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Review article

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

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ABSTRACT

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.

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 Pharmacopoeia*), 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

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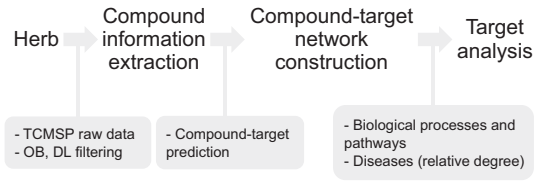

Fig. 1. Framework of network pharmacological analysis. DL, drug-likeness; OB, oral bioavailability, TCMSP, Traditional Chinese Medicine Systems Pharmacology.

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 [8–11]. However, *P. ginseng* reportedly contains various potentially bioactive ingredients such as phytosterols, sesquiterpenes, flavonoids, polyacetylenes, alkaloids, and phenolic compounds in addition to ginsenosides [12–15], 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 [16–18].

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" [19].

The aim of this article was to review the systems-level mechanism 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 Bioinformedicine and Translational Science (IBTS), Hong Kong], http://tcmspnw.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 triperpene 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).

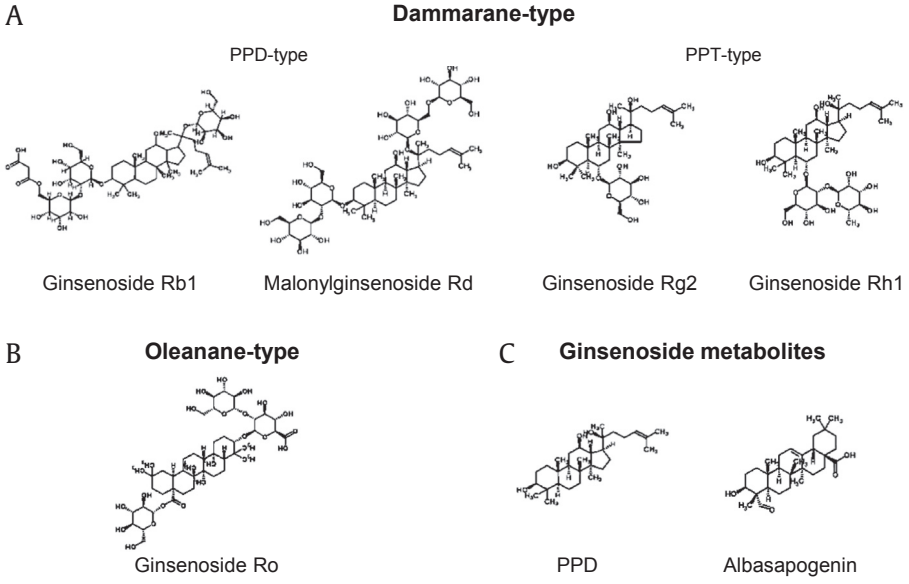

Fig. 2. Structures of selected ginsenosides. Dammarane-type is classified into two further types, PPD-type and PPT-type. PPD, protopanaxadiol; PPT, protopanaxatriol.

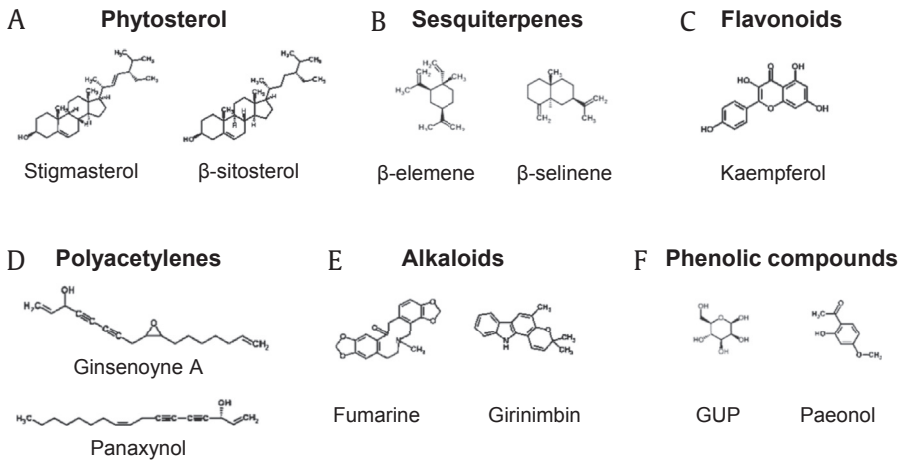

Fig. 3. Structures of selected non-ginsenoside constituents. GUP, β-D-mannopyranose.

