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Analysis of the New Progress in the Treatment of Parkinson's Disease from the Perspective of Antioxidant

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Abstract

Parkinson's disease (PD) is currently the second most common neurodegenerative disease. The pathological features of PD are degeneration of dopaminergic neurons in the brain, which leads to motor retardation, rigidity, quiescence, tremor, postural instability, smell disorders, pain, sleep disorders, depression and other non-motor symptoms Although the etiology of PD is still not fully understood, the occurrence of oxidative stress has been closely related to the pathogenesis of PD for a long time However, as there are many side effects of known PD treatment drugs, and there is a lack of effective treatment means to control the disease by inhibiting oxidative stress pathway, controlling the progression of PD disease by inhibiting oxidative stress has become a new direction of modification therapy. At present, a large number of studies have focused on the process of inhibiting oxidative stress. In this paper, a brief review of previous studies was made to provide new clinical ideas for the treatment of PD.

Keywords: Parkinson's disease, oxidative stress, antioxidant, research progress

1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease. At present mainly in the treatment of PD by symptomatic treatment, namely the effects on the dopamine neurons defect compensation, the clinical commonly used drugs including anticholinergic drugs, dopamine replacement therapy, dopamine agonists, etc., these drugs can relieve the patient's symptoms, but not positive effects on patients with disease process, at the same time, there are many side effects. Recent pathological studies have found that the characteristic pathological change of PD is the progressive loss of a large number of dopaminergic neurons in the substantia nigra pars compacta, and some relevant studies believe that this pathological feature is closely related to the motor symptoms of PD (Jiang P & Dickson DW., 2018). In recent years, in order to explore treatment methods that can delay or stop the process of the disease, the focus of research on PD treatment methods has gradually shifted from symptomatic treatment to modification treatment (Ellis JM & Fell MJ., 2017).

2. Oxidative Stress in PD Pathogenesis

At present, it is believed that oxidative stress is one of the regulatory factors of cell aging and various neurological disorders (Singh A, Kukreti R, Saso L & Kukreti S., 2019). Cells and tissues fight oxidative stress through a range of endogenous or exogenous redox-active substances, and targeting this pathway can help alleviate symptoms associated with neurodegeneration (Sbodio JI, Snyder SH & Paul BD., 2019). The occurrence of PD is associated with excessive production of reactive oxygen species (ROS) in neurons, proteolysis, mitochondrial dysfunction, neuroinflammation, substantia nigra iron accumulation and decreased enzyme activity (Segura-Aguilar J, Paris I, Muñoz P, Ferrari E, Zecca L & Zucca FA., 2014). A meta-analysis of PD patients showed that the concentrations of 8-OHdG, MDA, nitrite and ferritin in peripheral blood of PD

patients increased, which provided clinical evidence for oxidative stress in the process of PD (Wei Z, Li X, Li X, Liu Q & Cheng Y., 2018). T. N. Fedorova et al. speculated that PD patients are more sensitive to the effect of free radicals when the activity of the endogenous antioxidant system is reduced (Fedorova, T.N., Logvinenko, A.A., Poleshchuk, V.V. & et al., 2017).

2.1 Dopamine and Oxidative Stress

ROS produced by dopamine metabolism may have toxic effects on neurons (Wei Z, Li X, Li X, Liu Q & Cheng Y., 2018). SeguraAguilar et al. proposed that dopamine neurons in the substantia nigra pars compacta are selectively degenerated when PD occurs, suggesting that dopamine metabolism itself may be one of the sources of oxidative stress (Segura-Aguilar J, Paris I, Muñoz P, Ferrari E, Zecca L & Zucca FA., 2014). The metabolic process of dopamine takes tyrosine as the raw material, and synthesizes through tyrosine hydroxylase and aromatic amino acid decarboxylase to produce dopamine. The generated dopamine is taken up by vesicular monoamine transporter 2 (VMAT2) and stored in synaptic vesicles. Animal experiments have shown that if DA cannot be consumed normally in mice with decreased VMAT2 expression, the excess DA will mediate toxic reactions and lead to progressive loss of DA neurons (Caudle WM, Richardson JR, Wang MZ, & et al. 2007).

