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Recent trends of nano bioactive compounds from ginseng for its possible preventive role in chronic disease models

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Abstract

Ginseng medicine is popular around the world due to its medicinal properties including its anticancer, antidiabetic, and immunomodulatory effects as well as its contribution to stress relief. From ancient to modern times, medicinal ginseng has been proven to enhance immune function and cognition, and the bioactive compounds in ginseng, including ginsenosides, saponins, flavonoids polyphenols and volatile oils, greatly contribute to its health benefits. Several *in vitro* studies have found that ginsenosides such as Rg_3, Rb_1, Rh_1, Rh_2, and Ro as well as polyphenols have a relatively high anticancer and immune response activity. However, bioavailability of these bioactive compounds showed slightly lesser due to modifications in the gastro-intestinal environment. It is important to improve the bioavailability of those compounds, and this can be achieved by using nanotechnology to develop carrier delivery techniques for the bioactive compounds. The bioactive compounds in ginseng can be structurally modified in the nanometer regime to improve the bioactivity, including the anticancer, immunomodulatory, antidiabetic effects in addition to the activity against neurological disorders. Nano-sized ginseng particles are a very effective treatment against various diseases because they have a higher bioavailability, improved systemic circulation and lower toxicity. Therefore, the use of nano ginseng is expected to be effective against various types of disease in the future. Here thus focuses on recent progress and prospects on nano sizing crude ginseng extracts or pure bioactive compounds and various nano carrier delivery techniques for ginsenosides, including their bioavailability for treatment against various diseases.

Keywords: Ginseng, Ginsenosides, Nanoparticles, Nanocarrier, Bioavailability, Anticancer, Antidiabetic

1. Introduction

Ginseng has gained popularity in the world market as a plant-derived herbal medicine for various treatments, including anticancer, anti-ageing, anti-inflammatory, hepatoprotective, immune response, cognition and neurological disorders.[1-5] Traditional herbal medicines have gained importance in medicinal practice, with ginseng given as a drink-based supplement, tonic or as tablets due to its higher therapeutic values.[6-9] Most traditional herbal medicines contain crude extracts that have multiple potencies in treating various diseases, which reduces a multiple drug loading. Even though a ginseng supplement gradually increases with the oral dose, the bioaccessability and bioavailability of the bioactive compounds in ginseng is an important issue.[1, 10, 11] Bioactive compounds in ginseng, such as tannins and terpenoids, are water-soluble and may lead to a decreases in bioavailability. In addition, some of the active bioactive compounds from ginseng shows a lower membrane permeability and solubility for those compounds. Furthermore, variations in the gastric environment cause bioactive ginseng compounds to experience subsequent changes in their active sites, which decreases the health benefit of their treatment of various diseases.[4, 12]

In order to improve the effective delivery of crude or pure bioactive ginseng compounds and to improve the efficiency of ginseng therapy, the ginseng extracts have been nano sized and the many novel delivery carrier techniques have been developed over the last few years.[13-15] Nano sizing and new delivery carrier techniques have gained importance due to their multiple benefits, including higher permeability, fast delivery, improve circulation time and lower toxicity.[11, 16-20] Some nano sizing and delivery carrier techniques include the use of nanoparticles, nano liposomes, nano emulsions, nano niosomes, nano phytosomes and nano ginsosomes. Each nano sizing or delivery carrier technique has its own advantages and

disadvantages in the delivery of bioactive ginseng compounds to their target site. Most of the nano sizing and delivery carrier techniques solve the challenges and improve the bioavailability of bioactive ginseng compounds, improve the lipid membrane penetration, increase the sustainability in a gastric environment and reduce or eliminate the bioactive compound loss during oral supplementation.[11, 13-16, 18, 21-23] Overall, we have reviewed recent updates regarding nano sizing and delivery carrier techniques for bioactive ginseng compounds on chronic disease models and their possible preventive role in treating disease.

