

## Allelopathic Medicinal Plants: 2. Ginseng (*Panax*) species

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### ABSTRACT

Of the 12 ginseng medicinal species, only 3 spp. (*Panax ginseng*, *P. quinquefolium* and *P. notoginseng*) are important, due to their biological activities, hence, widely used worldwide. These are used for cardiovascular protection, immunomodulatory ability, antioxidants, antitumor, cholesterol lowering and anti-inflammatory activities. Hence, these are used in various products (food, health-food, daily necessities, cosmetics etc.). However, ginseng cultivation causes problems of replanting due to its allelopathic effects. This review provides a comprehensive insight of allelopathic ginseng plant and analyzes the allelopathic effects on soil diseases and soil microorganisms. More in-depth research is needed to reveal the mechanism of ginseng allelopathy.

**Key words:** Active ingredient, allelopathic effects, American ginseng biological activities, ginseng, ginseng spp., ginsenosides, medicinal plant, notoginseng, *Panax ginseng*, *P. quinquefolium*, *P. notoginseng*, replanting problem.

### 1. INTRODUCTION

Ginseng is one of the precious medicinal plants in the world. Its main component is ginsenoside, which has important pharmacological and medicinal uses. The ginseng products benefits 'Qi', invigorate spleen and replenishes blood to nourish heart. The ginseng roots contain saponins, polysaccharides, organic acids, proteins, volatile oils, trace elements etc. Hence, it is used to treat cardiovascular system and central nervous system diseases, improve myocardial function, improve memory, enhance immunity, improve sleep, anti-aging, anti-shock, anti-myocardial ischemia, etc.

Most of the ginseng species were wild and non-domesticated in the past, while, its cultivation has developed in past 50-60 Years. The ginseng needs specific climate and soil conditions, hence, its cultivation is done in China, South Korea, North Korea and Russia. *P.*

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*ginseng* is also planted in United States, Canada. The ginseng root exudates contain many chemicals (phenolic acids, organic acids, esters, alkanes, ginsenoside, etc.), which are not good for its continuous cropping. The roots secreted chemicals inhibits the growth of ginseng, disrupts the balance in soil microbial flora and causes soil diseases in its continuous cropped fields. Ginseng is a very good medicinal and commercial plant. Therefore, this review discusses ginseng chemical composition, medicinal values, cultivation and the allelopathic effects, these may be helpful for ginseng research and ginseng industry developments in future.

## 2. GINSENG SPECIES

Ginseng used for medicines may be a mixture from several species of *Panax* (from the Greek word : ‘Pan akheia’, meaning, "cure of all diseases") (103). In China, medicinal use of ginseng started > 6,000 years ago as per archaeological documents. Now China is the world's largest producer of ginseng, followed by South Korea, Canada and USA (4).

Twelve medicinal ginseng species are grown in different countries and used in traditional medicines (Table 1). Traditional Chinese medicinal plants of *Panax* are: Ginseng (*Panax ginseng*), American ginseng (*P. quinquefolium*) and Notoginseng (*P. notoginseng*) (80). They possessing various bioactivities such as cardiovascular protection, immunomodulatory ability, as antioxidants, antitumor, cholesterol lowering and anti-inflammatory activities. These are also beneficial to health, hence, commercialized and used worldwide as health-food, cosmetics etc. (26).

Table 1. List of 12-Ginseng spp. distributed in the world

S. No.	Botanical Name	English Name	Country	References
1	<i>P. ginseng</i>	Red ginseng	China, South Korea, North Korea	12
2	<i>P. ginseng</i> cv. <i>Chunpoong</i>	Chunpoong	South Korea	32
3	<i>P. ginseng</i> cv. <i>Yunpoong</i>	Yunpoong	South Korea	32
4	<i>P. ginseng</i> cv. <i>Gopoong</i>	Gopoong	South Korea	32
5	<i>P. quinquefolium</i>	American ginseng	United States	76
6	<i>Eleutherococcus senticosus</i>	Siberian ginseng	Russia	50,57
7	<i>P. japonicas</i>	Japanese ginseng	Japan	97
8	<i>Arctium lappa</i>	Burdock	Japan	62
9	<i>P. notoginseng</i>	Notoginseng	China	76
10	<i>P. omeiensis</i>	Omei ginseng	China	97
11	<i>P. vietnamensis</i>	Vietnamese ginseng	Vietnam	97
12	<i>P. wangianus</i>	Pseudoginseng	China	97

**Differentiation :** Ginseng species are difficult to distinguish, hence, some researches were done to distinguish them. Kim *et al.* (40) identified Korean *P. ginseng* from Chinese *P. ginseng* and *P. quinquefolius* by AFLP analysis. Wee *et al.* (94) identified anticoagulant components in Korean red ginseng due to the presence of phenolic compounds. Sun *et al.* (81) successfully used real time PCR and SNP Marker to distinguish ‘Chunpoong’ from many ginseng cultivars. Red ginseng monograph was prepared, showing components of red ginseng, functionality certified as health food by Korea Food and Drug Administration and information about red ginseng for businesses and consumers in South Korea and abroad (78).

Li *et al.* (54) developed a simple and reliable method to differentiate Russian wild ginseng from Chinese cultivated ginseng by analyzing the mitochondrial nicotinamide adenine dinucleotide (NADH) dehydrogenase subunit 7 (nad7) intron 3 regions of them. In *et al.* (30) used an amplification refractory mutation system (ARMS) to identify Korean mountain ginseng. Researchers not only differentiated the types of ginsengs from the perspective of morphology, but also distinguished the types of ginsengs from the molecular perspective.

