Role of Ginseng in therapeutic management of Alzheimer's Disease

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Abstract

While much of research progress has been achieved in last century on Alzheimer's Disease (AD), the conclusive therapy for the same is still unachieved. Several lines of therapeutic regimes have been introduced, which basically act on slowing down the disease progression. However, adverse side effects on lifelong use of such synthetic drugs are also inevitable. Rationale of such realization has attracted researchers to find alternative medicine for AD therapeutics. Natural products have shown promising response in this regard. Among handful of herbal products, Ginseng is notable and capable of recapitulating the equivalent functional attributes like other synthetic drugs available, with no side effects. In the present communication, based on available literature and reported data, we will discuss various aspects of Ginseng attribution as a potential alternative therapeutic approach for AD and whether it may serve as a novel pathway to treat AD.

Keywords: Ginseng, Alzheimer's Disease, Ginsenosides, MMSE, ADAS

Introduction

Alzheimer's Disease (AD) is one of the most dreaded neurodegenerative pathologies affecting ~2% of the global population especially in industrialized countries [1]. Clinically, still it remained a challenge to treat AD conclusively and most of the treatments rely on slowing down or stopping the disease progression [2]. These treatments may offer some relief but are largely ineffective in terms of long-term utility [3]. Hence, continuous effort to find adequate remedies through natural substances is going on, which if not cure, at least help in managing the symptoms of AD and may be utilized as adjuvants with other medications as well. Many studies have identified Ginseng as a potent herbal medicine for managing AD pathology and the evidence-based studies suggest the same [4-7]. Some studies showed promising results in terms of cognitive enhancement, while others found that it may act as an effective adjuvant when used with herbal mixtures [2]. Summing together, the contribution of Ginseng in the therapeutic possibilities for AD has been discussed here in the present discussion.

Ginseng in Alzheimer's Pathology

Many studies have been undertaken in the quest to understand the role of ginseng in AD pathology. Chen et al., in their 2006 paper, evaluated the efficacy of oral administered ginsenosides (one of the active components of ginseng) in Amyloid B peptide accumulation in one cell-based model. Although, various components in ginseng like ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids showed biological activity [8], its major pharmacological activities, are, however, credited to the ginsenosides, having similar architecture like steroid hormones [9]. The group identified that some ginsenosides, in a dose-dependent manner, lowered concentration of $A\beta$ and that too the ginsenoside Rg3 showed great promise with approximate IC_{50} of under 25 μM against $A\beta42$. They also unraveled that the ginsenosides viz., Rg1, Rg3, and RE cause significant reductions in the amount of $A\beta$ after giving single oral dose in the brains of study animals. From such findings, it can be concluded that ginseng in native form, or isolated and purified ginsenosides, may prove to be useful in treating human diseases [5].

To further evaluate the effects, Chen et al. utilized Tg2576 mouse model having familial Alzheimer's disease-linked Swedish mutation under control of the prion promoter. They evaluated the effect of 25 mg/kg of ginsenosides Rg3, Rg1, and Re on $A\beta$ concentration in the brain after a single oral dose. The results showed a significant reduction in $A\beta42$ concentration in the brain and in coherence with in-vitro model, Rg3 was found to be most effective in lowering $A\beta$ in vivo, with a $31.1 \pm 5\%$ reduction in $A\beta42$ relative to the vehicle control [5].

Another study by Lee et al., in 2008 evaluated the trophic effect of Panax ginseng in memory function of AD patients. The patients were given Ginseng power at 4.5 g/day for 12 weeks. Cognitive functions were evaluated using mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) index during 12 weeks of treatment and at the end 12 weeks when ginseng powder was discontinued. It has been shown that after ginseng treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks as compared to control groups. However, the improved ADAS and MMSE scores returned to baseline levels as control group when the Ginseng treatment was discontinued. This result suggests that continues use of ginseng could help in term of memory and cognition but upon withdrawal the effects drop drastically [4].

