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Chemical Composition, Pharmacological Actions and Clinical Applications of Duzhong's plants: A Comprehensive Review

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Abstract

Duzhong is a medicinal deciduous tree belonging to the genus Duzhong in the family of Duzhongceae, and is a third-century plant endemic to China and a national key protected plant of the second category. It is widely distributed in Henan, Shanxi, Shaanxi and Sichuan, and has a long history as a traditional Chinese herbal medicine. Modern phytochemical and pharmacological studies show that the main chemical constituents of Duzhong are lignans, cyclic enol ether terpenes, flavonoids, phenolic acids, steroids and terpenes, and studies have shown that Duzhong is mainly used in anti-osteoporosis, anti-inflammation, neuroprotection, lowering of blood pressure, lowering of blood glucose, anti-aging, and many other pharmacological effects. Cortex Duzhonge is currently used in large scale in pharmaceutical, chemical, food, feed and other industries, and the development prospect is promising. This review systematically organizes the current status of the traditional application, chemical composition, pharmacological effect and food processing of Cortex Duzhonge, reveals the pharmacological activity of Cortex Duzhonge and deeply understands its developmental value, which will provide a more scientific basis for the further study of its mechanism of action and the development of better Cortex Duzhonge therapeutic agents and health care products.

Keywords: Duzhong; Lignans;Iridoids; Flavonoids; Phenylpropanoids; Terpenoids; Steroids; Clinical applications; Exploitation and utilization

Introduction

Duzhong is a medicinal deciduous tree belonging to the Duzhongceae family and is unique in the plant kingdom, comprising only one genus and one species, endemic to China. As a tertiary relict plant, Duzhong is classified as a second-class nationally protected plant in China [1]. Historical records indicate its earliest origins in the regions of Henan, Shanxi, Shaanxi, and Sichuan. Since the Ming Dynasty, its production area has expanded throughout much of the country, with Sichuan, Shaanxi, Chongqing, and Guizhou being notable regions where high-quality Duzhong is cultivated, often associated with Taoist practices [2]. Duzhong was first documented in "Shennong's Classic of the Materia Medica," where it is classified as a top-quality herb. The text describes Duzhong as having a pungent flavor and a gentle texture, with applications for alleviating waist and spine pain, tonifying essence and energy, strengthening muscles and bones, enhancing willpower, relieving genital itching, and addressing urinary problems. It is also recognized for its anti-aging properties and is referred to as Si Xian, thriving in valley regions.To date, over 200 distinct chemical compounds have been identified in Duzhong [3]. The primary components include lignans, cyclic enol ether terpenoids, flavonoids, phenolic acids, steroids, and terpenoids. Modern pharmacological studies have demonstrated that Duzhong is effective in a variety of areas, including anti-osteoporosis, anti-inflammation, neuroprotection, antihypertensive, antihyperglycemic, antihyperlipidemic, immunoregulation, antibacterial, antiviral, anti-fatigue, antioxidant, anti-tumor, sedative-hypnotic, and anti-aging activities.Moreover, Duzhong is recognized as an economically valuable tree species. Its bark is used in traditional medicine, while extracts from its bark, leaves, and seeds find applications in the pharmaceutical, chemical, food, and feed industries, highlighting its significant development and utilization potential [4]. In this paper, we conducted a thorough literature review using the China Knowledge Information Network (CNKI) and the PubMed database, organizing, summarizing, and analyzing existing studies from various perspectives, including herbal uses, traditional applications, chemical composition, and pharmacological effects. By deepening our understanding of Duzhong and its pharmacological activities, this research aims to provide a solid scientific foundation for its future research, development, and utilization in diverse applications.

Textual research

The name “Duzhong” was primarily assigned based on its medicinal properties and morphological characteristics(Niu et al., 2020). It was first recorded in the "Shen Nong Ben Cao Jing," where "Duzhonge" is established as the proper name, while "Si Xian" serves as its alias. Over time, "Duzhonge" has been consistently used as the official name for this plant. The Qing Dynasty text "Ben Cao Chong Yuan" (Z. Zhang, 1996)explains that the term "Du" is derived from the earth, and "Zhong" refers to the central part. This wood originates from the Yuzhou valley, which is believed to capture the essence of the earth, hence its designation as "Du Zhong" in the "Ben Jing."Additionally, ancient medical records list several other aliases for Duzhonge, including Mu Mian, Mian Shu Pi, Si Mian Pi, Si Lian Pi, Si Lian Shu Pi, Si Xian, and Si Zhong.

Clinical Applications

Duzhong is a traditional Chinese tonic herb with a long history of medicinal use. Ancient medical texts recommend Duzhong for a variety of conditions, including lumbago, knee pain, osteoporosis, enhancement of learning and memory, liver protection, paralysis, intestinal hemorrhoids, vaginal bleeding, itching of the vagina or scrotum, wet and stagnant urinary flow, miscarriage, bleeding during pregnancy, spermatorrhea, aching feet, foot fungus, and anti-aging effects(L. Huang et al., 2021).Today, Duzhong is officially recognized as a medicinal plant and has been included in the "Chinese Pharmacopoeia."

Duzhong is commonly used in clinical practice and is referenced in the "Ming Yi Bie Lu" for "treating soreness and pain in the feet, which makes one not want to walk." It is also noted in the "Ben Cao Zheng" for "warming the uterus and stabilizing the fetus." Both ancient and modern prescriptions containing Duzhong share similar applications. Duzhong is known to nourish the

liver and kidneys and strengthen muscles and bones, making it particularly effective for treating lumbago and deficiency-related ailments.Historically, Duzhong has been an important remedy for stabilizing the fetus, frequently used in ancient formulas to address fetal restlessness and postpartum paralysis. In modern formulations, it is utilized for obstetric and gynecological conditions such as preeclampsia and labor pain, demonstrating the continuity of its efficacy from ancient times to the present.-Moreover, contemporary formulas containing Duzhong are often employed in the treatment of cardiovascular and cerebrovascular diseases, particularly hypertension—a use not typically found in ancient formulas. According to traditional Chinese medicine, hypertension is classified under conditions such as "headache" and "dizziness." The "Suwen - Zhi Zhen Yao Da Lun" states, "Wind-induced tremors and dizziness are all due to the liver," while the "Ling Shu - Hai Lun" mentions, "A lack of marrow causes vertigo and tinnitus." Given that the kidneys are responsible for producing marrow, this illustrates the close relationship between hypertension and the liver and kidneys(SU, 1988).Research has shown that traditional Chinese medicine therapies focusing on tonifying the liver and kidneys, calming the liver, and activating blood circulation are effective in managing hypertension(Kou, 2012). Duzhong, as a tonic for the liver and kidneys, has been found through modern pharmacological studies to have a significant blood pressure-lowering effect(L. Huang et al., 2021). This alignment with traditional Chinese medicine theory, coupled with contemporary research support, highlights its relevance in the treatment of hypertension.

Chemical composition

To elucidate the bioactive substances in Duzhong (Duzhong), numerous studies have been conducted both domestically and internationally. To date, over 200 chemical compounds have been isolated and identified from Duzhong, including lignans, cyclic enol ether terpenoids, flavonoids, phenylpropanoids, steroids, and various other compounds. Below is a summary of the current research on the chemical constituents of Duzhong from both Chinese and international studies.