Table 2. Medicinal ginseng species commonly used world wide

S. No.	Botanical Name	English Name	Distribution in Country	References
1	<i>P. ginseng</i>	Red ginseng	China, South Korea, North Korea	12
2	<i>P. quinquefolium</i>	American ginseng	United States	76
3	<i>P. japonicas</i>	Japanese ginseng	Japan	97
4	<i>P. notoginseng</i>	Notoginseng	China	76
5	<i>P. omeiensis</i>	Omei ginseng	China	97
6	<i>P. vietnamensis</i>	Vietnamese ginseng	Vietnam	97
7	<i>P. wangianus</i>	Pseudoginseng	China	97
8	<i>Eleutherococcus senticosus</i>	Siberian ginseng	Russia	50,57

Twelve ginseng spp have been identified (Table 1). Of these 8-Ginseng spp. (Table 2) have Medicinal uses in different countries. However, only following 3- major spp. are used for Medicinal purposes Worldwide.

- (i). *Panax ginseng* (or Korean ginseng) grown in China and Korea
- (ii). *Panax quinquefolius* (American ginseng) grown in USA (Virginia and Wisconsin) and Canada (Ontario, Quebec) (4)
- (iii). *Panax notoginseng* (Chinese ginseng) mostly grown in China

**2.1. *Panax ginseng* C.A. Meyer:** It is a perennial herb from genus *Panax* L and family Araliaceae (Figure 1). It is cultivated in China, Japan, North Korea, South Korea and Russia. It is called “King of Herbs” and has long history of medicinal uses. Medicines based on *P. ginseng* are available in market, e.g. Deng-Zhan-Sheng-Mai capsules, *Panax* provides vital energy, revitalize blood vessels, strengthen the spleen, benefit the lungs, increases body fluids, and calm nerves. The *P. ginseng* is used to treat various diseases, including cardiovascular disease and diabetes (39). In recent years, its chemical components (ginsenosides, polysaccharides, volatile oils, glycopeptides, amino acids and vitamins) are identified (10). Besides numerous ginsenoside monomers have been identified their structure, activity and structure- activity relationship of some ginsenosides have been confirmed (38,39). *P. ginseng* has 5-parts: root, stem, leaf, flower and berry. Roots are fusiform or cylindrical and contains polysaccharides.



Figure 1. Plant of *Panax ginseng* (25)

It is a perennial herb with stout rootstocks and is hermaphrodite or possibly andromonoecious. The stem is simple. The plants have 3 or 5 palmate compound leaves and leaflets that are serrated or dentated or pinnately lobed. The inflorescences are solitary umbel, with growth from the terminal end of stems. The pedicels are articulate below bisexual flowers and inarticulate below male flowers.

**2.2. *P. quinquefolium* :** American ginseng (*Panax quinquefolium* L., Araliaceae family) has originated in North America (Figure 2). It is found in Canada (Quebec to Manitoba) in USA (Georgia, Louisiana, Arkansas, and Oklahoma) (14). It is cultivated in Wisconsin, USA (31) and in China since 1980s (75). *P. quinquefolium* has the effect of replenishing 'Qi' and nourishing 'Yin'. It is used for 'Qi' deficiency, 'Yin' deficiency, heat tiredness, cough, asthma, phlegm and blood, internal heat to quench thirst, dry mouth and throat.

Its aromatic root resembles a small parsnip that forks as it matures or they appear to be spindle shaped. The plant grows 15 to 46 cm tall, have 3-leaves, each with 3-5 leaflets, 5 to 13 cm long and flowers are green white. It is a main herb in traditional medicinal practice in China. Its compounds are glycosides consisting of a non-sugar part-an aglycone and a sugar chain or chains. In ginsenosides 3-types of aglycones are identified (i). Tetracyclic of dammarane type, (ii). Pentacyclic of oleanolic acid type and (iii). Tetracyclic of the ocotillol type. The sugar part of saponins includes hexoses (glucose, galactose), 6-deoxyhexoses (furanose, rhamnose), pentoses (arabinose, xylose) and uronic acids (glucuronic acid). The sugars are usually in cyclic form and are associated to the aglycones through semi-acetal bonds (46,71). Apart from saponins and polysaccharides, American ginseng also contains terpenes, phenolic compounds, amino acids, flavonoids, volatile oils, vitamins and minerals (15). He *et al.* (27) identified numerous phenolic acids and aliphatic compounds from its fibrous roots and these inhibited its seedlings growth.



Figure 2. Plant and roots of *Panax ginseng* (Image from Google)

A



B



C



D



Figure 3. Plant (A), flowers (B), fresh fruits (C), and dried roots (D) of *P. japonicus* (91)

**2.3. *Panax japonicus* (T. Nees) C. A. Meyer:** It is a herbaceous perennial plant growing from a horizontal tuberous rhizome (Figure 3). It produces one or more straight, unbranched stems, 50-80 cm tall, with 3-5 leaves on stem tip.

It is commonly used medicinal herb in eastern Asia and cultivated in Japan, Korea and China (96). The major constituents in its roots are saponins. In the saponins, there are sapogenins, protopanaxadiol, protopanaxatriol and oleanolic acid, like those in the saponins of *P. ginseng*. The main saponins of *P. japonicus* are oleanolic acid-type saponins and their hydrolysis yields oleanolic acid, panaxadiol, and panaxatriol (83).

**2.4. *Panax notoginseng* (Burk.) F.H. Chen :** It is a medicinal specie of genus *Panax*, commonly called Chinese ginseng or notoginseng (Figure 4). The plant grows 20 to 60 cm tall, has 3-7 leaves, each with 5-7 leaflets and flower is green. It is distributed throughout the southwestern China, Japan, Burma, Nepal and Vietnam (86).



Figure 4. Plant and roots of *Panax ginseng* (86)

Its roots are harvested after 3- Years in autumn before flowering. After harvest, the roots are cleaned, divided into main root, branch root and rhizome, then dried under the sun or with artificial heating at low temperatures (88). Its roots phytochemical constituents are saponins, amino acids, polyacetylenes, volatile oils, polysaccharides and flavonoids. The dammarane-type saponins constitutes 12 % of the total root content. *Panax notoginseng* has the effects of dispersing blood stasis, reducing swelling and calming pain. It has been used in hemoptysis, exhalation, epistaxis, epX, hemorrhage, hemorrhage, trauma, thorax and abdomen, and edema and pain.

