Review Article

Regulation of appetite-related neuropeptides by Panax ginseng: A novel approach for obesity treatment ☆

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ABSTRACT

Obesity is a primary factor provoking various chronic disorders, including cardiovascular disease, diabetes, and cancer, and causes the death of 2.8 million individuals each year. Diet, physical activity, medications, and surgery are the main therapies for overweightness and obesity. During weight loss therapy, a decrease in energy stores activates appetite signaling pathways under the regulation of neuropeptides, including anorexigenic [corticotropin-releasing hormone, proopiomelanocortin (POMC), cholecystokinin (CCK), and cocaine- and amphetamine-regulated transcript] and orexigenic [agouti-related protein (AgRP), neuropeptide Y (NPY), and melanin-concentrating hormone] neuropeptides, which increase food intake and lead to failure in attaining weight loss goals. Ginseng and ginsenosides reverse these signaling pathways by suppressing orexigenic neuropeptides (NPY and AgRP) and provoking anorexigenic neuropeptides (CCK and POMC), which prevent the increase in food intake. Moreover, the results of network pharmacology analysis have revealed that constituents of ginseng radix, including campesterol, beta-elemene, ginsenoside Rb1, biotin, and pantothenic acid, are highly correlated with neuropeptide genes that regulate energy balance and food intake, including *ADIPOQ, NAMPT, UBL5, NUCB2, LEP, CCK, GAST, IGF1, RLN1, PENK, PDYN*, and *POMC*. Based on previous studies and network pharmacology analysis data, ginseng and its compounds may be a potent source for obesity treatment by regulating neuropeptides associated with appetite.

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1. Introduction

Obesity is a leading health concern worldwide, with a prevalence that has doubled in 73 countries since 1980 [1], and at least 2.8 million individuals dying each year as a result of being overweight or obese [2]. Obesity is associated with several chronic diseases, such as diabetes, cardiovascular disease (CVD), cancer, and mental diseases. It also increases the risk of infection and complications due to trauma [3]. A popular therapy for obesity includes weight loss via physical exercise and calorie-restricted dieting [4–6]. As part of a lifestyle change, "Eat less and move more" is considered a foundation for sustained weight loss. Although the principle of this therapy appears manageable and simple, it requires persistence and self-discipline to maintain and ensure the necessary beneficial weight loss. In fact, patients may face a number of challenges in terms of both physical and mental aspects when they follow a weight-loss program. For example, when food intake is dramatically restricted, the body has an evolutionary response of increasing the level of hormones mediating appetite signals, which causes the body to feel hungrier and more preoccupied with food [7,8].

In recent years, it has been discovered that hypothalamic and peripheral neuropeptides associated with appetite have a close evolutionary link. The principal feeding organ, the hypothalamus, regulates short- and long-term dietary intake by synthesizing numerous anorectic and orexigenic neuropeptides. The function

and structure of several hypothalamic peptides have been studied in rodent models, including melanin-concentrating hormone (MCH), cocaine- and amphetamine-regulated transcript (CART), orexins, neuropeptide Y (NPY), melanocortins, and agouti-related peptide (AGRP). In addition, peripheral neuropeptides including bombesin, amylin, peptide YY (PYY3-36), ghrelin, and cholecystokinin (CCK) govern essential gastrointestinal processes, such as absorption, secretion, and motility; offer feedback to the central nervous system on nutrition availability; and may help regulate food intake [9]. Thus, the interference of neuropeptides mediating appetite may contribute to supporting sustainable weight loss in addition to diet and physical activity. Natural products contain potential neuropeptide regulators of appetite control that are effective in reducing obesity markers in animal models [10]. For example, Kim et al. [11] reported that resveratrol found in *Vitis coignetiae* Pulliat suppresses AgRP and NPY expression, which induces a decrease in food consumption in C57BL/6 J mice.

Panax ginseng Meyer, also known as Korean ginseng, is the most highly regarded herb and has been widely used in herbal remedies in traditional Korean medicine for thousands of years. The Greek word "Panax" is derived from "panacea," which means "cure-all" [12]. As its name implies, the efficacy of *P. ginseng* has a wide impact on various chronic disease studies with respect to CVD, type 2 diabetes (T2D), immune function, and obesity [13]. Possessing sweet, mildly bitter, and slightly warm properties according to *Donguibogam* traditional Korean medicine literature, *P. ginseng* is prescribed to treat metabolic syndrome because of its traditional Korean medical effects, such as energy enhancement, *qi* tonification, and tranquilization [14,15]. *P. ginseng* crude extracts also have multiple effects, including anti-hyperglycemia, insulin sensitization, islet protection, anti-obesity, and anti-oxidation effects in many model systems [16]. The major active compounds of *P. ginseng* are ginsenosides (ginseng-specific saponins) (Fig. 1), gintonin (non-saponins) (Fig. 2) [16], polysaccharides, peptides, fatty acids, vitamins, and flavonoids, which are responsible for its diverse biological activities [13]. Ginsenosides are considered the

pharmacologically active constituents promoting various potential benefits to human health, especially to protect against obesity, which is defined as a "chronic, relapsing, multifactorial, neuro-behavioral disease" [17].

Moreover, ginseng has many benefits in supporting the treatment and prevention of obesity. The anti-obesity effects of ginseng have been described in relation to various mechanisms, including activation of the adenosine monophosphate-activated kinase (AMPK) pathway, a decrease in lipid accretion, or a decrease in the activity of pancreatic lipase [18]. In addition, ginseng and its compounds also impact neuropeptides regulating food intake, such as NPY, CCK, proopiomelanocortin (POMC), and AgRP, which promote weight loss [18,19]. This article aims to elucidate the potential of ginseng and its constituents as a neuropeptide-based therapy for appetite in the prevention and treatment of obesity via a literature review and network pharmacology analysis.

2. Study design and methods

A literature review and network pharmacological analysis were conducted to investigate the potential of ginseng and its components in obesity treatment targeting neuropeptides that regulate energy balance and food intake.

