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# Ethnobotanical Uses and Phytochemistry of *Eucommia ulmoides*: A Comprehensive Review

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**Abstract** *Eucommia ulmoides*, a widely used medicinal plant in traditional Chinese medicine, has a history of nearly two thousand years. This study systematically reviews the ethnobotanical uses and phytochemical properties of *E. ulmoides*, integrating historical knowledge with modern scientific research to explore its pharmacological activities and potential applications in modern medicine. The previous studies have demonstrated that *E. ulmoides* is rich in various bioactive compounds, including lignans, iridoids, flavonoids, and phenolic acids, which exhibit significant antioxidant, anti-inflammatory, antihypertensive and neuroprotective effects. Additionally, it reveals the potential applications of *E. ulmoides* extracts in treating cardiovascular diseases, neurodegenerative disorders and cancer. By thoroughly analyzing the traditional uses and phytochemical components of *E. ulmoides*, this study provides a scientific foundation for its application in modern medicine and identifies future research directions, particularly in the areas of bioactive compound isolation, pharmacological mechanisms, and clinical applications. This study is expected to promote the sustainable use and development of *E. ulmoides* in both traditional and modern medical systems.

**Keywords** *Eucommia ulmoides*; Ethnobotany; Phytochemistry; Pharmacological activity; Modern medical applications

## 1 Introduction

*Eucommia ulmoides*, commonly known as Dù-zhòng in traditional Chinese medicine (TCM), is the only species within the *Eucommia* genus, belonging to the family Eucommiaceae. It's endemic to China and has been highly valued for its medicinal properties for nearly two thousand years (Wang et al., 2019a). Renowned for its various therapeutic properties, *Eucommia ulmoides* has been extensively used in traditional Chinese medicine for centuries. The bark, leaves, and seeds of *Eucommia ulmoides* are commonly used to treat a range of ailments, including hypertension, arthritis, lower back pain, and immune deficiencies (Feng et al., 2020; Xing et al., 2020). The importance of *Eucommia ulmoides* in Chinese culture is significant, holding a revered position in traditional Chinese medicine and deeply embedded in cultural practices and beliefs related to health and wellness. Its reputation as a potent medicinal plant has been passed down through generations, becoming a crucial symbol of traditional herbal medicine. Additionally, the leaves, bark, and fruits of *Eucommia ulmoides* produce latex when torn, a unique characteristic historically documented (Wang et al., 2019a). Various parts of *Eucommia ulmoides* are widely used in traditional therapies in China, Japan, and Korea, underscoring its broad cultural and medicinal relevance (He et al., 2014).

The historical use of *Eucommia ulmoides* in ethnobotany is well-documented, with records spanning different historical periods. The plant has been a cornerstone in TCM, used to treat a variety of ailments such as hypertension, hyperlipidemia, diabetes, obesity, sexual dysfunction, osteoporosis, Alzheimer's disease, aging, lupus-like syndrome, and for immunoregulation (He et al., 2014; Huang et al., 2021; Sun et al., 2022). Besides, *Eucommia ulmoides* exhibits various pharmacological activities, including antioxidant, anti-inflammatory, neuroprotective, anti-fatigue, anti-aging, anticancer, and immunomodulatory effects. The pharmacological properties of *E. ulmoides* have been extensively studied, revealing a wide range of bioactive compounds including

lignans, iridoids, flavonoids, phenols, steroids, and terpenes (Wang et al., 2019a). These compounds contribute to the plant's diverse therapeutic effects, making it a valuable resource in both traditional and modern medicine.

This study provides a comprehensive review of the ethnobotanical uses and phytochemical properties of *Eucommia ulmoides*, combining historical knowledge with modern scientific research. It examines the traditional uses of *Eucommia ulmoides* and highlights the latest advances in phytochemistry, elucidating the therapeutic potential of the plant and its relevance in modern medicine. The study intends to identify gaps in current research and propose future research directions, particularly in areas such as the isolation of bioactive compounds, pharmacological mechanisms, and clinical applications. This study is expected to deepen the understanding of *Eucommia ulmoides* and its role in both traditional and modern medical systems, reinforcing its status as a medicinal plant of significant cultural and therapeutic value.

## 2 Traditional Ethnobotanical Uses of *Eucommia ulmoides*

### 2.1 Medicinal applications in traditional Chinese medicine

*Eucommia eucommia* is a kind of woody plant with high economic and medicinal value, which was listed as top quality medicine in *Shen Nong's Herbal Classics*. As a cornerstone of TCM, various parts of *Eucommia eucommia*, including the leaf, stem, bark and staminate flower, have been utilized to treat a wide array of ailments for nearly two thousand years. The earliest medical record about the bark of *Eucommia ulmoides* was found in the *Zhi Bai Bing Fang* in the Han Dynasty, which was about the treatment of internal injuries caused by consumptive diseases. The medicinal functions of *Eucommia eucommia* leaves, flowers, fruits and stems were similar to that of barks, which expounded in another pharmaceutical book named *Ben Cao Tu Jing* in the Song Dynasty (Wang et al., 2019b). Because of the *Eucommia eucommia*'s warm medicine nourishes the body, it can enter the liver meridian to tonify the kidneys and prevent miscarriage, was recorded in *Ben Cao Gang Mu* (Bao et al., 2024). China is a multi-ethnic country, in which people of all ethnic groups have accumulated a wealth of medical theories and drug experiences. Regarding the medicinal use of *Eucommia eucommia* by some ethnic minority groups in China, Jia and Li (2005) have summarized in the *Zhong Guo Min Zu Yao Zhi Yao* (Table 1).

Table 1 The traditional medicine application of *E. ulmoides* recorded by ethnic minority groups in China

| Ethnic minorities | Ethnic medicine names | Medicinal part | Medicinal value | Medicinal record |
|---|---|---|---|---|
| Yi | / | Stem/bark | Kidney vacuity, lumbar pain, inability of the extremities, rheumatism bone pain, ache all over, fetal irritability, sexual dysfunction | *Ai Lao* |
| Shui | Bimei Duzhong | Stem/bark | Hypotension, nephritis edema | *Shui Yi Yao* |
| Lisu | Sigongzi | Bark | Low back pain, rheumatism, dizziness, hypotension, restless fetus, falls | *Nu Jiang Yao* |
| Maonan | Meiduzhong | Bark | Kidney vacuity, lumbar pain | *Gui Yao Bian* |
| Miao | Ndui zhoux sod, Det dent, Det uab udfab | Stem/bark | Lumbar pain, fetal irritability | *Miao Yi Yao* |
| | | Bark | Kidney vacuity, lumbar pain, waist-leg weakness, fetal irritability, threatened abortion, hypertension | *Xiang Lan Kao* |
| | Det dent | Stem/bark | Lumbar pain, fetal irritability | *Miao Yao Ji* |
| | Keliu | Bark | External treatment of knife wounds | *Gui Yao Biao* |
| Hani | Qida | Stem/bark, leaves | Fracture | *Dian Yao Lu* |
| | | Bark | The Formula is used for the wound cure | *Dian Sheng Zhi* |
| De'ang | / | Bark | Knife wound, waist and knee pain, fetal irritability, hypertension | *Dian Sheng Zhi* |
| Jingpo | Sikjicq | / | Hypertension, giddy and dazzled, kidney deficiency and frequent micturition, fetal irritability | *De Hong Yao Lu* |
| Dai | Yaregao, Dedai | Bark | The formula is used for the wound cure | *Dian Sheng Zhi* |
| Dong | Meix sabt enl, Sangp meix sabt enl | Bark | Spermatorrhea | *Dong Yi Xue* |
| Tibetan | Dabusang | Bark | Stomach heat, eye disease, bone fracture, catagma, sore and ulcer | *Zang Ben Cao* |
| Va | Luokaoyangyi | Bark | Chronic kidney disease, hypertension | *Wa Zu Shi Liao (Ⅲ)* |

Note: /: No related information

Relevant statistics shown that, as of 2019, among the 9,985 varieties of proprietary Chinese medicines that have been already on the market, 220 of them contained *Eucommia eucommia*, which were mainly used in the fields of internal medicine, orthopedics, gynecology, ophthalmology and surgery (Li et al., 2021). Historical records highlight its use in managing conditions such as hypertension, hyperlipidemia, diabetes, obesity, sexual dysfunction, osteoporosis, Alzheimer's disease, aging, lupus-like syndrome, and immunoregulation (He et al., 2014; Wang et al., 2019a). For example, studies have found that *Eucommia ulmoides* extracts can alleviate the damage caused by hypertension by regulating blood pressure, improving kidney function, and reducing the levels of inflammatory factors. Specifically, by modulating the gut microbiota, *Eucommia ulmoides* extracts can enrich bacterial strains with antihypertensive effects, such as *Parabacteroides*, suggesting that *Eucommia ulmoides* exerts its antihypertensive effects through the regulation of gut microbiota (Yan et al., 2022). *Eucommia ulmoides* cortex extract inhibited palmitateinduced endoplasmic reticulum stress, reducing hepatic lipid accumulation through secretion of apolipoprotein B and associated triglycerides and cholesterol in hepatocytes (Lee et al., 2013). *Eucommia ulmoides* leaves extract may partly ameliorate hyperglycemia and hyperlipidemia with type 2 diabetes through increasing glycolysis, suppressing gluconeogenesis and the biosynthesis of fatty acid and cholesterol in the liver (Park et al., 2006). In addition, another research has revealed that the extracts of *Eucommia ulmoides* male flower ameliorated AD-like pathology in zebrafish possibly by inhibiting excessive autophagy and the abnormal expressions of *ache* and *slc6a3* genes (Sun et al., 2023).