Lignans

Lignans are a class of natural products formed in living organisms through the polymerization of two phenylpropanoid derivatives (C6-C3 units) via β,β' or 8,8-carbon linkages. In Duzhong (Duzhong) bark, these compounds predominantly occur in glycoside form. The lignans in Duzhong are classified into five main structural groups: di-epoxy lignans, mono-epoxy lignans, sesquiterpene lignans, neo-lignans, and cyclic lignans. The structural formula of the core lignan nucleus in Duzhong is presented in Fig. 1, and the various lignan components are listed in Table 2

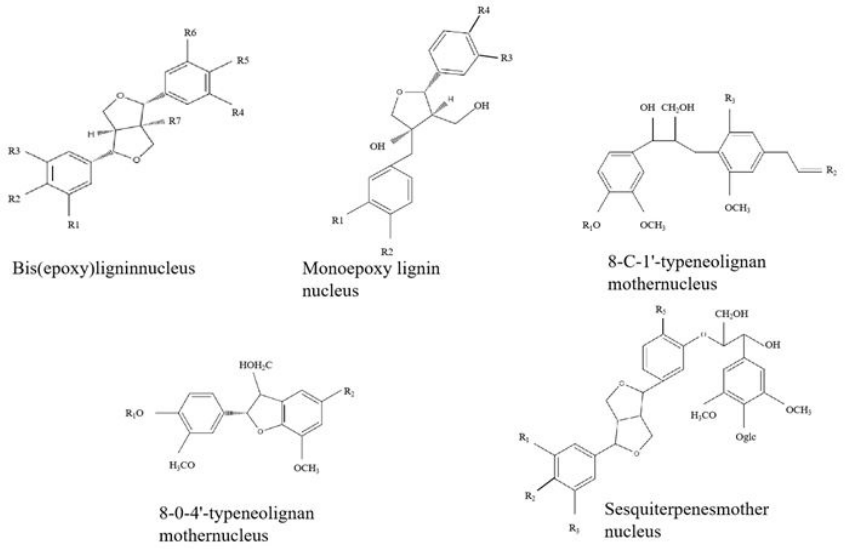

Figure 1: Structural formula of the mother nucleus of Duzhong lignin

Cyclic Enol Ether Terpenoids

Cyclic enol ether terpenes and their glycosides form a unique class of monoterpene compounds, widely distributed throughout the plant kingdom. They are biosynthesized from geranyl pyrophosphate, first forming an anotoxic di-formaldehyde intermediate, which is then converted through acetal derivatization. The basic structure of cyclic enol ether terpenes consists of a cyclic enol ether terpene alcohol, characterized by both an alcohol hydroxyl group and a cyclic enol ether. Due to the reactive nature of the alcohol hydroxyl group (which is hemiacetal in nature), these compounds primarily exist as glycosides in the leaves and bark of Duzhong (Duzhong). There are six main types of structural nuclei in this class. The structural formula of the cyclic enol ether terpenoids in Duzhong is shown in Fig. 2, and the individual compounds are listed in Table 3.

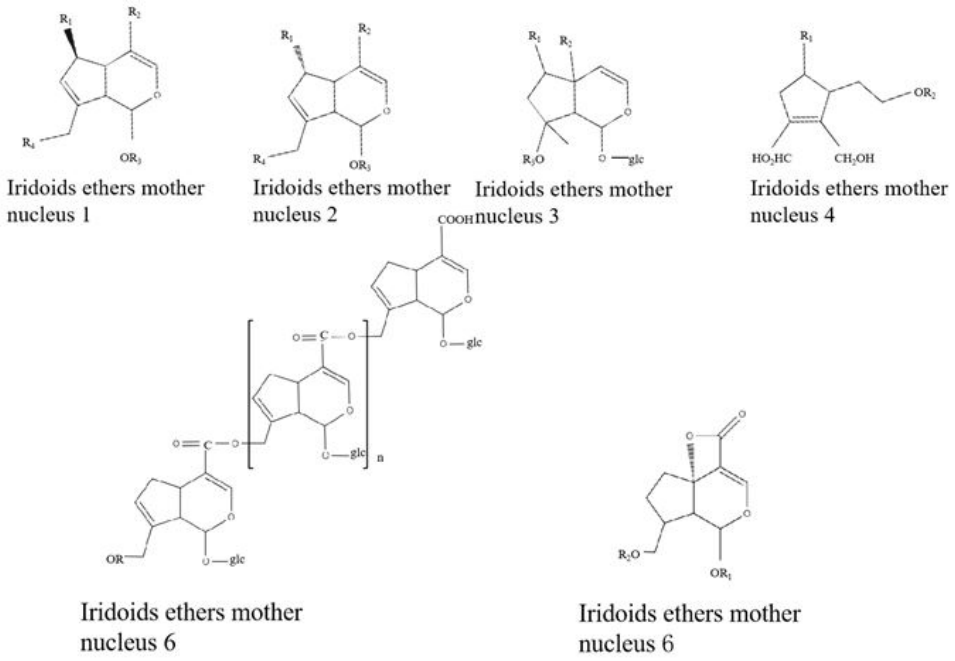

Figure 2: Structural formula of the mother nucleus of Duzhonge Cyclic enol ether

Flavonoids

Flavonoids are a class of compounds composed of two benzene rings with phenolic hydroxyl groups, linked by a central three--carbon chain. These compounds are predominantly found in the leaves and male flowers of Duzhong (Duzhong), with lower concentrations in the bark and fruit. The primary flavonoid structures, represented by F1, F2, and F3, are shown in Fig. 3, while the specific flavonoid compounds present in Duzhong are listed in Table 4 (see attached Table 4).

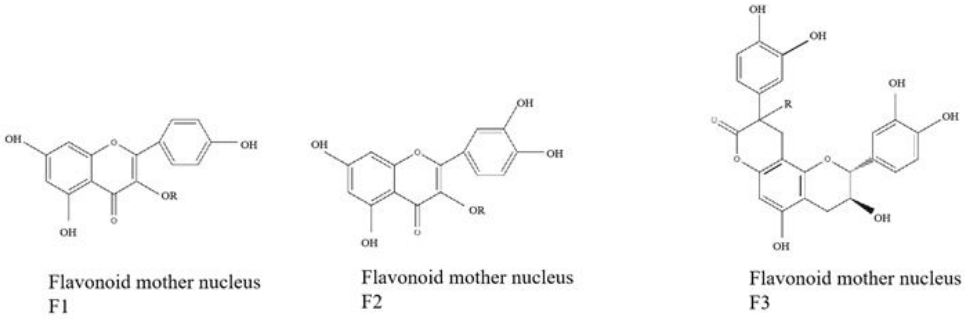

Figure 3: Structural formula of the mother nucleus of Duzhong flavonoids

Phenylpropanoid Compounds

Compounds consisting of a benzene ring and a three-carbon chain are collectively known as phenylpropanoids. These compounds serve as precursors to lignans and are widely found in Duzhong (Duzhong). The seven main structural nuclei of phenylpropanoids are depicted in Fig. 4, and the specific phenylpropanoid compounds are listed in Table 5 (see attached Table 5).

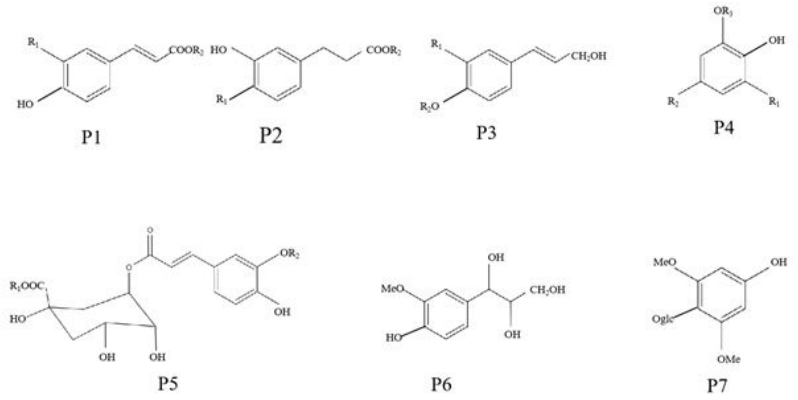

Figure 4: Structural mother nucleus of the phenylpropanoid analogs of Duzhong

Terpenoids and Steroids

Terpenoids and steroids are widely distributed classes of natural products with numerous varieties. In Duzhong (Duzhong), these compounds have been primarily isolated and identified from the leaves and male flowers. The core structures of these compounds are shown in Fig. 5, and the specific terpenoids and steroids are listed in Table 6 (see attached Table 6).