In 2009, Lee et al. reviewed some critical literature related to ginseng usage in AD pathology. They found that ginseng can be an adjunctive therapy when used with traditional medications. One possible theory has been put forward regarding such action, where it was argued that ginseng may improve cognitive function by interacting with the cholinergic and serotoninergic neurotransmitter systems. However, another study reported that ginseng treatment helps in managing glutamate-induced neurotoxicity by providing neuroprotection through anti-oxidation and anti-apoptosis pathways. But, regarding both the theories, more concluding evidence is required to prove the concept [7,10]. In another systemic review by Fu et al., they suggested that ginseng can enhance psychomotor and cognitive performance in AD patients. The possible mechanism is interaction with cholinergic functions, reducing the level of $A\beta$, and repairing networks of damaged neurons [6]. The studies reported however, were poorly executed with low sample size and insufficient controls, making it difficult to emphasize on the mechanism reported [6].
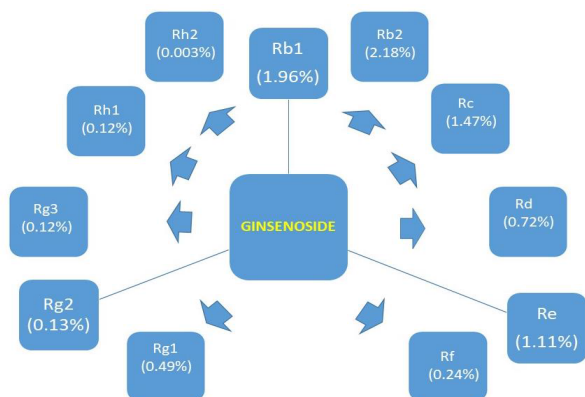

Figure 1: Different components of Ginsenoside (Based on data from Fu et al. [6]).

In a review by Tian et al., the protective action of ginseng component Panaxsaponin has been given importance. It has been found that it can help AD patients with improving cholinergic functions, reducing $A\beta$ deposition and activating repair of damaged neural networks. According to results from the study Chen et al. in 2006, the group which was given high-dose of ginseng showed statistically significant improvement on the Alzheimer Disease Assessment Scale (ADAS) and Clinical Dementia Rating, however, no significant change in the Mini-Mental State Examination (MMSE) at the end of the study, when compared with the control group. This study was poorly designed, with an insufficient description of randomization and without blinding. Furthermore, the sample size was small and hence conclusive remarks could not be drawn from this as well [2,11].

In 2011, Wang et al., studied the anti-neuroinflammatory function of ginseng component which is ginsenoside Rb1. They produced a rat model of AD through ventricle injection of $A\beta1-42$. They found that Rb1 treatment reversed the damage to learning and memory behavior of model rats. Rb1 also reversed the changes in neuroinflammatory markers (COX2, NF-kB etc.) found in hippocampus suggesting their role in anti-aging lead candidates as well [3].

The above-mentioned works were some of the earlier known trials towards establishing ginseng as a potential treatment option for AD pathology. Based on that, many studies were later undertaken and in this short communication, we also include some very recent studies on AD in light of ginseng action.

Kim et al. 2018, in their study found a new ginseng component called Gintonin, which contains lysophospatidic acid, to be very useful in AD related neuropathy attenuation. They decrease $A\beta$ formation either by inhibiting β- and γ-secretase or by activation of the nonamyloidogenic pathway. They also reduce $A\beta$ plaque induced reactive oxygen species and hence help in minimizing neuroinfammatory and neurotoxic outcomes [12].

The enzymes acetylcholinesterase (AChE) and butyrylcholines-terase (BChE) decrease Acetylcholine(Ach) concentration and are found to be one of the prominent causes of AD. In case of AD, the Ach levels are very low and it is attributed to the elevated levels of AchE and BChE enzymes. In a study by Razgonovoa et al., 2019, it has been found that some of the ginsenosides like Rb1, Rb2, Rc, Re, Rg1 and Rg3 pose major inhibitory effect on AChE and BChE. With the most optimal effect being shown by ginsenoside Re. In this way, they help to restore normal Ach levels which greatly helps in restoring cognitive functions in AD patients. The studies were done using molecular docking and in-vitro evaluation [13].