Additionally, *Eucommia ulmoides* has been employed to alleviate lumbar pain, knee pain, osteoporosis, hepatoprotection, paralysis, intestinal hemorrhages, vaginal bleeding, abortion, spermatorrhea, and foot fungus (Huang et al., 2021). For instance, *E. ulmoides* leaf extract may have curative properties for bone mineral density and body mass index in ovariectomy rats, and could provide an alternative therapy for the prevention of both postmenopausal osteoporosis and obesity (Zhang et al., 2012). Moreover, 5-(hydroxymethyl)-2-furaldehyde, isolated from *Eucommia ulmoides* Oliver Bark, not only inhibited the formation of adipose cells obviously, but also enhanced the osteoblastogenesis (Tan et al., 2014). The plant's extracts and active components have shown significant therapeutic effects, including antioxidant, anti-inflammatory, neuroprotective, anti-fatigue, anti-aging, anti-cancer, and immunoregulatory activities.

### 2.2 Non-medicinal uses in various cultures

Beyond its medicinal applications, *Eucommia ulmoides* has found various non-medicinal uses across different cultures. In traditional Chinese practices, the plant's latex, obtained by tearing its leaves, bark, and fruit, has been used for its unique properties (Huang et al., 2021). Compared with natural rubber, the chemical structure of Eucommia ulmoides rubber is trans-1, 4-polyisoprene, the structure is more regular to crystallize easyly, and has the double characteristics of plastic and rubber (Wei et al., 2021). Therefore, it has been developed for a variety of innovative applications, such as a thermoplastic material, thermoelastic shape memory material (Kang et al., 2022), vibrationand sound-absorbing materials (Su et al., 2022). It not only has enriched the research field of materials science, but also promoted the application and development of gutta-percha in textile, aerospace, transportation, sports and construction (Wang et al., 2019a; Yan et al., 2024).

Furthermore, the bioactive chemicals extracted from different parts of the plant, such as leaves, seeds, bark, and staminate flowers, are widely used as raw materials for food, powdery extracts and tinctures (Zhu and Sun, 2018; Ding et al., 2020). For instance, *Eucommia ulmoides* leaf superfine powder was used as an additive in the fermentation of glutinous rice (*Semen Oryzae Glutinosae*), could increase the contents of flavonoids, free amino acids, polyphenols and polysaccharides of sweet rice wine, and enhance its antioxidant activity (Ren et al., 2022). As a feed additive, it could increase the n-3 fatty acids content and decrease the n-6: n-3 PUFA ratio in egg yolk without affecting laying performance or egg quality (Feng et al., 2023). In flower preservation, pretreated with aqueous solution of Ag-NPs, synthesized with the leaf extract of *Eucommia ulmoides*, could effectively reduced bacteria-induced xylem blockage of cut tree peony, resulting in improved water uptake, extended vase life, and enhanced postharvest quality (Ma et al., 2023).

### 2.3 Conservation of traditional knowledge

Protecting traditional knowledge related to *Eucommia ulmoides* is of great significance in promoting its sustainable use and further research. As a traditional medicinal herb, *Eucommia ulmoides* has been extensively documented in historical literature, with its applications spanning multiple historical periods. Preserving and passing on this valuable ethnobotanical knowledge not only helps to understand how *Eucommia ulmoides* has been used in different cultural contexts but also provides valuable references for modern scientific research (Wang et al., 2019a). By documenting and deeply studying the traditional applications of *Eucommia ulmoides*, we can uncover its phytochemical components and pharmacological properties, laying the foundation for its applications in medicine and health care.

The protection of traditional knowledge related to *Eucommia ulmoides* involves not only the documentation of historical records but also the support of modern scientific research. Ongoing research can reveal potential new applications of *Eucommia ulmoides*, promoting its commercial development as a traditional medicine and health food (He et al., 2014; Wang et al., 2019a; Sayed et al., 2021). This study not only contributes to the inheritance and development of ethnobotanical knowledge but also brings new opportunities to the modern medical and health industries. Protecting and promoting the traditional knowledge of *Eucommia ulmoides* is not only a respect for history but also a drive for future innovation.

## 3 Phytochemistry of *Eucommia ulmoides*

### 3.1 Major chemical constituents

*Eucommia ulmoides* is rich in lignans and iridoids, which are among the primary bioactive compounds isolated from this plant, and contribute significantly to its pharmacological properties. Lignans such as pinoresinol diglucoside and syringaresinol have been identified, along with iridoids like geniposidic acid and aucubin (He et al., 2014; Wang et al., 2019a). *Eucommia* pinoresinol diglucoside is a natural blood pressure lowering compound. As a candidate drug for the treatment of cardiovascular diseases, it could prevent the dysfunction of venous endothelial cells induced by oxidized low density lipoprotein (Yao et al., 2016). It also could mitigate dexamethasone-induced osteoporosis and chondrodysplasia by promoting bone formation and activating Wnt signaling (Zuo et al., 2024). Study has shown that the glucoside structure of lignans was extremely important, it would lose the ability to regulate blood pressure without the glucoside structure (Sih et al., 1976). Geniposide is a bioactive iridoid glucoside, which has significant therapeutic effect on digestive, cardiovascular and central nervous system diseases. Through activating AMPK- $\alpha$ and Sirt1 pathways, it's able to reduce the heart damage caused by obesity symptoms (Ma et al., 2018), ameliorate DEX-induced osteoblast apoptosis by activating autophagy through GLP-1R/PI3K/AKT/mTOR pathway (Huang et al., 2022b), also could produce anti-inflammatory effects by reducing the release of inflammatory cytokines (Li et al., 2019), alleviate osteoarthritis through inhibiting inflammation and chondrocytes ferroptosis via Nrf2 signalling pathway (Sun et al., 2024).

Flavonoids and phenolic acids are also abundant in *E. ulmoides*. It contains 25 different flavonoids with different substituents, which have significant effects on treating cardiovascular diseases such as coronary heart disease and hypertension (Liu et al., 2020). Key flavonoids include quercetin and kaempferol, which have been shown to possess strong antioxidant and anti-inflammatory activities (Bai et al., 2015). The total flavonoids from *E. ulmoides* leaves can significantly alleviate neurological damage caused by ischemic stroke by inhibiting oxidative stress, including decrease the levels of reactive oxygen species, lactate dehydrogenase, and malondialdehyde, while increase catalase and glutathione (Qin et al., 2024). Quercetin glycoside, which from *E. ulmoides* leaves, could bind to insulin receptors, and improve insulin resistance as demonstrated by the increased uptake of glucose and glycogen production through a signaling pathway called IRS-1/PI3K/Akt/GSK-3 (Tang et al., 2023).

### 3.2 Bioactive compounds with therapeutic potential

The antioxidant properties of *E. ulmoides* are primarily attributed to its high content of flavonoids and phenolic acids. Compounds like quercetin and chlorogenic acid have demonstrated significant free radical scavenging activities, which help in mitigating oxidative stress-related damage (Bai et al., 2015; Gong et al., 2022). These antioxidants play a crucial role in the plant's ability to protect against various diseases, including

neurodegenerative disorders and cardiovascular diseases (Tang et al., 2021; Gong et al., 2022). Chlorogenic acid could cross the blood-cerebrospinal fluid barrier to exhibit its neuron protection and promotion of serotonin release through enhancing synapsin I expression, so that it may be developed as the natural drugs for the treatment of depression (Wu et al., 2016).

*E. ulmoides* contains several compounds with potent anti-inflammatory effects. Iridoids such as aucubin and geniposidic acid have been shown to inhibit the production of pro-inflammatory cytokines like TNF-α and IL-1β (Wang et al., 2016; Tang et al., 2021). Additionally, flavonoids like quercetin and kaempferol inhibit the NF-κB pathway, further contributing to their anti-inflammatory properties (Bai et al., 2015). These bioactive compounds are effective in treating conditions such as rheumatoid arthritis and gastric ulcers (Wang et al., 2016; Gong et al., 2022).

### 3.3 Methods of phytochemical analysis

Chromatography techniques are widely used for the analysis of phytochemicals in *E. ulmoides*. High-performance liquid chromatography (HPLC) is commonly employed to separate and quantify various bioactive compounds, including iridoids, flavonoids, and phenolic acids (Kim et al., 2009; Gong et al., 2022). Gas chromatography-mass spectrometry (GC-MS) has also been used to analyze the sterol profiles in *E. ulmoides* seed oil, identifying compounds such as β-sitosterol (Tang et al., 2021).

Spectroscopy methods, including nuclear magnetic resonance (NMR) and electrospray ionization mass spectrometry (ESIMS), are essential for the structural elucidation of bioactive compounds in *E. ulmoides*. These techniques have been used to identify and confirm the structures of various lignans, iridoids, and flavonoids isolated from the plant (Bai et al., 2015). Additionally, ultra-performance liquid chromatography (UPLC) coupled with mass spectrometry provides a rapid and accurate method for analyzing the main components in *E. ulmoides* extracts (Gong et al., 2022). By employing these advanced analytical techniques, researchers can better understand the complex phytochemical composition of *E. ulmoides* and its potential therapeutic applications.

