Effect of Ginkgo Biloba Extract (EGb761) on Cerebral Nervous System in Patients with ALzheimer's Disease

Yanlei Gu(✉)

Agricultural Science, University College Dublin, Dublin 04V1W8, Ireland
yanlei.gu@ucdconnect.ie

Abstract. Alzheimer's disease (AD) is a common neurodegenerative disease and a kind of dementia in the elderly. More and more studies have shown that using the standardized extract of Ginkgo biloba leaves (labeled EGb761) to intervene in the clinical treatment of AD patients can effectively improve their brain neuron damage. Although its biological mechanism and principle are still being explored. Among all kinds of research, the three most widely studied directions of scholars are: (i) EGb761 can prevent Aβ (1–42) oligomer induced results (ii) It can show anti neuroinflammatory toxicity (iii) It can produce natural acetylcholinesterase (AChE) inhibitors. The three directions simply analyze how EGb761 has a specific impact on the patient's brain nervous system after entering the human body. Based on the review of the above three directions, this paper will briefly discuss and review the specific effects of EGb761 on the brain nervous system of AD patients.

Keywords: EGb761 · AD · Aβ · AChE

1 Introduction

Ginkgo biloba extract (EGb761) is mainly composed of flavonoids and bilobalide compounds [1]. It is a dietary supplement taken orally by the elderly to improve memory and age-related cognitive loss [2]. At the same time, various experimental studies have shown that it is a substance that can inhibit the onset of nervous system diseases such as AD. As the most common senile dementia, the pathogenesis of AD has not yet been fully understood. But it is now believed that the disease is mainly caused by β- Amyloid (Aβ) Abnormal deposition leads to the destruction of blood-brain barrier (BBB), resulting in neuron death and cognitive impairment.

According to the statistics of scholars in 2010, the number of patients with ad in China has reached 56.9 million, accounting for 62% of the total number of all kinds of dementia in China in the same period, and is the main cause of dementia among people over 65 years old [3]. With the aging of the global population, the incidence rate of ad is also rising. In this case, as with other chronic diseases, effective preventive interventions can inhibit or delay the onset of the disease, and can greatly reduce the burden of the disease on society and the health system.

G. Ali et al. (Eds.): ISEMSS 2022, ASSEHR 687, pp. 267–273, 2022.
https://doi.org/10.2991/978-2-494069-31-2_33

As early as the end of the last century, EGb761 began to emerge in the treatment of AD and other dementia. For example, the experiment of kanowski et al. [4] in 1996. However, due to various conditions, the number of literatures on the specific effect in the Cerebral nervous system of EGb761 of AD patients in the world is still sparse and scattered. Most of them are that EGb761 can prevent different results induced by Aβ(1–42) oligomer, thus having a positive impact on the nervous system. At the same time, a small number of literatures have discussed the anti microglia induced neuroinflammatory toxicity of EGb761 and the effects of natural acetylcholinesterase (AChE) inhibitors produced by EGb761 on the nervous system of AD patients.

By reading and summarizing the above relevant literature, this paper will briefly review the specific effects of EGb761 on the brain nervous system of AD patients after entering the human body.

2 EGB761 Can Prevent Results of Aβ(1–42) Oligomer Induction

Aβ(Aβ (1–40) or Aβ (1–42)), is a 40 or 42 amino acid peptide β- Secretory enzymes and γ- The proteins [5, 6] produced by the sequential cleavage of amyloid precursor protein (APP) secreting enzymes, and it may interact with specific cell types after misfolding and cause dementia such as AD [7]. The formation and aggregation of Aβ and the neurotoxicity induced by related cells are the main signs and pathological principles of AD [8]. It can induce neuronal synaptic loss and neurodegeneration through several ways.

At present, people still can not clearly kown how can Aβ exert the cytotoxic effect, but according to the "Amyloid Cascade Hypothesis", the aggregation of Aβ will induce a series of downstream results, including tau protein hyperphosphorylation, neuronal damage and death, plaque deposition, destruction of neuronal Ca homeostasis [9] and RIP1 mediated mitochondrial dysfunction [10], which are the driving factors to aggravate the onset of dementia such as AD. However, several studies in recent years have shown that EGb761 can block the neurotoxicity of Aβ [2].