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, ginsenoyne 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 $\geq$ 30 (OB) and $\geq$ 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,

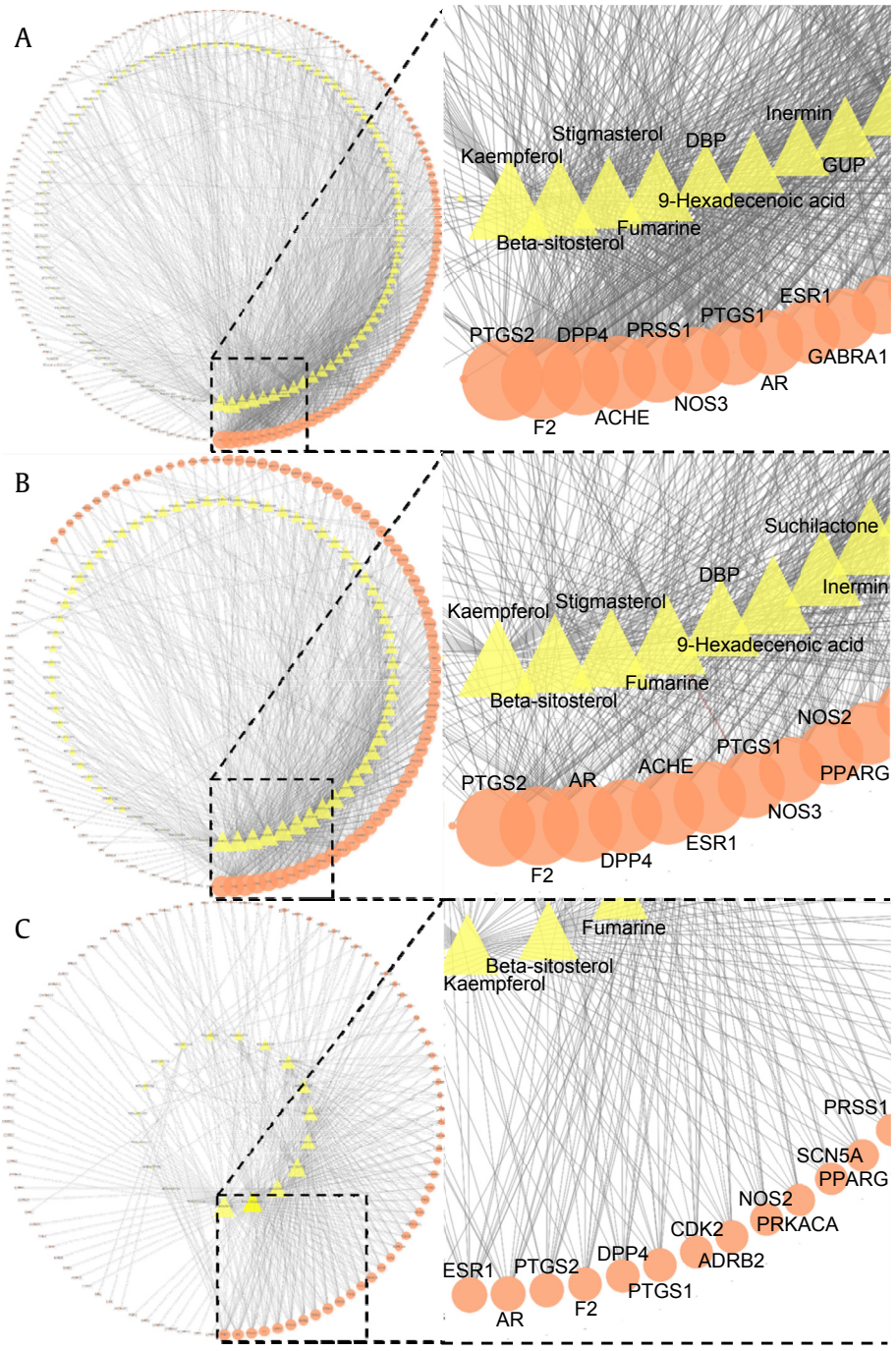

Fig. 4. The representative compound-target networks of *Panax ginseng* with different thresholds for OB and DL. (A) The networks are presented by applying no thresholds for OB and DL (105 compounds and 161 corresponding targets); (B) 13.56 and 0.09 for OB and DL, respectively (71 compounds and 116 corresponding targets); and (C) 30.27 and 0.19 for OB and DL, respectively (20 compounds and 100 corresponding targets). The yellow triangle represents compounds and the orange circle represents targets. The compounds and targets of each network were sorted in degree descending order from the bottom of the figure in a circular layout. The size of compound and target node is proportional to the degree in the network. Top 10 targets of each network are enlarged. ACHE, acetylcholinesterase; ADRB2, beta-2 adrenergic receptor; AR, androgen receptor; CDK2, cell division protein kinase 2; DBP, dibutyl phthalate; DL, drug-likeness; DPP4, dipeptidyl peptidase IV; ESR1, estrogen receptor; F2, thrombin; GABRA1, gamma-aminobutyric acid receptor subunit alpha-1; GUP, β-D-mannopyranose; NOS2, nitric oxide synthase (inducible); NOS3, nitric-oxide synthase (endothelial); OB, oral bioavailability; PTGS2, prostaglandin G/H synthase 2; PKACA, mRNA of PKA catalytic subunit C-alpha; PPARG, peroxisome proliferator activated receptor gamma; PRSS1, trypsin-1; PTGS1, prostaglandin growth hormone synthase 1; SCN5A, sodium channel protein type 5 subunit alpha.