2. Ginseng bioactive compounds and its bioavailability

Panax ginseng C.A. Meyer is the most commonly cultivated species in various countries, and it has various health benefits, including antiageing, anticancer and stress relief.[3, 10, 24] The health benefits of ginseng can be attributed to bioactive compounds such as ginsenosides, volatile oils, polyphenols, flavonoids, polysaccharides, and vitamins, irrespective of the processing and preparation methods.[25-29] Ginsenosides and polysaccharides are major bioactive compounds in ginseng, and these have exhibited anticancer, antioxidant, and anti-inflammatory effects in various *in vitro* and *in vivo* models.[26, 27, 29] Ginsenosides are steroidal saponins that differ based according to the type and location of sugar moieties and vary across 40 different ginsenosides. Ginsenosides can be classified into three types according to their aglycone structure: protopanaxadiol group like Rg_3, Rc, Rb_1, Rd and Rh_2; protopanaxatriol group like Rh_1, Re, Rg_1, Rf and Rg_2; and oleanane group like Ro.[30-33] In addition to the ginsenosides contents, ginseng polysaccharides also possess various anticancer characteristics. Most ginseng polysaccharides are water soluble and contain both acidic and neutral polysaccharides that are similar to pectin and starch, and these exhibit

anticancer activity by controlling the immune response in the host organism.[34-37] Pectin from ginseng can be able to bind to the β-galactoside-binding protein, thereby inhibiting the progression of cancer. In addition to the bioactive ginseng compounds that are naturally available, some metabolites from ginseng, such as ginsenoside CK, also possess multifunctional activity including anticancer, anti-inflammatory, anti-diabetic and hepatoprotective activity.[38-40] The bioavailability of the ginseng metabolites in blood plasma after oral administration leads to a reduction in the beneficial effects on the subjects.[4, 10, 12, 41] Some bioactive ginseng compounds and their bioavailability are shown in Table 1. To improve the bioavailability and sustainability of the bioactive ginseng compounds, nano sizing and carrier delivery techniques play a key role.

3. Nano technological approach for possible bioaccessability and bioavailability of ginseng

Nano sizing and carrier delivery techniques have sufficiently solved most bioavailability issues for various phytomedicinal compounds, crude extracts or individual compounds, including ginseng.[42-46] Various nano approaches includes reducing the size of ginseng particles into nano-size, improving the permeability by the aqueous solubility or by surface modifications.[13, 14, 19, 23, 47] Reducing the ginseng active particles to the nano size of 600 nm using ball milling technique enhanced the antioxidant activity of ginsenosides of exposing more active sites.[48] The same research group also successfully developed nano functional food product for the effective delivery and enhanced activity of various nanoparticles includes peanut sprout, oyster shell and ginseng using ball milling technique.[45, 48-51] Few nano carrier delivery systems also plays an extensive role in delivering ginseng bioactive compounds to the target site without much effect in the bioactivity of ginsenosides, such as,

nano niosomes,[43] polymer-loaded nanoparticles[42] and proliposomes.[52] Multi core novel nano niosomes were developed using ginsenosides Rh_2 showed enhanced antitumour efficiency with the size range of 100 to 300 nm.[43] Similarly, ginsenosides Rg_3 nanoparticle were constructed using poly(ethylene glycol)-poly(lactide-co-glycolide) with the particle size of 75-90 nm showed enhanced effect on the glioma cells apoptosis.[42] Recently, proliposome constructed with ginseng fruit saponins and sodium deoxycholate at the size range of 275 nm enhanced the oral bioavailability of ginseng fruit saponins.[52] Several nano carrier delivery systems also increase the bioavailability, reduce the toxicity, improve the stability and solubility, and prolong the delivery of the compounds to the target site.[44, 46, 53-56] The schematic role of nano ginseng bioactive compounds for various diseases is shown in Fig.1.

4. Nano ginseng possible preventive roles in various diseases

4.1 Nano ginseng role in anticancer activity

Active ginseng compounds include ginsenosides and saponins, and its metabolites have been reported to have anticancer properties by reducing the inflammation, oxidative stress, and cell death along while also having lower side effects, which makes these a suitable candidate for the treatment of various cancers.[11, 18, 57] Ginseng saponins, ginsenoside Rd, Rg_1 showed a significant effect in terms of their antiinflammatory activity in various *in vitro* and *in vivo* models by controlling the production of interleukin, cyclooxygenase-2 and tumor necrosis factor.[17, 18, 23] Individual compounds, such as Rg_3, Rh_2, Rb_2, Rc and Rg_1 exhibited excellent antioxidative activity, thereby reducing the onset of tumor growth. In addition, these compounds are also heat-treated with amino acids to form Maillard reaction products with excellent antioxidative activity in comparison to pure bioactive compounds.[58, 59] Even though the bioavailability of ginsenosides is low during oral administration, it is improved by nano

sizing the compounds.

