

Panax ginseng components and the pathogenesis of Alzheimer's disease (Review)

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Abstract. Ginseng is one of the main representatives of traditional Chinese medicine and presents a wide range of pharmacological actions. Ginsenosides are the main class of active compounds found in ginseng. They demonstrate unique biological activity and medicinal value, namely anti-tumour, anti-inflammatory and antioxidant properties, as well as anti-apoptotic properties. Increasing levels of stress in life are responsible for the increased incidence of nervous

system diseases. Neurological diseases create a huge burden on the lives and health of individuals. In recent years, studies have indicated that ginsenosides play a pronounced positive role in the prevention and treatment of neurological diseases. Nevertheless, research is still at an early stage of development, and the complex mechanisms of action involved remain largely unknown. This review aimed to shed light into what is currently known about the mechanisms of action of ginsenosides in relation to Alzheimer's disease. Scientific material and theoretical bases for the treatment of nervous system diseases with purified *Panax ginseng* extracts are also discussed.

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Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; ADAM, androgen deficiency of the aging male; ADAS, Alzheimer's disease assessment scale; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ADAS-non-cog, Alzheimer's disease assessment scale-non-cognitive subscale; AKT, protein kinase B; APP, amyloid β precursor protein; A β O, amyloid β oligomer; BACE1, beta-secretase 1; Bax, Bcl-2-associated X-protein; BChE, butyrylcholinesterase; Bcl-2-protein, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CDK, cyclin-dependent kinase; CDR, clinical dementia rating; ChAT, choline acetyltransferase; COX-2, cyclooxygenase 2; CREB, cAMP response element binding protein; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; FAB, frontal assessment battery; GSH, glutathione; GSK3, glycogen synthase kinase-3; GSSG, glutathione disulphide; HSP, heat shock protein; IDE, insulin-degrading enzyme; IGF-1, insulin-like growth factor 1; IL, interleukin; IRE-1, inositol-requiring enzyme-1; LDH, lactate dehydrogenase; LPAR, lysophosphatidic acid receptor;

LPC, lysophosphatidylcholine; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMSE, Mini-Mental Status Examination; MWM, Morris water maze; NEP, neprilysin; NF- κ B, nuclear factor- κ B; NFT, neurofibrillary tangle; NO, nitric oxide; NOS, nitric oxide synthase; NOS1, nitric oxide synthase 1 (neuronal); NOS2, nitric oxide synthase 2 (inducible); OKA, okadaic acid; p-AKT, phosphorylated protein kinase B; PI(4,5)P2, phosphatidylinositol 4,5-bisphosphate; PI3K, phosphoinositide-3-kinase; PI4KII α , phosphatidylinositol 4-kinase 2 α ; PI4P, phosphatidylinositol 4-phosphate; p-JNK, phosphorylated-c-Jun N-terminal protein kinase; PKA, protein kinase A; PP-2A, protein phosphatase 2A; PPAR, peroxisome proliferator activated receptor; PS1, presenilin-1; p- τ , phosphorylated Tau protein; ROS, reactive oxygen species; sAPP α , soluble amyloid precursor protein α ; SILAC, stable isotope labeling by amino acids in cell culture; SOD, superoxide dismutase; TNF- α , tumour necrosis factor α ; TRAF2, tumour necrosis factor receptor-associated factor 2; TrkB, tropomyosin-tyrosine kinase receptor; QXG, quercetin 3-O- β -D-xylopyranosyl- β -D-galactopyranosyl

Key words: ginseng, nervous system diseases, Alzheimer's disease, ginsenosides, β -amyloid level

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1. Introduction

Alzheimer's disease (AD), which is the most common form of dementia, is a neurodegenerative disease that was first described by the German psychiatrist, Alois Alzheimer in 1907 (1). Despite great progress being made in the understanding of the pathogenesis of AD, no cure has yet been found. Three main neuropathological signs characterize AD: The loss of neurons, amyloid plaques and neurofibrillary tangles (NFTs) (2). Amyloid plaques are predominantly composed of peptides, known as β -amyloid ($A\beta$), which are the main peptides to induce neuronal damage and apoptosis in patients with AD (3). NFTs are formed from the hyperphosphorylation of Tau protein (also known as τ protein) (4,5).

2. The history of ginseng as a drug

The ancient and rich experience of folk medicine in the countries of the Far East has paved the way for many valuable scientific medicines, and ginseng occupies a special place in this important group. The first information about this medicinal plant can be traced back into the distant past and is surrounded by an aura of legend and tradition. For dozens of centuries, ginseng has been the subject of worship for the peoples of the Far East and has played a significant role in the culture, commerce and even foreign policy of China and other East Asian states.

The first to discover the healing properties of ginseng, according to legend, is Lao Tzu (6th century BC), the founder of a religious and philosophical school in China. Ginseng has been known of for at least 4,000 years. The first mentions of it are found in the most ancient writings on medicinal plants, 'Shen-nun' and 'Shen-Lun-ben-cao', which date back to the 20th century BC. Numerous recommendations for the treatment of various diseases with ginseng are available in the new edition of the 'E-lin' medicine collection, compiled in China by Shi Bao-yuan in 2-1 BC. Ginseng is also described in several ancient Chinese sources from the 3rd century onwards (6,7).

Carl von Linné was the first to provide a systematic description of the genus and named it *Panax L.* (Linné, 1742; https://books.google.ru/books?id=30Y-AAAACAAJ&dq=Genera+Plantarum&printsec=frontcover&source=bl&ots=kI_cpWWP3x&sig=DballyFFHckeYxWqW-TegJC9iHs&hl=en&ei=07odS9_iE5HKsQPzotSECg&sa=X&oi=book_result&ct=result&redir_esc=y#v=onepage&q&f=false). This title [from the Greek words 'pan' (meaning all)

and 'asos' (meaning medicine)] reflects the idea of the all-healing properties of ginseng. Russian scientists have become increasingly interested in ginseng since the 19th century. The work of Kamensky (he studied Far Eastern ginseng for the first time) was followed by that of the Russian botanist and explorer, Carl Anton von Meyer (1841-1842) which deepened the knowledge of the taxonomy of the genus *Panax* and established the boundaries of the species, which are still accepted to this day. He described 5 types of ginseng and assigned the name of *Panax Ginseng C.A.Meyer* to true ginseng, and this name still holds to the present day (8,9; and Refs therein).

Reliable information on ginseng was provided by the writings of Far Eastern Russian researchers [Arsenyev (10), Przhevalsky (11), Maak (12), Maksimovich (13) and Komarov (14)]. In 1868, Y.K. Trapp (https://ru.wikipedia.org/wiki/Трапп,_Юлий_Карлович) included ginseng in his pharmacognosy guide.

Relevant studies on the biology and culture of ginseng [Shishkin (15), Gutnikova (16,17), Vysotsky (18), Bayanova (19) and Kurentsova (20)], have been carried out in the Far East of the former USSR since 1930. Several pharmacological [Zakutinsky (21), Burkat and Saksonov (22) and Kiselev (23)] and clinical works [Shapiro (24), Kuzminskaya (25) and Buturlin (26)] have been published since then. The Far Eastern academician scientists, Elyakov (founder of the Institute of the Far Eastern Branch of the Russian Academy of Sciences) and Brekhman provided significant contributions to the development of the science of Far Eastern medicinal plants, including ginseng (7,27).

The main active ingredients in ginseng are triterpene glycosides. These are ginsenosides, although they were more commonly known as panaxosides in the past. This was due to the fact that the pioneers of the study of ginseng saponins were domestic organic chemists under the guidance of the Academician of the Far East Branch of the Russian Academy of Sciences, G.B. Elyakov, who was the first to isolate 6 ginseng glycosides. The properties of an aglycone (a part of a glycoside that lacks a carbohydrate radical), led this group of scientists to term the glycosides of the protopanaxatriol group panaxosides, A, B and C, and the glycosides of the protopanaxadiol group panaxosides, D, E and F. Over time, other members of these groups were isolated; however, as there was no space left between C and D, the new opening compounds were termed ginsenosides and numbers that correspond to their mobility on chromatograms were assigned to them (7,28,29).

3. The chemical composition of *Panax Ginseng C.A. Meyer*

Saponins, which belong to the tetracyclic triterpene group, are among the biologically active substances (BAS) that are found in ginseng. Ginseng saponins are said to belong to the triterpenoid group of steroid origin (29).

Triterpene glycosides (ginsenosides) are considered the main active ingredients of ginseng, which were previously often termed panaxosides. The pioneers of the study of ginseng saponins are a group of Russian scientists led by the Academician Far Eastern Branch of the Russian Academy of Sciences, G.B. Elyakov. They were the first to isolate 6 glycosides of *Panax ginseng* in the 1960s (6,7). They termed the glycosides of the protopanaxatriol group, panaxosides A,

B, and C, based on the properties of the aglycone, and the glycosides of the protopanaxadiol group, the panaxosides D, E and F. Over time, other members of these groups were identified; however, since there was no space between C and D, newly discovered compounds began to be termed ginsenosides and assigned numbers to them corresponding to their mobility shown on the chromatograms.

When clarifying the structure of an aglycone that ginseng glycosides, it was found to contain 3-6 monosaccharide residues (glucose, rhamnose, arabinose and xylose). Almost all glycosides have two carbohydrate chains bound to aglycone through typical glycosidic bonds.

The systematization of the literature data on the chemical composition of ginseng has led to data that are presented in Table I.

It is now established that the composition of the dry root is approximately as follows: Ginsenosides, 1-6%; carbohydrates (polysaccharides, trisaccharides, disaccharides, monosaccharides, cellulose, pectins), 60-70%; nitrogen-containing compounds (amino acids, etc.), 12-16%; fat soluble components, 2%; vitamins, 0.05%; mineral substances 4-5% and moisture, 9-11% (28).

4. Ginsenosides and the acetylcholine level

Acetylcholine (ACh) is the main neurotransmitter in the parasympathetic nervous system and is rapidly destroyed by specific enzymes, known as cholinesterase, in the body. In addition to acetylcholinesterase (AChE), butyrylcholinesterase (BChE) can also destroy ACh (30). AChE and BChE play a significant role in AD. The inhibition of AChE and BChE provides additional benefits in the treatment of asthma. The cholinergic hypothesis, according to which the disease is caused by the reduced synthesis of ACh, was the first hypothesis to be proposed as the cause of AD. Indeed, the concentration of ACh in the brain during the first stages of AD is significantly below normal, and a decrease in the activity of cholinergic neurons is observed as a result (31). AChE inhibition-based therapy, which aims to increase the amount of ACh, is a method with which to alleviate AD in the initial and moderate stages (32). There are currently some doubts as to the cholinergic theory, as drugs that increase the level of ACh have a low efficiency. However, impelling methods of maintenance therapy have been created on this basis (33). Donepezil, galantamine and rivastigmine are three AChE inhibitors that form the basis of maintenance therapy for individuals with asthma. The continuous use of these drugs can lead to side-effects, such as headaches, constipation, dizziness, nausea, vomiting and a loss of appetite, which severely affect the quality of life of patients (34).

AD presents with both increased AChE activation and the inhibition of choline acetyltransferase (ChAT), which is the enzyme responsible for ACh biosynthesis (35).

Molecular docking and *in vitro* analyses have demonstrated that some of the ginsenosides that are obtained from ginseng root are AChE and BChE inhibitors. Ginsenosides Rb1, Rb2, Rc, Re, Rg1 and Rg3 have a significant inhibitory effect against AChE and BChE. The ginsenoside Re appears to provide the optimal AChE inhibitory activity from a series of ginsenosides (36).

The order of the inhibitory potential was as follows: Re>Rg3>Rg1>Rb1>Rb2>Rc for AChE, and Rg3>Rg1>Rb2>Rb1>Re>Rc

for BChE. Ginsenoside Rc exhibited a weak inhibitory activity against AChE, while ginsenosides Rc and Re did so against BChE, compared with the positive controls (36).

Five new ginsenosides that are derivatives of ursolic acid have been isolated from *Panax japonicus* (37). All five were identified as AChE inhibitors in an evaluation of AChE activity in a PC12 cell model (rat adrenal pheochromocytoma) that was treated with A β ₂₅₋₃₅. However, it was found that their inhibitory potential was lower than that of donepezilum.

An extract from *Panax quinquefolius* (Cereboost™) was shown to exhibit AChE inhibitory activity in a mouse model of AD (male ICR mouse that received A β ₁₋₄₂ intracerebroventricular) (38). Cereboost™ increased the level of ACh in the brain by inhibiting AChE and reduced the level of A β ₁₋₄₂, while it improved the cognitive abilities of mice. *In vitro*, Cereboost™ increased ChAT expression and reduced the cytotoxicity of A β ₁₋₄₂. Identical results have been observed in other studies on mouse models of AD (ICR mice injected with scopolamine) (38). Ginsenoside Rg1 has been proven to be a more potent AChE inhibitor than Rb1 (40). Furthermore, ginsenoside Rg5 has been observed to dose-dependently inhibit AChE and activate ChAT in another model of AD (Wistar rats, which were injected with intracerebroventricular streptozocin). It also increased the ability of rats to learn and memorize the Morris water maze (MWM) (41).

It was also previously shown that an extract from a 4-year-old *Panax ginseng* C.A. Meyer root inhibited the neurotoxicity of A β . Choi *et al* examined the effect of dried white ginseng extract (WGE) on neuronal cell damage and memory impairment in mice injected with intrahippocampal A β O (10 μ M). Mice were treated with WGE (100 and 500 mg/kg/day, p.o.) for 12 days after surgery. WGE improved memory impairment by inhibiting hippocampal cell death induced by A β O. In addition, the A β O-injected mice treated with WGE exhibited a restoration of reduced synaptophysin and ChAT intensity, and lower levels of ionized calcium-binding adaptor molecule 1 in the hippocampus compared with those of the vehicle-treated controls. These results suggest that WGE reverses memory impairment in AD by attenuating neuronal damage and neuroinflammation in the hippocampus of mice injected with A β O (42).

Some studies have shown that ginsenosides exert a neuroprotective effect by acting on neurotransmitters in AD. For example, ginsenosides can increase the levels of γ -aminobutyric acid, ACh and dopamine, and reduce the levels of glutamate and aspartic acid in the hippocampus and cerebral cortex. In addition, ginsenosides can increase the level of glycine and serotonin in the blood (43). Apparently, ginseng contains substances that can increase the level of ACh in the brain of people with AD. Ginseng extracts can thus be used as palliative treatment in the early stages of AD.

5. Ginsenosides and the β -amyloid level

A β is the common name for several peptides that consist of 36-43 amino acid residues. The main species are the following: One peptide with 40 amino acid residues (A β ₁₋₄₀) and another of 42 amino acid residues (A β ₁₋₄₂) (44). A β is formed in the body from A β precursor protein (APP), which is a transmembrane protein that is concentrated in neurons through sequential prote-

Table I. List of most known active components (ginsenosides) of *Panax Ginseng* C.A. Meyer.