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

Table 1
Top 10 targets in each network with different thresholds for OB and DL

Gene symbol	Target name	Degree (rank) according to each OB, DL threshold			Total degree
		0.00, 0.00	13.56, 0.09	30.27, 0.19	
PTGS2	Prostaglandin G/H synthase 2	54 (1)	35 (1)	11 (3)	100
F2	Thrombin	53 (2)	35 (1)	10 (4)	98
DPP4	Dipeptidyl peptidase IV	49 (3)	28 (4)	10 (4)	87
AR	Androgen receptor	35 (8)	33 (3)	12 (2)	80
ACHE	Acetylcholinesterase	45 (4)	27 (5)	7 (14)	72
ESR1	Estrogen receptor	34 (9)	27 (5)	13 (1)	74
PTGS1	Prostaglandin G/H synthase 1	36 (7)	23 (7)	10 (4)	69
PRSS1	Trypsin-1	41 (5)	16 (14)	8 (10)	49
NOS3	Nitric-oxide synthase, endothelial	38 (6)	22 (8)	4 (32)	60
NOS2	Nitric oxide synthase, inducible	27 (13)	21 (9)	9 (7)	30
GABRA1	Gamma-aminobutyric acid receptor subunit alpha-1	31 (10)	16 (14)	6 (22)	31
PPARG	Peroxisome proliferator activated receptor gamma	22 (14)	20 (10)	8 (10)	28
CDK2	Cell division protein kinase 2	15 (23)	14 (16)	9 (7)	9
ADRB2	Beta-2 adrenergic receptor	16 (21)	11 (20)	9 (7)	9
PRKACA	mRNA of PKA Catalytic Subunit C-alpha	11 (27)	11 (20)	8 (10)	8
SCN5A	Sodium channel protein type 5 subunit alpha	10 (31)	8 (32)	8 (10)	8

Targets are sorted according to their total degrees (sums of degrees in 3 networks). DL, drug-likeness; OB, oral bioavailability.

(http://www.genome.ad.jp/kegg/pathway.html) [39]. 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.

