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Review Article

Neuroprotective Effects of Edible Bird Nest Towards Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD), is closely related to the neurological disorder due to the degeneration of dopaminergic neurons caused by oxidative stress and nitrosative. Over the years, studies regarding the treatment for PD are continuously done as there is still no permanent cure for PD. Edible bird's nests, EBN are known for their neuroprotective effect which are used as the potential treatment for PD. This article aims to highlight the association of EBN and PD. EBN has the potential to inhibit the degeneration of the dopaminergic neurons against 6-OHDA, which causes production of nitric oxide and lipid peroxidation in SH-SY5Y cells. The bioactive ingredients that are responsible for the neuroprotective effect of EBN such as lactoferrin, ovotransferrin, melatonin, sialic acid and epidermal growth factor (EGF) are discussed. Moreover, suitable dosage forms of the EBN are required to serve the patients' needs as well as to deliver the content of EBN efficiently to the target. Hence, the dosage forms of EBN that are available in the market nowadays are addressed. The effects and mechanism of EBN as antioxidant and anti-apoptosis to treat PD are further elaborated. The concern regarding the toxicology of EBN is highlighted due the content of heavy metals such as arsenic, mercury, lead, cadmium, and tin in raw EBN that needs to be considered. This is because the accumulation of heavy metals in the body can lead to several health issues. The understanding and research between the background of PD and the promising effect of EBN may lead to the discovery of drugs for PD.

KEYWORDS: Parkinson's disease (PD), edible bird's nest (EBN), 6-OHDA, Lactoferrin, Ovotransferrin, Melatonin.

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1. Introduction

Parkinson's disease (PD) is a neurological disorder that causes involuntary or uncontrollable movements, such as shaking, rigidity, and difficulty balancing or coordinating [1]. The degeneration of dopaminergic neurons in the midbrain is the cause of Parkinson's disease [2]. People with Parkinson's disease may tremble in their hands, arms, legs, head, or jaw; they may also experience muscle rigidity, slowness of movement, and a decline in coordination and balance, which sometimes can cause falls [1]. Possible extra symptoms include skin problems, constipation or urination, difficulty speaking, eating, or swallowing, depression, and other mood swings [1]. Parkinson's disease affects each person differently, and so does the rate at which it progresses [1]. Treatments and medications can lessen symptoms, but there is no known cure [3]. Research has indicated that nitrosative and oxidative stress are major contributors to neurodegeneration [2]. In this study, researchers treated C57BL/6J mice with 6-hydroxydopamine (6-OHDA) and looked into the neuroprotective effects of edible bird's nest (EBN), (20 mg/kg and 100 mg/kg) [2]. Swiftlet species that were formerly resident in limestone caves secrete a hardened substance known as EBN [4]. The movement patterns of PD mice were significantly enhanced in terms of travel distance and balance after 28 days of oral EBN treatment. EBN also shielded substantia nigra dopaminergic neurons against 6-OHDA [2]. In PD mice, EBN restored both the increased activation of microglia and the decrease in the production of the antioxidant enzyme glutathione peroxidase 1 [2]. Additionally, the findings demonstrated that EBN successfully inhibited the generation of nitric oxide and lipid peroxidation in SH-SY5Y cells caused by 6-OHDA [2]. Overall, the data show that EBN exhibited neuroprotective effects by increasing the activity of antioxidant enzymes and reducing the activation of microglia, the production of nitric oxide, and lipid peroxidation in the Parkinson's disease model [2].