2.2 Mitochondrial Dysfunction and Oxidative Stress

Some studies have reported that the decreased activity of mitochondrial complex I in the substantia nigra pars compacta of PD patients may lead to excessive production of ROS and induce loss of dopaminergic neurons at the same time (Hauser DN & Hastings TG., 2013). Mitochondrial dysfunction affects the process of oxidative phosphorylation to produce superoxide and hydrogen peroxide (Hall CN, Klein-Flügge MC, Howarth C & Attwell D., 2012), and the production of these free radicals causes cytotoxicity and leads to the loss of dopaminergic neurons (Miyazaki I, Asanuma M, Diaz-Corrales FJ & et al., 2006). The production of ROS will affect the function of proteasome, lysosome and mitochondria, and further affect the oxidative damage of cells (Cook C, Stetler C & Petrucelli L., 2012). However, the functional abnormalities of the above structures will affect the normal metabolism of proteins and lead to protein misfolding, which plays a key role in the neurodegeneration of PD (Schapira AH, Olanow CW, Greenamyre JT & Bezard E., 2014). Cell experiments have shown that inhibition of ROS can produce neuroprotective effects on substantia nigra dopaminergic neurons cultured in vitro (Wang HL, Chou AH, Wu AS, & et al., 2011).

3. Neuroprotective Effects of Antioxidants

3.1 Coenzyme Q10

Coenzyme Q10 (CoQ10) is a component of the mitochondrial electron chain and plays a role in ATP production. It has been found that the level of CoQ10 in platelet mitochondria of PD patients is low (Shults CW, Haas RH, Passov D & Beal MF., 1997). CoQ10 on the inner mitochondrial membrane can help to remove ROS (Bentinger M, Tekle M & Dallner G., 2010). Animal experiments have shown that CoQ10 has a protective effect on dopaminergic neurons in PD model mice induced by 1-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine (MPTP) (Beal MF, Matthews RT, Tieleman A & Shults CW., 1998). A randomized controlled clinical observation involving 120 patients showed that, compared with the control group using basic drugs, after 6 months of conventional drugs combined with CoQ10 treatment, the effective rate reached 73.33%, while the effective rate of the control group was only 48.33% ($P < 0.05$) (Wang Lijuan, 2017). A randomized controlled clinical observation involving 66 patients showed that after 2 months of treatment with compound carbidopa tablets combined with CoQ10, the UPDRS scale scores of the two groups of patients were decreased, and compared with the control group using compound carbidopa tablets alone, the combined observation group had a lower score (Huang Li & Gong Xili, 2020).

3.2 Vitamin E

Vitamin E is a fat-soluble endogenous antioxidant, which can remove a variety of reactive oxygen radicals, including hydroxyl radicals and peroxyl radicals, to inhibit lipid peroxidation (Gong L, Daigneault EA, Acuff RV & Kostrzewa RM., 1991). Early animal experiments have shown that vitamin E has no neuroprotective effect on PD models. However, Lan et al. proposed that vitamin E has neuroprotective effect on MPTP-induced PD model mice in animal experiments (Lan J & Jiang DH., 1997). A systematic review study showed that people who had vitamin E intake in their diet were 19% less likely to develop PD than those who did not (Huang Yin, Yang Zheng, Zeng Li & Zhang Xiao, 2008). The results of a community study proved that vitamin E intake of about 10g per day can significantly reduce the prevalence of PD (Blesa J, Trigo-Damas I, Quiroga-Varela A & Jackson-Lewis VR., 2015). At present, the mechanism of vitamin E on PD is not completely clear, but many studies tend to act on PD through antioxidant. There is little clinical evidence for vitamin E in the treatment of PD, so its therapeutic effect is not certain.

