34. It is a versatile economic tree species endemic to China. Its distribution is primarily concentrated in the middle and lower reaches of the Yangtze River in China[1,2]. *E. ulmoides* likely exhibited broad adaptability in its evolutionary history[3]. Fossil evidence indicates that primitive *E. ulmoides* had a widespread distribution during the Miocene epoch, spanning nearly the entire Northern Hemisphere, but became restricted to central China following the Quaternary glaciation[4]. Consequently, this species can be introduced and cultivated in numerous regions worldwide. Presently, it is cultivated extensively across a vast geographic range in China, including between latitudes 22° N and 42° N and longitudes 100° E to 121° E, encompassing a planting area exceeding 400,000 hectares. This accounts for more than 99% of the global *E. ulmoides* resources[5]. Furthermore, the species has been successfully introduced to countries such as the United States, the United Kingdom, France, Ukraine, Russia, Australia, Japan, and South Korea.

E. ulmoides, a traditional and esteemed Chinese medicinal herb has a medicinal history spanning over two millennia (Fig. 1a). It was classified as a superior herb in the Han Dynasty's 'Shennong Ben Cao Jing' and is renowned for its antiaging properties[5]. Modern research has identified biologically active substances such as chlorogenic acid, aucubin, geniposidic acid, and geniposide in its bark, leaves, and fruits, which contribute to its efficacy in regulating blood pressure, preventing osteoporosis, improving neuroprotection, immune modulation, and antimicrobial and antiviral activities, enhancing hypoxia tolerance, and lowering blood lipids[1,2,5−7]. Furthermore, *E. ulmoides* shows promise as a temperate tree species for industrial gum production because its leaves contain 2%−3% gum (Fig. 1c), its bark contains 10%−12% gum (Fig. 1b), and its fruits contain 10%−18% gum[1,2]. The gum from *E. ulmoides* shares the same chemical composition as natural rubber but differs in its chemical structure, being trans-polyisoprene, which lacks elasticity. However, when modified, this compound combines the dual properties of rubber and plastic. It can be processed into sulfur-cured elastic rubber, like Hevea rubber, and possesses unique features such as low-temperature shape memory[8,9]. This finding demonstrates the extensive versatility and immense value of *E. ulmoides*, as every part of the plant is valuable. It shows significant potential for application and development in medicine, food, and the gum industry, as well as in materials, urban and rural landscaping, and soil and water conservation.

Since the 1950s, because of the significant development value of *E. ulmoides* in pharmaceuticals and rubber production, research has increasingly focused on pharmacological effects; extraction and identification of active components; rubber and drug manufacturing; germplasm resources; seedling breeding;

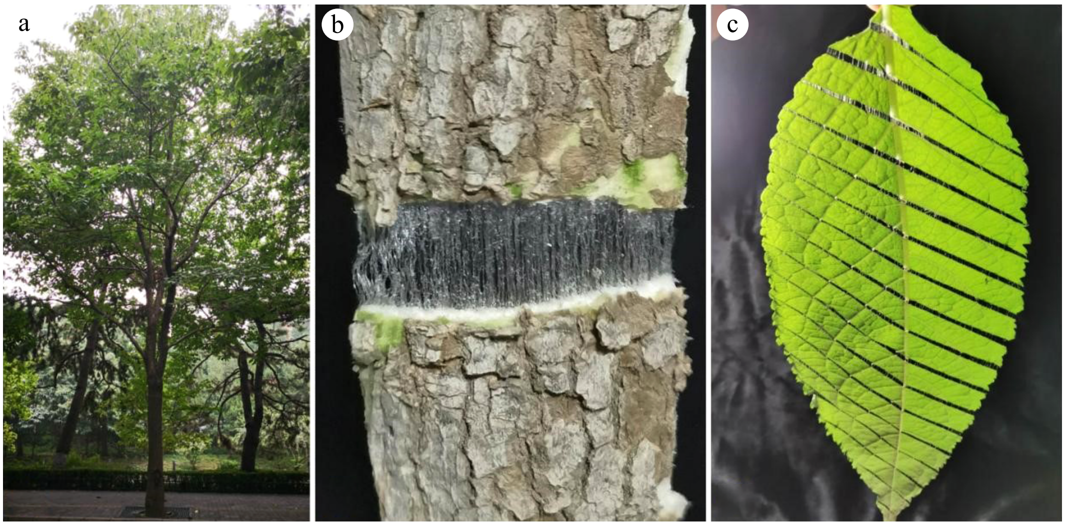


Fig. 1 Characteristics of the *E. ulmoides*, bark, and leaves. (a) The morphology of the adult *E. ulmoides.* (b) Gums contained in the bark of *E. ulmoides.* (c) Gums contained in the leaf of *E. ulmoides.*