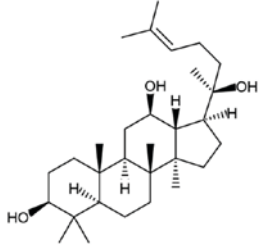
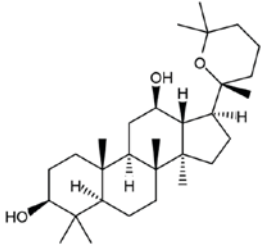
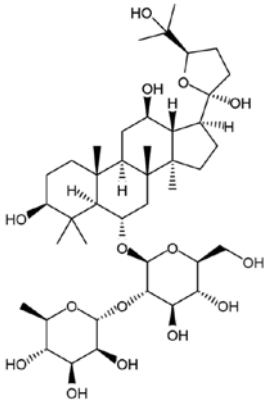
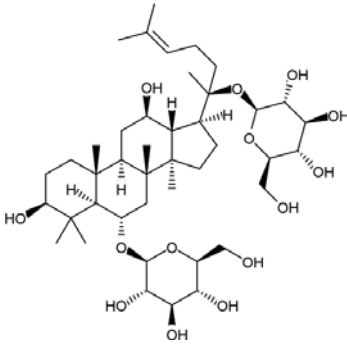
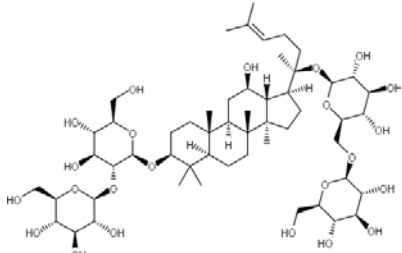
| No. | Chemical compounds | Structure |
|-----|--|---|
| 1 | <p>20S-protopanaxadiol (3S,5R,8R,9R,10R,12R,13R,14R,17S)-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,12-diol</p> <p>$C_{30}H_{52}O_3$ Mw = 460,743 g/mol</p> |  |
| 2 | <p>Panaxadiol (3S,5R,8R,9R,10R,12R,13R,14R,17S)-4,4,8,10,14-pentamethyl-17-[(2R)-2,6,6-trimethyloxan-2-yl]-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,12-diol</p> <p>$C_{30}H_{52}O_3$ Mw = 460,743 g/mol</p> |  |
| 3 | <p>Ginsenoside a1 (Panaxoside a1) (pseudoginsenoside F11) 2-[2-[[[(3S,6S,8R,10R,12R,13R,14R,17S)-3,12-dihydroxy-17-[(2S,5R)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy]-6-methyloxane-3,4,5-triol</p> <p>$C_{42}H_{72}O_{14}$ Mw = 801,024 g/mol</p> |  |
| 4 | <p>Ginsenoside a2 (Panaxoside a2) (Ginsenoside RG1) (2R,3R,4S,5S,6R)-2-[[[(3S,5R,6S,8R,9R,10R,12R,13R,14R,17S)-3,12-dihydroxy-4,4,8,10,14-pentamethyl-17-[(2S)-6-methyl-2-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy]hept-5-en-2-yl]-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol</p> <p>$C_{42}H_{72}O_{14}$ Mw = 801,024 g/mol</p> |  |
| 5 | <p>Ginsenoside Rb1 (Panaxoside Rb1) 2-O-β-Glucopyranosyl-(3β,12β)-20-[(6-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]-12-hydroxydammar-24-en-3-yl β-D-glucopyranoside</p> <p>$C_{54}H_{92}O_{23}$ Mw = 1109,307 g/mol</p> |  |

Table I. Continued.

| No. | Chemical compounds | Structure |
|-----|---|-----------|
| 6 | <p>Ginsenoside Rb2 (Panaxoside Rb2) (3β,12β)-20-[(6-<i>O</i>-α-L-Arabinopyranosyl-β-D-glucopyranosyl)oxy]-12-hydroxydammar-24-en-3-yl 2-<i>O</i>-β-D-glucopyranosyl-β-D-glucopyranoside, NSC 308878 $C_{53}H_{90}O_{22}$ Mw = 1079,281 g/mol</p> | |
| 7 | <p>Ginsenoside Rb3 (Panaxoside Rb3) (3β,12β)-3-[(2-<i>O</i>-β-D-Glucopyranosyl-β-D-glucopyranosyl)oxy]-12-hydroxydammar-24-en-20-yl 6-<i>O</i>-β-D-xylopyranosyl-β-D-glucopyranoside $C_{53}H_{90}O_{22}$ Mw = 1079,281 g/mol</p> | |
| 8 | <p>Ginsenoside Rg3 (Panaxoside Rg3) (2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-2-[(3S,5R,8R,9R,10R,12R,13R,14R,17S)-12-hydroxy-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol $C_{42}H_{72}O_{13}$ Mw = 785,025 g/mol</p> | |
| 9 | <p>Ginsenoside Rh2 (Panaxoside Rh2) (3β,12β)-12,20-Dihydroxydammar-24-en-3-yl-β-D-glucopyranoside, 20(S)-Ginsenoside-Rh2 $C_{36}H_{62}O_8$ Mw = 622,884 g/mol</p> | |
| 10 | <p>Ginsenoside Rh3 (Panaxoside Rh3) (3β, 12β,20Z)-12-Hydroxydammar-20(22), 24-dien-3-yl-β-D-glucopyranoside $C_{36}H_{60}O_7$ Mw = 604,869 g/mol</p> | |

Table I. Continued.

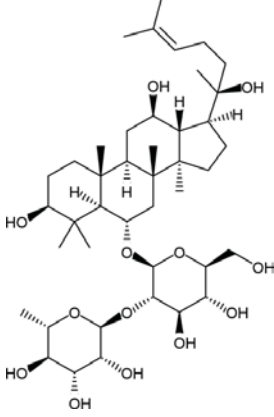
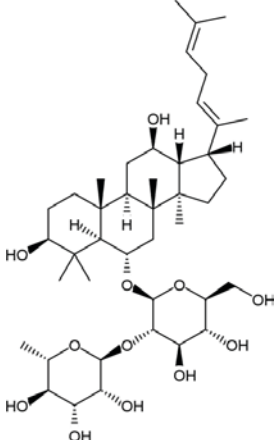
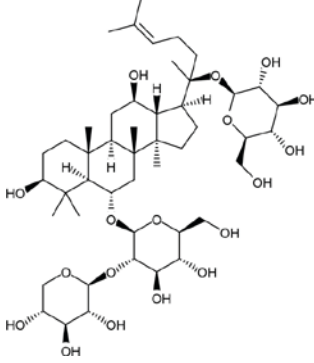
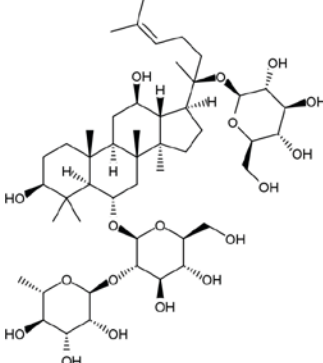
| No. | Chemical compounds | Structure |
|-----|---|---|
| 11 | <p>Ginsenoside Rg2 (Panaxoside Rg2) $(3\beta,6\alpha,12\beta)$-3,12,20-Trihydroxydammar-24-en-6-yl 2-<i>O</i>- (6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside $C_{42}H_{72}O_{13}$ Mw = 785,025 g/mol</p> |  |
| 12 | <p>Ginsenoside Rg4 (Panaxoside Rg4) $(2S,3R,4R,5R,6S)$-2-[(2R,3R,4S,5S,6R)-2-[(3S,5R,6S, 8R,9R, 10R, 12R, 13R,14R,17S)-3, 12-dihydroxy-4,4,8,10, 14-pentamethyl-17- [(2Z)-6-methylhepta-2,5-dien-2-yl]-2, 3,5,6,7, 9,11,12,13,15,16, 17-dodecahydro-1H-cyclopenta [a]phenanthren-6-yl]oxy]-4, 5-dihydroxy-6-(hydroxymethyl) oxan-3-yl] oxy-6-methyloxane-3, 4,5-triol $C_{42}H_{70}O_{12}$ Mw = 767,01 g/mol</p> |  |
| 13 | <p>Notoginsenoside R1 (Panaxoside R1) $(2S,3R,4S,5S,6R)$-2-[(2S)-2-[(3S,5R,6S,8R,9R,10R,12R, 13R, 14R,17S) -6-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(2S,3R,4S, 5R)-3,4,5-trihydroxyoxan-2-yl] oxyoxan-2-yl]oxy]-3, 12-dihydroxy-4,4, 8,10, 14-pentamethyl-2, 3,5,6,7,9,11,12,13,15,16, 17-dodecahydro-1H -cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-en- 2-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol $C_{47}H_{80}O_{18}$ Mw = 933,139 g/mol</p> |  |
| 14 | <p>Ginsenoside Re (Panaxoside Re) $3\beta,6\alpha,12\beta$)-20-(β-D-Glucopyranosyloxy)-3,12-dihydroxydammar-24- en-6-yl 2-<i>O</i>-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside, Chikusetsusaponin IVc, Ginsenoside B2, NSC 308877, Panaxoside Re $C_{48}H_{82}O_{18}$ Mw = 947,166 g/mol</p> |  |

Table I. Continued.

| No. | Chemical compounds | Structure |
|-----|--|-----------|
| 15 | Ginsenoside Rh1 (Panaxoside Rh1) (2R,3R,4S,5S,6R)-2-[[[(3S,5R,6S,8R,9R,10R,12R,13R,14R,17S)-3,12-dihydroxy-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol $C_{36}H_{62}O_9$ Mw = 638,883 g/mol | |
| 16 | Notoginsenoside ST4 (2S,3R,4S,5R)-2-[[[(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-2-[[[(3S,5R,8R,9R,10R,12R,13R,14R,17S)-12-hydroxy-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]-6-(hydroxymethyl)oxan-3-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy]oxyoxane-3,4,5-triol $C_{47}H_{80}O_{17}$ Mw = 917,14 g/mol | |

olysis with beta secretase 1 (BACE1) and γ -secretase (45). A β forms insoluble A β filaments, which subsequently stick together in the intercellular space into dense formations known as senile plaques (46). There is also an alternative, non-amyloidogenic pathway, in which the first cleavage of APP is catalysed, not by BACE1, but by α -secretase and the result is soluble amyloid precursor protein α (sAPP α), which exerts anti-apoptotic and neuroprotective effects (47,48).

Some ginsenosides are BACE1 inhibitors as molecular docking and *in vitro* studies have demonstrated. Their inhibitory ability decreases in a certain order: Rc>Rg1>Rb2>Rb1>Rg3>Re (36). Ginsenoside Re has not only been observed to reduce the activity of BACE1 and the expression of BACE1, but also to not affect the total levels of APP and sAPP α in a N2a/APP695 cell model (neuronal cells with an overexpression of APP) (49). It has also been shown that the decrease in BACE1 expression is associated with the activation of ginsenoside Re by peroxisome proliferator-activated receptor γ (PPAR γ). Ginsenoside Rg1 is also a stimulator of PPAR γ (50). The role of PPAR γ in the pathogenesis of AD is not yet fully known.

Yan *et al* (51) demonstrated that ginsenoside Rd promoted the activation of the non-amyloidogenic pathway by activating estrogen receptor (ER). The methods they used in their study were as follows: 10 mg/kg ginsenoside Rd in ovariectomy/ovariectomized (OVX) + ginsenoside Rd group and an equivalent volume of saline in the sham-operated group and OVX group were administrated intraperitoneally for two

months, respectively. The MWM was used to examine the cognitive function of rats, and the levels of sAPP α and A β in the hippocampi were measured. The culture medium of HT22 hippocampal neuronal cells was incubated with ginsenoside Rd, ER antagonist (ICI182,780), MAPK inhibitor (PD98059), or PI3K inhibitor (LY294002), respectively. The sAPP α levels were measured, and the expression levels of α -secretase, sAPP α , β -secretase, A β , phosphorylated AKT (p-AKT), total AKT, p-ERK, total ERK, p-ER α , total ER α , p-ER β and total ER β were examined by western blot analysis to investigate the estrogenic-like activity of ginsenoside Rd.

Accordingly, ginsenoside Rd was also found to attenuate cognitive and memory impairment, increase the levels of sAPP α and to reduce extracellular A β in OVX rats. In HT22 cells, ginsenoside Rd upregulated the sAPP α levels, which were inhibited by the inhibitors of the MAPK and PI3K pathways. In addition, the inhibitor of ER prevented the ginsenoside Rd-induced release of sAPP α and the activation of the MAPK and PI3K pathways. Ginsenoside Rd increased the expression of α -secretase and sAPP α , while it decreased the expression of β -secretase and A β . Moreover, ginsenoside Rd promoted the phosphorylation of ER α at the Ser118 residue (51). Similar results have also been obtained for ginsenoside Rg1 (52,53).

It has been demonstrated that ginsenosides Rd and Rg1 not only significantly reduce the level of A β , but also increase the level of sAPP α , as it has been shown in animal models of AD (54).

Huang *et al* (55) aimed to investigate the effects of *Panax notoginseng* saponins (PNS) on α -secretase and

β -secretase involved in A β generation in SAMP8 mice. The results of their study revealed that PNS increased α -secretase activity perhaps by enhancing the level of ADAM9 expression, which itself was achieved by the upregulation of the expression of the *ADAM9* gene. PNS significantly decreased the BACE1 protein level by downregulating the level of *BACE1* gene expression and consequently precluded the activity of β -secretase (56).

That study indicated that PNS modulated the expression levels of proteins and genes associated with α - and β -secretase, thereby increasing α -secretase activity and reducing β -secretase activity, which may be one of the mechanisms of action of PNS precluding A β generation. Accordingly, PNS may be a promising agent for AD (55).

Endres and Fahrenholz (57) noted in their research that a disintegrin and metalloproteinase domain 10 (ADAM10) presents a worthwhile target with respect to the treatment of a neurodegenerative diseases, such as AD. Animal models with an overexpression of ADAM10 revealed a beneficial profile of the metalloproteinase with respect to learning and memory, plaque load and synaptogenesis. Initially, ADAM10 was suggested to be an enzyme, shaping the extracellular matrix by cleavage of collagen type IV, or to be a tumour necrosis factor α (TNF- α) convertase. In a relatively short period of time, a wide variety of additional substrates [with amyloid precursor protein (APP) probably being the most prominent] have been identified and the search is still ongoing. Hence, any side-effects concerning the therapeutic enhancement of ADAM10 α -secretase activity have to be considered (57).

However, in another study, the level of sAPP α was found to be higher in mice that were treated with ginsenoside Rh2 than in the control group. Ginsenoside Rh2 inhibited the endocytosis of APP and increased the distribution of APP on the cell membrane, thereby reducing the amyloid and increasing the non-amyloid pathway of cleaving APP (58). It has been proven that the level of cholesterol in neurons is involved in the pathogenesis of AD (59), and that the C-terminus of APP contains a cholesterol-binding domain (60).

Since it is known that the lipid raft is a specific cell membrane that is enriched with cholesterol, which plays an important role in the endocytosis of transmembrane proteins (61), and treatment with ginsenoside Rh2 significantly reduces the level of cholesterol in neurons, it has been concluded that the distribution of APP over the cell membrane is determined by the cholesterol in neurons (58). In addition to cholesterol, other lipids, such as phosphoinositides, are also involved in the pathogenesis of AD (62). One of the key phospholipids, phosphatidylinositol 4,5-bisphosphate [PI(4,5)P₂], is formed by phosphatidyl inositol 4-phosphate (PI4P) phosphorylation using a specific enzyme, phosphatidyl inositol-phosphate-4 kinase type 1 γ . PI4P is formed via phosphatidylinositol by phosphatidylinositol-4-kinase 2 α (PI4KII α) (63). *In vitro* and *in vivo*, ginsenoside Rg3 has been observed to increase the levels of PI4P and PI(4,5)P₂ by activating PI4KII α (64). PI(4,5)P₂ contributes to the regulation of the mobility of transmembrane proteins in lipid rafts (65). In other words, PI(4,5)P₂ leads to changes in the fluidity and thickness of the membrane, and this, in turn, affects the activity of γ -secretase (66). Thus, high levels of PI4P and PI(4,5)P₂, induced by ginsenoside Rg3, reduce the generation of A β by altering the activity of γ -secretase. The cognitive abilities of the animals in the MWM test following

treatment with ginsenosides increased in all experiments, in relation to the control group with the AD model without treatment with ginsenosides (51-54,58).

Substances from ginseng extracts directly or indirectly affect the activity of secretases. However, such an approach to AD treatment appears to provide low-probability outcomes, as demonstrated by the fact that a number of large pharmaceutical companies have completed the clinical trials of various secretase inhibitors ahead of time: Verubecestat (67), lanabecestat (BACE1 inhibitors) (<https://www.astrazeneca.com/media-centre/press-releases/2018/update-on-phase-iii-clinical-trials-of-lanabecestat-for-alzheimers-disease-12062018.html>) and semagacestat (γ -secretase inhibitor) (68). There was no improvement in patients who were taking the BACE1 inhibitors compared to the placebo group. The first and second phases of the clinical trials of semagacestat revealed a decrease in the plasma A β ₁₋₄₂ concentration at 3 h after administration. However, the concentration increased by 300% after 15 h, while there was no reduction in the cerebrospinal fluid. Although semagacestat reduced the number of amyloid plaques, the cognitive functions of the patients taking semagacestat worsened compared with the placebo group (67,68; <https://www.astrazeneca.com/media-centre/press-releases/2018/update-on-phase-iii-clinical-trials-of-lanabecestat-for-alzheimers-disease-12062018.html>).

It has been proven *in vivo* that ginsenoside Rg3 reduces the level of A β by increasing the activity and expression of neprilysin (69). Ginsenoside Rg1 has also been shown to increase the activity and expression of neprilysin (70). Neprilizin is one of the main enzymes that is capable of destroying A β .

It is known that protopanaxadiol (PPD)-type saponins are completely metabolized to 20-*O*- β -D-glucopyranosyl-20(S)-p rotopanaxadiol (M1) by intestinal bacteria when taken orally; M1 and ginsenoside Rb1, as a representative of PPD-type saponins, were thus examined for cognitive disorders.