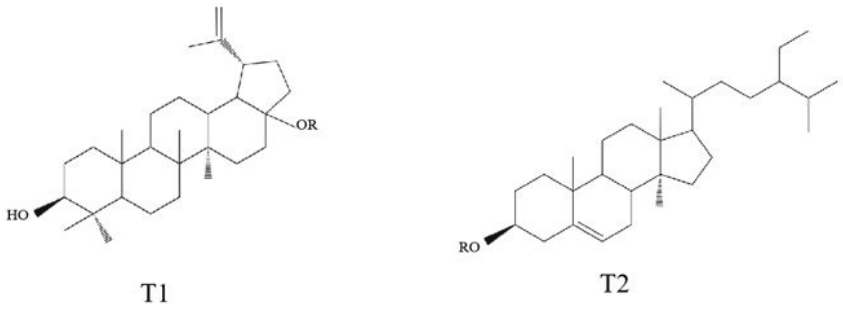

Figure 5: Structure mother nucleus of terpenoids and steroids of Duzhong

Other Types of Components

The polysaccharides in Duzhong dulcis are primarily composed of glucose, fructose, mannose, fucose, galactose, arabinose(Zeng et al., 2023), and other monosaccharides. Acidic polysaccharides isolated from Duzhong dulcis bark include Duzhong dulcis polysaccharide A and polysaccharide B[18].In terms of fatty acids, Duzhong seeds have the highest content, with linolenic acid (63.15%), oleic acid (16.9%), linoleic acid (10.66%), palmitic acid (6.03%), and stearic acid (1.96%) being the main components—most of which are unsaturated fatty acids(W. Huang P. et al., 2020; X. Liu et al., 2022a).The bark, leaves, male flowers, and seeds of Duzhong caryophyllata contain eight essential amino acids. The bark holds 17 free amino acids, with arginine and histidine being the most abundant. The leaves contain 15 amino acids, while the male flowers have 17, with glutamic acid and aspartic acid accounting for 20.81% and 14.47% of the total amino acids, respectively(Fan Y. et al., 2014). The seeds also contain 17 amino acids, with essential and semi-essential amino acids making up 33.6% and 11.2% of the total amino

acid content, respectively(W. Huang P. et al., 2020).

Analysis of differences in different parts of Duzhong

Lignans are most abundant in the bark of Duzhong (Duzhong), with the highest concentration and quantity found there. Flavonoids, cyclic enol ether terpenoids, and steroidal compounds are more prevalent in the leaves. In the male flowers, the primary components are cyclic enol ether terpenoids, flavonoids, and steroids, while the seeds are rich in unsaturated fatty acids and also contain significant amounts of cyclic enol ether terpenoids. A comparative analysis of these differences is shown in Figure 6.

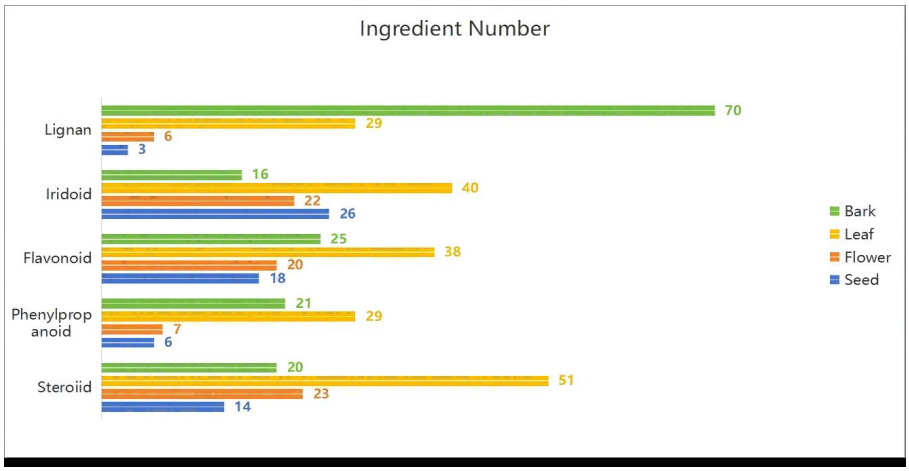

Figure 6: Chemical constituents in different parts of Duzhong

Pharmacological Effects

Modern pharmacological studies have demonstrated that Duzhong (Duzhong) exhibits a range of therapeutic effects, including anti-osteoporosis, anti-inflammatory, neuroprotective, antihypertensive, hypoglycemic, hypolipidemic, immunomodulatory, antibacterial, antiviral, anti-fatigue, antioxidant, anti-aging, and gut health improvement properties. The pharmacological effects of Duzhong are summarized in Figure 7.

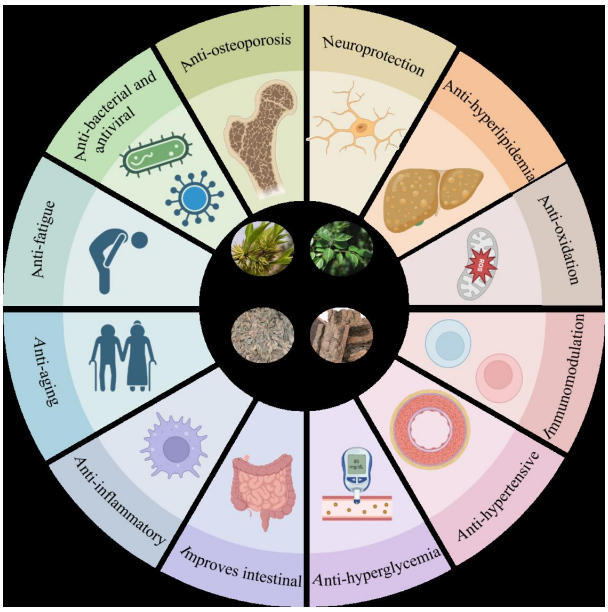

Figure 7: Pharmacological effects of Duzhong(Created in BioRender.com)