In 2010, Xiao and his colleagues used rats to study the effect of EGb761 on the hippocampus damaged in the pathogenesis of AD. The experiment shows that Ginkgolide B, the main component of EGb761, can protect hippocampal neurons from apoptosis and oxidative free radical damage by enhancing Brain-Derived Neurotrophic Factor (BDNF), which plays an important role in the regulation of synaptic function and plasticity [11]. This result is also consistent with that of Luo et al. Who carried out relevant in vitro experiments as early as 2002. They concluded that EGb761 can protect cells through a variety of neuroprotective mechanisms, including reducing apoptosis and directly inhibiting the conclusion of the neurotoxicity of Aβ [12].

In addition, in the field of in vivo experiments, Xu et al. Used rats in 2020 to clarify that the mitochondrial dysfunction accompanied by neuronal calcium imbalance induced by caspase mediated necrosis disease will further lead to oxidative stress in mitochondria and cell death. At the same time, they used in vitro and in vivo double experiments to verify that EGb761 can alleviate mitochondrial damage, inhibit necrosis and apoptosis, and improve the cognitive function of AD model [10].

3 EGB761 Can Show Anti Neuroinflammatory Toxicity

In addition to Aβ-related cytotoxicity, microglia, a resident immune cell in the central nervous system (CNS), can also lead to cellular and neurotoxic effects through over activation [13]. The data show that this significant and highly harmful neuroinflammatory toxicity is also one of the main causes of AD. At the same time, it is also considered to be an important factor leading to neuronal death and cognitive impairment in a variety of neurodegenerative diseases, including AD, traumatic brain injury, Parkinson's syndrome (PD) [14] ect.

Among the various results caused by excessive activation of microglia, the main manifestations of neuroinflammatory toxicity are potential neurotoxic molecules (such as inflammatory factors produced by microglia activation: tumor necrosis factor (TNFalpha), interleukin-1β (IL-1beta) and IL-6) [13], and arachidonic acid (AA)--a lipid metabolite that plays an important role in many inflammatory processes. In 2018, gargouri et al. Used the enzyme linked immunosorbent assay (ELISA) to measure the inflammatory factors such as TNFalpha, IL-1beta and IL-6 produced by the activation of in vitro cultured microglia treated with EGb761 solution of different concentrations and lipolysaccharide (LPS), and analyzed the gene expression in these cells by quantitative real time PCR (QRT PCR) and Western blot. The experimental results showed that EGb761, as a natural polyphenol of flavonoids with strong anti-inflammatory properties, had a strong inhibitory effect on the production of inflammatory factors. And it can reduce the production of AA by inhibiting the activation of cytoplasmic phospholipase A2 (cPLA2) and cyclooxygenase (COX). In addition, it can also reduce the activation ratio of microglia by targeting prostaglandin E (PGE), thus showing anti-inflammatory activity [15]. This further proves that EGb761 has inhibitory effect on a variety of neurotoxicity mediated by microglia, and can effectively inhibit or delay the onset of AD.

4 Egb761 Can Produce Natural Acetylcholinesterase (Ache) Inhibitors

Acetylcholine is an important neurotransmitter related to memory [16]. In the treatment of AD and other dementia, people need to use acetylcholinesterase (AChE) inhibitors to inhibit its decomposition. Studies have shown that EGb761 can reduce or delay the onset of AD patients by producing natural AChE inhibitors [17]. This is the latest conjecture in the research direction of treating degenerative diseases such as AD, and has been gradually confirmed in recent years. However, before this conjecture appeared, the therapeutic research of AChE inhibitors on ad has been widely studied since the introduction of the first cholinesterase inhibitor (ChEI) in 1997 [16]. At present, the International Pharmaceutical Association has approved the use of AChE inhibitors to treat mild to moderate AD symptoms, such as kabbalatine and donepezil [18]. In recent years, in order to reduce side effects and improve drug effects, people have tried to find a plant that can extract natural compounds to produce AChE inhibitors [18]. In 2018, Zhang et al. selected 21 EGb761 compounds and established a kinetic simulation model through molecular docking experiments to identify the ability of 21 compounds

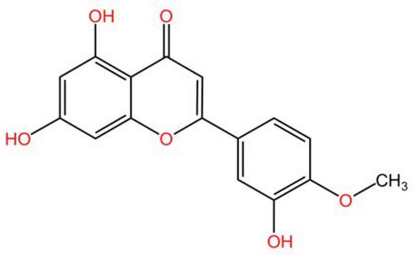

Fig. 1. 2D Structure of Diosmetin(Self-generated)