As a result, major diseases targeted by *P. ginseng* were analyzed as follows: angiogenesis, anxiety disorder, asthma, cough,

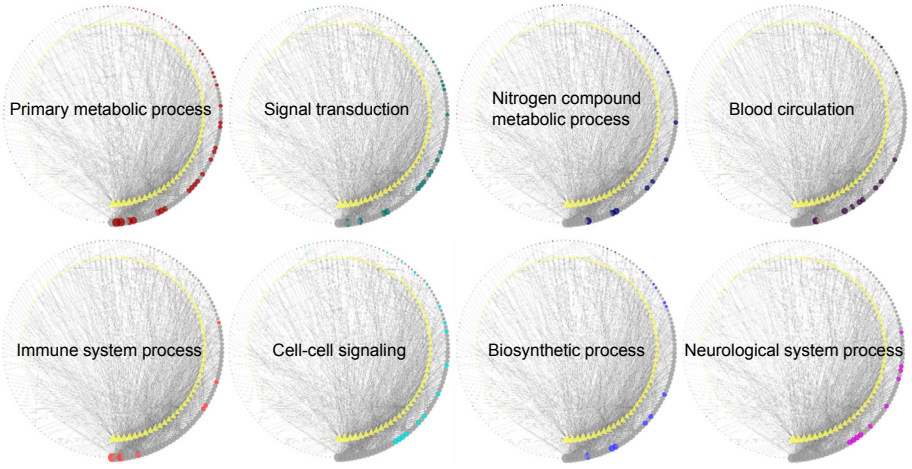

Fig. 5. Dominant biological processes of targets of *Panax ginseng*. Each target is classified using "PANTHER GO-slim Biological Process" in the PANTHER classification System. The top eight biological processes are presented according to the total degrees. The compounds and targets of each network are sorted in degree descending order from the bottom of the figure, in a circular layout. The size of compound and target node is proportional to the degree in the network. This analysis is conducted with unfiltered compound-target network.

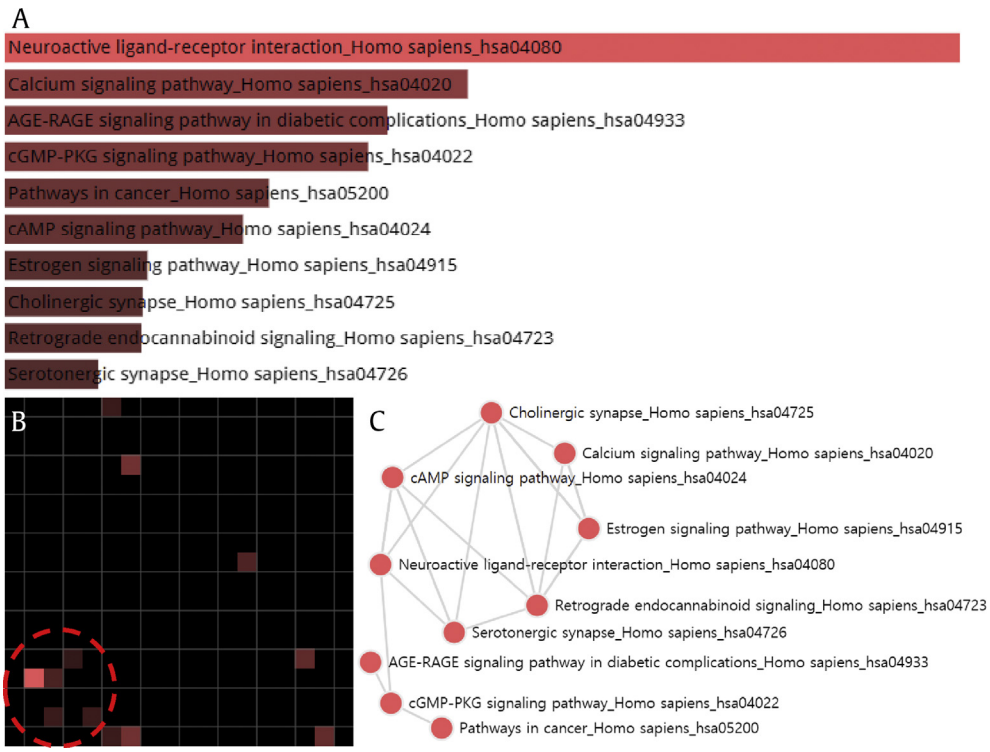

Fig. 6. Grid and network analysis of enriched terms using the KEGG 2016 library. The gene symbols of 161 targets are used as an input and the result is displayed in three different manners: a bar graph, a grid, and a network. (A) The top 10 terms are ranked as bar graph in descending order. The length of the bar represents the significance of the specific gene-sets represented by the terms. The brighter the color, the more significant that term is. (B) Each grid square represents a term and is arranged based on term-term similarity, which represents one term's gene-set content similarity with another term. It shows the top 10 terms sorted by enrichment score. The brighter the square, the more significant that term is. A circle is used to highlight the most dominant cluster of enriched terms: neuroactive ligand−receptor interaction, cAMP signaling pathway, serotonergic synapse, cholinergic synapse, and retrograde endocannabinoid signaling (displayed clockwise from the brightest grid). (C). In the network, each node represents the enriched term, and the edge between two nodes means that the two terms have some gene content similarity.

