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Advances in Pharmacological Mechanism of Eucommia Ulmoides in Treating Parkinson's Disease

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Abstract: Parkinson's disease is a common clinical neurodegenerative disease, mainly manifested by motor retardation, quiescence tremor, myotonia, etc., which seriously affects patients' physical and mental health and quality of life.Eucommia ulmoides is a commonly used traditional Chinese medicine for Parkinson's disease, which has the effect of tonifying liver and kidney, strengthening muscles and bones.Through the analysis of several drug components, animal and in vitro cell experiments, and the in-depth exploration of network pharmacology, it was found that Eucommia ulmoides contained a variety of effective active ingredients, such as peach-leaf corallin, eucommia ulmoides polysaccharide, protocatechuic acid, chlorogenic acid, caffeic acid, geniposide, etc.It can be used to treat Parkinson's disease by anti-neuroinflammation, anti-oxidative stress, inhibition of apoptosis and enhancement of nerve autophagy.In this paper, the active components of Eucommia ulmoides and their effects on receptor proteins and signaling pathways were summarized, so as to clarify the pharmacological mechanism of Eucommia ulmoides in the treatment of Parkinson's disease and provide reference for future research directions of Eucommia ulmoides in the treatment of Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that typically affects middle-aged and elderly individuals, characterized by symptoms such as slow movement, muscle rigidity, and resting tremors[1]. Epidemiological studies have shown that the proportion of PD patients among the population aged 65 and above in China exceeds 1%[2], with the prevalence increasing annually. By 2030, it is projected that there will be 5 million people with PD in China, nearly half of the global PD population[3]. The main pathological changes of PD include degeneration of

dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. The pathogenesis of PD is complex, involving multiple factors such as abnormal aggregation of α-synuclein, mitochondrial dysfunction, oxidative stress, immune response, and neuroinflammation[4]. The most commonly used treatment for PD is dopamine agonist replacement therapy, which can alleviate motor symptoms but cannot restore normal function of dopaminergic neurons or reverse disease progression. Moreover, the efficacy of these drugs diminishes over time, leading to adverse effects such as motor fluctuations and dyskinesias with long-term use[5], significantly impacting patients' physical and mental health as well as their quality of life. Therefore, there is an urgent need to explore treatment methods with long-term efficacy and reduced drug-related side effects.

PD traditional Chinese medicine can be classified under the category of "tremor syndrome". Contemporary doctors often believe that tremor syndrome is based on liver and kidney deficiency, producing wind, fire, phlegm, and blood stasis, leading to its onset[6].Traditional Chinese medicine has accumulated rich experience in treating tremor syndrome, and a large number of studies have shown that traditional Chinese medicine has the advantages of multiple components, pathways, and targets. Combining Western medicine treatment can not only improve efficacy, but also reduce adverse reactions of Western medicine and delay disease progression[7]. Among them, the traditional Chinese medicine Eucommia ulmoides has a history of more than 2000 years of use, which has the effects of nourishing the liver and kidney, strengthening muscles and bones, and relieving miscarriage. It is commonly used to treat liver and kidney deficiency, dizziness, and other symptoms.Modern pharmacological research has shown that Eucommia ulmoides contains various active substances, which exert antioxidative stress, anti-neuroinflammatory, and enhance neuronal autophagy effects[8]. Many classical and folk prescriptions used to treat central nervous system diseases include Eucommia ulmoides[9]. Some prescriptions for treating Parkinson's disease also contain Eucommia ulmoides[10-12], and studies have shown that Eucommia ulmoides can significantly improve Parkinson's disease-like behaviors and striatal dopamine levels in PD animals, alleviate dopamine neuron damage, thereby confirming its therapeutic effect on Parkinson's disease[13-15]. Network pharmacological studies suggest that Eucommia ulmoides may improve Parkinson's disease symptoms by upregulating PD-related genes such as DRD1 and DRD2[14].Professor Dong Shaolong, a nationally renowned traditional Chinese medicine practitioner, used Eucommia ulmoides as the monarch medicine in his prescription "Bushen Huoxue Decoction", advocating the treatment of Parkinson's disease with the method of "nourishing liver and kidney, dispelling blood stasis and calming wind". The therapeutic effect is significant [12].Therefore, this article retrieves relevant literature from databases such as Sci-Hub, Wanfang Data, and CNKI using "Parkinson's disease" and "Eucommia ulmoides" as search terms, to explore and summarize the pathogenesis of PD and the pharmacological effects of Eucommia ulmoides in treating PD, aiming to provide a basis for the development and application of Eucommia ulmoides in preventing and treating PD.