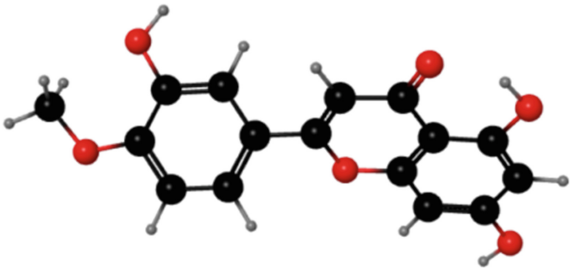

Fig. 2. 3D Structure of Diosmetin(Self-generated)

to bind to ache. The experimental results showed that four compounds showed activity in binding to ache active sites, and the compound named Diosmetin [Figs. 1–2] showed significant anti AChE activity [17]. Although only four of the 21 compounds showed activity, it also showed that it was very possible to extract natural AChE inhibitors from EGb761. This conclusion is the same as that of Birks in 2022 [16].

5 Discussion

Alzheimer's disease (AD) is a disease that mainly attacks neurons, and it can cause serious damage to the patient's brain, especially the hippocampus. With the aggravation of population aging, AD patients are also increasing. The report of Alzheimer's Disease International (ADI) in 2018 pointed out that the growth rate of AD patients averaged 1 new case every 3 s. It is estimated that by 2050, the global number of patients will exceed 150million. And based on the non recoverability of AD, the medical cost of AD patients is a heavy burden for both national medical institutions and patient's families.

Since the 1990s, the standardized extract of Ginkgo biloba leaves (EGb761) has been developed as a drug to delay and reduce the incidence of AD patients. However, there have been few studies on the specific effects of EGb761 on the brain nervous system of AD patients, and the research directions are scattered. At the same time, the clinical efficacy of EGb761 in the treatment of dementia such as AD is still elusive due to the complex pathogenesis and special nature of AD, as well as the difficulties in clinical trials caused by the difficulty in assessing the degree of disease.

Reducing the production of ROS, defending mitochondrial dysfunction, inhibiting the formation and aggregation of a, weakening cell damage and apoptosis, anti neuroinflammatory toxicity, and acting as an AChE inhibitor are all the mechanisms of EGb761 in various experiments of AD. Therefore, in this direction, a more comprehensive and clear literature review has been waiting to be produced.

6 Conclusion

In general, around the theme of EGb761's effect on cerebral nervous system of AD patients, this paper is divided into three parts: (a) EGb761 can prevent Aβ (1–42) oligomer induced results (b) EGb761 can show anti neuroinflammatory activity. (c) EGb761 can produce natural acetylcholinesterase (AChE) inhibitors. Through reading and summarizing the literatures in these three directions, this paper simply expounds the specific effects of EGb761 on the brain of AD patients. In addition to the several effects mentioned in this article, there are many related effects that worth to be explored, which will help to better understand the effectiveness and complexity of EGb761.

References

1. Müller, W. E., Eckert, A., Eckert, G. P., Fink, H., Friedland, K., Gauthier, S., Hoerr, R., Ihl, R., Kasper, S., & Möller, H. J. (2019). Therapeutic efficacy of the Ginkgo special extract EGb761® within the framework of the mitochondrial cascade hypothesis of Alzheimer's disease. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry, **20**(3), 173–189.
2. Singh, S. K., Srivastav, S., Castellani, R. J., Plascencia-Villa, G., & Perry, G. (2019). Neuroprotective and Antioxidant Effect of Ginkgo biloba Extract Against AD and Other Neurological Disorders. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics, **16**(3), 666–674.
3. Chan, K. Y., Wang, W., Wu, J. J., Liu, L., Theodoratou, E., Car, J., Middleton, L., Russ, T. C., Deary, I. J., Campbell, H., Wang, W., Rudan, I., & Global Health Epidemiology Reference Group (GHERG) (2013). Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet (London, England), **381**(9882), 2016–2023.
4. Kanowski, S., Herrmann, W. M., Stephan, K., Wierich, W., & Hörr, R. (1996). Proof of efficacy of the ginkgo biloba special extract EGb761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry, **29**(2), 47–56.
5. Liu, L., Zhang, C., Kalionis, B., Wan, W., Murthi, P., Chen, C., Li, Y., & Xia, S. (2016). EGb761 protects against Aβ1-42 oligomer-induced cell damage via endoplasmic reticulum stress activation and Hsp70 protein expression increase in SH-SY5Y cells. Experimental gerontology, **75**, 56–63.
6. Zhang, H. Y., Zheng, C. Y., Yan, H., Wang, Z. F., Tang, L. L., Gao, X., & Tang, X. C. (2008). Potential therapeutic targets of huperzine A for Alzheimer's disease and vascular dementia. Chemico-biological interactions, **175**(1-3), 396–402.
7. Gilbert B. J. (2013). The role of amyloid β in the pathogenesis of Alzheimer's disease. Journal of clinical pathology, **66**(5), 362–366.

