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Research Progress on the Mechanism of the Effective Components of Duzhong (Eucommiae Cortex) on Lumbar Disk Herniation

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Abstract

Duzhong (Eucommiae Cortex) is one of the most commonly used Chinese herb in the treatment of lumbar disk herniation (LDH). Both the single use of it and as a Chinese herbal compound have significant clinical efficacy. Its effective components including lignans, flavonoids, iridoid terpenes, polysaccharides, etc., participate in the treatment of LDH through multiple channels, which can effectively inhibit immune and inflammatory reactions, promote the repair of intervertebral disk bone tissues, protect neurological functions, enhance cell metabolism, regulate endocrine, etc. The signal pathways of Wnt/β-catenin, TNF, HL-1, MAPK, PI3K/AKT, and NF-κB may be also involved. The action mechanism of Duzhong (Eucommiae Cortex) on LDH is characterized by multiple paths, multiple targets, and multiple component cross-actions, but the direct effects of specific components of Duzhong (Eucommiae Cortex) on LDH pathological tissues have not been clarified in the existing studies. At present, the study on the efficacy of Chinese herbs has not yet included the chemical reactions among the pharmaceutical components and pharmaceutical processing, etc. Relevant experimental studies need to further extract the effective components through purification technology, analyze the target information between Duzhong (Eucommiae Cortex) and LDH through network pharmacology and biology, and strengthen the influence of different processing methods on the pharmaceutical effects of Chinese herbs to increase the choice of clinical medication. In the experimental study, the animal cell models were finely constructed, and the pathological targets of LDH were excavated, which was conducive to the development and application of new drugs.

Keywords
- lumbar disk herniation
- Duzhong (Eucommiae cortex)
- action mechanism

Lumbar disk herniation (LDH) is a disease in which the disk nucleus pulposus compresses the intraspinal dural sac or directly presses the nerve root through the ruptured disk fiber ring, causing lower back pain or syndromes of the leg or cauda equina nerves. The incidence of lumbago in manual workers in China is 16.4%,[1] of which LDH patients account for approximately 85%,[2] and the incidence is increasing. The pathogenesis of LDH is related to mechanical injury, inflammatory reaction, immune disorders, genetic factors, dysregulation of metalloproteinase expression, and abnormal

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lipid metabolism,[3] and it may also be the result of the combined action of multiple factors. At present, the clinical treatment is mainly symptomatic. With the continuous deepening of Chinese medicine application in clinical diagnosis and treatment, the treatment of LDH with a single Chinese herb or Chinese herb prescription has achieved a significant curative effect. Among them, the single use of Duzhong (Eucommiae Cortex) and its compound prescriptions are used more frequently, with higher confidence than other Chinese herbs, and they contain the most chemical components.[4] The clinical efficacy of the prescription related to Duzhong (Eucommiae Cortex) is prominent.[5] Modern pharmacological studies have found that the effective components of Duzhong (Eucommiae Cortex) such as lignans, flavonoids, iridoid terpenes, and polysaccharides have exact effects and the action mechanism is unique. To further study the mechanism of the effective components of Duzhong (Eucommiae Cortex) in LDH and expand its clinical application, relevant studies in recent years are summarized below.

Components and Pharmacological Effects of Duzhong (Eucommiae Cortex)