2. The Relationship Between Traditional Chinese Medicine Etiology and Pathogenesis of Parkinson's Disease (PD) and Liver and Kidneys

One of the main clinical manifestations of Parkinson's disease (PD) is involuntary movements of the limbs or head, resembling the shaking of trees and grass in the wind, attributed to endogenous wind. The occurrence of tremors affects the tendons, which, according to the theory of the Five Elements, belong to the liver system, whose normal function requires nourishment of liver qi and blood[16]. Internal wind is caused by visceral dysfunction and imbalance of yin and yang, closely related to the liver, also known as internal liver wind.Subsequently, tendon disorders occur, leading to PD-like symptoms.This pathogenesis is clearly described in the book "Standards of Diagnosis

and Treatment" by the famous Qing Dynasty physician Wang Kentang.The kidneys are the origin of congenital constitution and have the function of storing essence and regulating qi. Deficiency of kidney qi or essence affects water metabolism, blood production, and yin-yang balance, leading to corresponding pathological factors (i.e., phlegm, stasis, fire), ultimately resulting in endogenous wind and PD-like symptoms[17]. Therefore, the occurrence and development of PD are closely related to the liver and kidneys. Based on this pathogenesis, tonifying the liver and kidneys is one of the key methods for treating Parkinson's disease. Furthermore, the effectiveness of tonifying the liver and kidneys has been confirmed by extensive research[18-21].

3. Research Overview of Eucommia Ulmoides

Du Zhong refers to the dried bark of the Eucommia ulmoides Oliv., a plant belonging to the Eucommiaceae family.It is warm in nature, sweet in taste, and attributed to the liver and kidney meridians. It is a precious tonic herb in China[22]. First recorded in the "Sheng Nong's herbal classic," it is mentioned that Du Zhong has the efficacy of "treating lower back pain, nourishing the middle, enhancing essence and qi, strengthening tendons and bones." The "Mingyi Bielu" also states, "Du Zhong is warm in nature, sweet in taste, tonifies the liver and kidneys, and strengthens tendons and bones." Modern pharmacological studies have shown that Du Zhong contains over 100 chemical components, including sesquiterpenes, lignans, flavonoids, phenylpropanoids, polysaccharides, and antifungal proteins. The pharmacological effects of Du Zhong are extensive, including lowering blood pressure, anti-inflammatory, antioxidative, antitumor, and immune regulation properties[23]. However, there is currently limited research on the pharmacological mechanisms of Du Zhong in treating Parkinson's disease (PD). Therefore, by exploring the pathogenesis of PD and the pharmacological effects of Du Zhong, a systematic review of the mechanism of Du Zhong in treating PD is conducted.

4. The Mechanism of Action of Eucommia Ulmoides in the Treatment of Parkinson's Disease

4.1 Antioxidative Stress

Oxidative stress refers to a pathological state caused by an imbalance between the oxidative system and the antioxidative system. In Parkinson's disease (PD), this imbalance can occur due to mitochondrial dysfunction, increased dopamine oxidation metabolism, and decreased antioxidative enzyme activity. This leads to the excessive accumulation of reactive oxygen species (ROS), reactive nitrogen species (RNS), and other reactive polymers[24-25]. Dopamine (DA) is metabolized to produce hydrogen peroxide (H_2O_2), superoxide radicals (O^{2-}), and hydroxyl radicals (OH), which are cleared by glutathione (GSH). If GSH levels decrease, leading to an excess of ROS within cells, it can cause pathological reactions such as protein oxidation damage, lipid peroxidation, damage to the cell cytoskeleton and organelles, ultimately resulting in neuronal apoptosis[26]. Antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), and catalase (CAT) determine the rate of clearance of ROS and free radicals. Nitric oxide (NO) is a highly diffusible free radical synthesized by nitric oxide synthase (NOS). Upregulation of NOS expression leads to excessive NO production, which reacts with superoxide anions to form toxic peroxynitrite anions, thereby promoting oxidative damage[27].

Aucubin (AU) is a representative component of iridoids with neuroprotective effects, which are abundant in any extract of Eucommia ulmoides. Both in vivo and in vitro studies have confirmed AU's antioxidative effects, revealing its ability to reduce NOS generation, inhibit ROS production, decrease NO levels, and increase the activity of endogenous antioxidative enzymes such as SOD, GSH-PX, and CAT, thereby scavenging ROS and free radicals[8,22]. Additionally, in vitro

experiments have demonstrated that Eucommia ulmoides polysaccharides can scavenge DPPH radicals, with antioxidative activity depending on concentration and higher than that of VC at the same concentration[28]. Furthermore, chlorogenic acid can increase the activity of SOD, CAT, and GSH-Px, exhibiting antioxidative activity[29]. Malondialdehyde (MDA) is considered an indicator of lipid peroxidation caused by free radical release. AU, chlorogenic acid, and caffeic acid can all reduce MDA levels, further indicating that Eucommia ulmoides can reduce lipid peroxidation damage and attenuate cell apoptosis[26,30].