In a mouse model of AD induced by A β ₂₅₋₃₅ intracerebroventricular injection, impaired spatial memory was recovered by the p.o. administration of ginsenoside Rb1 or M1 (71). Although the expression levels of phosphorylated NF-H and synaptophysin were reduced in the cerebral cortex and the hippocampus of mice injected with A β ₂₅₋₃₅, their levels in the ginsenoside Rb1- and M1-treated mice were almost completely recovered to those of the control levels. The potencies of the effects did not differ between ginsenoside Rb1 and M1 when administered orally, suggesting that most of the ginsenoside Rb1 may be metabolized to M1, and M1 is an active principal of PPD-type saponins for memory improvement. M1 was shown to be effective *in vitro* and *in vivo*, indicating that ginseng drugs containing PPD-type saponins may reactivate neuronal function in AD by p.o. administration.

It has been demonstrated that AD is closely related to APP and presenilin-1 (PS1), which are overexpressed in AD (72). A study of UPLC/MS based metabolomics was conducted in order to better understand the mechanisms of action of ginsenoside Rg1 and Rg2, which counteract AD. The results revealed that ginsenosides Rg1 and Rg2 reduced rescue latency, compared to the AD model group, when cognitive function was tested in the MWM (71).

The impaired cognitive function and increased hippocampal A β deposition in mice with AD were ameliorated by ginsenoside Rg1 and Rg2. In addition, a total of 11 potential

biomarkers that are associated with the metabolism of lyso-phosphatidylcholines (LPCs), hypoxanthine and sphingolipids were identified in the brains of mice with AD and their levels were partly restored following treatment with ginsenoside Rg1 and Rg2. Ginsenoside Rg1 and Rg2 treatment influenced the levels of hypoxanthine, dihydrosphingosine, hexadec-asphinganine, LPC C 16:0, and LPC C 18:0 in mice with AD. Additionally, G-Rg1 treatment also influenced the levels of phytosphingosine, LPC C 13:0, LPC C 15:0, LPC C 18:1 and LPC C 18:3 in mice with AD (73).

A total of ten potential biomarkers were identified that were associated with the metabolism of lecithin, amino acids and sphingolipids in mice with AD. The peak intensities of LPC, tryptophan and dihydrosphingosine were lower, while those of phenylalanine were higher, in the mice with AD than in the control mice. Ginsenoside Rg1 treatment affected all three metabolic pathways, while ginsenoside Rb1 treatment affected lecithin and amino acid, but not sphingolipid metabolism. These data suggest that metabolomics has acquired a new method with which to discover the therapeutic benefits of ginsenosides in the treatment of AD (74).

Transgenic mice with AD have been used to study the protective properties of ginsenoside Rg1 on brain activity and synaptic plasticity, using conditional reflex fading and the western blotting technique. The results revealed that long-term memory improves following treatment with ginsenoside Rg1. Furthermore, ginsenoside Rg1 did not have a negative effect on normal diet and weight, while also inhibiting the levels of C-terminal fragments (CTF), phosphorylated τ -protein (p-Tau) and $A\beta_{1-42}$ in mice with AD. Ginsenoside Rg1 was also able to improve the expression of brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase B (TrkB) in the hippocampus. The results revealed that ginsenoside Rg1 exerted a neuroprotective effect via the activation of the BDNF-TrkB pathway and that weakened the expression of AD-associated proteins (75).

Furthermore, ginsenoside Rg1 has been found to increase the expression of N-methyl-D-aspartate receptor 1 (NR1) and N-methyl-2B D-aspartate (NR2B), while also attenuating the formation of NFTs, which directly affect the processes of learning and memory in mouse models with AD (76). It was discovered in recent studies that reproductive sex hormones, particularly oestrogen, play an important role in the pathogenesis of AD. The rapid decline in oestrogen levels in postmenopausal women increases susceptibility to AD (77-79).

Thus, the absence of oestrogen can be a risk factor for AD. Zhang *et al* conducted a successful study to examine the neuroprotective effects of ginsenoside Rg1 on an OVX and D-galactose (D-gal)-injected rat model of AD (54). The results revealed that ginsenoside Rg1 not only restored impaired cognitive activity and positively affected spatial learning and memory, but also reduced the production of $A\beta_{1-42}$ in the rats with AD. Seven weeks after surgery, ADAM10 expression in the hippocampus of the rats with AD was markedly decreased, while BACE1 expression increased compared with that in the sham-operated group ($P < 0.05$). The levels of cleaved caspase-3 were increased in the hippocampus of rats with AD. Ginsenoside Rg1 and E2 treatment increased the ADAM10 level, while it reduced the BACE1 level and apoptosis.

Moreover, moderate-dose i.e., 10 mg/kg/day and high-dose i.e., 20 mg/kg/day ginsenoside Rg1 exerted more potent effects than low-dose i.e., 5 mg/kg/day ginsenoside Rg1 (54). It is well known that chronic stress restrictions (in animals) can accelerate the process of AD generation and development. Ginsenoside Rg1 protects from oxidative damage by reactive oxygen species (ROS) and inhibits the expression of NADPH oxidase 2 (NOX2), p47phox and RAC1 (80).

The association between ginsenoside Rg1 and the endoplasmic apoptotic pathway, as mediated by the reticulum, has also been examined in a rat model of AD. The results revealed that ginsenoside Rg1 reduced the accumulation of NFTs and the number of terminal deoxynucleotide transferase-mediated dUTP filamentous ends that mark positive cells in mice with AD. More importantly, ginsenoside Rg1 inhibited the activation of apoptosis-associated phosphorylated-c-Jun N-terminal protein kinase (p-JNK) and reduced the expression of glucose-regulated protein 78 (Grp78). Consequently, ginsenoside Rg1 exerted a neuroprotective effect by inhibiting the accumulation of NFTs and $A\beta$ via inhibition of the ER stress-mediated pathway. The blocking of this pathway was triggered by the inositol-requiring enzyme-1 (IRE-1) and tumour necrosis factor receptor-associated factor 2 (TRAF2) pathway, as a result of the inhibition of the expression of p-JNK (81).

A scientific study found that pseudoginsenoside F_{11} (PF_{11}), one of the components of ginseng, exerted a neuroprotective effect and enhanced the activity of neurons (82). Another study demonstrated that PF_{11} reduced the latency of rescue in the MWM and blocked the reduction of stepwise latency in the step test for $A\beta_{11-42}$ and APP/PS1 mice. In addition, PF_{11} inhibited APP expression and the production of $A\beta_{11-42}$ in the hippocampus and cortex of APP/PS1 mice. PF_{11} significantly increased the activity of superoxide dismutase (SOD) and glutathione peroxidase and reduced the amount of malondialdehyde (MDA). In addition, PF_{11} reduced the expression of JNK2, p53 and cleaved caspase-3. Thus, the improved recognition that is observed when subjects are exposed to ginsenoside PF_{11} may be associated with anti-inflammatory, anti-apoptotic and inhibitory effects on amyloid genesis (83). By analogy, it has been found that ginsenoside R1 exerts a protective effect against $A\beta$ -neurotoxicity (84).

In a previous study, ginsenoside Rb1 also reduced the presence of $A\beta_{1-42}$ in the area of the cortex and hippocampus as well as improving the ability to learn in mice with AD (85). It is well known that cyclooxygenase 2 (COX-2), I κ B- α and neuronal nitric oxide (NO) synthase (nNOS) are markers of neuroinflammation. Ginsenoside Rb1 reduced the number of COX-2-positive cells and positive I κ B- α cells and increased the number of nNOS-positive cells in the hippocampus, as compared to the model group. The neuroprotective effect of ginsenoside Rb1 may thus be associated with anti-inflammatory markers in the hippocampus of mice with AD (85). More importantly, ginsenoside Rb1 has been observed to be more rapidly absorbed than ginsenoside Re and Rg1 (86). The effect of ginsenoside Rb1 may therefore be more potent than that of the other ginsenosides. In addition, ginsenoside Rb1 also demonstrated higher activity against neurotransmitters. For example, ginsenoside Rb1 has a higher absorbing activity against ONOO(-) than ginsenoside Rb2, Rc, Re, Rg1 and Rg3 (36).

Studies have shown that ginsenoside Rd can improve learning ability and memory, and can reduce neuronal death and loss in the CA1 region of the hippocampi of mice with AD. Moreover, ginsenoside Rd decreased the expression of ionized calcium-binding adaptor molecule 1 (Ibal), glial fibrillar acid protein (GFAP), interleukin (IL)-1 β , IL-6, TNF- α , caspase-3 and S100 β mRNA. Ginsenoside Rd has also been observed to increase IL-10 and HSP70 mRNA expression levels (87). Furthermore, ginsenoside Rd has been shown to inhibit the expression of NF- κ B p65, which is an important marker of the NF- κ B pathway (88). These findings indicate that the anti-inflammatory, antioxidant and anti-apoptotic effects of ginsenoside Rd are responsible for its neuroprotective effects.

AChE and BChE play a significant role in AD. The inhibition of AChE and BChE provides additional benefits to the treatment of AD. Ginsenosides Rb1, Rb2, Rc, Re, Rg1 and Rg3 have been shown to exert significant inhibitory effects against AChE and BChE. The Re compound of the series of ginsenosides inhibits the activity of AChE with optimal results (36). It has been demonstrated that ginsenosides exert neuroprotective effects via acting on neurotransmitters in AD. For example, ginsenosides can increase the levels of γ -aminobutyric acid, Ach and dopamine and reduce the levels of glutamate and aspartic acid in the hippocampus and cerebral cortex. Moreover, ginsenosides can increase the level of glycine and serotonin in the blood (43). These studies provide a novel method for AD treatment.

Apart from ginsenosides, the glycolipoprotein fractions of ginseng extracts (gintonin) have also been the subject of an AD model study, which made five observations to indicate that gintonin counteracts the development of AD: Gintonin has been shown to promote the production of sAPP α by activating ADAM10, inhibit A β production in a dose-dependent manner, activate PI3K and AKT, and also not only to alleviate memory impairment caused by A β neurotoxicity, but also reduces the deposition of amyloid plaques in a mouse model of AD (89).

6. Ginsenosides and calcium ion levels in neurons

The mechanism of the neuronal damage that is caused by an increase in the intracellular level of calcium ions (Ca²⁺), which is in turn induced by glutamate, has been well studied (90). An increase in Ca²⁺ levels leads to the excessive stimulation of proteolytic enzymes, an increase in lipid peroxidation and an increase in the generation of ROS and nitrogen (91,92), thereby contributing to the excitotoxic process. A β not only causes the addition of new ion channels in the cell membrane, but also promotes the phosphorylation of existing calcium channels, thereby increasing the flow of calcium and initiating neurodegeneration (93). A β increases the phosphorylation of membrane-bound proteins and decreases the phosphorylation of cytosolic proteins, via MAPK, with the result that the intracellular level of Ca²⁺ increases (94). Ginsenoside Rg2 can significantly reduce the intracellular level of Ca²⁺ and ROS that is caused by A β ₂₅₋₃₅ in the PC12 cell model (95). In another study, ginsenoside Rg2 has been found to reduce not only the level of Ca²⁺, but also the lipid peroxidation that is caused by glutamate (96).

Notably, while ginsenoside Rb1 can reduce the intracellular level of Ca²⁺ when it was increased by administering A β ₂₅₋₃₅, the intracellular level of Ca²⁺ in healthy cells is not affected (97).

Ginsenoside Rg1 has been observed to suppress the sensitivity of calcium channel activation to high values of membrane potential in an animal model of AD [Sprague Dawley (SD) rats administered A β ₂₅₋₃₅]. This effect disappears when ginsenoside Rg1 is used together with the MAPK inhibitor, PD98059 (98).

Quan *et al* (98) demonstrated that Rg1 treatment significantly reduced peak I_{Ca}, HVA densities, inhibited the sensitivity of channel activation to voltage, and enhanced the sensitivity of channel inactivation to voltage; these effects of Rg1 were effectively inhibited by the MAPK inhibitor, PD98059. This indicated that Rg1 reduced A β -induced HVA calcium channel currents via MAPK in hippocampal neurons. The resulting reduced calcium influx may downregulate the level of calcium ions in the neurons and attenuate the neurotoxicity of A β . In summary, the data of that study demonstrated that Rg1 can reduce HVA calcium channel currents via MAPK in hippocampal neurons in A β -exposed brain slices (98).

As mentioned above, the intracellular concentration of Ca²⁺ is an important indicator of neurological disorders. Increased Ca²⁺ levels may increase the manifestation of epilepsy. Ginsenosides, in general and ginsenoside Rg3, in particular, can inhibit an increase in Ca²⁺ that is induced by Mg²⁺. Ginsenosides can modulate the disrupted Ca²⁺ homeostasis by inhibiting the glutamate ionotropic receptors that selectively bind N-methyl-D-aspartate (NMDA receptors) (99). In addition, oxidative stress can lead to hippocampal degeneration. It is noteworthy that ginsenosides reduce the oxidative stress that acts upon the parts of the nerve ending that correspond to the synapse (synaptosomes), and reduce the synaptic vesicles of dose-dependent presynaptic terminations. Moreover, it is not adenosine A1 receptors or adenosine A2B receptors, but adenosine A2A receptors that play an important role in the fight against epilepsy. Thus, ginsenosides exert an antiepileptic effect that they exert by activating the Adenosine-A2A receptors (100) (Table II).

An increase in the intracellular levels of Ca²⁺ mediates the activation of calcium-dependent enzymes, such as calpain (calcium-dependent non-lysosomal cysteine proteases). Calpain II is involved in the regulation of the apoptosis of certain cell types and performs this role by interacting with cysteine protease caspase-3, which has been identified as a key factor in apoptosis (101). The expression of calpain II and caspase-3 *in vivo* has been found to be reduced under the influence of ginsenoside Rg2 (96). The decrease in the activity of caspase-3 is caused by an increase in the B-cell lymphoma protein 2 (Bcl-2)/Bcl-2-associated X-protein (Bax) ratio, which is caused by ginsenoside Rg2 (95).

Caspase-3 is involved not only in the regulation of cell apoptosis, but also in the proteolytic cleavage of APP, with the formation of A β . The caspase-3-mediated proteolysis site is located in the cytoplasmic tail of APP, and cleavage at this site occurs *in vivo* in the hippocampal neurons following acute excitotoxic or cerebral ischemia reperfusion injury (102). An increased caspase-3 activity and expression have been observed in rat models of AD; however, the activity and expression of caspase-3 decreases markedly following treatment with ginsenosides Rg1 and Rd (81,87). The protein fraction, extracted from 4-year-old ginseng root, is also able to reduce the expression of caspase-3, as well as increase the Bcl-2/Bax ratio (103).

Table II. Pharmacological activity and mechanism of ginsenoside action on epilepsy, depression and reperfusion injury of the brain.

| Pharmacological intervention | Ginsenosides | Impact mechanism | Authors/(Refs.) |
|---|------------------|---|--|
| Anti-epileptic effect | All ginsenosides | Activation of adenosine-A2A receptors | Shin <i>et al</i> (100) |
| | Rg3 | Modulation of Ca ²⁺ disrupted homeostasis via the inhibition of the nanomethylenediamine receptor | Doody <i>et al</i> (68) |
| Anti-depressant effect | Rg1 | Increased levels of phosphorylation of protein kinase A and levels of phosphorylation of the cAMP-response elements of the activating protein. Expression of the hippocampal transmission pathway of the neurotrophic factor of the brain, hippocampal neurogenesis | Jiang <i>et al</i> (160), Liu <i>et al</i> (161) |
| | All ginsenosides | Increased plasma ACTH levels and CORT blood levels | Wang <i>et al</i> (151), Kang <i>et al</i> (153) |
| | Rb1 | Activation 5-HT2A receptor | Yamada <i>et al</i> (152) |
| | Rb3 | Stops the process of reducing the mass of the hippocampus of the brain and the level of BDNF in the hippocampus | Cui <i>et al</i> (162) |
| | CK | Activation 5-HT2A receptor for the manifestation of the antidepressant effect, the regulation of levels of NA, ACTH and CORT in the brain. | Zhang <i>et al</i> (154), Yamada <i>et al</i> (152) |
| | Rg3 | Facilitation of the hippocampal-signalling pathway of BDNF, regulation of the levels of NA, ACTH and CORT in the brain area. | Zhang <i>et al</i> (154), You <i>et al</i> (155) |
| Protection against cerebral ischemia reperfusion injury | Rg1 | Decreases levels IL-1 β , TNF- α and HMGB1, suppresses the expression of cleaved caspase-3 and cleaved caspase-9. Downregulation of proteinase-activated receptor-1 (PAR-1) mRNA levels activated by protease | Bao <i>et al</i> (126), Zhou <i>et al</i> (127) Yang <i>et al</i> (129), Xie <i>et al</i> (131), Sun <i>et al</i> (132), Huang <i>et al</i> (150) |
| | Rb1 | Cancels the signalling pathway activation of NF- κ B and the increase in TNF- α and IL-6 levels in the ischemic hemisphere. It prevents the reduction of thioredoxin-1 and superoxide dismutase and improves the expression of HSP70, Akt and the p-NF- κ B p65 block when occluding the middle cerebral artery. | Huang <i>et al</i> (150) Zeng <i>et al</i> (149) |
| | Rd | Improves neuronal viability by inhibiting the overactive phosphorylation of NMDAR 2B and reducing levels of expression in the cell membrane | Liu <i>et al</i> (156), Xie <i>et al</i> (157) |
| | Re | Neuroprotective action by significantly reducing MDA and increasing the activity of H ⁺ -ATPase | Chen <i>et al</i> (158) |
| | Rg3 | Reduces the expression of calpain I and caspase-3 mRNA in the CA1 region of the hippocampus | He <i>et al</i> (159) |

BDNF, brain-derived neurotrophic factor; NA, noradrenaline; ACTH, adrenocorticotrophic hormone; CORT, corticosterone; HMGB1, high mobility protein group; PAR-1, protein and receptor-1 mRNA; NF, nuclear factor; HSP70, heat shock protein 70; NMDAR 2B, N-methyl-d-aspartate receptor 2B; MDA, malondialdehyde; TNF- α , tumour necrosis factor α .

