Review article

Systems-level mechanisms of action of Panax ginseng: a network pharmacological approach

Sa-Yoon Park 1,*, Ji-Hun Park 1,*, Hyo-Su Kim 1,*, Choong-Yeol Lee 1, Hae-Jeung Lee 2, Ki Sung Kang 3,*, Chang-Eop Kim 1,***

1 Department of Physiology, College of Korean Medicine, Gachon University, Seongnam, Republic of Korea
2 Department of Food and Nutrition, College of BioNano Technology, Gachon University, Seongnam, Republic of Korea
3 Department of Preventive Medicine, College of Korean Medicine, Gachon University, Seongnam, Republic of Korea

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A B S T R A C T

Panax ginseng has been used since ancient times based on the traditional Asian medicine theory and clinical experiences, and currently, is one of the most popular herbs in the world. To date, most of the studies concerning P. ginseng have focused on specific mechanisms of action of individual constituents. However, in spite of many studies on the molecular mechanisms of P. ginseng, it still remains unclear how multiple active ingredients of P. ginseng interact with multiple targets simultaneously, giving the multidimensional effects on various conditions and diseases. In order to decipher the systems-level mechanism of multiple ingredients of P. ginseng, a novel approach is needed beyond conventional reductive analysis. We aim to review the systems-level mechanism of P. ginseng by adopting novel analytical framework—network pharmacology. Here, we constructed a compound-target network of P. ginseng using experimentally validated and machine learning-based prediction results. The targets of the network were analyzed in terms of related biological process, pathways, and diseases. The majority of targets were found to be related with primary metabolic process, signal transduction, nitrogen compound metabolic process, blood circulation, immune system process, cell-cell signaling, biosynthetic process, and neurological system process. In pathway enrichment analysis of targets, mainly the terms related with neural activity showed significant enrichment and formed a cluster. Finally, relative degrees analysis for the target-disease association of P. ginseng revealed several categories of related diseases, including respiratory, psychiatric, and cardiovascular diseases.

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1. Introduction

Panax ginseng is one of the most widely used herbs in the world. It has been frequently used in East Asia since ancient times based on the traditional Asian medicine theory and clinical experiences. For instance, among herbal prescriptions in Shang-Han Lun (Treatise on Cold Damage Diseases) and Donguibogam (Korean Clinical Pharmacopeia), which are representative publications of traditional Asian medicine, 21 of 113 and 653 of 3,944 formulas (18.6% and 16.6%, respectively) contain P. ginseng [1]. Textbook of formula study that refers to herbal formula also has 78 prescriptions that contain P. ginseng out of the 438 total prescriptions (17.8%) [2]. In prescriptions, P. ginseng is mainly used as a tonic to boost the function of feeble bodies, and therefore applicable to a wide range of diseases [3]. In recent years, many clinical trials have been conducted to reveal the efficacy of P. ginseng for various diseases and symptoms. The results suggest that P. ginseng has effects on pathological conditions, such as ischemic heart disease, common cold, obstructive pulmonary disease, and erectile dysfunction [4–7]. Numerous studies have investigated the pharmacological mechanisms of P. ginseng. Most of the studies have focused on the actions of ginsenosides, the major active component of P. ginseng. It
is commonly believed that most pharmacological effects of *P. ginseng* are attributed to ginsenosides, including the stimulatory and inhibitory effects on the nervous system, antineoplastic effects, immunomodulatory effects, and nitric oxide release. However, *P. ginseng* reportedly contains various potentially bioactive ingredients such as phytosterols, sesquiterpenes, flavonoids, polyacetylenes, alkaloids, and phenolic compounds in addition to ginsenosides, and these ingredients may also work together with ginsenosides to contribute to the various effects of *P. ginseng*. Indeed, there have been reports that ginsenosides do not act alone; rather they function in concert with minor ingredients to perform their beneficial effects.