Anti-osteoporosis

A variety of components in Duzhong (Duzhong), including aucubin, iridoid glycosides, geniposide, geniposidic acid, acidic polysaccharides, quercetin, gardenia glycosides, chlorogenic acid, rutin, total lignans, pinocembrin diglucoside, and pinoresinol, exhibit anti-osteoporotic pharmacological effects. Duzhong has been shown to reduce calcium and phosphorus loss, activate the OPG/RANK/RANKL pathway, and alleviate symptoms of osteoporosis in rats, contributing to kidney tonification and bone formation(Zuo, Zhang, Li, et al., 2014).Aucubin enhances autophagy through AMPK signaling, preventing osteoblast apoptosis(Pan et al., 2021). It also promotes the proliferation, migration, and tube formation of HUVECs by mediating VEGFR2/MEK/ERK, Akt/mTOR, and Src/FAK signaling pathways(Deyama et al., 1985). The total glycosides in Duzhong seeds can enhance bone density and strength due to their high aucubin content(Gao H. et al., 2021). Cyclic enol ether terpene glycosides from Duzhong prevent osteoporosis primarily through the PI3K-Akt, MAPK, and estrogen signaling pathways(Wu G. et al., 2015). Geniposide significantly promotes calcified nodule formation and induces osteogenic differentiation(Zuo et al., 2022).EuOCP3, an acidic polysaccharide purified from Duzhong, restores cortical bone thickness, increases mineralized bone area, enhances osteoblast numbers, and reduces osteoclasts in dexamethasone-induced osteoporosis(S. Shi Y. et al., 2013). Analysis of mineralization data reveals that EuOCP3 has significant potential to promote the proliferation and osteogenic differentiation of MC3T3-E1 cells(Luo et al., 2019). In a model of iron overload induced by intraperitoneal injection of dextrose iron, quercetin has been found to prevent iron overload-induced osteoporosis by activating the Nrf2/HO-1 signaling pathway(Zuo, et al., 2014).In a mouse model of chronic kidney disease-mineral bone disorder (CKD-MBD), salt Duzhong significantly increases AMPK expression(Q. Huang et al., 2021a). In a D-galactose-induced senile osteoporosis model, salt Duzhong enhances BMP-2 activity in bone tissue, increases bone mineral density (BMD), promotes osteoblast metabolism, and facilitates bone mineralization, thereby treating senile osteoporosis(Guo Q. et al., 2022). Additionally, Duzhong can prevent or delay osteoporosis onset in ovariectomized rats by upregulating serum E2 levels and increasing serum IGF-I content(Deyama et al., 1987).In a DEX-induced rat osteoporosis model, gardenia glycoside (GEN), the main active compound in Duzhong, improves DEX-induced endoplasmic reticulum stress and mitochondrial apoptosis in osteoblasts. Duzhong also mitigates the adverse effects of kidney injury and bone damage in mice via the PPARG/AMPK signaling pathway(Zuo, Zhang, Wang, et al., 2014), regulating serum bone metabolism markers, promoting osteoblast differentiation, inhibiting bone resorption, and accelerating bone formation(R. Li et al., 2021b).Chlorogenic acid (CGA) from Duzhong bark promotes the proliferation of osteoblast precursors and the differentiation of BMSCs through the Shp2/PI3K/Akt/cyclin D1 pathway(Yan Y. et al., 2018), while geniposidic acid (GPA) stimulates bone formation via activation of the FXR/RUNX2 signaling pathway(Ning, 2008). Duzhong increases the expression of osteoblast gene markers such as Col5a2, Ubap2l, Dkk3, Foxm1, Col16a1, Col12a1, Usp7, Col4a6, Runx2, Sox4, and Bmp4, indicating promotion of osteoblast proliferation, differentiation, and mineralization, as well as prevention of osteoblast apoptosis(Y.-X. Ding et al., 2015b).Rutin, a key flavonoid in Duzhong, regulates FNCD1 levels and autophagy through the Akt/mTOR signaling pathway, significantly improving BMD and trabecular bone number in osteoporosis model rats(Takamura et al., 2007). In ovariectomized rats, total glucosides of Duzhong (TGEUS) enhance osteogenic differentiation and promote bone formation(Xu et al., 2021).The in vivo and in vitro effects of total lignans (TL) extracted from Duzhong have been demonstrated to induce the proliferation and differentiation of primary osteoblasts and inhibit osteoclastogenesis by increasing osteopontinogen (OPG) expression and decreasing RANKL expression(Yao et al., 2010). The total flavonoids from Duzhong leaves can regulate intestinal flora structure, inhibiting weight gain and increasing BMD(Ma et al., 2022b).Based on dual-energy X-ray bone scanning and HE staining of the distal femur, the aqueous extract of Duzhong leaves significantly enhances BMD(Xi et al., 2018)The aqueous extract of Duzhong bark promotes BMP2 gene expression in rat osteoblasts (Xi et al., 2018)and stimulates their proliferation through the ERK and AKT pathways(Bianco et al., 1974b). It also promotes the osteogenic differentiation of bone marrow mesenchymal stem cells by targeting the Fzd receptor, making it useful for treating osteoporosis and other orthopedic diseases.The alcoholic extract of Duzhong bark and leaves can regulate inflammatory bone metabolism associated with the NF-κB pathway, reducing joint inflammation in CIA rats, inhibiting pro-angiogenic factor expression, and delaying

cartilage and bone destruction in joints(Fu et al., 2012). It elevates the expression of the RhoA/ROCK signaling pathway, promoting osteogenic differentiation and proliferation of BMSCs(Jiang, 2018b).Both pinocembrin diglucoside and (+)-pinoresinol exert anti-osteoporosis effects by promoting osteoblast proliferation and differentiation, but through different mechanisms: pinocembrin diglucoside primarily promotes OPG secretion, while pinocembrin enhances both OPG secretion and inhibits RANKL expression(Tang F. et al., 2014). Quercetin further promotes BMSC proliferation by activating ERK phosphorylation(Yan J. et al., 2018).