2.1. Search strategy for review

A search was performed of the English literature in online databases such as PubMed, Google Scholar, and ScienceDirect. Various keywords were assessed, including "obesity," "obesity treatment," "neuropeptide," "appetite neuropeptide," "appetite signaling," "ginseng," "ginseng pharmacology activities," "ginseng obesity," "ginseng obesity neuropeptide," and "ginsenosides obesity neuropeptide."
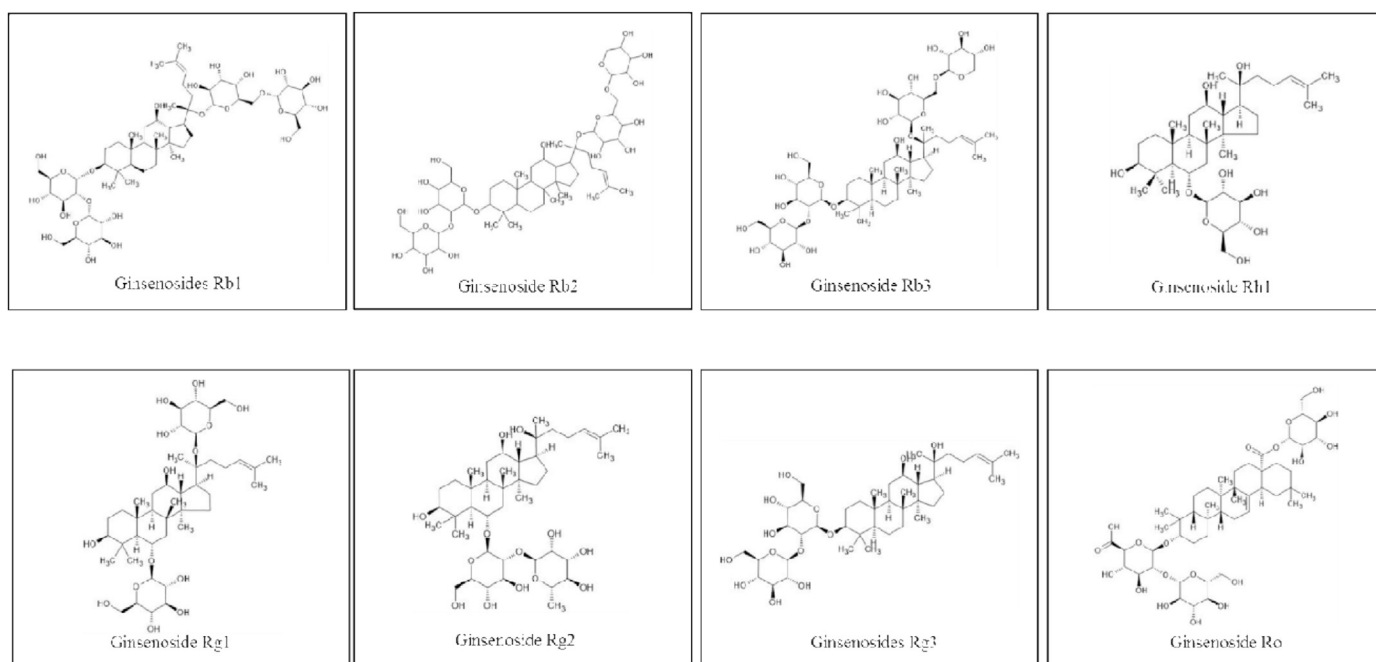

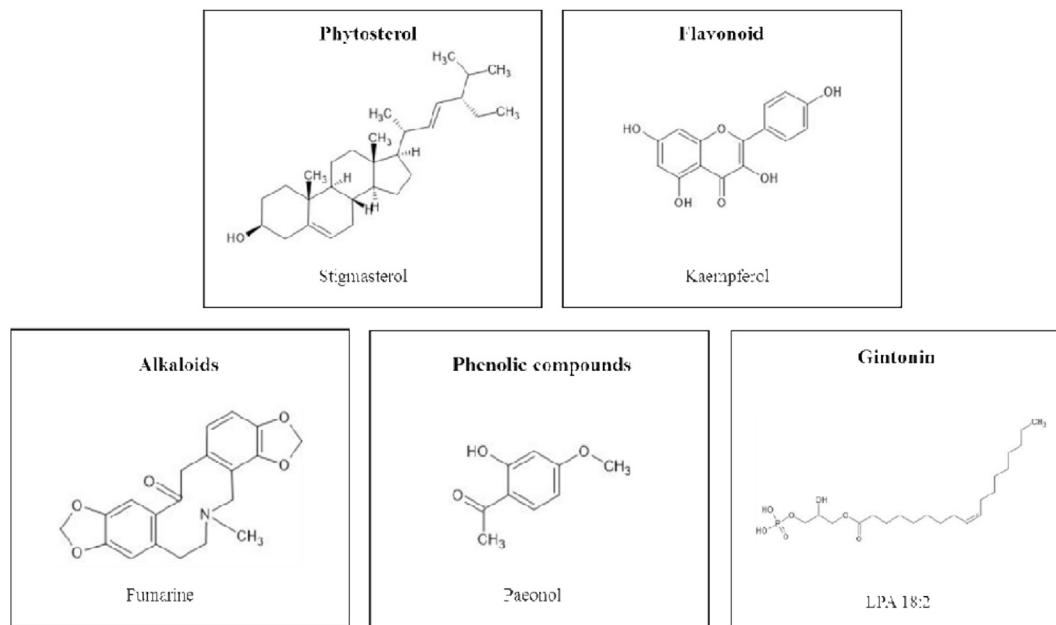**Fig. 1.** Structures of ginsenosides.

Fig. 2. Structures of non-ginsenosides.

2.2. Network proximity between targets of ginseng and neuropeptide genes

2.2.1. Human protein interactome

The human protein interactome was obtained from Valle et al. [20]. The interactome was assembled from 16 databases that included six different types of protein–protein interactions (PPIs): binary PPIs tested by high-throughput yeast two-hybrid experiments, kinase–substrate interactions, literature-curated PPIs, high-quality PPIs from three-dimensional protein structures, signaling networks from literature-derived low-throughput experiments, and protein complexes. The interactome included 351,444 PPIs between 17,706 proteins.