Despite the previous efforts to understand the molecular mechanisms, it is still unclear how the combinations of multiple ingredients work together to produce clinical effects of *P. ginseng*. The conventional pharmacological approaches are unable to capture the systems-level mechanism of herbs; therefore, novel methods are needed. In recent years, emergence of network pharmacology is shedding light on understanding the mechanism of the herbal medicine at the systems level. Network pharmacology integrates computational and experimental methods, focusing on the "multi-component, multi-target effects".

The aim of this article was to review the systems-level mechanisms of *P. ginseng* by adopting network pharmacological analysis, providing new insights into the effects and mechanisms of *P. ginseng*. First, we briefly reviewed the chemical constituents of *P. ginseng* including the minor components in addition to the ginsenosides. Next, we constructed a compound-target network using the information from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSp [Institute of Integrated Bio-informicine and Translational Science (IBTS), Hong Kong, http://tcmspw.com]) [20]. In order to review the related processes and pathways of the compound-network of *P. ginseng*, the PANTHER [Protein ANalysis THrough Evolutionary Relationships (Paul Thomas, in Keck School of Medicine of USC, Los Angeles, USA), http://pantherdb.org] classification system [21,22] and Enrichr method were employed, respectively. Finally, the relative degree matrix was constructed from the network of *P. ginseng* to investigate the related diseases (Fig. 1).

### 2. The chemical constituents of *P. ginseng*

#### 2.1. Ginsenosides

Ginsenosides were isolated in the 1960s for the first time [23], and many types of ginsenosides have been identified. Ginsenosides are triterpene saponins that originated from 2, 3-oxidosqualene. They can be divided into two groups by their skeletal structures: dammarane-type ginsenosides and oleanane-type ginsenosides.

##### 2.1.1. Dammarane-type ginsenosides

Dammarane-type ginsenosides are biosynthesized from protopanaxadiol (PPD) or protopanaxatriol (PPT), both of which are formed when dammarenediol-II is hydroxylated. They can be classified into two groups, PPD-type and PPT-type. PPD-type has the attachment of saccharides to C-3 and/or C-20 and includes ginsenosides Ra1, Rb1, Rc, Rd, etc. PPT-type has the attachment of saccharides to C-6 and/or C-20 and includes ginsenosides Re, Rg2, Rh1, etc. [24] (Fig. 2A).

##### 2.1.2. Oleanane-type ginsenosides

Oleanane-type ginsenosides are biosynthesized from β-amyrin, which are also formed from dammarenediol-II. They have a pentacyclic structure, whereas dammarane-type ginsenosides have a tetracyclic structure. Ginsenoside Ro (Fig. 2B) is a compound that is commonly detected in *P. ginseng*, and other oleanane-type ginsenosides are rare [25].

##### 2.1.3. Ginsenoside metabolites

The majority of ginsenosides are deglycosylated in the gastrointestinal tract by colonic bacteria. Most of them are finally metabolized to PPD, PPT, compound K, or other compounds [26,27] (Fig. 2C).
2.2. Phytosterols

Phytosterols are a type of alcohol that has the steroid skeleton and are naturally present in plants. Phytosterols are generally considered to lower the cholesterol level [28]. The representative phytosterol, stigmasterol, and β-sitosterol (Fig. 3A) are commonly detected in P. ginseng.

2.3. Sesquiterpenes

Sesquiterpenes are volatile C15-terpenoids originating from three isoprene units. Many sesquiterpenes including β-elemene and β-selinene (Fig. 3B) have been isolated and identified as compounds of P. ginseng [13,29].

2.4. Flavonoids

Flavonoids are a group of polyphenolic compounds that consist of two phenyl rings and a heterocyclic ring and are universally present in plants. It is believed that flavonoids have health-promoting properties due to antioxidant activities [30]. Kaempferol (Fig. 3C) is the representative flavonoid in P. ginseng.

2.5. Polyacetylenes

Plenty of polyacetylenes have been identified since the first polyacetylene panaxynol was extracted from P. ginseng [31]. These include panaxynol, ginsenoyn e A, etc. (Fig. 3D). Several studies revealed that polyacetylenes in P. ginseng show cytotoxic activity at high concentrations and possess antitumor properties [32].