**2.5. *Panax vietnamensis* Ha et Grushv. (Family Araliaceae):** It is a wild and endemic *Panax* species, called Vietnamese ginseng discovered at Ngoc Lay, Gia Lai-Kontum, Central Vietnam (Figure 5). In 2003, it was named as *Panax vietnamensis* var. *fuscidiscus* K. Komatsu, S. Zhu & S.Q. Cai. It is distributed in Yunnan province, China and Lai Chau province, Vietnam (74,109).



Figure 5. Plant of *Panax vietnamensis* (Image from Google)

In Vietnam, it is a perennial plant, grows 40-100 cm tall. It differs from other ginseng species by the notches on its roots. It contains saponins found in *P. ginseng* [protopanaxadiol (PPD) and protopanaxatriol (PPT) saponins (i.e. ginsenoside Rb1, Rg1, Rd, and Re)], and also contains dammarane saponins with an ocotillol side-chain, such as majonoside R1 and R2, vina-ginsenoside R1 and R2 (19,20,21).

**2.6. *Eleutherococcus senticosus* (Araliaceae family):** It is a species of small, woody shrub native to Northeastern Asia. It is called ‘Siberian ginseng’ and uses in folklore and traditional Chinese medicine (Figure 6). Its root extracts are sold as dietary supplement or cosmetic, under the name *Siberian ginseng*.



Figure 6. Plant of *Eleutherococcus senticosus* (Image from Google)

Its native habitat is East Asia, China, Japan, and Russia. *E. senticosus* is a deciduous shrub slowly grows 200 cm tall. It flowers in July, flowers are hermaphroditic

and pollinated by insects. Its active components are eleutherosides (28), their acid hydrolysis forms the glycosides viz., rhamnose, arabinose, xylose, mannose, galactose and glucose. Wagner *et al.* (87), also detected the phenylpropanes compounds, lignans, coumarins, polysaccharides and other compounds, such as oleanolic acid, aromatic oils and sugar (82). *Eleutherococcus* not only produces lignans, but also siringina, syringaresinol and sesamin. It also produces precursors of lignans, such as hydroxycinnamic, caffeic acid and other intermediate compounds, as coniferaldehyde. These have significant antioxidant activity (17).

### 3. GINSENG CULTIVATION

China is major producer of different Ginseng spp. these are grown in many Chinese provinces (Fig. 7). The major producers of Ginseng in China are following provinces. Worldwide Ginseng is grown in 35 Countries (Figure 8)



Figure 7. Ginseng growing Chinese provinces - commercial grown ginseng spp.

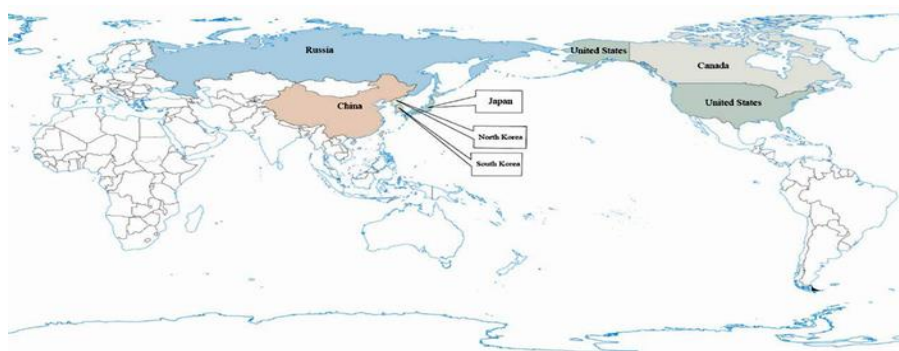


Figure 8. Ginseng growing countries - commercial grown ginseng spp.

### 3.1. Culture methods

The growth, soil microbial quantity and nutrients content of *Panax notoginseng* were investigated using 3-soil drainage treatments: control (CK), eucalyptus bark (SP), corn stalk (YM), tobacco stem (YG) (100). The results showed that the soil water content was CK, YG, SP, YM, and the addition of drainage reduces the incidence of *Panax notoginseng* (100).

Kim *et al.* (41) investigated the physiochemical properties of cultivated *P. ginseng* sprouts with nano-bubble water and antioxidative activity of its enzymatic hydrolysates. Nano-bubble water promoted the height and thickness of *P. ginseng* sprouts compared to normal water. The cultivated *P. ginseng* sprout composition (ash, crude fat and crude protein) are similar to other groups (41). The contents of crude saponin, total ginsenoside, total polyphenol and flavonoid were higher in NB-4 than in NA-4. The viscozyme hydrolysate has the highest DPPH radical scavenging activity and the fungamyl hydrolysate has the highest ABTs radical scavenging activity among the hydrolysates (41). Lee *et al.* (53) compared the growth characteristics and quality of *P. ginseng* grown in upland and in lowland paddy field after paddy harvest (53). The upland ginseng has higher survival rate and shoot growth than grown in lowland paddy field. The lowland paddy field ginseng taproot was hard and rusty than upland ginseng. Dry weight of taproot in upland ginseng was lower than paddy ginseng (53).

Song *et al.* (79) established an *in-situ* system for production of N-containing water production using plasma technology and evaluated the effects of the Plasma-treated water on ginseng growth and its bioactive phytochemicals (76). The results showed that plasma-treated water could be used as a liquid N fertilizer for *P. ginseng* growth and phytochemical accumulation during sprout under aeroponic conditions (79). Different cultivation methods of ginseng greatly affects the ginseng biomass and active substances.