2.2.2. Bioactive compounds, compound targets, and neuropeptide genes

We collected 151 compounds of ginseng radix from the TCM-Mesh database. To filter out compounds that rarely play a role of drugs via oral administration, a quantitative estimate of drug-likeness (QED) was used, which measures drug-likeness based on molecular descriptors [21]. The QED ranges from 0 to 1, and we considered 87 compounds with QEDs greater than 0.35 as drug-like chemicals (the method outperformed other drug-like prediction tools, such as Lipinski's rule of 5, the Ghose rule, and the Veber rule [21]). Seven ginsenosides and their metabolites, which are generally considered bioactive compounds of ginseng radix [22], were included in our analysis, although their QEDs were lower than 0.35. We considered 29 bioactive compounds available in PubChem as the final list of bioactive compounds of ginseng radix (Fig. 3A). The protein targets of the bioactive compounds were retrieved from STITCH [23]. We collected 94 neuropeptide genes, which were classified into 24 gene families according to shared structural properties retrieved from Burbach [24] (Table 1).

2.2.3. Network proximity between compound targets and neuropeptide genes

The proximity between a family of neuropeptide genes and compound targets in the human protein interactome was evaluated using a distance metric proposed by Valle et al. [20]. Given S, the set of neuropeptide genes in a family, T, the set of compound targets and $d(s, t)$, the shortest path length between a gene node s and target node t in the interactome, the average proximity between S and T, $d_c(S, T)$, is defined as follows [25]:

$$d_c(S, T) = \frac{1}{T} \sum_{t \in T} \min_{s \in S} d(s, t)$$

We compared the absolute distance $d_c(S, T)$ with a reference distribution describing the random expectation. The reference distribution was determined by calculating the proximity between randomly selected proteins matching the degrees of the original neuropeptide genes and compound targets across 1000 iterations. We defined the relative distance metric Z_{d_c} as.

$Z_{d_c} = \frac{d - \mu_{d(S,T)}}{\sigma_{d(S,T)}}$ where $\mu_{d(S,T)}$ is the mean and $\sigma_{d(S,T)}$ is the standard deviation $\sigma_{d(S,T)}$ of the reference distribution. For our analysis, we considered only the neuropeptide family–compound association with a relative distance $Z_{d_c} < -0.5$ [25].

3. Obesity, etiology, and current treatments

Obesity is a medical condition in which an excessive amount of body fat increases to the point of being harmful to one's health [18]. Individuals are generally considered obese when their body mass index (BMI), which is calculated as the body weight in kilograms divided by the square of the height in meters, is 30 kg/m² or greater. BMIs ≥25 kg/m² are classified as overweight, which is distinguished from obesity [3]. An epidemiological study of 68.5 million individuals in 195 countries showed that the overall prevalence of obesity was 5.0% among children and 12.0% among adults in 2015 [1]. Following secular trends, a forecasted 38% of the world's adult population will be overweight and 20% will be obese by 2030 [26].

Regarding the etiology of obesity, there are three primary causes of obesity progression, including the environment, genetic factors, and energy balance dysregulation (Fig. 4). The popular environmental reasons for weight gain include the consumption of high-calorie foods, sedentary activities, inadequate sleep, and side effects of some medicines. Furthermore, heterozygous mutations in
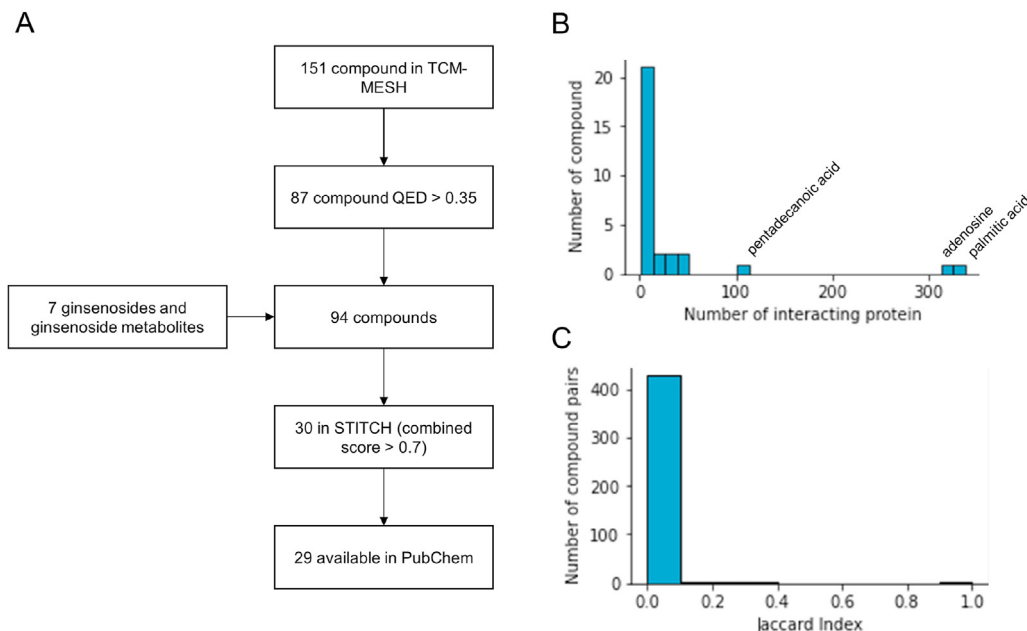
Fig. 3. Description of compounds analyzed in this study. (A) Selection criteria for the compounds evaluated in this study. (B) Distribution of the number of targets of compounds.

Table 1
Neuropeptide gene families analyzed in this study.