Other components of ginseng, apart from ginsenosides, are capable of influencing the intracellular level of Ca²⁺. Quercetin 3-O- β -D-xylopyranosyl- β -D-galactopyranosyl (QXG) has been isolated from *Panax notoginseng* root.

Of note, a previous study demonstrated that following the introduction of A β into cortical neurons and PC12 cells alone, the intracellular level of Ca²⁺ was not altered. However, following pre-treatment with QXG, the level of Ca²⁺ which

was increased by A β was decreased by 50%. QXG also reduced the A β levels and caspase-3 activity *in vivo* (104).

7. Ginsenosides and neuroinflammatory processes

NF- κ B is a transcription factor with various functions that is closely associated with the inflammatory response, the immune response and other pathological and physiological processes. NF- κ B is in the cytoplasm in an inactive form in a normal state. When NF- κ B is activated and enters the nucleus, it binds to target genes and induces transcription (105). NF- κ B activates the transcription of TNF- α , various ILs (IL-1 β and IL-6) and other target genes during inflammation, and contributes to the production of cytokines. It has also been found that NF- κ B is associated with neurodegenerative diseases and is activated in the cerebral cortices of patients with AD (106). It has been shown, for ginsenoside Rb1 (107) and Rg5 (41) *in vitro* and for ginsenoside Rd (88) *in vivo*, that these ginsenosides are capable of reducing the expression of anti-inflammatory factors (IL-1 β , IL-6 and TNF- α) and increasing the expression of IL-10 (for Rb1 and Rd) by suppressing the activation of NF- κ B.

COX-2 is a key enzyme in the synthesis of prostaglandins and is an important mediator of inflammation (108). NO is a short-lived neurotransmitter that plays an important role in learning and memory mechanisms. As a result, impaired NO synthesis can lead to memory impairment and a decrease in learning ability (109). The fact that a number of inflammatory molecules can regulate the expression of NO synthases [NO synthase 1 (neuronal) (NOS1) and NO synthase 1 (inducible) (NOS2)] suggests that NOS should be considered a neuroinflammatory marker (110). The levels of COX-2 and NOS2 have been observed to increase significantly in models of AD (Wistar rats, administration of either A β or streptozocin), while the level of NOS1 decreases compared to the control group. However, treatment with ginsenoside Rg5 lowers the levels of COX-2 and NOS2 compared to the control values (41), and the level of COX-2 also decreases following treatment with ginsenoside Rb1, and the level of NOS1 increases (85).

Li *et al* examined the effect of ginsenoside Rg2 on neurotoxic activities induced by glutamate in PC12 cells (96). The results revealed that glutamate decreased cell viability, increased intracellular Ca²⁺ lipid peroxidation (the excessive production of MDA and NO) and the protein expression levels of calpain II, caspase-3 and A β ₁₋₄₀ in PC12 cells. Ginsenoside Rg2 significantly attenuated the glutamate-induced neurotoxic effects upon these parameters at all doses tested. Their study suggested that ginsenoside Rg2 exerted a neuroprotective effect against glutamate-induced neurotoxicity through mechanisms related to anti-oxidation and anti-apoptosis. In addition, the inhibitory effect of ginsenoside Rg2 against the formation of A β ₁₋₄₀ suggested that ginsenoside Rg2 may also represent a potential treatment strategy for AD (96).

Li *et al* investigated and evaluated the neuroprotective effects of ginseng protein (GP) and its possible mechanisms of action in a cellular and animal model of AD. The results demonstrated that GP (10-100 μ g/ml) significantly improved the survival rate of neurons and reduced cell apoptosis and the mRNA expression of caspase-3 and Bax/Bcl-2. In addition, GP (0.1 g/kg) significantly shortened the escape latency, prolonged the crossing

times and the percentage of residence time; reduced the level of A β ₁₋₄₂ and p-Tau, the activity of t-NOS and iNOS, and the content of MDA and NO, improved the activity of SOD, the concentration of cyclic adenosine monophosphate (cAMP) and the protein expression of p-PKA/PKA and cAMP response element binding protein (p-CREB/CREB) (103).

Ginseng extracts also exhibit antioxidant properties in AD models. In fact, ginsenoside Rg2 has been shown to decrease the concentration of MDA (a marker of lipid peroxidation) (96) and the level of ROS *in vivo* (95). The GP fraction activates SOD (antioxidant enzyme) and reduces the concentration of MDA *in vitro* (103). Furthermore, QXG prevents the formation of H₂O₂-induced ROS generation in a dose-dependent manner *in vitro* (104).

8. Ginsenosides and the PI3K/Akt signalling pathway

As mentioned above, ginseng root components are able to affect the PI3K/Akt signalling pathway. The PI3K/Akt signalling pathway is one of the most important signalling pathways with which cells can avoid apoptosis and it plays a significant role in oxidative stress in AD. Kashour *et al* (110) examined the role of the late Simian virus 40 transcription factor (LSF), in anti-apoptotic APP pathways. The expression of wild-type human APP (hAPPwt) inhibited staurosporine (STS)-induced apoptosis and this inhibition was further enhanced by the expression of LSF. Thus, Kashour *et al* (111) established a connection between APP, LSF and AD. Akt (p-Akt) hyperphosphorylation regulates apoptotic factors, such as Bcl-2 and Bax, downstream signalling pathways, which allows for the regulation of apoptosis (112). The suppression of the PI3K/Akt signalling pathway promotes cell apoptosis, while the activation of the PI3K/Akt signalling pathway leads to the phosphorylation of the Akt cascade, which, in turn, protects the cells from oxidative stress (113).

Cui *et al* examined the protective effects of ginsenoside Rg2 on A β ₂₅₋₃₅-induced neurotoxicity to PC12 cells and identified a potential molecular signalling pathway involved. Ginsenoside Rg2 attenuated the cleavage of caspase-3 induced by A β ₂₅₋₃₅ thereby improving cell survival and significantly enhanced the phosphorylation of Akt in PC12 cells. Additionally, pre-treatment with PI3K inhibitor, LY294002, completely abolished the protective effects of ginsenoside Rg2 against A β ₂₅₋₃₅-induced neuronal cell apoptosis. These findings unambiguously suggested that the protective effect of ginsenoside Rg2 against the A β ₂₅₋₃₅-induced apoptosis of PC12 cells was associated with activation of the PI3K/Akt signalling pathway (95).

Li *et al* examined the therapeutic effect of GP on AD and its association with the PI3K/Akt signalling pathway in order to elucidate the mechanisms underlying the neuroprotective effects of ginseng (114). It was found that the cognitive abilities of the rats with AD were increased and the level of A β was also reduced by treatment with GP. GP also reduced the content of A β ₁₋₄₂ and p-Tau, and increased the mRNA and protein expression of PI3K, p-Akt/Akt and Bcl-2/Bax in the hippocampus (114).

9. Ginsenosides and the formation of neurofibrillary tangles

As mentioned above, AD is characterized by the accumulation of NFTs in cerebral tissue. NFTs are mainly composed of

hyper p-Tau. τ -protein is a microtubule-related protein that is expressed in the central nervous system. It induces microtubule assembly and stabilisation. However, excessive p-Tau forms NFTs and leads to synaptic dysfunction, neuronal degeneration and cognitive impairment (115). In addition, abnormal hyperphosphorylation renders the τ -protein resistant to proteolytic degradation, which leads to the gradual accumulation of p-Tau in the cell and promotes the formation of NFTs. The inhibition of p-Tau can therefore be a potential therapeutic strategy for the prevention of AD.

Okadaic acid (OKA), a potent phosphatase inhibitor, often used to mimic the symptom of AD damaged by NFTs, was used in the study by Song *et al* to examine the effects of ginsenoside Rg1 on memory improvement and related mechanisms in SD rats. According to their study, it can be concluded that ginsenoside Rg1 protects rats from OKA-induced neurotoxicity. The possible neuroprotective mechanisms may be that Rg1 decreases OKA-induced memory impairment through the glycogen synthase kinase 3 (GSK3) β /Tau signalling pathway and/or by attenuating A β formation. Thus, their study indicates that ginsenoside Rg1 may be a potential prophylactic drug for AD (116).

Plattner *et al* noted in their study that the hyperphosphorylation of the microtubule-associated protein Tau is a characteristic feature of neurodegenerative tauopathies, including AD (117). The overactivation of proline-directed kinases, such as cyclin-dependent kinase (CDK)5 and GSK3, has been implicated in the aberrant phosphorylation of Tau at proline-directed sites. The results obtained in the study by Plattner *et al* prove the role of GSK3 as a key mediator of Tau hyperphosphorylation, whereas CDK5 acts as a modulator of Tau hyperphosphorylation via the inhibitory regulation of GSK3 (117).

Li *et al* (118) convincingly proved in their study that pretreatment of adult male SD rats with ginsenoside Rd (10 mg/kg for 7 days) or that of cultured cortical neurons (2.5 or 5 mol/l for 12 h) reduced OKA-induced neurotoxicity and Tau hyperphosphorylation by enhancing the activities of protein phosphatase 2A. The results of their study implied that ginsenoside Rd protected the SD rats and cultured cortical neurons against OA-induced toxicity (118).

Zhang *et al* (119) subjected SD rats to focal cerebral ischemia. Treatment with ginsenoside Rd attenuated the ischemia-induced enhancement of Tau phosphorylation and ameliorated behavioral impairment. Furthermore, they revealed that ginsenoside Rd inhibited the activity of GSK-3 β , the most important kinase involved in Tau phosphorylation, but enhanced the activity of PKB/Akt, a key kinase suppressing GSK-3 β activity (119).

A decrease in the activity of protein phosphatase 2A (PP-2A) in the cerebrum of individuals with AD is another cause of τ -protein hyperphosphorylation. PP-2A is the key serine/threonine phosphatase and presents broad substrate specificity. It is involved in the dephosphorylation of the τ -protein (120). It has been proven that ginsenoside Rd is capable of activating PP-2A *in vitro* and *in vivo*, and thereby reducing the level of p-Tau (121).

It has also been demonstrated that various ginsenosides can reduce the level of p-Tau and prevent the formation of p-Tau (43). However, to date, there is no clear understanding of the mechanisms through which this occurs.

Ginsenoside Rg1 has been observed to reduce the formation of NFTs in a study on transgenic rats that have increased APP and A β production. The authors of that study associated the accumulation of NFTs with brain-cell apoptosis (81). Furthermore, it was shown that ginsenoside Rg1 blocked the stress-apoptotic pathway that was caused by the disruption of the endoplasmic reticulum. The blocking of this pathway was initiated by the inhibition of the expression of IRE-1, factor 2, which is associated with TRAF2 and p-JNK. Moreover, as mentioned above, ginsenoside Rg1 inhibited apoptosis by increasing the Bcl-2/Bax ratio (81,119).

In another study, it was assumed that the mechanism of NFTs accumulation was mediated by the influence of nephrilysin and protein kinase A (PKA) on the phosphorylation of the τ -protein. Ginsenoside Rg1 reduced the activity and expression of PKA and increased the activity and expression of NEP at the same time, thereby inhibiting τ -protein hyperphosphorylation (70).

10. Ginsenosides and other factors

Elevated levels of A β can inhibit the expression of neurotrophic factors, such as BDNF and insulin-like growth factor-1 (IGF-1). It has been found that BDNF is a synaptic-plasticity regulator that is involved in memory and cognitive functions. It plays a role in several events that constitute the pathological cascade in AD (122). A decrease in the level of IGF-1 in the brain is considered an important factor in the development of cognitive impairment and A β deposition (123). Ginsenoside Rg5 is able to increase the expression of BDNF and IGF-1, as shown in a study on a mouse model of AD. Ginsenoside Rg1 has not only been recorded to increase BDNF expression in a transgenic mouse model of AD, but also to activate TrkB, which acts as the BDNF receptor, thereby activating the BDNF/TrkB pathway (75). The effective transcription of BDNF only occurs following the activation of four transcription factors, including CREB (124). In most cases, CREB dysfunction plays a significant role in alterations in BDNF expression. The activation of CREB occurs mainly via phosphorylation at Ser133 by PKA, the activity of which is suppressed in the model of AD induced by A β . In fact, it has been shown that ginsenoside Rg1 increases the expression of BDNF via the phosphorylation of CREB and the activation of PKA (125).

Bone marrow stem cell (BMSC) transplantation is currently used in the treatment of cerebral ischemic disease. However, this method also presents some disadvantages, such as the low conversion rate of neural cells and weak proliferation ability (126). Ginsenoside Rg1 is a possible therapeutic agent for cerebral ischemia as its molecules are small enough to pass through the blood-brain barrier (127).

Reperfusion in cerebral ischemia can cause a significant disruption to the nervous system, and can increase the water content in the brain and the volume of infarction. Notably, ginsenoside Rg1 can improve nervous system deficiency, reduce cell apoptosis and increase the sensitivity of neuron-specific cell enolase and the gliofibrillary acidic protein of cells. Moreover, ginsenoside Rg1 not only significantly increases the protein level of Bcl-2, but also lowers the protein level of Bax (126).

The combined use of ginsenoside Rg1 and BMSC transplantation improves the quality of brain tissue by enhancing

the neuro-like cell differentiation and the anti-apoptotic effect of ginsenoside Rg1 in reperfusion injury in cases of cerebral ischemia (126).

Ginsenoside Rg1 has also been found to improve neurological injury conditions by suppressing the expression of aquaporin 4 (127).

It is well known that the inflammation and apoptosis of neurons often occur with reperfusion injury following cerebral ischemia. Kashour *et al* clearly indicated in their study that the expression of dominant-negative late Simian virus 40 transcription factor (LSF) led to a marked increase in staurosporine-induced cell death that was significantly blocked by hAPPwt. These effects of Alzheimer's APP were accompanied by LSF nuclear translocation and dependent gene transcription. The activation of LSF is dependent on the expression of hAPPwt and is inhibited by the expression of dominant-negative forms of either phosphoinositide 3-kinase or Akt. These results demonstrate that LSF activation is required for the neuroprotective effects of APP via PI3K/Akt signalling (111).

Chem-oxygenase-1 (HO-1) is one of the downstream effectors of PPAR γ . The PPAR γ /HO-1 signalling system can inhibit apoptosis and inflammation. The association between ginsenoside Rg1 and the PPAR γ /HO-1 signalling system in cerebral ischemic reperfusion injury has been investigated. Li *et al* (128) hypothesized that the neuroprotective effects of ginsenoside Rg1 occur through PPAR γ signaling in the ischemic brain. They demonstrated that Rg1 markedly increased PPAR γ expression in ischemic rats and in the cortical neurons of cerebral cortical neuron ischemic injury model rats. They also found that the selective PPAR γ antagonist, GW9662, reduced PPAR γ expression, suggesting that Rg1 may be a potent PPAR γ agonist.

With the use of the middle cerebral artery occlusion rat model with cerebral ischemia/reperfusion injury, Li *et al* (128) also observed that Rg1 effectively reduced neurological disorders and swelling of the brain in cerebral ischemic injury. These results are in accordance with those of other studies which demonstrated the effectiveness of Rg1 as a neuroprotector in various models of cerebral ischemic injury, including neurological deficits (129,130).

