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Research Article

An Investigation of the Molecular Mechanisms Underlying the Analgesic Effect of Jakyak-Gamcho Decoction: A Network Pharmacology Study

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Herbal drugs have drawn substantial interest as effective analgesic agents; however, their therapeutic mechanisms remain to be fully understood. To address this question, we performed a network pharmacology study to explore the system-level mechanisms that underlie the analgesic activity of Jakyak-Gamcho decoction (JGd; Shaoyao-Gancao-Tang in Chinese and Shakuyaku-Kanzo-To in Japanese), an herbal prescription consisting of *Paeonia lactiflora* Pallas and *Glycyrrhiza uralensis* Fischer. Based on comprehensive information regarding the pharmacological and chemical properties of the herbal constituents of JGd, we identified 57 active chemical compounds and their 70 pain-associated targets. The JGd targets were determined to be involved in the regulation of diverse biological activities as follows: calcium- and cytokine-mediated signalings, calcium ion concentration and homeostasis, cellular behaviors of muscle and neuronal cells, inflammatory response, and response to chemical, cytokine, drug, and oxidative stress. The targets were further enriched in various pain-associated signalings, including the PI3K-Akt, estrogen, ErbB, neurotrophin, neuroactive ligand-receptor interaction, HIF-1, serotonergic synapse, JAK-STAT, and cAMP pathways. Thus, these data provide a systematic basis to understand the molecular mechanisms underlying the analgesic activity of herbal drugs.

1. Introduction

Pain is a major healthcare and socioeconomic issue worldwide that severely affects the overall health, quality of life, daily activities, and productivity of patients, and it places a substantial financial burden on healthcare systems and society [1–6]. Based on the pathophysiological mechanisms, pain is classified into (i) nociceptive and (ii) nonnociceptive neuropathic pain [7–21]. Nociceptive pain is caused by the activation and stimulation of nociceptors and pain pathways driven by inflammation, chemicals, or physical events, and it is subdivided into somatic and visceral [7–21]. Neuropathic pain develops due to damage, injury, dysfunction, or disease of the somatosensory nervous system, and it is further classified into central and peripheral [7–21]. At present, opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and non-anti-inflammatory antipyretic analgesic agents serve as primary therapies for pain alleviation [6, 15, 22–28]. However, current treatment options for pain management are still associated with limited efficacy and unwanted adverse effects [6, 15, 22–28]. Meanwhile, herbal drugs and multicomponent-multitarget-multipathway polypharmacological therapeutics have received considerable attention for pain treatment because of their important analgesic effects with fewer side effects and toxicity [29–36].

Jakyak-Gamcho decoction (JGd; Shaoyao-Gancao-Tang in Chinese and Shakuyaku-Kanzo-To in Japanese) is an herbal drug that consists of *Paeonia lactiflora* Pallas and

Glycyrrhiza uralensis Fischer, which has been prescribed for the treatment of various types of pain, gynecological diseases, arthritic diseases (e.g., osteoarthritis and arthralgia), and muscular diseases (myalgia, muscle tension, spasm, and cramps) [30, 37–48]. Previous studies have demonstrated the various therapeutic properties of JGd, including its analgesic, anti-inflammatory, antispasmodic, and anti-allergic effects [30, 37–40, 43, 44, 46–55]. Among the diverse effects of this herbal drug, the most common therapeutic use of JGd is to alleviate pain arising from cancer, diabetes, neuropathy, and muscle and arthritis diseases [30, 37–40, 44, 46–48], which makes it one of the most frequently prescribed oral analgesic agents in East Asia [56]. The analgesic mechanisms of JGd include the modulation of spinal α2-adrenoceptors, transient receptor potential vanilloid 1 (TRPV1) channels, calcium and Sirt1 signalings, muscle contraction and relaxation, and chemokine and cytokine expression [39, 44, 46, 51, 57–60]. However, the pharmacological properties of JGd at the systemic level need to be explored.

Because of the complex pharmacological nature of multicompound-multitarget-multipathway agents, there is often a fundamental limitation in investigating their comprehensive mechanisms of action based only on conventional biological experimental methodologies [61–68]. To overcome such challenges, network pharmacology, an integrative research field that systematically combines computational systems biology, network science, medicine, pharmacology, mathematics, and physics, has emerged as one of the most effective approaches for the mechanistic exploration of polypharmacological drugs, such as herbal medicines [61–68]. The goal of this integrative science is to unveil the mechanisms of disease pathogenesis and drug activity that are coordinated through the interactions among diverse biological components such as genes, proteins, cells, tissues, and organs [61–68]. Previous network pharmacology studies successfully investigated the polypharmacological properties of herbal drugs by identifying their active compounds and key therapeutic targets and further elucidating the distinct system-level pharmacological effects and mechanisms (e.g., therapeutic modulation of biological processes such as proliferation, apoptosis, cell cycle regulation, angiogenesis, oxidation and reduction, insulin metabolism, and inflammation) for the treatment of various diseases, including cancer, diabetes, arthritis, and ischemic stroke, which are exerted by the synergistic interplay between multiple compounds and targets contained in herbal drugs [61–79]. In the present network pharmacology study, we aimed to uncover the molecular mechanisms that underlie the analgesic properties of JGd with a system's perspective.