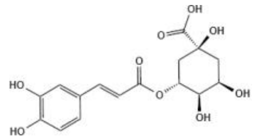
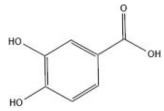
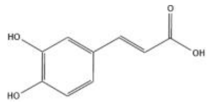
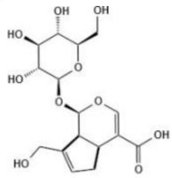
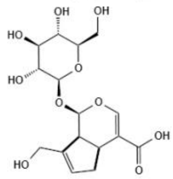
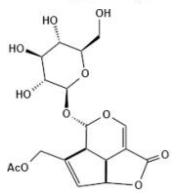
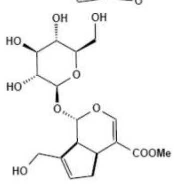
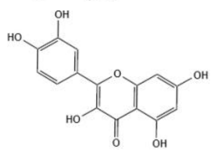
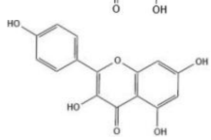
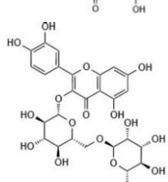
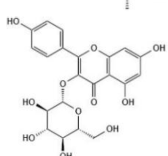
introduction and cultivation; genetic foundation; and selection of improved varieties[1,2]. *E. ulmoides* has become one of the most widely studied and highly regarded tree species globally. Building on existing research, it is crucial to address and overcome the theoretical and technical bottlenecks in the development and utilization of *E. ulmoides* resources. Enhancing the precision and efficiency of industrial development, reducing the production costs of rubber and pharmaceuticals, and promoting the development of a green circular economy centered on the active components of *E. ulmoides* are vital goals. These efforts aim to meet the significant demands of human economic development and health. This review aims to provide a comprehensive overview of recent advancements in the identification, distribution, synthesis, and genetic regulation of bioactive components in *E. ulmoides*. It also seeks to explore the challenges and issues associated with the industrial application of these active ingredients and to propose future research directions. Ultimately, the goal is to offer significant references for the sustainable industrial utilization of *E. ulmoides.*

Bioactive components and pharmacological effects of *E. ulmoides*

Modern medical research has shown that the medicinal value of *E. ulmoides* is associated primarily with the rich bioactive components found in its bark, leaves, male flowers, and seeds. To date, more than 200 compounds have been isolated from various parts of *E. ulmoides*, with the leaves containing the greatest variety and quantity of bioactive components, followed by the male flowers, with relatively fewer in the bark and seeds. These components include mainly flavonoids, iridoids, lignans, phenylpropanoids, phenolic acids, terpenes, and steroids[5,7,10] (Table 1). The flavonoids in *E. ulmoides* include quercetin, rutin, astragulin, kaempferol, hyperoside, isoquercitrin, catechin, and others, most of which are flavonoids of the quercetin and kaempferol glycoside types. Present lignans are mostly glycosides, including pinoresinol, olivine, dehydrodiconiferyl alcohol, and directed lipoxyglucoside, with the major component being pinoresinol diglucoside (PDG). Present iridoids are primarily monoterpene compounds, such as geniposidic acid, aucubin, asperuloside, harparin acetate, ajugoside, eucommiol, and reptoside. Phenylpropanoids have a C6-C3 structure and are precursors to lignans and flavonoids, including chlorogenic acid, caffeic acid, isochlorogenic acids A and C, guaiacylglycerol, and cobrazin[5,7,10]. Research has shown that *E. ulmoides* is rich in many bioactive components with high utilization values.