In addition, ginsenoside Rg1 has not only been found to reduce the levels of IL-1 β , TNF- α and high mobility group box protein 1 (HMGB1), but also to suppress the expression of cleaved caspase-3, cleaved caspase-9 and the receptor for advanced glycation end products (RAGE) in rat models (129). The infarct volume of the cerebrum and the permeability of the blood-brain barrier decreases with cerebral ischemic disease following exposure to ginsenoside Rg1. Ginsenoside Rg1 may attenuate neurological injury, the brain infarct volume and the blood-brain barrier permeability induced by focal cerebral ischemia in rats, and its neuroprotective mechanism is related to the downregulation of protease activated receptor-1 (PAR-1) expression. The permeability of the blood-brain barrier also increases with an increase in PAR-1 expression (131).

Moreover, astrocytes play an important role in the ischemic death of neurons. Although ginsenoside Rg1 does not alter the viability of astrocytes, its effect can weaken apoptosis and inhibit the intracellular overload of Ca²⁺ in astrocytes. In addition,

ginsenoside Rg1 can reduce the loss of the transmembrane potential of the mitochondria and ROS production in astrocytes (132).

Metabolomic analyses have been performed in a number of studies, and substances whose level varied in the AD model have been identified and recovered under the action of various ginsenosides. In a previous study, a total of 10 potential biomarkers that were associated with the metabolism of lecithin, amino acids, and sphingolipids were identified in mice with AD based on metabolomics. These biomarkers in the plasma of mice with AD were disrupted. Following treatment with ginsenoside Re, the disrupted metabolic profiling was restored back to control-like levels, indicating that the protective effect of ginsenoside Re in AD was exerted through these pathways (133). In that study (133), the levels of hexadecaspinganine and phytosphingosine were both decreased in the plasma of mice with AD as compared to the control mice. Following treatment with ginsenoside Re, the levels of these two metabolites were significantly elevated. Thus, the results suggest that mice with AD have impaired sphingolipid metabolism, and therefore plasma sphingolipids can also be utilized as indicators of therapeutic response. The therapeutic effects of ginsenoside Re on mice with AD are exerted through the modulation of sphingolipid metabolic processes (133).

Ginsenosides Rg1 and Rb1 increase the concentrations of tryptophan, di-hydrospingosine (Rg1 only), various lysosfatidylcholines (C22: 6, C20: 4, C18: 2, C16: 0, C18: 1 and C18: 0), and lower the levels of phenylalanine (53). Ginsenoside Rg2 increases the concentrations of hypoxanthine, dihydrospingosine, hexadecaspinganine and lysosfatidylcholine C16: 0 and C18: 0 (73).

A comparative proteomics analysis was performed on a model of AD using the stable isotope labelling by amino acids in cell culture (SILAC) in order to examine the potential defence mechanisms of ginsenoside Rb1. Forty proteins were found that exhibited significant changes after the treatment of cells, into which A β had previously been introduced, with ginsenoside Rb1. As a result, the authors suggested that proteins, such as adenylyl cyclase associated protein 1, the isoform 2, the subunit β F-actin-closure protein and the subunit of the mitochondrial receptor TOM40, can act as potential biomarkers and regulatory proteins in protector mechanisms that prevent AD (134).

11. Ginsenosides and individuals with Alzheimer's disease

The American National Institute of Neurological and Communication Disorders and Stroke, and the Alzheimer's Disease Association formed the most commonly used set of criteria for the diagnosis of AD. The following neuropsychological tests are therefore widely used to assess cognitive impairment: i) Mini-Mental Status Examination (MMSE); ii) AD assessment scale (ADAS), which includes the cognitive subscale (ADAS-cog) and the non-cognitive subscale (ADAS-non-cog); iii) 'Frontal Assessment Battery' (FAB) Test and iv) clinical dementia rating (CDR) (135).

Studies have been conducted to assess the effects of ginseng components on the course of AD in humans. The clinical efficacy of heat-processed ginseng with the novel ginsenoside

complex, SG-135, was confirmed in relation to cognitive function in patients with moderately severe disease. An increase in the ADAS-cog, ADAS-non-cog and MMSE tests has been proven to occur as a function of the SG-135 dose (136).

The groups treated with the higher dose exhibited an improvement in cognitive improvement as early as at 12 weeks, which was sustained for 24 weeks of follow-up. The SG-treated patients also exhibited an improving trend over time. Improvement in cognitive function following SG treatment supports the findings that ginsenosides Rg3(R), Rg3(S) and Rg5/Rk1 exert memory-enhancing effects due to their neuroprotective actions against excitotoxicity (136).

Yang *et al* (137) investigated the neuroprotective and antioxidant effects of ginsenoside compound K (CK) on a mouse model of memory impairment induced by scopolamine hydrobromide. It should be noted that protopanaxadiol saponin is degraded by the intestinal flora into ginsenoside CK (20-*O*- β -D-glucopyranosyl-20-(S)-protopanaxadiol) (CK). The role of CK in the regulation of A β and its ability to activate the Nrf2/Keap1 signaling pathway have also been studied due to their great significance for AD. It has been proven that ginsenoside CK improves memory function, inhibits the expression of A β and activates the Nrf2/Keap1 signaling pathway in animals exposed to scopolamine. Based on these results, Yang *et al* (137) concluded that ginsenoside CK can improve memory function by regulating A β aggregation and facilitating the transduction of the Nrf2/Keap1 signaling pathway, thereby reducing oxidative damage to neurons and inhibiting neuronal apoptosis. Rg3 is the most effective ginsenoside having an A β -lowering effect, and the effect is correlated with the dose of Rg3. Similarly, Heo *et al* observed dose-related cognitive improvements following SG treatment (136).

Of note, Korean white ginseng root powder was previously shown to improve the performance of the ADAS-cog and MMSE tests. However, the ADAS-non-cog test scores remained unaltered, and the test scores evened out with those of the control group after the drug was discontinued (138). An increase in indicators was only found in the ADAS-cog and CDR tests, while the indicators of the ADAS-non-cog and MMSE tests were the same as those of the control group in a similar study using Korean red ginseng (KRG) root powder (139). Moreover, electroencephalography was used to assess the effectiveness of KRG root powder in relation to cognitive functions. An increase in relative alpha power was found in patients with AD who were treated with KRG root powder, which indicates an improvement in the functions of the frontal lobe. The FAB test scores also increased, although the MMSE scores remained unaltered (140).

In a different study, cognitive functions were assessed every 12 weeks, using the ADAS and the Korean version of the Mini-mental status examination (K-MMSE), to investigate maintenance doses of 4.5 and 9.0 g of KRG per day (141). A significant improvement was observed in groups that took KRG for 24 weeks. The improved MMSE score did not exhibit significant decreases at the 48th and 96th week, in a long-term assessment of the impact effectiveness of KRG. Similar results were obtained in the ADAS-assessment. The maximum improvement was found on the 24th week (141).

In another study, improved cognitive function was demonstrated with KRG treatment as was the sustainability

of the achieved clinical goals in patients with AD. Previously, data on the long-term effects of KRG in patients with AD were limited, and studies did not exceed a few months (138), meaning that these shorter-term studies did not exactly indicate whether the effect of ginseng is temporary or whether it is able to continue to suppress the progressive course of AD. The results obtained in the long-term KRG study indicated that the effectiveness of KRG on cognitive function during the course of AD can be maintained for at least 2 years (141).

Several long-term (over 2 years) tests on AChE inhibitors have demonstrated that, although the efficacy of the drugs is evident, they were not able to block or reverse cognitive decline (142,143). The 2-year MMSE decline typically ranged from 2.5 to 4.0 points compared to the initial estimate. The usual picture of cognitive decline shows an initial improvement of 3 or 6 months, and then decreases to baseline over about a year in patients taking conventional medication. The disease then progresses again. By contrast, the ADAS-cog and K-MMSE scores were stable and did not exhibit an obvious decrease at the registration times over 2 years (141). This clinical picture can be explained by the difference in the main mechanisms of action of ginseng and anticholinesterase. The effect of ginseng on cognitive function with underlying specific mechanisms of influence has been considered (144). It is known that ginsenoside Rb1 improves learning and memory in tasks that are dependent on the hippocampus, and that it increases cell survival in the dentate gyrus of the medial and lower hemispheres of the large brain and in the hippocampal subregion CA3 (145). Ginsenoside Rg1 has been observed to weaken A β_{1-42} -induced neurotoxicity and τ -hyperphosphorylation, in a dose-dependent manner, at several sites that are associated with AD (146). Moreover, it has been suggested that ginsenoside Rg1 and Rb1 potentiate cholinergic pathways in the central nervous system and it was found that both ginsenosides Rg1 and Rb1 enhance the activity of ChAT and inhibit the activity of AChE, thereby enhancing the function of the cholinergic system (147).

The introduction of Rg1 and Rb1 to mice in the post-weaning period has been shown to increase the thickness and density of the cerebral cortex in the CA3 region of the hippocampus, which is believed to modulate synaptic plasticity, regarded as one of the most important learning and memory mechanisms (148).

12. Conclusion

We herein present a literature survey on the ginseng components that have exhibited biological activity on the pathogenesis of AD. Information on the effects of ginseng components on the signs of AD is depicted in Table III. The same symptoms that are observed in patients with AD are artificially created in animal models of AD; the mechanisms that trigger AD have not yet been confirmed with all possible accuracy. However, BAS found in ginseng can have a significant protective and inhibitory effect on the further development of AD, as shown by the foregoing review and general research data, summarized in Table III. The data obtained in studies on the effects of ginseng components on patients with AD have shown that ginseng preparations can be used for maintenance therapy.

Table III. Effect of the components of ginseng on the pathogenesis of AD.

| Model AD | Treatment | Research results | Authors/(Refs.) |
|--|--|--|------------------------|
| Enzyme activity measurement (without models) | Ginsenosides Rb1, Rb2, Rc, Re, Rg1 and Rg3 | ↓ Activity AChE (except Rc); ↓ Activity BChE (except Rc and Re); ↓ Activity BACE1 (except Rg3 and Re); Neutralization of pyroxyinitrite; ↓ Nitrotyrosine formation; | Shin <i>et al</i> (38) |
| Rat PC12 cells; Introduction A β ₂₅₋₃₅ | Extract <i>Panax japonicus</i> | 5 Components that are inhibitors of AChE were selected | Li <i>et al</i> (37) |
| Male ICR mice (6 weeks); Intracerebroventricular injection A β ₁₋₄₂ | Cereboost™ (extract <i>Panax quinquefolius</i>) | ↑ Cognitive abilities of mice; ↓ Activity AChE; ↓ Cytotoxicity A β ₁₋₄₂ in stem cell; ↑ Expression ChAT; ↓ Level A β ₁₋₄₂ ; ↑ Level MAP2; ↑ Synaptophysin level; ↑ ACh level; | Li <i>et al</i> (103) |
| Wistar rats Streptozocin administration | Ginsenoside Rg5 | ↑ Cognitive abilities of rats; ↑ Expression BDNF; ↑ Expression IGF-1; ↓ Level A β ₁₋₄₂ ; ↓ Activity AChE; ↑ Activity ChAT; ↓ Level TNF- α ; ↓ Level IL-1 β ; ↑ Expression COX-2; ↓ Expression NOS2; | Chu <i>et al</i> (41) |
| ICR male mice (7 weeks, 30-33 g); Intragypocampal injection A β O | White ginseng root extract (age 4 years) | Suppression of the activation of microglia; ↑ Memory function in mice; ↓ Neuron death; ↑ Cholinergic degeneration in the hippocampus | Choi <i>et al</i> (42) |
| N2a/APP695 cell line; | Ginsenoside Re | ↓ Substance production A β ; Activation PPAR γ ; ↓ Activity BACE1; | Cao <i>et al</i> (49) |
| Male Sprague-Dawley rats Intragypocampal injection A β ₁₋₄₂ | Ginsenoside Rg1 | ↑ Cognitive abilities of rats; ↓ Level A β ₁₋₄₂ ; ↑ Expression IDE; Activation PPAR γ | Quan <i>et al</i> (50) |
| Female rats with ovaries removed (280-300 g) HT22 hippocampal neuronal cell line expressing ER | Ginsenoside Rd | ↑ Cognitive abilities of rats; ↓ Level A β ₁₋₄₂ ; ↑ Level sAPP α ; ↑ Activity of signalling pathway MAPK/ERK; ↑ Activity of signalling pathway PI3K/AKT; ↑ Expression α -secretase; ↓ Expression BACE1; ↑ Level p-ERK, total level ERK was not altered; ↑ Level p-AKT, total level AKT was not altered; ↑ Expression p-ER α , total expression ER α , ER β levels not altered; | Yan <i>et al</i> (51) |
| Line of neuronal cells of the hippocampus HT22 Human neuroblastoma cells SH-SY5Y | Ginsenoside Rg1 | ↑ Cognitive abilities of rats; ↑ Level sAPP α ; ↑ Activity α - secretase; | Shi <i>et al</i> (52) |

Table III. Continued.

| Model AD | Treatment | Research results | Authors/(Refs.) |
|--|--|---|-------------------------|
| Female Wistar rats with ovaries removed (9 months) | | ↓ Level A β_{1-42} ; ↑ Level p-ERK and ERK; ↑ Level p-AKT and AKT; ↑ Expression p-ER α and ER α ; | |
| 12 women with menopause Platelet rich plasma taken | Ginsenoside Rg1 | ↑ Level sAPP α ; ↓ Level A β_{1-42} ; ↑ Activity α -secretase; ↑ Level p-ERK1/2, without affecting the overall level ERK1/2; | Shi <i>et al</i> (53) |
| Female Wistar rats (10 weeks, 260-300 g) Ovarian removal Injection of D-galactose | Ginsenoside Rg1 | ↑ Cognitive abilities of rats; ↓ Generation A β_{1-42} ; ↓ Activity caspase-3; ↓ Cell apoptosis; ↑ Expression ADAM10; ↓ Expression BACE1; | Zhang <i>et al</i> (54) |
| Mice SAP8 (with elevated level APP and A β_{1-42}) | Saponins from <i>Panax notoginseng</i> | ↑ Activity α -secretase; ↓ Activity BACE1; Activity of γ -secretase was not altered | Huang <i>et al</i> (55) |
| Cortical neurons from mouse embryos Tg2576 | Ginsenoside Rh2 | ↑ Cognitive abilities of mice; ↓ Level A β_{1-42} ; Activity of α -secretase and BACE1 was not altered; ↑ Level sAPP α ; Total level of APP was not altered; ↑ Cholesterol level in neurons; | Qiu <i>et al</i> (58) |
| Neuronal differentiated mouse embryonic stem cells Transgenic APP/PSI mice | Ginsenoside Rg3 | ↓ Level A β_{1-42} ; ↑ Activity of PI4KII α ; | Kang <i>et al</i> (64) |
| Human neuroblastoma cells SH-SY5Y Transgenic mice (with elevated level A β_{1-42}) | Gintonin (glyco-lipoprotein fraction of ginseng extract) | ↑ Activity LPAR ↓ Level A β_{1-42} ; ↑ Level sAPP α ; ↓ Cytotoxicity A β_{1-42} in cells; ↑ Cognitive abilities of mice; ↓ Microglial activation; | Hwang <i>et al</i> (89) |
| Cell PC12 Injection A β_{25-35} | Ginsenoside Rg2 | ↑ Cell viability; ↓ Level LDH; ↓ Level ROS; ↓ Intracellular level Ca ²⁺ ; ↓ Activity of caspase-3; ↑ Ratio Bcl-2/Bax; ↑ Level p-Akt; ↓ Cytotoxicity A β_{1-42} in cells; | Cui <i>et al</i> (95) |
| Cells PC12 Injection of glutamate | Ginsenoside Rg2 | ↑ Neuroprotective properties; ↓ Intracellular level Ca ²⁺ ; ↓ Level MDA; ↓ Level NO; ↓ Level A β_{1-42} ; ↓ Expression caspase-3; ↓ Expression calpain II; | Li <i>et al</i> (96) |
| Primary cortical neurons Sprague-Dawley rats Injection A β_{25-35} | Ginsenoside Rb1 | ↓ Level p-tau; ↓ Cytotoxicity A β_{25-35} in cells; ↓ Level and expression CDK5; ↓ Calpain activity; ↓ Intracellular level Ca ²⁺ ; | Chen <i>et al</i> (97) |

Table III. Continued.