2. Materials and Methods

2.1. Screening of Active Chemical Compounds in Jakyak-Gamcho Decoction. Information on chemical compounds comprising the herbal constituents of JGd was investigated using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database [80]. Then, based on their absorption, distribution, metabolism, and excretion (ADME) properties (i.e., oral bioavailability (OB), Caco-2 permeability, and drug-likeness (DL)), chemical compounds that satisfy the following criteria were screened and determined to be bioactive as previously suggested [63, 80, 81] using the TCMSP [80]: OB $\geq$ 30%, Caco-2 permeability $\geq$ -0.4, and DL $\geq$ 0.18. In brief, OB is the proportion of orally administered drug compounds that enter the general circulation, and it is one of the most crucial considerations in the design and development of a drug [80, 82]. Of note, compounds with an OB larger than 30% are commonly regarded as effectively absorbed in the human body [80, 82]. Caco-2 permeability is an important index for the investigation of intestinal permeability and drug efflux that is based on an evaluation of the rate of absorption and diffusion of a compound across Caco-2 human intestinal cells [80, 83–85]. In general, a chemical compound is considered not permeable in the intestinal epithelium if its Caco-2 permeability is lower than −0.4 [86, 87]. DL is a widely used measurement that qualitatively assesses whether a certain compound is physicochemically and structurally suitable for use as a drug [80, 88]. Note that the average DL of all drugs is 0.18, and therefore, it is commonly used as the threshold to determine the pharmacological potential of a compound [80, 88].

2.2. Target Identification. Human targets of the active chemical compounds of JGd were investigated using various databases and models, including the PharmMapper [89], search tool for interactions of chemicals (STITCH) 5 [90], Swiss Target Prediction [91], similarity ensemble approach (SEA) [92], systematic drug targeting tool (SysDT) [93], and weighted ensemble similarity (WES) [94]. The pain-associated human genes and proteins were investigated from the DisGeNET [95], Therapeutic Target Database [96], GeneCards [97], Comparative Toxicogenomics Database [98], Human Genome Epidemiology Navigator [99], Online Mendelian Inheritance in Man [100], Pharmacogenomics Knowledgebase [101], and DrugBank [102], using the medical subject headings term "Pain" (ID: D010146) for *Homo sapiens* species.

2.3. Network Construction. The herbal medicine-active chemical compound (H-C), active chemical compound-target (C-T), and target-pathway (T-P) networks were generated by connecting the herbal medicines with their active chemical compounds, the compounds with their targets, and the targets with the signaling pathways in which they are enriched. The protein-protein interaction (PPI) network was generated using the STRING database (interaction confidence score $\geq$ 0.9) [103]. Analysis and visualization of networks were performed with Cytoscape software [104]. A network is composed of nodes (e.g., herbal medicines, chemical compounds, targets, or pathways) and edges (or links) describing the interactions among the nodes [105]. The degree is defined as the number of links of a node [105].

2.4. Contribution Index Evaluation. The network-based efficacy-based contribution index (CI) of active chemical

compounds of JGd was evaluated following previous procedures as follows [81]:

$$\mathrm{NE}(j) = \sum_{i=1}^{n} d_i,$$
$$\mathrm{CI}(j) = \frac{c_j \times \mathrm{NE}(j)}{\sum_{i=1}^{m} c_i \times \mathrm{NE}(i)} \times 100\%, \quad (1)$$

where m is the number of chemical compounds, n is the number of targets of chemical compound j, d_i is the number of links of target i of chemical compound j, and c_i (or c_j) is the number of previous studies having "pain" and component i (or j) in their title or abstract searched from the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). The chemical compounds with the highest CIs were regarded as contributing more to the pharmacological activity of a certain herbal drug [81].

2.5. Functional Enrichment Analysis. Gene ontology (GO) enrichment analysis was performed with g:Profiler [106]. Pathway enrichment analysis was performed with Kyoto Encyclopedia of Genes and Genomes database [107]. Functional association analysis was conducted using GeneMANIA [108].

2.6. Molecular Docking Analysis. The structures of chemical compounds of JGd and their targets were obtained from the PubChem [109] and RCSB Protein Databank [110] databases, respectively. Then, the molecular docking scores between the chemical compounds and the targets were assessed using AutoDock Vina [111]. Of note, a certain chemical compound is regarded as having high binding affinity to a target if the corresponding docking score is less than or equal to −5.0 [112, 113].