Gene family	Gene
Opioid gene family	PENK, POMC, PDYN, PNOC
Vasopressin/oxytocin gene family	AVP, OXT
CCK/gastrin gene family	GAST, CCK
Somastostatin gene family	SST, CORT
F- and Y-amide gene family	NPVF, NPFF, NPY, PPY, PYY, PRLH
Calcitonin gene family	CALCA, CALCB, IAPP, ADM, ADM2
Natriuretic factor gene family	NPPA, NPPB, NPPC
Bombesin-like peptide gene family	GRP, NMB
Endothelin gene family	EDN1, EDN2, EDN3
Glucagon/secretin gene family	GCG, SCT, VIP, ADCYAP1, GHRH, GIP
CRH-related gene family	CRH, UCN, UCN2, UCN3, UTS2, UTS2B
Kinin and tensin gene family	TAC1, TAC3
Neuromedins	NMS, NMU
Tensins and Kinins	KNG1, AGT, NTS
Granins	CHGA, CHGB, SCG2, SCG3, SCG5, VGF
Motilin family	MLN, GHRL
Galanin family	GAL, GALP
GnRH family	GNRH1, GNRH2
Neuropeptide B/W family	NPB, NPW, NPS
Neurexophilins	NXPH1, NXPH2, NXPH3, NXPH4
Insulin family	INS, IGF1, IGF2, RLN1, RLN2, RLN3
No-family neuropeptides	TRH, PTHLH, PMCH, HCRT, CARTPT, AGRP, PRL, APLN, KISS1, DBI
Cerebellins	CBLN1, CBLN2, CBLN3, CBLN4
Adipose neuroepeptides	LEP, ADIPOQ, NAMPT, RETN, RETNLB, NUCB2, UBL5

the melanocortin-4 receptor gene, which affects 2%–5% of children with severe obesity, are the most prevalent cause of monogenic obesity. In addition, body weight, related physiological processes, and energy balance are all regulated by a complicated system in which the environment and genes interact. Energy expenditure and food intake are controlled by two groups of neurons in the hypothalamus arcuate nucleus, which are suppressed or stimulated by circulating neuropeptide hormones. The cells and microbiota in the pancreas, adipose tissue, stomach, and other organs manage long- and short-term energy balance through a coordinated network of peripheral signals and central processes. Energy balance control is also aided by brain areas other than the hypothalamus via attention, memory, the hedonic effects of food intake, cognitive

processes, and sensory signal input. If for any reason these energy balance mechanisms are disrupted, it will lead to a series of dysregulations in food intake, which provokes overweightness and obesity [3]. Based on the causes and levels of obesity, patients are prescribed dietary modifications, medicines, or surgery to reduce weight [3].

Lifestyle changes, including dieting and physical exercise, are the main treatments for overweightness and obesity. Dietary plans can help patients lose weight in the short and long term, but they work the most effectively when combined with counseling and exercise [3].

Bariatric surgery is the most effective treatment for obesity in severely obese individuals (BMI >40 kg/m^2) who have failed to
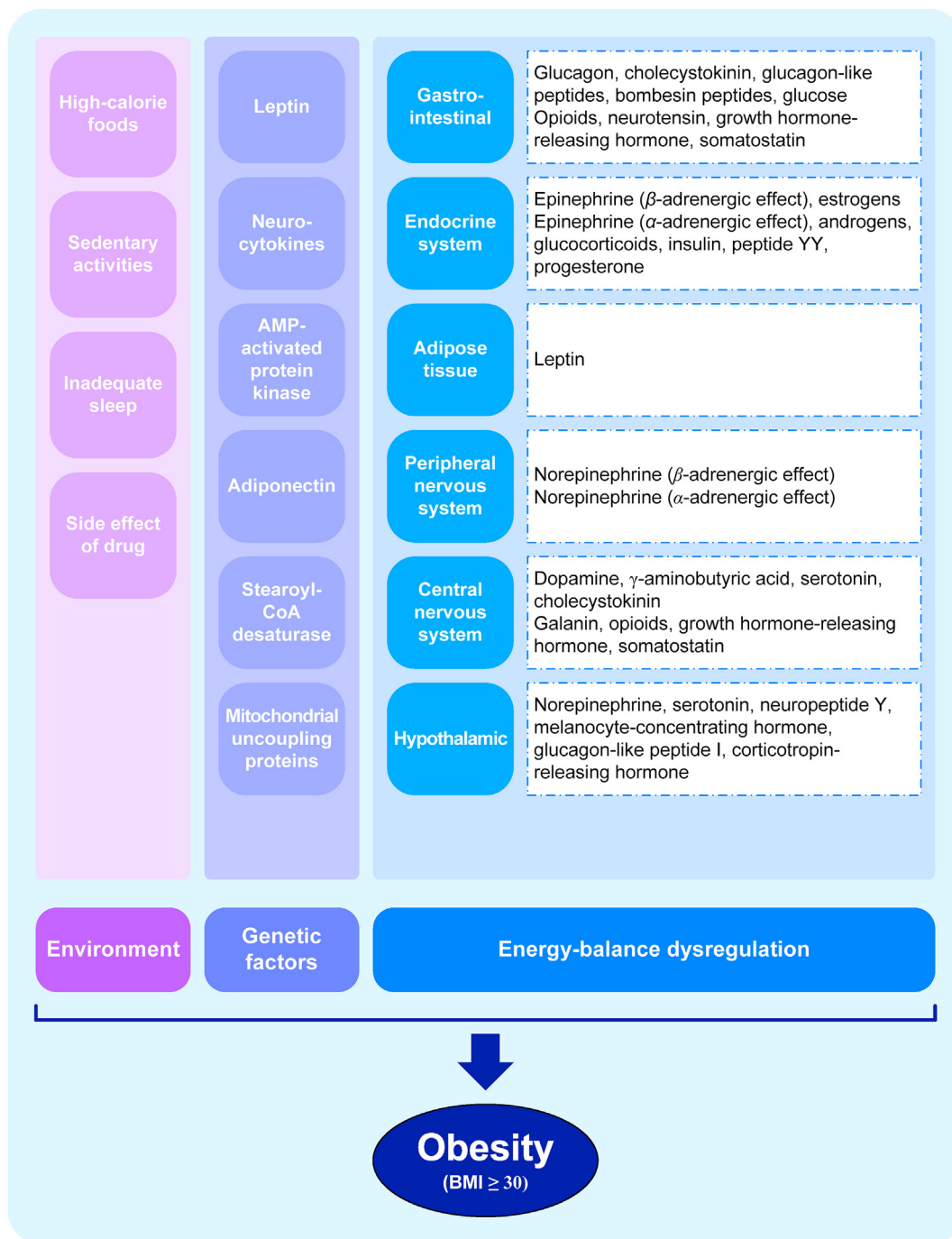
Fig. 4. Etiology of obesity.

reduce weight after dietary changes and pharmaceutical treatment. Surgery for severe obesity is correlated with reduced overall mortality and long-term weight loss. One year after gastric banding, patients lose 15%–20% of their body weight. Vertical-sleeve gastrectomy and Roux-en-Y operations produce larger weight loss reductions of approximately 25% and 30%, respectively. More than half of all patients who underwent Roux-en-Y gastric bypass lost at least 25% of their body weight one year postoperatively [3]. Although surgery is the most effective means to lose weight, it may face relatively large risks and complications, such as metabolic bone disease, gallstones, and gastrointestinal side effects, compared to those of other treatments for obesity [27–29].