Poly (ethylene glycol)-poly(D,L-lactide-co-glycolide) ginseng nano particle with an average size of 75 to 90 nm exhibited an improvement in antitumor activity in the brain cells.[60] Nano-sized ginsenoside compounds from Chinese white ginseng exhibited a 2.5 times increase in anticancer activity against normal bioactive ginsenoside compounds.[17] The conjugation of ginsenoside compounds with gold to form nano sized particles ranging from 4.3 nm via heptaethylene glycol exhibited an improved anticancer activity. Novel green techniques can thus be used for a supercritical antisolvent process with total panax notoginsenoside nano particle synthesized with a size ranging from 141.5 nm with a higher bioavailability of the compounds during *in vitro* studies.[61]

In a manner similar to the sizing, some delivery carrier techniques have also improved the anticancer activity. Recently, 20(s)-ginsenoside Rg_3, an active ginseng compound, was constructed with magnetic particles with an easy delivery system of human serum albumin to form nanospheres using the desolvation-crosslinking technique, and when tested with HeLa cervical cancer cells, these showed a higher anti-cancer activity. The results showed that the bioactive ginseng compounds had a higher delivery of the compounds with greater apoptosis.[15] Similarly, the oral delivery of ginsenoside 25-OCH_3-PPD, a novel ginsenoside compound that is nano encapsulated with PEG-PLGA to form nanoparticles, showed an improvement in activity against prostate cancer *in vitro* and *in vivo.*[62]

4.2 Nano ginseng role in immunomodulatory effects

Crude ginseng extracts and pure compounds have shown variations in their modulatory immune effects as the concentration of the crude extracts and pure compounds varies with animal model studies.[63-66] Polysaccharide and saponin fractions as well as aqueous extracts of

158 ginseng are major bioactive compounds involved in the modulatory function of the immune
159 system.[35, 67-69] Crude ginseng extracts administrated along with inactivated influenza virus A
160 showed a high level of production of antibodies such as IL-4 and IL-5 cytokines when
161 compared to that of inactivated influenza virus, which confirmed that the ginseng extract has
162 an immunomodulatory function via intranasal administration.[70, 71] Similarly, ginseng saponin
163 end products, such as M_4 also showed a higher immune response and antitumor activity
164 against cancer cells.[72] When the individual saponin components Re, and other are co
165 administrated with ovalbumin in BALB/c mice, a higher antibody response was observed
166 than with other saponin components such as Rb_2, Rc and Rd.[73] These studies confirm that the
167 individual components of ginseng saponins exhibit various immunomodulatory effects. Nano
168 sizing and delivery carrier techniques of these compounds were recently studied to improve
169 the activity of the individual bioactive ginseng compounds, and a higher immune response
170 was confirmed in various animal and cell models.[74, 75] Ginsenoside-based nanoparticles were
171 recently constructed with a size ranging from 70 to 107 nm with a uniform spherical shape
172 with Rb_2, Rc, Rb_1 and Rd and were administrated in mice.[74] The mice co-administered with
173 ginsosome nanoparticles and antigen ovalbumin exhibited a higher level of proliferation of
174 the B and T lymphocytes and specific antibodies, such as IgG_3, IgG_2a, IgG_1 and IgG_2b.[19]
175 Nano sizing was confirmed to greatly improve the Th_1 and Th_2 immune responses. Similarly
176 to sizing, delivery carrier techniques, such as nano emulsion with a droplet size of 72 nm,
177 showed a higher production of IgG_2 immunoglobulins in ovalbumin antigen induced mice.[76]
178 This confirmed that ginseng saponin could act as a vaccine adjuvant. Similarly, the adjuvant
179 effect was studied for nano ginsosomes along with the recombinant vaccine against *Eimeria*
180 *tenella* in chickens, and the nano ginsosomes were found to induce the subunits of the
181 vaccine with the lymphocyte proliferation and IL-1 secretion[75]. These research studies

confirmed that nano sizing and delivery carrier techniques for bioactive ginseng compounds have a positive effect on their use as a vaccine adjuvant and improve the immune response.

