



RESEARCH ARTICLE

Utilizing data mining and network pharmacology to analyze the formulation rule and function of enhancing immunity of *Acanthopanax Radix et Rhizoma*-containing health products

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Funding information

The CAMS Innovation Fund for Medical Sciences, Grant/Award Number: CIFMS 2021-I2M-1-031; The Key Project at Central Government Level: the ability establishment of sustainable use for valuable Chinese medicine resources, Grant/Award Number: 2060302; The National Natural Science Foundation of China, Grant/Award Number: 82174046

Abstract

Objective: This study aims to analyze the formulation rules of Ciwujia (*Acanthopanax Radix et Rhizoma*)-containing health products and investigate the potential mechanisms.

Methods: By searching the Ciwujia-containing health products from the special food information inquiry platform of the State Administration for Market Regulation and MedSciNet, the basic information, including efficacy, tropism of taste, dosage form, health function etc., was analyzed using R language software packages and Excel. The formulation rules and core drug combinations were analyzed using the Apriori algorithm of IBM SPSS Modeler 18.0. By searching TCMID and other databases and reviewing relevant literature, the chemical components and potential targets database of Ciwujia was constructed. The protein–protein interaction network was analyzed using R package, String database, and Cytoscape software to screen for key components and targets related to health functions. Gene ontology functional annotation and Kyoto encyclopedia of genes and genomes pathway enrichment analysis were performed. Finally, molecular docking was used to verify the binding affinity of core targets and key components.

Results: A total of 315 cases of Ciwujia-containing health products were collected. The major health functions were to relieve physical fatigue and immune enhancement. A total of 205 effective components and 775 targets related to Ciwujia were obtained. By intersecting the genes related to Ciwujia and immune enhancement, 212 key target genes were identified. Ciwujia has an effect on immune enhancement through signaling pathways such as C-type lectin receptor, toll-like receptor, and NOD-like receptor. Molecular docking results also indicated a spontaneous and stable binding between the key components of Ciwujia and the core targets.

Conclusions: Through data mining, network pharmacology, and molecular docking research, this study analyzed the relevant information of Ciwujia-containing health products, preliminarily revealing its potential targets and mechanism pathways of immune enhancement and providing a theoretical basis for the development of future health products.

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KEYWORDS

Acanthopanax Radix et Rhizoma, data mining, health products, immune enhancement, network pharmacology

INTRODUCTION

Acanthopanax senticosus (Rupr. et Maxim.) harms is a plant in the Araliaceae family that can be used to make health food products. Ciwujia is the dried root, rhizome, or stem of this plant [1]. It has a pungent and slightly bitter and warm taste. Ciwujia enters the spleen, kidney, and heart meridians. It has the effects of promoting qi, strengthening the spleen, tonifying the kidney, and calming the mind [2]. Glycosides, polysaccharides, flavonoids, coumarins, lignans, and trace elements are among Ciwujia's primary chemical components [3]. The central nervous system, cardiovascular system etc., are the primary subjects of contemporary pharmacological research. Its primary constituents exhibit favorable effects in immunomodulation, liver protection, cardio protection, central nervous system protection, anticancer, antioxidant, antidiabetic, and other areas [4].

Ciwujia was first mentioned in *Shennong Ben Cao Jing* (Classic of the Materia Medica of the Divine Husbandman). It is frequently used as a ginseng alternative and is considered a good medicine with antiaging and immune-enhancing properties. Total glycosides and polysaccharides, the primary ingredients in Ciwujia-containing health food, have been shown, in studies, to have a number of health benefits, including boosting immunity, reducing physical exhaustion, and promoting better sleep [5–7]. These compounds can have the greatest health effects when judiciously combined with different raw materials. Therefore, Ciwujia as a health food is not only welcomed in the domestic market but also has a good sales volume in East Asia, Southeast Asia, as well as the America, Europe and other countries and regions [8], which has a good prospect of market application. Research on the law of medication in health foods and the mechanism of their health function has not yet been published, despite reports on health foods containing Ciwujia. This study aims to provide a theoretical foundation and point of reference for the research and development of Ciwujia-containing products, using data mining, network pharmacology, and molecular docking technology to examine the compositional rules of health foods containing Ciwujia as well as the mechanism of its health-care function.

MATERIALS AND METHODS

Inclusion and exclusion criteria

(1) The product information contains health function claims and they satisfy the standards for nonnutrient

supplements in the list of health functions that health foods are allowed to claim (2023 edition). (2) The product information clearly identifies the primary raw components. (3) Only products declared for the first time are counted. Excluding the renewal of registration, changed products and other products that do not meet the above criteria.

Data organization and establishment of database

We used “Ciwujia” as a key word to find health food products on the Pharmaceutical Intelligence Network and the State Administration for Market Supervision and Administration's Special Food Information Query Platform, which were approved before 9 August 2024.