3. Results

The network pharmacology study for the exploration of analgesic mechanisms of JGd was conducted as follows (Figure 1). Detailed information regarding the chemical constituents of JGd was obtained from the comprehensive biomolecular databases, and the bioactive compounds were investigated using their ADME characteristics (Figure 1). The human targets of the active chemical compounds were identified from various databases and models that assess chemical-protein interactions (Figure 1). Then, we integrated the extensive herbal drug-related data into networks and performed network pharmacology analysis (Figure 1).

3.1. Active Chemical Compounds of Jakyak-Gamcho Decoction. Detailed information regarding the chemical compounds present in JGd was obtained from TCMSP [80] (Supplementary Table S1), and the active compounds were defined as those with OB ≥ 30%, Caco-2 permeability ≥ −0.4, and DL ≥ 0.18, as described previously [63, 80, 81]. Some components were also determined to be active because of the

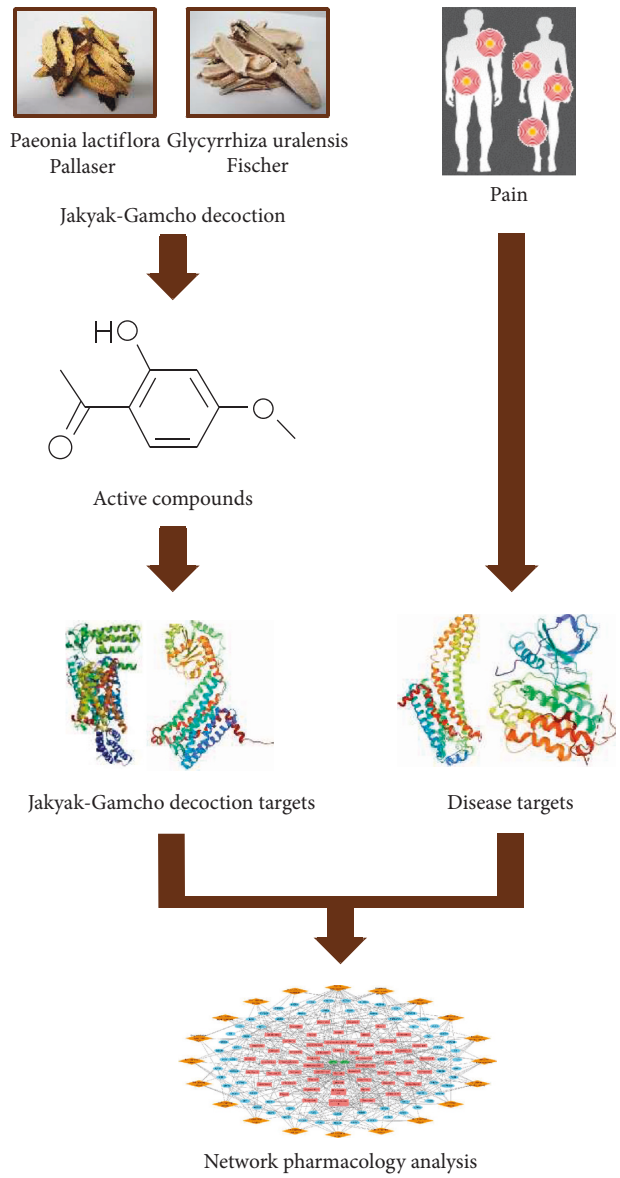

Figure 1: A schematic diagram illustrating the network pharmacology exploration of the analgesic mechanisms of Jakyak-Gamcho decoction.

substantial amount contained in JGd and their reported relevant pharmacological activity [42, 57, 114–128], although they did not meet the criteria. As a result, 111 active chemical compounds were obtained for JGd (Supplementary Table S2).

3.2. Targets of Jakyak-Gamcho Decoction. We identified the targets of the active chemical compounds of JGd using the following databases and models for the investigation of chemical-protein interactions: Swiss Target Prediction [91], STITCH 5 [90], PharmMapper [89], SEA [92], SysDT [93], and WES [94]. Therefore, 70 human pain-associated and 137 nonpain-associated targets were obtained for JGd (Supplementary Table S3).

3.3. Network Pharmacology-Based Analysis of Jakyak-Gamcho Decoction. To perform network pharmacology-based analysis of the pharmacological features of JGd, we constructed an herbal medicine-active chemical compound-target (H-C-T) network composed of 129 nodes (two herbal medicines, 57 active chemical compounds, and 70 pain-associated targets) and 217 links (Figure 2 and Supplementary Table S3) using comprehensive information regarding the herbal drug. We found that quercetin (number of targets = 36) and kaempferol (number of targets = 11) have relatively many targets (Figure 2 and Supplementary Table S3), implying that they might be important active compounds for the therapeutic activity of JGd. In addition, 27 human genes/proteins were found to be targeted by two or more active chemical compounds of JGd (Figure 2), suggesting a polypharmacological mechanism.

