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REVIEW ARTICLE

Anti-neurodegenerative activity of *Panax ginseng*, a Review

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ABSTRACT

Panax ginseng, P. quinquefolius and *P. notoginseng* including white ginseng and red ginseng prepared by air-drying and steaming or heating processes, respectively, are widely used herbal medicines which require rigorous quality control to assure their consistent bioactivities. Therefore, many analytical methodologies have been developed, primarily with a focus on high performance liquid chromatography. On the contrary, monoclonal antibodies against ginsenosides such as ginsenosides -Rb1, -Rg1, -Re, and notoginsenoside R1 were applied to newly developed techniques like the eastern blotting system, one-step separation method, and preparation of knockout extract from ginseng. Cognitive activities of major ginsenosides and their mechanisms were also widely confirmed. Clinical trials of ginseng administered to Alzheimer's patients confirmed its activity without side effects, with the result that ginseng may be a potential new medicine to treat Alzheimer's disease.

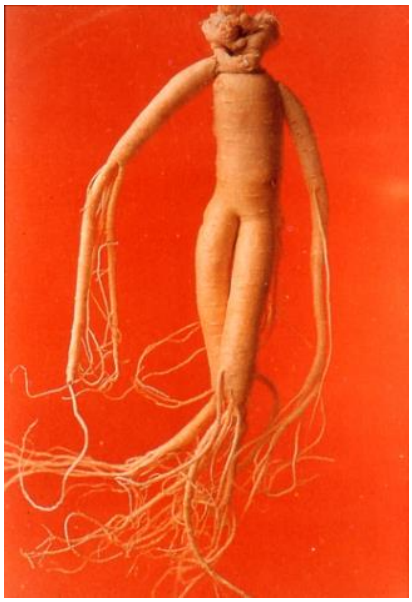
1. Introduction

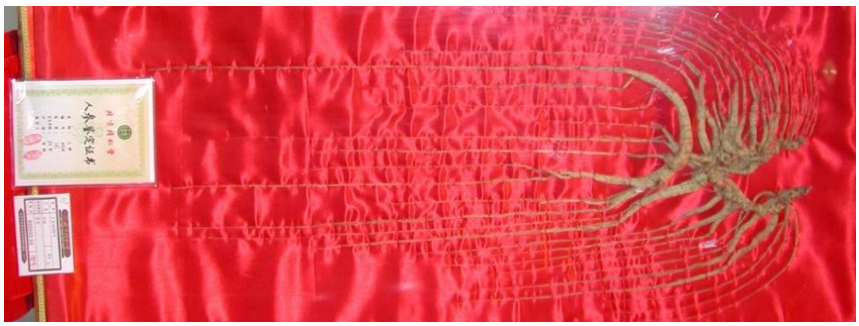
The genus *Panax* belongs to the family Araliaceae and is divided into 11 species, 9 of which are native to Asia and 2 to North America. Of these, the *P. ginseng* and the *P. quinquefolius* (American ginseng) are almost exclusively collected from their native habitats, and are considered to be endangered species. Currently, the main markets are ginseng, *P. notoginseng* (Tenshichi ginseng), and American ginseng which is produced in large quantities in the northern United States and Canada and exported to China.

The origin of *P. ginseng* C.A. Meyer (Figs. 1) has been known since the Later Han Dynasty and has been treated as an important drug in China ever since. It is thought to have been written between 100 and 200 A.D. The 365 herbal medicines listed in the Shen Nung Hon Zo Jing, are classified into three categories: refined (120 items), intermediate (120 items), and inferior (125 items). Ginseng has many spiritual benefits, such as supplementing the five organs, calming the spirit, stopping palpitations, opening the mind, benefiting the wisdom, removing evil spirits, and clarifying the eyes which are seemed to be closely related to cognitive function.

Fig.1. Roots of *Panax ginseng*

Left: Ordinal 5 years old fresh root, Right: 90 years old root filmed at Beijing Tong Ren Tang Pharmacy, Botom: Red ginseng produced in Korea





P. ginseng is used as an important medicine in China, Korea, Japan and other Asian countries, and many are listed in pharmacopoeias. *P. ginseng* is formulated in traditional Chines medicine (TCM) and Kampo medicine or used in combination with chemical medicines. In Japan ginseng and its processing products such as red ginseng is covered by national health insurance. Europe, especially in Germany where phytotherapy is popular, *P. ginseng* is treated as a medicinal product but is not covered by health insurance. *P. ginseng* is also often used as a food to maintain and promote health in the world. In USA ginseng is used as a botanical without health insurance.