depression, dyspnea, hypertension, ischemia, mood disorder, myocardial infarction, opioid dependence, pain, Parkinson's disease, and schizophrenia (Fig. 7). These diseases could be categorized into respiratory, psychiatric, cardiovascular, and miscellaneous diseases (Table 2).

Interestingly, the results of systems-level target diseases analysis were found to be consistent with the published studies on diseases with the extract of *P. ginseng*.

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.

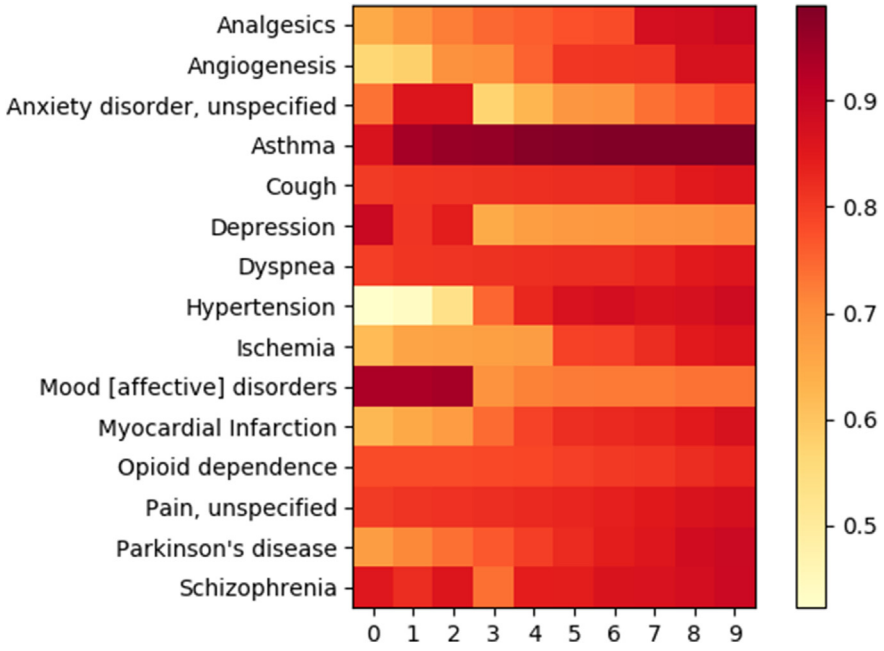

Fig. 7. Relative degree matrix of major diseases. Each row and column represents the disease name and threshold level of oral bioavailability and drug-likeness, respectively. Only the top 30% of diseases by total degrees across thresholds are presented. Color bar indicates relative degrees.

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

Table 2
Category of diseases and corresponding disease names

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 animal 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, signal transduction, nitrogen compound metabolic process, blood circulation, immune system process, cell-cell signaling, biosynthetic process, and neurological system process. In more detailed pathway enrichment analysis of targets using KEGG pathway database, mainly the terms related with neural activity showed significant enrichment and formed a cluster. Furthermore, relative degrees analysis for target-disease association of *P. ginseng* revealed several categories of related diseases including respiratory, psychiatric, and cardiovascular diseases. However, it is worthy to note that the network pharmacological approach adopted in this review largely depends on the *in silico* predictions although the training dataset for the prediction models are experimentally validated. Currently, many different methods exist for each network pharmacological analysis step, such as the prediction of OB, DL, and drug-target interactions [35], and it is not clear which methods are ideal for understanding the systems-level, multidimensional mechanisms of herbs with multiple ingredients. In spite of the limitations of *in silico* analysis, our results were consistent with the previous researches on diseases with the extract of *P. ginseng*. The network pharmacological approach will help to comprehensively understand the systems-level mechanism of *P. ginseng* by combining experimental validation and optimizing the analytical methodologies in future studies.

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Conflicts of interest

The authors declare no conflicts of interest.

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