Kil et al., studied the learning and memory enhancing capability of ginseng in an $A\beta$ induced Alzheimer's mouse model. They used double processed ginseng berry extract (PGBC) and found that it has high content of ginsenosides Re, Rd and Rg3, which were instrumental in clearing the $A\beta$ plaques. It also showed reduced level of Acetylcholine esterase enzyme and high acetyltransferase enzyme suggesting its cognitive protection in AD pathology. All the above-mentioned data suggested a positive role of ginseng in improving cognitive function in the AD mouse model [14].

Conclusion

Ginseng has shown many promising avenues towards improving AD pathology, however, conclusive data and properly designed studies are still lacking. The components of ginseng showed very promising results in some studies which are very encouraging. The side effects found were also very low as compared to traditional drugs. Hence, ginseng holds the potential to act as an adjuvant treatment modality in AD pathology. Hence, properly designed investigations in future are highly warranted to establish the clinical significance and utility of ginseng in AD pathology.

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References

1. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004 Aug;430(7000):631.

2. Tian J, Shi J, Zhang X, Wang Y. Herbal therapy: a new pathway for the treatment of Alzheimer's disease. Alzheimer's research & therapy. 2010 Oct;2(5):30.

3. Wang Y, Liu J, Zhang Z, Bi P, Qi Z, Zhang C. Anti-neuroinflammation effect of ginsenoside Rbl in a rat model of Alzheimer disease. Neuroscience letters. 2011 Jan 3;487(1):70-2.

4. Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer disease & associated disorders. 2008 Jul 1;22(3):222-6.

5. Chen F, Eckman EA, Eckman CB, Chen F, Eckman EA, Eckman CB. Reductions in levels of the Alzheimer's amyloid β peptide after oral administration of ginsenosides. The FASEB Journal. 2006 Jun;20(8):1269-71.

6. Fu LM, Li JT. A systematic review of single Chinese herbs for Alzheimer's disease treatment. Evid Based Complement Alternat Med. 2009.

7. Lee MS, Yang EJ, Kim JI, Ernst E. Ginseng for cognitive function in Alzheimer's disease: a systematic review. J Alzheimers Dis. 2009, 18: 339-344.

8. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 1999; 58:1685-1693.

9. Liu ZQ, Luo XY, Liu GZ, Chen YP, Wang ZC, Sun YX. In vitro study of the relationship between the structure of ginsenoside and its antioxidative or prooxidative activity in free radical induced hemolysis of human erythrocytes. Journal of agricultural and food chemistry. 2003 Apr 23;51(9):2555-8.

10. Li N, Liu B, Dluzen DE, Jin Y. Protective effects of ginsenoside Rg2 against glutamate-induced neurotoxicity in PC12 cells. Journal of ethnopharmacology. 2007 May 22;111(3):458-63.

11. Chen F, Eckman EA, Eckman CB. Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides. Faseb J. 2006, 20: 1269-1271.

12. Kim HJ, Jung SW, Kim SY, Cho IH, Kim HC, Rhim H, Kim M, Nah SY. Panax ginseng as an adjuvant treatment for Alzheimer's disease. Journal of ginseng research. 2018 Oct 1;42(4):401-11.

13. Razgonova MP, Veselov VV, Zakharenko AM, Golokhvast KS, Nosyrev AE, Cravotto G, Tsatsakis A, Spandidos DA. Panax ginseng components and the pathogenesis of Alzheimer's disease. Molecular medicine reports. 2019 Apr 1;19(4):2975-98.

14. Jang SK, Ahn JW, Jo B, Kim HS, Kim SJ, Sung EA, Lee DI, Park HY, Jin DH, Joo SS. Double-processed ginseng berry extracts enhance learning and memory in an Aβ42-induced Alzheimer's mouse model. Korean Journal of Food Science and Technology. 2019;51(2):160-8.