P. notoginseng (Burk.) F.H. Chen (Fig. 2), is a plant endemic to Yunnan Province, China, and was discovered in the 16th century. The root morphology is different from other *Panax* species. The medicinal properties of *P. notoginseng* are different from those of ginseng. It is said to stop blooding, improve blood flow, and relieve internal bleeding due to contusions.

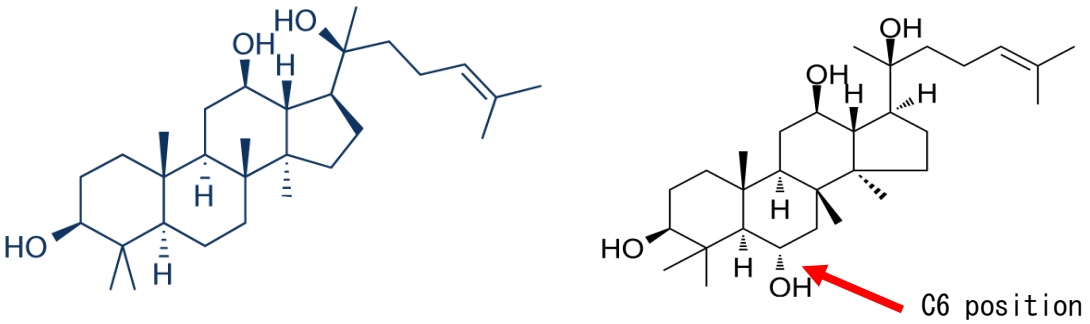
Fig.2. Root of *Panax notoginseng*

On the other hand, the information of the American ginseng, *P. quinquefolius* Linne received in 1711 to Canada when a French missionary sent details of its biology and the environment of its native habitat of ginseng (*P. ginseng*) in Chaina, and discovered it in 1716. This indicates that American ginseng is resembled to ginseng in both arial and root parts. In the early 1800s, mass collection of native species led to the endangerment of the species. The cultivation of the plant (Fig.3) has gradually progressed, and today, about 1,000 tons of dried roots are produced annually in the United States and Canada, and is exported to China.

Fig.3. Cultivation of *Panax quinquefolius* in Canada

P. ginseng contains flavonoids, lignans, polyacetylene compounds, sterols, essential oil components, fatty acids, polysaccharides, alkaloids and vitamins. It also contains ginsenosides, which are unique to plants of the genus *Panax*. Ginsenosides were isolated from the *P. qinquefolius* in 1854 and named panaxylon[1] Subsequently, Shibata et al. started these structure elucidation[2-4]. The characteristic feature of this compound is that it has a dammarane skeleton in a molecule. The ginsenosides are divided into two types such as protopanaxadiol type with no hydroxyl group attached at the C6 resulting that ginsenosides Rb1, Rb2, Rc and Rd are the major ginsenosides of this series. On the other hand the protopanaxatriol type ginsenosides such as ginsenosides Rg1, Re, Rf and Rh1 have a hydroxy group at the C6 position as indicated in Fig.4.

Fig.4. Structures of protopanaxadiol (a) and protopanaxatriol (b)



With the rapid development of analytical instruments, 257 dammarane saponins, 14 octylol saponins and 18 oleanane saponins have been isolated and structurally elucidated[5]. In addition, the ginseng root is air-dried or steaming and processing red ginseng, respectively. As mentioned above, plants of the genus *Panax* contain a wide variety of components. Therefore, this paper introduces an analytical method using a monoclonal antibody (MAb). Among the various pharmacological activities of ginsenosides. *P.*

ginseng and ginsenosides are effective against dementia. The number of dementia patients in Japan continues to increase, with projections predicting an increase to 8.3 million by 2030 and 10 million by 2050. Such a rapid increase in the number of dementia patients is expected in many countries around the world. The number of patients requiring nursing care is the second highest after stroke at nearly 15.8 % in Japan[6]. Given this situation, ginseng is considered to be a useful herbal medicine, especially for the elderly. The contribution of *P. ginseng* to such a highly needed area in the medical field will also be discussed. When discussing the pharmacological activity of *P. ginseng*, especially its neurogenerative activity, a simple and easy analytical methodology is essential, since many ginsenosides have been isolated. For this reason, the following new analytical methods and methods that can easily isolate a single ginsenoside and methods to remove specific ginsenosides were also discussed.