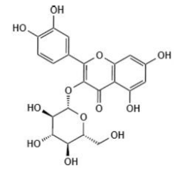
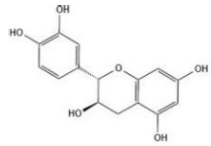
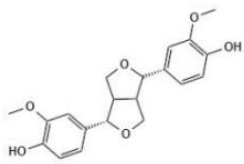
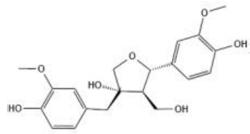
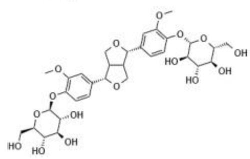
Ancient Chinese medical practices and modern pharmacological studies have indicated that *E. ulmoides* contains several important bioactive components with various beneficial effects, including blood pressure regulation, osteoporosis prevention, neuroprotection, immune modulation, and antibacterial and antiviral properties[1,2,5,7]. Among these compounds, lignan compounds such as pinoresinol diglucoside, dehydrodiconiferyl alcohol, and pinoresinol monoglucoside; phenylpropanoid compounds such as chlorogenic acid and caffeic acid; iridoid compounds such as geniposidic acid, geniposide, and aucubin; and flavonoid compounds such as quercetin and rutin all exhibit blood pressure-regulating effects. The mechanisms involve promoting nitric oxide (NO) release and inhibiting angiotensin II, calcium (Ca^{2+}) influx, and phosphodiesterase synthesis[19−21]. *E. ulmoides* compounds such as pinoresinol diglucoside, kaempferol, rutin, quercetin, and geniposidic acid can promote osteoblast formation[22,23], whereas aucubin can prevent steroid hormone-induced osteoblast apoptosis, thereby helping to prevent osteoporosis[24]. Lignans from *E. ulmoides* bark, geniposide, and aucubin also have neuroprotective effects, such as inhibiting acetylcholinesterase activity to protect ganglion cells from damage[25], reducing the loss of dopaminergic neurons[26], and alleviating neuroinflammatory responses[27]. These compounds are potentially beneficial in treating neurodegenerative diseases such as glaucoma, Parkinson's disease, epilepsy, and Alzheimer's disease. Additionally, extracts from *E. ulmoides* bark and leaves exhibit varying degrees of inhibition against fungi such as *Candida albicans* and bacteria such as *Staphylococcus aureus, Escherichia coli*, and *Salmonella typhimurium*[28,29]. Compounds such as chlorogenic acid and caffeic acid from *E. ulmoides* have been shown to protect HIV-infected cells from pathological changes to a certain extent[30]. Furthermore, pinoresinol monoglucoside

Table 1. Key active components, main existing parts, and pharmacological effects of *E. ulmoides*.

	Compound name	Molecular formula	Molecular structural formula	Main existing parts	Pharmacology	Ref.
Phenolic acid monomer compounds	Chlorogenic acid	$C_{16}H_{18}O_9$		Leaves, bark, fruit pods, male flowers	Antioxidant, anti-inflammatory, anti-tumor, etc	[11]
	Protocatechuic acid	$C_7H_6O_4$		Leaves, bark, fruit pods, male flowers		[12]
	Caffeic acid	$C_9H_8O_4$		Leaves, bark, fruit pods, male flowers		[13]
Cyclohexene ether terpenes	Geniposidic acid	$C_{16}H_{22}O_{10}$		Leaves, bark, fruit pods, male flowers	Anti-inflammatory, promoting wound healing, diuresis, etc.	[13]
	Aucubin	$C_{15}H_{22}O_9$		Leaves, bark, fruit pods, male flowers		[14]
	Asperuloside	$C_{18}O_{11}H_{22}$		Leaves, bark, fruit pods, male flowers		[13]
	Geniposide	$C_{17}H_{24}O_{10}$		Leaves, bark, male flowers		[13]
Flavonoids	Quercetin	$C_{15}H_{10}O_7$		Leaves, fruit pods, male flowers	Antioxidant, blood lipid-lowering, anti-allergy, anti-inflammatory, antiviral, anticancer, etc.	[12]
	Kaempferol	$C_{15}H_{10}O_6$		Leaves, fruit pods, male flowers		[11,15]
	Rutin	$C_{27}H_{30}O_{16}$		Leaves, bark, fruit pods, male flowers		[11]
	Astragalin	$C_{21}H_{20}O_{11}$		Leaves, male flowers		[11]