Health functions are standardized with reference to the catalog of health functions allowed to be claimed by health food products as nonnutrient supplements (2023 edition), for example, “immunomodulation” is uniformly categorized as “helping to enhance immunity”, “anti-fatigue” as “relieving physical fatigue”, and “improving tolerance to hypoxia” as “tolerance to hypoxia”. The names of traditional Chinese medicines (TCMs), their efficacies, the four qi five flavors, and categorization of Chinese medicines were standardized with reference to *the 2020 edition of the Chinese Pharmacopoeia* [2] and *the Encyclopedia of Traditional Chinese Medicine (ETCM) v2.0* [9]; the artillery products were standardized according to the names of the raw medicines, for example, “Zhihuangqi” was standardized as “Huangqi”; raw material extracts are standardized as raw material names, for example, “Wujia extract” is standardized as “Wujia”; Chinese medicine aliases and common names are standardized as standard names, for example, “Chinese yam” is standardized as “yam”. The auxiliary materials and chemical components in the formula were removed, such as microcrystalline cellulose, magnesium stearate, and corn starch. The data of suitable and unsuitable groups are standardized, for example, “lactating women” is standardized as “lactating mothers”.

The data were standardized using the back-to-back double entry method. The product name, dosage form, primary raw materials (including efficacy, four qi, five flavors, and attribution of channels of TCM), health functions, and appropriate and inappropriate groups were all uniformly entered into Excel and the Chinese Medicine Inheritance Calculation Platform V3.5. A third party then verified and integrated the data to create the database of health food products that contained Ciwujia.

Data statistical analysis

Frequency analysis and formula analysis

Microsoft Excel was used to analyze the efficacy of TCM, the four qi, the five flavors, the categorization, the dosage form, the health-care function, the frequency, and the frequency of suitable and unsuitable people. The Apriori algorithm of IBM SPSS Modeler18.0 and the formula analysis module in the Chinese Medicine Heritage Computing Platform V3.5 software were used to analyze the pattern of formulas.

Network pharmacology research

Collection and screening of active ingredients and target genes of Ciwujia

Ciwujia's active ingredients and target genes were screened and gathered using the keyword "Ciwujia" in the TCMID database [10], HERB database [11], ETCM database [9], and HIT database [12]. The chemical composition and target information were gathered by searching China Knowledge, PubMed, and other relevant literature. Duplicate compounds were removed, and the integrated data were corrected by a PubChem database [13]. The target sites of Ciwujia's active components were obtained using the Swiss Target Prediction platform. The UniProt database normalized and rectified the data after duplicates were removed.

Screening of potential targets for health functions

GeneCards database [14], PathCards database [15], and DrugBank database [16] were searched for disease protein targets related to health-care functions. The targets were merged and de-weighted and corrected by the Uniprot database.

Acquisition of key targets for health function of Ciwujia

The intersection of potential targets of Ciwujia active ingredients and potential targets for health functions was taken to obtain common targets, which were used as key targets for the health function of Ciwujia. A venn diagram visualization was drawn using the jvenn website to obtain a map of intersecting targets for health-care functions of Ciwujia.

PPI network construction and core target screening

The key targets were imported into STRING, the protein species limited to "homo sapiens", and the required score limited to high confidence (0.900) to analyze the protein interactions. The protein-protein interaction (PPI) network was visualized using the cytoHubba plugin [17] in Cytoscape 3.10.0 software, and then the core targets were filtered according to the degree value size.

GO functional annotation and KEGG signaling pathway enrichment analysis

The core target genes of Ciwujia were imported into DAVID, and gene ontology (GO) biological process (BP), molecular function (MF) and cellular component (CC) analyses and Kyoto encyclopedia of genes and genomes (KEGG) signaling pathway enrichment analyses were carried out and visualized by using the ggplot2 software package.

Molecular docking validation

The most prevalent and dominating Ciwujia components were chosen after the results and reports were examined, and the relevant sdf files were obtained from the PubChem database. The target protein structure was optimized by eliminating the original ligands and water molecules and adding hydrogen atoms after the three-dimensional structural data were obtained from the PDB library. The AutoDock Vina software was used to analyze binding energy data and perform molecular docking after the screened key components and core target information were entered.

RESULTS

Distribution of annual and provincial approved quantity of health products containing Ciwujia

A total of 353 health food products were obtained through the search option, and with reference to the inclusion and exclusion criteria, a total of 315 health food products were included in the statistical analysis. They included 10 types of imported health food goods and 305 types of domestic health food products. As shown in Figure 1, 2004–2006 (31, 31, and 22 products), 2014–2015 (28 and 17 products), and 2022 (17 products) were the three stages with more approved products; Beijing (64 products), Shaanxi (31 products), Heilongjiang (28 products), and Jilin (21 products) were the four provinces and municipality with more approved products. Additionally, 9 health products were imported.

Frequency and efficacy analysis of TCM

In the formulas of 315 different health foods containing Chinese medicines (ranging from 1 to 18), the usage percentages of raw materials with four flavors, five flavors, six flavors, and three flavors were 28.25%, 24.76%, 14.92%, and 13.33%, respectively. There were also two types of primary raw materials for a single Ciwujia. Besides Ciwujia, 110 different TCM raw materials were used, with a total frequency of 1070 times. Those with frequencies higher than the average of 9.73 times are listed in Table 1.