2.6. Alkaloids

Alkaloids are one of the non-saponin constituents in P. ginseng, including fumarine and girinimbin (Fig. 3E). P. ginseng alkaloids are minor components; they were isolated later than other compounds [15] and relatively less investigated.

2.7. Phenolic compounds

There are > 10 identified phenolic compounds in P. ginseng, such as elemicin and dauricine (Fig. 3F). Numerous studies have reported various biological properties of phenolic compounds, including antitumor, antioxidant, and anti-inflammatory activities [33,34].

3. Network construction

Compound-target networks are bipartite networks in which the nodes represent compounds and targets, and the edges (links, connections) are defined as compound-target interactions (1 or 0). In order to construct networks, oral bioavailability (OB) and drug-likeness (DL) index information were extracted from TCMSP for each compound of P. ginseng (a total of 190 compounds including 18 microbiota-derived metabolites). OB and DL are calculated by machine learning methods or Tanimoto coefficient, using diverse drugs and drug-like molecule datasets [35]. They are commonly used for filtering out compounds that are unlikely to be drugs and the thresholds are set to > 30 (OB) and ≥ 0.18 (DL) as default suggestive values of TCMSP.

In this review, a wide range of thresholds of OB and DL (10 bins between minimum and maximum values of OB and DL) were applied for compound filtering instead of a single value of threshold since it is not clear to what extent the compounds will be utilized as active compounds. Compound-target interaction information was also extracted from TCMSP for all pairs of candidate compounds and target proteins in the database. It includes experimentally validated interactions, but most of the interactions were predicted ones, based on the machine learning methods (Support Vector Machine and Random Forest) with validated drug-target interaction datasets. The performance of this predictive method for compound-target interactions are proven to be reliable [36].

For the purpose of visualization, three representative networks among threshold networks were presented using Cytoscape (Cytoscape Consortium, San Diego, California, USA) [37] (Fig. 4, Table 1).

4. Pathway analysis

To capture the related biological functions of P. ginseng at coarse-grained level, every target of the compound-target network was assigned to biological processes using the PANTHER classification system [21]. This system provides tools for large-scale gene function analysis by combining information of gene functions, ontology, and pathways. In this review, an ontology system named “PANTHER GO-Slim Biological Process” was used. For the interpretability, 74 biological processes were manually extracted from the first to third level nodes of the taxonomy of PANTHER GO-Slim Biological Process. The majority of targets were included in eight categories as follows: primary metabolic process (55 targets, total degrees = 471), signal transduction (36 targets, total degrees = 313), nitrogen compound metabolic process (27 targets,
total degrees = 195), blood circulation (15 targets, total degrees = 191), immune system process (14 targets, total degrees = 186), cell-cell signaling (20 targets, total degrees = 180), biosynthetic process (22 targets, total degrees = 180), and neurological system process (15 targets, total degrees = 155) (Fig. 5).

In order to determine the significantly enriched pathways in the targets of the network, pathway enrichment analysis was performed with Enrichr (Avi Ma’ayan in Ma’ayan Laboratory, Center for Bioinformatics, Icahn School of Medicine at Mount Sinai, New York, USA) [38] using the KEGG pathway database.
As a result, the top 10 terms were ranked in the descending order as follows: neuroactive ligand–receptor interaction, calcium signaling pathway, advanced glycation end-products (AGEs) and receptor for advanced glycation end-product signaling pathway in diabetic complications, cGMP-PKG signaling pathway, pathways in cancer, cAMP signaling pathway, estrogen signaling pathway, cholinergic synapse, retrograde endocannabinoid signaling, and serotonergic synapse. These enriched terms were visualized as a bar graph, grid, and network using the KEGG 2016 library (Fig. 6). Specifically, it was found that the terms related with neural activities such as neuroactive ligand–receptor interaction, serotonergic synapse, and cholinergic synapse form a cluster, suggesting multidimensional therapeutic effects of *P. ginseng* on the nervous system.