(to be continued)

Table 1. (continued)

	Compound name	Molecular formula	Molecular structural formula	Main existing parts	Pharmacology	Ref.
	Hyperoside	$C_{21}H_{20}O_{12}$		Leaves, bark		[16]
	Catechin	$C_{15}H_{14}O_6$		Leaves, bark, fruit pods, male flowers		[17]
Lignans	Pinoresinol	$C_{20}H_{22}O_6$		Leaves, bark	Blood pressure-lowering, neuroprotective, etc.	[18]
	Olivil	$C_{20}H_{24}O_7$		Leaves, bark		[18]
	Pinoresinol diglucoside	$C_{32}H_{42}O_{16}$		Leaves, bark, fruit pods, male flowers		[13]

inhibits H1N1 virus[31]. In the realm of pharmacological effects, the leaves and bark of *E. ulmoides* exhibit similar activities, which include antioxidant, hypoglycemic, and hypotensive properties[32]. However, there may be differences in the intensity and efficacy of certain pharmacological actions between the two. For instance, the leaves of *E. ulmoides* are more prominent in antioxidant activity, while the effects of mature leaves are superior to those of tender and old leaves in terms of central sedation, and also superior to the bark[32]. The outcomes of modern pharmacological research have illuminated the direction for the in-depth development and utilization of *E. ulmoides* resources. The specific pharmacological effects of *E. ulmoides* fruit have not been extensively discussed in existing evidence, and future research can further explore the pharmacological effects of the fruit and its differences and connections with the leaves and bark of *E. ulmoides*.

Distribution and harvesting of the bioactive components of *E. ulmoides*

The bark, leaves, male flowers, and seeds of *E. ulmoides* all contain bioactive components, but there are significant differences in the concentrations of these components across different tissues and organs[9,10,33–35]. In general, the leaves of *E. ulmoides* are rich in flavonoids, iridoids, phenolic acids, terpenoids, and steroids[32]. The male flowers primarily contain iridoids, flavonoids, and triterpenoids. Seeds are rich in iridoids, whereas bark has the highest content of lignans[4,5,8,33,36]. Flavonoids are relatively most abundant in the leaves, followed by the male flowers, with lower concentrations in the bark and seeds[8,33,34,36]. The determination of total flavonoids in *E. ulmoides* leaves, male flowers, bark, and seeds collected from various regions in China, such as Hanzhong in Shaanxi, Yichang in Hubei, and Changzhi in Shanxi, revealed that their average contents decreased in the following order: 9.02%, 3.02%, 1.33%, and 1.22%, respectively[34]. The measurement of the total flavonoid content of various tissues and organs at different growth stages revealed that mature leaves presented the highest total flavonoid content, which was significantly different from that of young leaves. In contrast, the flavonoid contents in branches, trunks, bark, and roots at different parts or developmental stages show little variation[35]. Phenylpropanoid components are most abundant in the leaves, followed by the fruit pods, with the lowest content in the bark[9,10,32]. For example, chlorogenic acid is present in all parts of *E. ulmoides*, but its content in the leaves is the highest, reaching approximately 2.5%[10,33,36,37]. Lignan components are most abundant in the bark, followed by the leaves, and are least abundant in the fruit pods. For example, the content of pinoresinol diglucoside in dried bark is approximately 0.5%, which is significantly greater than that in other parts[10,33,36,38]. Iridoid components are most abundant in the fruit pods, followed by the bark and male flowers, with relatively lower leaf content. For example, the content of geniposidic acid in the leaves of *E. ulmoides* is approximately 1.5%, whereas in the bark of branches, it can reach up to 6.71%[10,33,36]. The spatial and temporal distribution characteristics of bioactive components in *E. ulmoides* suggest that in the industrial development process of this plant, it is necessary to determine the direction of utilization of different organs and tissues and the corresponding cultivation and utilization methods according to the differences in the content of the main active components.