2. MAb as analytical tool against ginsenosides

There was almost nothing of MAb against natural product except medicine such as morphine in 1980s. One of the reasons for this is that natural products having small molecular weight cannot be immunized directly, therefore it is necessary to prepare a conjugate with a carrier protein and administer it to mice for immunization. Since there was no method to accurately detect the number of natural products conjugates bound to the protein, the antibody titer could not be reliably raised, and few cases of successful MAb production were considered to have occurred. For this reason, matrix-assisted laser desorption ionization mass spectrometry was introduced to accurately analyze the number of bound natural products in carrier protein-natural product conjugates[7-9]. This enabled us to accurately detect the number of haptens, which greatly increased the speed of MAb preparation and led to the preparation of MAbs for more than 40 natural products[10].

Two hundred fifty seven dammarane saponins have been isolated and structure elucidated from ginseng as previously described[5]. Among them anti-ginsenosides Rb1[11], Rg1[12], Re[13], Rg3[14] and notoginsenoside R1[15] MAbs were prepared. Newly developed methods using these MAbs will be introduced following.

2-1. Eastern blotting as visual method for natural products

Although the analytical method by ELISA has been established as usual with each MAb, we have developed a visualized analytical method and succeeded in developing a method named eastern blotting as the next method after Northern, Southern, and Western blotting[16]. First, the main saponins of ginseng, ginsenoside Rb1 and ginsenoside Rg1 (Fig.5), are introduced.

When ginsenosides are spotted on thin-layer-chromatography (TLC) and developed with an appropriate solvent system, the ginsenosides are separated. By covering the TLC plate with a PVDF membrane and heating it for several tens of seconds, all components on the TLC are transferred to the membrane. In this state, the components on the membrane are dissolved by the washing solution, therefor a sodium periodide solution is added to the membrane to open the sugar moiety of the ginsenosides to form aldehyde groups in a molecule. At this point, the addition of the protein solution binds to the aldehyde groups to form a Schiff base on the membrane resulting adsorption capacity

on the PVDF membrane. The subsequent coloration with MAb follows Western blotting. Fig.6 shows eastern blotting by anti-ginsenoside Rb1 and Rg1 MAbs.

Fig.5. Structures of ginsenoside Rb1 (left) and Rg1 (right)

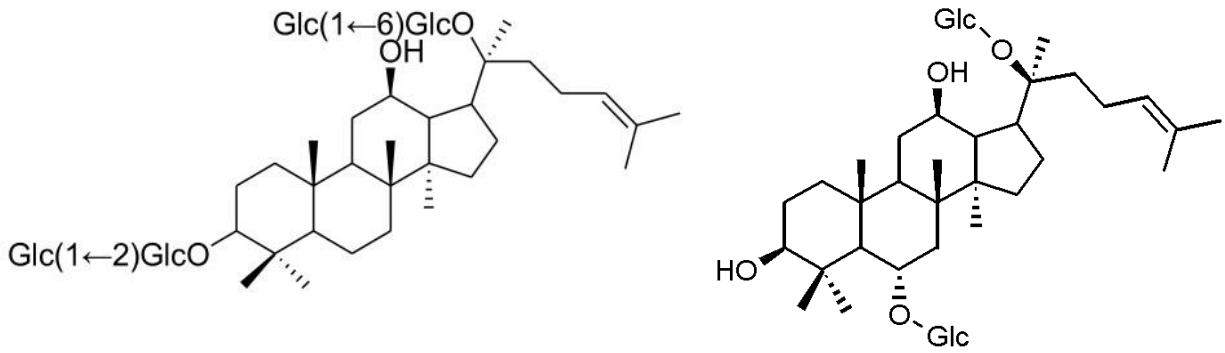


Figure 6. Eastern and double eastern blotting of ginsenosides.
1: sulfuric acid staining, 2: eastern blotting with anti-ginsenoside Rb1 MAb, 3: eastern blotting with anti-ginsenoside Rg1 MAb, 4: double eastern blotting with both antibodies.
G: ginsenoside Sample left to right: white ginseng, red ginseng, fibrous ginseng (*P. ginseng*), *P. notoginseng, P. quinquefolium* and *P. japonicus.*

