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Review Article

Attractiveness of Ginseng, Quality Control and Pharmacological Activity, a Review

Shiho Kito[1] and Yukihiro Shoyama[2]*

[1]*Association for Health Economics Research and Social Insurance and Welfare, Tokyo, Japan*

[2]*Faculty of Pharmacy, Nagasaki International University, Sasebo, Nagasaki, Japan*

Abstract

Panax ginseng, P. quinquefolius and P. notoginseng including white ginseng and red ginseng prepared by air-drying and steaming or heating process, respectively are widely used herbal medicines, and their quality control are necessary for their constant activities. Monoclonal antibodies (MAbs) against ginsenosides such as ginsenosides-Rb1, -Rg1, -Re and notoginsenoside R1 were applied to open newly developed techniques like eastern blotting system and one step separation method of ginsenoside. The anticancer activities of red ginseng are significantly increased due to the production of active anticancer ginsenosides during the steaming processing compared to white ginseng resulting in the induction of apoptosis and inhibition of angiogenesis. Future studies should focus on characterizing active red ginseng derivatives as potential anticancer drugs. Cognitive activities of major ginsenosides and their mechanisms were widely confirmed. Clinical trials of ginseng for Alzheimer's patients were performed to be confirmed its activity without side effects resulted that ginseng might be deserved as a new medicine for Alzheimer disease.

Keywords: Anti-cancer activity; Anti-dementia activity; *Araliaceae*; Ginsenoside; *Panax species*

Introduction

Plants of the genus *Panax* belonging to the family *Araliaceae* and are classified into 11 species, nine of which are native to Asia and two to North America. Of these, *Panax ginseng C.A. Meyer and P. quinquefolius Linne* have been almost exclusively collected from native plants and are considered to be very endangered species. Currently, the main markets are for three species: *P. ginseng, P. quinquefolius*, of which American ginseng is produced in large quantities in the northern USA and Canada, and exported to China and *P. notoginseng (Burk.) F.H.Chen* which is cultivated in southern part of Chine.

The origin of *P. ginseng* has been known since the Later Han period and has been treated as an important drug in China ever since. The 365 herbal medicines listed in the New Farming and Herbal Medicine Sutra, which is thought to have been written between 100 and 200AD, are classified into three categories: refined (120 items), intermediate (120 items) and inferior (125 items), and ginseng is classified as refined, Ginseng has many mental benefits, such as aiding the five organs, calming the mind, stopping heart palpitations, opening the mind and benefiting the mind, eliminating evil spirits and clarifying the eyes, and is also a herbal medicine closely related to cognitive functions. It was first introduced to Japan from China in the Nara period (710-794), during the reign of Emperor Shomu, and is included in the 60 Shosoin medicinal herbs.

Tanshichi ginseng, *P. notoginseng* is a plant endemic to Yunnan Province, China, and was first discovered in the 16th century. The form of the root is different from that of other Panax plants, and the medicinal properties described in the Honzo Tome differ from those of ginseng: it stops bleeding, disperses blood and relieves pain. The discovery of the American ginseng, *P. quinquefolius*, is the most recent, dating from 1711, when a French missionary sent details of the ecology of the ginseng and its native habitat in China to a Canadian missionary, leading to the discovery of the American ginseng in 1716, which was named by Linne in 1735. In the early 1800s, American ginseng was endangered due to mass collection of native species, but it was gradually cultivated and today approximately 1,000 tones of dried roots are produced annually in the USA, Canada and northern China, and exported to China. American ginseng has long been traded in the Guangdong market in China and are therefore also known as Cantonese ginseng or Western ginseng.