2. Bioactive Ingredients of EBN

Edible bird's nest (EBN) has gained widespread recognition in the Chinese community for medicinal purposes since the Tang and Sung dynasties, given that it is believed to have nutritional and therapeutic benefits [5]. These effects are caused by the nutritional composition and bioactive substances discovered in EBN. Several studies have been conducted to investigate EBN as a potential therapy for neurodegenerative disorders such as Parkinson's disease. According to the research, EBN is abundant in protein and carbohydrate, as well as other components, including trace elements such as iron, sodium, manganese, zinc, calcium, and magnesium [5]. Proteins and carbohydrates are the two most prevalent biological active components in EBN. About 50-60% of EBN's weight is made up of proteins, and EBN contains 18 of the 20 types of amino acids necessary by humans, with significant concentrations of serine, threonine, and aspartic acid [5]. Amino acids are essential for cell development and regeneration, as well as the synthesis of brain chemical messengers (neurotransmitters), immunoglobulin, and antibodies. Lactoferrin and ovotransferrin, two glycoproteins produced from EBN, have been shown to have neuroprotective action [6]. Carbohydrate components of EBN include N-acetylneuraminic acid (sialic acid), galactosamine, N-acetylglucosamine, N-acetylgalactosamine, galactose, and fructose [6,7]. Sialic acid is the most abundant component in the brain, accounting for around 10% of the EBN, and it has significant pharmacological effects on human health by encouraging neuronal development, synaptic transmission, and brain development [6]. Consuming sialic acid stimulates brain cell activity and boosts cognitive ability [6]. Furthermore, sialic acid is an important precursor for polysialic acid glycan, which modifies the neural cell adhesion molecule on the cell membrane (NCAM), and NCAM, in conjunction with ganglioside, mediates cell-to-cell interactions for neuronal outgrowth, synaptic connectivity, axonal formation and elongation, and memory formation [7]. In addition, the neuroprotective and neurotrophic components in EBN are epidermal growth factor (EGF) and melatonin [7]. EGF promotes the proliferation of neural stem cells (NSC), as well as active neurogenesis in the mammalian subventricular zone and the survival of striatal dopaminergic neurons in the Parkinson's disease model [7]. It communicates with a multipotent progenitor cell in the striatum, facilitating the development of both neurons and astrocytes. Meanwhile, melatonin can protect against neurodegenerative disorders, with the main contributor to its neuroprotective action being

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its antioxidant capacity against oxidative stress, which is known to be a risk factor for Parkinson's disease [7]. Melatonin protects neuronal cells from programmed cell death and provides a safer process in which it is transformed into a stable end-product after being oxidized in the presence of free radicals [7]. Melatonin has also been shown to minimize lipid peroxidation, resulting in fewer damaged and dead nigral cells and increased levels of superoxide dismutase, glutathione, and catalase [7]. It is a possible bioactive chemical for neurodegeneration in PD by encouraging neuronal differentiation of survival and dopaminergic neural stem cells [7].

3. Dosage Form of EBN

EBN is commercialized in the market as a dry powder, capsule, or liquid beverage, such as a ready-to-drink EBN beverage consisting of light syrup [8]. In the Chinese community, EBN has been a well-known traditional delicacy. It is most often consumed in the form of a soup called bird's nest soup, mixing rock sugar with herbs and double-boiling it to achieve a gelatinous-like consistency. The freeze-dried EBN has been used in cosmetics, ready-to-drink beverages, tonics, and baking powder, among other products, in industrial settings [9]. Moreover, EBN is also consumed as flakes. Some EBN products developed recently include bird's nest instant energy drink, instant Malaysian cubilose nourishing tonic, and Vietnam bird's nest powder [10].

4. Effect and Mechanism of EBN in PD

The development of PD is influenced by a complex interaction between oxidative stress and apoptosis [2]. Its interaction with mitochondrial functionality is crucial for neuronal survival in PD [11]. The depletion of dopaminergic neurons in the substantia nigra causes a decline in dopamine levels in the striatum, resulting in deterioration of motor functions [11]. An excess of ROS elevates the oxidative stress which specifically targets electron-rich biological components such as DNA, protein, and lipid. More ROS generation renders neurons, more prone to oxidative stress. [11]. Increased lipid peroxidation and high nitrite levels have also been identified in PD brains [2,5].