The medicinal parts of Duzhong (Eucommiae Cortex) are mostly the bark and leaves of Eucommia ulmoides Oliv. The earliest record of it can be found in the medical wood slips unearthed from the Eastern Han Dynasty Tomb on the dry beach slope of Wuwei City, Gansu Province, and it was used for the treatment of "seven injuries—spermatogenesis."[6] It is recorded in the *Pharmacopoeia of the People's Republic of China* that the bark of Duzhong (Eucommiae Cortex) is used, also known as Sixian and Mumian. It is sweet in taste and neutral in nature. It pertains to the liver and kidney meridians and is classified as a warm and sweet nontoxic Chinese herbs. It has the efficacy of strengthening muscles and bones, tonifying the liver and kidney, and calming the fetus.[7] Xing et al[8] found that there were no significant differences in different parts of Duzhong (Eucommiae Cortex) through modern pharmacological studies, mainly including phenolic acids, flavonoids, iridoid, polysaccharides, steroids, lignans, amino acids, plant proteins, etc. Among them, quercetin, kaempferol, wogonin, baicalin, etc., are the main pharmaceutical components, which have anti-inflammatory, immunomodulatory, antiosteoporosis, antioxidant, blood pressure, blood glucose and lipid regulation, liver protection, sedation, and hypnosis effects.[9,10] Its anti-inflammatory, immune regulation, bone metabolism regulation, and neuroprotection effects are closely related to LDH.

Mechanism of the Effective Components of Duzhong (Eucommiae Cortex) in Intervening LDH

Anti-inflammatory and Immune Regulation

It was found that the inflammatory factors involved in LDH mainly included tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2), interleukin (IL), nuclear transcription factor ß (NF-κβ), P38 mitogen-activated protein kinase (P38 MAPK), matrix metalloproteinase (MMP), etc. The inflammatory reaction promoted the degeneration and dehydration of intervertebral disk tissues and ultimately caused cell lysis of endplate cartilage, fibrous ring, and protrusion of nucleus pulposus.[11,12] Anti-inflammatory and immunomodulatory effects are of great significance for relieving LDH. Sun et al[13] found that the aucubin of Duzhong (Eucommiae Cortex) mainly played anti-inflammatory, immunomodulatory, and antioxidant roles in LDH, and its extract could down-regulate TNF-α and IL-1β, block miR-140–5p/CREB1 axis, and inhibit the expression of cartilage inflammatory factors, thus improving clinical pain symptoms.[14] Zhang et al[15] used Duzhong (Eucommiae Cortex) extract to intervene in arthritis in rats and found that TNF-α and IL-6 in serum were decreased; the expression of vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 mRNA was in a horizontal state, which might be related to the inhibition of inflammatory factors by Duzhong (Eucommiae Cortex). Deng et al[16] found in the network pharmacology study that components including kaempferol in Duzhong (Eucommiae Cortex) exerted anti-inflammatory, immunomodulatory, and analgesic effects on the treatment of LDH.

Immune and inflammatory reactions occurred almost simultaneously in the course of LDH. Hai et al[17] found by detection that immune genes associated with intervertebral disk degeneration (IDD) were highly aggregated in immune-related pathways, among which genes of MSH2, LY96, ANXA3, PIK3CD, and ZBTB16 might change the immune and bone marrow cell composition of IDD patients by triggering various immune-related pathways and participate in the pathogenesis of IDD. Sun et al[18] found that various downstream cascade immune reactions occurred in the nucleus pulposus when the blood nucleus pulposus barrier was damaged by analyzing the relationship between the structure of the intervertebral disk and the autoimmune response. Di et al[19] found that nerve root pain was closely related to the autoimmune reactions of intervertebral disks and nerve roots. Zhang et al[20] performed immunohistochemical treatment through the protruding intervertebral disk of pigs. The antibody CD68 and monoclonal antipig IgG antibody of the protruding intervertebral disk macrophages were both positive, indicating that inflammatory and immune reactions were present in LDH tissues at the same time. Both reactions also caused pain by promoting the demyelination of nerve roots. Wang et al[21] found reduced expression of cyclic guanosine phosphate (cGMP), decreased activity of Na^+-K^+-ATPase, increased ratio of cyclic adenosine phosphate and cGMP, and increased ratio of $CD4^+/CD8^+$ of T lymphocytes in Duzhong (Eucommiae Cortex)-intervened rats, indicating that Duzhong (Eucommiae Cortex) could effectively improve the immunity of the body. Kim et al[22] used Duzhong (Eucommiae Cortex) to study the inflammatory reaction of mouse peritoneal macrophages induced by lipopolysaccharide (LPS) and found that the LPS could inhibit the production of TNF-α and IL-6 induced by LPS, reduce the elevated level of COX-2 induced by inflammation and the production of peptidoglycan (PG)