Furthermore, the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) axis also plays a crucial role in counteracting oxidative stress damage by inhibiting inflammation, oxidation, mitochondrial damage, calcium influx, apoptosis, and autophagy. Nrf2 is typically sequestered in the cytoplasm by the regulatory protein Kelch-like ECH-associated protein 1 (Keap1). Oxidation induces structural modifications in Keap1, releasing Nrf2, which translocates to the nucleus, binds to antioxidant response elements (ARE), and induces the expression of glutathione (GSH), SOD, and downstream proteins such as NADPH quinone oxidoreductase 1 (NQO1) and HO-1. Therefore, upregulation of the Nrf2-dependent HO-1 pathway promotes the expression of the antioxidative system, alleviating cellular oxidative stress damage. ROS can mediate oxidative-reductive reactions by activating the NF-κB pathway. Meanwhile, NF-κB activation stimulates cells to produce more ROS. Upregulation of NF-κB in PD leads to a decrease in Nrf2-mediated target transcription. ROS can also decrease cytoplasmic Nrf2, causing mitochondrial dysfunction and subsequent cell apoptosis. Therefore, inducing Nrf2 activation may be a target for treating oxidative stress and mitochondrial dysfunction. Mitogen-activated protein kinase (MAPK) is an upstream pathway controlling inflammation and ROS production. Elevated intracellular ROS levels mediate the activation of the MAPK signaling pathway, leading to various cellular effects such as proliferation, differentiation, and apoptosis. MAPK is also regulated by ROS and is involved in Nrf2 nuclear translocation. Increasing evidence suggests that MAPK regulates the activation of Nrf2, and p38 is an upstream regulator of Nrf2 that can inhibit the activation of the Nrf2 pathway. Studies have shown that AU can upregulate Nrf2, promote the expression of HO-1 and NQO-1 proteins, while downregulating the phosphorylation level of p38, confirming that AU can enhance cellular antioxidative capacity and alleviate oxidative stress by downregulating the MAPK signaling pathway and activating the Nrf2 signaling pathway[25,31-39].

Lactate dehydrogenase (LDH) is a stable cytoplasmic enzyme, which rapidly releases into the surrounding medium when the cell membrane is damaged by oxidative stress. Therefore, the concentration of LDH in the extracellular space corresponds to the proportion of dead or membrane-damaged cells[40]. In vitro cell studies[41] have shown that Eucommia ulmoides bark extract (EUE) pretreatment significantly reduces H2O2-induced LDH release and inhibits the marked increase in ROS, demonstrating that EUE can protect cells from oxidative damage. The degeneration of dopaminergic neurons and the aggregation of α-synuclein (α-syn) are closely related to the occurrence of Parkinson's disease (PD). The oxidation products of dopamine (DAQ) and/or dopamine quinone (DAch) can directly bind to α-syn, promoting α-syn oligomerization in vitro, leading to cytotoxicity. Chlorogenic acid can significantly inhibit DA oxidation and its direct binding with α-syn, suppress DA-induced α-syn oligomerization, thereby protecting neurons from α-syn toxicity[42].

In summary, Eucommia ulmoides primarily exerts its antioxidative effects by activating the nNOS/NO, Nrf2/HO-1, and Nrf2-ARE signaling pathways, while downregulating the NF-κB and MAPK signaling pathways. This leads to the inhibition of LDH release and dopamine oxidation, thereby regulating ROS or NOS and exerting antioxidative effects.

4.2 Anti Neuroinflammation

Neuroinflammation is a complex process coordinated by different glial cell populations in the central nervous system and peripheral immune cells. It is a key player in various neurological disorders and contributes to the production and aggregation of abnormal proteins, disruption of the blood-brain barrier, and acceleration of neuronal degeneration and death. Under pathological conditions of Parkinson's disease (PD), microglia and astrocytes can be activated and release large amounts of pro-inflammatory and cytotoxic factors, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), NO, ROS, and prostaglandin E2 (PGE2), thereby triggering or exacerbating inflammatory responses, causing neuronal dysfunction, and worsening PD[43-46].

Studies have shown that AU can significantly reduce the activation of astrocytes and microglia in the hippocampus of epileptic mice and the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) mice. It can decrease the levels of Iba-1 (a microglial marker) and GFAP (an astrocytic marker), and significantly inhibit the release of pro-inflammatory cytokines (HMGB1, RAGE, TLR4, MyD88, NF-κB p65, TNF-α, IL-1β, IL-6)[47-52]. Additionally, researchers have found that Eucommia ulmoides exerts anti-inflammatory activity on lipopolysaccharide (LPS)-stimulated BV-2 microglial cells, inhibiting the production of NO, ROS, and PGE2 mediated by LPS. Chlorogenic acid has also been shown to exert similar effects[53-54].

The mechanisms involved in the above effects mainly include the inactivation of the NLRP3/ASC/caspase-1 inflammasome, inactivation of the NF-κB signaling pathway, and activation of the Keap1/Nrf2 signaling pathway[55-56]. AU can improve the inflammatory state by inhibiting the NLRP3 inflammasome (including NLRP3, ASC, and caspase-1). Eucommia ulmoides can inhibit the generation of NO and PGE2 by activating the Keap1/Nrf2/HO-1 pathway. In addition, it can significantly increase the degradation of IκBα, inhibit IκBα phosphorylation, suppress MAPKs, phosphoinositide 3-kinase (PI3K)/Akt, glycogen synthase kinase-3β (GSK-3β), and downstream transcription factor NF-κB phosphorylation, and markedly inhibit p-NF-κB/NF-κB, COX-2, and iNOS protein expression, thereby downregulating the NF-κB pathway. Experiments have shown that geniposide can inhibit PI3K/Akt to suppress the production of inflammatory mediators, thereby inhibiting NF-κB and iNOS expression and NO synthesis, exerting anti-inflammatory effects[57]. Phosphorylation levels of p38 and JNK are significantly increased in the brains of PD patients, which can further lead to inflammatory responses[58]. AU can reduce the phosphorylation levels of p38 and JNK, decreasing the production of IL-1β, IL-6, and TNF-α[25].