### 5. Disease analysis

Finally, potential target diseases of *P. ginseng* were analyzed based on the target-disease information from TCMSP, where the information is extracted from PharmGKB (http://www.pharmgkb.org) and Therapeutic Targets Database (http://bidd.nus.edu.sg/BIDD-Databases/TTD/TTD.asp). First, degrees were calculated for all diseases in TCMSP by counting the number of associations with targets in the constructed compound-target networks of *P. ginseng*. Since the results differ with the changes in the threshold level, the degrees of diseases were calculated across a wide range of thresholds of OB and DL, resulting in the degree matrix of diseases. However, it turned out that the degrees of diseases tend to be biased to specific diseases (e.g., unspecific cancer) because previous studies about target genes are not evenly distributed for diseases. To avoid this bias, relative degrees were calculated by dividing degrees by the maximum degree of the corresponding disease. The relative degree matrix of major diseases targeted by *P. ginseng* shows a comparative advantage of this herb over others on various diseases (Fig. 7). Comparative advantage means that *P. ginseng* has more protein targets than other herbs for the same disease, thereby making the probability of targeting corresponding disease higher.
5.1. Respiratory effects

P. ginseng is known to produce numerous actions on the respiratory system, especially on asthma related with anti-allergic properties [40]. For example, Babayigit et al. [41] investigated the anti-asthmatic activity of P. ginseng in a murine model of chronic asthma sensitized by ovalbumin. When compared with the placebo group, all the chronic histopathologic changes of airways (thicknesses of basement membrane, epithelium, and subepithelial smooth muscle, goblet cell number, and mast cell number) in P. ginseng group were significantly ameliorated. In accordance with this, it was reported that P. ginseng suppressed airway hyperresponsiveness, ovalbumin-specific IgE levels, and inflammatory cytokine production [42]. Kim and Yang [43] demonstrated that P. ginseng reduced airway inflammation in allergic asthma mice model and investigated the underlying mechanism. The P. ginseng-treated group restored not only the expression of inflammatory cells, such as EMBP, Muc5ac, CD40, and CD40L, but also the mRNA and protein levels of the cytokines [interleukin (IL)-1β, IL-4, IL-5, and tumor necrosis factor-α].

5.2. Psychiatric effects

Several studies have described the beneficial effects of P. ginseng on various psychiatric diseases such as depression and schizophrenia. It has been reported that P. ginseng has curative effects on depression by a plethora of studies. For instance, a report states that the wild P. ginseng extract suppressed the expression of corticotrophin-releasing factor and neuropeptide Y, significantly reducing depression-like behavior in morphine withdrawal rat model [44]. Furthermore, numerous studies revealed the clinical effects of herbal formulas containing P. ginseng on depression, e.g., Kai-Xin-San [45–49], Sanyuansan [50], Xiaochaihutang [51], and Sho-ju-sen [52]. In parallel with this, there have been several clinical trials on depression. Lee and Ji [53] showed that fermented red P. ginseng had beneficial effects on depression by altering lipids. In addition, Jeong et al. [54] reported that Korean Red P. ginseng at a dose of 3 g/d significantly decreased residual symptoms of major depression in an 8-wk study with 35 female outpatients remitted from major depression.

Several recent studies have suggested that P. ginseng has beneficial effects on schizophrenia. For instance, Tran et al. [44] reported that wild P. ginseng was found to ameliorate phencyclidine-induced schizophrenia-like behavior in mice by positive modulation of glutathione. Kim et al. [55] investigated the influence of P. ginseng on offspring of pregnant rats exposed to prenatal stress. The influence of P. ginseng was examined in the behavioral activity and protein expression analysis. The results demonstrated that the downregulation of some genes after exposure to prenatal stress had influences on behavioral changes, and these phenomena were recovered following the treatment with P. ginseng (300 mg/kg) during pregnancy.
5.3. Cardiovascular effects

P. ginseng also produces numerous effects on the cardiovascular system [6]. There have been studies suggesting the efficacy of P. ginseng on hypertension [56–60]. It is known that P. ginseng regulates blood pressure to normal and thereby helps to elevate low blood pressure and to lower high blood pressure [61]. It was reported that the effect of regulating high blood pressure is mediated by promoting vascular endothelial cell-derived nitric oxide secretion [62–64].