## 4 Pharmacological Activities of *Eucommia ulmoides*

### 4.1 Anti-inflammatory and antioxidant properties

*Eucommia ulmoides* exhibits significant anti-inflammatory properties through various mechanisms. The polysaccharides derived from *E. ulmoides* (EUP) have been shown to reduce inflammation by modulating the TLR-4-NF-κB pathway, which is crucial in the inflammatory response. Specifically, these polysaccharides decrease the levels of pro-inflammatory cytokines such as TNF-α and IL-1β, thereby mitigating inflammation in hepatic ischemia-reperfusion injury (Figure 1) (Gao et al., 2020). Additionally, the iridoid glycosides present in *E. ulmoides* seeds, such as aucubin, have demonstrated inhibitory effects on nitric oxide (NO) production in LPS-stimulated microglial cells, further contributing to their anti-inflammatory potential (Tang et al., 2021).

The antioxidant properties of *E. ulmoides* are primarily attributed to its ability to enhance the activity of antioxidant enzymes and reduce oxidative stress markers. Studies have shown that *E. ulmoides* leaf extracts (ELE) increase the levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) while decreasing malondialdehyde (MDA) levels in various tissues, indicating a reduction in oxidative stress (Ding et al., 2020; Liao et al., 2021). These antioxidant effects are crucial in preventing diseases associated with oxidative stress, such as cardiovascular diseases and neurodegenerative disorders (Huang et al., 2021; Huang et al., 2022a).

### 4.2 Cardiovascular and metabolic health benefits

*E. ulmoides* has been traditionally used to manage hypertension, and modern research supports its efficacy in lowering blood pressure. The bark extract of *E. ulmoides* has been shown to reduce blood pressure in high-salt diet and L-NAME-induced hypertensive mice by modulating the gut microbiota and reducing inflammatory cytokines (Yan et al., 2022). Additionally, the leaf extract enhances NO production in endothelial cells, which plays a critical role in vasodilation and blood pressure regulation (Lee et al., 2018).

*E. ulmoides* also contributes to metabolic health by regulating lipid metabolism. The extracts from *E. ulmoides* have been found to improve lipid profiles by reducing serum cholesterol and triglyceride levels. This effect is partly due to the enhancement of lipid metabolism enzymes and the modulation of gut microbiota, which collectively help in maintaining healthy lipid levels (Wang et al., 2019a; Zhao et al., 2022).

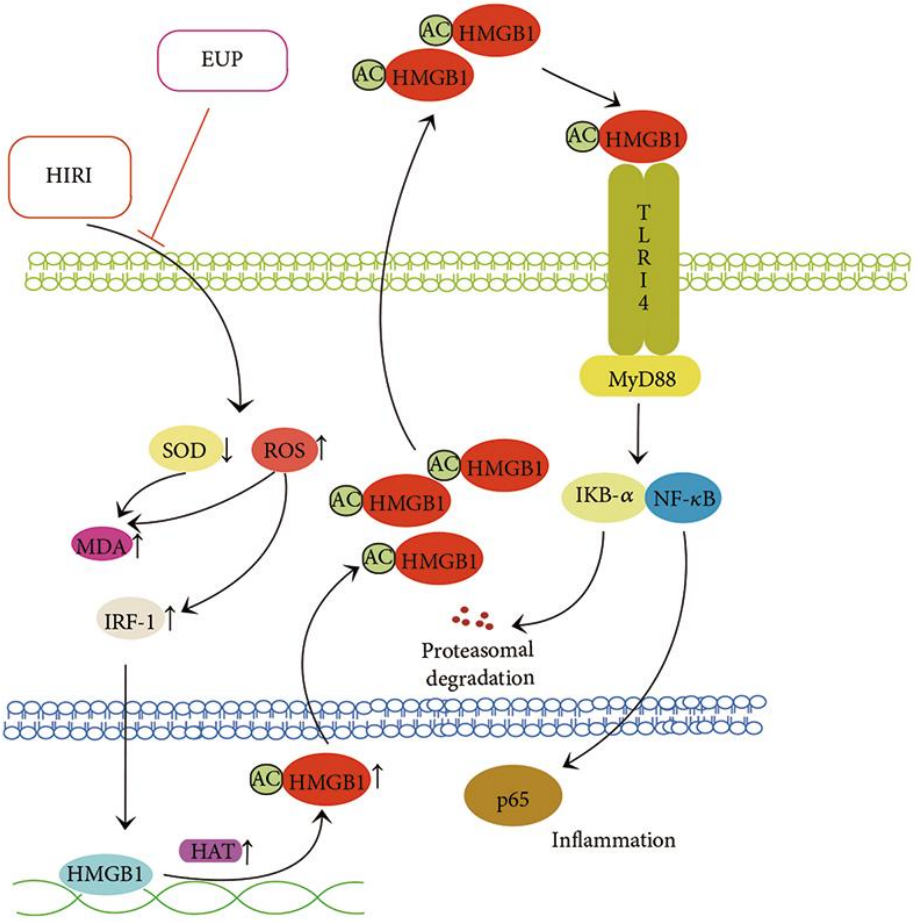


Figure 1 The role of EUP in hepatic ischemia-reperfusion injury (Adopted from Gao et al., 2020)

Image caption: The figure indicates that EUP reduces ROS production, inhibits HMGB1 release and the activation of its downstream TLR-4-NF-κB signaling pathway, thereby alleviating inflammation and oxidative stress caused by ischemia-reperfusion, ultimately reducing hepatocyte damage and liver necrosis. This result confirms the significant anti-inflammatory and antioxidant effects of EUP, supporting its potential application in preventing and treating hepatic ischemia-reperfusion injury (Adapted from Gao et al., 2020)

### 4.3 Neuroprotective and anticancer activities

*E. ulmoides* exhibits neuroprotective properties that are beneficial in the context of neurodegenerative diseases. The iridoid glycosides, particularly aucubin, have been shown to protect neuronal cells by inhibiting oxidative stress and inflammation. These compounds reduce NO production and enhance the expression of antioxidant genes, thereby protecting against neurodegenerative conditions such as Parkinson's and Alzheimer's diseases (Huang et al., 2021; Tang et al., 2021).

The anticancer potential of *E. ulmoides* is attributed to its ability to modulate various cellular pathways involved in cancer progression. The extracts from *E. ulmoides* have been shown to inhibit cancer cell proliferation and induce apoptosis through mechanisms involving the regulation of the NEI network and inflammatory pathways (Zhao et al., 2022). Additionally, the phytosterols and iridoids present in *E. ulmoides* seeds have demonstrated significant anti-inflammatory and anticancer activities, suggesting their potential use in cancer prevention and therapy (Tang et al., 2021). By understanding these pharmacological activities, researchers can further explore the therapeutic potential of *E. ulmoides* in various diseases, providing reference for new clinical applications and drug development.

## 5 Mechanisms of Action of *Eucommia ulmoides*

### 5.1 Cellular pathways

*Eucommia ulmoides* exerts its pharmacological effects through various cellular pathways, prominently involving the PI3K/Akt signaling pathway. For instance, the flavonoids from *Eucommia ulmoides* leaves (TFEL) have been shown to regulate the PI3K/Akt pathway, which plays a crucial role in improving insulin resistance and regulating glucose and lipid metabolism in polycystic ovary syndrome (PCOS) models (Peng et al., 2021). Additionally, *Eucommia ulmoides* flavones have demonstrated protective effects against enterocyte damage induced by lipopolysaccharide (LPS) by modulating the PI3K-NFκB signaling pathway, enhancing cell viability, and reducing apoptosis (Hussain et al., 2020). These pathways are critical in mediating the anti-inflammatory and cytoprotective effects of *Eucommia ulmoides*.

### 5.2 Molecular targets

The active compounds in *Eucommia ulmoides* target several key molecular entities. For example, in the treatment of Parkinson's disease (PD), *Eucommia ulmoides* downregulates the expression of p38 and JNK, which are upstream genes of the *Fosl2*, thereby reducing neuroinflammation (Fan et al., 2020). In the context of nonalcoholic fatty liver disease (NAFLD), *Eucommia ulmoides* components, particularly flavonoids, interact with lipid metabolism-regulating core proteins such as PPARγ, enhancing lipid metabolism and autophagy (Gong et al., 2021). The study found that *Eucommia ulmoides* leaf extract 50 significantly reduced lipid accumulation in HepG2 cells by regulating PPARγ expression and activating autophagy (Figure 2).