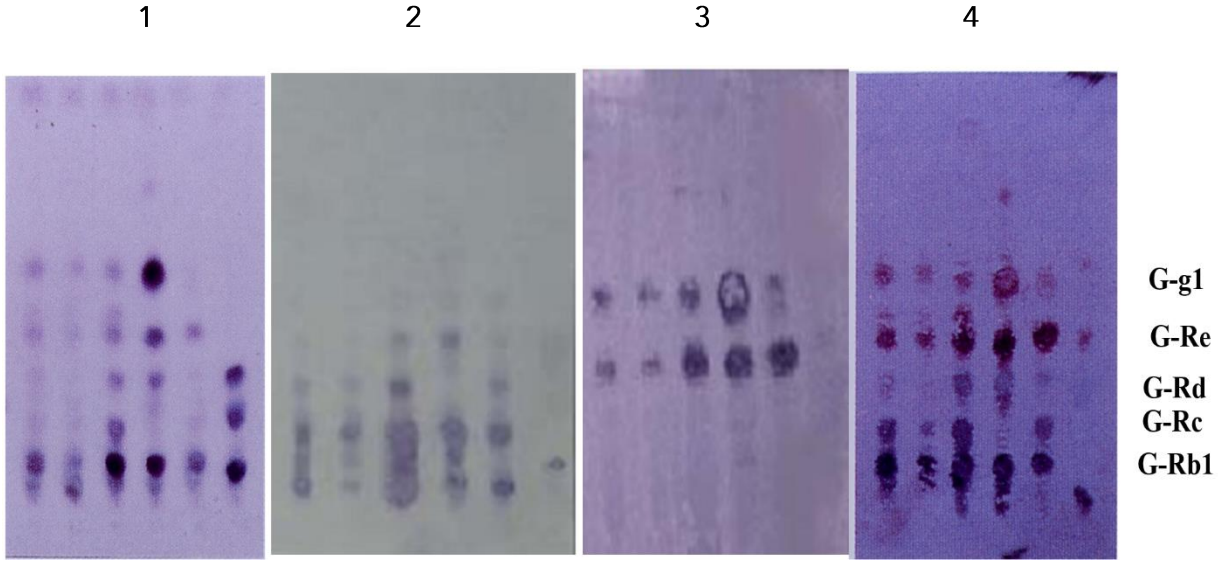


Fig.6-1 shows TLC profile stained by sulfuric acid. All compounds are detected and it is not possible to identify ginsenosides. Fig.6-2 is stained with anti-ginsenoside Rb1 MAb indicating protopanaxadiol type ginsenosides such as ginsenoside Rb1. The question will arise as to why various components are detected by MAb. The reason for this phenomena is that the specific affinity of MAb is reduced by ring-opening of the sugar moiety with sodium periodide on the membrane, resulting in the detection of ginsenosides having the same

aglycon part (protopanaxadiol). F-g.6-3 shows the staining profile by anti-ginsenoside Rg1 MAb. In this case protopanaxatriol type ginsenosides such as ginsenoside Rg1 and the other related ginsenosides can be stained by anti-ginsenoside Rg1 MAb. Fig.6-4 is doble eastern blotting using anti-ginsenoside Rb1 and Rg1 which resemble to the addition of 2 and 3 profiles. Furthermore, ginsenoside Rg1 and Re show reddish spots and ginsenoside Rd, Rc and Rb1 are blush spots, respectively. It is therefore possible to recognize either protopanaxadiol or protopanaxatriol ginsenosides by their staining color. Protopanaxadiol type ginsenosides are known to have strong anti-cancer activity[17] and protopanaxatriol-based ginsenosides have strong anti-recognition activity[18]. On the other hand, with regard to the Rf value, it can be seen that the Rf value is inversely proportional to the number of sugars bound. When comparing ginsenosides of the same aglycone, it is known that the greater the number of sugar linkages, the stronger the physiological effect[19-23]. From the above, the creation of MAbs for the two ginsenosides has provided a lot of information.

