Chapter 13
Edible Bird's Nest as Brain Food

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Abstract Edible bird nest (EBN) is a natural food substance derived from edible velvet nest saliva consisting of glycoproteins as one of its key components; these glycoproteins contain an excess of sialic acid. Dietary EBN supplementation has been documented to promote brain development in mammals. The bioactivity and nutritional benefit of EBN are significant during periods of rapid brain development, especially in preterm infants. However, the impact of EBN on learning and memory control remains unknown. This chapter aims to illustrate the benefits of EBN and its potential effects as a neuroprotective supplement for adults.

Keywords Edible Bird Nest (EBN) · Herbal Medicine · Brain · Neuroprotection · Antioxidant · Oxidative stress

13.1 Introduction and Historical Background of EBN

Swiftlet is a unique small insectivorous bird using its specialize salivary glands secretion in building its nest. Swiftlet species mainly live in the South East Asia region (Macron 2005; Chua et al. 2016). Its nest; edible bird's nest (EBN) is a valuable precious natural food built from the salivary secretion of glutinous glycoprotein through sublingual glands, mainly by the male swiftlet during their nesting and breeding season. The glutinous secretion solidified when exposed to air and form a strong structure to support the birds during their breeding season (Fig. 13.1). The nest in the shape of a bowl is built high on the wall and roof of the cave. It takes over 35 days to complete the nest construction. The solidified secretion enables the

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Fig. 13.1 A pair of swiftlets in the nest

nest to carry the swiftlets and their eggs remaining attached to the wall during the whole breeding season (Macron 2005; Ma and Liu 2012; Ramji et al. 2013). Studies showed swiftlets are cave dweller animals mainly located at the limestone caves. They live in large numbers in a colony, and they can fly in the dark as they can produce echolocation calls. The echo sounds help them navigate in the dark to get to their nests and hunting insects (Medway 1967; Brinkløv et al. 2013). The nest is always mixed with feathers and twigs. EBN harvester will have to do some intensive processing and cleaning works before it can be packaged and introduced to the customers in the shape of a bowl (Wong 2013; Jong et al. 2013).

Swiftlet's nest is produced by more than 24 different species all over the world. However, only few of them are edible. The Collocalia, Aerodramus, and Hydrochous are the three main geniuses of swiftlets that produce edible bird's nest (Wong 2013). *Aerodramus fuciphagus* produces white nest, *Aerodramus maximus* produces black nest; both are the two highly exploited species of Aerodramus and the most widely identified swiftlets in Malaysia. *Aerodramus fuciphagus* is the most valuable type; it contains about 70–90% mucous secretion with small percentages of feathers and insects that feed on the nest (Wong 2013; Chua et al. 2016). The highest quality of white nest attracts the commercial interest of the EBN industry. While the black nest, the edible part is only 10–15% and the rest are impurities. Therefore, the commercial value of the black nest is low since it needs intensive cleaning before it can sell to consumers. According to the harvest location, either cave or house, EBN is available in three different colors; white, orange, and red. The red EBN is the more costly type in the market because traditionally, people believe in its health advantages (Macron 2005). Some scientists suggested that the red color may be due to the blood of swiftlets mixed with their saliva secretion or the food source, which mainly comes from the insect with minerals (But et al. 2013). Others linked the red color with the oxidation of iron and the minerals found on the cave wall. Interestingly, some investigators suggested a correlation between the red color of EBN and nitrate oxidation (But et al. 2013; Paydar et al. 2013; Quek et al. 2015; Shim and Lee 2018).