3.3 Iron Chelators

Iron is of great significance in maintaining the normal physiological function of the human brain. It is involved in the transport and utilization of oxygen. When the human body cannot effectively remove the excess iron, its aggregation will produce the Fenton reaction in the body, which will cause damage to the mitochondrial electron transport system, enhanced membrane lipid peroxidation and other damages. Eventually, it leads to cell death and causes central system diseases (Moos T & Morgan EH., 2004). Therefore, many iron chelators have been used in the clinical studies of PD, among which desferrixamine (DFO) is one of the most studied iron chelators. In the MPTP-induced mouse model, the use of DFO inhibits striatal iron accumulation. Thus, it inhibits the production of oxidized glutathione (GSSG) and hydroxyl radicals, reduces the ratio of oxidized glutathione to glutathione (GSSG/GSH) and the level of lipid peroxides (Lan J & Jiang DH., 1997). However, for the 6-hydroxydopamine (6-OHDA) -induced rat model, intraventricular injection of DFO can reduce the dopamine level in part of the striatum (Ben-Shachar D, Eshel G, Riederer P & Youdim MB., 1992). However, because DFO is a hydrophilic macromolecular substance, it is difficult to pass the blood-brain barrier, which limits its possibility as an oral drug (Richardson, D.R., 2004). Iron chelator VK28 is a non-toxic iron chelator that can pass the blood-brain barrier, and it also produces neuroprotective effect in 6-OHDA-induced rat model (Shachar DB, Kahana N, Kampel V, Warshawsky A, Youdim MB., 2004). The results of a randomized, double-blind, placebo-controlled trial showed that after 6 months and 12 months of iron chelator treatment, the motor function of patients was significantly improved compared with that of the control group, but only after 6 months of treatment had obvious effect (Devos D, Moreau C, Devedjian JC & et al., 2014). At present, the clinical research evidence of iron chelator treatment for PD is insufficient, but C sustained and moderate iron chelator treatment may delay the process of the disease by avoiding abnormal iron metabolism, which may be a new way to treat PD.

3.4 Sarcosine (Cr)

Sarosine (Cr) is a nitrogen-based guanidine molecule that is widely found in vertebrates and provides energy for muscle and nerve cells. Evidence has shown that Cr has antioxidant properties and can reduce mitochondrial dysfunction, showing neuroprotective properties in PD mouse models (Beal MF., 2011). It has been demonstrated that for MPTP-induced PD mouse models, Cr supplementation reduces dopaminergic neuronal deformation and dopamine consumption (Matthews RT, Ferrante RJ, Klivenyi P & et al., 1999). Animal experiments have shown that the combination of Cr and CoQ10 can block nitropropionic acid (3-NP) -induced glutathione homeostasis damage and reduce striatal lipid peroxidation and DNA oxidative damage in MPTP-induced mouse model (Yang L, Calingasan NY, Wille EJ & et al., 2009). However, in the clinical observation of PD patients, the therapeutic effect of Cr is not obvious. The results of a randomized controlled study involving 60 patients for up to 2 years showed that there was no significant difference in the UPDRS score of PD patients after taking Cr compared with the control group (Bender A, Koch W, Elstner M & et al., 2006). In a randomized controlled study involving more than 1700 patients, there was no significant difference in the therapeutic effect between patients who consumed 10g Cr per day and placebo for 5 consecutive years ($P < 0.01$) (Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators, Kieburtz K, Tilley BC & et al., 2015). Thus, previous clinical observations cannot directly prove the therapeutic effect of Cr on PD, and its therapeutic effect needs to be further studied.