Regards pharmacotherapy, the Food and Drug Administration has authorized various anti-obesity medicines for long-term use, such as orlistat, lorcaserin, phentermine, naltrexone, and liraglutide [30]. Among them, orlistat is one of the most common drugs approved for long-term use in obesity treatment. Orlistat is a reversible inhibitor of gastric and pancreatic lipases that, at the recommended dosage, inhibits dietary fat absorption by 30%. It is linked to a reduction in fat mass in obese adolescents and adults, as well as lower levels of the hormone leptin, as patients lose weight. However, anti-obesity medications still have side effects, such as gastrointestinal, renal, and musculoskeletal adverse reactions [31].

Consequently, the development of safe, effective, and easily accessible agents is critical.

Phytochemistry has emerged as an abundant and nontoxic source of anti-obesity compounds. Moreover, apart from their anti-obesity effects, these plant-derived medications provide a slew of other health advantages [32]. *P. ginseng* is a well-known traditional Korean medicine that is widely used in various chronic disease studies with respect to CVD, T2D, immune function, and obesity [13]. The anti-obesity effect of *P. ginseng* has been demonstrated in various *in vivo*, *in vitro*, and preclinical studies on multiple targets [18].

4. Ginseng and obesity

4.1. Effect on digestion and absorption systems

Ginseng inhibits the digestion and absorption of food. In rats, amino acid derivatives, such as arginyl-fructose and arginyl-fructosyl-glucose, which are generated during the heat processing of raw ginseng to red ginseng, block carbohydrate absorption in the gastrointestinal tract, hence lowering blood glucose levels [33]. Similar to the high-fat diet (HFD) control mice, black ginseng ethanol extract (1%, 3%, and 5% diet for 12 weeks) decreases fat digestion and absorption, as evidenced by increased fecal weight and fecal fat excretion [34]. The suppression of pancreatic lipase by ginseng consumption might result in a lack of carbohydrate and fat absorption [33–35]. However, in HFD-induced obese rats, Rb1 (intraperitoneal injections, 20 mg/kg, daily for 4 weeks) has no effect on lipid absorption while decreasing weight and fat content [36]. Furthermore, although the extract reduces the fat pad in HFD-induced mice, it does not inhibit pancreatic lipase *in vitro* [37].

4.2. Effect on adipocyte

In cell experiments, the AMPK pathway is also activated in fat cells by ginseng or ginsenosides. In 3T3-L1 cells, the ginsenosides Rg1, Rg3, Rh2, and cK increase phospho (p)-AMPK levels while inhibiting triglyceride (TAG) production [38–40]. In fat cells, peroxisome proliferator-activated receptor (PPAR) promotes lipid absorption, fatty acid storage, and adipogenesis, and PPAR-mutant animals fail to develop adipose tissue when fed an HFD [41]. Ginsenosides Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, and cK also decrease adipogenesis in 3T3-L1 cells by suppressing PPAR and CCAAT/enhancer-binding protein (C/EBP) [39,42–45].

In animal models, Korean ginseng whole extract reduces bodyweight and fat pads in obese mice with a 0.8–1.6% (w/w) KGE diet for 8 weeks [46] or 5, 10, and 30 g/kg diet for 13 weeks [47], as well as in rats with a 0.2 g/kg diet for 12 weeks [48]. Ginsenoside Rh1 (20 mg/kg/day, 4 weeks) reduces body and epididymal fat weight, as well as plasma TAG levels in mice. Oral administration of compound K (400 mg/kg, 6 times per week) significantly reduces HFD-induced increases in body weight, liver weight, and subcutaneous fat weight in mice [49]. Dietary consumption of Chinese ginseng extract (0.5 g/kg diet, 15 weeks) decreases body fat mass, enhances glucose tolerance and whole-body insulin sensitivity, and prevents hypertension in HFD-induced obese mice [50].

4.3. Effect on the liver

Activation of the enzyme AMPK regulates cellular energy balance by stimulating fatty acid oxidation, ketogenesis, mitochondrial biogenesis, and glucose uptake while inhibiting cholesterogenesis, lipogenesis, and TAG production [51].

Ginseng and ginsenosides activate the AMPK pathway in liver HepG2 cells, resulting in elevated levels of *p*-AMPK and phospho-

acetyl-CoA carboxylase [52–60]. Ginseng and ginsenosides decrease the expression of fatty acid synthase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, phosphoenolpyruvate carboxykinase, and glucose 6-phosphatase *in vitro*, decreasing TAG synthesis [52,53,56], cholesterogenesis [53,58], and gluconeogenesis [54,55,59].

Various *in vivo* animal investigations have revealed that ginseng and ginsenosides activate the AMPK pathway in the liver in HFD-fed models, which is consistent with the results of *in vitro* research [54,61]. HFD-fed mice treated with ginseng extract have a lower liver weight [47,62], which might be due to a reduction in hepatic lipid deposition. Ginseng supplementation lowers hepatic lipid content and alleviates liver steatosis, supporting this theory [47,62–68].

4.4. Effect on skeletal muscle

Skeletal muscle is the most important tissue for the oxidation of glucose and fatty acids, making it a viable target for anti-obesity and anti-diabetes drugs. AMPK is involved in an essential energy-sensing and signaling mechanism in skeletal muscle that, when activated, promotes glucose transporter type 4 and mitochondrial biogenesis and improves glucose uptake and acute fatty acid oxidation by phosphorylating acetyl-coenzyme A-carboxylase and lowering malonyl-coenzyme A levels [69].

Ginsenosides Rc, Re, Rg1, Rg3, and Rh2, as well as ginseng extracts, activate the AMPK signaling pathway in C2C12 myoblast cells *in vitro*. Furthermore, ginseng radix activates AMPK in the skeletal muscle of mice fed an HFD. In skeletal muscle and cultured C2C12 cells, Korean Red Ginseng boosts mitochondrial biogenesis and fatty acid oxidation by increasing the expression of PPAR-coactivator-1, nuclear respiratory factor 1, cytochrome *c*, and cytochrome *c* oxidase [18].