2-2. One step isolation of ginsenoside using MAb and preparation of knockout extract

Isolation of specific ginsenosides from ginseng which contain a wide variety of ginsenosides, is very labor intensive. We have therefore developed a one-step isolation method using MAb-based affinity columns. Anti-ginsenoside Rb1MAb is adsorbed on Affigel to prepare affinity column. After complete washing with a washing solvent the column was eluted by the elution solvent containing methanol to isolate ginsenoside Rb1. The affinity of this method is that the column can be used more than a dozen times repeatedly, so in vitro pure and sufficient ginsenoside Rb1 is obtained for the experiment. On the other hand, the washing fraction contains all compounds except ginsenoside Rb1[24]. The washing solution was named knockout extract because it resembles the knockout of ginsenoside Rb1 in ginseng extract. Although research has not yet been conducted, it is anticipated that comparing this washed fraction extract with the original ginseng extract will clarify the role of ginsenoside Rb1 in ginseng. A similar study on the role of glycyrrhizin in licorice extract could also be conducted and proved[25,26].

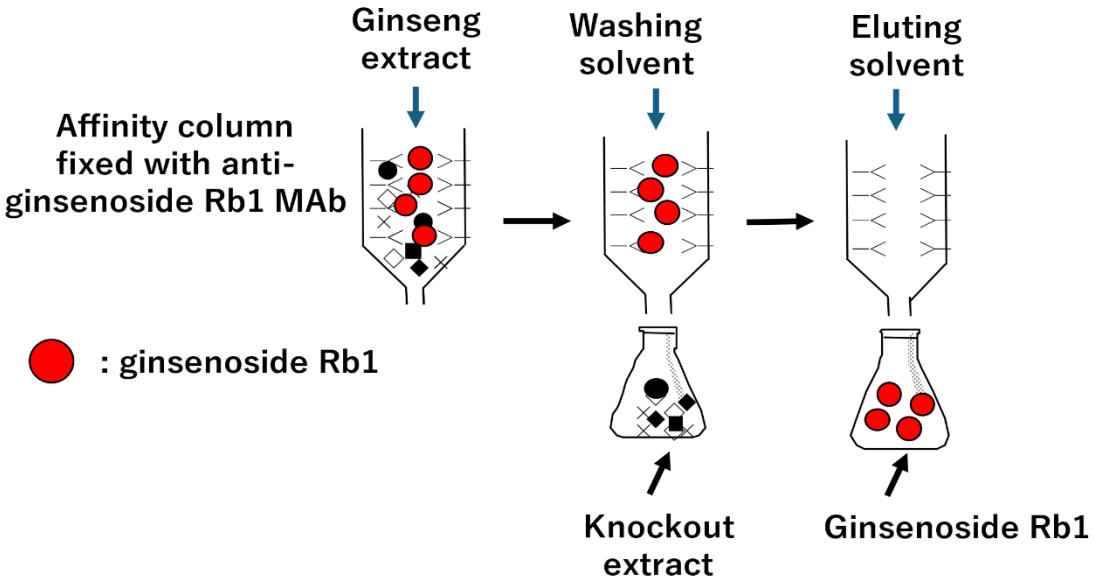
3. Pharmacological activities of ginsenosides

The Chinese have a wide range of ginseng's known seven-effect theory, including the following.

1. Supplementing vitality and promoting physical strength in acute and chronic illnesses.
2. It improves abnormalities in the metabolism of the whole body and facilitates haematopoiesis and blood circulation.
3. It has a tranquilising effect and relieves various types of stress.
4. To cure diabetes by improving the functions of the whole body and supplying sufficient body fluid.
5. Effective in stopping asthma and coughs, and in respiratory diseases.
6. Stopping diarrhoea, strengthening the digestive tract and improving digestive functions.
7. It improves resistance to illnesses caused by poor metabolic functions, normalises

skin functions and is effective against tumours. Among them 3 might be able to relate to anti-dementia activity which will be document. Also safety is the most necessary requirement when applied to human being. *P. ginseng* has been used clinically in China for thousands of years and is probably the safest herb medicine.