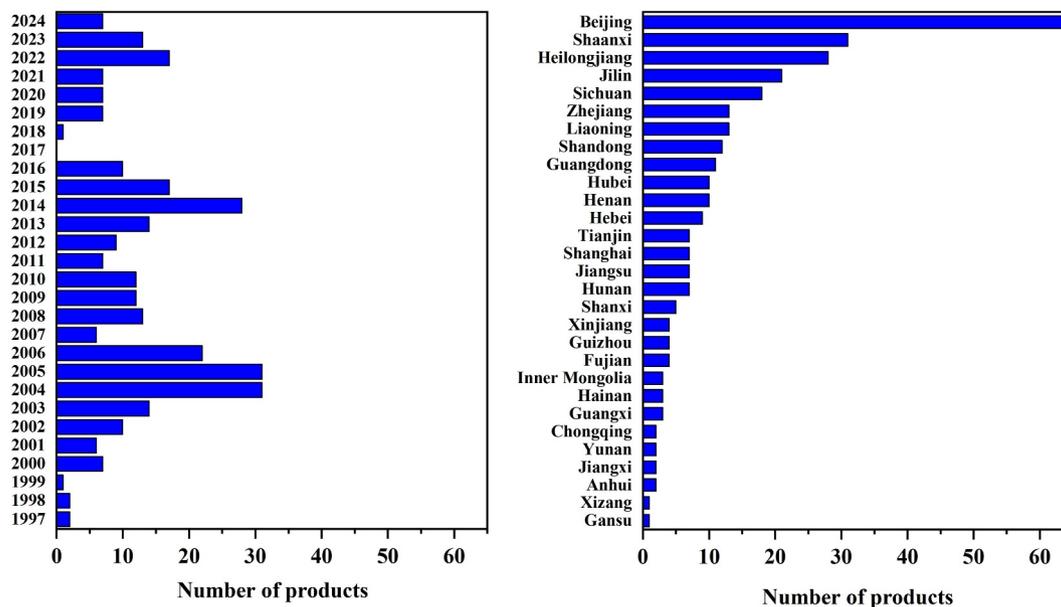


FIGURE 1 Distribution chart of annual and provincial approved quantity of health products containing Ciwujia.

TABLE 1 Frequency statistics of raw materials in health products containing Ciwujia (frequency >10).

No.	Herbs	Frequency (N)	Percentage (%)	No.	Herbs	Frequency (N)	Percentage (%)
1	Gouqizi	108	10.09	13	Shanyao	26	2.43
2	Xiyangshen	77	7.20	14	Maidong	23	2.15
3	Renshen	76	7.10	15	Danggui	17	1.59
4	Suanzaoren	69	6.45	16	Dazao	14	1.31
5	Hongjingtian	57	5.33	17	Shanzhuyu	14	1.31
6	Wuweizi	52	4.86	18	Gegen	14	1.31
7	Huangqi	50	4.67	19	Yuanzhi	14	1.31
8	Fuling	42	3.93	20	Tianma	13	1.21
9	Yinyanghuo	41	3.83	21	Boziren	11	1.03
10	Huangjing	35	3.27	22	Yinxingye	11	1.03
11	Lingzhi	32	2.99	23	Rougui	10	0.93
12	Lurong	27	2.52	24	Sangshen	10	0.93

The efficacy of the raw materials covers 17 kinds, including astringents, purgatives, antipyretics, deficiency tonics etc., which are listed in Table 2. Figure 2 shows how frequently different effective Chinese medicines are used in each product's formula. The most commonly used Chinese medicines in health products are astringents, tranquilizers, and deficiency tonics. Deficiency tonics are more common in formulas with different ingredients, whereas tranquilizers and

astringents are more common in health products made up of 4–6 types of TCMs.

Flavors and meridians analysis

Among the 110 raw ingredients, the four qi were primarily flat (44.30%), warm (20.65%), and slightly warm (15.23%) according to Figure 3a; the five flavors were

TABLE 2 Statistics on the efficacy of TCM raw materials.

Serial number	Efficacy	Number of types
1	Tranquillizers	7
2	Deficiency tonics	50
3	Heat-clearing	8
4	Exterior-releasing	7
5	Astringent	6
6	Phlegm-reducing, cough-relieving, and asthma-suppressing	4
7	Blood-stasis-removing	4
8	Qi-regulating	4
9	Water-permeating and dampness-eliminating	4
10	Liver-calming and wind-suppressing	4
11	Wind-dampness-expelling	2
12	Interior-warming	2
13	Digestion-promoting	2
14	Purgative	2
15	Hemostatic	2
16	Antitoxic, insecticidal, and antipruritic	1
17	Dampness-transforming	1

Abbreviation: TCM, traditional Chinese medicines.

primarily sweet (55.89%), lightly bitter (10.42%), and acidic (9.62%) according to Figure 3b; the kidney (23.22%), lung (20.95%), and heart (20.13%) were the primary meridians according to Figure 3c.

Frequency analysis of dosage forms of health products

Among the 315 kinds of Ciwujia-containing products, there are 9 dosage forms including capsule, tablet, wine, oral liquid, granule, drink rinse, tea, pill, and powder, which are listed in Table 3.

Frequency and correlation analysis of health functions

Of the 315 different kinds of health products that included Ciwujia, 1 type claimed to have 3 different health functions, 82 types claimed to have 2 different health functions, and 232 types claimed to have 1 health function. Detailed health functions are listed in Table 4. According to Figure 4, relieving physical fatigue, enhancing immunity products, and improving sleep are common functions of health-care products, and formulas including 3–7 TCMs are more common.