Chinese community has regarded EBN since the Tang dynasty in AD681 as a precious food and medicine known as "Caviar of the East" (Macron 2005). The EBN soup was prepared by double boiling with rock sugar and was only available for the emperor and wealthy people in the olden days. Traditionally, it was widely used by the Chinese for its nutritional value and health beneficial effect for a thousand years despite being regarded as a costly traditional medicine. They maintain the convention that EBN is a balanced food and beauty improver, effective for various diseases of respiratory and gastrointestinal systems. Additionally, it increases immunity and improves aging skin. Studies also showed that EBN is a potential curative agent in cancer, stomach ulcers, asthma, and cough (Kong et al. 1987; Ma and Liu 2012; Hobbs 2004; Macron 2005). Lately, EBN was showed to have antiviral effect by inhibiting influenza infection (Haghani et al. 2016, 2017) and neuroprotective activity (Xie et al. 2018). EBN also benefits as an antioxidant, anti-inflammatory agent and can improve bone strength (Matsukawa et al. 2011; Yida et al. 2014). Today the awareness toward EBN has been increased worldwide as this salivary secretion is valuable for its therapeutic effect and delicacy (Ma and Liu 2012). With the aid of modern technology, EBN has been produced as one of the key ingredients in health supplementation food, drinks, and cosmetics products (Kong et al. 1987).

13.2 Preparation and Extraction of EBN

The valuable nutrition and functional entity in the EBN is not the only cause for the high price of EBN. The labor intensive EBN cleaning process to remove all its impurities such as feather, twigs, and dirt, making its high production cost (Fig. 13.2a). Many tedious steps are involved in cleaning the raw EBN before going into the market. The first step of raw EBN cleaning is by soaking the raw EBN in cold water (10–15 °C) to get the gelatinous material to expand for 6 h. Some feathers and twigs will be floated on the water surface and can be easily removed by changing the water (Fig. 13.2b). However, many impurities remain inside the EBN which can only be removed using tweezers. The cleaned EBN is then layered on the plastic mold to get the bowel shape for drying before packing in a container and introduced to the customers (Fig. 13.2c,d) (Jong et al. 2013). Different methods are used for checking the authentication and the quality of the processed EBN. These include physical examination, chemical analysis, fluorescent microscope viewing, FTIR microscopic, and chromatography determination (Wong et al. 2017; Zainab et al. 2013; Yang et al. 2014; Chua et al. 2016). However, there is still no established method to identify its authentication since all methods used are time-consuming and need special instruments.

An effective scientific tool for extensive analysis of small molecules in EBN is through metabolites profiling. This technique has been conducted to estimate the biological components that can potentially treat the diseases (Chua et al. 2014; Amiza et al. 2019). The biological effects and biomolecules of EBN are different when different methods are used for its extraction. So far, heat extraction is the