Research indicates that as the age of *E. ulmoides* trees increases, the contents of flavonoids and phenylpropanoids in the leaves tend to decrease, whereas the content of lignans increases. Conversely, the contents of lignans and protocatechuic acid in the branch bark and trunk bark of *E. ulmoides* tend to increase[33]. Moreover, the active components of *E. ulmoides* vary depending on the harvest time. For example, the total flavonoid content in *E. ulmoides* leaves is highest in April and May, decreases in June and July, and then slightly increases and then stabilizes after that. Consequently, this suggests that the optimal time for harvesting leaves is April and May[35]. Notably, variations in the contents of the bioactive components of *E. ulmoides* can be attributed to differences in planting location, tree age, organ or tissue, developmental stage or position, and preservation and processing methods[10,33,35,39−41]. This results in different optimal harvesting times; for example, the highest average content of chlorogenic acid in *E. ulmoides* leaves was observed in July in Zhangjiajie, Hunan, China[39], whereas in Xi'an, the highest content was found in August and September[30]. The significant differences in the bioactive component contents and optimal harvesting times of *E. ulmoides* are likely due to variations in the natural environments of different planting locations[10,41].

Additionally, there are differences in the bioactive components between leaves from current-year seedling forests and those from arboreal forests. Compared with those from arboreal forests, the leaves from current-year seedling forests contain significantly greater levels of various active components, such as total flavonoids, chlorogenic acid, geniposidic acid, aucubin, and pinoresinol diglucoside. These levels were several times greater than those of *E. ulmoides* leaves collected from arboreal forests at the same time, indicating substantial potential for wider application[36]. Importantly, newly emerged young leaves accumulate lower levels of bioactive components. Harvesting in a leaf-oriented tree model should be based on changes in the bioactive component contents of the leaves. This can be accomplished by selecting leaves of suitable age for batch harvesting or by performing concentrated coppicing when most leaves have matured.

Synthesis and genetic regulation of the bioactive components of *E. ulmoides*

E. ulmoides has achieved high-quality chromosome-level genome assembly and functional annotation via a haploid approach[42]. Concurrently, studies have been conducted on the key enzymes involved in the synthesis of bioactive components such as lignans, phenylpropanoids, terpenoids, and flavonoids, as well as their genetic regulation. Lignans are the principal medicinal compounds in *E. ulmoides*, whereas lignin plays a role in the plant's defense against pests and diseases. Both lignans and lignin share the common precursor pineol. Research indicates that the formation of pinoresinol is a critical step in the biosynthetic pathway of lignans[43]. The dirigent protein oxidase (DIR)-encoding gene plays a critical role in the biosynthesis of lignans[44]. The transcriptome of *E. ulmoides* contains 58 unigenes encoding the ten key enzymes involved in the biosynthetic pathways of lignans and lignin. These unigenes encompass critical processes in the biosynthesis of lignans and lignin in *E. ulmoides*. The expression levels of 4-coumarate-CoA ligase (*4CL)*, hydroxycinnamoyl-CoA (HCT), cinnamoyl CoA reductase (*CCR)*, cinnamyl alcohol dehydrogenase (*CAD)*, caffeoyl-CoA 3-O-methyltransferase (CCoAOMT), *DIR*, and peroxidase (*POD)* are greater in the stem than in the leaves, whereas PAL and C4H are expressed at higher levels in the leaves than in the stem[44].

The primary flavonoids in *E. ulmoides* are quercetin and kaempferol[45]. The biosynthetic pathways of these two bioactive substances are highly similar. Initially, phenylalanine is converted into p-coumaroyl-CoA by phenylalanine ammonia-lyase (PAL) and 4-coumaroyl-CoA ligase (4CL). This process is subsequently catalyzed by chalcone synthase (CHS) to produce chalcone, which is then converted into naringenin by chalcone isomerase (CHI). Naringenin undergoes consecutive catalysis by flavanone 3-hydroxylase (F3H) and flavonoid 3'-hydroxylase (F3'H) to form dihydroquercetin, which ultimately transforms into quercetin[46]. Additionally, dihydrokaempferol can be directly converted into kaempferol by flavonol synthase (FLS)[47]. Studies have shown that there are three and four family members of CHS and *E. ulmoides* FLS, respectively, in *E. ulmoides*. In contrast, CHI and flavanone F3H are highly conserved, with only one gene identified in both the fruits and leaves of *E. ulmoides*[48]. The gene expression of these two enzymes shows significant tissue specificity. For example, within the CHS gene family, *EuCHS1* is expressed primarily in the leaves, whereas *EuCHS2* is expressed mainly in the fruits[48]. In the FLS gene family, *EuFLS3* and *EuFLS4* have much higher expression levels in leaves than in young fruits, whereas *EuFLS1* and *EuFLS2* show the opposite trend[48]. Transcription factors such as MYBs and bHLHs may play crucial regulatory roles in the flavonoid synthesis and phenylpropanoid synthesis pathways in *E. ulmoides* leaves[49].