In addition, recent advances in the understanding of the peptidergic mechanism of satiety and hunger from the gastrointestinal tract mediated by ghrelin, PYY, CCK, and LP-1 and the homeostatic signaling of leptin and its upstream pathways in the hypothalamus regulated by neuropeptides, such as α-melanocyte-stimulating hormone (MSH), AgRP, and NPY, have introduced new approaches for obesity treatment [70]. The combined regulation of neuropeptides in appetite with dietary changes and physical exercise may be a promising strategy, which not only supports safe and sustainable weight loss, but also helps patients feel less hungry and preoccupied with food when following a weight loss program. Ginseng and ginsenosides also control appetite and prevent the overconsumption of food energy via neuropeptides. In the following sections, the potential of ginseng and its constituents in regulating neuropeptides associated with appetite will be reviewed and analyzed in depth.

5. 5. ginseng and neuropeptides regulating food intake

5.1. Neuropeptides

Neuropeptides are small proteinaceous substances produced and released by neurons through the regulated secretory route that act on neural substrates [71]. The hallmarks of neuropeptides are gene expression and biosynthesis by neurons, storage and regulated release upon demand, and the ability to modulate or mediate neural functioning directly through neural receptors [72].

Neuropeptides mediate various regulatory activities involving all organ systems and drive a wide range of biological responses. They influence central and peripheral nervous system intercellular signaling, as well as signal transduction crosstalk among endocrine and neurological systems. Indeed, neuropeptides function as

peptide hormones that regulate physiological homeostasis (response to stress, pain, cognition, glucose metabolism, water balance, feeding behavior, and blood pressure), immunomodulation, and neuroprotection [73]. In energy homeostasis, neuropeptides play an important role in mediating food intake via appetite signal transduction. Disruption of these signaling pathways may induce eating disorders such as obesity and anorexia [74].

5.2. Role of neuropeptides in appetite regulation and obesity

A complicated neuroendocrine system that includes peripheral signals, such as leptin and cerebral signals, particularly neuropeptides, regulates dietary behaviors. Many neuropeptides with anorexigenic (corticotropin-releasing hormone, CART, and POMC) and orexigenic (MCH, AgRP, and NPY) activities are involved in this regulatory system [75].

When energy stores are low due to diet or physical activity, leptin is released from adipose tissue and circulating leptin concentrations decrease, leading to the increased production of hypothalamic orexigenic neuropeptides that strongly increase food intake, such as NPY, galanin, and AgRP, and decreased levels of anorexigenic neuropeptides, including α-MSH, cocaine, and CART, which stimulate appetite and food intake [9].

This energy balance regulation mechanism may be why some individuals applying diet or physical activities fail to lose weight. Thus, the regulation of neuropeptides in food intake may be a promising therapy for sustainable weight loss in addition to dietary changes and physical activity.

5.3. P. ginseng and its compounds, a potential anti-obesity source via the regulation of neuropeptides in food intake

P. ginseng is a well-known traditional Korean medicine with diverse pharmacological effects, including those in cancer, diabetes, Alzheimer's disease, stroke, skin aging, and CVD [12,76–79]. The root extracts of *P. ginseng* and its main bioactive constituent, saponins (ginsenosides), have been widely studied in overweightness and obesity treatments. Li et al. [18] indicated that ginseng and constituent ginseng-specific saponins (ginsenosides) express an anti-obesity effect via various mechanisms including activation of the AMPK pathway, a reduction in lipid accretion, and a reduction in the activity of pancreatic lipase.

In addition, the potential of ginseng and its compounds in the regulation of neuropeptides related to appetite and food intake have been reported recently. As shown in Table 2, the orexigenic neuropeptide NPY is the most studied subject in ginseng research. Crude saponin, wild ginseng, and ginsenosides (GRb1, protopanaxadiol, and protopanaxatriol) are effective in suppressing hypothalamic NPY expression. In addition, Rb1 treatment increases anorexigenic POMC and decreases orexigenic AgRP mRNA expression in HFD-induced obese mice. Furthermore, the protopanaxadiol- or protopanaxatriol-type saponins in red ginseng treatment also stimulate anorexigenic CCK expression.

It seems clear that studies on the anti-obesity effects of ginseng and its compounds related to neuropeptides associated with appetite are limited. Hence, we subsequently assessed the network proximity between the targets of ginseng and neuropeptide genes to investigate potent ginseng constituents in mediating neuropeptides associated with appetite.

5.4. Network pharmacology analysis

We collected the potential targets of 29 bioactive compounds in ginseng radix in the STITCH database. Twenty-one compounds had fewer than 10 targets, while pentadecanoic acid, adenosine, and palmitic acid had more than 100 targets (Fig. 3B). Next, we computed the Jaccard index between pairs of target sets of two different compounds. We found that most pairs had very low Jaccard indices. These results indicate that each compound in ginseng radix has specific targets that are specific and do not overlap with the targets of other compounds.

We investigated the compounds associated with neuropeptide families. We calculated the network proximity scores between 29 bioactive compounds in ginseng radix and 24 neuropeptide families. This analysis was based on the assumption that the proximity of the targets of a compound to proteins in a neuropeptide family was inversely correlated with the likelihood that the compound affects the physiology of the neuropeptide family. We found that half of the families were relatively close to the targets of any compound (Fig. 5). A set of gene families, including the granin, glucagon/secretin, opioid, CCK/gastrin, and kinin and tensin gene families, were observed to be similar to those of similar bioactive compounds, indicating that the set of gene families may be modulated by similar compounds in ginseng radix. In Tables 3–6,

Table 2
Summary of relevant *in vivo* studies on the regulation of neuropeptides by ginseng and its constituents in obesity treatment.