Fig 7. Scheme on one-step isolation of ginsenoside Rb1 and preparation of knockout extract from ginseng extract



3-1. Anti-cognitive active ginsenoside

Ginseng, as mentioned above, is placed in the refined class of the Shen Nung Hon Ching. It can be said to be a herbal medicine that has effects on the mind and improves cognitive functions, such as calming the mind, stopping heart palpitations, opening the mind and improving wisdom. The following in vitro experimental systems and studies using laboratory animals and clinical studies are presented in this order.

3-1-1 in vitro study

Using PC-12 cells the addition of ginsenoside Rb1 and Rg1 to the medium showed that neurite outgrowth was observed. SN-K-SH cells were used to investigate the effects of ginsenoside Rb1 and Rg1. The results showed that neuronal cell death by dopaminergic neuronal degeneration-depleting neurotoxin (MPTP) and β-amyloid peptides were slightly inhibited by ginsenoside Rb1. This is why ginsenoside Rb1 and Rg1 as a neuronal trophic factor and ginsenoside Rb1 has a protective effect on brain neurons[27]. Lee et al. used rat hippocampal slices to measure the effect of β-amyloid peptide as an indicator of the inhibitory effect of the addition of acetylcholine release. The results of this study showed that ginsenoside Rb1 inhibits the inhibitory effect of β-amyloid peptides on memory learning and averts memory loss[28].

3-1-2 In vivo study

Ethanol, acetoaldehyde, scopolamine, etc. are used to create models of memory impairment.

Yamaguchi et al. investigated the cognitive function of ginsenosides in old and brain-damaged rats with memory impairment induced by scopolamine administration. The ginsenoside Re, Rg1 of the protopanaxatriol family had a memory- and learning-promoting effect whereas the protopanaxadiol ginsenosides did not[18]. Itoh et al. used mice as an experimental system and found that ginsenosides induced cortical dopamine and norepinephrine resulting that ginseng contributes to cognitive processing and the integration of sensory-motor functions[29]. In mouse models of cerebrovascular dementia, apoptotic inhibitory factors, e.g. BCL-2 and HSP-70, are reduced, whereas the facilitating factors BAX and p53 are increased. On the other hand, ginsenoside Rg2 (2.5, 5 and 10 mg/kg) increased BCL-2 and HSP-70, while the facilitators BAX and P53 increased. These results suggest that ginsenoside Rg2 improves neural activity and memory by a mechanism involving anti-apoptotic memory[30].

In China, injections of *P. notoginseng* extract are often used to recover from neurological disorders. However, the mechanism is unclear. Rats underwent middle cerebral artery occlusion and brain function and the expression of Nago-A and other related factors (inhibition of neuron axon outgrowth) at 7, 14 and 28 days post-operation were observed. The results showed that controls showed an increase in brain function at 7 days, but not at 14 and 28 days after surgery. On the other hand, the above factors were reduced in the group treated with *P. notoginseng* saponin. The results show that *P. notoginseng* saponin is a potent inhibitor of the Nogo-A protein and improves cerebral infarction[31]. Since cerebral infarction is the main cause of vascular dementia, it became evident that *P. notoginseng* saponin has indirect anti cognitive activity. The effect of notoginsenoside R1 (a component unique to *P. notoginseng* ginseng) on Alzheimer's disease was investigated in a mouse model. Following oral administration of 5 mg or 50 mg/kg/day of notoginsenoside R1 for 3 months, the kinetics, cerebral neuropathology and amyloid protein were surveyed. As a result the cognitive function was enhanced, and acetylcholinesterase, amyloid protein accumulation and insulin degrading enzymes were inhibited[32]. Rats were subjected to cerebral infarction and notogincenoside R1 was orally preadministration and apoptosis at the infarct site was surveyed. The results showed that notoginsenoside R1 inhibited apoptosis and prevented cerebral infarction[33]. The authors have also prepared a MAb against notoginsenoside R1[15] and plan to conduct further research on cerebral infarction prevention and etc.

3-1-3 Clinical trial

A 12-week double-blind clinical trial (58 patients in the ginseng powder 4.5 g/day group and 39 patients in the no-treatment placebo group) was conducted in 97 Alzheimer's patients. The assessment was based on a mini-mental state examination (MMSE), an Alzheimer's disease assessment (ADA), and an Alzheimer's disease examination (MMSE) and Alzheimer disease assessment scale (ADAS). The ginseng powder group showed improvement in the above assessment, and when ginseng administration was discontinued, the improvement was the same as in the control group. Based on the above, a daily dose of 4.5 g of ginseng powder is clinically applicable to cognitive function in Alzheimer's disease[34]. Forty patients with Alzheimer's disease were administered a daily dose of 1.5 g, 3 g, 4.5 g and 0 g of red ginseng.