4.3 Nano ginseng role in antidiabetic effects

Ginseng saponin components and polysaccharides are well known to be useful in the treatment of diabetes and its complications.[77-79] Crude ginseng extracts, individual components such as compound K, Rg_1, and the combination of two pure compounds have been proven to have synergistic effects in the ailment of diabetic disease models with an improvement in antidiabetic activity and a reduction in side effects.[80-84] However, to sustain and enhance the effect of those bioactive compounds, the bioavailability is a greater issue for modern medicine. Nano sizing the particles or nano encapsulating the bioactive ginseng compounds is a relatively newer treatment for diabetes with various complications, and such treatment has been found to have an improved effect.[85] Recently, gold nanoparticles synthesized with *Gymnema sylvestre R. Br* bioactive compounds of around 50 nm in size were tested for their antidiabetic activity in Wistar albino rats, and this treatment resulted in lower blood glucose levels along with improved anti-inflammatory activity[86]. Nano sizing of the phyto constituents allowed these to cross the blood brain barrier, and this can control the production of insulin to a certain limit, thereby maintaining the supply of brain glucose.[87] These studies thus confirmed that there are possible roles for the use of nano-sized bioactive ginseng compounds in treating diabetes and its associated disorders. Recently, ginseng nano particles were synthesized using gold and silver with an average particle size of 40 and 30 nm, and each showed a higher activity.[87] In another study, proliposome developed using ginseng fruit saponins along with sodium deoxycholate showed enhanced oral delivery which will be fruitful in future for various therapeutic effects.[85]

4.4 Nano ginseng role in aphrodisiac effects

The aphrodisiac effects of ginseng are mostly related to the bioactive compounds, such as ginsenosides, and these have been well studied in various animal models.[88, 89] Ginsenosides increased the hormone secretion by the central nervous system, which leads to a higher production of nitric oxide and the activation of gonadal tissue.[88-91] Irrespective of type, the origin and concentration of ginseng improves the aphrodisiac effect by activating the pituitary gland and secreting hormones mediated by nitric oxide. Animal studies in rats and rabbits have shown a higher positive effect on penile erection by treating with an oral dose of ginsenosides.[92, 93] Even though these have a positive effect on sexual performance, treatment is mostly through oral means and the constituents subsequently vary in gastric environmental conditions, which leads to a reduction in the bioavailability of the bioactive ginseng compounds to the target site. Recently, some researcher[52] reported that ginseng nanoparticle constructed using poly-lactic-co-glycolic acid were used to treat albino rats against nicotine toxicity. The nanoparticles were confirmed to increase the secretion of testicular hormones, decrease the DNA damage and reduce sperm abnormalities. However, studies related to other nano delivery carrier techniques such as fabricated ginseng nanoparticles[94] for sexual improvement have yet to be performed. This will also pave the way to develop various nano carriers for bioactive ginseng compounds, thereby improving the bioavailability of various bioactive ginseng compounds and providing a greater protective role against sexual disorders.

4.5 Nano ginseng role in cardiovascular effects

Bioactive ginseng compounds have various protective effects on the cardiovascular system by increasing vasodilation and preventing nitric oxide degradation through super oxide free radicals.[95, 96] Several animal models have confirmed that ginseng feeding improves the

protective cardio vascular effects by improving the release of endothelial nitric oxide by controlling the cGMP and cAMP levels.[95-99] Crude saponin fractions form ginseng improve the cerebral blood flow in the rats[100], and Korean patients with hyper tension who were treated with crude ginseng extracts exhibited a relatively lower blood pressure, which is possibly a result of the enhanced production of nitric oxide.[101] Individual ginseng compounds have a protective role in cardiovascular systems, and among these, ginsenosides Rg_1 has a predominant role in cardiovascular improvement.[99] The anti-atherosclerotic action of ginseng is mostly a result of controlling the cGMP and cAMP levels, inhibiting 5-hydroxytryptamine (5-HT) release, balancing hormone level of prostacyclin and thromboxane, and extending the time between the conversion of fibrinogen to fibrin.[99] Even though various beneficial effects of ginseng on the cardiovascular system were observed, the bioavailability is relatively low when orally administered, and nano sizing was recently observed to greatly improve the bioavailability and sustained protective effect on the cardiovascular system[5]. Liposomal nano vesicles and nano particles were recently constructed with panax notoginsenoside compounds in the size range from 117 to 147 nm, and these exhibited a protective effect that was higher than native bioactive compounds in an acute myocardial ischemia rat model.[5] The study thus confirmed that the nano carrier delivery techniques have a protective effect on the cardiovascular function, and this will pave the way for further research to provide various molecular effects when feeding either crude extract or individual bioactive ginseng compounds at the nano size.