To investigate the biological interaction relationship between the JGd targets, we generated a PPI network (58 nodes and 174 links) comprising the targets (Figure 3). Next, we searched for hubs, specific nodes with a high degree in the network that are shown to have crucial biological functions and promising therapeutic potential [129, 130]. In the analysis, hubs were determined as nodes for which the degree was greater than or equal to twice the average node degree of the network [131, 132]. The results showed that PIK3R1 (degree = 25), HSP90AA1 (degree = 15), EGFR (degree = 14), AKT1 (degree = 13), LPAR1 (degree = 13), LPAR2 (degree = 13), and LPAR3 (degree = 13) were hubs (Figure 3), implying that they might be the key targets responsible for the analgesic activity of JGd. These hubs were shown to be involved in the regulation of pain-related processes and could function as potent targets to induce analgesic effects. The *PIK3R1* gene was suggested to have the potential to function as a pain-related regulator according to the genetic interaction analysis [133], and its expression level might be associated with osteoarthritis pathogenesis [134]. Upregulation of the *HSP90AA1* gene was observed in patients with fibromyalgia [135–137], and pharmacological inhibition of heat shock protein 90 (HSP90; encoded by *HSP90AA1*) was shown to alleviate monoarthritis-induced pain [138]. The activation of epidermal growth factor receptor (EGFR; encoded by *EGFR*) and AKT (encoded by *AKT1*) is associated with the development and enhancement of diverse types of pain, and their therapeutic modulation might be associated with analgesic properties [139–156]. Lysophosphatidic acid receptor 1 (encoded by *LPAR1*) activity is involved in pain behavior arising from bone cancer, inflammation, diabetes, and neuropathy, and its pharmacological or genetic ablation might reduce the pain response [157–165]. Lysophosphatidic acid receptor 3 (encoded by *LPAR3*) plays crucial roles in the development and maintenance of neuropathic pain, and its blockade exerts analgesic effects [163, 166, 167].

We further assessed the CIs of the active chemical compounds of JGd to assess their pharmacological contribution to the analgesic effect of the herbal drug as described earlier [81, 168]. As a result, quercetin was shown to have the highest CI (91.83%) (Supplementary Figure S1), which suggests that this chemical compound might be the primary contributor to the analgesic activity of JGd.

Together, these data indicate the system-level pharmacological properties of the analgesic activity of JGd.

3.4. Functional Enrichment Investigation of Jakyak-Gamcho Decoction Networks. To investigate the molecular mechanisms underlying the analgesic effect of JGd, we carried out GO enrichment analysis of the targets. As a result, the JGd targets were enriched in GO terms involved in the modulation of a variety of biological activities, such as calcium- and cytokine-mediated signalings, calcium ion concentration and homeostasis, cellular behaviors of muscle and neuronal cells, inflammatory response, and response to chemical, cytokine, drug, and oxidative stress (Supplementary Figure S2), which are in accordance with the previously reported molecular mechanisms of the herbal drug [40, 41, 44, 46, 49, 55, 58–60, 169–172]. In addition, GeneMANIA analysis indicated that the JGd targets might functionally interact via diverse mechanisms (Supplementary Figure S3), implying the similarity in their pharmacological roles.

Because various signaling pathways were reported to be associated with the initiation, transmission, perception, and maintenance of pain [12, 14, 20, 144, 155, 173–186], we carried out pathway enrichment analysis. We found that the JGd targets were enriched in the following signalings: "PI3K-Akt signaling pathway," "Neuroactive ligand-receptor interaction," "Estrogen signaling pathway," "cAMP signaling pathway," "Chemokine signaling pathway," "JAK-STAT signaling pathway," "Neurotrophin signaling pathway," "AMPK signaling pathway," "Dopaminergic synapse," "ErbB signaling pathway," "HIF-1 signaling pathway," "Insulin signaling pathway," "mTOR signaling pathway," "Serotonergic synapse," "Adipocytokine signaling pathway," "Drug metabolism - cytochrome P450," "IL-17 signaling pathway," "TNF signaling pathway," "Arachidonic acid metabolism," and "VEGF signaling pathway" (Figure 4 and Supplementary Figure S2). These signalings are well-known pain-regulating pathways and function as therapeutic targets of analgesic and pain-relieving drugs. The activities of adenosine monophosphate-activated kinase (AMPK), ErbB, mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K)-Akt, tumor necrosis factor (TNF), or vascular endothelial growth factor (VEGF) signaling pathways are involved with the development and maintenance processes of various types of pathological pain, and their functional modulation might relieve neuropathic, nociceptive, and bone cancer pain [144, 149, 150, 155, 156, 187–226]. Furthermore, the activity of PI3K-Akt and the adipocytokine pathway further correlates with the severity of neuropathic and inflammatory pain, and their targeting agents exert analgesic effects [227–229]. The estrogen pathway serves as a modulator of the processing and sensitivity of visceral and mechanical pain responses [230–235]. Previous studies have shown the involvement of cyclic adenosine monophosphate (cAMP), chemokine, Janus kinase-(JAK-) signal transducer and activator of transcription (STAT), neurotrophin, and hypoxia-inducible factor (HIF) pathways in the initiation and persistence of inflammatory, cancer, and neuropathic pain, as well as their role as pharmacological mediators of analgesic approaches [141, 224, 236–265]. The