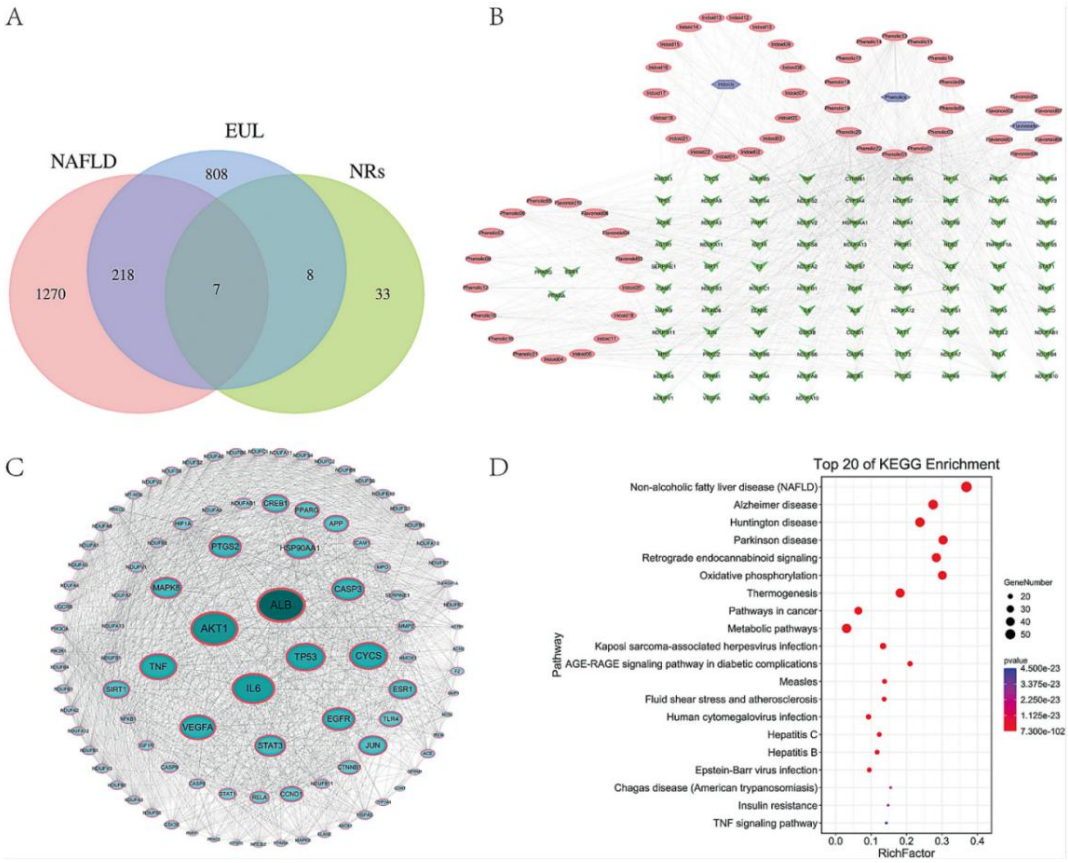


Figure 2 Network pharmacology analysis of *Eucommia ulmoides* leaves (Adopted from Gong et al., 2021)

Image caption: Figure A shows the target analysis of *Eucommia ulmoides* leaves related to NAFLD, while Figure B presents the composition-target network, revealing the association between multiple active components and the core targets of NAFLD. Figure C displays the protein-protein interaction (PPI) network, highlighting key targets such as PPARγ, ESR1, and PPARA. Figure D shows the KEGG enrichment analysis, indicating that these targets are primarily involved in metabolic pathways related to NAFLD. These analyses suggest that the flavonoid and phenolic components in *Eucommia ulmoides* leaves may exert therapeutic effects by modulating these key targets (Adapted from Gong et al., 2021)

Additionally, in a study on diabetic nephropathy, Do et al. (2018) found that *E. ulmoides* effectively reduced the accumulation of advanced glycation end-products (AGEs) and mitigated renal damage in streptozotocin-induced diabetic mice. Notably, *E. ulmoides* treatment did not alter blood glucose levels but significantly upregulated the expression of glyoxalase 1 (Glo1) and nuclear factor erythroid 2-related factor 2 (Nrf2), both of which play crucial roles in detoxifying AGEs and reducing oxidative stress. Histological analysis revealed that *E. ulmoides* significantly reduced glycation and oxidative damage in kidney tissues. This suggests that *E. ulmoides*, through its antioxidative and anti-glycation properties, may be a potential therapeutic agent for preventing or treating diabetic complications, particularly in protecting kidney function.

### 5.3 Synergistic effects

The therapeutic efficacy of *Eucommia ulmoides* is often attributed to the synergistic interactions between its various bioactive compounds. For instance, the combination of *Eucommia ulmoides* and *Dipsaci Radix* (EU-DR) has been shown to exert a multi-component, multi-target, and multi-pathway interaction mechanism in the treatment of osteoporosis. The flavonoids in EU-DR play a significant role in regulating osteoclast differentiation-related signaling pathways, demonstrating strong binding efficiency to target proteins involved in bone metabolism (Feng et al., 2022).

Similarly, the multitarget mechanism of *Eucommia ulmoides* in treating ankylosing spondylitis involves the interaction of its bioactive molecules with multiple targets such as IL-1B, PTGS2, and IL-8, mediated through interleukin-17 and TNF-α signaling pathways (Zhang et al., 2022). These synergistic effects highlight the complex interplay of *E.ulmoides*'s compounds in modulating various biological processes and enhancing therapeutic outcomes.

## 6 Case Studies

### 6.1 The antihypertensive effects of *Eucommia ulmoides* extract through gut microbiota modulation

The lignans, flavonoids, and iridoids in *E. ulmoides* extracts are considered the primary active components responsible for its antihypertensive effects. However, the significant antihypertensive effects remain difficult to fully explain due to the low oral bioavailability of these compounds. In recent years, researchers have begun to focus on the relationship between *E. ulmoides* extracts and the gut microbiota, hypothesizing that gut microbiota may play a key role in the antihypertensive effects.

Yan et al. (2022) explored the mechanism by which *E. ulmoides* extracts exert their antihypertensive effects by regulating the gut microbiota, particularly by enriching *Parabacteroides* strains. In a six-week treatment of hypertensive mouse models induced by a high-salt diet and N(omega)-Nitro-L-arginine methyl ester, *E. ulmoides* extracts were administered. The results showed that *E. ulmoides* extracts significantly lowered blood pressure, improved kidney function, and reduced inflammation. Moreover, the study found that *E. ulmoides* extracts significantly altered the diversity and composition of the gut microbiota, especially by enriching *Parabacteroides* strains. Further animal experiments confirmed the crucial role of the *Parabacteroides* strain XGB65 in reducing blood pressure and renal inflammation (Figure 3).

The study provides the first evidence that *E. ulmoides* reduces blood pressure through the regulation of gut microbiota, revealing the important role of the *Parabacteroides* strain XGB65 in this process. This discovery offers significant theoretical and practical references for the development of novel antihypertensive probiotics and prebiotic therapies, with potential clinical application value.

### 6.2 Effects of *Eucommia ulmoides* male flower extracts on Alzheimer's disease

*E. ulmoides*, a traditional Chinese medicinal herb, has garnered significant attention for its various bioactive components, known for their antioxidant and anti-inflammatory effects. Research indicates that the male flowers of *E. ulmoides* also contain abundant active compounds, which hold therapeutic potential for Alzheimer's disease (AD) (Huang et al., 2021; Sun et al., 2022).

Sun et al. (2022) investigated the therapeutic effects of *E. ulmoides* male flower extracts (EUMF) in a zebrafish model of Alzheimer's disease, focusing particularly on its impact on β-amyloid (Aβ) deposition, the expression of autophagy-related genes, and acetylcholinesterase (AChE) activity. The study found that EUMF significantly alleviated AD-like symptoms induced by aluminum chloride (AlCl3) in zebrafish. This was evidenced by a reduction in Aβ plaques in the zebrafish brain, inhibition of AChE activity, and decreased brain cell apoptosis (Figure 4). Additionally, EUMF modulated the expression of autophagy-related genes (such as *ambra1a*, *atg5*, *ulk1b*, and *lc3b*) and neurotransmitter regulation-related genes (*ache* and *slc6a3*), which play critical roles in AD pathology.