In summary, Eucommia ulmoides exerts its anti-neuroinflammatory effects by inactivating the NLRP3/ASC/caspase-1 inflammasome, regulating MAPKs, PI3K/Akt, and GSK-3β to inhibit pro-inflammatory responses, thereby suppressing NF-κB activation and inducing Keap1/Nrf2/HO-1 pathway activation.

4.3 Enhanced Neuroautophagy

Autophagy is defined as a lysosomal degradation pathway that degrades cytoplasmic components and facilitates waste recycling, playing a crucial role in nutrient cycling, energy production, and clearance of damaged proteins. Parkinson's disease (PD) is characterized by Lewy bodies, with α-synuclein as its main component. Autophagy can target the degradation of α-synuclein; in the presence of ROS production, autophagy can be triggered by upstream activators such as AMPK or increased ATG protein activity, removing damaged mitochondria, limiting further damage from ROS production, thereby inhibiting cell apoptosis and necrosis, and preventing early progression of PD. As the disease progresses, protein accumulation increases, leading to sustained activation of

autophagy, inducing cell death. Furthermore, abnormal protein aggregation in PD damages autophagosome formation and impairs lysosomal function, inhibiting the elimination of abnormal proteins, leading to autophagosome accumulation, and ultimately resulting in neuronal cell death[59].

The PD-related gene PTEN-induced kinase 1 (PINK1) binds to E3 ubiquitin ligase Parkin, phosphorylating Parkin. Subsequently, phosphorylated Parkin is recruited to damaged mitochondria, where it interacts with Beclin1 to activate mitochondrial autophagy[60]. In PD, decreased activity of Beclin-1 (a mammalian homolog of Atg6), as well as defects in Parkin and PINK1, can all lead to impaired mitochondrial autophagy, resulting in reduced clearance of aggregates and ROS, and causing neuronal damage. Microtubule-associated protein light chain 3 (LC3) in its lipidated form, LC3-II, is considered a marker for autophagosome formation or autophagy activation[61]. Research by Wang et al. suggests that the active component aucubin (AU) from Eucommia ulmoides activates the AMPK signaling pathway, upregulating the expression of Beclin-1, p-AMPK, and LC3-II, thereby enhancing autophagy. When AMPK is knocked out, these effects are partially reversed[59].

Research has shown that α-synuclein overexpression can decrease autophagic activity[60]. ROS is also closely related to autophagy, as reduced autophagy can induce ROS and oxidative stress[61]. Accumulation of LC3-II may occur due to either autophagy activation or failure in autophagosome clearance. P62, a multi-domain protein, can form oligomers with LC3-II, targeting autophagosomes for degradation in lysosomes. In zebrafish models of Parkinson's disease (PD), significant upregulation of LC3-II mRNA expression is observed, possibly due to the inability of P62 to attach to LC3-II and form oligomers for autophagy participation. Extension and closure of isolation membranes during autophagy require Atg5 and Atg7, making them essential for autophagosome formation. Ulk1b, a protein kinase, phosphorylates various substrates, activating autophagy through the mTor complex 1 (mTorc1) and AMPK pathways. Zebrafish PD models and in vitro experiments with SHSY5Y cells suggest that chlorogenic acid improves PD by promoting neuronal autophagy. The specific mechanisms include: upregulating Ulk1b expression to activate autophagy; reducing α-synuclein expression to enhance autophagic activity; enhancing P62 binding to LC3-II to promote autophagy and reduce ROS levels; additionally, regulating the expression of Atg5, Atg7, and LC3B to promote elongation and closure of isolation membranes, facilitating autophagosome formation and restoring the autophagic process[15].

4.4 Antiapoptosis

Apoptosis Is A Typical Form Of Programmed Cell Death, Which Is A Precisely Regulated Process Controlled By Genes And Serves As The Final Pathway For Cell Death In Parkinson's Disease (Pd). Proteins Involved In The Apoptotic Pathway Mainly Include Caspases, Adaptor Proteins, Bcl-2, And The Iap Protein Family. A Key Target Of Ros-Induced Cytotoxicity Is The Mitochondria. Mitochondria Are Highly Sensitive To Oxidative Stress And Respond To Changes In Mitochondrial Membrane Potential (Mmp) And Mitochondrial Membrane Permeability[62].Cytochrome C Release From Damaged Mitochondria Activates A Signaling Cascade That Leads To Cell Apoptosis. Following Its Release From Mitochondria, Cytosolic Cytochrome C Interacts With Bcl-2 Family Proteins (Downregulating The Anti-Apoptotic Factor Bcl-2 Expression) And Activates Caspase-3 Cleavage To Initiate Apoptosis[63,64].Caspases Are Key Signals In The Early Stages Of Apoptosis. Ros Can Promote The Expression Of Apoptosis Factors Such As Caspase-9, Caspase-3, And Bax, Among Which Caspase-3 Is The Ultimate Effector Of Apoptosis Cell Death[25,65-66].Caspase Cleavage Also Renders Parp Inactive. Ros Is Also A Well-Known Factor Driving Jnk Activation, Whose Activity Typically Participates In The Process Of