Recent studies found a close relationship between angiogenesis and P. ginseng [65,66]. P. ginseng and its ginsenosides reportedly modulate multiple steps of angiogenesis, such as inhibiting endothelial cell proliferation, formation of capillary tube, and vascular endothelial growth factor (VEGF)-induced chemoinvasion [67,68]. According to Choi et al. [69], Korean Red Ginseng extracts efficiently decrease several angiogenic factors such as IL-8, hypoxia inducible factor-1a, VEGF, IL-6, and matrix metalloproteinases, implying the underlying mechanism of anti-angiogenesis.

Many studies suggest that P. ginseng has protective effects on ischemia and reperfusion (I/R), especially on the myocardial I/R [70,71]. Recently, Aravinthan et al. [72] reported that ginseng total saponin ameliorated myocardial injury by improving hemodynamics, such as aortic flow, coronary flow, and cardiac output. Thus, ginseng total saponin significantly suppressed the biochemical parameters, oxidative stress markers, and inflammatory indicators. In consistent with this, Luo et al. [73] suggested that the long-term consumption of P. ginseng lowers the susceptibility of acute myocardial I/R injury in intermediate-aged rats. P. ginseng-treated heart reportedly showed reduced infarct size, improved cardiac performance, and increased survival signals.

5.4. Parkinson’s disease

Several studies have recently reported that P. ginseng has a wide range of actions in the central nervous system, with promising effects on Parkinson’s disease. Van et al. [74] demonstrated neuroprotective effects of the P. ginseng extract. It significantly reduced dopaminergic cell loss, preventing the development of locomotor deficits in chronic Parkinson’s disease model animals. Hu et al. [75] demonstrated that the water extract of P. ginseng has significant protective effects against parkinsonism-inducing cytotoxic agents, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and its active metabolite 1-methyl-4-phenylpyridinium, in mice. It increased the Bax/Bcl-2 ratio, decreased cell death, promoted the release of cytochrome C, and suppressed the overproduction of reactive oxygen species.

5.5. Pain

There have been reports on pain-relieving effects of P. ginseng [76–78]. Nah et al. [76] reported that ginsenosides could regulate the pain-related behavior of mice with capsaicin-induced pain in a dose-dependent manner. Lee et al. [79] demonstrated analgesic and

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**Table 2**

| Category of diseases | Disease name |
|---------------------|--------------|
| Respiratory diseases | asthma, cough, dyspnea |
| Psychiatric diseases | anxiety disorder, depression, mood disorder, opioid dependence, schizophrenia |
| Cardiovascular diseases | angiogenesis, hypertension, ischemia, myocardial infarction |
| Miscellaneous diseases | pain, Parkinson’s disease |
anti-inflammatory effects of the fraction of P. ginseng in inflammatory pain mice models. Wang et al. [80] showed that glycoproteins extracted from P. ginseng exhibited a dose-dependent analgesic effect in mice by conducting acetic acid-induced writhing and hot-plate. Recently, a study also showed analgesic effect of P. ginseng in neuropathic pain animals models [81].

6. Concluding remarks and future directions

P. ginseng contains various ingredients in addition to ginsenosides, and these components might interact with multiple targets and pathways simultaneously in a complex manner. It is difficult to understand the complex mechanisms of the action of P. ginseng at systems-level using the conventional reductive analysis. Here, we attempted to review the systems-level mechanism of P. ginseng by applying a novel analytical framework, network pharmacology. The constructed compound-target network of P. ginseng based on validated datasets and predictive models provided potential target proteins of P. ginseng. The multiple targets of the network were analyzed in terms of related biological process, pathways, and diseases, revealing the systems-level mechanism of P. ginseng. The majority of targets were related with primary metabolic process, proteins of P. ginseng contains various ingredients in addition to ginsenosides on the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1. Drug Metab Dispos 2002;30:378–84

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Conflicts of interest

The authors declare no conflicts of interest.

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