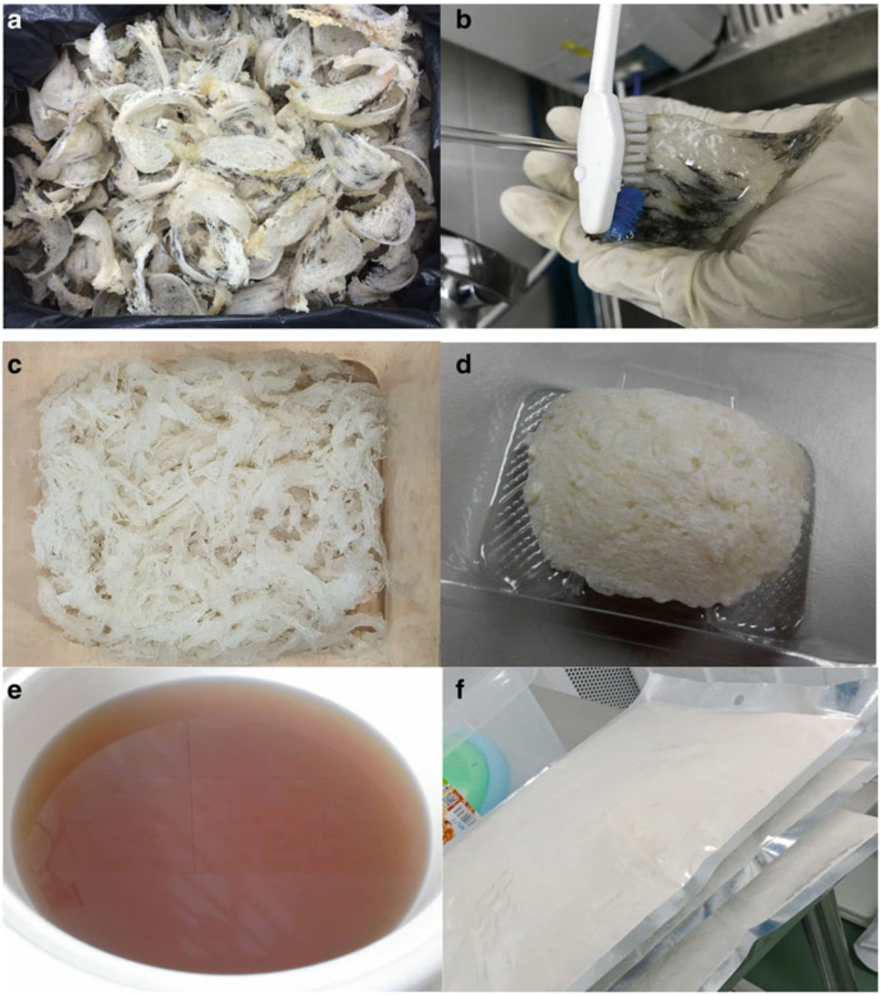

Fig. 13.2 Edible bird's nest (EBN) cleaning and extraction. (**a**) RAW EBN. (**b**) Cleaning the surface of EBN. (**c**) The cleaned EBN. (**d**) Dry EBN in bowel shape. (**e**) The liquid extract of EBN. (**f**) The freeze dried EBN extract in powder form

cheapest and the easiest way to extract glycoprotein, especially for water-soluble glycoproteins from EBN (Fig. 13.2e,f) (Zhang et al. 2012). The glycoprotein structures change according to the different colors of EBN, and also affected by its boiling time. The red EBN has a higher resistance to protein digestion and solubility, so it needs more time in the extraction (Wong et al. 2017). The study done by Tong et al. (2020) testing on different methods of EBN extraction revealed that eHMG was the optimal technique that can obtain the highest amount of water-soluble metabolites. In addition, sialic acid was presented as the main component in the extraction, indicating the effectiveness of eHMG (Tong et al. 2020). This extraction process was efficient in enhancing the proliferation of corneal keratocytes (Zainal Abidin et al. 2011). Furthermore, it has shown good anti-osteoarthritis effect when tested on human chondrocytes isolated from arthritic knee joint (Chua et al. 2013a, b). In 2020, Zameri group revealed no difference in the amount of protein and antioxidant property of EBN by using different extraction methods (Zamri et al. 2020). The enzymatic hydrolysis method using enzymes such as pepsin, pancreatin, pancreatin F, alcalase, and papain could result in more bioactive compounds such as antioxidant peptides in the extract (Amiza et al. 2019; Nadia et al. 2017; Wong et al. 2017). It was also reported that enzymatic hydrolysis could improve the solubility of EBN and enhance the bioactivity of the product (Ghassem et al. 2017; Amiza et al. 2019). Matsukawa group has shown that the pancreatin F hydrolysis of EBN could improve the anti-osteoarthritis effect, inhibit influenza virus, reduce neuronal apoptosis, and decrease oxidative stress (Guo et al. 2006; Matsukawa et al. 2011; Yew et al. 2014). Furthermore, the antioxidant property of EBN can be enhanced by papain and alcalase enzymatic partial digestion (Nadia et al. 2017; Babji et al. 2018).