Cell Apoptosis. The Mapk Signaling Pathway Also Regulates Neuronal Death. An Increase In Tunel-Positive Cells In The Brain Can Be Used To Assess The Occurrence Of Cell Apoptosis.

Possible mechanisms of AU's anti-apoptotic effects are as follows: (1) Downregulation of the Bax/Bcl-2 pathway: Significant inhibition of Bax and necrosis proteins (MLKL and RIP1) overexpression, as well as caspase-3, PARP, and caspase-9 cleavage, while enhancing Bcl-2 expression[67-69]; (2) Reduction of MAPK signaling pathway activation: Decreased phosphorylation levels of cellular JNK, p38, and ERK. Additionally, studies have demonstrated that AU can significantly reduce TUNEL-positive cells and increase the number of neurons[26]. Other research has shown that aside from the aforementioned effects, Eucommia ulmoides (EU) can also inhibit MMP loss, cytochrome c release, indicating that EU may exert its neuroprotective effects by directly acting on the H2O2-mediated mitochondrial apoptotic pathway, and blocking PI3K/Akt phosphorylation may also be one of its anti-apoptotic mechanisms[41].

5. Conclusion and Outlook

Parkinson's disease (PD) affects a large population, has a high disability rate, and its pathogenesis is complex, influenced by various factors, making clinical treatment challenging. Currently, Western medicine is the mainstay of treatment, aimed at slowing disease progression, but it cannot provide permanent or sustained relief for patients and often entails significant side effects. Eucommia ulmoides (EU) has broad pharmacological effects, and through systematic review and analysis, it has been found that its iridoid compounds, notably aucubin, can modulate multiple target molecules and signaling pathways, exerting multiple anti-PD effects. It shows promising therapeutic effects and significant potential for application, offering assistance in the development of new drugs and therapies for PD prevention and treatment.

After summarizing and analyzing, it can be concluded that Eucommia ulmoides (EU) mainly treats Parkinson's disease (PD) by antioxidative stress, anti-neuroinflammation, regulating neuronal autophagy, and inhibiting cell apoptosis. Its mechanisms of action are extensive, but involve complex molecular pathways with interactions between them, lacking a complete systematic analysis. Furthermore, current research on the mechanism of EU in treating PD mainly focuses on animal and in vitro cell studies. Future endeavors should involve large-sample randomized controlled trials (RCTs) to provide clinical evidence and comprehensively explore the effective chemical components in EU for treating PD, clarifying their pharmacological mechanisms. Based on this, refinement and comparative studies can be conducted on the preparation and extraction techniques of EU components to increase the yield of effective components, providing new directions for further research and development of EU.

References

[1] *Chinese Society of Parkinson's Disease and Movement Disorders, Parkinson's Disease and Movement Disorder Section of Neurologist Branch of Chinese Medical Doctor Association. Chinese guidelines for theTreatment of Parkinson's disease (fourth edition). Chinese Iournal of Neurology, 2020,53(12):973-986.*

[2] *Zhang Z, Roman G C, Hong Z, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. The Lancet, 2005,365(9459):595-597.*

[3] *Li G, Ma J, Cui S, et al. Parkinson's disease in China: a forty‐year growing track of bedside work. Transl Neurodegener, 2019, 8: 22. DOI: 10.1186/s40035‐019‐0162‐z.*

[4] *Zhang Sen, Zhao Xiaoyue, Liang Yu, et al. Advances in understanding the pathogenic factors and pathogenesis of Parkinson's disease. Acta Pharmaceutica Sinica, 2020,55(10):2264-2272.*

[5] Li Lin, Zhang Rui, Suo Xiaoyan, et al. Clinical effect of levodopa combined with pramipexole in the treatment of Parkinson's disease and its influence on UPDRS score of patients. Clinical Research and Practice, 2021,6(21):80-82.

[6] Wei Yufan, Zhang Yunke, Fan Feiyan, et al. Meta Analysis and Data Mining of Chinese Medicine Compounds in the Treatment of Sleep Disorders in Parkinson's Disease. Acta Chinese Medicine, 2022,37(1):216-226.

[7] Bao Qian, Zhao Yawei, Huo Xiaoxiao, et al. Research progress of traditional Chinese medicine for Parkinson's disease treatment. Modern Journal of Integrated Traditional Chinese and Western Medicine, 2019,28(30):3416-3420.