and nitric oxide (NO) in mouse peritoneal macrophages, inhibit inflammatory reaction, and regulate immune response. Xie et al[23] found that Eucommia bark extract could reduce arthritis reaction and immune response deposition in rats, decrease MMP-3 secretion and alleviate osteoarthritis symptoms by inhibiting phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signal pathway. In summary, the components of Duzhong (Eucommiae Cortex) such as kaempferol, quercetin, and chlorogenic acid act on various organs of the immune system, inhibit the inflammatory immune responses expression of IL-17, TNF, and MAPK through the targets of IL-6, IL-1β, TNF, and VEGFA.[24]

Promotion of Bone Cell Metabolism and Repair

The disorder of bone metabolism is one of the important causes of LDH. Wang and Sun[25] found that Duzhong (Eucommiae Cortex) could increase the expression of immune cells $CD4^+/CD8^+$, $CD3^+$ and $CD4^+$ in human body, inhibit osteoclasts, accelerate bone metabolism, promote fracture healing, and effectively treat disk herniation. Zhao et al[26] found that after the intervention of Duzhong (Eucommiae Cortex) extract, osteoblasts proliferated, osteoclasts decreased, and bone tissues was significantly repaired. The mechanism may be that Duzhong (Eucommiae Cortex) extract induced the proliferation of bone marrow mesenchymal stem cells (BMSCs), promoted the differentiation of bone cells, and MAPK, Wnt/β-catenin, RhoA/ROCK, and other intervertebral disk-related signal pathways could also promote the metabolism and repair of bone tissues under the effect of Duzhong (Eucommiae Cortex) extract. Li et al[27] found that Eucommia polysaccharide reduced IL-1β-induced apoptosis of chondrocytes ATDC5 by inhibiting NF-κβ and inhibited the expression of TNF-α, NO, IFN-γ, and IL-6 in mouse chondrocytes ATDC5 culture medium, reduced inflammatory response. The decreased MMP-13 and P-P65 protein expression could also effectively alleviate the destruction of extracellular matrix and chondrocytes. Zhang et al[28] found that the regulation of Duzhong (Eucommiae Cortex) on osteoporosis involved the signal pathways of MAPK, Estrogen, FoxO, and VEGF through enrichment analysis of target genes. The main targets of action were MAPK1, EGFR, MAPK8, ESR1, ALB, etc., which could increase the proliferation of osteoblasts, inhibit osteoclasts, promote the metabolism, and repair of bone and slow down the degeneration of intervertebral disks.

Studies have shown that Duzhong (Eucommiae Cortex) has 19 active components that play a role in bone metabolism, which may exert effects through signal pathways of p53, MAPK, PI3K-Akt and NF-κβ. The effective chemical components in the treatment of osteoporosis are mainly the extracts of sebum alcohol, betulinic acid, kaempferol, eucommia gum, etc.[29] Wang et al[30] studied osteoporosis rats by extracting the components of Duzhong (Eucommiae Cortex) with 75% ethanol and found that the tryptophan level was significantly increased, which could inhibit bone cell generation and metabolism; among its flavonoids, kaempferol, rutin, and quercetin had inhibitory effects on bone marrow stem cells and promoted bone differentiation. They could promote bone metabolism and increase bone tissue repair and kaempferol had the strongest effect.[31] Xie et al[32] also found that lignans, iridoid terpenes, and flavonoids in the chemical components of Duzhong (Eucommiae Cortex) could directly act on osteoclasts and osteoblasts, affect the absorption and production of bone matrix, and effectively stimulate the osteogenic differentiation of BMSCs, activate signal pathways of Wnt/β-catenin, OPG/RANKL/RANK, BMP/Smad and MAPK, and regulate bone metabolism. Tang and Zou[33] found that Duzhong (Eucommiae Cortex) could promote the expression of VEGF and improve local circulation and bone metabolism during fracture healing. Yang et al[34] found through experimental studies that the alcohol extract of Duzhong (Eucommiae Cortex) played an inhibitory role in Janus kinase 1 (JAK1) signal transduction, signal transducer and activator of transcription 3 (STAT3), and suppressor of cytokine signaling 3 (SOCS3), which could reduce cartilage inflammatory response and cell damage. Gui and Xu[35] observed the regulatory effect of quercetin on the differentiation of articular cartilage cells in rats. They found that quercetin could promote the expression of target genes and enhance the metabolism and proliferation of bone tissues by activating the signal pathways of ERK, P38, and ATK in the downstream of MAPK pathway. Therefore, quercetin contained in Duzhong (Eucommiae Cortex) also had a repair effect on the endplate cartilage of the intervertebral disk and could slow down the degeneration of the spinal unit.