4.1. Sialic acid in EBN alleviates mitochondrial dysfunction

Mitochondria are required for neural processes such as ATP generation, calcium buffering, and epigenetic signaling. In PD, mitochondrial dysfunction has a substantial influence on dopaminergic neuron function [12]. This malfunction causes increased ROS and baseline mitochondrial oxidant stress, which damages cellular components [12]. Studies have demonstrated that inhibiting mitochondrial complex I in dopaminergic neurons can result in a disease phenotype similar to idiopathic PD [12]. Moreover, genetic studies have shown that altering mitochondrial complex I function in dopaminergic neurons can result in progressive, L-DOPA-responsive parkinsonism [12]. The potential use of sialic acid from EBN in alleviating mitochondrial dysfunction was explored [13]. In vitro cytotoxicity and cell viability tests were performed, which revealed that sialic acid enhanced cell viability without cytotoxicity up to a specific dose. When treated with EBN-derived sialic acid, differentiated SH-SY5Y cells showed a considerable increase in active mitochondria [13].

4.2. EBN as an antioxidant

EBN increases the expression of antioxidant glutathione peroxidase 1 which protects cells from oxidative damage [2]. Glutathione peroxidase (GPX1) is a key antioxidant enzyme in mammalian cells, protecting against oxidative stress and inactivating hydrogen peroxide [14]. GPX1 is needed to maintain redox balance in cells and has been linked to PD due to decreased brain glutathione levels in the early stage of PD [15]. In the PD mouse model, 6-OHDA injection led to a decrease in GPX1 expression, but EBN treatment has increased GPX1 expression, suggesting potential neuroprotective effects. Furthermore, EBN treatment reduced neuroinflammation by decreasing the expression of microglia marker CD11b and ameliorating reactive nitrogen species, nitrosative stress, and lipid peroxidation [2]. Neurodegeneration in

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substantial nigra is accompanied by a robust microglial reaction in PD. These cells produce protective or toxic substances like cytokines, neurotrophins, and ROS, which may initially be neuroprotective but can become neurotoxic due to toxic change, leading to the death of CA neurons in late stage [16]. Hence, reduced expression of microglia by EBN shows good neuroprotective activity. Moreover, the glycoproteins lactoferrin and ovotransferrin in EBN were proposed to contribute synergistically to its antioxidant activity, upregulating antioxidant genes and protecting against oxidative stress-induced cell death [2].

4.3. EBN as an anti-apoptosis

Apoptosis, a process characterized by high levels of intracellular proteolysis, is often observed in brains undergoing neurodegeneration [5]. Apoptosis is one of the causes of neuronal loss in PD, as demonstrated by DNA fragmentation and apoptotic chromatin changes in dopaminergic neurons [17]. The intrinsic apoptotic pathway is the predominant mechanism of neuronal death where this mitochondria-mediated apoptosis involves the increased generation of reactive oxygen species. Wild-type α-synuclein accumulation in dopaminergic neurons leads to decreased mitochondrial complex I activity and increased ROS generation whereby a defect of mitochondrial complex I is observed in PD patients' substantia nigra [17]. A study regarding the effects of different treatments on the cellular morphology of SH-SY5Y cells, has revealed that 6-OHDA-induced cell death is mediated through apoptosis [11]. Nuclear apoptotic changes were less prominent in cells pre-treated with EBN, revealing that EBN may be effective in mitigating the cytotoxic effects of 6-OHDA. 6-OHDA is a neurotoxin that is used to create an in vivo model of PD [11].