### 3.2. Field management

Field soils were silt loam, loam and sandy loam in less slope, alluvial or local valley. Soil pH ranged 5.0~5.2 and soil EC was 0.93~3.78 ds m<sup>-1</sup>. Organic matter was 37~35 g kg<sup>-1</sup>, nitrate nitrogen was 63~490 mg kg<sup>-1</sup> and available P<sub>2</sub>O<sub>5</sub> was 55~163 mg kg<sup>-1</sup>. Soil fertility is better than Korean ginseng cultivation (58). Ginseng planting also involves the steps of transplanting. Before transplanting, fully decomposed organic fertilizer (2500 kg/667 m<sup>2</sup>) was evenly applied on the surface as the base fertilizer, and 5% occiphos granules (3 600 ~ 4 800 g/667 m<sup>2</sup>) were sprinkled to disinfect the soil, and the soil was mixed (91). The planting density was 10 cm x 15 cm, and the hole depth was 5 ~ 8 cm. After the seedlings were transplanted, the non-exposed bud heads were used as the standard soil cover. A layer of pine needles was spread as mulch (91). The ginseng cultivation scales are : (i). Small scales of 0.5~3.0 ha, (ii). Middle scales of 4.0 ~ 10.0 ha and (iii). Large scales of 30~700 ha. Ginseng is cultivated in newly reclaimed forest land by two methods: Direct seeding and transplanting of ginseng seedlings. The field beds of ginseng are shaded with different coloured vinyl films in arch design of 100 ~ 130 cm height.

Kim *et al.* (43) showed that soil organic matter (OM), total nitrogen (TN) and cation exchangeable capacity (CEC) were significantly higher in ginseng cultivation regions, where, ginseng has been grown for 13-years compared to 7-years. Ginsenoside G-Rb1, Rb2, Rc, Rd, Re, Rf, Rg1 were significantly higher in these soils. Soil OM, TN and CEC of the cultivated regions were positively correlated with the growth of ginseng. The root length showed positive correlation with ginsenoside content (43). Different field management also

has a great impact on the accumulation of ginseng biomass and active substances, hence, the traditional field management needs to be improved.

### 3.3. Rhizosphere microbes

Most ginseng plants have continuous cropping obstacles. Jin's research found that different years of *Panax notoginseng* root had significant effects on the diversity of fungal community. The diversity index, richness index and evenness index of fungi in the soil of biennial *Panax notoginseng* were higher than those of annual and triennial (34). Inoculating *Glomus intraradices* improved the abundance and Shannon diversity of bacteria, facilitated the colonization rate of ginseng lateral roots, increased the levels of monomeric and total ginsenosides, enhanced root activity, polyphenol oxidase and catalase activities of ginseng (84). *G. intraradices* inoculation increases some beneficial bacterial species and decreases pathogenic fungi in rhizosphere soil of ginseng, benefiting ginseng crop (84). Various abiotic stresses such as high content of heavy metals in ginseng cultivation area reduces the quality of *Panax ginseng*. Ginseng seedlings treated with *Rhizobium panacihumi* DCY116T produced higher biomass, proline, total phenolic, total soluble sugar contents and related gene expressions, while, decreased the H<sub>2</sub>O<sub>2</sub> level than non-bacterized Al-stressed seedlings. It could be used as growth promoting rhizobacteria for future cultivation of ginseng in regions with heavy metal exposure (37).

### 3.4. Diseases

Rust rot and sclerotinia are the two major soil borne root diseases of ginseng, these reduces the growth, yield and quality of its ginseng roots (72). Besides, other pathogens in soil are: *Fusarium solani*, *Rhizoctonia solani*, *Alternaria panax*, *Pythium debaryanum*, *Phytophthora cactorum*. In addition, there are about 20 kinds of parasitic nematodes harmful to ginseng growth, but *M. changbaiensis* and *Meloidogyne hapla* two major groups and the mite (*H. sapronyzarum*, *Hisriostoma feroniarum*, *Rizoglyphus echiphus*] are harmful to ginseng growth (5). The pathogenic mechanism of nematodes and mites is to make the wound on the ginseng root epidermis, opening it for pathogens infection causing root diseases.

**Diseases control :** During 3- or 5-years of ginseng cultivation in Korea, various diseases reduces the *P. ginseng* yield up to 30-60 %. Bae (3) suggested that some rhizobacteria could induce resistance against various plant diseases in ginseng. Characterization of resistance to multiple fungicides in *Botrytis cinerea* populations from Asian ginseng in northeastern China was tested and determined. The multi-fungicide resistance of *B. cinerea* to fungicides decreased the efficacy of current fungicides (68). Lee et al. (51) summarized the possible defense-related genes in ginseng based on the expression patterns against biotic and abiotic stresses and described their functional roles. Ginseng's proteins biological activities affects the salicylic acid/jasmonic acid dependent defense responses. However, some genes suppress the specific pathogens and others restrict their growth (51). Inoculation with beneficial bacteria in the rhizosphere soil of ginseng promotes the growth of mycorrhiza, which is conducive to the cultivation of ginseng.

## 4. CONTINUOUS CROPPING PROBLEM

Ginseng cannot be replanted in the same field within 10-20 years, because it causes roots rot, frequent diseases and reduces the yield and quality. The problem of ginseng continuous cropping has become the main limitation for ginseng industry development. The reasons for continuous cropping soil sickness problem are very complex, hence, till now, following factors have been studied: The (i). aggravation of soil-borne pathogens, (ii). autotoxicity (allelopathic toxicity of root exudates) and (iii). imbalance of soil microorganisms.