The main phenylpropanoid compound is chlorogenic acid[50]. Three biosynthetic pathways for chlorogenic acid have been identified in plants[51]. The latest genome data for *E. ulmoides* indicate that only two pathways are involved in the biosynthesis of chlorogenic acid[42]. One pathway involves the hydroxylation of *p*-coumaroylquinic acid by *p*-coumaroylquinic acid/shikimate 3'-hydroxylase (C3'H)[52], and the other pathway involves synthesis from caffeoyl-CoA and quinic acid catalyzed by hydroxycinnamoyl-CoA quinate hydroxycinnamoyl transferase (HQT)[53]. In the *E. ulmoides* genome, 23 candidate genes related to six key enzyme-encoding gene families involved in the chlorogenic acid biosynthesis pathway were identified. These genes included seven PAL genes, eight 4CL genes, two C4H genes, two C3'H genes, one HCT gene, and three HQT genes[42]. Analysis of gene expression profiles in leaves and bark revealed that the expression levels of PAL (PAL2 and PAL5), C3'H2, C4H6, HQT2, and HCT are significantly greater than those of other genes[42]. Some transcription factors (TFs) from the MYB, ZIP, ERF, and WRKY families may be involved in regulating the biosynthesis of chlorogenic acid in *E. ulmoides*[54].

The biosynthetic pathway of terpenoids in plants can generally be divided into three stages: the mevalonate (MVA) pathway in the cytoplasm and the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway in plastids, which synthesize the five-carbon skeleton isopentenyl diphosphate (IPP) and dimethylallyl pyrophosphate (DMAPP)[55,56]. DMAPP and IPP, under the catalysis of geranyl diphosphate synthase (GPS), synthesize geranyl diphosphate (GPP). GPP is then converted to farnesyl diphosphate (FPP) under the catalysis of farnesyl diphosphate synthase (FPS), and finally, geranylgeranyl diphosphate (GGPP) is synthesized under the catalysis of geranylgeranyl diphosphate synthase (GGPS)[57]. Under the action of various terpenoid synthases and modifying enzymes, structurally and functionally specific terpenoid compounds are produced[58]. In *E. ulmoides*, 13 genes involved in the six reactions of the MVA pathway and 11 genes involved in the seven reactions of the MEP pathway were identified. Additionally, the genes involved in the catalytic synthesis of FPP, GPP, and GGPP include three GPS genes, seven GGPS genes, and four FPS genes[42]. HMGR is the first rate-limiting enzyme in the MVA pathway and serves as a crucial regulatory point in cytoplasmic terpenoid metabolism[58]. Members of the EuHMGR gene family in the MVA pathway, along with other genes such as EuMK, EuPMK, and EuMDP, show significant differential expression in young and mature fruits of *E. ulmoides*[59].