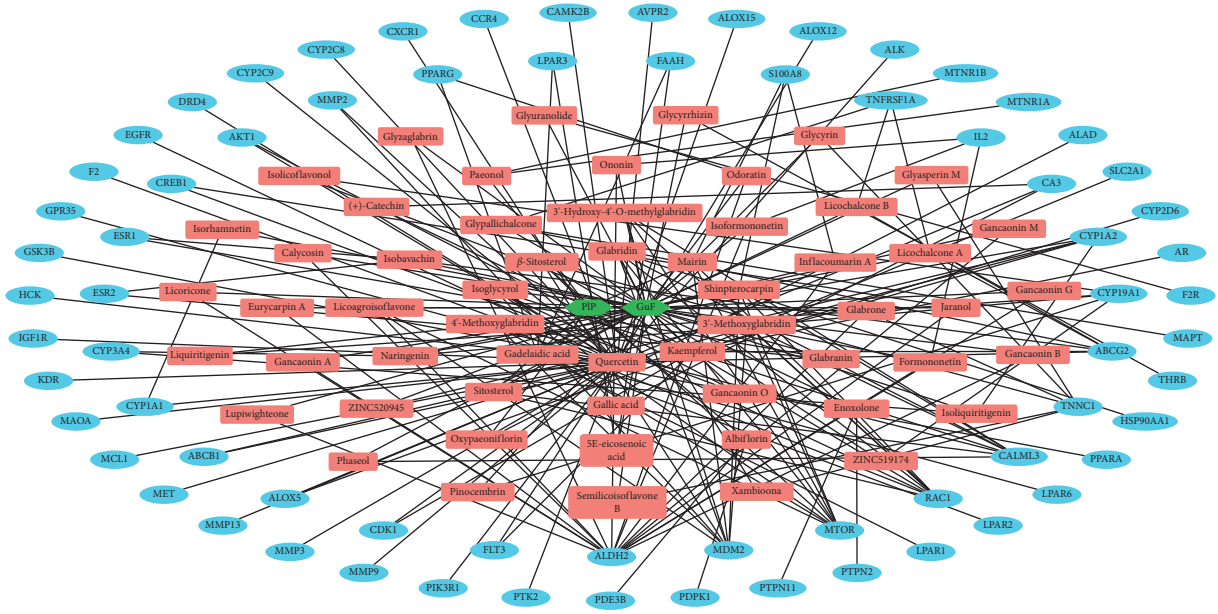

Figure 2: The herbal medicine-active chemical compound-target network of Jakyak-Gamcho decoction. Green nodes, herbal medicines; red nodes, active chemical compounds; blue nodes, pain-related targets.