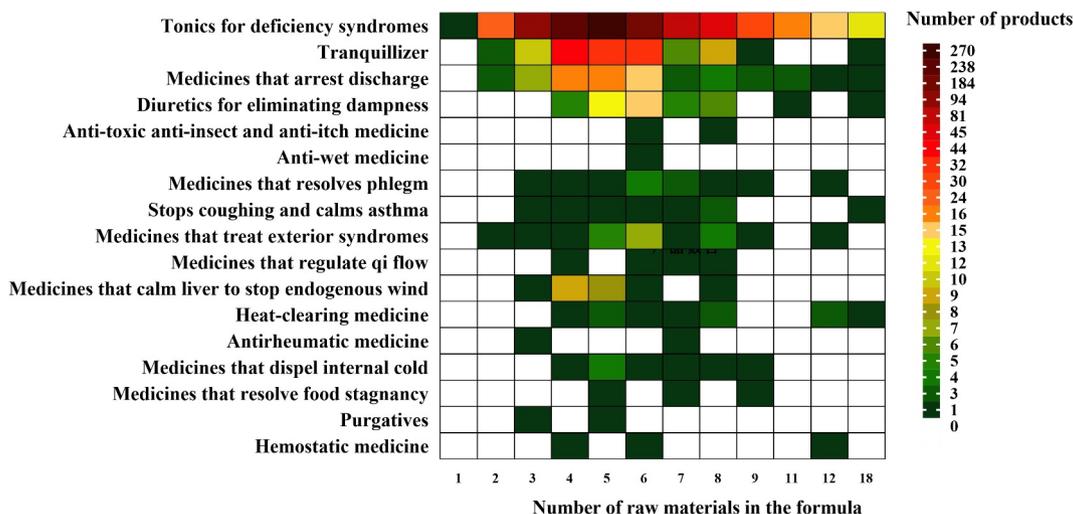


FIGURE 2 Heat map of correlation between the number of Chinese medicines in the formula of health products containing Ciwujia and the frequency of use of Chinese medicines with various effects.

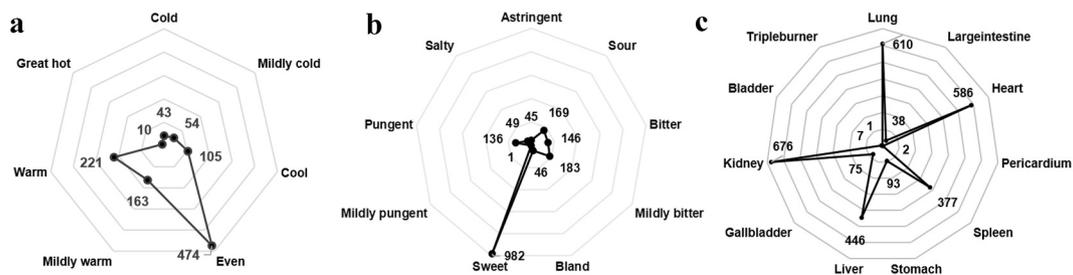


FIGURE 3 Radar plot of four qi, five flavors, and meridian distribution of raw materials in health products containing Ciwujia.

Frequency analysis of suitable and unsuitable people

Among the 315 types of Ciwujia-containing products, the total number of suitable people was 396 times, and inappropriate people accumulated 744 times, which are listed in Tables 5 and 6 in detail.

Association analysis of health products

SPSS software Apriori modeling was used to perform association analysis on the pairing relationship

TABLE 3 Frequency analysis of dosage forms of health products.

Serial number	Dosage form	Frequency (N)	Percentage (%)
1	Capsule	176	55.87
2	Tablet	47	14.92
3	Wine	20	6.35
4	Oral liquid	32	10.16
5	Granule	18	5.71
6	Drink rinse	12	3.81
7	Tea	7	2.22
8	Pill	2	0.63
9	Powder	1	0.32

TABLE 4 Frequency analysis of health functions in products.

Serial number	Health function	Frequency (N)	Percentage (%)
1	Relieve physical fatigue	151	39.02
2	Enhance immunity	84	21.71
3	Improve sleep	84	21.71
4	Resistance to hypoxia	30	7.75
5	Auxiliary protection against the hazards of ionizing radiation	11	2.84
6	Maintain a healthy level of blood lipids	6	1.55
7	Maintain a healthy blood sugar level	5	1.29
8	Auxiliary protection against chemical liver damage	3	0.78
9	Auxiliary improvement of memory	3	0.78
10	Help antioxidant	2	0.52
11	Help to improve chloasma	2	0.52
12	Help to improve bone density	2	0.52
13	Auxiliary protection of gastric mucosa	1	0.26
14	Help to improve the skin moisture condition	1	0.26
15	Improve iron-deficiency anemia	1	0.26
16	Help to moisten the intestine and laxative	1	0.26

between drugs, and the support level was set at 10% and the confidence level at 100% to analyze and excavate potential drug combinations. Core combinations are listed in Table 7. A total of 313 Ciwujia health foods were included. Sorted by the support degree, the results obtained 13 core drug combinations. Meanwhile, the network topology module was used to draw the raw material relationship diagram, the bubble size indicates the support degree, and the bubble color shade indicates the enhancement degree, as shown in Figure 5a. A total of 151 health food products for relieving physical fatigue were included, which obtained 15 core drug combinations, and the network topology module is shown in Figure 5b. A total of 84 immune-enhancing health food products were included, which obtained 14 core drug combinations, and the network topology module is shown in Figure 5c. A total of 84 health food products for improving sleep were included, which obtained 15 core drug combinations, and the network topology module is shown in Figure 5d.