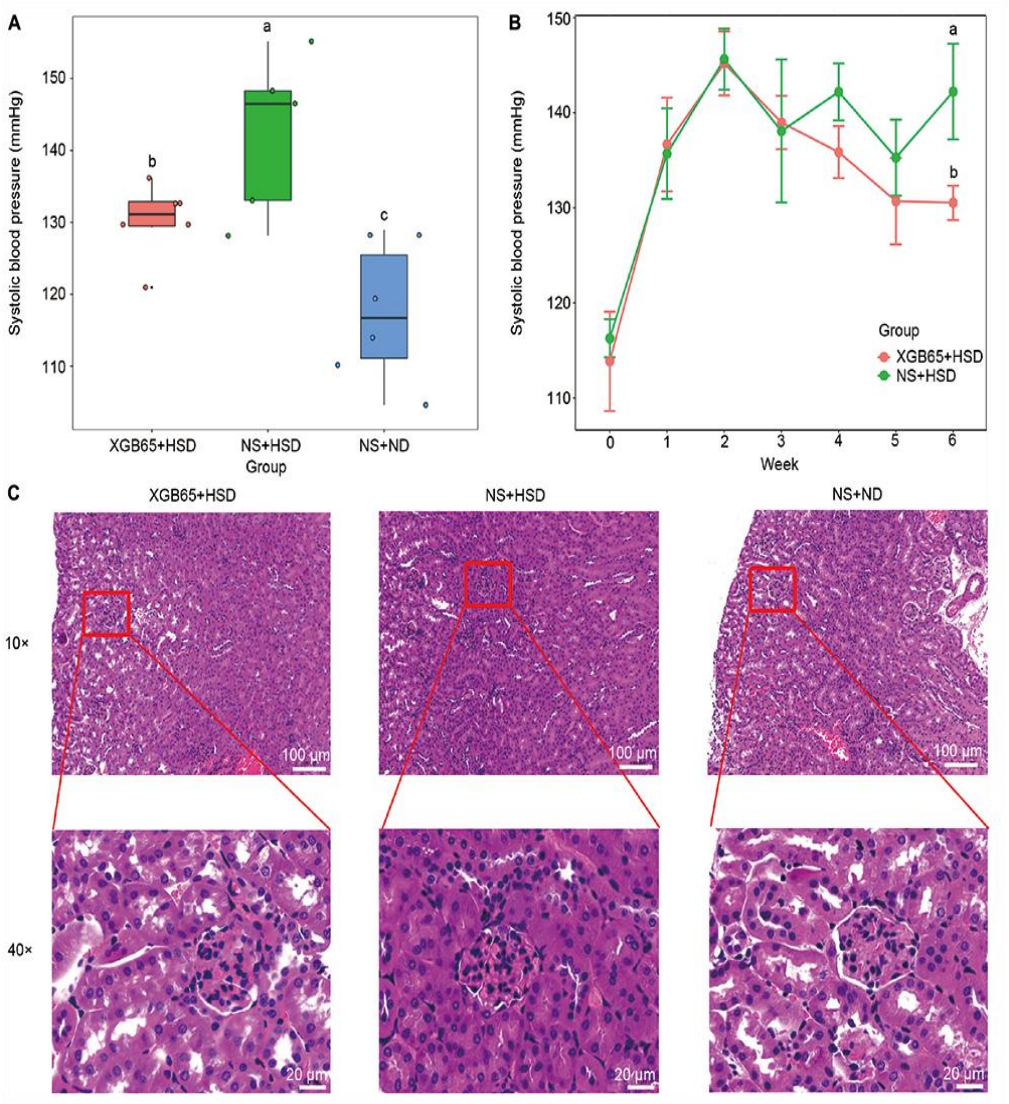


Figure 3 *Parabacteroides* strain XGB65 reduces blood pressure. Blood pressure (A) in the XGB65 + HSD, NS + HSD, and NS + ND groups in week 6 and (B) in the XGB65 + HSD and NS + HSD groups from the beginning of the experiment to the end of week 6 (2-week L-NAME treatment, 1-week washout period, XGB65 + HSD treatment from week 4 to week 6). (C) HE staining of kidney tissues in the XGB65 + HSD, NS + HSD, and NS + ND groups (10 × , scale bars = 100 μm; 40 × , scale bars = 20 μm) (Adopted from Yan et al., 2022)

Image caption: The figure demonstrates the antihypertensive effects and the improvement of kidney inflammation in high-salt diet-induced hypertensive mice treated with *Parabacteroides* strain XGB65. The results show that compared to the control group, the blood pressure in the XGB65-treated group was significantly reduced, and the expression of IL-17A in the kidneys was also significantly decreased. Histological analysis of the kidneys revealed that pathological damage was improved in the XGB65-treated group. These findings confirm that *Parabacteroides* strain XGB65 has antihypertensive and anti-inflammatory effects, further supporting the crucial role of gut microbiota in the antihypertensive mechanism of *E. ulmoides* and highlighting the therapeutic potential of the XGB65 strain (Adapted from Yan et al., 2022)

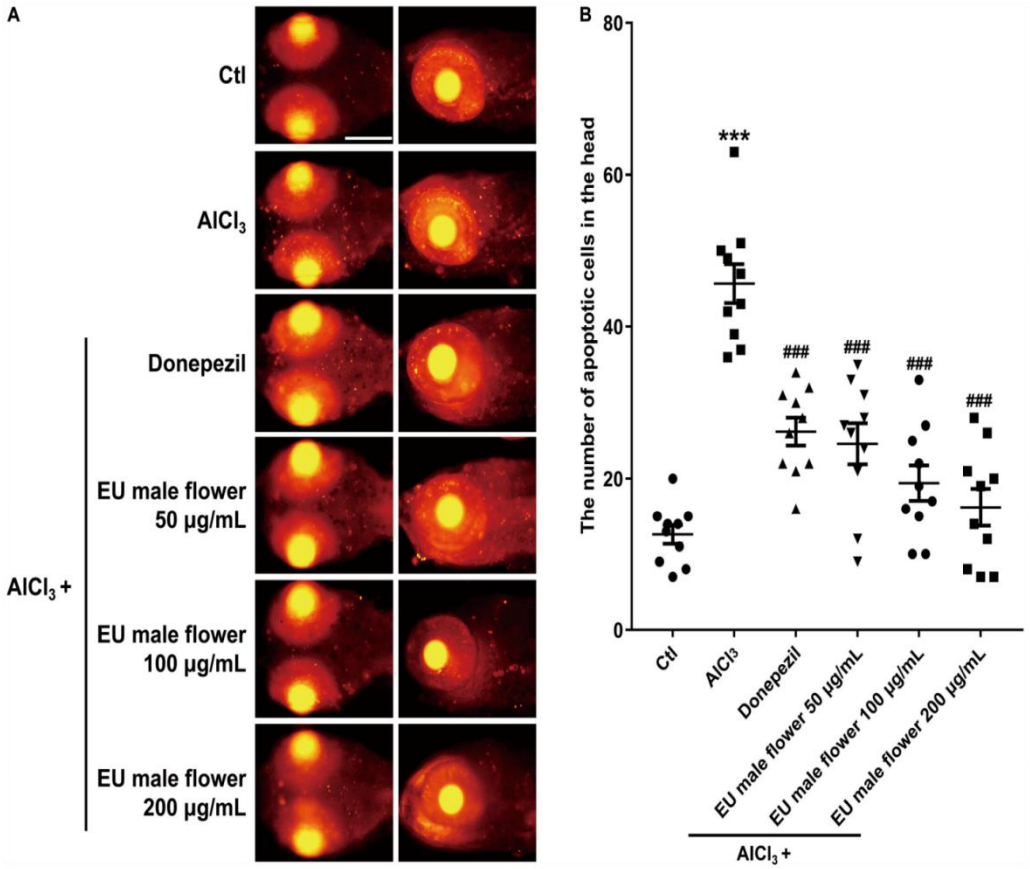


Figure 4 Effect of EUMF on apoptosis in the brains of the AlCl3-modeled zebrafish (Adopted from Sun et al., 2022)

Image caption: Figure A shows the location of apoptotic cells in the zebrafish brain through TUNEL staining, while Figure B quantifies the number of apoptotic cells in each treatment group. The results indicate that AlCl3 treatment significantly increased the number of apoptotic cells in the zebrafish brain, whereas EUMF treatment significantly reduced these numbers. This figure reveals the protective effect of EUMF against AlCl3-induced apoptosis, further validating its potential as an anti-Alzheimer's disease agent (Adapted from Sun et al., 2022)

The study suggests that *E. ulmoides* male flower extracts have a significant ameliorating effect on Alzheimer's disease-like pathology, with mechanisms potentially involving the inhibition of excessive autophagy and the regulation of acetylcholinesterase and dopamine transporter gene expression. The flavonoids in EUMF are likely the key compounds responsible for its therapeutic effects. *E. ulmoides* male flower extracts show promise as a potential therapeutic agent for Alzheimer's disease, acting through multiple pathological pathways and offering new perspectives and directions for the comprehensive treatment of AD.

### 6.3 Clinical trials involving *E. ulmoides* extracts

Clinical trials have further substantiated the therapeutic potential of *E. ulmoides* extracts. In one study, the administration of *E. ulmoides* leaf extract to ox-LDL-treated human endothelial cells resulted in a significant recovery of nitric oxide levels and a reduction in oxidative stress, suggesting its potential in preventing vascular endothelial dysfunction (Lee et al., 2018). Another clinical investigation demonstrated that *E. ulmoides* extract could lower blood pressure in hypertensive patients by improving renal hemodynamics and reducing oxidative stress (Ishimitsu et al., 2021). These findings are consistent with traditional uses and provide a scientific basis for the continued use of *E. ulmoides* in cardiovascular treatments.

*E. ulmoides* has shown significant promise in cardiovascular treatments, particularly in reducing blood pressure and improving vascular health. Its traditional uses are supported by modern research, which has elucidated the mechanisms behind its antihypertensive effects and highlighted its potential in clinical applications (Ishimitsu et al., 2021; Yan et al., 2022).

## 7 Environmental and Ecological Impacts on *Eucommia ulmoides*

### 7.1 Ecological requirements for *E. ulmoides* cultivation

*E. ulmoides*, a dioecious and pharmaceutically significant tree species, is endemic to China and thrives in specific ecological conditions. The species is predominantly found in the Wuling Mountains and other regions with similar geoclimatic conditions. Studies have shown that the average annual temperature and rainfall are critical factors influencing the phenotypic traits of *E. ulmoides* (Xie et al., 2023). These climatic conditions significantly affect leaf, fruit, and seed sizes, which are essential for the plant's growth and medicinal properties (Wang et al., 2023). Additionally, the annual sunshine duration has been identified as a crucial factor, positively correlating with economic traits and leaf yield, while negatively correlating with growth traits (Deng et al., 2022). Therefore, selecting appropriate cultivation areas with optimal temperature, rainfall, and sunshine duration is vital for the successful cultivation of *E. ulmoides*.