### 4.1. Soil-borne Pathogens

Continuous cropping of ginseng (*P. ginseng*) in farmlands causes soil-borne diseases mainly due to the changes in the soil microbial composition. We studied the impact of cultivation methods and duration on the diversity and composition of *P. ginseng* rhizosphere microbial community and to develop suitable technology for its cropping. There are significant variations in richness, diversity and relative abundances of microbial taxa between the farmland and forest field plantation. The bacterial communities of LCK (forest soil, where *P. ginseng* was not grown) possessed higher richness and diversity than NCK (farmland soil, where *P. ginseng* was not grown). The increase in cultivation years of *P. ginseng* in farmland and deforestation fields remarkably altered the diversity of soil microbial communities. In addition, the accumulation of *P. ginseng* soil-borne pathogens (*Monographella cucumerina*, *Ilyonectria mors-panacis*, *I. robusta*, *Fusarium solani* and *Nectria ramulariae*) varied with the cropping age of *P. ginseng* (85).

Lu *et al.* (69) studied the Taxonomy of fungal complex causing red-skin root disease of ginseng in China. A total of 230 isolates were obtained from 209 disease samples, which were classified into 12 specie (*Dactylonectria* sp., *D. hordeicola*, *Fusarium acuminatum*, *F. avenaceum*, *F. solani*, *F. torulosum*, *Ilyonectria mors-panacis*, *I. robusta*, *Rhexocerosporidium panacis*, and three novel species *I. changbaiensis*, *I. communis*, and *I. qitaiheensis*). Furthermore, *I. communis* (36.1 %), *I. robusta* (20.9 %), and *F. solani* (23.9 %) were major fungi. All these species were pathogenic to ginseng roots and caused red-skin root disease under certain conditions. *Fusarium oxysporum* is common pathogenic fungus in ginseng cultivation. In the adventitious roots of *P. ginseng* the antagonistic fungi, *Penicillium* sp. YJM-2013 was more conducive to the accumulation of ginsenosides compared with *F. oxysporum*. It increases the production of signal molecules and activates the expression of transcription factors and functional genes (92).

The ginseng pathogen, *Cylindrocarpon destructans* and 5-non-pathogens were examined for their sensitivities to total ginsenoside fraction (T-GF), protopanaxadiol-type ginsenoside fraction (PPD-GF) and protopanaxatriol-type ginsenoside fraction (PPT-GF) from the roots of *P. ginseng*. The results showed that ginsenosides might act as host chemical defences, while the ginseng root pathogenic fungi were harmful by converting the PPD-type ginsenosides into growth or host recognition factors. The ability of ginseng root pathogens to deglycosylate PPD-type ginsenosides may be a pathogenicity factor (106).

### 4.2. Autotoxicity

*Panax ginseng* is a perennial medicinal plant, which cannot be replanted in the same field within 10-20 years. Otherwise, there will be problems such as roots rot, frequent diseases etc., resulting in poor yields. The roots of ginseng secrete some chemical substances

(Salicylic acid, gallic acid, benzoic acid, 3-phenyl propionate and cinnamic acids the main allelochemicals). These affect the abundance and diversity of soil microorganisms through allelopathic effects, thereby affecting the re-planting problems of ginseng. Li *et al.* (62) did research on autotoxic compounds and their mitigation method to solve the Ginseng continuous cropping problem. Metagenomic molecular sequencing was used to determine the autotoxic phenolic acids produced by ginseng roots, which can change the fungal structure and diversity in ginseng rhizosphere soil. *Trichoderma harzianum* 41 effectively inhibits the growth of main disease (*C. destructans*) in ginseng continuous cropping, reduces the autotoxic phenolic acids present in the soil and was colonized in the soil-fertilizer mixture for a long time. This study proposed a set of disease prevention and control technology of “physical disinfection + chemical elimination + biological fertilizer recovery”. This technology can improve the soil microorganisms, reduce the incidence of ginseng diseases and improve the yield and quality of ginseng (62).

Li *et al.* (60) studied allelopathic effects of ginsenoside Rg1 on seed germination and seedling growth of *P. ginseng* and found that rhizosphere soil of 5-year-old ginseng mainly contained ginsenosides viz., Rb1 (2.69 mg L<sup>-1</sup>), Rg1 (1.94 mg L<sup>-1</sup>), Re (1.84 mg L<sup>-1</sup>), Rb2 (1.56 mg L<sup>-1</sup>) and Rc (1.12 mg L<sup>-1</sup>). High concentration of Rg1 (2.00 mg L<sup>-1</sup>) inhibited the seed germination and seedling growth, while wax was stimulatory at low concentration (0.25 mg L<sup>-1</sup>). The Rg1 at 1.00 mg L<sup>-1</sup> concentration stimulated the superoxide dismutase, peroxidase and ascorbic peroxidase activities of seedlings, but 2.00 mg L<sup>-1</sup> concentration decreased their activities (60).

#### 4.3. Soil microorganisms

The effects of successive cropping on microecology of ginseng rhizosphere soil and the mechanisms were studied. The results revealed that the numbers and population of microorganisms as well as enzyme activities changed remarkably in continuous cropped ginseng soil. The *Medicago sativa*, *Fructus perillae* and *Trifolium repens* increased the microorganisms population in the ginseng soil (59). The abundance and diversity of soil microorganisms in continuous ginseng cropping have undergone significant changes, thus causing the problem of continuous ginseng cropping.

*P. ginseng* plants could release antimicrobial polyacetylenes into the surrounding soil from the roots as defence compounds (23). Along with dihydropanaxacol (I), panaxacol (II), two new polyacetylenes, 1-hydroxydihydropanaxacol (III) and 17-hydroxypanaxacol (IV) and ginsenoside D (V), were isolated from *Panax ginseng* hairy root culture. Among them, compounds I-IV showed antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. Liu *et al.* (64) examined the soil microbial composition, total number, diversities and the characteristics of soil microflora of *P. notoginseng* in relation to their increase in the continuous cropping years (50). The results showed that bacteria and fungi were the dominant groups in *P. notoginseng* microbial communities. Moreover, the soil microflora changed significantly with the seasons and cropping years, resulting in the failure of replanted *P. notoginseng* (64).