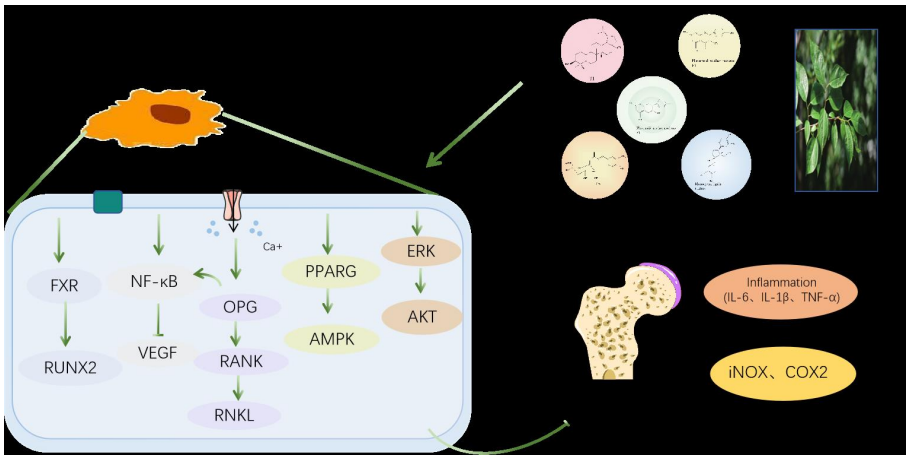

Figure 8: Anti-osteoporosis of Duzhong

Anti-inflammatory

Modern pharmacological research indicates that Duzhong (Duzhong) exhibits significant anti-inflammatory effects, along with certain analgesic and decongestive properties(Ding Y.-X., Guo, et al., 2014). Active ingredients in Duzhong, such as total Duzhong glycosides, iridoid glycosides, flavonoid glycosides, genipin glycosides, total glycosides from Duzhong seeds, Duzhong polysaccharides, myrtillus coralloidus glycosides, turpentine glucosides, genipin, and aucubin, as well as alcoholic extracts of Duzhong bark and leaves, have demonstrated anti-inflammatory pharmacological effects.Total Duzhong glycosides may promote the proliferation of osteoarthritic chondrocytes while inhibiting their apoptosis by upregulating Prdx5(Peng et al., 2013). The total glycosides from Duzhong seeds also exhibit strong anti-inflammatory and analgesic effects(Yang F. et al., 2014b). Two iridoid glycosides and a flavonoid glycoside extracted from the male flowers of Duzhong caryophyllantha effectively inhibit nitric oxide (NO) production in RAW 264.7 cells(Z. Wang et al., 2023). Additionally, Duzhong flavonoids (EUF) can intervene in intestinal inflammatory diseases via the PI3K-NF-κB signaling pathway(Dong et al., 2014).Alcoholic extracts of Duzhong bark and leaves can reduce joint inflammation, inhibit the expression of pro-angiogenic factors, and delay the destruction of intra-articular cartilage and bone in collagen-induced arthritis (CIA) rats by regulating NF-κB pathway-related inflammatory bone metabolism(Zhao N., 2021). In a rat model of osteoarthritis, Duzhong bark extract inhibited disease progression by delaying cartilage degeneration, reducing inflammatory cytokines, and blocking MMP-3 secretion through the inhibition of the PI3K/Akt pathway[55].Geniposide acid significantly downregulates the secretion of inflammatory factors such as IL-6, IL-1β, and TNF-α, while attenuating the phosphorylation of nuclear transcription factors MAPK p38 and NF-κB p65(Zhang Z. et al., 2019). Duzhong polysaccharides also regulate macrophage immune function, which is associated with osteoarthritis and synovial inflammation(Z. Wang & CLIFFORD, 2008). EUP (an extract) promotes articular cartilage repair and subchondral bone reconstruction, while another anti-inflammatory polysaccharide, EUP1, effectively inhibits major inflammatory cytokines in a lipopolysaccharide-induced mouse model of sepsis(C. Si et al., 2008).In vitro studies show that aucubin, pinoresinol diglucoside, genipin, and their combinations effectively inhibit the proliferation of MH7A cells, reduce NO release, and lower inflammatory factor levels(Zhang Z. et al., 2014). Long-leaf Duzhong exhibits anti-inflammatory activity by inhibiting pro-inflammatory mediators (NO, iNOS, and COX-2) and protecting mice from LPS-induced mortality in a septic shock model(Chen J. et

al., 2002).Inhibition of pro-inflammatory responses occurs through modulation of the MAPK, PI3K/Akt, and GSK-3β pathways, which inhibit NF-κB activation and induce Nrf2-dependent HO-1 activation(Chen C. et al., 2012). Iridoids (EU-Idd) exert anti-inflammatory and osteoprotective effects by modulating the JAK2/STAT3 pathway in rheumatoid arthritis(Nakamura et al., 1997). Aucubin reduces inflammation in rheumatoid arthritis by decreasing NO levels(Lin M. et al., 2007) and exhibits anti-apoptotic properties(Li K. et al., 2016). Specifically, aucubin inhibits chondrocyte apoptosis and excessive ROS production, reverses IL-1β-induced cytotoxicity, and alleviates OA symptoms by attenuating IL-1β-induced chondrocyte apoptosis in a mouse model of osteoarthritis(Wang S. et al., 2014).

Neuroprotection

Active ingredients such as myricetin, β-sitosterol, genipin glycosides, propolis, pinoresinol diglucoside, lignans, diepoxy lignans, aucubin, chlorogenic acid, and macranthoin G (MCG), along with aqueous and alcoholic extracts from the bark, leaves, and flowers of Duzhong (Duzhong), all exhibit significant neuroprotective effects. Duzhong has been shown to exert neuroprotection in cerebral ischemia models by regulating the expression of Beclin-1 and LC3II proteins, thereby inhibiting autophagy(-Dong et al., 2020). In a scopolamine-induced Alzheimer's disease (AD) mouse model, it significantly inhibited acetylcholinesterase (AChE) and thiobarbituric acid reactive substances (TBARS) in the hippocampus and frontal cortex, while increasing hippocampal BDNF levels and enhancing scopolamine-induced phosphorylation of cAMP response element-binding protein (CREB), thus improving memory by supporting cholinergic signaling(Zhou Y. L., 2016).Duzhong bark has been found to reduce neuroinflammation by down-regulating the p38/JNK-Fosl2 gene expression(Ding Y.-X., Wang, et al., 2014). Additionally, its extracts show anti-Parkinson's disease (PD) effects by modulating autophagy(C. Li et al., 2012b), and exhibit strong anti-AD activity in hydrogen peroxide (H2O2)-induced SH-SY5Y cells, a neuroblastoma cell line. The extracts attenuate the phosphorylation of JNK, p38 MAPK, ERK1/2, and PI3K/Akt, enhance cellular viability, reduce cytotoxicity and DNA condensation, mitigate reactive oxygen species (ROS) production, preserve mitochondrial membrane potential (MMP), and regulate Bcl-2 and Bcl-xL expression(Shi X. et al., 2021).Duzhong foetida (EF), an edible herb, contains four active compounds—oleamide, catechol, chlorogenic acid, and kaempferol—that have neuroprotective effects by preventing mitochondrial dysfunction and calcium overload in epileptic hippocampal neurons in a pentetrazole-induced epilepsy model(Yan J., 2022). Thirteen compounds isolated from ethanolic extracts of EF were shown to have anti-neuroinflammatory activity by inhibiting lipopolysaccharide (LPS)-induced NO release in BV-2 mouse microglial cells(J. Yan et al., 2017b). The ethyl acetate extract of Duzhong reduces the expression of inflammatory mediators nitric oxide (NO) and prostaglandin E2 (PGE2) by inhibiting the expression of inducible nitric oxide synthase (iNOS) and COX-2[61].Edible Duzhong seeds, a potential dietary source of myricetin and β-sitosterol, may reduce the risk of neurodegenerative diseases(J.-K. Yan et al., 2019). Aucubin, one of the major compounds in Duzhong, has been shown to improve symptoms and prognosis in conditions such as Parkinson's disease, Alzheimer's disease, cerebral hemorrhage, diabetic encephalopathy, epilepsy, anxiety, depression, and traumatic brain injury. It promotes the repair of damaged neurons, increases γ-aminobutyric acid (GABA) levels in synapses, promotes the differentiation of neural precursor cells into GABAergic neurons, and provides antioxidant and anti-neuroinflammatory effects, in addition to enhancing autophagy and inhibiting apoptosis(Yang R. & Guan, 2023).Geniposidic acid, another active compound extracted from Duzhong, has demonstrated anti-aging, anti-oxidative, anti-inflammatory, and neurotrophic effects on neurons. In APP/PS1 mice, it significantly improved spatial learning and memory abilities and reduced cerebral amyloid-β deposition(Zhao L. et al., 2017). Propolis, another bioactive compound found in Duzhong, reduces inflammation and oxidative stress through the NF-κB, Nrf2/HO-1, and MAPK pathways(He et al., 2023). Pinoresinol diglucoside (PDG), a major lignan isolated from Duzhong, reduces neuroinflammation, neuronal apoptosis, and oxidative stress by modulating the TLR4/NF-κB and Nrf2/HO-1 pathways, and improves Aβ1-42-induced memory dysfunction in mice(Y. Li et al., 2011).Lignans in Duzhong also exert neuroprotective effects by activating AMPK signaling, which improves glaucoma-associated optic neuropathy(T. Wang et al., 2022). The aqueous extract of Duzhong antagonizes the activity of acetylcholinesterase(Xie et al., 2019), while the crude extract improves neurotransmitter levels in the striatum, enhancing motor function in Parkinson's disease models(J. Song et al., 2023). Duzhong leaves

inhibit brain damage by reducing oxidative stress(Thu et al., 2017), while epoxylated lignans from the leaves provide neuroprotection by activating the PI3K/Akt/GSK-3β/Nrf2 signaling pathway(J. Xiao et al., 2023). Aucubin has been shown to ameliorate brain injury in a rat model of status epilepticus by inducing autophagy, inhibiting necrotic apoptosis, reducing the number of apoptotic neurons, and increasing the number of surviving neurons(Shen et al., 2023).Oxidative stress-mediated cellular injury is a major cause of neurodegenerative diseases such as Alzheimer's and Parkinson's. Antioxidant strategies, including the scavenging of ROS, may help delay disease progression. Macranthoin G (MCG), isolated from Duzhong, exhibits antioxidant effects by downregulating the NF-κB pathway and activating the phosphorylation of IκBα, p38, and ERK(Zhao L. et al., 2017). Rich in chlorogenic acid (CGA), Duzhong improves learning, memory, and cognitive performance, and alleviates anxiety, depression, and symptoms of post-traumatic stress disorder (PTSD) by enhancing neuronal cell function(Tong et al., 2013). It also helps alleviate Parkinson's disease by enhancing autophagy in neuronal cells(Y. Xiao et al., 2022)Lastly, Duzhong polysaccharides exhibit immunomodulatory and neuroprotective effects. In a study on adolescent mice fed an obesity-inducing diet (OD), which is linked to low-grade chronic inflammation and neurodevelopmental disorders, Duzhong polysaccharides improved cognitive and social behaviors by modulating the gut microbiota and tryptophan metabolism(Zhao L. & Chen, 2019).