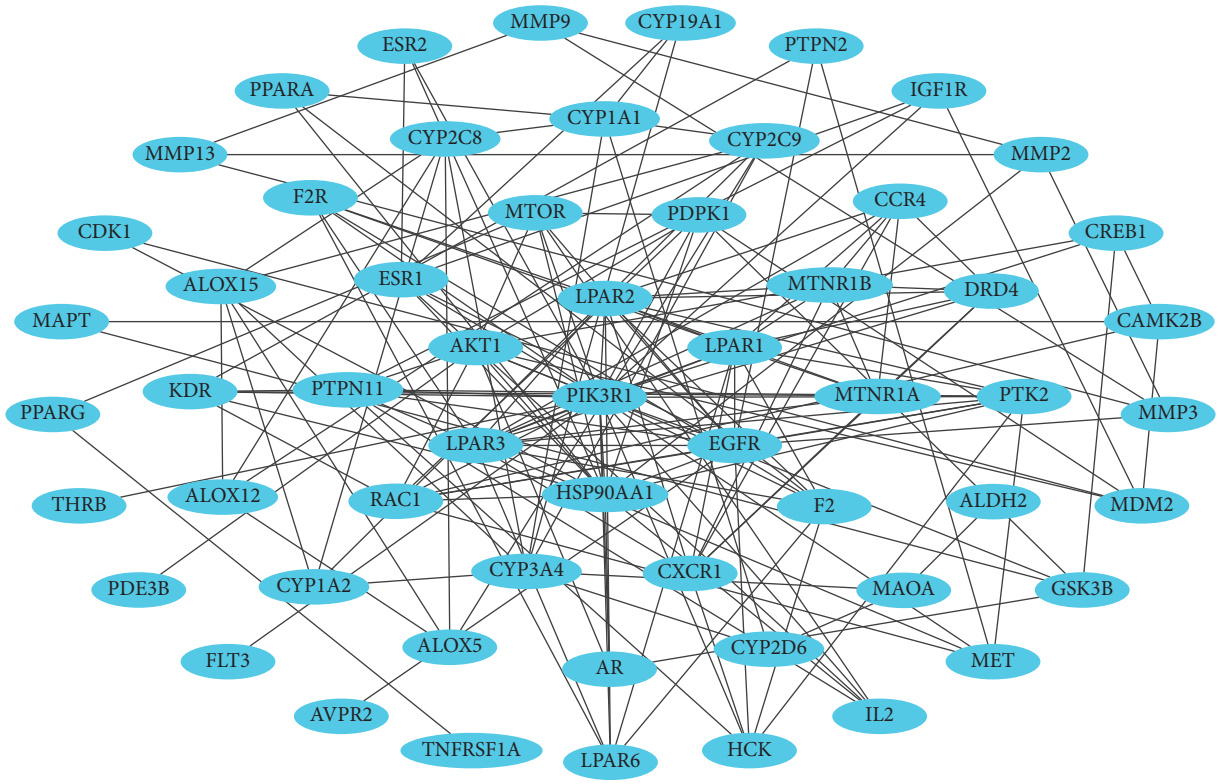

Figure 3: The protein-protein interaction network for the pain-related targets of Jakyak-Gamcho decoction. Blue nodes, pain-related targets.

impaired regulation of insulin signaling might promote the development of and pain sensation with diabetic neuropathy, which can be alleviated by its functional restoration [266–269]. The interleukin- (IL-) 17 pathway plays a crucial role in cellular mechanisms of pain pathogenesis and maintenance in various diseases including multiple sclerosis, prostatitis, intervertebral disk degeneration, femoral head osteonecrosis, and neuropathy; its inhibition might block the generation and persistence of pain [270–282]. Arachidonic acid metabolism is associated with the generation and secretion of diverse biomolecular substances

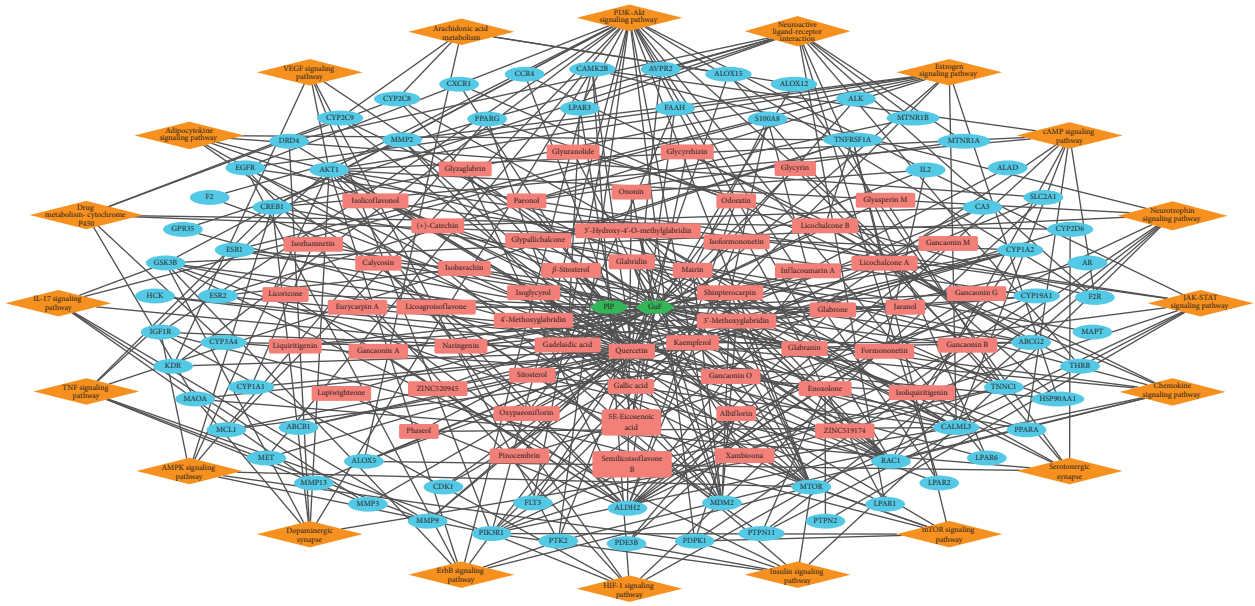

FIGURE 4: The herbal medicine-active chemical compound-target-pathway network of Jakyak-Gamcho decoction. Green nodes, herbal medicines; red nodes, active chemical compounds; blue nodes, pain-related targets; orange nodes, signaling pathways.

responsible for the induction of inflammation and pain, and it is mainly involved in the mechanisms of action of NSAIDs [283–288]. Moreover, the serotonergic and dopaminergic synapse pathways are key neurotransmitters responsible for modulating the intensity and duration of pain, and their therapeutic interventions have been shown to attenuate pain behaviors [289–292].

Collectively, these results demonstrate the molecular- and pathway-level mechanisms underlying the analgesic activity of JGd.