Genetic variation and breeding of superior *E. ulmoides* varieties

Currently, natural forests of *E. ulmoides* are extremely rare, with only a few ancient trees occasionally found in their original habitats[60,61]. Although *E. ulmoides* is cultivated primarily in plantations, its dioecious nature and cross-pollination, coupled with seed propagation, result in significant trait variation both within and between half-sibling and full-sibling families[62,63]. Therefore, the species still maintains relatively rich genetic diversity within its populations, with the semiwild population in Shennongjia exhibiting a relatively high level of genetic diversity[62−66]. *E. ulmoides* exhibits rich morphological variation, with genetic differences observed in traits such as bark, leaves, branches, and fruits, leading to the formation of unique natural types. For example, bark characteristics can be categorized into smooth-barked and rough-barked types. Leaf shape variations can be classified into types such as small leaves, long leaves, and dense leaves, among others[1,2,66−68]. Under the influence of different environmental selection pressures across its vast cultivation areas, *E. ulmoides* has developed various geographic provenances. These geographic provenances differ in terms of leaf and seed morphology; Eucommia rubber; and the contents of bioactive compounds, such as aucubin, chlorogenic acid, total flavonoids, geniposidic acid, and geniposide[66,69,70]. Notably, *E. ulmoides* from southern Shaanxi, northeastern Sichuan, northwestern Hunan, and northwestern Guizhou are considered superior provenances[66].

Cross-pollination in *E. ulmoides* results in abundant genetic variation within the species, allowing significant results to be achieved by directly selecting for natural variations. Currently, a series of superior varieties, such as 'Huazhong' and 'Qinzhong', have been selected from natural populations. These varieties are characterized by fast growth and high yields of leaves, male flowers, samaras, and effective compounds[71−76], thereby promoting the improvement of *E. ulmoides* cultivars. Because *E. ulmoides* is a relict tree species that is dioecious and wind-pollinated, the superior types found in nature are themselves products of intraspecific hybridization. Elite trees bred through intensive selection from large natural populations should exhibit greater genetic gains. Consequently, the difficulty of breeding new, improved *E. ulmoides* varieties through simple parental hybridization is very high, making it challenging to surpass the existing selected varieties. Due to the doubling of chromosome numbers, polyploid plants often exhibit significant morphological and physiological changes, such as increased cell volume, larger and thicker leaves, and higher metabolite content. Therefore, polyploid breeding has always been a promising approach for the genetic improvement of *E. ulmoides*[2]. Researchers have conducted extensive studies on the doubling of chromosomes in both somatic and germ cells of this species. These studies include inducing triploidy through endosperm culture[77], treating germinating seeds and seedling growth points with colchicine solution to induce tetraploidy[78,79], and doubling pollen chromosomes[80,81]. Additionally, a series of triploid *E. ulmoides* plants were successfully obtained by inducing the doubling of chromosomes in female gametes through high-temperature treatment[82,83]. These triploid *E. ulmoides* plants often exhibit excellent characteristics, such as larger leaves, faster growth, and significantly increased contents of Eucommia rubber and medicinal components[84], highlighting the potential for the genetic improvement of *E. ulmoides*.

Problems and prospects

The bark of *E. ulmoides* has been a well-established medicinal herb for centuries; however, the utilization of other plant parts has not been as extensively explored. Unlike the bark, the leaves of *E. ulmoides* are a renewable resource that is abundantly available. Therefore, the efficient exploitation of *E. ulmoides* leaves is crucial for the sustainable exploitation of this plant's resources. In 2005, the leaves of *E. ulmoides* were officially recognized in the Chinese Pharmacopoeia. Subsequent studies have revealed that these leaves contain a plethora of physiologically active compounds, often in higher concentrations than those present in the bark. Moreover, in terms of pharmacological efficacy, the leaves and bark of *E. ulmoides* have been found to possess comparable potency[41]. In 2023, the leaves of *E. ulmoides* were officially included in the catalog of substances recognized as both food and traditional Chinese medicinal materials by the National Health Commission and the State Administration for Market Regulation of China. This recognition has opened up significant opportunities for the research, development, and application of *E. ulmoides* leaves across diverse industries, including pharmaceuticals, food products, dietary supplements, animal feed additives, and chemical products.