[8] Yang P, Zhang Q, Shen H, et al. Research progress on the protective effects of aucubin in neurological diseases. Pharmaceutical Biology, 2022,60(1):1088-1094.

[9] Ji Xiaomin. Exploring the Mechanism of Yougui Pill's "Seeking Yang from Yin" Promoting Neural Regeneration in EAE Mice through Neurodirectional Factors[D]. Capital Medical University, 2016.

[10] Jing Lei, Ma Yunzhi. Summary of Professor Ma Yunzhi's Experience in Treating Middle and Late Stage Parkinson's Disease. Guangming Journal of Chinese Medicine, 2018,33(19):2813-2815.

[11] Yang Kai, Zou Jiuli, Ji Yongxiang. Clinical effect observation of Tianma Gouteng decoction in the treatment of Parkinson's disease. Clinical Research and Practice, 2017,2(9):97-98.

[12] Dou Weihua, Diao Limei. Clinical study of Bushen Huoxue decoction in the treatment of Parkinson disease. Journal of Changchun University of Chinese Medicine, 2010,26(4):501-502.

[13] Li Lili, Ma Ningning, Fan Shanshan, et al. Therapeutic effects and spectra-effect relationship of different extracts of Eucommia ulmoides on Parkinson's disease mice. Chinese Traditional and Herbal Drugs, 2019,50(6):1400-1406.

[14] Zhang Pengyu, Jin Meng, Shang Xueliang, et al. Study on anti-Parkinson's disease activity of Eucommia ulmoides based on network pharmacology and zebrafish model. Chinese Pharmacological Bulletin, 2022,38(7):1081-1087.

[15] Gao, X., et al., Neuroprotective effect of chlorogenic acid on Parkinson's disease like symptoms through boosting the autophagy in zebrafish. European Journal of Pharmacology, 2023. 956: p. 175950.

[16] Ning Gang, Wu Hui, Li Bonan, et al. Hepatocyte growth factor being the possible material basis for"homogeny of Yi and Gui". Journal of Hunan University of Chinese Medicine，2022,42(10): 1720-1724.

[17] Cao Bingqian. TAN Feng's Experience in Treating Early Parkinson's Disease Based on the Pathogenesis of Kidney Deficiency with Marrow Hollow and Internal Stirring of Liver Wind. Journal of Guangzhou University of Traditional Chinese Medicine,2022,39(8):1906-1910.

[18] Chen Shi-ya, Xiao Shao-jian, Lin You-ning, et al. Clinical Efficacy and Transcriptomic Analysis of Congrong Shujing Granules in Patients with Parkinson's Disease and Syndrome of Shen (Kidney) Essence Deficiency. Chinese Journal of Integrative Medicine, 2020,26(6):412-419.

[19] Jin Z, Liu Z, Kang L, et al. A randomized double-blind placebo-controlled multicenter trial of Bushen Yisui and Ziyin Jiangzhuo formula for constipation in Parkinson disease. Medicine, 2020,99(28):e21145.

[20] Zhang L, Yang H. Promotive effects of tetrahydroxystilbene glucoside on the differentiation of neural stem cells from the mesencephalon into dopaminergic neurons. Neuroscience Letters, 2021,742:135520.

[21] Dong H, Zhang J, Rong H, et al. Paeoniflorin and Plycyrrhetinic Acid Synergistically Alleviate MPP+ /MPTP-Induced Oxidative Stress through Nrf2-Dependent Glutathione Biosynthesis Mechanisms. ACS Chemical Neuroscience, 2021,12(7):1100-1111.

[22] Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China: Volume 1, 2020 [S]. Beijing:China Medical Science Press，2020.

[23]Gao Hongwei, Li Yuping, Li Shouchao. Study Advances in Chemical Constituents and Pharmacological Effects of Eucommia Ulmoides Oliv.Information on Traditional Chinese Medicine,2021,38(06):73-81.DOI:10.19656/j.cnki.1002-2406.210615.

[24] Trist, B.G., D.J. Hare and K.L. Double, Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell, 2019. 18(6): p. e13031.

[25] Li Y C, Hao J C, Shang B, et al. Neuroprotective effects of aucubin on hydrogen peroxide-induced toxicity in human neuroblastoma SH-SY5Y cells via the Nrf2/HO-1 pathway. Phytomedicine, 2021,87:153577.

[26] Xue H, Jin L, Jin L, et al. Aucubin prevents loss of hippocampal neurons and regulates antioxidative activity in diabetic encephalopathy rats. Phytotherapy Research, 2009,23(7):980-986.

[27] Hink U, Li H, Mollnau H, et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus. Circ Res, 2001,88(2):E14-E22.

[28] Sun Xixiao, Liu Zaizhi, Du Xinqi, et al. Ultrasonic-assisted Extraction of Polysaccharide from Eucommia ulmoides and Evaluation of its Antioxidant Activity. Bulletin of Botanical Research, 2014,34(3):428-432.