| Model AD | Treatment | Research results | Authors/(Refs.) |
|--|--|--|-------------------------|
| SD rats A β_{25-35} injection | Ginsenoside Rg1 | ↓ Current density through high-threshold calcium channels through MAPK; | Quan <i>et al</i> (98) |
| Female Wistar rats (3 months), Tg APP/PSI rats | Ginsenoside Rg1 | ↓ Accumulation of NFTs; ↓ Level of A β_{1-42} ; ↓ Apoptosis; ↓ Expression of IRE-1; ↓ Expression of TRAF2; ↓ Expression of p-JNK; | Mu <i>et al</i> (81) |
| Male Sprague-Dawley rats Intracerebroventricular injection A β_{1-42} Liu J | Ginsenoside Rd | ↑ Cognitive abilities of rats; ↑ Neuroprotective properties; ↓ Cytotoxicity of A β_{1-42} ; ↓ Expression IL-1 β ; ↓ Level and expression of IL-6; ↑ Level and expression of IL-10; ↓ Level and expression of TNF- α ; ↑ Expression of HSP70; ↓ Ratio of GSSG/GSH; ↓ Expression of caspase-3; | Liu <i>et al</i> (87) |
| Primary cortical neurons from the brain of newborn (0-24 h) mice; Female rats (260-280 g); Injection of D-galactose and aluminum chloride | <i>Panax ginseng</i> <i>C.A. Meyer</i> root extract (aged 4 years) | ↑ Survival rate ↓ Neuronal apoptosis <i>in vitro</i> ; ↑ Ratio of expression p-PKA/PKA and p-CREB/CREB; ↓ Concentration of MDA; ↓ Concentration of NO; ↑ Ratio of Bcl-2/Bax; ↓ Expression of caspase-3; ↓ Level of p-Tau; ↑ Activity of SOD; ↓ Activity of NOS2 and NOS; ↑ Level of cAMP; | Li <i>et al</i> (103) |
| Cortical cortical neurons (PC12 cells) | Radix Notoginseng flavonol glycoside (RNFG), quercetin 3-O- β -D-xylo- pyranosyl- β -D- galactopyranoside | ↓ Cytotoxicity A β_{1-42} in cells; ↓ Level of A β_{1-42} ; ↓ Level of ROS; | Choi <i>et al</i> (104) |
| APP transgenic mice (10 months) | Ginsenoside Rd | ↑ Cognitive abilities of mice; ↓ Expression and activity of NF- κ B p65; ↓ Level of IL-1 β ; ↓ Level of TNF- α ; d ↓ Level of IL-6; ↓ Level of IL-10; | Liu <i>et al</i> (88) |
| Male Wistar rats (3-4 weeks, 250-300 g) Intracerebroventricular injection A β_{1-42} | Ginsenoside Rb1 | ↑ Cognitive abilities of rats; ↓ Level of A β_{1-42} ;0 ↓ Level of COX2; ↑ Level of iNOS; | Wang <i>et al</i> (85) |
| Female Wistar rats (260-280 g); Injection of D-galactose and aluminum chloride | <i>Panax ginseng</i> C.A. <i>Meyer</i> root extract (age 4 years) | ↑ Cognitive abilities of rats; ↓ Quantity A β_{1-42} ; ↓ Quantity p-tau; ↑ Activity of PI3K/Akt signalling pathway; | Li <i>et al</i> (114) |

Table III. Continued.

| Model AD | Treatment | Research results | Authors/(Refs.) |
|---|----------------------------|---|---------------------------|
| Male Sprague-Dawley rats (200-240 g) Intracerebroventricular injection OKA | Ginsenoside Rg1 | ↓ Cognitive abilities of rats; ↓ Level of p-Tau; ↑ Level of GSK3β-Tyr216; ↑ Level of Aβ ₁₋₄₂ ; | Song <i>et al</i> (118=6) |
| Male Sprague-Dawley rats (270-320 g) Artificial cerebral ischemia | Ginsenoside Rd | ↑ Cognitive abilities of mice; ↓ Level p-Tau; ↑ Activity of AKT | Zhang <i>et al</i> (119) |
| Male Sprague-Dawley rats Cortical neurons Injection OKA | Ginsenoside Rd | ↑ Weight of rats without changing morphology in the hippocampus and cerebral cortex; ↑ Neuroprotective properties <i>in vitro</i> ; ↓ Phosphorylation of Tau <i>in vitro</i> ; ↑ Activity of PP-2A | Li <i>et al</i> (121) |
| APP/PS1 mice | Ginsenoside Rg1 | ↑ Memory function of mice; ↓ Level p-Tau; ↓ Level of Aβ ₁₋₄₂ ; Expression of APP was not altered; ↓ Level of APP; ↑ Expression of BDNF; ↑ Level of p-TrkB; | Li <i>et al</i> (75) |
| Male Wistar rats weighting 180-220 g Injection of D-galactose (D-gal) with AlCl ₃ (Al) for 60 days | Ginseng extract | ↑ Cognitive abilities of mice; ↓ Neuronal death; ↓ Level of Aβ ₁₋₄₂ ; ↓ Level of p-Tau; ↑ Blood glycine level; ↑ Level of 5- hydroxytryptamine in blood; | Zhang <i>et al</i> (43) |
| Male SAMP8 and SAMR1 mice (6 months) | Ginsenoside Rg1 | ↑ Cognitive abilities of mice; ↓ Level of Aβ ₁₋₄₂ ; ↓ Level of PKA RIIα; ↑ Level of p-CREB; ↑ Level of BDNF | Shi <i>et al</i> (125) |
| 12-Month-old mice (18-22 g); Intracerebroventricular injection | Ginsenoside Re | ↑ Cognitive abilities of mice; ↑ Hexadecanosphinganine and phytosphingosine concentrations; ↑ Phenylalanine concentration; ↓ Tryptophan concentration | Li <i>et al</i> (133) |
| Male Kunming mice (12-month-old mice, 18-22 g) Intragypocampal injection Aβ ₁₋₄₂ | Ginsenosides Rg1 and Rb1 | ↑ Level of LPC; ↓ Level of phenylalanine; ↑ Tryptophan level; ↑ Dihydrosphingosine for Rg1 (unaltered level for Rb1) | Li <i>et al</i> (74) |
| Male mice APP/PS1 and C57BL/6j | Ginsenosides Rg1 and Rg2 | ↑ Cognitive abilities of mice; ↓ Level Aβ ₁₋₄₂ ; ↑ Hypoxanthine level; ↑ Level LPC; Change in metabolic profile for sphingolipids | Li <i>et al</i> (73) |
| SH-SY5Y cells Exposure to Aβ ₂₅₋₃₅ | Ginsenoside Rb1 SILAC | Change in levels of 40 proteins in response to Rb1 pretreatment in β-amyloid-treated cells | Hwang <i>et al</i> (134) |
| 40 Individuals with AD (72.9 ± 9.4 years old) | Ginsenoside complex SG-135 | ↑ Indicators ADAS-cog; ↑ Indicators ADAS-non-cog; ↑ Indicators K-MMSE | Heo <i>et al</i> (136) |

Table III. Continued.

| Model AD | Treatment | Research results | Authors/(refs.) |
|---|--|---|------------------------|
| 97 Individuals with AD (47-83 years old) | Ginseng root powder (age 6 years) | ↑ indicators MMSE; ↑ indicators ADAS-cog; Indicators ADAS-non-cog did not change The MMSE and ADAS-cog rates were the same as in the control group 12 weeks after discontinuation of the ginseng drug | Lee <i>et al</i> (138) |
| 61 Individuals with AD (50-80 years old) | Red Korean Ginseng root powder (age 6 years) | ↑ Indicators ADAS-cog; ↑ Indicators CDR; Indicators ADAS-non-cog were not altered; Indicators MMSE were not altered | Heo <i>et al</i> (139) |
| 14 Individuals with AD (74.93±7.63 years old) | Red Korean Ginseng root powder (age 6 years) | ↑ test results FAB; ↑ the power of the alpha rhythm in the right temporal, parietal and occipital regions of the brain; K-MMSE did not change | Heo <i>et al</i> (140) |
| 61 Individuals with AD (60-80 years old) | Red Korean Ginseng root powder (age 6 years) | ↑ indicators ADAS-cog; ↑ indicators MMSE | Heo <i>et al</i> (141) |

AD, Alzheimer's disease; Ach, Acetylcholine; Ache, acetylcholinesterase; BChE, butyrylcholinesterase; APP, amyloid precursor protein; sAPP α , water soluble α -amyloid; ER, estrogen receptor; PI4KII α , phosphatidylinositol-4-kinase 2 α ; LPC, lysophosphatidylcholines; TrkB, tyrosine receptor kinase B; ADAM10, a-secretase a disintegrin and metallopeptidase domain 10; ROS, reactive oxygen species; TNF- α , tumour necrosis factor α ; NO, nitric oxide; NOS2, synthase nitric oxide 2, induced; SD, Sprague-Dawley; CDK5, cyclin-dependent kinase 5; GSK3, glycogen synthase kinase 3; TRAF2, tumour necrosis factor receptor 2; p-JNK, phosphorylated-c-Jun N-terminal protein kinase associated with apoptosis; IGF-1, insulin-like growth factor-1; cAMP, cyclic adenosine monophosphate; CREB, cAMP response-element-binding protein; SILAC, stable isotope labelling of amino acids in a cell culture; MMSE, Mini-Mental Status Examination; K-MMSE Korean MMSE; CDR, Clinical Evaluation of Dementia; PPAR, peroxisome proliferator activated receptor.

At the same time, a drug that consists of correctly selected ratios of the various components of ginseng is likely to be more effective than a simple ginseng root extract. However, the creation of such a drug will entail large-scale studies on the effects of individual components of ginseng on patients with AD.

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Data sharing is not applicable to this review article, as no datasets were generated or analyzed during the current study.

Authors' contributions

MPR, AT and KSG conceptualized and designed the study. MPR, DAS and AMZ collected, organized and drafted the information. AEN and GC collected information on the introduction and history of ginseng. MPR and VVV collected data and prepared tables. MPR, KSG and AEN wrote the manuscript. KSG, AMT and DAS revised the manuscript critically and advised revisions. All authors have read and approved the manuscript.

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References

- Alzheimer A, Stelzmann RA, Schnitzlein HN and Murtagh FR: An English translation of Alzheimer's 1907 paper, 'Über eine eigenartige Erkrankung der Hirnrinde'. *Clin Anat* 8: 429-431, 1995.
- Hardy J and Allsop D: Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* 12: 383-388, 1991.
- Donev R, Kolev M, Millet B and Thome J: Neuronal death in Alzheimer's disease and therapeutic opportunities. *J Cell Mol Med* 13: 4329-4348, 2009.
- Liu Z, Li T, Li P, Wei N, Zhao Z, Liang H, Ji X, Chen W, Xue M and Wei J: The ambiguous relationship of oxidative stress, tau hyperphosphorylation, and autophagy dysfunction in Alzheimer's disease. *Oxid Med Cell Longev* 2015: 352723, 2015.
- Hernández F and Avila J: Tauopathies. *Cell Mol Life Sci* 64: 2219-2233, 2007.
- Brekhman II, Dardymov IV and Dobriakov II: On the pharmacology of individual glycosides from the roots of *Panax ginseng* C.A. Mey. *Farmakol Toksikol* 29: 167-171, 1966 (In Russian).
- Elyakov G, Strigina L, Khorlin A and Kochetkov H: Glycosides of ginseng (*Panax ginseng* C. A. Mey). *Bulletin of the Academy of Sciences of The USSR, Division of Chemical Science*. Vol 11, Issue 6, pp1055-1055, 1p, 1962. https://searchworks.stanford.edu/articles/edb_72505988.
- Brekhman II: Ginseng. Government publisher of medicine literature. Medgiz, Saint Petersburg, pp 3-163, 1957 (Translated from Russian). <http://moodle.pharmi.uz/library/books/Рус/Күшимча%20адабиётлар/Жень-шень.pdf>.
- Fischer FEL and Meyer CA: *Enumeratio plantarum novarum a cl. Schrenk lectarum [Flora change from Cl. Schrenk Lectarum]*. Petropoli Publishers, 1841-1842.
- Arsenyev VK: Myths, legends, traditions, and fables of peoples of Far East. Monograph Series, International Institute of Ethnolinguistic and Oriental Studies (IIEOS), ISSN 1230-3283; 10, ISBN 83-902273-4-7, 1995.
- Przhevalsky N: Mongolia, The Tangut Country and the Solitudes of Northern Tibet. Translated by E.D. Morgan. Editor (Yule H). London: Sampson Low, Marston, Searle & Rivington, 2; 24, 1876.
- Maak R: Journey through the Ussuri river valley. The Siberian Department of the Imperial Russian Geographical Society, 1-2. V. Bezobrazov and Co Printers, Saint Petersburg, 1861.
- Maximowicz CJ: Diagnoses des nouvelles plantes du Japon et de la Mandjourie [Diagnoses of the new plants of Japan and Mandjourie]. In: *Bulletin de l'Academie Imperiale des Sciences de St. Petersburg*. Tome dix-huitieme. Saint Petersburg, XII decade, p 41.1873.
- Komarov VL: Coniferae of Manchuria. *Trudy Imp. Saint Petersburg. Obsc.* 32: 230-241, 1902.
- Shishkin IK: Studies about the flora of Iman River. *Materials of the Vladivostok, Branch of the Russian Geographical Society* 5: 128-130, 1930.
- Gutnikova ZI: Ginseng in Suputinsky reserve. *Materials of the Academy of Sciences of the USSR* 4: 257-267, 1941.
- Gutnikova ZI: Preliminary data on the culture of ginseng in the conditions of Suputinsky reserve. *Materials of the Academy of Sciences of the USSR* 1955.
- Vysotsky KK: To the question of the biology of wild ginseng. *Main Directorate of USSR Reserves* 7: 254-262, 1940.
- Bayanova VB: Conditions of ginseng growth in the 'Kedrovaya Pad' reserve. *Materials of the mountain taiga station of the Academy of Sciences of the USSR* 4: 217-231, 1941.
- Kurentsova GE: Medicinal plants of the Soviet Far East. *Materials of the mountain taiga station of the Academy of Sciences of the USSR* 4: 15-97, 1941.
- Zakutinsky DI: Pharmacology of ginseng root. *Pharmacol Toxicol* 7: 13-16, 1944.
- Burkat ME and Saksonov P: Materials for the pharmacological characterization of ginseng root. *Pharmacol Toxicol* 10: 7-16, 1947.
- Kiselev VS: Pharmacological study of the ginseng root. *Pharmacol Toxicol* 11: 50-57, 1948.
- Shapiro ML: Ginseng is an active therapeutic drug. *J Sov Med* 6: 17-19, 1947.
- Kuzminskaya RA: Treatment of vegetative dystonia with ginseng root. *Neuropathol Psych* 2: 62-63, 1949.
- Buturlin VV: The use of ginseng root in clinical practice. *Sov Med* 5: 34-36, 1950.
- Brekhman II and Dardymov IV: Pharmacological investigation of glycosides from ginseng and eleutherococcus. *Lloydia* 32: 46-51, 1969.
- Elyakov GB, Strigina LI, Uvarova NI, Vaskovsky VE, Dzizenko AK and Kochetkov NK: Glycosides from ginseng roots. *Tetrahedron Lett* 5: 3591-3597, 1964.
- Elyakov GB, Strigina LI and Kochetkov NK: Glycosides from ginseng roots. VI. Structure of the carbohydrate chain of panaxoside A. In: *Chemistry of Natural Compounds*. Vol. 1, Issue 3, pp114-116, 1965.
- Chen Y, Sun J, Fang L, Liu M, Peng S, Liao H, Lehmann J and Zhang Y: Tacrine-ferulic acid-nitric oxide (NO) donor trihybrids as potent, multifunctional acetyl- and butyrylcholinesterase inhibitors. *J Med Chem* 55: 4309-4321, 2012.
- Geula C and Mesulam MM: Cholinesterases and the pathology of Alzheimer disease. *Alzheimer Dis Assoc Disord* 9 (Suppl 2): 23-28, 1995.
- Wilkinson DG, Francis PT, Schwam E and Payne-Parrish J: Cholinesterase inhibitors used in the treatment of Alzheimer's disease: The relationship between pharmacological effects and clinical efficacy. *Drugs Aging*: 21, 453-478, 2004.
- Raschetti R, Albanese E, Vanacore N and Maggini M: Cholinesterase inhibitors in mild cognitive impairment: A systematic review of randomised trials. *PLoS Med* 4: e338, 2007.
- Collins LE, Paul NE, Abbas SF, Leser CE, Podurciel SJ, Galtieri DJ, Chrobak JJ, Baqi Y, Müller CE and Salamone JD: Oral tremor induced by galantamine in rats: A model of the parkinsonian side effects of cholinomimetics used to treat Alzheimer's disease. *Pharmacol Biochem Behav* 99: 414-422, 2011.
- Ikonomovic MD, Mufson EJ, Wu J, Bennett DA and DeKosky ST: Reduction of choline acetyltransferase activity in primary visual cortex in mild to moderate Alzheimer's disease. *Arch Neurol* 62: 425-430, 2005.
- Choi RJ, Roy A, Jung HJ, Ali MY, Min BS, Park CH, Yozozawa T, Fan TP, Choi JS and Jung HA: BACE1 molecular docking and anti-Alzheimer's disease activities of ginsenosides. *J Ethnopharmacol* 190: 219-230, 2016.
- Li S, Liu C, Liu C and Zhang Y: Extraction and *in vitro* screening of potential acetylcholinesterase inhibitors from the leaves of *Panax japonicus*. *J Chromatogr B Analyt Technol Biomed Life Sci* 1061-1062: 139-145, 2017.
- Shin K, Guo H, Cha Y, Ban YH, Seo W, Choi Y, Kim TS, Lee SP, Kim JC, Choi EK, *et al*: Cereboost™, an American ginseng extract, improves cognitive function via up-regulation of choline acetyltransferase expression and neuroprotection. *Regul Toxicol Pharmacol* 78: 53-58, 2016.
- Lee MR, Yun BS, Liu L, Zhang DL, Wang Z, Wang CL, Gu LJ, Wang CY, Mo EK and Sung CK: Effect of black ginseng on memory improvement in the amnesic mice induced by scopolamine. *J Ginseng Res* 34: 51-58, 2010.
- Wang Q, Sun LH, Jia W, Liu XM, Dang HX, Mai WL, Wang N, Steinmetz A, Wang YQ and Xu CJ: Comparison of ginsenosides Rg1 and Rb1 for their effects on improving scopolamine-induced learning and memory impairment in mice. *Phytother Res* 24: 1748-1754, 2010.
- Chu S, Gu J, Feng L, Liu J, Zhang M, Jia X, Liu M and Yao D: Ginsenoside Rg5 improves cognitive dysfunction and beta-amyloid deposition in STZ-induced memory impaired rats via attenuating neuroinflammatory responses. *Int Immunopharmacol* 19: 317-326, 2014.
- Choi JG, Kim N, Huh E, Lee H, Oh MH, Park JD, Pyo MK and Oh MS: White ginseng protects mouse hippocampal cells against amyloid-beta oligomer toxicity. *Phytother Res* 31: 497-506, 2017.
- Zhang Y, Pi Z, Song F and Liu Z: Ginsenosides attenuate d-galactose- and AIC13-induced spatial memory impairment by restoring the dysfunction of the neurotransmitter systems in the rat model of Alzheimer's disease. *J Ethnopharmacol* 194: 188-195, 2016.
- Karp G (ed): *Cell and Molecular Biology: Concepts and Experiments*. 6th edition. John Wiley & Sons, New York, NY, 2009.
- Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, *et al*: Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 286: 735-741, 1999.
- Ohnishi S and Takano K: Amyloid fibrils from the viewpoint of protein folding. *Cell Mol Life Sci* 61: 511-524, 2004.