Network pharmacology research

Collection and screening of active ingredients and target genes of Ciwujia

A total of 205 active ingredients of Ciwujia and 775 potential target genes were collected through various databases and retrieved literature related to Ciwujia.

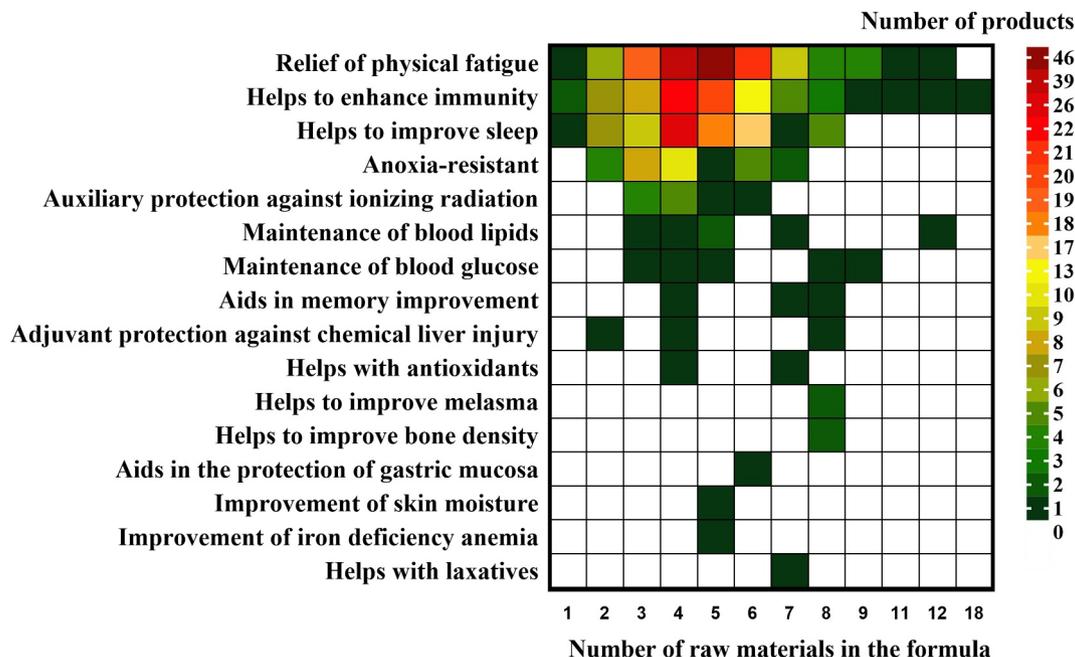


FIGURE 4 Heat map of correlation between the number of Chinese medicine and health function in the formula of health products containing Ciwujia (including Ciwujia).

TABLE 5 Frequency analysis of suitable people.

Serial number	Target group	Frequency (N)	Percentage (%)
1	People who are easily fatigued	152	38.38
2	People with low immunity	76	19.19
3	People with poor sleep conditions	67	16.92
4	People in an oxygen-deficient environment	35	8.84
5	Middle-aged and elderly people	26	6.57
6	People exposed to radiation	13	3.28
7	People with slightly high blood sugar	7	1.77
8	People with slightly high blood lipids	6	1.52
9	People who need to improve memory	4	1.01
10	People with weak constitution	2	0.51
11	People with nutritional anemia	2	0.51
12	People at risk of chemical liver damage	2	0.51
13	People with chloasma	2	0.51
14	People with dry skin	1	0.25
15	People with mild gastric mucosa susceptible to damage	1	0.25

Screening of potential targets for health functions

Relieving physical fatigue, helping to enhance immunity, and helping to improve sleep were the top three health benefits identified in “2.6” above. Considering that studies have been conducted on Ciwujia for relieving physical fatigue [18, 19] and helping to

improve sleep [20, 21], and that 80% of the core pairs of physical fatigue and immunity enhancement in Table 2 are the same, the health function of Ciwujia for immunity enhancement was selected for the follow-up network pharmacology study in this study.

We searched the GeneCards, PathCards, and DrugBank databases for immunity-related targets, de-emphasized and corrected the target gene information

TABLE 6 Frequency analysis of unsuitable people.

Serial number	Unsuitable group	Frequency (N)	Percentage (%)
1	Juveniles and children	301	40.46
2	Pregnant women	197	26.48
3	Nursing mothers	176	23.66
4	Infants and young children	2	0.27
5	People with impaired liver and kidney function	12	1.61
6	Women during menstruation	5	0.67
7	Patients with cardiovascular and cerebrovascular diseases	9	1.21
8	Diabetic patients	1	0.13
9	People with chronic diarrhea	4	0.54
10	People allergic to bee products	3	0.40
11	Patients with gynecological tumors	2	0.27
12	People allergic to alcohol	28	3.76
13	People with a family history of liver disease	2	0.27
14	People with excessive stomach acid	2	0.27

through the Uniprot database, and obtained a total of 2100 immunity-related targets.