The above introduction focuses on the historical background of plants of the genus *Panax*. Ginseng contains flavonoids, lignans, polyacetylenic compounds, sterols, essential oil components, fatty acids, polysaccharides, alkaloids, vitamins and ginsenosides unique to *Panax* spp. Ginsenosides were isolated from the American ginseng in 1854 and named panaxylon [1]. Subsequently, Shibata et al. started structural analysis [2-4]. Biosynthetic pathway is a triterpenoid via squalene and is characterised by its dammaran skeleton. The ginsenosides with no hydroxyl group at the C6 position are referred to as the protopanaxadiol type and those with a hydroxyl group at the C6 position as the protopanaxatriol group. Ginsenoside Rb1 and ginsenoside Rg1 are shown as the main ginsenosides of each group. The protopanaxatriols and protopanaxadiols are structurally different and many of them show different pharmacological activities. In recent years, with the rapid development of analytical instruments, 257 dammarane saponins, 14 octylol saponins and 18 oleanane saponins have been

***Corresponding author:** Yukihiro Shoyama, Faculty of Pharmacy, Nagasaki International University, Sasebo, Nagasaki, Japan, E-mail: shoyama@niu.ac.jp

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isolated and their structures determined [5]. As will be discussed later, heat processing produces secondary ginsenosides by changing genuine ginsenosides to secondary ginsenosides. When these ginsenosides are added, a very large number of ginsenosides are present.

As part of their research on crude drugs, Kitagawa et al. conducted a detailed comparison of the constituents of ginseng. As a result, it was found that the malonyl group of the malonyl ginsenosides found in white ginseng was released. It was also found that 20(R)-ginsenoside Rg2, 20(S)-ginsenoside Rg3, ginsenoside Rg3, ginsenoside Rh1, 20(R)-ginsenoside Rh1 and ginsenoside Rh2 were newly formed by coordination transformation and sugar elimination at 20 positions [6] (Figures 1 & 2).

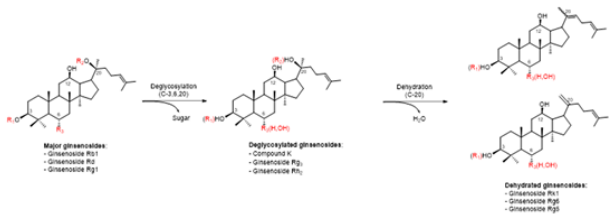

Figure 1: Transformation of ginsenosides in red ginseng.

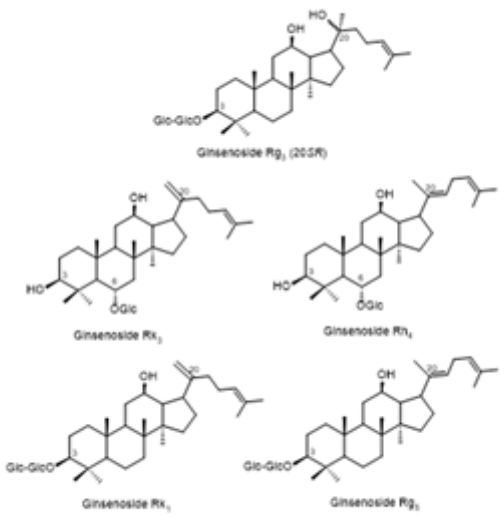

Figure 2: Artificial ginsenosides in red ginseng.

As mentioned above, *Panax* spp. contain a wide variety of constituents and a simple and rapid analytical methodology is desired, so this paper introduces an analytical method using Monoclonal Antibodies (MAb). Among the various pharmacological activities of ginsenosides, this paper introduces research on their activity against cancer, which is still a serious disease, and on ginseng and ginsenosides, which are effective against dementia, a rapidly growing disease with a care requirement rate of just under 16%, second only to stroke, and a situation that has become so severe that it is causing a squeeze on medical costs [7].

Quality control by MAbs against ginsenosides

As indicated above nearly 300 structurally resembled saponins are contained in *Panax* species. Therefore, simple and quick analytical methodology is required. The authors succeeded to prepare 4 MAbs against ginsenosides such as ginsenoside Rb1 [8], ginsenoside Rg1 [9], ginsenoside Rc [10] and notoginsenoside R1 [11]. As ginsenosides are one of the main medicinal constituents of ginsengs, the development of analytical methods related to the quality control of ginsenosides using MAbs for the above-mentioned ginsenosides is presented.