47. Fahrenholz F: Alpha-secretase as a therapeutic target. *Curr Alzheimer Res* 4: 412-417, 2007.
48. Gubandru M, Margina D, Tsitsimpikou C, Goutzourelas N, Tsarouhas K, Ilie M, Tsatsakis AM and Kouretas D: Alzheimer's disease treated patients showed different patterns for oxidative stress and inflammation markers. *Food Chem Toxicol* 61: 209-214, 2013.
49. Cao G, Su P, Zhang S, Guo L, Zhang H, Liang Y, Qin C and Zhang W: Ginsenoside Re reduces A β production by activating PPAR γ to inhibit BACE1 in N2a/APP695 cells. *Eur J Pharmacol* 793: 101-108, 2016.
50. Quan Q, Wang J, Li X and Wang Y: Ginsenoside Rg1 decreases A β ₁₋₄₂ level by upregulating PPAR γ and IDE expression in the hippocampus of a rat model of Alzheimer's disease. *PLoS One* 8: e59155, 2013.
51. Yan X, Hu G, Yan W, Chen T, Yang F, Zhang X, Zhao G and Liu J: Ginsenoside Rd promotes non-amyloidogenic pathway of amyloid precursor protein processing by regulating phosphorylation of estrogen receptor alpha. *Life Sci* 168: 16-23, 2017.
52. Shi C, Zheng DD, Fang L, Wu F, Kwong WH, and Xu J: Ginsenoside Rg1 promotes nonamyloidogenic cleavage of APP via estrogen receptor signaling to MAPK/ERK and PI3K/Akt. *Biochim Biophys Acta* 1820: 453-460, 2012.
53. Shi C, Na N, Zhu X and Xu J: Estrogenic effect of ginsenoside Rg1 on APP processing in post-menopausal platelets. *Platelets* 24: 51-62, 2013.
54. Zhang X, Wang J, Xing Y, Gong L, Li H, Wu Z, Li Y, Wang J, Wang Y, Dong L and Li S: Effects of ginsenoside Rg1 or 17 β -estradiol on a cognitively impaired, ovariectomized rat model of Alzheimer's disease. *Neuroscience* 220: 191-200, 2012.
55. Huang J, Wu D, Wang J, Li F, Lu L, Gao Y and Zhong Z: Effects of *Panax notoginseng* saponin on α , β , and γ secretase involved in A β deposition in SAMP8 mice. *Neuroreport* 25: 89-93, 2014.
56. Zetterberg H, Alexander DM, Spandidos DA and Blennow K: Additional evidence for antagonistic pleiotropic effects of APOE. *Alzheimers Dement* 5: 75, 2009.
57. Endres K and Fahrenholz F: Upregulation of the α -secretase ADAM10-risk or reason for hope? *FEBS J* 277: 1585-1596, 2010.
58. Qiu J, Li W, Feng SH, Wang M and He ZY: Ginsenoside Rh2 promotes nonamyloidogenic cleavage of amyloid precursor protein via a cholesterol-dependent pathway. *Genet Mol Res* 13: 3586-3598, 2014.
59. Reiss AB and Voloshyna I: Regulation of cerebral cholesterol metabolism in Alzheimer disease. *J Investig Med* 60: 576-582, 2012.
60. Barrett PJ, Song Y, Van Horn WD, Hustedt EJ, Schafer JM, Hadziselimovic A, Beel AJ and Sanders CR: The amyloid precursor protein has a flexible transmembrane domain and binds cholesterol. *Science* 336: 1168-1171, 2012.
61. Korade Z and Kenworthy AK: Lipid rafts, cholesterol, and the brain. *Neuropharmacology* 55: 1265-1273, 2008.
62. Di Paolo G and De Camilli P: Phosphoinositides in cell regulation and membrane dynamics. *Nature* 443: 651-657, 2006.
63. Balla A and Balla T: Phosphatidylinositol 4-kinases: Old enzymes with emerging functions. *Trends Cell Biol* 16: 351-361, 2006.
64. Kang MS, Baek SH, Chun YS, Moore AZ, Landman N, Berman D, Hyun Ok Yang, Morishima-Kawashima M, Osawa S, Funamoto S, *et al*: Modulation of lipid kinase PI4KIIa activity and lipid raft association of presenilin 1 underlies γ -secretase inhibition by ginsenoside (20S) Rg3. *J Biol Chem* 288: 20868-20882, 2013.
65. Kwik J, Boyle S, Fooksman D, Margolis L, Sheetz MP and Edidin M: Membrane cholesterol, lateral mobility, and the phosphatidylinositol 4,5-bisphosphate-dependent organization of cell actin. *Proc Natl Acad Sci USA* 100: 13964-13969, 2003.
66. Fraering PC, Ye W, Strub JM, Dolios G, LaVoie MJ, Ostaszewski BL, van Dorsselaer A, Wang R, Selkoe DJ and Wolfe MS: Purification and characterization of the human γ -secretase complex. *Biochemistry* 43: 9774-9789, 2004.
67. Barber J: Merck & Co. terminates Phase III study of verubecestat in prodromal Alzheimer's disease. *First Word Farma*, Feb 13, 2018. <https://www.firstwordpharma.com/node/1542930>.
68. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, *et al*: Alzheimer's Disease Cooperative Study Steering Committee; Semagacestat Study Group: A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med* 369: 341-350, 2013.
69. Yang L, Hao J, Zhang J, Xia W, Dong X, Hu X, Kong F and Cui X: Ginsenoside Rg3 promotes beta-amyloid peptide degradation by enhancing gene expression of neprilysin. *J Pharm Pharmacol* 61: 375-380, 2009.
70. He Y, Zhao H and Su G: Ginsenoside Rg1 decreases neurofibrillary tangles accumulation in retina by regulating activities of neprilysin and PKA in retinal cells of AD mice model. *J Mol Neurosci* 52: 101-106, 2014.
71. Tohda C, Matsumoto N, Zou K, Meselhy MR and Komatsu K: Abeta(25-35)-induced memory impairment, axonal atrophy, and synaptic loss are ameliorated by M1, A metabolite of protopanaxadiol-type saponins. *Neuropsychopharmacology* 29: 860-868, 2004.
72. Androutsopoulos VP, Kanavouras K and Tsatsakis AM: Role of paraoxonase 1 (PON1) in organophosphate metabolism: Implications in neurodegenerative diseases. *Toxicol Appl Pharmacol* 256: 418-424, 2011.
73. Li N, Liu Y, Li W, Zhou L, Li Q, Wang X and He P: A UPLC/MS-based metabolomics investigation of the protective effect of ginsenosides Rg1 and Rg2 in mice with Alzheimer's disease. *J Ginseng Res* 40: 9-17, 2016.
74. Li N, Zhou L, Li W, Liu Y, Wang J and He P: Protective effects of ginsenosides Rg1 and Rb1 on an Alzheimer's disease mouse model: A metabolomics study. *J Chromatogr B Analyt Technol Biomed Life Sci* 985: 54-61, 2015.
75. Li F, Wu X, Li J and Niu Q: Ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in an Alzheimer's disease model. *Mol Med Rep* 13: 4904-4910, 2016.
76. Li X, Liu Y, Zhang X, Yuan H and Quan Q: [Effect of ginsenoside Rg1 on expressions of phosphory protein tau and N-methyl-D-aspartate receptor subunits NR1 and NR2B in rat brain slice model of Alzheimer's disease]. *Zhongguo Zhong Yao Za Zhi* 35: 3339-3343, 2010 (In Chinese).
77. Roberson ED, Halabisky B, Yoo JW, Yao J, Chin J, Yan F, Wu T, Hamto P, Devidze N, Yu GQ, *et al*: Amyloid- β /Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *J Neurosci* 31: 700-711, 2011.
78. Broestl L, Worden K, Moreno AJ, Davis EJ, Wang D, Garay B, Singh T, Verret L, Palop JJ and Dubal DB: Ovarian Cycle Stages Modulate Alzheimer-Related Cognitive and Brain Network Alterations in Female Mice. *eNeuro* 5: pii: ENEURO.0132-17.2018, 2018.
79. Yang JT, Wang ZJ, Cai HY, Yuan L, Hu MM, Wu MN and Qi JS: Sex Differences in Neuropathology and Cognitive Behavior in APP/PS1/tau Triple-Transgenic Mouse Model of Alzheimer's Disease. *Neurosci Bull* 34: 736-746, 2018.
80. Wang Y, Kan H, Yin Y, Wu W, Hu W, Wang M, Li W and Li W: Protective effects of ginsenoside Rg1 on chronic restraint stress induced learning and memory impairments in male mice. *Pharmacol Biochem Behav* 120: 73-81, 2014.
81. Mu JS, Lin H, Ye JX, Lin M and Cui XP: Rg1 exhibits neuroprotective effects by inhibiting the endoplasmic reticulum stress-mediated c-Jun N-terminal protein kinase apoptotic pathway in a rat model of Alzheimer's disease. *Mol Med Rep* 12: 3862-3868, 2015.
82. Wang ZJ, Sun L, Peng W, Ma S, Zhu C, Fu F and Heinbockel T: Ginseng derivative ocotillol enhances neuronal activity through increased glutamate release: A possible mechanism underlying increased spontaneous locomotor activity of mice. *Neuroscience* 195: 1-8, 2011.
83. Wang C-M, Liu M-Y, Wang F, Wei MJ, Wang S, Wu CF and Yang JY: Anti-amnesic effect of pseudoginsenoside-F11 in two mouse models of Alzheimer's disease. *Pharmacol Biochem Behav* 106: 57-67, 2013.
84. Yan S, Li Z, Li H, Arancio O and Zhang W: Notoginsenoside R1 increases neuronal excitability and ameliorates synaptic and memory dysfunction following amyloid elevation. *Sci Rep* 4: 6352, 2014.
85. Wang Y, Liu J, Zhang Z, Bi P, Qi Z and Zhang C: Anti neuroinflammation effect of ginsenoside Rb1 in a rat model of Alzheimer disease. *Neurosci Lett* 487: 70-72, 2011.
86. Lv C, Li Q, Zhang Y, Sui Z, He B, Xu H, Yin Y, Chen X and Bi K: A UPLC-MS/MS method with a switching ionization mode for simultaneous quantitation of polygalaxanthone III, four ginsenosides and tumulosic acid in rat plasma: Application to a comparative pharmacokinetic study in normal and Alzheimer's disease rats. *J Mass Spectrom* 48: 904-913, 2013.
87. Liu J, Yan X, Li L, Zhu Y, Qin K, Zhou L, Sun D, Zhang X, Ye R and Zhao G: Ginsenoside rd attenuates cognitive dysfunction in a rat model of Alzheimer's disease. *Neurochem Res* 37: 2738-2747, 2012.