Screening of key target genes and PPI network analysis

Two hundred and twelve common targets, which were Ciwujia's primary targets for enhancing immunity, were obtained by drawing a Venn diagram utilizing the target genes and immunity-related target genes (Figure 6). With the 212 common targets, the PPI network graph was constructed using 212 nodes and 994 edges (Figure 7). By using the cytoHubba plugin of Cytoscape software to filter the topological parameters, 10 core targets of Ciwujia for enhancing immunity were found. These core targets were then sorted by degree values, which were RAC-alpha serine/threonine-protein kinase (AKT1), cellular tumor antigen p53 (TP53), signal transducer and activator of transcription 3 (STAT3), proto-oncogene tyrosine protein kinase (SRC), mitogen-activated protein kinase 1 (MAPK1), mitogen-activated protein kinase 3 (MAPK3), Jun proto-oncogene (AP-1 transcription factor subunit, JUN), tumor necrosis factor (TNF), interleukin-6 (IL6), and epidermal growth factor receptor (EGFR).

GO function and KEGG enrichment analysis of key target genes

One hundred and sixty-two entries were found in the GO enrichment analysis results from Ciwujia's biological processes to improve immunity, primarily in the

areas of positive regulation of miRNA transcription, cellular reaction to cadmium ions, and cellular response to reactive oxygen species; 29 entries were found in the MF, involving homoprotein binding, enzyme binding, and transcription cis-regulatory region binding; 21 entries were found in the cellular localization, involving plasma membrane caveola, focal adhesion, and late-stage adherence. In cellular localization, 21 entries were obtained, involving caveola, focal adhesion, and late endosome. The top 10 entries were selected according to the order of each functional result (Figure 8).

Ciwujia's immunity-enhancing main target genes were subjected to KEGG pathway analysis, and 134 KEGG pathways were found to be enriched; after removing the pathways that were not related to immunity enhancement of Ciwujia, such as hepatitis B and tuberculosis, the immunity-enhancing key pathways of Ciwujia were obtained. The top 30 core pathways are shown in Figure 9.

Molecular docking validation results

Based on the outcomes of the literature search and database organization, as well as with reference to *the 2020 edition of the Chinese Pharmacopoeia*, the key components of Ciwujia were determined to be syringin (the content assay control), eleutheroside E (the main pharmacological active ingredient), and chlorogenic acid (a quality marker of flavonoids) [2, 22, 23]. The binding of Ciwujia's key components (syringin, eleutheroside E, and chlorogenic acid) and core targets (AKT1, TP53, STAT3, SRC, MAPK1, MAPK3, JUN, TNF, IL6, and EGFR) was confirmed using the

TABLE 7 Analysis of association rules of high-frequency raw materials in health products containing Ciwujia and health products with different health functions.

Association rule	Herbs	Herbs	Frequency (N)	Confidence level (%)	Association rule	Herbs	Herbs	Frequency (N)	Confidence level (%)
Containing Ciwujia	Gouqizi	Ciwujia	108	100	Relieving physical fatigue	Gouqizi	Ciwujia	72	100
	Xiyangshen	Ciwujia	77	100		Xiyangshen	Ciwujia	60	100
	Renshen	Ciwujia	76	100		Renshen	Ciwujia	41	100
	Suanzaoren	Ciwujia	69	100		Yinyanghuo	Ciwujia	34	100
	Hongjingtian	Ciwujia	56	100		Gouqizi, Xiyangshen	Ciwujia	33	100
	Wuweizi	Ciwujia	52	100		Huangqi	Ciwujia	32	100
	Huangqi	Ciwujia	49	100		Hongjingtian	Ciwujia	30	100
	Gouqizi, Xiyangshen	Ciwujia	43	100		Huangjing	Ciwujia	25	100
	Fuling	Ciwujia	42	100		Gouqizi, Renshen	Ciwujia	25	100
	Yinyanghuo	Ciwujia	41	100		Gouqizi, Yinyanghuo	Ciwujia	21	100
Immune-enhancing	Gouqizi	Ciwujia	30	100	Improving sleep	Suanzaoren	Ciwujia	66	100
	Renshen	Ciwujia	22	100		Wuweizi	Ciwujia	35	100
	Xiyangshen	Ciwujia	21	100		Suanzaoren, Wuweizi	Ciwujia	30	100
	Huangqi	Ciwujia	19	100		Fuling	Ciwujia	22	100
	Hongjingtian	Ciwujia	13	100		Fuling, Suanzaoren	Ciwujia	21	100
	Wuweizi	Ciwujia	11	100		Lingzhi	Ciwujia	17	100
	Lingzhi	Ciwujia	11	100		Lingzhi, Suanzaoren	Ciwujia	15	100
	Huangjing	Ciwujia	11	100		Yuanzhi	Ciwujia	13	100
	Gouqizi, Renshen	Ciwujia	11	100		Tianma	Ciwujia	12	100
	Gouqizi, Xiyangshen	Ciwujia	10	100		Renshen	Ciwujia	12	100

molecular docking technique. Syringin, eleutheroside E, and chlorogenic acid were able to bind spontaneously and had a high affinity for the core targets, as illustrated in Figure 10. Under the optimal mode, the binding energies of the key components of Ciwujia and the core targets are shown in Table 8.

DISCUSSION

In this study, deficiency tonic is the most common among 315 health food products containing Ciwujia. Examining the causes, deficiency tonic medications are used to cure a variety of deficiencies by supplementing the body's qi, blood, yin, and yang, and the top three health-care functions of health food products containing

Ciwujia are to alleviate physical fatigue, to help enhance immunity, and to help improve sleep. All of the above indications are predominantly for deficiency syndromes; therefore, deficiency tonic drugs are symptomatic treatments based on the basic theory of Chinese medicine. According to recent pharmacological research, deficient tonics can improve the body's immune system and control its immune homeostasis via a number of mechanisms, including immune system and cytokine regulation [24].