Wang *et al.* (90) determined the antifungal activities of six major ginsenosides (Rb1, Rb2, Rc, Rd, Re and Rg1), along with the metabolites of ginsenoside Rb1 (Gypenoside XVII (G-XVII) and F2), against the ginseng root pathogen *C. destructans* and non-ginseng pathogens *Fusarium graminearum*, *Exserohilum turcicum*, *Phytophthora megasperma* and *Pyricularia oryzae* (90). It was concluded that the pathogenicity of *C. destructans* against

ginseng root was independent of its ability to deglycosylate ginsenosides (84). Jiao *et al.* (33) analyzed nutrients, phenolic acids and microbial communities in soils from the fields with continuous maize, monoculture ginseng, and 1-, 3-, and 5-year maize rotation after ginseng; and the results showed that at least a 3-years maize rotation was necessary to overcome the replant failure of American ginseng (33). Li *et al.* (40) investigated the effects of continuous cropping of *P. notoginseng* on the properties of rhizosphere soil and found that pH change and nutrients imbalance might be causing the continuous cropping problem of *P. notoginseng*. Ginsenosides and its metabolites have antibacterial activity against pathogens, changing soil nutrients and pH, thereby, changing the diversity of soil microorganisms.

## 5. MEDICINAL USES

Of the 8-Ginseng spp. (Table 2) with medicinal uses in different countries. Only 3-major spp. [(i). *Panax ginseng* (or Korean ginseng), (ii). *Panax quinquefolius* and (iii). *Panax notoginseng* (Chinese ginseng)] are used for Medicinal purposes Worldwide. Its pharmacological activities have been studied worldwide. Ginseng is of great importance in medicinal uses because it possesses a number of active substances useful for human health, resulting in the development of numerous health products.

### 5.1. Metabolic physiology

Many studies have reported various pharmacological effects of ginseng roots on human health, including immunostimulant, anticancer, antiaging, anti-oxidative activities and cardiovascular control of blood pressure (7). These pharmacological effects were due to presence of ginsenosides, polysaccharides, polyacetylenic alcohols and peptides (2). Recently, metabolomics studies revealed that ginseng metabolome varied according to different plant parts, various geographical origins and cultivation ages (45,65). The metabolic consequences in ginseng during their growing seasons are poorly understood. Lee *et al.* (47) explored metabolic variations in ginseng roots and leaves during their growing seasons using proton NMR (<sup>1</sup>H NMR)-based metabolomics approach. There are few data on ginseng metabolomics and more research is needed.

### 5.2. Ginseng for human health

Ginseng is believed to suppress the growth and metastasis of cancer cells, activate glutathione peroxidase and superoxide dismutase to protect against damage caused by free radicals, decrease malondialdehyde levels and increase the activity of catalase. Non-saponins in red ginseng may improve learning and memory, while acidic polysaccharides increase the production of interferons (29,49). Kim (30) reported that extract of Korean red ginseng protected cells against peroxynitrite-induced genotoxicity by increasing cell viability through modulating the expression of p53 signaling intermediates.

Raw ginseng can be processed to red or white ginseng to increase its efficacy and preservation properties. Black ginseng is a new kind of processed ginseng manufactured from white ginseng with nine steaming cycles, which turns the ginseng black in color. Black ginseng can reduce reactive oxygen species (ROS) and nitric oxide (NO) production followed by inflammation in IRE1 $\alpha$ -dependent and XBP1-independent manners. Black ginseng provides antioxidant and anti-inflammatory effects through the endoplasmic reticulum stress mechanism (1).

Lee *et al.* (49) showed that red ginseng (*P. Ginseng*) extract suppressed the acute gout inflammation by suppressing NLRP3 inflammasomes in animal models. Clinically, red ginseng tablet suppressed NLRP3 expression in gout patients. It suggested that red ginseng may exert an additive benefit in gout treatment.

Protein components were extracted from ginseng and antitumor activity in human breast cancer cell line MCF-7 was investigated. It revealed that ginseng proteins could elicit antitumor activity by inhibiting cell proliferation and migration and inducing cell cycle arrest and apoptosis in MCF-7 cells and might act via the Bcl-2 and Bax apoptotic pathway (67).

Isolated from white, red, and black ginseng, 21 fractions were screened and their antioxidant effects on AAPH- or H<sub>2</sub>O<sub>2</sub>-induced damage were investigated to find new anti-UV and whitening agents. F10, whose main active compound was disaccharide sucrose, was used as an ingredient for whitening cosmetics and is an anti-UV filter (16).

### 5.3. Active substances

Ginsenoside is essential compound responsible for the pharmaceutical activities in ginseng (Table 3). Their structures and bio-activities have been studied during the past decades (57,93). Li *et al.* (56) reported oligosaccharides in ginseng and developed a procedure to detect and analyze these. Fu *et al.* (22) studied the anticancer effects of ginseng leaves crude polysaccharides on human hepatoma cell SMMC-7721. It revealed that GLCP promoted autophagy and apoptosis in human hepatoma cell SMMC-7721. Moreover, the mechanism may be associated with the caveolin-1, which was an essential structural molecule of caveolae. Although the inhibition of ginseng leaves to liver cancer was not very strong, however, it suppressed the tumor (22).

Table 3. Ginseng chemical compounds useful in Medicine, Food and health related products.