13.3 Active Compounds in Edible Bird's Nest

The composition of the edible bird's nest (EBN) is different according to the source (Macron 2005: Quek et al. 2018). The major biologically active compound in EBN is protein and carbohydrates that are important in assessing the efficacy of EBN. The average raw protein in EBN is about 60% of its weight. The protein is made up of 17 different types of amino acids that are essential for the cells growth, regeneration, production of the brain neurotransmitter, antibodies production, and immunoglobulin that help the immune system (Wang 1921; Macron 2005; Chua et al. 2014). The variation in EBN amino acid composition is mainly due to the different collection locations and types of cave or EBN's man-made houses (Macron 2005; Seow et al. 2016). Study showed serine, threonine, aspartic acid, glutamic acid, proline, and valine are the most abundant amino acid in EBN (Babji et al. 2018; Kathan and Weeks 1969). The aromatic amino acid (tyrosine and phenylalanine) is highly present in white EBN, which has anti-depressant and pain-alleviating effects (Macron 2005). It was found that EBN also contains a 77KDa protein, which has the same properties like the ovotransferrin in chicken egg. It is responsible for the allergic reactions in children that consume EBN (Macron 2005). The unique combination of protein and carbohydrates in the EBN provides remarkable health benefits to humans (Wang 1921; Macron 2005; Xin et al. 2014; Babji et al. 2018; Kathan and Weeks 1969). In 2017, a report indicated that mucin-like protein is the main hallmark peptide of EBN, which may help for the classification of EBN via its colure and collection places (Wong et al. 2017). The gastric fluid and acidic enzyme digestion of EBN causes the release of protein that enhances the nutritional value of the EBN (Wong et al. 2018).

Carbohydrates are considered the second major component of EBN. According to Kathan and Weeks, 28% of EBN is made up of carbohydrates, including 9% N-acetylneuraminic acid (sialic acid), Galactosamine, glucosamine, and galactose N-acetylglucosamine and N-acetyl galactosamine. These compounds are known as glyconutrients that give the unique value of EBN (Wong et al. 2017, 2018; Ma and Liu 2012; Chua et al. 2015; Norhayati Jr et al. 2010; Macron 2005; Kathan and Weeks 1969).

The unique indicator that allows the grading of various EBNs is its sialic acid, which has the pharmacological effects on human health (Quek et al. 2018). N-acetylneuraminic acid (Neu5Ac or NANA) is the main type of sialic acid found in EBN (Pozsgay et al. 1987; Guo et al. 2006; Yida et al. 2015a, b, c; Zhao et al. 2016). It plays an essential role in brain development, neuronal outgrowth, and synaptic transmission. Diet rich in sialic acid helps in increasing brain cell activity level and improving cognitive functions (Wang 2009, 2012; Khalida et al. 2019). The amount of sialic acid in EBN is higher than the sialic acid-rich foods such as human milk and chicken egg yolk (Quek et al. 2018). This high content explains the beneficial effect of EBN in brain development, prevention of influenza virus infection, immunity enhancement, cell proliferation, and neurological improvement (Aswir and Wan Nazaimoon 2011a; Hou et al. 2017; Wong et al. 2018; Xie et al. 2018; Khalida et al. 2019).

Minerals are micronutrients received from natural food, which are important elements for the human body and brain functions. The ashes in EBN contain minerals, and it was reported that the amount of nitrate and nitrite in the cave is higher than house EBN (Zainab et al. 2013; But et al. 2013). The white EBN contains fewer amounts of nitrite and nitrate than the red EBN, which can be further reduced by overnight soaking with water (Paydar et al. 2013; Quek et al. 2015). Other minerals such as sodium, magnesium, potassium, and calcium are abundant as well, while iron, copper, phosphorus, and zinc are found in low traces amount in EBN (Norhayati Jr et al. 2010). The variation in the food sources and the environment of swiftlets may explain the difference in ashes content. For example, a higher calcium and sodium concentration is found in EBN harvested from limestone caves (Quek et al. 2018; Norhayati Jr et al. 2010; Macron 2005).

EBN is widely used worldwide with its tremendous value. The nutritional benefits and pharmacological activity are necessary for developing the promising EBN product to customers. It is important to use scientific research data to boost the EBN value to increase customer trust in EBN's products.