Neuroprotection

Ethanol-extracted compounds such as baicalin, betulin, chlorogenic acid, and gardenia acid contained in Duzhong (Eucommiae Cortex) can effectively reduce oxidative stress-mediated cell damage, improve the symptoms of Parkinson's disease (PD) or Alzheimer's disease (AD) caused by immune inflammation, and protect dopaminergic neurons.[36] Studies have found that Duzhong (Eucommiae Cortex) can also exert neuroprotective effects on amyloidß (25–35)-induced learning and memory dysfunction in mice by inhibiting the AChE activity in the hippocampus and frontal cortex.[37] Fan et al[38] studied whether Duzhong (Eucommiae Cortex) extract could inhibit the expression of proinflammatory cytokines in dopaminergic neuron degeneration and found that it could down-regulate the expression of p38/JNK-Fosl2 gene and relieve neuroinflammation. In the treatment of painful LDH, it is most important to prevent the sensitization of sensory nerve fibers that dominate the intervertebral disks, inhibit the pathogenic increase of cytokines, and reduce the excessive activity of the intervertebral disks.[39] Aucubin in Eucommia bark can attenuate the activation of astrocytes, reduce the expression levels of IL-1β, HMGB1, TNF-α and glutamic acid, and protect neuronal cells.[40] Duzhong (Eucommiae Cortex) extract can alleviate pain symptoms by inhibiting the inflammatory response and antioxidant effect of nerve roots, such as inhibiting the release of TNF-α, TNF-β, and PGE mediators, or by inhibiting the expression of immune complexes and inflammatory responses in intervertebral disks. Kobayashi et al[41] observed an increase in the expression of CD45, IL-1β, TNF-α, I-NOS, and COX-2 after compression of dog nerve roots, in which the immunoinflammatory

response complex can stimulate peripheral nerves. Miyagi et al[42] used recombinant human TNF-α and IL-1β to stimulate $CD14^-$ and $CD14^+$ cells cultured in IVD and qPCR to determine the levels of pain-related molecules calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF). It was found that $CD14^+$ cells had higher TNF-α, IL-1β, IL-6, and NGF expression in human degenerative IVD than $CD14^-$ cells. $CD14^+$ cells directly and indirectly promoted the expression of inflammatory cytokines and pain-related molecules in human degenerative IVD. Zhang et al[43] found that VEGF mediated pain together with immune T cells and B cells, while Duzhong (Eucommiae Cortex) could effectively regulate inflammatory and immune responses and produce analgesic effects on peripheral nerve roots. Guo et al[44] found that the iridoid components contained in Eucommia bark, flowers, and leaves could exert analgesic effects by regulating sodium ions and glutamate receptors. Si et al[45] studied quercetin and sciatic nerve pain in rats and found that quercetin could inhibit the signal pathway Wnt/β-catenin and downstream COX-2 and iNOS targets, and alleviate sciatic nerve pain.