Ginsenoside Rg1 and ginsenoside Rb1 (Figure 3) are the main components of ginseng which structurally have four and three OH groups respectively, and are called protopanaxatriol type and protopanaxadiol type, **re**spectively (Figure 3).

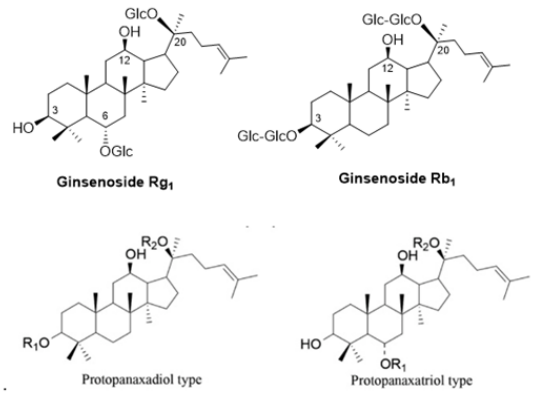

Figure 3: Ginsenoside Rg1 and Rb1 and pare of protopanaxidiol and protopanaxatriol type.

It often has different medicinal properties, and a wide range of quality variations have been observed. For this reason, an analytical method using anti-ginsenoside Rb1 and anti-ginsenoside Rg1 MAbs, double eastern blotting method [12,13], was developed as indicated in figure 4.

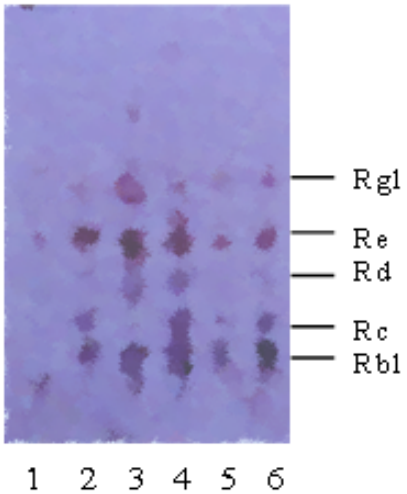

Figure 4: Double staining of ginsenosides using anti-ginsenoside Rb1 and Rg1 monoclonal antibodies.

R indicates ginsenoside. 1: P. japonicus, 2: P. quinquefolius, 3: P. notoginseng, 4: hairly root of P. ginseng, 5: red ginseng, 6: P. ginseng . In this staining, the reddish color is P.ginsenoeide and the blue-color components are protopanaxadiol ginsenosides. Furthermore, the Rf value indicates the number of sugars bound, e.g. Rg1 has two sugars and Rb1 has four (Figure 4). The higher the number of sugars, the smaller the Rf value and the lower the number of sugars, the larger the Rf value.

The ginsenosides of the various ginseng species are found to vary widely in composition. This means that it is easy to predict that there will be no small amount of variation in the various ginseng species, so quality control is important when conducting pharmacological studies. Another advantage of MAb is that the MAb-mounted affinity column allows one-step isolation of antigenic ginsenosides, and a single purification step can isolate a sufficient amount of ginsenoside for in vitro experiments on the bench [14].

Pharmacological Activities of Ginseng

In China, ginseng is known to have a wide range of medicinal effects, known as the Seven Effects of Ginseng, including: 1. supplementing energy and promoting physical strength when physical strength is weakened due to acute or chronic diseases; 2. improving abnormal metabolism throughout the body and facilitating blood formation and circulation; 3. having a tranquilising effect and relieving various stresses; 4. improving general body functions and curing diabetes by providing sufficient body fluid; 5. It is effective in curing diabetes by improving the functions of the whole body and providing a sufficient supply of body fluid; 5. It is effective in stopping asthma and coughs and in diseases of the respiratory system; 6. It stops diarrhoea, strengthens the digestive tract and improves digestive functions; 7. It improves resistance to diseases caused by poor metabolic functions, normalises skin functions and is effective in treating cancer, The following are the most common reasons for the use of this herb. Of these, 3. and 7. may be relevant to this article.