Material (extraction method)	Animal Model	Sex	Age (weeks)	Weight (g)	N per group	Administration Route	Dose or Concentration	Treatment Period (days)	Mechanism	Reference
CS (EE)	SD rat with HFD	M	3	Unknown	Unknown	Intraperitoneal injection	200 mg/kg	21	↓NPY	[85]
WG (ME)	SD rat	M	Unknown	260–280	5	Intraperitoneal injection	50, 100, and 200 mg/kg	5	↓NPY	[86]
PD and PT (EE)	SD rat with HFD	M	3	Unknown	6	Intraperitoneal injection	50 mg/kg (/day)	21	↓NPY ↑CCK	[87]
GRb1	SD rat	M	6	200–220	6–7	Intraperitoneal injection	10 and 30 mg/kg	14	↓NPY	[88]
GRb1	C57Bl mice with HFD	M	6	Unknown	5, 8, and 10	Intraperitoneal injection	20 mg/kg	21	↓NPY	[89]
GRb1	Long-Evans rats with HFD	M	Unknown	Unknown	6–8	Intraperitoneal injection	0, 2.5, 5, 10, or 20 mg/kg	28	↓NPY ↑POMC ↓AgRP	[36]
GS	SD rat with HFD	M	4	90–100	5	Intraperitoneal injection	10 mg/kg	21	↓NPY ↑CCK	[90]
GRb1	C57Bl/6 mice with HFD	M	6	19.66 ± 1.4	16	Intraperitoneal injection	14 mg/kg	21	↑POMC ↓AgRP	[19]

SD rats: Sprague-Dawley rats, HFD: high-fat diet, CS: crude saponin, EE: ethanol extracted, WG: wild ginseng, ME: methanol extracted, PD: protopanaxadiol-type, PT: protopanaxatriol-type, GRb1: ginsenoside Rb1, NPY: neuropeptide Y, POMC: proopiomelanocortin, AgRP: agouti-related protein, CCK: cholecystokinin, GS: ginsenosides.
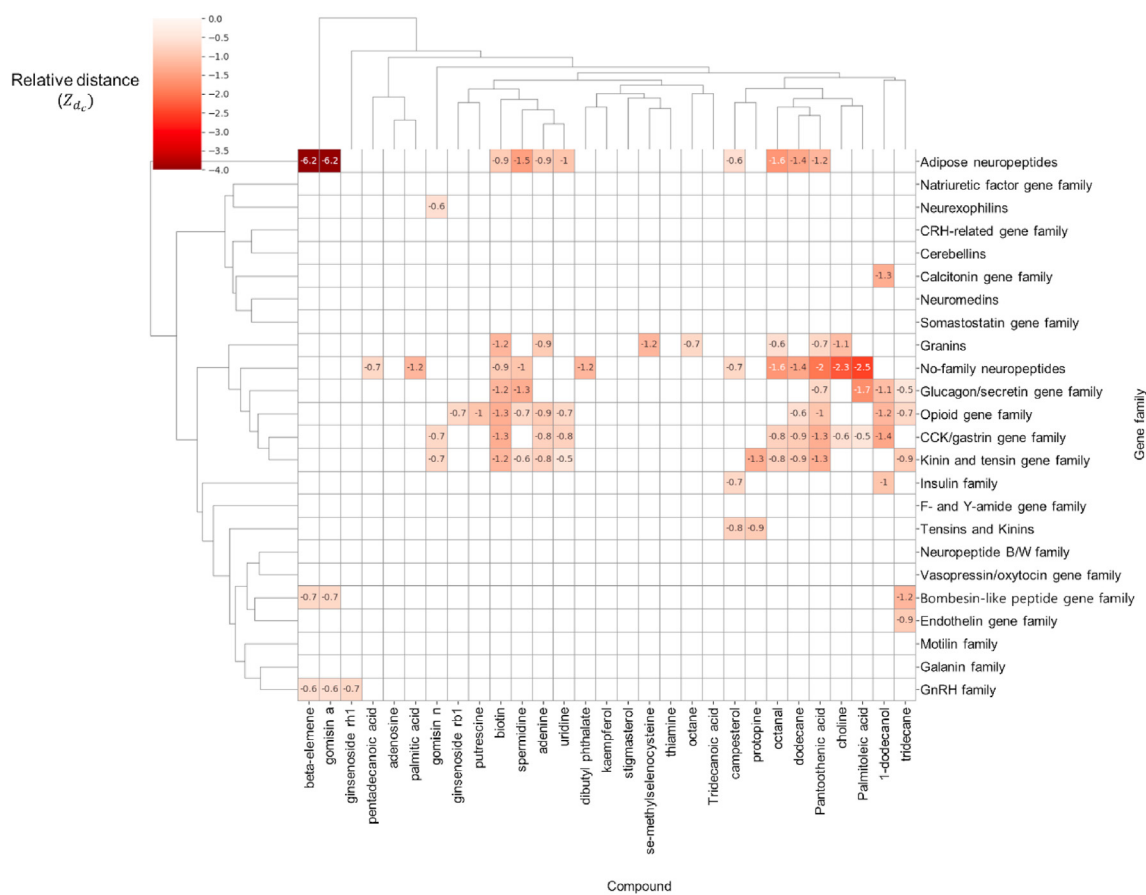
Fig. 5. Proximity between neuropeptide family genes and targets of compounds. Relative distances higher than −0.5 are masked.

Table 3
Predicted therapeutic association between the CCK/gastrin gene family and compounds.

Compound	Distance $d_c(S,T)$	Significance Z_{d_c}
1-dodecanol	2	−0.99
campesterol	2	−0.70

Table 4
Top 10 predicted therapeutic associations between the opioid gene family and compounds.

Compound	Distance $d_c(S,T)$	Significance Z_{d_c}
biotin	2	−1.26
1-dodecanol	2	−1.19
pantothenic acid	2.25	−0.99
putrescine	2.23	−0.98
adenine	2.15	−0.90
spermidine	2.18	−0.75
ginsenoside rb1	2	−0.71
uridine	2.2	−0.69
tridecane	2	−0.65
dodecane	2.2	−0.64

Table 5
Predicted therapeutic associations between the glucagon/secretin gene family and compounds.

Compound	Distance $d_c(S,T)$	Significance Z_{d_c}
palmitoleic acid	2	−1.71
spermidine	2.09	−1.32
biotin	2	−1.16
1-dodecanol	2	−1.12
pantothenic acid	2.25	−0.72
tridecane	2	−0.55

Table 6
Predicted therapeutic associations between the insulin family and compounds.