Other Effects

It was found that the height of the intervertebral disk decreased and the risk of fracture increased in patients with type 1 and type 2 diabetes mellitus, which might be related to hyperglycemia affecting the metabolism of the extracellular matrix of the intervertebral disk, resulting in dystrophy of the intervertebral disk cells.[46,47] The extracellular matrix of the intervertebral disk was in a hyperglycemia environment for a long time, the oxidative stress response increased, and the acidic substances increased in anoxia environment, which promoted the aging apoptosis of the intervertebral disk cells and the autophagy of the nucleus pulposus cells. The reduction of the oxidative stress response and improvement of the nutritional metabolism were conducive to the treatment of LDH. Wang et al[48] intervened with Eucommia polysaccharide in diabetic rats and found that the serum superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) increased, and the blood glucose concentration and MDA decreased significantly. Wang et al[49] also found that Eucommia polysaccharide could reduce the blood urea nitrogen concentration and creatine kinase activity in swimming mice. It was speculated that Eucommia polysaccharide participated in LDH to exert antioxidant and antifatigue effects and could effectively improve disk degeneration. There are many factors involved in the pathological process of LDH. Yang et al[50] found that estrogen had a protective effect on intervertebral disk cells, which could inhibit the expression of inflammatory factors of IL-1β, TNF-α, etc., and the synthesis of MMPS, up-regulate the synthesis and metabolism of integrin α2β1 and IVD, and activate the signal pathway of PI3K/Akt to reduce oxidative damage of intervertebral disk cells. At the same time, Saravi et al[51] found that the renin-angiotensin system (RAS) was also involved in the degeneration process of IVD, and its angiotensin II type 2 receptors (Agtr2)/angiotensin-converting enzyme 2 (ACE2)/angiotensin 1–7/MasReceptor regulatory pathway might be a protective anti-inflammatory pathway. The effective components of Duzhong (Eucommiae Cortex), such as wogonin and baicalin, could activate endogenous target genes of estrogen receptor (ER), mediate estrogen effect through the genomic action of ER subtype ERα and had the effects of reducing LDH tissue damage.[52] The lignans of Duzhong (Eucommiae Cortex) can also regulate the protective pathway of RAS. Luo et al[53] found that Duzhong (Eucommiae Cortex) may be involved in the regulation of NO level and RAS to participate in protective anti-inflammatory effect. Duzhong (Eucommiae Cortex) may play an important role in the inflammation and immune response of LDH tissues through the protection of estrogen and the regulation of RAS system. Obesity is one of the causes of LDH. Segar et al[54] found that the metabolism of NP decreased after the increase of leptin and other cytokines in fat in obese patients, the secretion of lactic acid also increased, NO, MMP-3 and MMP-9, TNF-α, IL-6 were also synthesized in large quantities, but the concentration of glycosaminoglycan (GAG) was reduced. Zheng et al[55] found that by regulating lipid metabolism, the compounds in Eucommia leaves could inhibit the synthesis of free fatty acids and leptin in mice and reduce fat deposition. Lei and Zhang[56] found through animal experiments that Eucommia total flavonoids could reduce the serum triglyceride, cholesterol concentration, increase the concentration of high-density lipoprotein and apolipoprotein A, and effectively regulate the abnormal state of blood lipids in vivo. Therefore, Eucommia flavone may indirectly improve the pathological process of LDH by regulating blood lipids.

In summary, although there is no experimental evidence that specific components of Duzhong (Eucommiae Cortex) directly intervene in the pathological process of the intervertebral disks, it is believed that the effective components of Duzhong (Eucommiae Cortex) may actively participate in the treatment process of LDH through blood glucose, blood lipid, RAS system, estrogen, etc.