Anti-tumor activity of ginseng and ginsenoside

As part of their research on crude drugs, Kitagawa et al. conducted a detailed comparison of the constituents of ginseng. As a result, it was found that the malonyl group of the malonyl ginsenosides found in white ginseng was released. It was also found that 20(R)-ginsenoside Rg2, 20(S)-ginsenoside Rg3, ginsenoside Rg3, ginsenoside Rh1, 20(R)-ginsenoside Rh1 and ginsenoside Rh2 were newly formed by coordination transformation and sugar elimination at 20 positions [15].

The anti-tumour activity of ginseng extract has been widely tested in various human organ cells [16-20]. Ren et al., [21] and Yun et al., [22] have shown that the components of red ginseng differ from those of white ginseng and have high anti-tumour activity. Lee et al. also confirmed that red ginseng has high anti-tumour activity and produces ginsenosides Rg3, Rh1 and Rh2, similar to the results of Kitagawa et al. mentioned above [23]. Recently, Lin et al., [24] also reported that red ginseng activates caspases 3 and 9 and promotes cytochrome c secretion by increasing mitochondrial Bak and Bax in human cervical cell carcinoma cells, thereby inducing apoptosis of the cancer cells. From the above, it is clear that red ginseng is effective against lung, breast and colon cancer. From above data the chemical changes shown in figure 5 during the production of red ginseng give rise to the components shown in figure 5, which have strong anti-cancer activity.

Next, ginsenoside Rg3, one of the secondary components of red ginseng, was evaluated by Shinkai et al., [25] using rat ascites cancer cells, melanoma cells, human small lung cancer cells and human pancreatic ciliated cancer cells, and found to have a strong inhibitory effect, while the other ginsenoside 20(R)-Rh2, which is unique to red ginseng, was also found to be effective. ginsenoside Rg2 and the isomer 20(S)-ginsenoside Rg3 also showed some inhibitory activity.

Based on the above results, the following animal studies with red ginseng have been conducted. Studies have been conducted on the preventive effect of red ginseng on the development of liver cancer in rats [26]. Rats were randomly divided into 15 animals each, acclimatised for 1 week and fed a diet containing 0.5 and 1% red ginseng for 10 weeks. The carcinogenic compound Dimethylnitrosamine (DEN) was administered two weeks after the start, and the number of tumours and tumour area were investigated using glutathione S-transferase placental-type molecular species (tumour marker) as an indicator, and the results showed that the 0.5 and 1% red gum ginseng-added areas were all inhibited. Lipid peroxidation reactions were also reduced in the 0.5 and 1% red ginseng-added zones, while glutathione and related enzyme levels were all increased in the 1% red ginseng-added zone. Furthermore, cDNA microarray analysis showed that Cyp2e1, Cyp2c1, Cyp3a9, Mgst1 and others were down-regulated in the 1%-added zone. These results indicate that red ginseng contributes to cancer prevention by inhibiting lipid oxidation reactions, increasing glutathione levels and activating related enzymes, and inducing inhibition of Cyp system factors on the cytochrome 450 signalling pathway.

The following is an example of the proven anti-tumour effect of red ginseng in humans. Yun [27] conducted an epidemiological study between 1987 and 1992 on 4,634 ginseng users aged 40 years or older. Questions included when they started taking ginseng, frequency of ginseng use, duration of use and type of ginseng. The ginseng group clearly had a lower specific risk than the group not taking ginseng. The ginseng-only group had a lower specific risk than the groups taking various diets, and the group of 24 taking red ginseng had no deaths from cancer. The risk was also lower the more frequently the ginseng was taken, indicating that the risk decreases in proportion to the dose taken. The specific risk of stomach cancer was 0.33 and that of lung cancer 0.30. In addition, the group taking fresh ginseng clearly had a lower incidence of stomach cancer. These results indicate that ginseng has a non-organ-specific preventive effect.