13.4 Pharmacological Effect of Edible Bird's Nest

13.4.1 Antiviral Effect of EBN

Study done by Guo et al. in 2006 showed that the enzymatic hydrolysis of EBN with protease pancreatin F has potent antiviral properties (Guo et al. 2006). EBN has the ability to inhibit influenza viruses from hemagglutination of red blood cells and neutralizes influenza virus infection on Madin Darby Canine Kidney (MDCK) epithelial cells (Guo et al. 2006; Haghani et al. 2016). It was suggested that the inhibition of viral infection might be related to sialic acid content in EBN (Guo et al. 2006; Yagi et al. 2008). Another study also reported the antiviral efficacy of EBN against the influenza virus relate to its high level of sialic acid (Haghani et al. 2017).

13.4.2 Effect of EBN on Cell Proliferation

Studies showed that EBN has the potential mitogenic effect on cell proliferation. Kong et al. indicated that EBN exhibits EGF like activity to promote cell growth (Kong et al. 1987). Following that, many studies were conducted to verify the existence and possibility of using EBN in cell proliferation. Aswir and Nazaimoon studied the effect of EBN on cell proliferation in Caco-2 culture and the tumor necrosis factor-alpha (TNF- α) release in RAW cells. The results indicated an increase in Caco-2 cell proliferation and reduction in TNF- α release in RAW cells. The efficacy of EBN varied according to its type and origin (Aswir and Wan Nazaimoon 2011b). As there are no adequate therapies for corneal wound healing, the study done by Zainal Abidin showed a significant advancement using EBN extract. The results demonstrated that a low concentration of EBN (0.05% and 0.1%) is sufficient to enhance cell proliferation of corneal keratocytes derived from rabbits (Zainal Abidin et al. 2011). The presence of a growth factor-like substance in EBN, the avian EGF, contributed to the cell proliferation improvement (Kong et al. 1987; Zainal Abidin et al. 2011). EBN plays a vital role in tissue regeneration and promotes Human Adipose-Derived Stem Cells (hADSCs) (Roh et al. 2012; Wong et al. 2012). Roh et al. (2012) reported that interleukin 6 (IL6) and vascular endothelial growth factor (VEGF) expression by the cells were triggered by EBN supplementation (Roh et al. 2012). A similar study by Albishtue supported that the presence of EGF, VEGF, and IL6 play an important role in cell proliferation of uterine. The finding demonstrated the possible effect of EBN supplementation on improving fertility and uterine functions by increasing uterus growth and enhancing the anti-oxidation activities (Albishtue et al. 2018, 2019).

13.4.3 Antioxidant Effect of EBN

EBN has been recorded as an antioxidant with the amino acids present in the edible bird nest after hydrolysis. After gastrointestinal digestion, the antioxidant effect of EBN will be enhanced (Yew et al. 2014; Yida et al. 2014). A research carried out by Yida et al. reported that EBN has the ability to reduce the risk of hypercoagulation associated with cardiovascular disease (CVD). The results showed that the EBN treated group can improve the lipid profile, lower the blood sugar level, and total cholesterol by reducing oxidative stress compared to the control group (Yida et al. 2015c). In 2015, the same research group demonstrated the effect of EBN on high-fat diet (HFD) induced oxidative stress in a rat model. The result showed EBN could reduce the oxidative stress and inflammation triggered by HFD via transcriptional control of hepatic antioxidant genes expression related to inflammation (Yida et al. 2015b). The results support the effectiveness of EBN in the prevention of inflammation and oxidative stress induced by obesity. In addition, a study done by Ghassem et al. suggested protein hydrolysate of EBN possesses antioxidant properties and can scavenge the free radical (Ghassem et al. 2017). A similar study was reported on the improvement of the level of superoxide dismutase (SOD), estrogen, malondialdehyde, and lipid profile of the ovariectomized rats with 12 weeks of EBN supplementation in the diet (Z. Hou et al. 2017). These finding highlights the value of EBN to prevent the cardio metabolic disease induced by estrogen deficiency. Hu et al. studied the anti-aging effect of EBN in the *Drosophila melanogaster* model. The study showed EBN could decrease mortality rates and lipid peroxidation via increasing the antioxidant enzyme activity (Q. Hu et al. 2016). Likewise, research carried out by Albishtue and colleagues to evaluate the effect of EBN supplementation on uterine function and embryo implantation rate proven that EBN enhances anti-oxidative activity and decreases oxidative stress level, which enhances embryo implantation (Albishtue et al. 2019).