3.5 Melatonin

In mammals, melatonin is produced by the pineal gland and released directly into the cerebrospinal fluid of the third ventricle, where it subsequently diffuses into peripheral nerve tissues (Tricoire H, Locatelli A, Chemineau P & Malpaux B., 2002). Studies have proved that the expression of melatonin receptors in the amygdala and central nervous system of PD patients is decreased compared with normal (Adi N, Mash DC, Ali Y, Singer C, Shehadeh L & Papapetropoulos S., 2010). Melatonin can increase antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutamylcysteine synthetase in cells (Reiter, R. J., Mayo, J. C., Tan, D. X., Sainz, R. M., Alatorre-Jimenez, M., & Qin, L., 2016). Animal studies have shown that melatonin can inhibit MPTP-induced oxidative stress (Thomas B & Mohanakumar KP., 2004) and nitrification stress (Tapias, V.; Escames, G.; Lopez, L.C.; Lopez, A.; Camacho, E.; Carrion & M.D., 2009) in mouse models, which exert protective effects on dopaminergic neurons in the nigrostriatum. However, in the paraquat-induced PD mouse model (Singhal NK, Srivastava G, Patel DK, Jain SK & Singh MP., 2011), oxidative damage was significantly reduced after melatonin treatment compared with the control group. The experimental results of 6-NHDA-induced PD model in rats have proved that melatonin can produce neuroprotective effect by inhibiting ROS (Jia Linju, Chen Si, Huang Ziyun, Zhu Yaofeng, Zheng Xuefeng, Chen Tao & Lei Wanlong., 2021). In a randomized, double-blind, placebo-controlled study involving 18 PD patients, after 4 weeks of melatonin treatment, the sleep quality of one group of patients was significantly improved compared with that of the placebo group, but their motor symptoms did not change significantly (Randhir, R., Y. Lin & K. Shetty, 2004). Since melatonin is amphipathic and can easily cross the blood-brain barrier, and it can inhibit the occurrence of oxidative stress, these properties make melatonin a potential therapeutic modality for neurodegenerative diseases.

However, due to the lack of long-term clinical observation evidence, its therapeutic effect remains skeptical.

4. Natural Antioxidants

4.1 Plant Polyphenols

Plant polyphenols are secondary metabolites produced through the plant pentose phosphate, shikimate, and phenylpropionic acid pathways (Heim KE, Tagliaferro AR & Bobilya DJ., 2002), which have antioxidant activity. Green tea polyphenols are plant polyphenols from the tea tree. It has been pointed out that after PD patients continue to drink green tea, the levels of antioxidant enzymes catalase and superoxide dismutase are significantly increased, and the oxidation levels of proteins and lipids are decreased (Danaraddi, S.; Koneru, A.; Hunasgi, S. & Ramalu, S., 2014). In the PD transgenic fly model, epicatechin gallate (EGCG), a catechin monomer isolated from tea, restored part of the motility activity of α-synuclein mutant flies to a certain extent, and reduced lipid peroxidation and oxidative stress-mediated apoptosis (Siddique YH, Jyoti S & Naz F., 2014). EGCG can selectively locate in mitochondria, target and protect nerve cells to avoid apoptosis, and this mechanism can interfere with ROS generation and maintain cell homeostasis (Schroeder EK, Kelsey NA, Doyle J & et al., 2009). Studies have confirmed that a diet rich in polyphenols can effectively prevent various diseases related to aging (Park HA & Ellis AC., 2020). Dietary polyphenols have a variety of targets, which can effectively inhibit the verification pathway, ROS generation, and at the same time maintain the protein balance of diseases related to amyloid dysfunction (Leri M, Scuto M, Ontario ML & et al., 2020). As a natural antioxidant, polyphenols can be supplemented through diet, which is an advantage of polyphenols as a treatment for PD. However, due to the low bioavailability of dietary polyphenols, it is still difficult to apply them in the clinical treatment of PD.