### 7.2 Impact of environmental factors on phytochemical profiles

Environmental factors play a significant role in determining the phytochemical profiles of *E. ulmoides*. Variations in genotype, site, and genotype × environment interactions have been shown to influence the phenotypic traits and, consequently, the phytochemical composition of the plant. For instance, the gutta-percha content, total number of leaves, and chlorogenic acid content exhibit significant differences based on these environmental interactions (Deng et al., 2022). The phenotypic differentiation among populations of *E. ulmoides* is significantly correlated with geographic and climatic distances, indicating that environmental factors such as temperature and rainfall are crucial in shaping the phytochemical profiles (Wang et al., 2023). These findings suggest that environmental conditions must be carefully managed to optimize the production of valuable phytochemicals in *E. ulmoides*.

### 7.3 Conservation strategies for wild populations

Conserving wild populations of *E. ulmoides* is essential for maintaining genetic diversity and ensuring the species' long-term survival. The phenotypic variation within and among natural populations highlights the need for targeted conservation strategies (Wang et al., 2018; Kardos et al., 2021). The significant phenotypic differentiation driven by geographic and climatic factors suggests that conservation efforts should focus on preserving diverse habitats that support various phenotypic traits (Wang et al., 2023). Additionally, the identification of key environmental factors, such as average annual temperature and rainfall, can inform the development of conservation plans that prioritize areas with optimal conditions for *E. ulmoides* growth (Deng et al., 2022; Wang et al., 2023). Implementing genetic improvement programs and resource management strategies can further enhance the conservation of this valuable species, ensuring its continued availability for medicinal and economic uses.

## 8 Challenges and Future Research Directions

### 8.1 Challenges in sustainable cultivation

Sustainable cultivation of *E. ulmoides* faces several significant challenges, primarily due to the plant’s specific environmental requirements and the increasing demand for its medicinal properties. The cultivation of *E. ulmoides* requires specific soil types, optimal temperature ranges, and careful management of water resources to ensure healthy growth and high yield of bioactive compounds (Su et al., 2021; Dong et al., 2022). Climate change, with its unpredictable weather patterns, poses a threat to these conditions, potentially leading to reduced productivity (Wang et al., 2023). Additionally, as demand for *E. ulmoides* continues to grow, over harvesting and unsustainable agricultural practices risk depleting natural resources and compromising the genetic diversity of the species. There is a pressing need for developing sustainable agricultural practices that balance the need for high yield with environmental conservation, including the promotion of agroforestry systems, organic farming, and the development of resistant varieties through advanced breeding techniques.

### 8.2 Opportunities for new pharmacological discoveries

Despite the challenges in sustainable cultivation, *E. ulmoides* presents numerous opportunities for new pharmacological discoveries. The plant’s rich phytochemical profile, which includes iridoids, lignans, flavonoids, and phenolic acids, offers a promising foundation for the development of new therapeutic agents (Liu et al., 2020).

Recent research has identified the potential of *E. ulmoides* extracts in treating a range of conditions, including hypertension, osteoporosis, and neurodegenerative diseases (Han et al., 2021; Liu et al., 2022). With the advancement of modern analytical techniques, there is an opportunity to explore lesser-known compounds in *E. ulmoides*, elucidating their mechanisms of action and potential therapeutic benefits. Furthermore, the integration of traditional knowledge with modern scientific research can lead to the discovery of novel bioactive compounds, contributing to the development of new drugs and health supplements.

### 8.3 Future research directions in ethnobotany and phytochemistry

Future research on *E. ulmoides* should focus on bridging the gap between ethnobotanical knowledge and modern phytochemistry to fully harness the plant's medicinal potential. In ethnobotany, there is a need for comprehensive studies documenting traditional uses of *E. ulmoides* across different cultures, as well as the ecological knowledge associated with its cultivation and harvest. This information is crucial for informing sustainable use practices and for identifying new applications of the plant in modern medicine. In phytochemistry, future research should prioritize the identification and characterization of bioactive compounds, as well as their pharmacokinetics and pharmacodynamics. Additionally, exploring the synergistic effects of multiple compounds found in *E. ulmoides* could lead to the development of more effective multi-target therapies. Collaborative research between ethnobotanists, chemists, pharmacologists, and agricultural scientists will be essential in advancing our understanding of *E. ulmoides* and its applications in both traditional and modern medicine.

## 9 Concluding Remarks

*E. ulmoides*, a valuable medicinal plant endemic to China, has been extensively studied for its ethnobotanical uses and phytochemical properties. The plant has a rich history in traditional Chinese medicine, with various parts such as the leaves, bark, and fruit being utilized for their medicinal properties. Research has identified over 200 natural compounds in *E. ulmoides*, including lignans, iridoids, flavonoids, phenols, steroids, and terpenes, which exhibit a wide range of pharmacological activities such as antihypertensive, antihyperglycemic, antihyperlipidemic, antioxidative, anti-osteoporotic, antitumor, immunomodulatory, and neuroprotective effects. Additionally, studies have shown that the leaves of *E. ulmoides* are particularly effective in regulating lipid metabolism and treating nonalcoholic fatty liver disease through mechanisms involving flavonoids and phenolics. The comprehensive utilization of different parts of the plant, including leaves and bark, has been explored to improve its economic value and conservation.

The extensive pharmacological properties of *E. ulmoides* suggest several potential applications in modern medicine and industry. The antihypertensive, antihyperglycemic, and antihyperlipidemic properties make it a promising candidate for developing treatments for cardiovascular diseases and metabolic disorders. The antioxidative and neuroprotective activities indicate potential uses in preventing and treating neurodegenerative diseases. Furthermore, the plant's antitumor and immunomodulatory effects could be harnessed in cancer therapy and immune system support. The identification of bioactive compounds and their mechanisms of action also opens avenues for the development of new drugs and therapeutic agents. Additionally, the comprehensive utilization of *E. ulmoides*, including its leaves and bark, can enhance its economic value and promote sustainable use of this valuable resource.

Future research on *E. ulmoides* should focus on several key areas to fully realize its potential. For example, More in-depth studies on the pharmacological mechanisms of its bioactive compounds are needed to develop targeted therapies for specific diseases. Efforts should be made to standardize the quality and composition of *E. ulmoides* products to ensure their efficacy and safety. This includes developing reliable methods for quality control and authentication of different varieties and parts of the plant. Exploring the comprehensive utilization of *E. ulmoides*, including its leaves, bark, and other parts, can lead to more sustainable and economically viable practices. Furthermore, Interdisciplinary research combining ethnobotany, phytochemistry, pharmacology, and modern biotechnology will be essential to unlock the full potential of *E. ulmoides* and translate traditional knowledge into modern medical applications.

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## Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

### References

Bai M.M., Shi W., Tian J.M., Lei M., Kim J.H., Sun Y.N., Kim Y., and Gao J.M., 2015, Soluble epoxide hydrolase inhibitory and anti-inflammatory components from the leaves of *Eucommia ulmoides* Oliver (Duzhong), Journal of Agricultural and Food Chemistry, 63(8): 2198-2205. https://doi.org/10.1021/acs.jafc.5b00055

Bao L., Sun Y., Wang J., Li W., Liu J., Li T., and Liu Z., 2024, A review of "plant gold" *Eucommia ulmoides* Oliv.: A medicinal and food homologous plant with economic value and prospect, Heliyon, 10(2): e24851. https://doi.org/10.1016/j.heliyon.2024.e24851

Deng P., Wang Y., Hu F., Yu H., Liang Y., Zhang H., Wang T., Zhou Y., and Li Z., 2022, Phenotypic trait subdivision provides new sight into the directional improvement of *Eucommia ulmoides* Oliver, Frontiers in Plant Science, 13: 832821. https://doi.org/10.3389/fpls.2022.832821

Ding H., Cao A., Li H., Zhao Y., and Feng J., 2020, Effects of *Eucommia ulmoides* leaf extracts on growth performance, antioxidant capacity and intestinal function in weaned piglets, Journal of Animal Physiology and Animal Nutrition, 104(4): 1169-1177. https://doi.org/10.1111/jpn.13333

Do M.H., Hur J., Choi J., Kim M., Kim M.J., Kim Y., and Ha S.K., 2018, *Eucommia ulmoides* ameliorates glucotoxicity by suppressing advanced glycation end-products in diabetic mice kidney, Nutrients, 10(3): 265. https://doi.org/10.3390/nu10030265

Dong C., Shao Q., Ren Y., Ge W., Yao T., Hu H., Huang J., Liang Z., and Han Y., 2022, Assembly, core microbiota, and function of the rhizosphere soil and bark microbiota in *Eucommia ulmoides*, Frontiers in Microbiology, 13: 855317. https://doi.org/10.3389/fmicb.2022.855317

Fan S., Yin Q., Li D., Ma J., Li L., Chai S., Guo H., and Yang Z., 2020, Anti-neuroinflammatory effects of *Eucommia ulmoides* Oliv. in a Parkinson's mouse model through the regulation of p38/JNK-Fosl2 gene expression, Journal of Ethnopharmacology, 260: 113016. https://doi.org/10.1016/j.jep.2020.113016

Feng H., Yang X., Fan J., Zhang L., Liu Q., and Chai D., 2020, DEC-205 receptor-mediated long-circling nanoliposome as an antigen and *Eucommia ulmoides* polysaccharide delivery system enhances the immune response via facilitating dendritic cells maturation, Drug Delivery, 27(1): 1581-1596. https://doi.org/10.1080/10717544.2020.1844343

Feng S., Wang T., Fan L., An X., Ding X., Wang M., Zhai X., Cao Y., He J., and Li Y., 2022, Exploring the potential therapeutic effect of *Eucommia ulmoides*–Dipsaci Radix herbal pair on osteoporosis based on network pharmacology and molecular docking technology, RSC Advances, 12(4): 2181-2195. https://doi.org/10.1039/d1ra05799e