Summary and Outlook

LDH belongs to the categories of lower back pain, flaccidity syndrome, and bi syndrome in Chinese medicine. Its pathogenesis is related to liver and kidney deficiency, wind-cold-dampness pathogen, trauma, etc. In *Plain Conversation of Yellow Emperor's Inner Classic (Huang Di Nei Jing):Discussion on the Essentials of Pulse (Huang Di Nei Jing Su Wen: Mai Yao Jing Wei Lun)*, it records that "The waist is the area covered by the essence of the kidney. So inability of the waist to turn around indicates that the kidney is declining." In *Treatise on the Origins and Manifestations of Various Diseases:Manifestation of Lumbago (Zhu Bing Yuan Hou Lun:Zu Yao Tong Hou)*, it states that "For a man with injury, the kidney qi is deficient, and the kidney governs the waist and feet…The wind pathogen thus enters the kidney meridian, so the waist hurts." In *Wondrous Lantern for Peering into the Origin and Development of Miscellaneous Diseases:Origin of Lumbar and Naval Disease (Za Bing Yuan Liu Xi Zhu:Yao Qi Bing Yuan Liu)*, it says that "Lumbago is due to essence deficiency and invasion of

pathogenic qi, and kidney deficiency is its origin." In *Treatise on the Origins and Manifestations of Various Diseases:Manifestation of Waist and Foot Pain (Zhu Bing Yuan Hou Lun:Yao Jiao Tong Tong Hou)*, it states that "Kidney qi is insufficient and wind pathogen attacks. Overstrain causes kidney deficiency, and cold wind further attacks, which will cause struggling between cold wind and healthy qi, so the waist and feet will be painful." Clinically, the internal causes of LDH are mainly liver–kidney deficiency, external wind-cold-dampness pathogens, etc. The liver–kidney deficiency syndrome, cold-dampness obstruction, and intermingling deficiency-excess syndrome are often common. Duzhong (Eucommiae Cortex) has the effects of tonifying liver and kidney, strengthening muscles and bones, etc., and is a high-frequency herb for the clinical treatment of LDH. It was found that the inflammatory immune response, bone metabolic disorders, neurological dysfunction, etc., were involved in the pathological process of LDH, and the factors of blood glucose, estrogen, blood lipid, RAS system, etc. were also involved. The main components of Duzhong (Eucommiae Cortex) such as kaempferol, quercetin, lignan, aucubin, flavonoids, polysaccharides, chlorogenic acid, etc., are involved in the pathological process of LDH, which can effectively inhibit the inflammatory immune response, regulate bone metabolism, protect nerve function, and promote extracellular matrix formation. The signal pathways of Wnt/β-catenin, TNF, HL-1, MAPK, PI3K/AKT, and NF-κB may also be involved. The action mechanism of Duzhong (Eucommiae Cortex) on LDH is characterized by multiple paths, multiple targets, and multiple component cross-action, which provides the basis for clinical medication and direction for relevant experimental studies. However, most of the existing studies are related to inflammation and bone metabolism and the direct effects of specific components of Duzhong (Eucommiae Cortex) on LDH pathological tissues have not been clarified. However, the current studies on the efficacy of Chinese herbs have not yet included the factors such as chemical reactions between pharmaceutical components and herb processing. In the future, the experimental study can further extract the effective components of Duzhong (Eucommiae Cortex) through purification technology. At the same time, the target information between Duzhong (Eucommiae Cortex) and LDH will be analyzed through network pharmacological and biological research, so as to promote the development and utilization of the effective components and improve the herb development value of different parts of Duzhong (Eucommiae Cortex). Chinese herbal processing technology is closely related to pharmaceutical effects. The study on the effects of different processing methods on the pharmaceutical effects of Chinese herbs should be strengthened to increase the choice of clinical medication. In addition, the pathological mechanism of LDH is complex, and a variety of biomolecules, signal pathways, and genes are involved. The animal cell model can be refined in the experiment to explore the pathological targets of LDH, and it is also conducive to the development and application of new drugs

CRediT Authorship Contribution Statement
B.Y. and Y.Z, were responsible for writing—original draft, investigation, and conceptualization. H.Q. and Y.Z. were responsible for supervision, funding acquisition, and writing—review and editing.

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Conflict of Interest
The authors declare no conflict of interest.

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