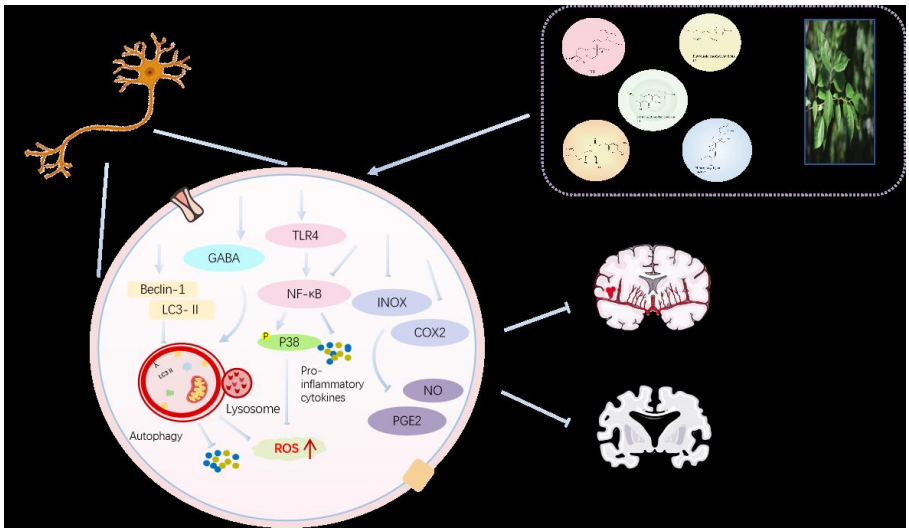

Figure 9: Neuroprotection of Duzhong

Anti-hypertensive

The active ingredients found in Duzhong bark, leaves, male flowers, and seeds—such as pinoresinol diglucoside, geniposidic acid, chlorogenic acid, and total flavonoids—exhibit significant antihypertensive effects(R. P. Zhou et al., 2016). Pinoresinol diglucoside and geniposidic acid, two key active compounds, have been shown to significantly reduce hypertension in spontaneously hypertensive rats (SHR)(M. Liu et al., 2022). In a study with a high-dose group (20 mg/kg) of chlorogenic acid extract, the main active ingredient of Duzhong, a stable and effective reduction in blood pressure was observed in SHR(Guan et al., 2021). Geniposidic acid exerts its effects by inhibiting NADPH oxidase, increasing endothelial nitric oxide synthase (eNOS), and improving both blood pressure and renal hemodynamics(Y. Xiao et al., 2019).The antihypertensive components of Duzhong leaves (EF) are classified into four categories: flavonoids, iridoids, lignans, and phenylpropanoids. These include compounds like chlorogenic acid, geniposidic acid, and pinoresinol diglucoside, which work by regulating biological processes such as inhibiting inflammation, modulating the nitric oxide synthase pathway, reducing oxidative stress, and regulating endothelial vasoactive factors(Y. Zhou & Xie, 2021). Additionally, the male flowers of Duzhong have been found to lower blood pressure in SHR in a dose-dependent manner. Mechanistic studies suggest that the aqueous extract of the male flowers exerts its antihypertensive effects by activating the ACE2-Ang-(1-7)-Mas signaling pathway in SHR(R. Zhang et al., 2014).

Anti-hyperglcemic

Duzhong polysaccharides, aqueous extracts, and quercetin, key active ingredients in Duzhong, exhibit notable hypoglycemic properties. Polysaccharides from Duzhong leaves significantly reduce fasting blood glucose (FBG) levels in diabetic rats, offering antioxidant benefits and providing a certain degree of protection to pancreatic islet cells in diabetic conditions(Zhang Y. et al., 2022). The aqueous extract of Duzhong demonstrates anti-hypoglycemic effects in diabetic mice, potentially through enhancing the body's antioxidant capacity and decreasing the protein content of caspase-3 and caspase-7 in the pancreas(X. Zhao et al., 2020). Additionally, the ethanol extract of Duzhong leaves exhibits anti-hyperglycemic properties by inhibiting α-glucosidase activity and reducing glucose absorption(Xing & Feng, 2022). Duzhong polysaccharides also display hypoglycemic effects in diabetic mice induced by tetracosan(Zhang L. et al., 2013). Quercetin, another key active compound in Duzhong, significantly targets DPP-IV to increase insulin sensitivity, further contributing to its hypoglycemic effects(Tang J. et al., 2013).

Anti-hyperlipdemic

Duzhong leaf extract, polysaccharides, total flavonoids, chlorogenic acid, and seed oil all exhibit significant hypolipidemic effects. Duzhong leaves help control hyperlipidemia by regulating the composition of intestinal microbiota(Zhang Y. et al., 2021). The extract of Duzhong aurantium leaves has been shown to correct the dysregulated gut flora caused by hyperlipidemia in rats(Lin Q. et al., 2019). Duzhong polysaccharides lower serum lipid levels, improve liver lipid metabolism, and have a potent lipid-lowering effect(Hu Q. et al., 2018). The total flavonoids of Duzhong leaves effectively reduce blood lipids in hyperlipidemic mice and rats(Chen L. et al., 2014), decreasing serum levels of total cholesterol, triglycerides, lipoproteins, apolipoprotein B, and LDL cholesterol, while significantly increasing high-density lipoprotein cholesterol and apolipoprotein levels(Wu H. et al., 2021).Chlorogenic acid from Duzhong leaves effectively reduces the accumulation of lipids in both blood and liver, enhances antioxidant activity in serum and liver, and regulates lipid metabolism(Ren H. et al., 2021). Duzhong seed oil also plays an important role in regulating lipid metabolism and serves as a supportive treatment for hyperlipidemia(Song L. et al., 2009). Duzhong bark and leaves have been shown to improve lipid metabolism by modulating the gut microbiota, which may contribute to treating hyperlipidemia(R. Li et al., 2021b). Additionally, Duzhong leaf extract stimulates lipolysis and thermogenesis by increasing sympathetic nerve activity in white adipose tissue (WAT-SNA) and brown adipose tissue (BAT-SNA), while reducing appetite through parasympathetic nerve inhibition, resulting in a decrease in abdominal fat and body weight(Hussain et al., 2020).