S. No.	Ginsenoside Compounds	Medicinal Properties
1	Rb1,Rb2,Rc,Rd	Anti-arthritis, anti-injury, anti-inflammatory, anti-oxidant
2	Re,Rf,Rg1,Rg2	Anti-diabetic, anti-injury, anti-platelet, anti-oxidant
3	Ro	Inhibit the replication of HIV-1

Lee *et al.* (52) studied the water extraction (90 °C for 14-16 h) and concentration process (until the final concentration is 70-73 Brix at 50-60 °C) and found that the ginsenoside contents of *P. ginseng* were Rg1: 1.3 mg/g, Re: 1.3 mg/g, Rb1: 6.4 mg/g, Rc: 2.5 mg/g, Rb2: 2.3 mg/g and Rd: 0.9 mg/g, respectively. Traditional method should be well preserved as it had its own chemical characteristics (39). Li *et al.* (55) developed an effective purification method of ginsenosides from cultured wild ginseng roots, red ginseng and white ginseng with microporous resins. Choi *et al.* (11) compared the ginsenoside and phenolics contents in hydroponically-cultivated ginseng leaves, fruits and roots. The study showed that hydroponically-cultivated ginseng leaves contained higher levels of ginsenosides (Rg1, Rg2+Rh1, Rd, and Rg3) and p-coumaric acid than field grown ginseng plants. At the same time, the 2, 2'-azino-di-(3-ethylbenzothiazoline)-6-sulfonic acid radical scavenging activities of leaves were the highest. Accordingly, hydroponically-grown ginseng leaves possessed the environmentally-friendly natural antioxidant (11). Siddiqi *et al.* (77) summarized the evidence supporting the therapeutic properties of ginsenosides both *in-vivo* and *in-vitro*, focusing on the different molecular agents comprising receptor activator of

nuclear factor kappa-B ligand, receptor activator of nuclear factor kappa-B, matrix metalloproteinase-9 as well as the bone morphogenetic protein-2 and Smad signaling pathways.

The active substances of *Panax ginseng* could be changed by steaming or sun drying. Six malonyl-ginsenoside (Rg1, Rb1, Rb3, Rc, Rd, Rb2) and 15 amino acids contents were decreased by steaming. In contrast, ginsenoside-Rh1, 20(S)-Rg2, 20(S, R)-Rg3 and Maillard reaction product such as AF (arginine-fructose), AFG (arginine-fructose glucose) and maltol concentrations were increased. These results are helpful for quality control and standardization of *P. ginseng*, which provided a scientific basis for pharmacological research of processed ginseng (29).

To evaluate 14-ginsenosides in ginseng collected from 66-producing areas in Northeast China, a practical liquid chromatography diode array detection (LC-DAD) method was developed. It revealed that the quality of ginseng roots and rhizomes from various sources differed due to various growing environments, cultivation technology, etc. The developed LC-ESI-IT-TOF-MSn method may identify more ginsenosides. The LC-DAD method assesses the ginseng quality and optimize the cultivation conditions to produce ginsenosides (89). Compound K (CK; 20-O- $\beta$ -(d-glucopyranosyl)-20(S)-protopanaxadiol) metabolites of ginsenosides was found in red ginseng root and possesses high bioavailability. Park *et al.* (73) determined the characteristics of bio-converted ginsenosides in red ginseng extract.

Fermentation technology is widely used to alter active substances of ginseng. Lee *et al.* (50) analyzed the characteristics and antioxidant activity of ginseng seeds fermented by *Bacillus*, *Lactobacillus* and *Pediococcus* strains, showing that 3-ethylbenzothiazoline-6-sulfonic acid and SOD were higher in fermented ginseng seeds in comparison with non-fermented ginseng seeds. Wang *et al.* (89) developed a new high-performance liquid chromatography coupled with electrospray ionization ion trap time-of-flight multistage mass spectrometry (LC-ESI-IT-TOF-MS/MS) method to identify the triterpenoids in ginseng. From the ginseng cultivated in China, 60-compounds including 58 triterpenoids were identified, of these 20 substances were identified for the first time (89).

Ginseng berry pomace (GBP) is a byproduct of ginseng berry processing, which contains numerous bioactive components (ginsenosides and their derivatives). The application of GBP as a beneficial biomaterial is currently limited but is promising source of bioactive compounds. The Phenolics, less polar ginsenosides and fatty acids were positively correlated with the antioxidant activity of GBP (48). The results demonstrated that the relative abundance of primary metabolites and a few ginsenosides was higher in the control, whereas, UHP treatment contained higher levels of fatty acids and sugars.

Yao *et al.* (98) conducted the study to qualitatively and quantitatively elucidate dynamic changes of ginsenosides in ginseng (*P. ginseng*) pulp steamed at 100 or 120 °C for different durations (1-6 h) through UPLC-QTOF-MS/MS and HPLC with the aid of 18 authentic standards of ginsenosides. It revealed that levels of 8-polar ginsenosides (i.e., Rg1, Re, Rb1, Rc, Rb2, Rb3, F1, and Rd) declined, while, those of 10 less-polar ginsenosides [i.e., Rf, Rg2, 20(S) Rh1, 20(R)-Rg2, F4, 20(S)-Rg3, 20(R)-Rg3, PPT, Rg5, and 20(R)-Rh2] elevated with increases of both steaming temperature and duration. The optimum steaming conditions for achieving the highest total ginsenosides were 100 °C for 1 h.

Rd, a protopanaxadiol (PPD) type ginsenoside, has relative low content in ginseng. However, it was more active than another protopanaxadiol ginsenoside Rb1, which has high content in ginseng. *Cladosporium fulvum* could convert Rb1 to Rd. G-I and G-II, isolated from the culture filtrate of *C. fulvum*, was purified and characterized. Both could selectively convert Rb1 to Rd and would be useful in industrial application (24,107,108).

Since each ginsenoside shows different medical activity and metabolic pathway, a quantitative analysis of ginsenoside is very important for ginseng studies. Therefore, a rapid, simultaneous and quantitative analysis of 26 ginsenosides (Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2(R), Rg2(S), Rg3(S), Rg3(R), Rg5, Rg6, Rh1(R), Rh1(S), Rh2(R), Rh2(S), F1, F2, F3, F4, K, Mc, PPT(S), XVII and Y) in white and red *Panax ginseng* was done by Lee *et al.* (35) using multiple reaction monitoring (MRM) mode on ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) (48).