The results indicated that the majority of the dosage form of the health food containing Ciwujia was in the form of capsules, and the reason for this was determined to be that the soft gelatin capsule's wall was thick and impermeable, separating the contact between Chinese medicinal preparations and the air and

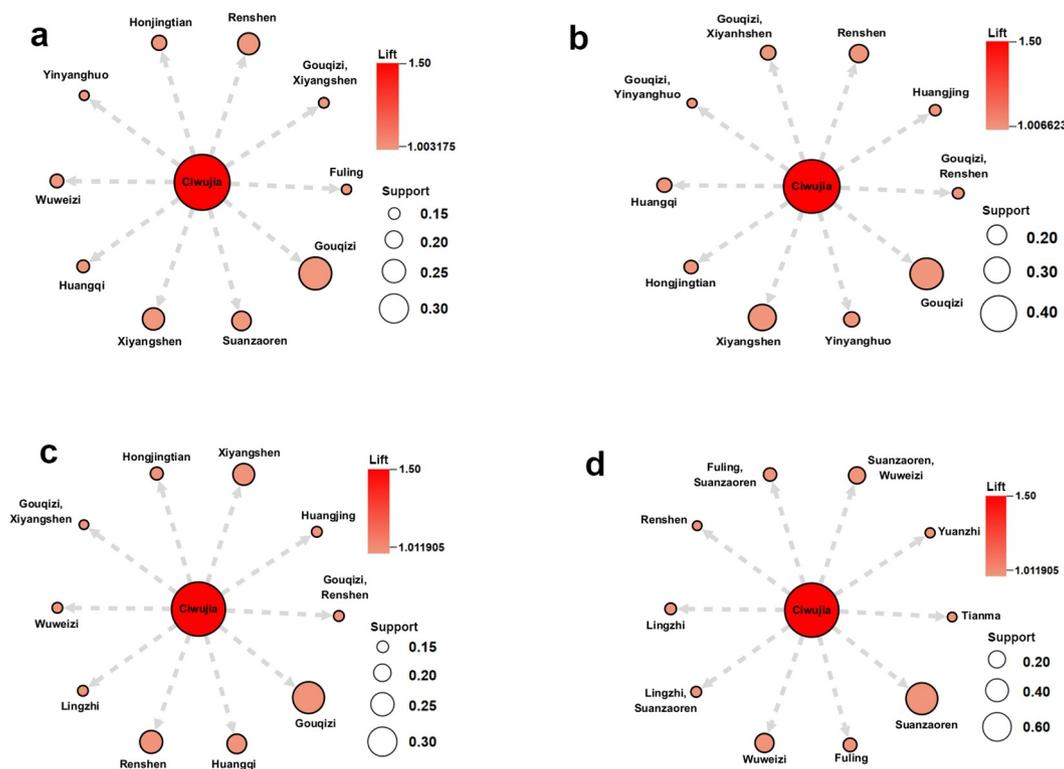


FIGURE 5 Relationship between high-frequency raw materials in health products containing Ciwujia and health products with different health functions. (a) Containing Ciwujia; (b) Helps to relieve physical fatigue; (c) Helps to strengthen immunity; (d) Helps to improve sleep.

Ciwujia-related targets Immunity related targets

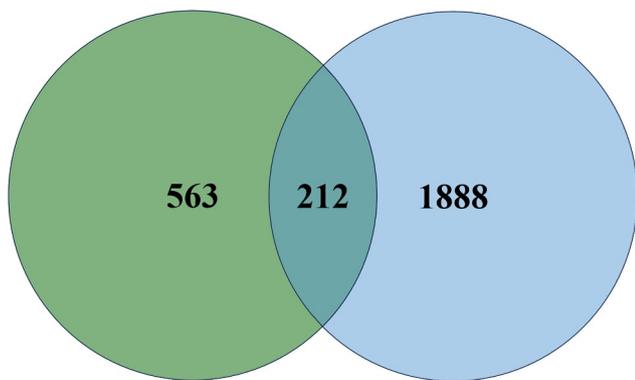


FIGURE 6 Venn diagram of common target genes related to Ciwujia and immunity.

effectively preventing either the oxidative breakdown of the medications or the deterioration of their hygroscopic absorption [25, 26].

The typical combinations of TCMs in health foods that contain Ciwujia to help improve immunity were examined. They were Ciwujia-Gouqizi, Ciwujia-Renshen, Ciwujia-Xiyangshen, Ciwujia-Huangqi, Ciwujia-Hongjingtian, Ciwujia-Wuweizi, Ciwujia-Lingzhi, and Ciwujia-Huangjing, and these combinations of TCMs ranked high in the frequency statistics of ingredients, belonging to the high-frequency use of TCM.