13.4.4 Bone Regeneration Effect of EBN

The effect of EBN on bones and cartilage has been investigated through many studies. It has been showed that oral administration of EBN extract increases bone strength and calcium concentration, improves skin aging and dermal thickness in ovariectomized rats (Matsukawa et al. 2011). The presence of non-sulfated chondroitin proteoglycans in EBN may contributed in the enhancement of bone strength. The outcomes indicate that women can use EBN after menopause in improving bone strength (Matsukawa et al. 2011). Furthermore, hot water extraction of EBN enhances the proliferation of human articular chondrocytes. The sialoglycoprotein found in EBN can be used to manage the progression of osteoarthritis and enhance the regeneration of cartilage cells (Chua et al. 2013a,b). Both findings supported the nutritional supplementation effect of EBN in reducing the progression of osteoarthritis.

13.5 Effects of EBN on Learning and Memory

Nutrient is the essential factor for the development and growth of the newborn. Any nutrient deficiency deeply affected brain development. EBN has been documented as a natural glycoprotein containing sialic acid that can boost up brain function. Study has shown sialic acid can increase the intelligence and the brain functions of a child by increasing the synaptic pathway and ganglioside distribution (Wang 2009, 2012). Dietary supplementation of sialic acid causes upregulation of some genes involved in the physiological pathway related to cognitive development (Wang et al. 2007). The study conducted by Xie et al. (2018) showed that the administration of EBN into the mother during pregnancy or lactation could increase the level of sialic acid and enhance BDNF expression in the hippocampus. EBN increases the number of neuronal cells in the hippocampal CA1, CA2, and CA3 regions. EBN improved the offspring's learning and memory skills by increasing superoxide dismutase (SOD), choline acetyltransferase (ChAT) activities but decreased its acetylcholinesterase (AChE) (Xie et al. 2018). Another study showed EBN supplementation in the maternal mice during pregnancy and lactation could improve the learning and memory function of the newborn by BDNF gene attribution (Mahaq et al. 2020). BDNF expression has the potential to boost neurogenesis in hippocampal area by triggering mitochondrial biogenesis and neuronal plasticity (Xie et al. 2018; Mahaq et al. 2020). The high level of sialic acid in EBN supplementation increases the expression of brain genes correlated to the improvement of cognitive outputs in Y maze in both generations of the animal (Mahaq et al. 2020). Nevertheless, the gene expression in brain due to EBN supplementation is still uncertain since the content of sialic acid is different from various locations of EBN origin. It was showed that the mice treated with different concentrations of sialic acid derived from EBN showed improvement in cognitive impairment. In a cellular study, EBN was shown to increase the proliferation of pheochromocytoma and neuroblastoma cells (Khalida et al. 2019). The study revealed that the higher concentration of sialic acid might correlate with the development and functioning of the brain (Khalida et al. 2019). In the previous study conducted on the Wistar rat model, EBN can enhance the learning and memory of the LPS-induced neuro-inflammation. This work demonstrated that the anti-inflammatory effect of sialic acid in EBN might enhance the memory by inhibiting neuro-inflammation. The potential neuroprotective effect of EBN could become a promising strategy for the treatment of menopause related cognitive dysfunction. Zhiping et al. have indicated a novel approach using EBN as a natural supplementation to overcome menopause cognitive disability. This finding demonstrated that EBN could reduce neurological dysfunctions cause by estrogen deficiency and downregulation of genes in the hippocampus and frontal cortex related to neurodegeneration. In addition, EBN greatly diminished the increased level of advanced glycation end-products (AGEs) associated with estrogen deficiency. EBN also increase the antioxidant enzyme activity to decrease oxidative stress in the hippocampal and frontal cortex (Zhiping et al. 2015). The results in the study are consistent with another study done in 2017, showing the cognitive ability in hippocampus of ovariectomized rats could improve by the administration of EBN. The beneficial effect of EBN could be accomplished by improving the neuronal plasticity mediated by SIRT1 in the hippocampus that correlates with cognitive skills. Besides, EBN is a safer alternative treatment compare to the estrogen. Estrogen administration can cause undesirable effects in the ovariectomized rat's kidney and liver although it can enhance cognitive functions (Z. Hou et al. 2017). The ability of