Feng Y., Dai G., Han X., Li M., Zhao D., Wu J., Wu Y., and Wen Z., 2023, Feeding laying ducks *Eucommia ulmoides* Oliv. leaves increases the n-3 fatty acids content and decreases the n-6: n-3 PUFA ratio in egg yolk without affecting laying performance or egg quality, Foods, 12(2): 287. https://doi.org/10.3390/foods12020287

Gao W., Feng Z., Zhang S., Wu B., Geng X., Fan G., Duan Y., Li K., Liu K., and Peng C., 2020, Anti-inflammatory and antioxidant effect of *Eucommia ulmoides* polysaccharide in hepatic ischemia-reperfusion injury by regulating ROS and the TLR-4-NF-κB pathway, BioMed Research International, 1: 1-11. https://doi.org/10.1155/2020/1860637

Gong M., Li Q., Guo H., Cui B., Liu Y., Wang P., Zhu H., Liu X., Dai L., and Wang Z., 2022, Protective effect of active components of *Eucommia ulmoides* leaves on gastric ulcers in rats: Involvement of the PI3K/Akt/NF-κB pathway, Journal of Food Science, 87(7): 3207-3222. https://doi.org/10.1111/1750-3841.16214

Gong M., Su C., Fan M., Wang P., Cui B., Guo Z., Liang S., Yang L., Liu X., Dai L., and Wang Z., 2021, Mechanism by which *Eucommia ulmoides* leaves regulate nonalcoholic fatty liver disease based on system pharmacology, Journal of Ethnopharmacology, 282: 114603. https://doi.org/10.1016/j.jep.2021.114603

Han R., Yuan T., Yang Z., Zhang Q., Wang W., Lin L., Zhu M., and Gao J., 2021, Ulmoidol, an unusual nortriterpenoid from *Eucommia ulmoides* Oliv. leaves prevents neuroinflammation by targeting the PU.1 transcriptional signaling pathway, Bioorganic Chemistry, 116: 105345.
https://doi.org/10.1016/j.bioorg.2021.105345

He X., Wang J., Li M., Hao D., Yang Y., Zhang C., He R., and Tao R., 2014, *Eucommia ulmoides* Oliv.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine, Journal of Ethnopharmacology, 151(1): 78-92.
https://doi.org/10.1016/j.jep.2013.11.023

Huang D., Zhu J., Zhang L., Ge X., Ren M., and Liang H., 2022a, Dietary supplementation with *Eucommia ulmoides* leaf extract improved the intestinal antioxidant capacity, immune response, and disease resistance against Streptococcus agalactiae in genetically improved farmed tilapia (GIFT; Oreochromis niloticus), Antioxidants, 11(9): 1800.
https://doi.org/10.3390/antiox11091800

Huang J., Ye Y., Xiao Y., Ren Q., Zhou Q., Zhong M., Jiao L., and Wu L., 2022b, Geniposide ameliorates glucocorticoid-induced osteoblast apoptosis by activating autophagy, Biomedicine and Pharmacotherapy, 155: 113829.
https://doi.org/10.1016/j.biopha.2022.113829

Huang L., Lyu Q., Zheng W., Yang Q., and Cao G., 2021, Traditional application and modern pharmacological research of *Eucommia ulmoides* Oliv., Chinese Medicine, 16: 73.
https://doi.org/10.1186/s13020-021-00482-7

Hussain T., Yuan D., Tan B., Murtaza G., Rahu N., Kalhoro M., Kalhoro D., and Yin Y., 2020, *Eucommia ulmoides* flavones (EUF) abrogated enterocyte damage induced by LPS involved in NF-κB signaling pathway, Toxicology in Vitro: An International Journal Published in Association with BIBRA, 62: 104674.
https://doi.org/10.1016/j.tiv.2019.104674

Ishimitsu A., Tojo A., Satonaka H., and Ishimitsu T., 2021, *Eucommia ulmoides* (Tochu) and its extract geniposidic acid reduced blood pressure and improved renal hemodynamics, Biomedicine & Pharmacotherapy, 141: 111901.
https://doi.org/10.1016/j.biopha.2021.111901

Jia M., and Li X., 2005, Zhong Guo Min Zu Yao Zhi Yao, China Medical Science and Technology Press, Beijing, pp. 258-259.

Kang H., Luo S., Du H., Han L., Li D., Li L., and Fang Q., 2022, Bio-based *Eucommia ulmoides* gum composites with high electromagnetic interference shielding performance, Polymers, 14(5): 970.
https://doi.org/10.3390/polym14050970

Kardos M., Armstrong E., Fitzpatrick S., Hauser S., Hedrick P., Miller J., Tallmon D., and Funk W., 2021, The crucial role of genome-wide genetic variation in conservation, Proceedings of the National Academy of Sciences, 118(48): e2104642118.
https://doi.org/10.1101/2021.07.05.451163

Kim B., Park K., and Chang I., 2009, Elucidation of anti-inflammatory potencies of *Eucommia ulmoides* bark and *Plantago asiatica* seeds, Journal of Medicinal Food, 12(4): 764-769.
https://doi.org/10.1089/jmf.2008.1239

Lee G., Lee H., Choi M., Choi A., Shin T., and Chae H., 2018, *Eucommia ulmoides* leaf (EUL) extract enhances NO production in ox-LDL-treated human endothelial cells, Biomedicine & Pharmacotherapy, 97: 1164-1172.
https://doi.org/10.1016/j.biopha.2017.11.035

Lee H., Lee G., Lee M., Kim H., Kim N., Kim H., Lee Y., Kim H., and Chae H., 2013, *Eucommia ulmoides* Oliver extract, aucubin, and geniposide enhance lysosomal activity to regulate ER stress and hepatic lipid accumulation, PLoS ONE, 8(12): e81349.
https://doi.org/10.1371/journal.pone.0081349

Li G., Li Z., Li H., Xiao J., Xu Y., Chen J., Wu W., and Yang H., 2021, Study on development strategy of *Eucommia ulmoides* Chinese medicine industry, Modern Chinese Medicine, 23(4): 567-586.
https://doi.org/10.13313/j.cnki.issn.1673-4890.20201016001

Li Y., Pan H., Zhang X., Wang H., Liu S., Zhang H., Qian H., Wang L., and Ying H., 2019, Geniposide improves glucose homeostasis via regulating FOXO1/PDK4 in skeletal muscle, Journal of Agricultural and Food Chemistry, 67(16): 4483-4492.
https://doi.org/10.1021/acs.jafc.9b00402

Liao W., Zhao S., Yang Z., Yang W., Huang L., Liu F., Liu M., Ge J., Wang Y., and Jiang S., 2021, *Illicium verum* and *Eucommia ulmoides* leaf extracts promote nutrient availability and antioxidant capacity in piglets by upregulating duodenal and jejunal Nrf2/TNF-α, Journal of Animal Physiology and Animal Nutrition, 105(5): 916-926.
https://doi.org/10.1111/jpn.13534

Liu C., Guo F., Xiao J., Wei J., Tang L., and Yang H., 2020, Research advances in chemical constituents and pharmacological activities of different parts of *Eucommia ulmoides*, Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China Journal of Chinese Materia Medica, 45(3): 497-512.
https://doi.org/10.19540/j.cnki.cjcmm.20191108.201

Liu T., Cao X., and Cao D., 2022, Combination of UHPLC-Q Exactive-Orbitrap MS and network pharmacology to reveal the mechanism of *Eucommia ulmoides* leaves in the treatment of osteoarthritis, Journal of Food Biochemistry, 46: e14204.
https://doi.org/10.1111/jfbc.14204

Ma Z., Kong C., Song P., Zhang X., Yuan Y., and Tang Q., 2018, Geniposide protects against obesity-related cardiac injury through AMPKα- and SIRT1-dependent mechanisms, Oxidative Medicine and Cellular Longevity, 2018: 6053727.
https://doi.org/10.1155/2018/6053727

Ma Z., Zhang K., Guo W., Yu W., Wang J., and Li J., 2023, Green synthesis of silver nanoparticles using *Eucommia ulmoides* leaf extract for inhibiting stem end bacteria in cut tree peony flowers, Frontiers in Plant Science, 14: 1176359.
https://doi.org/10.3389/fpls.2023.1176359

Park S., Choi M., Kim M., Jung U., Kim H., Park K., Noh H., Park H., Park Y., Lee J., and Lee M., 2006, Hypoglycemic and hypolipidemic action of Du-zhong (*Eucommia ulmoides* Oliver) leaves water extract in C57BL/KsJ-db/db mice, Journal of Ethnopharmacology, 107(3): 412-417.
https://doi.org/10.1016/j.jep.2006.03.034

Peng M., Tian S., Song Y., Li C., Miao M., Ren Z., and Li M., 2021, Effects of total flavonoids from *Eucommia ulmoides* Oliv. leaves on polycystic ovary syndrome with insulin resistance model rats induced by letrozole combined with a high-fat diet, Journal of Ethnopharmacology, 273: 113947.
https://doi.org/10.1016/j.jep.2021.113947

Qin J., Chen K., Wang X., He S., Chen J., Zhu Q., He Z., Lv P., and Chen K., 2024, Investigating the pharmacological mechanisms of total flavonoids from *Eucommia ulmoides* Oliver leaves for ischemic stroke protection, International Journal of Molecular Sciences, 25(11): 627.
https://doi.org/10.3390/ijms25116271