5. Potential Health Risks Concerns

In Southeast Asian nations like Malaysia, Indonesia, and Thailand, edible bird's nest (EBN) is a customary food item. The solidified swiftlet's saliva, or EBN, has a high nutritional value, per a study published in the Evidence-Based Complementary and Alternative Medicine journal [18]. However, EBN has been associated with safety concerns like higher nitrate and nitrite levels, stimulation of cancer cells, fungal infection, heavy metal presence, and adulteration [18]. Heavy metals are toxic elements that can accumulate in the body over time and cause serious health problems [19]. An investigation into the presence and concentration of heavy metals in EBNs originating from multiple main Indonesian islands was carried out by the Veterinary World journal [20]. The majority of the raw, unclean EBNs that originated from the main Indonesian island where they were produced had low levels of heavy metals (arsenic, mercury, lead, cadmium, and tin) detected in them, according to the study [21]. After washing, the concentrations of every heavy metal examined in the raw, dirty EBNs samples dramatically dropped [21]. Another study conducted by the Department of Veterinary Services Malaysia found that heavy metals were not detected in raw cleaned EBNs [21]. The other study found that EBNs are very safe to eat because the nitrate level is within government-set limits, the microbiology profile is acceptable, and no other heavy metals were found [21].
Though the World Health Organization has set a maximum level of 34 parts per million for all food products, there have been instances where the nitrite levels in some nests have exceeded this limit. To address this issue, a strong framework of Standard Operating Procedures and regulations has been put in place. The establishment of the Malaysia Bird Nest Alliance in 2015 shows the commitment to monitor and ensure the quality of the EBN industry in Malaysia [21]. A recent protocol outlining the requirements for exported EBNs was mutually agreed upon and ratified by the Agriculture and Agro-Based Industry Department of Malaysia and the authorities of China in September 2012 [21, 22]. The Standards and Industrial Research Institute of Malaysia (SIRIM) has established particular upper limits for microbial components like bacteria, mold, and yeast, as well as heavy metals like mercury, lead, cadmium, and arsenic in Edible Bird's Nests (EBNs) in order to strengthen safety measures. The Malaysian Ministry of Health's Food Safety and Quality Division rigorously enforces these standards, which were developed by the nation's Department of Standards between 2010 and 2012. This demonstrates the nation's steadfast dedication to upholding standards and guaranteeing the quality and security of Edible Bird's Nests. The Chinese government outlawed the import of EBN products from outside in August 2011 because of the

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higher nitrite (NO^{2-}) content of these consumable bird's nest products [22]. One naturally occurring substance found in EBN is nitrite. The presence of ammonia (derived from bird droppings) in the bird's house or cave environment, which eventually converted to nitrite in EBN, is one of the factors that contribute to the natural occurrence of nitrite in EBN. Other factors include the presence of nitrite in bird saliva and the formation of ammonia in the nest. Nitrite has the potential to cause cancer because it can combine with other substances in the body for the production of nitrosamines that can cause cancer [23]. A standard operating procedure (SOP) has been developed by the Food Safety and Quality Division of the Ministry of Health Malaysia to regulate the amount of nitrite in EBN [24]. The SOP outlines how to decrease the amount of nitrite in raw EBN during the raw clean EBN processing and primary production stages. Thirty parts per million (ppm) is the maximum amount of nitrite that is permitted in bird nests in Malaysia. As a result of the higher nitrate levels found in raw EBN, the Malaysian EBN market experienced a decline in prices in 2011. Chinese authorities thus forbade EBN from Malaysia from joining their market [25]. Nitrite may naturally form in bird nests as a result of fermentation at particular temperatures and humidity levels, according to some scientific studies [26]. Numerous studies have suggested that environmental contamination, such as nitrate-rich bird droppings, could be the cause of elevated nitrate levels in a nest. Research on the amount of nitrite in EBN made in Malaysia has been carried out by the Ministry of Health Malaysia. The research came to the conclusion that nitrite naturally occurs in EBN due to a number of factors, including nitrite found in bird saliva, ammonia formed in the nest, ammonia (derived from bird droppings) present in the bird's home or cave environment, which is eventually converted to nitrite in EBN, and nitrite-containing bird droppings that contaminate the EBN.

6. Conclusion

EBN can be classified as a natural remedy for PD. The ability of EBN to protect the dopaminergic neurons from the toxins, 6-OHDA makes it a promising treatment as the root cause of Parkinson's Disease is the deterioration of the dopaminergic neurons in substantia nigra. Rich content of bioactive compounds in EDN have therapeutic properties as the antioxidant and anti-apoptosis which results in less stress-induced cell death and neurodegeneration. This can indirectly reduce the symptoms of PD, such as stiffness, shaking and coordination problems. The preparation process of raw EBN is crucial to eliminate the presence of heavy metals and to ensure the EBN is safe to be consumed. It can be summarized that EBN brings a new hope for the patients suffering from PD and also as the possible starting material in the development of drugs for PD in the future.

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