3.5. Molecular Docking Evaluation. To investigate the binding potential of the chemical compounds of JGd components for the targets, we evaluated their molecular docking activity. As a result, 95.09% of the binding interactions between the active chemical components of JGd and the hub targets was found to have docking scores equal to or lower than −5.0 (Figure 5 and Supplementary Table S4), indicating their therapeutic binding potential. Of note, the protein structures for LPAR2 and LPAR3 were unavailable in the RCSB Protein Databank [110]; therefore, they were excluded from the analysis.

4. Discussion

Herbal medicines are increasingly being acknowledged as effective analgesic and pain-relieving agents owing to their promising therapeutic activity with fewer side effects [29–36]. JGd is a well-known herbal drug that alleviates pain induced by multiple diseases such as peripheral neuropathy, myalgia, arthralgia, and diabetes [30, 37–40, 44, 46–48], and it is one of the most frequently prescribed oral analgesics in East Asia [56]. Previous studies have attempted network pharmacology analyses to investigate the mechanisms underlying JGd for the treatment of osteoarthritis and Parkinson's disease [293, 294]; however, its network-perspective analgesic properties have not been fully elucidated. Therefore, this network pharmacology study attempted to investigate system-level mechanisms that underlie the analgesic activity of JGd. The ADME evaluation and network pharmacology investigation identified 57 active chemical compounds in JGd and their 70 pain-associated human molecular targets. Further enrichment analysis indicated that JGd targets were enriched with GO terms related to the modulation of biological activities, involving calcium- and cytokine-mediated signalings, calcium ion concentration and homeostasis, cellular behaviors of muscle and neuronal cells, inflammatory response, and response to chemical, cytokine, drug, and oxidative stress, consistent with the previously reported molecular mechanisms of the herbal drug [40, 41, 44, 46, 49, 55, 58–60, 169–172]. We further showed that JGd might target various pain signalings to exert its analgesic and pain-relieving effects, which involve the PI3K-Akt, estrogen, ErbB, neurotrophin, neuroactive ligand-receptor interaction, HIF-1, serotonergic synapse, JAK-STAT, and cAMP pathways.

The analgesic activity of the chemical components of JGd has been previously reported. (+)-Catechin and pinocembrin produce analgesic, antineuropathy, and antinociceptive effects [295–297]. Albiflorin might play a pharmacological role as an analgesic, antineuropathy, and antinociceptive compound that can reduce pain intensity via the functional modulation of calcium channels, mitogen-activated protein kinase (MAPK) pathways, and various cytokines and chemokines [127, 298]. Moreover, formononetin, glabridin, glycyrrhizin, and paeonol exhibit anti-inflammatory, antinociceptive, and analgesic activities by inhibiting the generation of inflammatory cytokines and signaling molecules, thereby attenuating the pain responses [117, 120, 299–302]. Gallic acid could also have potential anti-

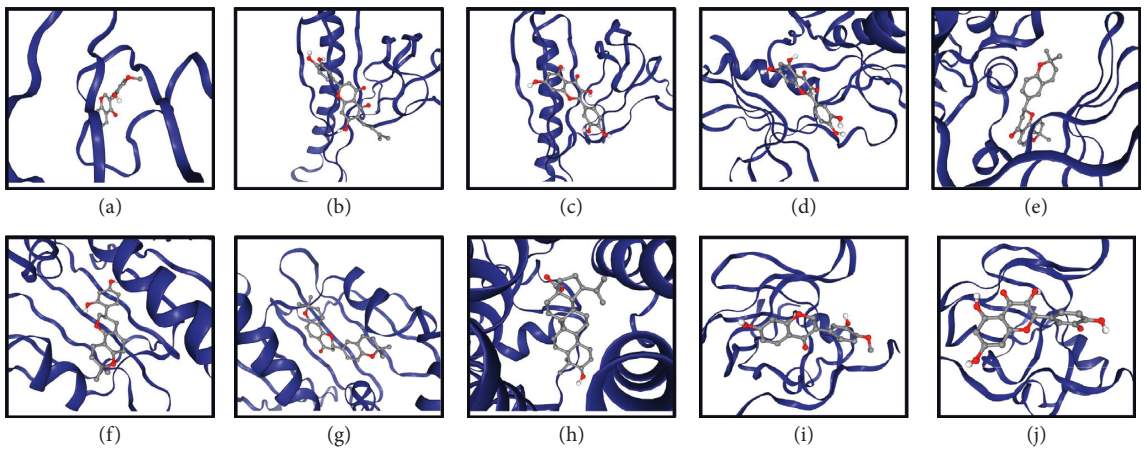

Figure 5: Molecular docking analysis of interactions between the active chemical compounds of Jakyak-Gamcho decoction and hub targets. (a) Calycosin-AKT1 (score = −7.5). (b) Gancaonin O-AKT1 (score = −5.7). (c) Quercetin-AKT1 (score = −6.4). (d) Quercetin-EGFR (score = −8.0). (e) Xambioona-EGFR (score = −10.5). (f) Glabridin-HSP90AA1 (score = −8.3). (g) Xambioona-HSP90AA1 (score = −9.1). (h) Mairin-LPAR1 (score = −8.4). (i) Calycosin-PIK3R1 (score = −7.9). (j) Quercetin-PIK3R1 (score = −6.3).