Since ginsenoside Rg3, a component of red ginseng, has been shown to have an inhibitory effect on cancer cells [25], the clinical trial is as follows. Lu et al., [28] randomly divided 133 patients with small cell lung cancer into three groups: ginsenoside Rg3 capsule group (I: 43 patients), ginsenoside Rg3 capsule plus anti-cancer drug. The results of the 2-year treatment are as follows: survival rate of patients in the ginsenoside Rg3 capsule group (I: 43 patients), the ginsenoside Rg3 capsule group (II: 46 patients) and the anti-cancer drug group (III: 44 patients) was randomly divided into three groups. Survival rates were 67.4% for I, 71.7% for II and 70.5% for III. 3-year survival rates were 46.5%, 54.3% and 47.7%, respectively. The NK cells were variable in each group, but CD4/CD8 was normal in groups I and II; group III had increased vascular endothelial growth factor and a lower 3-year survival rate, but no statistical difference was observed. The results of the study showed that the ginsenosides were not statistically different from those in group III. The results show that the ginsenoside Rg3 plus anticancer group improves the lifespan of

cancer patients with elevated vascular endothelial growth factor after surgery. They concluded that the mechanism was due to an improved immune system and control of angiogenesis. Based on these results, ginsenoside Rg3 has been on the market in China since 2008 as a drug that can be used in combination with anti-cancer drugs to reduce cancer recurrence, known as 参一胶囊 (Figure 5).

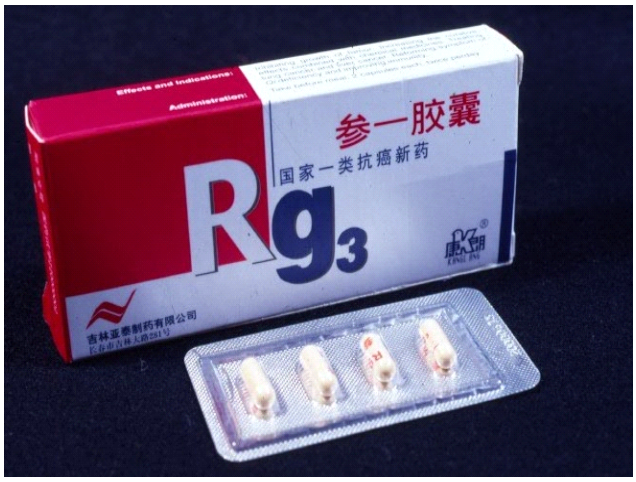

Figure 5: Anti-cancer agent from ginsenoside Rg3 in China.

Anti-cognitive activity of ginseng extract and ginsenosides

As mentioned above, ginseng is a classy herbal medicine in the Honzo Gynogenetic Index, and can be said to act on the mind and improve cognitive functions by calming the spirit, stopping palpitations, opening the mind and benefiting the wisdom. According to the Encyclopedia of Traditional Chinese Medicine, ginseng is listed under anti-cancer drugs, American ginseng as a sedative and antispasmodic and Danshichi ginseng as a haemostatic. The strong anti-tumour activity of ginseng, especially the red ginseng that has undergone a cure, has already been mentioned. This section mainly introduces ginseng and ginsenosides for improving cognitive function.

Brain function promoting effects using an in vitro experimental system: PC-12 cells (mouse-derived neuron-like cells) do not grow without Neuronal Growth Factor (NGF), but the addition of ginsenoside Rb1 and Rg1 to NGF-free medium resulted in neurite outgrowth; the effects of ginsenoside Rb1 and Rg1 were investigated using SN-K-SH cells. Ginsenoside Rb1 slightly suppressed neuronal cell death induced by dopaminergic neuronal degeneration-depleting neurotoxin (MPTP) and β-amyloid peptide [29]. Lee et al. investigated the effects of ginsenosides in rat hippocampal slices, using the inhibition of acetylcholine release by the addition of β-amyloid peptide as an indicator of the effects of ginsenosides. The results of this study showed that ginsenosides inhibit the release of acetylcholine. The results showed that ginsenoside Rb1 inhibited the inhibitory effect of β-amyloid peptide on memory learning and averted memory loss [30].