Compound	Distance $d_c(S,T)$	Significance Z_{d_c}
1-dodecanol	2	−0.99
campesterol	2	−0.70

we summarize compounds that are predicted to be associated with adipose neuropeptides and the CCK/gastrin gene, opioid gene, glucagon/secretin gene, and insulin families, which may have roles in food intake, energy balance, and metabolism. Among the

compounds, campesterol [80,81], beta-elemene [82], ginsenoside Rb1 [18], biotin [83], and pantothenic acid [84] are bioactive compounds that may have functional roles in ginseng radix.

We next sought to discover the molecular mechanisms underlying the regulatory effects of campesterol, beta-elemene, ginsenoside Rb1, biotin, and pantothenic acid on neuropeptides. We found that neuropeptide genes were connected with targets of compounds via the interactome (Fig. 6). The following
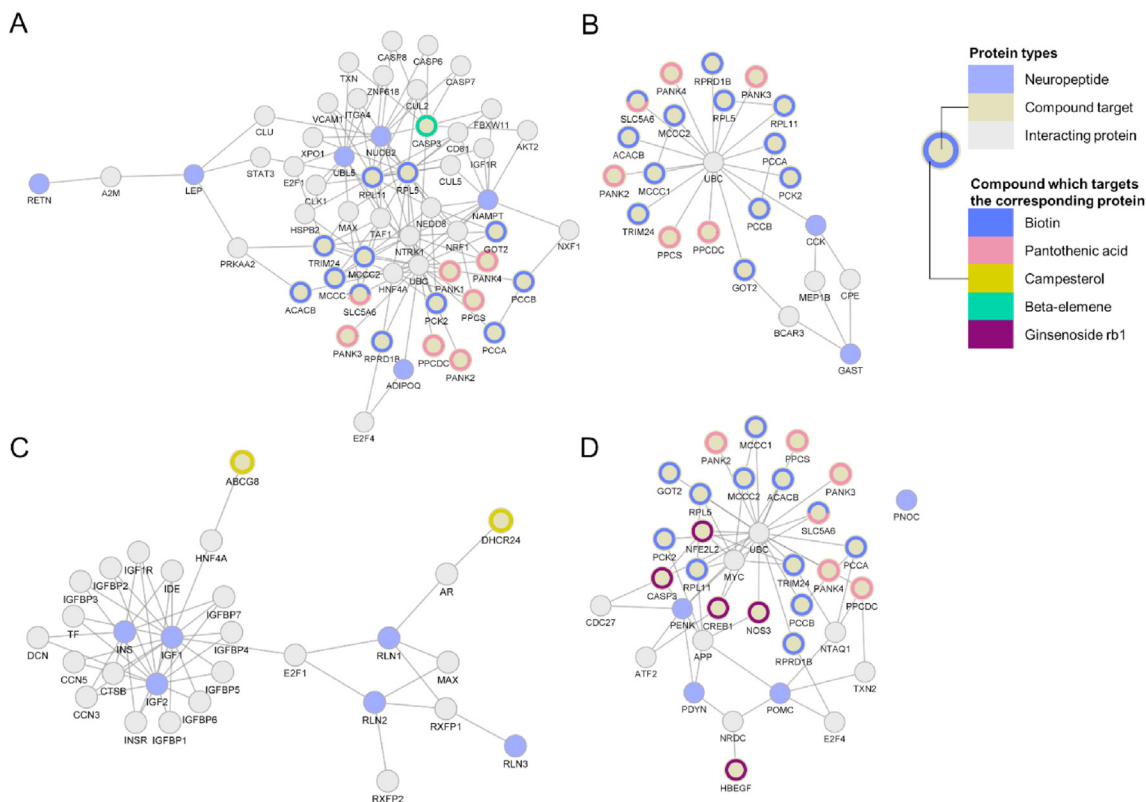
Fig. 6. Interactome neighborhood showing associations between the neuropeptide gene families including the (A) adipose neuropeptide gene family, (B) CCK and gastrin gene family, (C) insulin family, and (D) opioid gene family and compounds in ginseng radix. Nodes and edges indicate proteins and their interactions, respectively. Colors filled in nodes indicate whether the protein belongs to the neuropeptides, compound targets, or proteins that connect signaling between neuropeptides and compound targets. Colors filled in borders of nodes indicate the compound that targets the protein.

neuropeptide genes were found to be in the neighborhood of targets of the compounds within absolute distance $d_c(S,T) \leq 2$: *ADIPOQ*, *NAMPT*, *UBL5*, *NUCB2*, and *LEP* in the adipose neuropeptide gene family; *CCK* and *GAST* in the CCK and gastrin gene family; *IGF1* and *RLN1* in the insulin family; and *PENK*, *PDYN*, and *POMC* in the opioid gene family. This suggests that these neuropeptides are regulated by compounds with targets that are proximal to these neuropeptide genes.

6. Conclusion

Ginseng and its main bioactive constituents (ginsenosides) may be a potential anti-obesity source via the regulation of neuropeptides in food intake. Ginseng extract and ginsenosides such as ginsenoside Rb1, protopanaxadiol, and protopanaxatriol-type ginsenosides are effective in inhibiting the expression of orexigenic neuropeptides (NPY and AgRP) and stimulating the expression of anorexigenic neuropeptides (CCK and POMC), which prevents the increase in food intake, as observed previously. Furthermore, the data obtained from network pharmacology analysis indicated that compounds of ginseng radix, which are predicted to be associated with adipose neuropeptides, the CCK/gastrin gene family, the opioid gene family, the glucagon/secretin gene family, and the insulin family, may have roles in food intake, energy balance, and metabolism. Among the compounds, campesterol, beta-elemene, ginsenoside Rb1, biotin, and pantothenic acid are strongly correlated with neuropeptide genes regulating energy balance and food intake, including *ADIPOQ*, *NAMPT*, *UBL5*, *NUCB2*, *LEP*, *CCK*, *GAST*, *IGF1*, *RLN1*, *PENK*, *PDYN*, and *POMC*. Based on previous reports and network pharmacology analysis data, ginseng and its compounds

may be a potent source for obesity treatment by regulating neuropeptides associated with appetite.

Declaration of competing interest

All the authors have no conflicts of interest to declare.

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