inflammatory, antioxidant, and neuroprotective effects that could improve neuropathic pain, neuronal damage, and injury [119, 303, 304]. Glycyrrhizin and naringenin reduce inflammatory and neuropathic pain-like behaviors by modulating the secretion of inflammation-associated cytokines and mediators, as well as the activities of cyclic guanosine monophosphate (cGMP) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalings [120, 301, 305–314]. Isoliquiritigenin was reported to possess analgesic, antispasmodic, and relaxant properties [315, 316]. Isorhamnetin ameliorates the pain intensity of diabetic neuropathy via its neuroprotective, antioxidative, and anti-inflammatory effects [317]. Kaempferol shows anti-inflammatory, antioxidant, and analgesic effects, which relieve the pain symptoms of gastritis, pancreatitis, and diabetic neuropathy [318–320]. In addition, liquiritigenin might suppress neuropathic pain by improving thermal, cold, and mechanical hyperalgesia [116]. Mairin (betulinic acid) has been shown to exert anti-inflammatory, antinociceptive, antipyretic, and analgesic effects, thereby alleviating visceral pain and chemotherapy-, infection-, and diabetes-associated neuropathies [321–326]. Quercetin reduces pain arising from inflammation, cancer, chronic prostatitis/chronic pelvic pain syndrome, arthritis, and muscle injury by inhibiting the induction of oxidative stress and activating inflammatory and adrenergic pathways, neurotransmitters, and cytokines [327–334]. In addition, quercetin further modulates the activity of a variety of pathways, including Toll-like receptor, mTOR, protein kinase Cε (PKCε)-TRPV1, p70 ribosomal S6 kinase (p70S6K), and $P2X_4$ receptor signalings, as well as oxidative stress- and inflammation-associated mediators to exert its analgesic effects against diverse types of neuropathic pain [214, 335–347]. β-Sitosterol shows analgesic, antinociceptive, and anti-inflammatory activities [348–353]. These studies regarding the chemical components of JGd provide the pharmacological basis for the analgesic activities of this herbal drug.

Based on the network pharmacological analyses, the following studies would contribute to the improvement of herbal drug therapies: (i) an assessment of the therapeutic efficacy of JGd analgesic activity in specific diseases that are associated with distinct types of pain, such as cancer, osteoarthritis, myalgia, arthralgia, and diabetes; (ii) a comprehensive exploration of the system-level mechanisms of analgesic properties of the herbal drug from diverse pharmacological perspectives, involving antinociceptive, anti-inflammatory, muscle relaxant, and antipyretic effects; and (iii) an investigation of the safety and effectiveness of combined treatment with JGd and widely used analgesic agents, including celecoxib, tramadol, and acetaminophen [24, 56, 354].

To conclude, we investigated the systems' perspective pharmacological properties of JGd, a widely prescribed analgesic herbal drug [56]. Based on the network pharmacological approach, we investigated 57 active chemical compounds and their 70 pain-related targets responsible for the analgesic activity of JGd. The targets of JGd were associated with the modulation of biological functions such as calcium- and cytokine-mediated signalings, calcium ion concentration and homeostasis, cellular behaviors of muscle and neuronal cells, inflammatory response, and response to chemical, cytokine, drug, and oxidative stress, which suggests the molecular mechanisms of JGd treatment. In addition, the enrichment analysis indicated that the targets are involved in various pathways that are associated with the pathophysiology of pain, including the PI3K-Akt, estrogen, ErbB, neurotrophin, neuroactive ligand-receptor interaction, HIF-1, serotonergic synapse, JAK-STAT, and cAMP pathways. The overall data offer a novel systematic view of the polypharmacological characteristics of herbal drugs and a mechanistic basis for their clinical implications for pain treatment.

Data Availability

The data used to support the findings of this study are included within the article and supplementary materials file.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Supplementary Materials

Supplementary Figure S1: contribution index analysis for the analgesic activity of active chemical compounds of Jakyak-Gamcho decoction. Supplementary Figure S2: functional enrichment analyses for the pain-associated targets of Jakyak-Gamcho decoction. Supplementary Figure S3: functional interaction analysis of the pain-associated targets of Jakyak-Gamcho decoction. Supplementary Table S1: list of the chemical compounds contained in Jakyak-Gamcho decoction. Supplementary Table S2: list of the active chemical compounds contained in Jakyak-Gamcho decoction. Supplementary Table S3: list of the targets of active chemical compounds of Jakyak-Gamcho decoction. Supplementary Table S4: docking scores of the active chemical compounds of Jakyak-Gamcho decoction with the hub targets. (*Supplementary Materials*)

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