#### 5.4. Pharmacological activity

Sathiyamoorthy *et al.* (76) obtained 6,226 expressed sequence tags (ESTs) from cDNA libraries of *P. ginseng* and conducted Insilico analysis to annotate the putative sequences using gene ontology functional, Kyoto Encyclopedia of Genes and Genomes. The orthologs biochemical and InterProScan protein functional domain analysis, revealing that genes were responsible for growth, pathogenicity, pigments, ginsenoside pathway and development of ginseng. Potential 346 targets were identified for the predicted 69 conserved miRNAs by searching the ginseng EST database and the predicted targets concentrated involved in secondary metabolic processes, responses to biotic and abiotic stress, transcription regulator activities as well as a variety of other metabolic processes (70).

High temperature and pressure-treated red ginseng (HRG) was produced at high temperature (140 °C) and high pressure (3 kg/cm<sup>2</sup>). Moreover, the HRG included higher phenolic acids content, for instance, maltol (6213.2 µg/100 g), p-hydroxybenzoic acid (823.3 µg/100 g) and syringic acid (6938.8 µg/100 g) than that found in white ginseng or commercial red ginseng (CRG) (35). Furthermore, the change of phenolic acids in HRG lead to the inhibition of oxidative stress in C2C12 muscle cells and 3T3-L1 adipocytes by up-regulation of the mRNA expression levels of copper and zinc (Cu/Zn)-SOD and catalyst (99).

The effects of HRG on oxidative stress was investigated using a mouse model. It showed that the levels of glutamic oxaloacetic transaminase, glutamic pyruvic and transaminasehepatic malondialdehyde in the HRG group were significantly lower than in exercise groups supplemented with commercial red ginseng (CRG) or not supplemented. The activities of muscular glycogen level, glucose-6-phosphate dehydrogenase and lactate dehydrogenase of the HGR group were higher than CR G group. Moreover, the HRG treatment group showed up-regulated mRNA expression of Cu/Zn-SOD and muscle regulatory factor 4. These results indicated that HRG might protect oxidative stress induced by exercise and improve exercise performance capacity (101).

In particular 20(R)-Rg3, represents less-polar ginsenoside with high bioactivity such as potent anti-cancer effects increased significantly. However, Re (the most abundant polar ginsenoside in fresh ginseng pulp), decreased remarkably. More importantly, ginsenoside species increased from 18 to 42 after steaming. Demalonylation and acetylation of ginsenosides were the dominant underling mechanisms for transformation of polar into less-polar ginsenosides (98).

Yuan *et al.* (102) studied the overexpression and characterization of a glycoside hydrolase family 1 enzyme from *Cellulosimicrobium cellulans* sp. 21 and its application for minor ginsenosides production, suggesting that CcBg11A would be potentially useful to prepare the pharmacologically active minor ginsenosides Gyp XVII, CO, Mb and F2. American ginseng (*P. quinquefolium*), originated from Northeast America, is also an important traditional herbal medicine in China. Ginsenosides are mainly responsible for the pharmacological activities of American ginseng (6). Effects of *Fusarium solani* and *F. oxysporum* infection on the metabolism of ginsenosides in American ginseng roots were studied. The pathogenic *Fusarium* spp. reduces ginsenoside levels by consuming them (44).

### 5.5. Ginseng products

Ginseng is distributed in about 35 countries around the world (Table 4, Figure 8). In general, four countries : China, South Korea, Canada and US are the biggest producers. Ginseng is used in various forms such as fresh, dried, boiled, red ginseng etc. It is consumed as food, dietary supplements and, functional food. World ginseng market including ginseng root and the processed products are estimated to be worth \$2,084 million (4). As the interests in alternative medicine and healthy food are increasing all over the world, the consumer markets of ginseng-processed products are expected to expand continuously. With *Panax ginseng* as the main raw materials that products are ginseng Guipi pill, ginseng Yangrong pill and ginseng tonic pill. The main raw materials of *Panax notoginseng* include Sanqi Xuefangning capsule, compound Danshen Tablet, Xiaoshuantongluo capsule and Naodesheng tablet. The products with *Panax quinquefolium* as the main raw material are beneficial to Anning, Longshen tonic ointment and American ginseng pill.

Table 4. Products manufactured from Ginseng spp.

Ginseng spp	Products
<i>Panax ginseng</i>	Guipi pill, ginseng Yangrong pill and ginseng tonic pill
<i>Panax notoginseng</i>	Sanqi Xuefangning capsule, compound Danshen Tablet, Xiaoshuantongluo capsule and Naodesheng tablet.
<i>Panax quinquefolium</i>	Longshen tonic ointment and American ginseng pill.

As interest in health issues steadily grows, demand for ginseng products to prevent and treat illness is also increasing and ginseng's pharmacological efficacy and function have been investigated extensively. The ginseng also goes well with many foods (drinks, rice cakes, cakes, jelly, salad dressing) (12). Choi *et al.* (12) found good quality of ginseng coffee produced via the processing of various types of coffee bean with a micro-coating solution containing ginseng extract derived from a variety of ginseng types combined with hydroxypropyl methyl cellulose.

## 6. FUTURE LINES OF RESEARCH

Much researches have been done on ginseng till date, but its allelopathic mechanisms remain unclear. For example:

- (i). the role of specific individual allelochemical is not clear, suggests the complexity of problem. Hence, more in-depth studies, are required to understand the mechanisms and the role of individual allelochemical.

(ii). The allelopathic molecular mechanism of ginseng may change crop traits through genetic control. Some emerging technologies, such as SWATH-MS, are used to analyze the upregulation and downregulation of stress proteins in ginseng, to identify ginseng functional membrane or cell wall proteins and complex signalling pathways, to study the molecular mechanisms of ginseng's allelopathic effects. (8,105).

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### DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

### CONFLICT OF INTEREST

The authors announce that they have no conflict of interest.

### ETHICAL APPROVAL

The authors declare that the study was carried out following scientific ethics and conduct. However, this study did not involve any use of animals, hence no ethical approval has been obtained from the concerned committee.

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