4.2 Marine-Derived Compounds

With the deepening of Marine exploration, many studies have focused on the treatment of PD by Marine compounds in recent years. At present, it has been found that Marine compounds that may have therapeutic effects on PD include bacteria, algae, mollusks, etc., and their extracts (Huang C, Zhang Z, Cui W., 2019). NP7 is a phospho-containing antioxidant extracted from Streptomyces marinum, which can inhibit microglia activation and prevent H2O2-induced ERK phosphorylation (Mena, M.A., Casarejos, M.J., Solano, R., Rodríguez-Navarro, J.A., Gómez, A., Rodal, I., Medina, M. & de Yebenes, J.G., 2009). Therefore, it may play a neuroprotective role in PD by inhibiting oxidative stress, but there is still a lack of experimental or clinical observation of NP7. Whether it can play a role in the treatment of PD remains to be further confirmed. Candida A and 4-dehydroxycandidusin A, extracted from the Marine fungus Aspergillus candida sp.KM4676, can eliminate ROS (Ivanets EV, Yurchenko AN, Smetanina OF & et al., 2018) and avoid 6-OHDA and paraquat-mediated cytotoxicity in in vitro culture, thus producing neuroprotective effects (Yurchenko EA, Menchinskaya ES, Pislyagin EA & et al., 2018). Astaxanthin extracted from seaweed is believed to prevent and delay the progression of neurodegenerative diseases (Yuan JP, Peng J, Yin K & Wang JH., 2011). Animal experiments have shown that after feeding with astaxanthin for 4 weeks, it can reduce the dopaminergic cell death induced by MPTP in PD mice (Grimmig, B., Daly, L., Hudson, C., Nash, K.R. & Bickford, P.C., 2017). At present, it has been found that artificial astaxanthin has better anti-inflammatory and antioxidant effects than natural astaxanthin (Galasso C, Orefice I, Pellone P & et al., 2018). Therefore, artificial astaxanthin may be an effective way to treat PD in the future. Fucoidan is a natural antioxidant extracted from algae. Fucoidan extracted from brown algae can inhibit the neurocytotoxicity of MPTP by removing ROS (Luo, D., Zhang, Q., Wang, H., Cui, Y., Sun, Z., Yang, J., Zheng, Y., Jia, J., Yu, F., Wang, X. & et al., 2009), while fucoidan can inhibit the NO production of microglia induced by lipopolysaccharide (Cui YQ, Jia YJ, Zhang T, Zhang QB & Wang XM., 2012). The protein extracts of spirulina and cyanobacteria can improve the activity of biological antioxidant enzymes, produce antioxidant effects, and thus have neuroprotective effects on PD mouse models induced by MPTP (Zhang F, Lu J, Zhang JG & Xie JX., 2015) and 6-OHDA (Lima FAV, Joventino IP, Joventino FP & et al., 2017). There are many Marine compounds that can exert antioxidant effects, and the research on many compounds that may have positive effects on PD is still at the theoretical stage, lacking enough experimental data as evidence. Therefore, the anti-PD effect of Marine compounds still has great research potential.

5. Antioxidant Effect of Active Ingredients of Chinese Herbal Medicine

5.1 Ginkgo Extract

Ginko biloba extract (GBE) is a compound derived from dried ginkgo leaves. EBG pretreatment can dose-dependently restore the activities of GSH-dependent enzymes, catalase, superoxide dismutase (SOD) and the expression level of dopamine D2 receptor in the striatum of 6-OHDA rat PD model (Ahmad M, Saleem S, Ahmad AS & et al., 2005). Another rat study showed that GBE could effectively activate the endogenous NrF2-ARE antioxidant pathway in the brain and improve the oxidative stress of neurons in PD model (Zhang Hui, Ma Huiqing & Wang Xiaojuan., 2018). A clinical observation of PD dementia patients showed that after 8

weeks of GBE combined with butylphthalide treatment, the cognitive function and neurological function of the patients were significantly improved compared with the control group, and the levels of recombinant human Parkinson's disease protein 7(PARK7) and serum C-reactive protein (CRP) in the observation group were significantly lower than those in the control group. Neurotrophin-3 (NT-3) was increased compared with the control group, which may be the result of the neuroprotective effect of GBE by reducing oxidative stress (Liu Ru, LI Hong-Jun, GU Yu-qin, HUANG Run-Xia, BAI Yi-wen & LIU Jun-Xian., 2017). In addition, compared with the control group, the glucose-regulated protein (GRP75), SOD, and glutathione peroxide dismutase (GSH-Px) in PD patients were significantly increased after GBE combined with levodopa and serazide treatment, and the level of malondialdehyde (MDA) was decreased, which indicated that GBE could inhibit oxidative stress in PD patients (Xu Haogang, Chen Zhengping, Xia Qiuyu & Sang Muhui., 2019).

5.2 Ginsenoside

Ginsenosides are the active components of ginseng, which have antioxidant stress and anti-aging pharmacological activities (Song Jia, HE Junhuan, Wang Xienting, Zhu Shimin & Tang Genyun., 2021). There are three main types of ginsenosides: propanaxtriol (PPTs; Ginsenosides Rg1, Re, Rg2, Rh1, Rf), propanaxidiol (PPD; Ginsenosides Rb1,Rb2,Rd,Rg3 and Rh2) and oleanolic acid derivative (ginsenoside Ro) (Hou J, Xue J, Lee M & Sung C., 2017). Ginsenosides Rd and Re can inhibit neuronal apoptosis in PD by inhibiting oxidative stress and inflammatory responses (Li Dong, Wang Xindi, Guo Daoyu & Liu Hao., 2020).