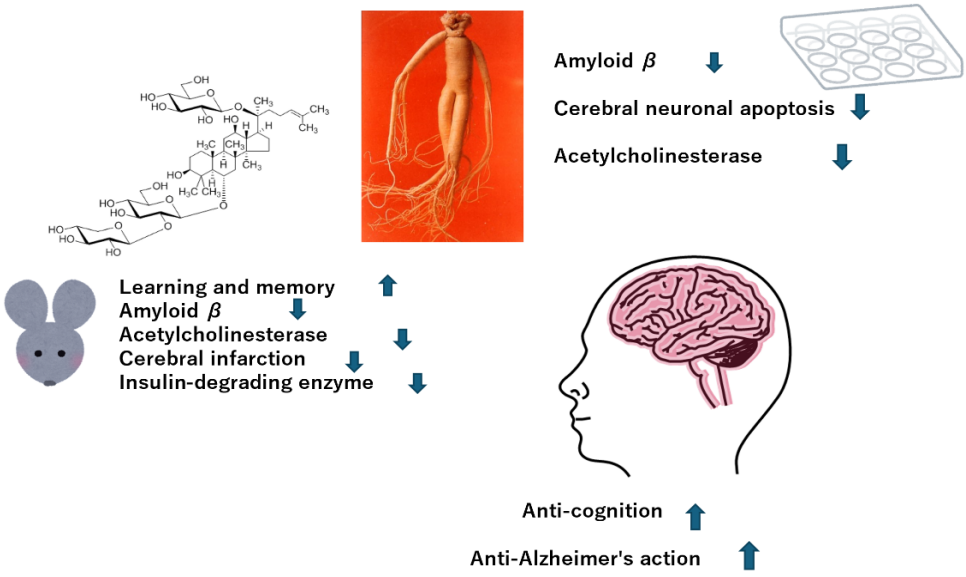
They were randomly divided into four groups and judged by MMSE, ADAS. The 4.5 g dose group showed improvement in ADAS cognitive function and MMSE scores after 12 weeks. The improvement continued with consecutive doses for a further 12 weeks[35]. Recently, Huang et al. confirmed that ginsenoside Rc has affinity with SIRT1 protein in docking experiments[36]. They have carried out experiments using cardiomyocytes and neurons. They have demonstrated that ginsenoside Rc is an activator of the SIRT1 protein, which is responsible for mitochondrial damage resulting in protection of neuronal energy metabolism. Among SIRT1 protein has been linked to dementia[37,38]. The report that ginsenoside Rc activates brain function by a new mechanism may lead to the development of a new type of anti-dementia drug, and further research is expected in the future. Based on these results, the author provides a comprehensive explanation of the effect of ginsenosides on SIRTprotein and their anti-dementia activity[39].

As previously indicated that Yang et al. investigated ginsenosides in various ginseng species (plants of the genus Panax) and reported that 257 ginsenosides were contained[5]. Therefore, when ginseng is used for the clinical trial, we should select *Panax* species containing higher amount of ginsenoside. For example *P. notoginseng* must be selected if the medicinal effect of notoginsenoside R1 is to be expected.

4. Conclusion

The number of people with dementia is expected to increase to 7 million by 2025 and 10 million by 2050 in Japan[40]. A survey of the healthcare costs of care in Japan revealed that the cost of care for dementia is the second highest after stroke, at 15.8%. The number of people in need of care is expected to increase rapidly by 2025[6]. Dementia can take many years to develop. It is hoped that measures will be taken as soon as possible, as dementia can take many years to develop. Since ginseng has been shown to be beneficial both mentally and physically, ginseng is recommended as a preventive measure, as it has been shown to improve cognitive function as indicated in Fig.9.

Fig.9 Anti-dementia activities of ginseng



On the other hand, the side effects of ginseng include insomnia, menstrual problems, breast pain, increased heart rate, high/low blood pressure, headache, etc[41]. Therefore, it is advisable to take the right amount of ginseng according to the advice of a doctor or pharmacist.

Conflict of Interest Statement:

None

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