4.6 Nano ginseng protective role in neurodegenerative diseases

Regarding natural medicines, ginseng has a well-known role in neuroprotection, and the possible mechanisms in which crude extract or pure compound of ginseng act involve anti-

apoptosis, antioxidant, anti neuroinflammatory and immune stimulatory activities.[7, 102-105] The delivery of bioactive ginseng compounds to the brain is most difficult for various neurological diseases, including Alzheimers, Parkinson's and Huntington's disease. [103, 106-110] Nano sizing and carrier deliver techniques were applied to ginsenosides to improve the delivery of bioactive ginseng compounds to the brain by crossing the blood brain barrier and the blood cerebrospinal fluid barrier, and this had a higher protective effect against certain neurological diseases. Recently, panax notoginsenoside compounds with a range in size of 147 and 117 nm exhibited higher protective effects than native bioactive compounds in an acute cerebral ischemia rat model.[111] In another study[13], black red ginseng powder was pulverized to a nano size with the range of 350 nm, and it showed a higher antioxidant activity that may be useful in further studies on their role in various neurological disorders. Ginseng-rGO films showed an accelerated differentiation of stem cells in neurons with a higher antioxidant activity.[16] Similarly, ginsenoside nanoparticles were synthesized and studied *in silico,*[112] and these showed higher protective effects on amyotrophic lateral sclerosis, a neuro degenerative disease that causes severe damage to the brain and spinal cord. Few bioactive ginseng compounds were studied for their effective antioxidative mechanism on several neurological disorders or other oxidative stress-related disorders. 20(R)-Ginsenoside Rg_3 (G-Rg_3) was effectively constructed to form mixed micelles with a size of about 20 nm, and these were shown to have a higher delivery of bioactive compounds to the target site.[113] Overall, nano sizing and delivery carrier techniques were studied for certain neurological disorders and were confirmed to result in a higher protectivity and a sustained effect, and this may help in near future for scientist to focus on individual neurological disorders.

5. Nano ginseng toxic effects

Ginseng is considered to be safe when taken in large amounts, and such doses are well tolerated by humans, dogs, rabbits and rats.[114-120] A two year study[121] involving human trials showed that 14 out of 133 individuals exhibited sleeplessness, dizziness, hypertension and nervousness after consuming ginseng at a level higher than 15 g per day. This also varies with types and varieties of ginseng.[122-129] At very higher doses this may lead to breast pain, chest pain and breathing problems in human subjects.[115] Higher doses of ginseng also lead to nervousness and excitability, so nano ginseng particles should be developed at lower concentrations to ensure safe use of the ginseng compounds. A higher bioavailability of these ginseng nano compounds may lead to other complications, and their toxicity is yet to be studied.

6. Conclusions

Ginseng is a medicine that possess strong therapeutic efficiency, and it should be properly utilized with the corresponding nanotechnology. Current research indicates that ginseng medicine has an excellent *in-vitro* bioactivity but poor bioavailability due to gastric digestion, loss of active sites, and a larger size that leads to a lower bioavailability of these compounds when given orally, which results in a reduction in the potential health benefits. Nanosizing greatly improves the bioavailability of water-soluble bioactive ginseng compounds, and a modification at the surface leads to an improvement in the absorption in the gastric systems and a greater delivery of these compounds to the target site.

Among the nanotechnologies, nano carrier delivery techniques of ginseng compounds have shown a higher target specific activity. As we discussed, various nano delivery techniques confirmed that sustained delivery of ginseng compounds or pure extract to various diseases

like anticancer, immunomodulatory and so on in various animal models. In addition, nano delivery approaches of various diseases also enhances the food sectors in the development of various nano sized functional food. However, nano ginseng research is in a budding stage, and it should focus on various disease models to improve the bioavailability while diminishing side effects. This will enhance the utility of natural bioactive compounds to the future patients. Future nano ginseng research developments are expected with co loading of two or more ginseng compounds or mixed plant bioactive compounds to various disease treatments with reduced drug loads.