Ren N., Gong W., Zhao Y., Zhao D., and Xu Y., 2023, Innovation in sweet rice wine with high antioxidant activity: *Eucommia ulmoides* leaf sweet rice wine, Frontiers in Nutrition, 9: 1108843.
https://doi.org/10.3389/fnut.2022.1108843

Sayed S., Siems K., Schmitz-Linneweber C., Luyten W., and Saul N., 2021, Enhanced healthspan in *Caenorhabditis elegans* treated with extracts from the traditional Chinese medicine plants *Cuscuta chinensis* Lam. and *Eucommia ulmoides* Oliv., Frontiers in Pharmacology, 12: 604435.
https://doi.org/10.3389/fphar.2021.604435

Sih C.J., Ravikumar P.R., Huang F.C., Buckner C., and Whitlock H., 1976, Isolation and synthesis of pinoresinol diglucoside, a major antihypertensive principle of tu-chung (*Eucommia ulmoides* Oliver), Journal of the American Chemical Society, 98(17): 5412-5413.
https://doi.org/10.1021/ja00433a070

Su L., Wang Q., Xiang P., Yin D., Ding X., Liu L., and Zhao X., 2022, Development of nitrile rubber/*Eucommia ulmoides* gum composites for controllable dynamic damping and sound absorption performance, Royal Society of Chemistry Advances, 33(12): 21503-21511.
https://doi.org/10.1039/d2ra03597a

Su Y., Pei Y., Towson A., He Y., Nie J., and Wang B., 2021, Physiological alterations of *Eucommia ulmoides* Oliv. seedlings under saline water stress and nitrogen fertilizer application, Pakistan Journal of Botany, 53(5): 1539-1544.
https://doi.org/10.30848/PJB2021-5(27)

Sun C., Zhang S., Ba S., Dang J., Ren Q., Zhu Y., Liu K., and Jin M., 2022, *Eucommia ulmoides* olive male flower extracts ameliorate Alzheimer's disease-like pathology in zebrafish via regulating autophagy, acetylcholinesterase, and the dopamine transporter, Frontiers in Molecular Neuroscience, 15: 901953.
https://doi.org/10.3389/fnmol.2022.901953

Sun J., Song X., Wang C., and Ruan Q., 2024, Geniposidic acid alleviates osteoarthritis progression through inhibiting inflammation and chondrocyte ferroptosis, Journal of Cellular and Molecular Medicine, 28(8): e18228.
https://doi.org/10.1111/jcmm.18228

Tan X., Zhang Y., Cai J., Zhu L., Ge W., and Zhang X., 2014, 5-(Hydroxymethyl)-2-furaldehyde inhibits adipogenic and enhances osteogenic differentiation of rat bone mesenchymal stem cells, Natural Product Communications, 9(4): 529-532.
https://doi.org/10.1177/1934578X1400900427

Tang J., Zhao N., Gao Y., Han R., Wang X., Tian J., and Gao J., 2021, Phytosterol profiles and iridoids of the edible *Eucommia ulmoides* Oliver seeds and their anti-inflammatory potential, Food Bioscience, 43: 101295.
https://doi.org/10.1016/J.FBIO.2021.101295

Tang P., Tang Y., Liu Y., He B., Shen X., Zhang Z., Qin D., and Tian J., 2023, Quercetin-3-O-α-L-arabinopyranosyl-(1→2)-β-D-glucopyranoside isolated from *Eucommia ulmoides* leaf relieves insulin resistance in HepG2 cells via the IRS-1/PI3K/Akt/GSK-3β pathway, Biological and Pharmaceutical Bulletin, 46(2): 219-229.
https://doi.org/10.1248/bpb.b22-00597

Wang C., Gong H., Feng M., and Tian C., 2023, Phenotypic variation in leaf, fruit, and seed traits in natural populations of *Eucommia ulmoides*, a relict Chinese endemic tree, Forests, 14(3): 462.
https://doi.org/10.3390/f14030462

Wang C., Tang L., He J., Li J., and Wang Y., 2019a, Ethnobotany, phytochemistry and pharmacological properties of *Eucommia ulmoides*: A review, The American Journal of Chinese Medicine, 47(2): 259-300.
https://doi.org/10.1142/S0192415X19500137

Wang J., Yuan Y., Chen X., Fu S., Zhang L., Hong Y., You S., and Yang Y., 2016, Extract from *Eucommia ulmoides* Oliv. ameliorates arthritis via regulation of inflammation, synoviocyte proliferation, and osteoclastogenesis in vitro and in vivo, Journal of Ethnopharmacology, 194: 609-616.
https://doi.org/10.1016/j.jep.2016.10.038

Wang W., Chen S., and Zhang X., 2018, Whole-genome comparison reveals heterogeneous divergence and mutation hotspots in chloroplast genome of *Eucommia ulmoides* Oliver, International Journal of Molecular Sciences, 19: 1037.
https://doi.org/10.3390/ijms19041037

Wang Y., Liu J., X L., Shen M., Wei L., and Xin Z., 2019b, Fully biobased shape memory thermoplastic vulcanizates from poly(lactic acid) and modified natural *Eucommia ulmoides* gum with co-continuous structure and super toughness, Polymers, 11(12): 2040.
https://doi.org/10.3390/polym11122040

Wei X., Peng P., Peng F., and Dong J., 2021, Natural polymer *Eucommia ulmoides* rubber: A novel material, Journal of Agricultural and Food Chemistry, 69(13): 3797-3821.
https://doi.org/10.1021/acs.jafc.0c07560

Wu J., Chen H., Li H., Tang Y., Yang L., and Cao S., 2016, Antidepressant potential of chlorogenic acid-enriched extract from *Eucommia ulmoides* Oliver bark with neuron protection and promotion of serotonin release through enhancing synapsin I expression, Molecules, 21(3): 260.
https://doi.org/10.3390/molecules21030260

Xie S., Si H., Sun H., Zhao Q., Li X., Wang S., Niu J., and Wang Z., 2023, Predicting the potential distribution of the endangered plant *Eucommia ulmoides* in China under the background of climate change, Sustainability, 15(6): 5439.
https://doi.org/10.3390/su15065349

Xing Y.Y., Wang J.Y., Wang K., Zhang Y., Liu K., Chen X.Y., and Yuan Y., 2020, Inhibition of rheumatoid arthritis using bark, leaf, and male flower extracts of *Eucommia ulmoides*, Evidence-Based Complementary and Alternative Medicine, 2020: 3260278.
https://doi.org/10.1155/2020/3260278

Yan D., Si W., Zhou X., Yang M., Chen Y., Chang Y., Lu Y., Liu J., Wang K., Yan M., Liu F., Li M., Wang X., Wu M., Tian Z., Sun H., and Song X., 2022, *Eucommia ulmoides* bark extract reduces blood pressure and inflammation by regulating the gut microbiota and enriching the *Parabacteroides* strain in high-salt diet and L-NAME-induced mice, Frontiers in Microbiology, 13: 967649.
https://doi.org/10.3389/fmicb.2022.967649

Yan S., Cui S., Guo N., Chu Z., Zhang J., Yan S., and Jin X., 2024, Research on the performance and modification mechanism of gutta-percha-modified asphalt, Polymers, 16(13): 1860.
https://doi.org/10.3390/polym161318600

Yao J., Zou Z., Wang X., Ji X., and Yang J., 2016, Pinoresinol diglucoside alleviates oxLDL-induced dysfunction in human umbilical vein endothelial cells, Evidence-Based Complementary and Alternative Medicine, 2016: 3124519.
https://doi.org/10.1155/2016/3124519

Zhang H.S., Zhang S.N., Guo W.K., and He S.H., 2022, *Eucommia ulmoides* Oliver's multitarget mechanism for treatment of ankylosing spondylitis: A study based on network pharmacology and molecular docking, Evidence-Based Complementary and Alternative Medicine, 2022: 3699146.
https://doi.org/10.1155/2022/3699146

Zhang W., Fujikawa T., Mizuno K., Ishida T., Ooi K., Hirata T., and Wada A., 2012, *Eucommia* leaf extract (ELE) prevents OVX-induced osteoporosis and obesity in rats, The American Journal of Chinese Medicine, 40(4): 735-752.
https://doi.org/10.1142/S0192415X12500553

Zhao Y., Tan D., Peng B., Yang L., Zhang S., Shi R., Chong C., Zhong Z., Wang S., Liang Q., and Wang Y., 2022, Neuroendocrine–immune regulatory network of *Eucommia ulmoides* Oliver, Molecules, 27(12): 3697.
https://doi.org/10.3390/molecules27123697

Zhu M., and Sun R., 2018, *Eucommia ulmoides* Oliver: A potential feedstock for bioactive products, Journal of Agricultural and Food Chemistry, 66(22): 5433-5438.
https://doi.org/10.1021/acs.jafc.8b01312

Zuo Y., Chen C., Liu F., Hu H., Dong S., Shen Q., Zeng J., Huang L., Liao X., Cao Z., Zhong Z., Lu H., and Chen J., 2024, Pinoresinol diglucoside mitigates dexamethasone-induced osteoporosis and chondrodysplasia in zebrafish, Toxicology and Applied Pharmacology, 484: 116484.
https://doi.org/10.1016/j.taap.2024.116884