Immunomodulation

Duzhong total polysaccharides and extracts exhibit significant immunoregulatory effects. Different active components of Duzhong have been shown to improve sleep and modulate immune function in mice(Zhang Y. et al., 2021), with the ethyl acetate fraction demonstrating the most potent regulatory effect. Duzhong total polysaccharides enhance immune responses by increasing the phosphorylation levels of p38, ERK1/2, and JNK, and enhancing cyclic AMP activity[109]. These polysaccharides have also been shown to improve immune function in cyclophosphamide-induced immunocompromised mice(Yang Z. et al., 2020). Furthermore, Ali-1, a polysaccharide isolated from the roots of longleaf Duzhong, significantly increased the phagocytic activity of RAW264.7 cells and promoted cytokine secretion(Y. Sun et al., 2021), further supporting its role in enhancing immune function.

Antibacterial, Antiviral

Duzhong extracts, including those from its leaves(Q. Li et al., 2017), male flowers, and active ingredients such as chlorogenic acid, total flavonoids, and lignans, exhibit notable antibacterial and antiviral properties. EuCHIT1, an antibacterial peptide derived from Duzhong, has demonstrated effectiveness against Candida albicans. Its mechanism is thought to involve the destruc-

tion of the fungal cell wall, leading to membrane depolarization, increased permeability, and a reduction in IL-6 and TNF-α levels in lung epithelial cells infected with Candida albicans(R. Yang et al., 2023). The leaf extract of Duzhong has also shown inhibitory effects on intestinal bacteria, including Escherichia coli. Furthermore, metabolites from the endophytic fungus DZ05, isolated from Duzhong, exhibit broad-spectrum antibacterial activity(Hien et al., 2019). Total flavonoids from Duzhong have been found to inhibit the replication of hepatitis B virus (HBV) DNA and reduce the secretion of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg)(Kwon et al., 2016). Duzhong also significantly inhibits the growth of Fusarium spinosum(L.-D. Tang et al., 2023). Chlorogenic acid (CGA) has demonstrated a potent inhibitory effect on Salmonella spp(Tang L. et al., 2022), and the male flower extract of Duzhong effectively inhibits Staphylococcus aureus(Duan et al., 2019). Additionally, the antiviral compound (+)-pinoresinol-O-β-D-glucopyranoside from Duzhong has been shown to suppress H1N1 virus activity, potentially by inactivating the nuclear factor-κB, p38 MAPK, and AKT signaling pathways(B.-W. Wang et al., 2019)

Anti-fatigue

Duzhong extract, male flowers, isoquercitrin, polysaccharides, and leaf flavonoid glycosides all exhibit anti-fatigue pharmacological effects. Isoquercitrin (IQ) has been shown to enhance the exercise capacity of rats by improving energy metabolism, boosting antioxidant defenses, and reducing exercise-induced injury, thereby contributing to a strong anti-fatigue effect. Duzhong polysaccharides also display anti-fatigue properties, likely through mechanisms involving the regulation of glucose metabolism and protein conservation(S. Fan et al., 2020; Kwon et al., 2013). Duzhong extract can elevate hormone levels in rats subjected to exhaustive exercise, improving substance metabolism, extending exercise duration, and enhancing physical performance(S. Zhang et al., 2020). The anti-fatigue effects of Duzhong leaf flavonoid glycosides are linked to an increase in energy reserves, a reduction in the production of undesirable metabolites during over-exercise, improved tissue tolerance, and the removal of free radicals generated during exercise(Kwon et al., 2012). The extract from Duzhong male flowers (MFEU) and its seven active compounds may exert anti-fatigue effects by regulating testosterone secretion(S.-N. Zhang et al., 2023). Additionally, polyphenols, isolated and purified from Duzhong caryophyllantha resin, are thought to be the key components responsible for its anti-fatigue effects(Hu F. et al., 2023; Kwon et al., 2016).

Antioxidant

The total flavonoids of Duzhong, Duzhong seed meal protein, chlorogenic acid, and aucubin all exhibit potent antioxidant properties. The antioxidant capacity of Duzhong total flavonoids increases in a concentration-dependent manner, demonstrating strong in vitro antioxidant activity(J.-J. Tang et al., 2021). Hydrolyzed peptides derived from Duzhong seed meal protein also show significant scavenging effects on DPPH radicals, superoxide anions, and ABTS radicals, indicating their promising antioxidant potential(P. Yang et al., 2022). Chlorogenic acid from Duzhong leaves has been shown to effectively scavenge DPPH, ABTS, and hydroxyl radicals(Z. Zhou et al., 2020). Additionally, rutin, isoquercitrin, and astragalin from Duzhong leaves may be key components responsible for its radical scavenging activity(Y. C. Li et al., 2021).

Anti-aging

Duzhong demonstrates significant anti-aging effects, with its key active compounds, geniposidic acid (GPA) and polyphenols, playing crucial roles in protecting the nervous system and acting as antioxidants. Studies have shown that Duzhong leaf extract at doses of 3 g/kg and 1.5 g/kg can increase the binding rate of erythrocyte C3b receptors and immune complexes, enhancing immune function in the elderly and delaying the aging process(S. Lei et al., 2021). The alcoholic extract of Duzhong bark improves the antioxidant capacity of brain tissue, thereby protecting brain nerve DNA, with polyphenols being especially important in this neuroprotective and antioxidant role(C.-P. Li et al., 2016). Additionally, the kynurenic acid in Duzhong regulates the levels of Aβ in the brain by affecting its production and degradation, reducing neuroinflammation in transgenic mice, and providing neuroprotection, making it a key anti-aging metabolite(Kwon et al., 2011).Duzhong leaves primarily exert their an-

ti-aging effects by boosting immune function, scavenging free radicals, promoting collagen synthesis, and reducing collagen degradation. Li Xiaoan(H. Guo et al., 2015)'s research on a subacute aging model, induced by D-galactose in mice, revealed that the powdered extract of Duzhong bark has anti-aging properties, likely by improving central neurotransmitters, erythrocyte immunity, and antioxidant capacity. Zhao Hui(Y. Ding et al., 2022) discovered that iridoid monoglycosides such as geniposidic acid and aucubin could dose-dependently accelerate collagen synthesis, enhance skin renewal, and slow the aging process, without adverse effects. Further studies by Li(R. Han et al., 2022)demonstrated that aucubin, geniposidic acid, and genipin promoted collagen synthesis and the formation of granulomas in aged rat models, with geniposidic acid also boosting skin renewal and counteracting skin aging.Zhang Huan(J. Wang et al., 2017)found that compounds such as EUB-4 (Aucubin), EUB-2 (Asperuloside), and EUB-17 (Duzhong A) had significant protective effects on human embryonic skin fibroblast cells (ESF-1) damaged by H_2O_2 and UV radiation(W. Hu et al., 2014). Research has shown that the decline in collagen synthesis is directly linked to aging. Animal experiments suggest that aucubin from Duzhong promotes collagen production and slows the decline in physiological function associated with aging(X.-D. Chen et al., 2021).

Improvement of intestinal function

Duzhong flavonoids, polysaccharides, chlorogenic acid, bark extract, and leaf extract exhibit pharmacological effects that enhance intestinal function. Duzhong flavonoids have been shown to inhibit lipopolysaccharide (LPS)-induced inflammation in porcine small intestinal epithelial cells (IPEC-J2) and to repair intestinal damage by reducing the protein expression of PI3K, p-Akt, p-IKKα/β, and p-NF-κB(X. Gao et al., 2023). This action helps alleviate oxidative stress and intestinal damage in piglets through the Nrf2 signaling pathway(P. Sun et al., 2022). Additionally, modifications of selenium nanoparticles (SeNP) by Duzhong caryophyllantha polysaccharides (EUP) inhibited LPS-induced activation of the TLR-4/NF-κB signaling pathway in intestinal epithelial cell lines. This enhancement improves colonic antioxidant capacity and modulates the composition of the intestinal microbiome, mitigating the severity of DSS-induced colitis in mice(Lei Y. N. & Zhang, 2016). Furthermore, fecal microbiota transplantation (FMT) experiments have demonstrated that fecal bacterial suspensions containing chlorogenic acid (CGA), Duzhong bark extract (EBE), and Duzhong leaf extract (ELE) can ameliorate high-fat diet (HFD)-induced obesity via the Fiaf-LPL intestinal-hepatic axis and the SCFAs-GPR43 intestinal fat axis(R. Li et al., 2021b). However, evidence regarding the effects of plant polysaccharides on age-related gut dysbiosis and reactive oxygen species (ROS) accumulation during aging is limited. Notably, chlorogenic acid (CGA) appears to offer superior protective effects on the intestine(Gong et al., 2016).