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Disclosure

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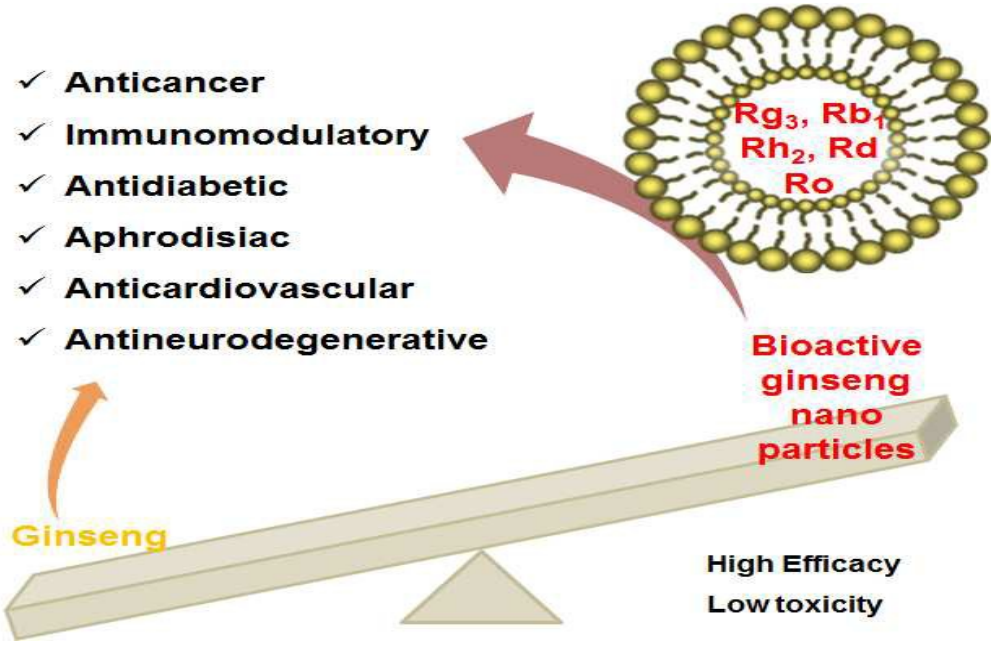

Fig. 1 Schematic representation of bioactive ginseng nanoparticle role in chronic diseases

Table 1 Bioavailability of bioactive ginseng compounds in various animal models

Ginseng bioactive compounds	Dosage	Bioavailability	Animal model	Reference
Crude extract		Low permeability	Caco-2 cell culture model	58
5-OH-PPD	10 mg/kg	64.80%	Rat plasma/oral	5
$Rg_{1,}$ Rb_1	50 mg/kg	18.4% (Rg_1) 4.35% (Rb_1)	Rat plasma/oral	131
25-hydroxyprotopanaxadiol	10 and 20 mg/kg	2 μg/ml	Nude mice/ intravenous and oral	26
Rd	10 mg/kg	0	Human	40
Multiple	300mg/kg	0	Rat	26
20(S)-Ginsenoside Rh_1		1.01%	Rat/intragastrical	27
Compound K	20 mg/Kg	35%	Rat	131
Ginsenoside Re	Oral	0%	Mice/oral	102
Rg_1	50mg/kg	1.52-6.60%	Rat/oral	97
Rh_2+D5:E20D4D2:E20	100mg/Kg	0.25%	Rat/oral	98

577 Table 2 Nano delivery methods for bioactive ginseng compounds to treat various chronic

578 diseases

Biological activity	Bioactive compounds	Nano delivery methods	References
Antitumor or Anticancer			
	Ginseng crude extract	Poly (ethylene glycol)-poly(D,L-lactide-co-glycolide) coated ginseng nano particle	42
	White ginseng crude extract	Ginseng nanoparticles	20
	Chinese white ginseng	Nano ginsenosides	17
	Ginsenosides	Gold nanoparticle	13
	20(s)-ginsenoside Rg_3	Nanospheres	15
	25-OCH_3-PPD	PEG-PLGA nanoparticles	62
	Ginseng extract	Liposome nano vesicles	130
	Ginsenoside Rg_3	Mixed Micelles	131
Immunomodulatory effects			
	Ginsenosides	Ginsosomes	19
	Ginseng saponin	Nano emulsion	20
	Ginseng extracts	Nano ginsosomes	75
Antidiabetic effects	Ginsenoside Rb_1	Not applicable	132
	Ginseng fruit saponins	Proliposomes	85
Aphrodisiac effects			
	Ginseng extract	Poly-lactic-co-glycolic acid nanoparticles	91
Cardiovascular effects			
	Notoginsenoside	Nano liposomes	5

	compounds		
Neurodegenerative diseases			
	Notoginsenoside compounds	Nano liposomes	5
	20(R)-Ginsenoside Rg_3 ($G\text{-}Rg_3$)	Mixed miscelles	131

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