88. Liu J, Yan X, Li L, Li Y, Zhou L, Zhang X, Hu X and Zhao G: Gingsenoside Rd Improves Learning and Memory Ability in APP Transgenic Mice. *J Mol Neurosci* 57: 522-528, 2015.
89. Hwang SH, Shin EJ, Shin TJ, Lee BH, Choi SH, Kang J, Kim HJ, Kwon SH, Jang CG, Lee JH, *et al*: Gintonin, a ginseng-derived lysophosphatidic acid receptor ligand, attenuates Alzheimer's disease-related neuropathies: Involvement of non-amyloidogenic processing. *J Alzheimers Dis* 31: 207-223, 2012.
90. Choi DW and Rothman SM: The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. *Annu Rev Neurosci* 13: 171-182, 1990.
91. Braugher JM and Hall ED: Central nervous system trauma and stroke. I. Biochemical considerations for oxygen radical formation and lipid peroxidation. *Free Radic Biol Med* 6: 289-301, 1989.
92. Sousa SC, Maciel EN, Vercesi AE and Castilho RF: Ca²⁺-induced oxidative stress in brain mitochondria treated with the respiratory chain inhibitor rotenone. *FEBS Lett* 543: 179-183, 2003.
93. Dante S, Hauss T and Dencher NA: β -amyloid 25 to 35 is intercalated in anionic and zwitterionic lipid membranes to different extents. *Biophys J* 83: 2610-2616, 2002.
94. Ekinci FJ, Malik KU and Shea TB: Activation of the L voltage-sensitive calcium channel by mitogen-activated protein (MAP) kinase following exposure of neuronal cells to β -amyloid. MAP kinase mediates β -amyloid-induced neurodegeneration. *J Biol Chem* 274: 30322-30327, 1999.
95. Cui J, Wang J, Zheng M, Gou D, Liu C and Zhou Y: Ginsenoside Rg2 protects PC12 cells against β -amyloid 25-35-induced apoptosis via the phosphoinositide 3-kinase/Akt pathway. *Chem Biol Interact* 275: 152-161, 2017.
96. Li N, Liu B, Dluzen DE and Jin Y: Protective effects of ginsenoside Rg2 against glutamate-induced neurotoxicity in PC12 cells. *J Ethnopharmacol* 111: 458-463, 2007.
97. Chen X, Huang T, Zhang J, Song J, Chen L and Zhu Y: Involvement of calpain and p25 of CDK5 pathway in ginsenoside Rb1's attenuation of β -amyloid peptide 25-35-induced tau hyperphosphorylation in cortical neurons. *Brain Res* 1200: 99-106, 2008.
98. Quan QK, Li X, Yuan HF, Wang Y and Liu WL: Ginsenoside Rg1 inhibits high-voltage-activated calcium channel currents in hippocampal neurons of beta-amyloid peptide-exposed rat brain slices. *Chin J Integr Med*: Jan 15, 2016. (Epub ahead of print)
99. Kim S and Rhim H: Ginsenosides inhibit NMDA receptor-mediated epileptic discharges in cultured hippocampal neurons. *Arch Pharm Res* 27: 524-530, 2004.
100. Shin E-J, Koh YH, Kim A-Y, Nah SY, Jeong JH, Chae JS, Kim SC, Yen TP, Yoon HJ and Kim WK: Ginsenosides attenuate kainic acid-induced synaptosomal oxidative stress via stimulation of adenosine A(2A) receptors in rat hippocampus. *Behav Brain Res* 197: 239-245, 2009.
101. Blomgren K, Zhu C, Wang X, Karlsson JO, Leverin AL, Bahr BA, Mallard C and Hagberg H: Synergistic activation of caspase-3 by m-calpain after neonatal hypoxia-ischemia—a mechanism of pathological apoptosis. *J Biol Chem* 276: 10191-10198, 2001.
102. Gervais FG, Xu D, Robertson GS, Vaillancourt JP, Zhu Y, Huang J, LeBlanc A, Smith D, Rigby M, Shearman MS, *et al*: Involvement of caspases in proteolytic cleavage of Alzheimer's amyloid- β precursor protein and amyloidogenic A β peptide formation. *Cell* 97: 395-406, 1999.
103. Li H, Song J, Zhang J, Wang T, Yan Y, Tao Z, Li S, Zhang H, Kang T and Yang J: Ginseng protein reverses amyloid beta peptide and H₂O₂ cytotoxicity in neurons, and ameliorates cognitive impairment in AD rats induced by a combination of D-galactose and A β 1-42. *Phytother Res* 31: 284-295, 2017.
104. Choi RY, Zhu JT, Leung KW, Chu GK, Xie HQ, Chen VP, Zheng KY, Lau DT, Dong TT, Chow PC, *et al*: A flavonol glycoside, isolated from roots of *Panax notoginseng*, reduces amyloid- β -induced neurotoxicity in cultured neurons: Signaling transduction and drug development for Alzheimer's disease. *J Alzheimers Dis* 19: 795-811, 2010.
105. May MJ and Ghosh S: IkappaB kinases: Kinsmen with different crafts. *Science* 284: 271-273, 1999.
106. Boissière F, Hunot S, Faucheux B, Duyckaerts C, Hauw JJ, Agid Y and Hirsch EC: Nuclear translocation of NF-kappaB in cholinergic neurons of patients with Alzheimer's disease. *Neuroreport* 8: 2849-2852, 1997.
107. Park EK, Shin YW, Lee HU, Kim SS, Lee YC, Lee BY and Kim DH: Inhibitory effect of ginsenoside Rb1 and compound K on NO and prostaglandin E2 biosyntheses of RAW264.7 cells induced by lipopolysaccharide. *Biol Pharm Bull* 28: 652-656, 2005.
108. Kim SF, Huri DA and Snyder SH: Inducible nitric oxide synthase binds, S-nitrosylates, and activates cyclooxygenase-2. *Science* 310: 1966-1970, 2005.
109. Prast H and Philippu A: Nitric oxide as modulator of neuronal function. *Prog Neurobiol* 64: 51-68, 2001.
110. Li Y, Zhao Y, Li G, Wang J, Li T, Li W and Lu J: Regulation of neuronal nitric oxide synthase exon 1f gene expression by nuclear factor-kappaB acetylation in human neuroblastoma cells. *J Neurochem* 101: 1194-1204, 2007.
111. Kashour T, Burton T, Dibrov A and Amara FM: Late Simian virus 40 transcription factor is a target of the phosphoinositide 3-kinase/Akt pathway in anti-apoptotic Alzheimer's amyloid precursor protein signalling. *Biochem J* 370: 1063-1075, 2003.
112. van der Heide LP, Ramakers GMJ and Smidt MP: Insulin signaling in the central nervous system: Learning to survive. *Prog Neurobiol* 79: 205-221, 2006.
113. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, *et al*: Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 60: 759-767, 2001.
114. Li H, Kang T, Qi B, Kong L, Jiao Y, Cao Y, Zhang J and Yang J: Neuroprotective effects of ginseng protein on PI3K/Akt signaling pathway in the hippocampus of D-galactose/A β 1-42 inducing rats model of Alzheimer's disease. *J Ethnopharmacol* 179: 162-169, 2016.
115. Kanemaru K: Immunotherapy targeting misfolded proteins in neurodegenerative disease. *Brain Nerv* 65: 469-474, 2013 (In Japanese).
116. Song XY, Hu JF, Chu SF, Zhang Z, Xu S, Yuan YH, Han N, Liu Y, Niu F, He X and Chen NH: Ginsenoside Rg1 attenuates okadaic acid induced spatial memory impairment by the GSK3 β /tau signaling pathway and the A β formation prevention in rats. *Eur J Pharmacol* 710: 29-38, 2013.
117. Plattner F, Angelo M and Giese KP: The roles of cyclin-dependent kinase 5 and glycogen synthase kinase 3 in tau hyperphosphorylation. *J Biol Chem* 281: 25457-25465, 2006.
118. Li L, Liu Z, Liu J, Tai X, Hu X, Liu X, Wu Z, Zhang G, Shi M and Zhao G: Ginsenoside Rd attenuates beta-amyloid-induced tau phosphorylation by altering the functional balance of glycogen synthase kinase 3beta and protein phosphatase 2A. *Neurobiol Dis* 54: 320-328, 2013.
119. Zhang X, Shi M, Ye R, Wang W, Liu X, Zhang G, Han J, Zhang Y, Wang B, Zhao J, *et al*: Ginsenoside Rd attenuates tau protein phosphorylation via the PI3K/AKT/GSK-3 β pathway after transient forebrain ischemia. *Neurochem Res* 39: 1363-1373, 2014.
120. Liu F, Shi J, Tanimukai H, Gu J, Gu J, Grundke-Iqbal I, Iqbal K and Gong CX: Reduced O-GlcNAcylation links lower brain glucose metabolism and tau pathology in Alzheimer's disease. *Brain* 132: 1820-1832, 2009.
121. Li L, Liu J, Yan X, Qin K, Shi M, Lin T, Zhu Y, Kang T and Zhao G: Protective effects of ginsenoside Rd against okadaic acid-induced neurotoxicity *in vivo* and *in vitro*. *J Ethnopharmacol* 138: 135-141, 2011.
122. Xu B, Gottschalk W, Chow A, Wilson RI, Schnell E, Zang K, Wang D, Nicoll RA, Lu B and Reichardt LF: The role of brain-derived neurotrophic factor receptors in the mature hippocampus: Modulation of long-term potentiation through a presynaptic mechanism involving TrkB. *J Neurosci* 20: 6888-6897, 2000.
123. Sakata K, Mastin JR, Duke SM, Vail MG, Overacre AE, Dong BE and Jha S: Effects of antidepressant treatment on mice lacking brain-derived neurotrophic factor expression through promoter IV. *Eur J Neurosci* 37: 1863-1874, 2013.
124. West AE, Chen WG, Dalva MB, Dolmetsch RE, Kornhauser JM, Shaywitz AJ, Takasu MA, Tao X and Greenberg ME: Calcium regulation of neuronal gene expression. *Proc Natl Acad Sci USA* 98: 11024-11031, 2001.
125. Shi YQ, Huang TW, Chen LM, Pan XD, Zhang J, Zhu YG and Chen XC: Ginsenoside Rg1 attenuates amyloid- β content, regulates PKA/CREB activity, and improves cognitive performance in SAMP8 mice. *J Alzheimers Dis* 19: 977-989, 2010.
126. Bao C, Wang Y, Min H, Zhang M, Du X, Han R and Liu X: Combination of ginsenoside Rg1 and bone marrow mesenchymal stem cell transplantation in the treatment of cerebral ischemia reperfusion injury in rats. *Cell Physiol Biochem* 37: 901-910, 2015.

127. Zhou Y, Li HQ, Lu L, Fu DL, Liu AJ, Li JH and Zheng GQ: Ginsenoside Rg1 provides neuroprotection against blood brain barrier disruption and neurological injury in a rat model of cerebral ischemia/reperfusion through downregulation of aquaporin 4 expression. *Phytomedicine* 21: 998-1003, 2014.
128. Li Y, Guan Y, Wang Y, Yu CL, Zhai FG and Guan LX: Neuroprotective effect of the ginsenoside Rg1 on cerebral ischemic injury in vivo and in vitro is mediated by PPAR γ -regulated antioxidative and anti-inflammatory pathways. *Evid Based Complement Alternat Med* 2017: 7842082, 2017. doi: 10.1155/2017/7842082.
129. Yang Y, Li X, Zhang L, Liu L, Jing G and Cai H: Ginsenoside Rg1 suppressed inflammation and neuron apoptosis by activating PPAR γ /HO-1 in hippocampus in rat model of cerebral ischemia-reperfusion injury. *Int J Clin Exp Pathol* 8: 2484-2494, 2015.
130. Lin M, Sun W, Gong W, Ding Y, Zhuang Y and Hou Q: Ginsenoside Rg1 protects against transient focal cerebral ischemic injury and suppresses its systemic metabolic changes in cerebral injury rats. *Acta Pharmaceutica Sinica B* 5: 277-284, 2015.
131. Xie CL, Li JH, Wang WW, Zheng GQ and Wang LX: Neuroprotective effect of ginsenoside-Rg1 on cerebral ischemia/reperfusion injury in rats by downregulating protease-activated receptor-1 expression. *Life Sci* 121: 145-151, 2015.
132. Sun C, Lai X, Huang X and Zeng Y: Protective effects of ginsenoside Rg1 on astrocytes and cerebral ischemic-reperfusion mice. *Biol Pharm Bull* 37: 1891-1898, 2014.
133. Li J, Liu Y, Li W, Wang Z, Guo P, Li L and Li N: Metabolic profiling of the effects of ginsenoside Re in an Alzheimer's disease mouse model. *Behav Brain Res* 337: 160-172, 2018.
134. Hwang JY, Shim JS, Song MY, Yim SV, Lee SE and Park KS: Proteomic analysis reveals that the protective effects of ginsenoside Rb1 are associated with the actin cytoskeleton in β -amyloid-treated neuronal cells. *J Ginseng Res* 40: 278-284, 2016.
135. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, *et al*: Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 6: 734-746, 2007.
136. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY and Kim M: Heat-processed ginseng enhances the cognitive function in patients with moderately severe Alzheimer's disease. *Nutr Neurosci* 15: 278-282, 2012.
137. Yang Q, Lin J, Zhang H, Liu Y, Kan M, Xiu Z, Chen X, Lan X, Shi X, Li N and Qu X: Ginsenoside compound K regulates amyloid β via the Nrf2/Keap1 signalling pathway in mice with scopolamine hydrobromide-induced memory impairments. *J Mol Neurosci* 67: 62-71, 2019.
138. Lee ST, Chu K, Sim JY, Heo JH and Kim M: *Panax ginseng* enhances cognitive performance in Alzheimer disease. *Alzheimer Dis Assoc Disord* 22: 222-226, 2008.
139. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY and Kim M: An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. *Eur J Neurol* 15: 865-868, 2008.
140. Heo JH, Park MH and Lee JH: Effect of Korean red ginseng on cognitive function and quantitative EEG in patients with Alzheimer's disease: A preliminary study. *J Altern Complement Med* 22: 280-285, 2016.
141. Heo JH, Lee ST, Oh MJ, Park HJ, Shim JY, Chu K and Kim M: Improvement of cognitive deficit in Alzheimer's disease patients by long term treatment with korean red ginseng. *J Ginseng Res* 35: 457-461, 2011.
142. Burns A, Gauthier S and Perdomo C: Efficacy and safety of donepezil over 3 years: An open-label, multicentre study in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 22: 806-812, 2007.
143. Minthon L, Wallin AK, Eriksson S, Wattmo C and Andreason N: Long-term rivastigmine treatment in a routine clinical setting. *Acta Neurol Scand* 119: 180-185, 2009.
144. Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, Roller M and Stough C: Effects of American ginseng (*Panax quinquefolius*) on neurocognitive function: An acute, randomised, double-blind, placebo-controlled, crossover study. *Psychopharmacology (Berl)* 212: 345-356, 2010.
145. Liu L, Hoang-Gia T, Wu H, Lee MR, Gu L, Wang C, Yun BS, Wang Q, Ye S and Sung CK: Ginsenoside Rb1 improves spatial learning and memory by regulation of cell genesis in the hippocampal subregions of rats. *Brain Res* 1382: 147-154, 2011.
146. Huang T, Fang F, Chen L, Zhu Y, Zhang J, Chen X and Yan SS: Ginsenoside Rg1 attenuates oligomeric A β 1-42-induced mitochondrial dysfunction. *Curr Alzheimer Res* 9: 388-395, 2012.
147. Zhang JT, Liu Y, Qu ZW, Zhang XL and Xiao HL: [Influence of ginsenoside Rb1 and Rg1 on some central neurotransmitter receptors and protein biosynthesis in the mouse brain]. *Yao Xue Xue Bao* 23: 12-16, 1988 (In Chinese).
148. Ying Y, Zhang JT, Shi CZ, Qu ZW and Liu Y: [Study on the nootropic mechanism of ginsenoside Rb1 and Rg1--influence on mouse brain development]. *Acta pharmaceutica Sinica* 29: 241-245, 1994 (In Chinese).
149. Zeng XS, Zhou XS, Luo FC, Jia JJ, Qi L, Yang ZX, Zhang W and Bai J: Comparative analysis of the neuroprotective effects of ginsenosides Rg1 and Rb1 extracted from *Panax notoginseng* against cerebral ischemia. *Can J Physiol Pharmacol* 92: 102-108, 2014.
150. Huang XP, Ding H, Lu JD, Tang YH, Deng BX and Deng CQ: Effects of the combination of the main active components of *Astragalus* and *Panax notoginseng* on inflammation and apoptosis of nerve cell after cerebral ischemia-reperfusion. *Am J Chin Med* 43: 1419-1438, 2015.
151. Wang X, Zeng C, Lin J, Chen T, Zhao T, Jia Z, Xie X, Qiu Y, Su M, Jiang T, *et al*: Metabonomics approach to assessing the modulatory effects of St John's wort, ginsenosides, and clomipramine in experimental depression. *J Proteome Res* 11: 6223-6230, 2012.
152. Yamada N, Araki H and Yoshimura H: Identification of antidepressant-like ingredients in ginseng root (*Panax ginseng* C.A. Meyer) using a menopausal depressive-like state in female mice: Participation of 5-HT $_2A$ receptors. *Psychopharmacology (Berl)* 216: 589-599, 2011.
153. Kang A, Hao H, Zheng X, Liang Y, Xie Y, Xie T, Dai C, Zhao Q, Wu X, Xie L and Wang G: Peripherally anti-inflammatory effects explain the ginsenosides paradox between poor brain distribution and anti-depression efficacy. *J Neuroinflammation* 8: 100, 2011.
154. Zhang H, Li Z, Zhou Z, Yang H, Zhong Z and Lou C: Antidepressant-like effects of ginsenosides: A comparison of ginsenoside Rb3 and its four deglycosylated derivatives, Rg $_3$, Rh $_2$, compound K, and 20(S)-protopanaxadiol in mice models of despair. *Pharmacol Biochem Behav* 140: 17-26, 2016.
155. You Z, Yao Q, Shen J, Gu Z, Xu H, Wu Z, Chen C and Li L: Antidepressant-like effects of ginsenoside Rg3 in mice via activation of the hippocampal BDNF signaling cascade. *J Nat Med* 71: 367-379, 2017.
156. Liu X-Y, Zhou X-Y, Hou J-C, Zhu H, Wang Z, Liu JX and Zheng YQ: Ginsenoside Rd promotes neurogenesis in rat brain after transient focal cerebral ischemia via activation of PI3K/Akt pathway. *Acta Pharmacol Sin* 36: 421-428, 2015.
157. Xie Z, Shi M, Zhang C, Zhao H, Hui H and Zhao G: Ginsenoside Rd protects against cerebral ischemia-reperfusion injury via decreasing the expression of the NMDA receptor 2B subunit and its phosphorylated product. *Neurochem Res* 41: 2149-2159, 2016.
158. Chen LM, Zhou XM, Cao YL and Hu WX: Neuroprotection of ginsenoside Re in cerebral ischemia-reperfusion injury in rats. *J Asian Nat Prod Res* 10: 439-445, 2008.
159. He B, Chen P, Yang J, Yun Y, Zhang X, Yang R and Shen Z: Neuroprotective effect of 20(R)-ginsenoside Rg(3) against transient focal cerebral ischemia in rats. *Neurosci Lett* 526: 106-111, 2012.
160. Jiang B, Xiong Z, Yang J, Wang W, Wang Y, Hu ZL, Wang F and Chen JG: Antidepressant-like effects of ginsenoside Rg1 are due to activation of the BDNF signalling pathway and neurogenesis in the hippocampus. *Br J Pharmacol* 166: 1872-1887, 2012.
161. Liu Z, Qi Y, Cheng Z, Zhu X, Fan C and Yu SY: The effects of ginsenoside Rg1 on chronic stress induced depression-like behaviors, BDNF expression and the phosphorylation of PKA and CREB in rats. *Neuroscience* 322: 358-369, 2016.
162. Cui J, Jiang L and Xiang H: Ginsenoside Rb3 exerts antidepressant-like effects in several animal models. *J Psychopharmacol* 26: 697-713, 2012.