EBN glycoprotein to suppress the oxidation stress contributes to the prevention of the disease. Various researches indicated the neuroprotective and antioxidant effect of lactoferrin (LF) and ovotransferrin (OVF) which are also glycoproteins (Ibrahim et al. 2007; Rousseau et al. 2013). Hou et al. revealed that the antioxidant and protective effects of EBN against hydrogen peroxide induced apoptosis and oxidative stress to SHSY5Y cells were also contributed by its component of LF and OVF (Zhao et al. 2015). These findings demonstrated the antioxidant ability of EBN in combat aging and associated neurodegeneration disorder. It also found that the EBN extract has a neuroprotective effect against degeneration of dopaminergic neurons caused by 6 hydroxdopoamine. It inhibits apoptosis in human neuroblastoma SH-SY5Y cells and improved cell viability (Yew et al. 2014). Consequently, EBN may be suggested as a new alternative treatment in neurodegeneration diseases such as Alzheimer's Disease (AD) and Parkinsonism induced by oxidative stress.

13.6 EBN and AD Rat Model

Aging is the one of the major contributing factors in AD dementia. Reduction in cerebral blood flow (CBF) may initiate cascade of inflammatory reaction and oxidative stress that causes neuronal loss which triggers cognitive deterioration. Recently the medicinal concept is emphasizing the role of natural antioxidant product as nutritious compound in protecting the physiological changes of the brain that cause aging or any neurological disorder. In one of our studies, we induced bilateral occlusion of the common carotid arteries (2VO) in the rat model, which mimic the decrease in CBF in the human aging brain (Farkas et al. 2007). This occlusion is irreversible and permanent thus contributing in pathophysiological changes with increase oxidative stress level that leads to neuronal damage (Liu and Zhang 2012; Zhang et al. 2018). The most affected area in brain is CA1 region in hippocampus. The neuronal death contributes to serious functional and morphological disorders that correlate with gradual memory and cognitive deterioration. The treatment of EBN was given first day after surgery by oral gavage for eight consecutive weeks. The treatment used to protect neuronal cell from damaging related to the chronic reduction in CBF. The finding showed that the long-term ischemia induced by occlusion of bilateral carotid arteries induced neuronal damage and increased oxidative stress in the untreated group. While in 2VO treated groups with EBN showed an improvement in pathological changes of neuronal cells associated with an increased in viable neuronal cells count in CA1 hippocampal area. In addition, there was a decrease of the oxidative stress level of F2-isoprostane in hippocampus compared to untreated groups. The pharmacological intervention of EBN based on antioxidant and anti-inflammatory properties furthermore showed the valuable nutritious components in EBN may have the ability to enhance cognitive functions. The consumption of food with therapeutic benefits could be a great plan to slow the progression of AD. Since EBN has been consumed for its enormous medical and health reason, our result highlighted the potential effect of EBN in delaying the progression of dementia-related to AD if taken early before the onset of the disease. It can be a daily supplement to protect neurons from aging process.

13.7 Conclusions and Recommendations

The above mentioned was the first study demonstrating the effect of EBN on the brain ischemic rat model; however, the study has some limitations. Our recommendation is to conduct a behavior test on the rat to assess the animal's cognitive ability after EBN supplementation. In addition, inflammatory markers could be measured to clarify the anti-inflammatory effect of the EBN. Finally, it would be useful if future research carries out to assess the gene and protein expression in the hippocampus and brain cortex of the same animal model.

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