[29] Yin Xue, Su Xinyun, Wang Xiuhua, et al. Effects of protocatechuic acid on expression of D2DR, iNOS, and TH in striatum and midbrain of Parkinson's disease model mice. Chinese Traditional and Herbal Drugs, 2015,46(06):866-870.

[30] Oboh G, Agunloye O M, Akinyemi A J, et al. Comparative Study on the Inhibitory Effect of Caffeic and Chlorogenic Acids on Key Enzymes Linked to Alzheimer’s Disease and Some Pro-oxidant Induced Oxidative Stress in Rats’ Brain-In Vitro. Neurochemical Research, 2013,38(2):413-419.

[31] Jeayeng S, Wongkajornsilp A, Slominski A T, et al. Nrf2 in keratinocytes modulates UVB-induced DNA damage and apoptosis in melanocytes through MAPK signaling. Free Radical Biology and Medicine, 2017,108:918-928.

[32] Qu Z, Sun J, Zhang W, et al. Transcription factor NRF2 as a promising therapeutic target for Alzheimer’s disease. Free Radical Biology and Medicine, 2020,159:87-102.

[33] Huang, T., et al., The therapeutic effect of aucubin-supplemented hyaluronic acid on interleukin-1beta-stimulated human articular chondrocytes. Phytomedicine, 2019. 53: p. 1-8.

[34] Buelna-Chontal M, Zazueta C. Redox activation of Nrf2 & NF-κB: A double end sword?. Cellular Signalling, 2013,25(12):2548-2557.

[35] Qiu Y, Cheng X, Bai F, et al. Aucubin protects against lipopolysaccharide-induced acute pulmonary injury through regulating Nrf2 and AMPK pathways. Biomedicine & Pharmacotherapy, 2018,106:192-199.

[36] de Oliveira M R, de Bittencourt Brasil F, Fürstenau C R. Sulforaphane Promotes Mitochondrial Protection in SH-SY5Y Cells Exposed to Hydrogen Peroxide by an Nrf2-Dependent Mechanism. Molecular Neurobiology, 2018,55(6):4777-4787.

[37] Bao S, Lin J, Xie M, et al. Simvastatin affects Nrf2/MAPK signaling pathway and hepatic histological structure change in Gambusia affinis. Chemosphere, 2021,269:128725.

[38] Lefaki M, Papaevgeniou N, Tur J A, et al. The dietary triterpenoid 18 α －Glycyrrhetinic acid protects from MMC-induced genotoxicity through the ERK/Nrf2 pathway. Redox Biology, 2020,28:101317.

[39] Li Z, Wang Q, Luan H, et al. A novel target TAX1BP1 and P38/Nrf2 pathway independently involved in the anti-neuroinflammatory effect of isobavachalcone. Free Radical Biology and Medicine, 2020,153:132-139.

[40] Lu Y H, Su M Y, Huang H Y, et al. Protective effects of the citrus flavanones to PC12 cells against cytotoxicity induced by hydrogen peroxide. Neurosci Lett, 2010,484(1):6-11.

[41] Kwon S, Kim M, Ma S, et al. Eucommia ulmoides Oliv. Bark. protects against hydrogen peroxide-induced neuronal cell death in SH-SY5Y cells. Journal of Ethnopharmacology, 2012,142(2):337-345.

[42] Teraoka M, Nakaso K, Kusumoto C, et al. Cytoprotective effect of chlorogenic acid against α-synuclein-related toxicity in catecholaminergic PC12 cells. Journal of Clinical Biochemistry and Nutrition, 2012,51(2):122-127.

[43] Yang Q Q, Zhou J W. Neuroinflammation in the central nervous system: Symphony of glial cells. Glia, 2019,67(6):1017-1035.

[44] Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain, Behavior, and Immunity, 2017,60:1-12.

[45] Giovannoni F, Quintana F J. The Role of Astrocytes in CNS Inflammation. Trends in Immunology, 2020,41(9):805-819.

[46] Diaz-Castro B, Bernstein A M, Coppola G, et al. Molecular and functional properties of cortical astrocytes during peripherally induced neuroinflammation. Cell Reports, 2021,36(6):109508.

[47] Chen S, Zeng X, Zong W, et al. Aucubin Alleviates Seizures Activity in Li-Pilocarpine-Induced Epileptic Mice: Involvement of Inhibition of Neuroinflammation and Regulation of Neurotransmission. Neurochemical Research, 2019,44(2):472-484.

[48] Zhu Y, Sun M, Jia X, et al. Aucubin alleviates glial cell activation and preserves dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonian mice. NeuroReport, 2018,29(13):1075-1083.

[49] Shen B, Zhao C, Wang Y, et al. Aucubin inhibited lipid accumulation and oxidative stress via Nrf2/HO －1 andAMPK signalling pathways. Journal of Cellular and Molecular Medicine, 2019,23(6):4063-4075.

[50] Wang H, Zhou X, Wu L, et al. Aucubin alleviates oxidative stress and inflammation via Nrf2-mediated signaling activity in experimental traumatic brain injury. Journal of Neuroinflammation, 2020,17(1):188.