In reviewing current research, development, and utilization of the bioactive components of *E. ulmoides*, significant milestones have been achieved through collaborative endeavors of all scientific researchers and industrial developers. These advancements encompass the identification of bioactive compounds and their pharmacological properties, the genetic underpinnings of biosynthesis, the spatiotemporal distribution characteristics of these components, the implementation of efficient agricultural practices, the cultivation of new varieties, and the development of comprehensive extraction techniques. These breakthroughs have laid a foundational framework for the comprehensive development of the *E. ulmoides* industry, contributing to the promotion of the entire industrial chain for *E. ulmoides*. However, it is important to recognize that current research on the bioactive substances of *E. ulmoides* still faces several restrictive challenges, which hinder its development and efficient utilization. For instance, current pharmacological research is predominantly confined to ethanol or water extracts of mixed components from *E. ulmoides*. While these extracts have shown notable pharmacological activities in areas such as antioxidant effects, blood pressure reduction, and lipid-lowering, studies on individual components are comparatively limited, and there is a significant lack of in-depth research and understanding of the synergistic effects among the various components. Although the genome sequencing of *E. ulmoides* has been completed, the genetic regulatory mechanisms of most of its bioactive components are still not clearly understood, primarily due to the lack of an established system for *ex vitro* regeneration and genetic function validation of *E. ulmoides*. Research on allelic variations related to relevant traits is rare, and there is a need to enhance the supportive role of basic research in breeding and its applications. The limited size of the remaining wild populations of *E. ulmoides* trees restricts the effectiveness of simple crossbreeding; despite breakthroughs in polyploid breeding, these advancements still depend on a somewhat random selection of parent varieties, indicating a substantial room for improvement in seed selection. The traditional cultivation of *E. ulmoides* as a tree crop involves long cycles, and the mechanization of harvesting is challenging, leading to high labor costs for raw material collection. Meanwhile, the cultivation model for leafy forests is still in the early stages of exploration. The utilization of bioactive substances from *E. ulmoides* is rudimentary, and the benefits are minimal; a comprehensive strategy for the preparation and utilization of various types of bioactive compounds has yet to be fully developed, which represents a key challenge for future industrial applications.

Thus, it is imperative to fully acknowledge and address the restrictive challenges hindering the development of the *E. ulmoides* industry. Focused efforts should be directed toward key medicinal properties and other major target traits, emphasizing efficient detection, and precise assessment of active ingredients in *E. ulmoides*. This approach should build upon the comprehensive collection and preservation of superior genetic resources of *E. ulmoides*, exploring advanced techniques for high-throughput screening and accurate evaluation of active components. Research initiatives should also delve into population genetic diversity, allelic variation patterns of key traits, regulatory networks of genes related to target traits, distinctive gene expression characteristics, and their genetic effects. Such endeavors will effectively promote the integration of conventional breeding with unconventional approaches such as chromosome doubling, genetic transformation, or gene editing, aiming to cultivate new *E. ulmoides* varieties characterized by high yields and elevated levels of medicinal components. Moreover, enhancing the foundational work on the isolation, purification, and pharmacology of key active compounds in *E. ulmoides* is crucial. This includes comprehensive research on the mechanisms of action of individual active compounds and their synergistic effects when used in combination, thereby establishing a robust basis for the development of *E. ulmoides*-derived biopharmaceuticals. Furthermore, there is a pressing need to enhance the foundational work related to the separation, purification, and pharmacological investigation of the key active components of *E. ulmoides*, particularly regarding the mechanisms of action of individual bioactive compounds. A comprehensive understanding of the synergistic effects among various active ingredients and their collective impact on human and animal physiology is equally imperative. Such efforts are essential for establishing a robust foundation for the development of biopharmaceuticals derived from *E. ulmoides*.

By adopting superior varieties, ultrashort-cycle leaf forest cultivation, and mechanized harvesting, raw material costs can be significantly reduced. Additionally, the comprehensive utilization of different plant parts will help distribute raw material costs more effectively. Specifically, leaf veins and bark can be used for gum production and extraction of medicinal compounds, whereas leaf mesophyll can be utilized for pharmaceutical production or as a feed additive or health supplement. The stems can be used for manufacturing particleboard, reconstituted wood, or as substrates for edible fungi, thereby achieving multiple benefits from a single source of raw material. Resolving these issues will undoubtedly catalyze the efficient development of a green circular economy centered on *E. ulmoides*, with a primary focus on pharmaceutical and rubber production. This advancement will propel the *E. ulmoides* industry into a new phase of accelerated growth, fostering sustainable innovation and economic progress.

Author contributions

The authors confirm contribution to the paper as follows: writing - original draft preparation: Li Y; writing - review & editing: Kang X. Both authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare that they have no conflict of interest.

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