Recently, Huang et al. confirmed in docking experiments using cells that ginsenoside Rc has affinity with SIRT1 protein [31]. They have conducted experiments with cardiomyocytes and neurons and interpret ginsenoside Rc as an activator of the SIRT1 protein, which protects mitochondrial damage, thereby promoting neuronal energy metabolism and enhancing cognitive function [32,33]. While reports of SIRT1 protein being associated with dementia, the report that ginsenoside Rc activates brain function by a novel mechanism may lead to the development of a new type of dementia drug, and further research is expected in the future [34].

Studies using laboratory animals: Ethanol, acetaldehyde and scopolamine are used to create models of memory impairment, and Yamaguchi et al. investigated the cognitive function of ginsenosides in old and brain-damaged rats with memory impairment induced by scopolamine administration and found that the protopanaxatriol ginsenosides Re and Rg1 have anti-cognitive activity [35]. Itoh et al. found that ginsenosides increase dopamine and norepinephrine in the cerebral cortex in mice, indicating that ginsenoside contributes to cognitive processing and the integration of sensory-motor functions [36].

In mouse models of cerebrovascular dementia, apoptosis inhibitors, e.g., BCL-2 and HSP-70, are decreased, while the facilitators BAX and P53 are increased. On the other hand, when ginsenoside Rg2 (2.5, 5, 10 mg/kg) was administered, BCL-2 and HSP-70 increased, while BAX, P53 decreased. It was concluded that ginsenoside Rg2 improves neural activity and memory through an anti-apoptotic mechanism [37].

In China, tanshichi ginseng, *P. notoginseng* extract is often injected for the recovery of neurological disorders, but the mechanism is unknown. Rats were operated on for occlusion of the middle cerebral artery, and brain function and the expression of Nogo-A and other related factors (inhibition of neuroaxonal elongation) were observed 7, 14 and 28 days later. The results showed that in controls, the factors increased after 7 days, peaked at 21 days and remained at high levels thereafter. On the other hand, the above-mentioned factors decreased in the group treated with *P. notoginseng* saponin. This suggests that *P. notoginseng* saponin suppresses the expression of Nogo-A protein and other factors and ameliorates cerebral infarction [38]. Since cerebral infarction is the main cause of vascular dementia, this indirectly proves its anti-cognitive activity.

The effect of notoginsenoside R1 (an intrinsic component of *P. notoginseng*; Figure 6) on Alzheimer's disease was investigated in an Alzheimer's model mouse: 5 mg or 50 mg/kg/day was administered orally for 3 months and the dynamics, cerebral neuropathology and amyloid protein status were investigated. Enhanced cognitive function, increased expression of acetylcholinesterase, inhibited amyloid protein accumulation and inhibited insulin degrading enzymes. Based on these results, it was concluded that notoginsenoside R1 is effective in preventing dementia [39].

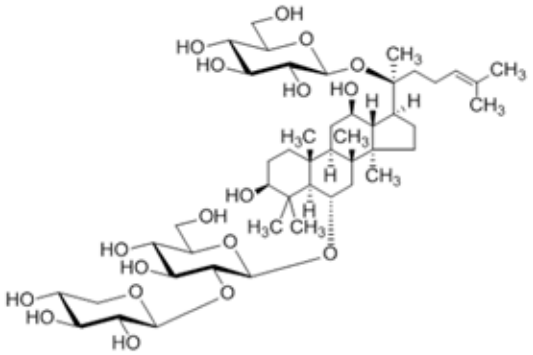

Figure 6: Structure of notoginsenoside R1.

Rats were subjected to cerebral infarction and notoginsenoside R1 was orally pre-administered and apoptosis at the infarct site was checked. The results showed that notoginsenoside R1 inhibited apoptosis and thus prevented cerebral infarction [40].

The authors have also generated a monoclonal antibody against notoginsenoside R1 [11] and plan to conduct further research on the prevention of cerebral infarction by using immunostaining technique.