[51] Zhang S, Feng Z, Gao W, et al. Aucubin Attenuates Liver Ischemia-Reperfusion Injury by Inhibiting the HMGB1/TLR-4/NF- κB Signaling Pathway, Oxidative Stress, and Apoptosis. Frontiers in Pharmacology, 2020,11:544124.

[52] Li Y C, Hao J C, Shang B, et al. Neuroprotective effects of aucubin on hydrogen peroxide-induced toxicity in human neuroblastoma SH-SY5Y cells via the Nrf2/HO-1 pathway. Phytomedicine, 2021,87:153577.

[53] Kwon S, Ma S, Hwang J, et al. The Anti-Inflammatory Activity of Eucommia ulmoides Oliv. Bark. Involves NF- κB Suppression and Nrf2-Dependent HO-1 Induction in BV-2 Microglial Cells. Biomolecules & Therapeutics, 2016,24(3):268-282.

[54] Shen W, Qi R, Zhang J, et al. Chlorogenic acid inhibits LPS-induced microglial activation and improves survival of dopaminergic neurons. Brain Research Bulletin, 2012,88(5):487-494.

[55] Duan M, Yuan Y, Liu C, et al. Indigo Fruits Ingredient, Aucubin, Protects against LPS-Induced Cardiac Dysfunction in Mice. Journal of Pharmacology and Experimental Therapeutics, 2019,371(2):348-359.

[56] Gao F, Li H, Feng Y, et al. Aucubin ameliorates the LPS‐induced inflammatory response in bovine endometrial epithelial cells by inhibiting NF‐κB and activating the Keap1/Nrf2 signalling pathway. Reproduction in Domestic Animals, 2021,56(7):972-982.

[57] Shi Huiyan, He Xin, Ouyang Dongsheng, et al. Progress in pharmacological research on geniposide and its derivatives. Chinese Pharmaceutical Journal, 2006,41(1):4-6.

[58] Chongthammakun V, Sanvarinda Y, Chongthammakun S. Reactive oxygen species production and MAPK activation are implicated in tetrahydrobiopterin-induced SH-SY5Y cell death. Neuroscience Letters, 2009,449(3):178-182.

[59] Wang J, Li Y, Huang W, et al. The Protective Effect of Aucubin fromEucommia ulmoides Against Status Epilepticus by Inducing Autophagy and Inhibiting Necroptosis. The American Journal of Chinese Medicine, 2017,45(03):557-573.

[60] Button, R.W., S. Luo and D.C. Rubinsztein, Autophagic activity in neuronal cell death. Neuroscience Bulletin, 2015. 31(4): p. 382-394.

[61] Kazlauskaite A, Muqit M M K. PINK 1 and Parkin – mitochondrial interplay between phosphorylation and ubiquitylation in Parkinson's disease. The FEBS Journal, 2015,282(2):215-223.

[62] Wu Maodong, Su Qinglun, Liu Zhen, et al. Recent advance in pathophysiological mechanism of micro RNAs regulating autophagy in ischemic stroke. Chinese Journal of Neuromedicine, 2020,19(12):1277-1282.

[63] Erustes, A.G., et al., Overexpression of α‐synuclein in an astrocyte cell line promotes autophagy inhibition and apoptosis. Journal of Neuroscience Research, 2018. 96(1): p. 160-171.

[64] Li, L., et al., ROS and Autophagy: Interactions and Molecular Regulatory Mechanisms. Cellular and Molecular Neurobiology, 2015. 35(5): p. 615-621.

[65] Ly J D, Grubb D R, Lawen A. The mitochondrial membrane potential (deltapsi(m)) in apoptosis; an update. Apoptosis, 2003,8(2):115-128.

[66] Merry D E, Korsmeyer S J. Bcl-2 gene family in the nervous system. Annual Review of Neuroscience, 1997,20(1):245-267.

[67] Fan T, Han L, Cong R, et al. Caspase Family Proteases and Apoptosis. Acta Biochimica et Biophysica Sinica, 2005,37(11):719-727.

[68] Hartmann A, Hunot S, Michel P P, et al. Caspase-3: A vulnerability factor and final effector in apoptotic death of dopaminergic neurons in Parkinson's disease. Proceedings of the National Academy of Sciences, 2000,97(6):2875-2880.

[69] Xue H, Jin L, Jin L, et al. Neuroprotection of aucubin in primary diabetic encephalopathy. Science in China Series C: Life Sciences, 2008,51(6):495-502.

[70] Wang B, Jiang Y, Yao Z, et al. Aucubin Protects Chondrocytes Against IL-1β-Induced Apoptosis In Vitro And Inhibits Osteoarthritis In Mice Model . Drug Des Devel Ther, 2019,Volume 13:3529-3538.

[71] Wang J, Li Y, Huang W, et al. The Protective Effect of Aucubin fromEucommia ulmoides Against Status Epilepticus by Inducing Autophagy and Inhibiting Necroptosis. The American Journal of Chinese Medicine, 2017,45(03):557-573.