8. Kumar, S., Okello, E., Harris, J. (2012). Experimental Inhibition of Fibrillogenesis and Neurotoxicity by amyloid-beta (Aβ) and Other Disease-Related Peptides/Proteins by Plant Extracts and Herbal Compounds. In: Harris, J. (eds) Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease. Subcellular Biochemistry, vol **65**. Springer, Dordrecht.
9. Shi, C., Wu, F., & Xu, J. (2010). H2O2 and PAF mediate Abeta1-42-induced Ca2+ dyshomeostasis that is blocked by EGb761. Neurochemistry international, **56**(8), 893–905.
10. Tu, J. L., Chen, W. P., Cheng, Z. J., Zhang, G., Luo, Q. H., Li, M., & Liu, X. (2020). EGb761 ameliorates cell necroptosis by attenuating RIP1-mediated mitochondrial dysfunction and ROS production in both in vivo and in vitro models of Alzheimer's disease. Brain research, 1736, 146730.
11. Xiao, Q., Wang, C., Li, J., Hou, Q., Li, J., Ma, J., Wang, W., & Wang, Z. (2010). Ginkgolide B protects hippocampal neurons from apoptosis induced by beta-amyloid 25-35 partly via up-regulation of brain-derived neurotrophic factor. European journal of pharmacology, **647**(1-3), 48–54.
12. Luo, Y., Smith, J. V., Paramasivam, V., Burdick, A., Curry, K. J., Buford, J. P., Khan, I., Netzer, W. J., Xu, H., & Butko, P. (2002). Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. Proceedings of the National Academy of Sciences of the United States of America, **99**(19), 12197–12202.
13. Wan, W., Zhang, C., Danielsen, M., Li, Q., Chen, W., Chan, Y., & Li, Y. (2016). EGb761 improves cognitive function and regulates inflammatory responses in the APP/PS1 mouse. Experimental gerontology, **81**, 92–100.
14. Yang, C., Yu, L., Kong, L., Ma, R., Zhang, J., Zhu, Q., Zhu, J., & Hao, D. (2014). Pyrroloquinoline quinone (PQQ) inhibits lipopolysaccharide induced inflammation in part via down-regulated NF-κB and p38/JNK activation in microglial and attenuates microglia activation in lipopolysaccharide treatment mice. PloS one, **9**(10), e109502.
15. Gargouri, B., Carstensen, J., Bhatia, H. S., Huell, M., Dietz, G., & Fiebich, B. L. (2018). Anti-neuroinflammatory effects of Ginkgo biloba extract EGb761 in LPS-activated primary microglial cells. Phytomedicine : international journal of phytotherapy and phytopharmacology, **44**, 45–55.
16. Birks J. (2006). Cholinesterase inhibitors for Alzheimer's disease. The Cochrane database of systematic reviews, **2006**(1), CD005593.
17. Zhang, L., Li, D., Cao, F., Xiao, W., Zhao, L., Ding, G., & Wang, Z. Z. (2018). Identification of Human Acetylcholinesterase Inhibitors from the Constituents of EGb761 by Modeling Docking and Molecular Dynamics Simulations. Combinatorial chemistry & high throughput screening, **21**(1), 41–49.
18. Batawi A. H. (2022). Ginkgo biloba extract mitigates the neurotoxicity of AlCl in alzheimer rat's model: role of apolipoprotein E4 and clusterin genes in stimulating ROS generation and apoptosis. The International journal of neuroscience, **1–11**. Advance online publication.