Clinical trial: A 12-week double-blind clinical trial was conducted in 97 Alzheimer's patients (58 in the ginseng powder 4.5 g/day group and 39 in the no-dose placebo group), with assessment using the Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale (ADAS). The ginseng powder group showed improvement in the above assessment, which was similar to the control group when ginseng administration was discontinued. From the above, it was concluded that a daily dose of 4.5 g of ginseng powder can be clinically applied to cognitive function in Alzheimer's disease [41].

Forty patients with Alzheimer's disease were randomly divided into four groups with daily doses of 1.5 g, 3 g, 4.5 g and 0 g of red ginseng, and MMSE and ADAS were used to judge the results. 4.5 g dose group improved ADAS cognitive function and MMSE scores in 12 weeks, and the improvement effect continued after another 12 weeks of continuous administration The improvement continued after 12 weeks of continuous administration [42].

The number of people suffering from dementia continues to increase and is expected to reach 7 million by 2025 and exceed 10 million by 2050 in Japan [43] as shown in figure 7.

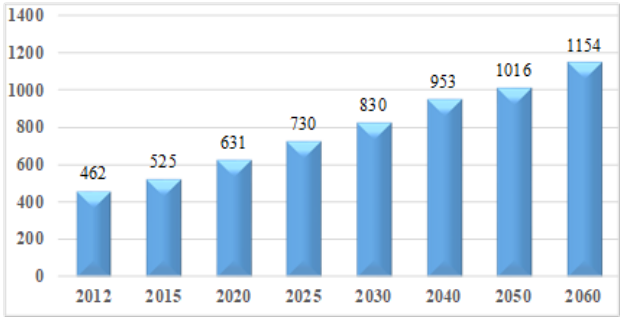

Figure 7: Increase in the dementia population in Japan.

Since dementia is second only to stroke at 15.8%, the number of people requiring care is expected to increase more rapidly than stroke by 2025 in Japan [44], leading to a sharp rise in healthcare costs. Dementia develops over many years, so it is hoped that measures will be taken as soon as possible.

Yang et al. investigated ginsenosides in various ginseng species (*Panax spp*.) and reported that 257 ginsenosides were contained [5]. Gingsenoside Rc, Rd, Rg1, Rh, etc., which are the main ginsenosides, are considered to be the best choice for clinical use. On the other hand, if the above-mentioned medicinal effects of notoginsenoside R1, etc. are expected, it would be advisable to select *P. notoginseng*, which specifically contains them. These would result in higher clinical efficacy. However, quality control is essential for clinical use, as *Panax* species are known to show qualitative and quantitative variations in ginsenosides depending on age, growing region, collection time, etc [45,46]. As already mentioned, ginsenoside Rg3, which is not found originally but only in red ginseng, has recognised anti-tumour effects and is currently used in China as an anti-cancer drug, cancer metastasis inhibitor and in combination with chemical anti-cancer drugs. In this case, ginseng extract is mass-produced by microbial (*Lactococcus lactis*) fermentation and enzymatic treatment of ginsenoside Rb1 for use as a pharmaceutical ingredient.

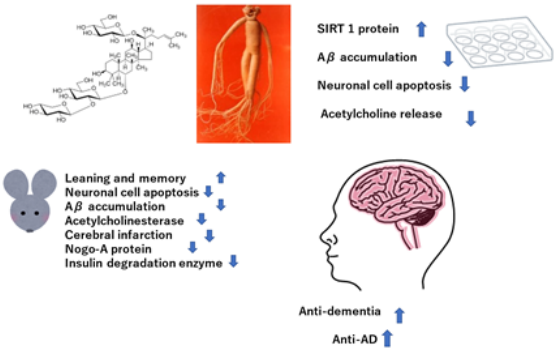

Figure 8: Anti-cognitive activities of ginseng and ginsenosides.

Conclusion

Ginseng has been shown to be beneficial both mentally and physically, and it has also been shown to improve cognitive function, as indicated in figure 8 so we recommend ginseng as a preventive measure.

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