Applications of Duzhong in Food Processing

In 2023, the National Health Commission and the State Administration for Market Regulation jointly issued the “Notice on the Announcement of 9 Substances That Are Both Food and Traditional Chinese Medicine” (No. 9 of 2023). This notice includes Codonopsis pilosula, Cistanche deserticola, and Duzhong leaves among the nine substances classified as both food and traditional Chinese medicine (commonly referred to as food-medicine substances). Duzhong leaves, recognized for their medicinal and edible properties, exhibit high safety and find various applications in the food industry.Duzhong tea, prepared from fresh Duzhong leaves through stir-frying, demonstrates notable antioxidant activity. Ye Wenfeng(Ye et al., 2004)et al. developed a unique and flavorful health beverage using Duzhong leaves as the primary ingredient. The addition of degummed Duzhong leaf powder during biscuit production significantly enhanced the color, flavor, and texture of the biscuits(Chen S. & Zhang, 2023). Similarly, incorporating Duzhong powder into bread improved its texture, firmness, and chewiness, while also extending its shelf life(S. Han et al., 2024).Ren(N. Ren et al., 2023)et al. utilized Duzhong ultrafine powder as an additive in glutinous rice fermentation, resulting in rice wine with significantly higher levels of flavonoids and polysaccharides compared to ordinary sweet wine, alongside strong antioxidant properties. Zhang discovered that adding Duzhong leaf ultrafine powder to fermented apple juice not only improved its color and flavor but also increased its nutrient content.Beyond its role as a food additive, research indicates that dietary supplementation with Duzhong leaf aqueous extract can significantly enhance egg production and

quality in aged laying hens, prolonging their peak production period. Han(M. Han et al., 2024)et al. demonstrated that incorporating 0.1% to 0.2% Duzhong leaf aqueous extract into pig feed improved pork flavor and meat quality. This highlights the substantial potential of Duzhong leaves as both a food additive and a feed supplement, showcasing their remarkable benefits in enhancing food quality, nutritional value, and health advantages.However, to successfully commercialize Duzhong leaf food additives and ensure their safe and effective application in food production, rigorous quality control and safety evaluation studies are essential. Developing diverse forms, flavors, and effective food products and additives derived from Duzhong leaves represents a promising endeavor.

Among the various Duzhong products available, Duzhong tea stands out as a prominent example. Depending on fermentation levels—unfermented, semi-fermented, and post-fermented—and variations in raw materials, commercially available Duzhong teas can be broadly categorized into Duzhong green tea, Duzhong black tea, Duzhong dark tea, and Duzhong flower tea. Notably, Duzhong flower was officially approved as a novel food ingredient by the National Health and Family Planning Commission of China in 2014.Duzhong flower is a valuable resource, characterized by a short blooming period of just 3 to 7 days and a high pollen yield that is easily harvested. It is regarded as a precious source of medicinal pollen in China. Nutritionally, Duzhong flower is rich in protein, containing 32.9% crude protein, 21.41% amino acids (with 40.4% being essential amino acids), 31.5 mg/100g of vitamin C, and 3.53% total flavonoids, contributing to its high nutritional value and medicinal benefits.Research has demonstrated that Duzhong flower pollen enhances dietary fiber content in noodles(Hong, 2024). This increase in dietary fiber is associated with a slower staling rate for the noodles. Additionally, Duzhong flower pollen is advantageous due to its high fiber and low fat content, allowing for a reduction in fat while increasing dietary fiber when incorporated into noodle recipes.In a study focusing on Duzhong flower nutrient meal replacement powder, efforts were made to improve its dispersibility. Through single-factor and orthogonal experiments, optimal addition levels of polydextrose, mono- and diglycerides, and hydroxypropyl starch were determined. The results indicated that the best dispersibility was achieved with 2% polydextrose, 0.1% mono- and diglycerides, and 2% hydroxypropyl starch. Human trials assessing the glycemic index (GI) showed that the meal replacement powder had a GI of 45.8, indicating its effectiveness in stabilizing postprandial blood glucose levels. Classified as a low-GI food, it is particularly suitable for individuals with diabetes, as well as those with high blood pressure, high cholesterol, and elevated triglyceride levels(Zhong et al., 2020).

Summary and Outlook

Duzhong has been used in China for thousands of years as a traditional medicine, establishing itself as a unique and precious resource. It accounts for over 99% of the world's Duzhong production and is extensively utilized in clinical settings. The bark, leaves, male flowers, and seeds of Duzhong all possess significant medicinal and edible value.With ongoing advancements in analytical technology and in-depth research into its modern pharmacological effects and chemical compositions, our understanding of Duzhong has deepened. This review systematically summarizes over 200 chemical constituents isolated from Duzhong, primarily including lignans, iridoids, flavonoids, phenolic acids, steroids, and terpenoids. We comprehensively discuss the chemical compositions, pharmacological effects, and mechanisms of action associated with Duzhong.There are notable differences in the chemical compositions and concentrations of the various parts of Duzhong, resulting in varying therapeutic effects in clinical applications. Modern pharmacological studies have demonstrated that the constituents of Duzhong are particularly effective in anti-osteoporosis, anti-inflammatory, and neuroprotective mechanisms.

Modern pharmacological studies have shown that Duzhong extract is remarkable in anti-osteoporosis, anti-inflammatory and neuroprotective mechanisms, and is clinically used in the treatment of osteoporosis and neurodegenerative diseases with promising efficacy(Y. Zhang, 2024).Among them, Duzhong polysaccharides play a significant role in modifying the skeletal system, while the medicinal use Duzhong polysaccharides is safe and effective without side effects(X. Liu, 2025).

The potential application of Duzhong in the field of functional food has also attracted more and more scholars to study. In recent years, it has been found that Duzhong extract has a variety of efficacies such as lowering blood pressure, lowering blood lipids, lowering blood glucose, anti-aging, etc., which makes it suitable for the development of health food. As a traditional Chinese medicine with the same origin of medicine and food, Duzhong has spawned a series of products based on the concept of "treating the future disease" in traditional Chinese medicine. For example, Duzhong tea made from Duzhong leaves, which is professionally processed, has the efficacy of lowering blood lipids, blood sugar and weight loss. In addition, Duzhong wine made from the skin of Duzhong has the effects of tonifying the liver and kidney and strengthening the muscles and bones, and Duzhong series of health food derived from Duzhong is gradually coming to the public's view.

This paper summarizes the structural characteristics, pharmacological components and clinical applications of Duzhong. The potential application of Duzhong in the fields of food, health food and medicine is further understood. At the same time, the basic research on Duzhong is summarized. In the coming time, as more pharmacological mechanisms of Duzhonge are revealed and health food products of Duzhonge are developed, more clinical indications will be found, and the concept of"treating the future disease"of Chinese medicine will be implemented. We hope that this review will provide a scientific basis for the further study of the effects of Duzhonge and its clinical applications.

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Conflict of Interest section

The authors declare that there is no conflict of interest

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