5.3 Extract of Polygonum Cuspidatum

Polydatin (PLD) and Resveratrol (Res) are the active ingredients in Polygonum cuspidatum, among which Resveratrol has strong antioxidant properties (Jang M, Cai L, Udeani GO & et al., 1997). Pretreatment with resveratrol can reduce 6-OHDA-induced cytotoxicity and increase neuronal DJ-1 expression (Yang Rui-xin, GAO Li, Huang Lu, LI Yu-qian & GAO Guo-dong., 2017).

5.4 Other Traditional Chinese Medicine Extracts

Irisinoside is an effective component of traditional Chinese medicine, which can inhibit hydrogen peroxide-induced production of reactive oxygen species (ROS) and ROS-induced cell death in rat primary astrocytes (Park JS, Jung JS, Jeong YH & et al., 2011). The cell experiments of Li Qian et al. proved that irisaglycone could down-regulate Mir-103a-3p /SHC to protect nerve cells in PD model (Qian, Fu Zijuan, Sun Peng & Cao Yibin., 2021). Astragaloside iv can protect PC12 cells treated with 6-OHDA by inhibiting oxidative stress (Huang Wangang, Yang Dongfeng, Feng Jialiang, Huang Huai, Gao Gao & Xu Zhenghu., 2021). It has been documented that icaritin, lycium barbarum polysaccharide, triptolide and other traditional Chinese medicine ingredients can also inhibit oxidative stress in PD (Zhou Xinyu, Ba Zhisheng, Zhu Li & Luo Yong, 2019; Chen Hao, Zhang Haojie, Shi Liang, Li Yinghao, Ren Yankang, Jing Wei, Wang Yanhong & Li Xinyi, 2018; Dong Lin, An Haiting, Tong Yulong, Zhang Wenjing, Wang Qi, Zhang Feilong, Zheng Yan & Wang Xiaomin, 2014).

6. Summary and Prospect

Previous studies on antioxidants for PD were mainly vitamin E, Coenzyme Q10, iron chelators and other drugs. With the in-depth study of natural compounds in recent years, natural compounds that have been proved to inhibit oxidative stress and affect the pathogenesis of PD have gradually entered our field of view. The anti-PD effect of many compounds with antioxidant effects is still in the theoretical stage, which indicates that these natural antioxidants have great research potential. At the same time, with the in-depth study of the effective ingredients of traditional Chinese medicine with clinical effects, more and more traditional Chinese medicine that can have positive effects on PD patients through antioxidant are known to us. These studies provide a certain theoretical basis for the potential targets of traditional Chinese medicine in the treatment of PD from the perspective of pharmacology, but there are also many problems. Due to the blood-cerebrospinal fluid barrier, most drugs cannot penetrate into the brain well and are difficult to exert their effects. There are few clinical observations related to many new compounds, and there is a lack of evidence-based basis to formulate reasonable use methods and therapeutic doses, which are the theoretical difficulties that need to be solved in their preclinical application. Therefore, the combination of antioxidants with the current clinical routine treatment of PD to form a systematic treatment needs further research. At the same time, if these drugs want to play a role in the future clinical, their dosage forms and use methods also need to be further studied.

At present, a large number of studies have focused on the modification therapy of PD. Nerve cells consume high oxygen and are more sensitive to oxidative stress. Therefore, it is a feasible modification therapy to control the course of PD by inhibiting oxidative stress. Though current research of antioxidants in the treatment of PD has been a lot, but most still stays in the experimental stage, lack of reliable clinical evidence, many cells in the experiment, the results of animal experiments and clinical observation results deviation, this may be because the cells and the building process of the animal experiment and human disease process is not the same, Therefore,

there is great potential for further research on the model of human pathogenesis and the clinical application of antioxidants.

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