The results showed that the pattern of TCM in health food products containing Ciwujia complied with the basic theory of Chinese medicine. Among them, Gouqizi nourishes the liver and kidneys, tonifies renal essence, and brightens the eyes; Renshen greatly replenishes vital energy, restores the veins, and stabilizes loss; Xiyangshen tonifies qi, nourishes yin, clears heat, and generates body fluid; Huangqi replenishes qi and elevates yang, consolidates the exterior, and stops sweating; Hongjingtian benefits qi, promotes blood circulation, opens the veins, and calms asthma; Wuweizi is used for astringency, benefiting the vital energy and promoting the production of body fluid; Lingzhi tonifies qi, calms the spirit and relieves cough and asthma; and Huangjing tonifies qi, nourishes yin, benefits the kidneys, and strengthens the spleen. At the same time, modern pharmacological studies have also confirmed that the above components can play a role in enhancing immunity through different pathways. Polysaccharides in Gouqizi can enhance immunity through the activation of T lymphocytes and B lymphocytes [27]; polysaccharides in ginseng can activate and induce the proliferation of T and B lymphocytes and promote the activation of splenocytes, thereby promoting the specific or nonspecific immune effect [28]; Saponins and polysaccharides in Xiyangshen can enhance the immune function of the body by promoting cell proliferation, regulating pro-inflammatory mediators, and enhancing the phagocytosis of macrophages to produce biologically active

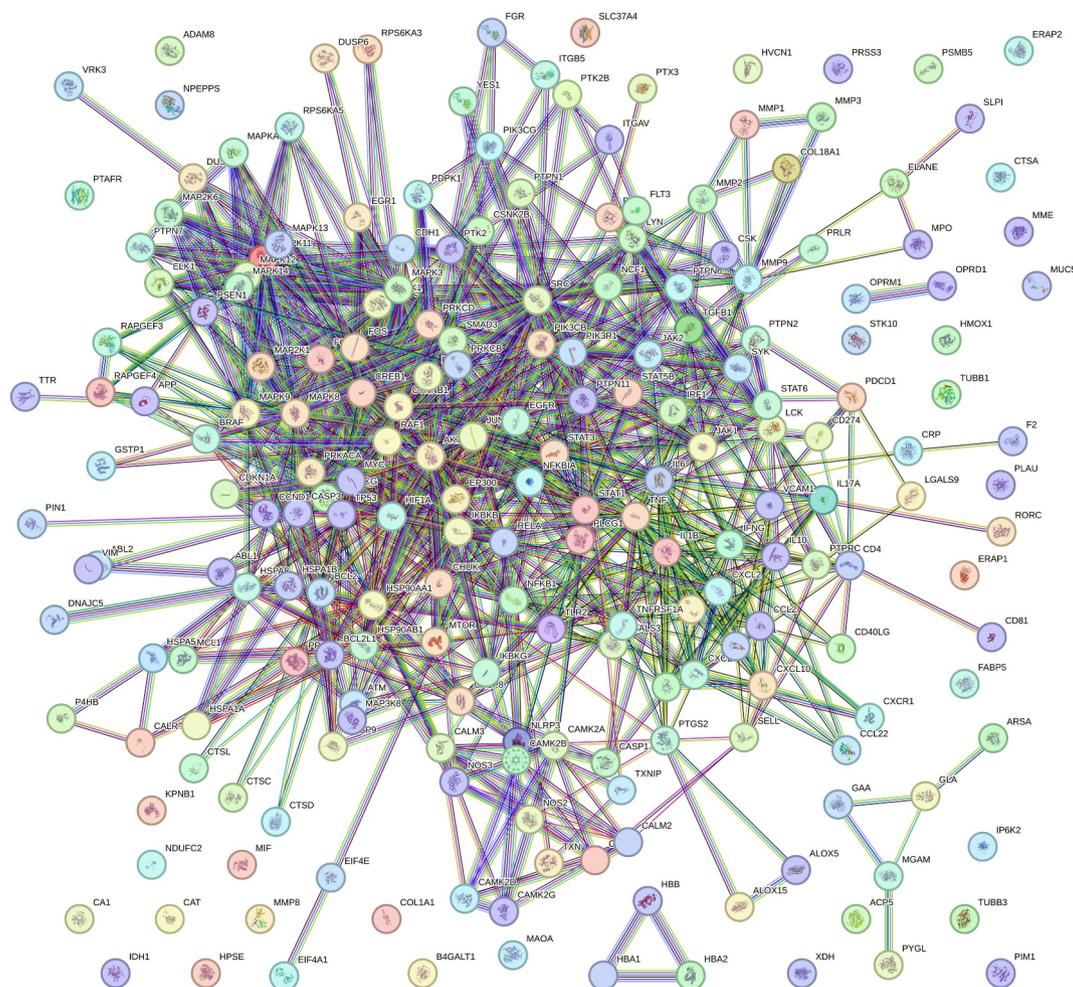


FIGURE 7 Protein–protein interaction network of common target genes related to Ciwujia and immunity.

substances [29]; polysaccharides in Huangqi can inhibit the proliferation of tumor cells by regulating the immune system [30]; glycosides in Hongjingtian can regulate the immune function by alleviating the stimulation of inflammation [31]; polysaccharides and lignans in Wuweizi can enhance immunity by increasing the number of immune cells and enhancing the function of immune cells [32]; polysaccharides in Lingzhi can comprehensively and efficiently affect immune cells while releasing a variety of chemokines, cytokines, and growth factors, thus regulating innate and adaptive immunity of the body [33]; and polysaccharides in Huangjing have significant antitumor and immunomodulating activities [34]. The results of the above analyses indicate that the herbal compositions in the health food products containing Ciwujia have immune-enhancing effects in both the basic theories of TCM and modern pharmacological studies.

In this study, 207 active components of Ciwujia were obtained by searching various databases and related literatures, and 212 potential targets for immunity enhancement were identified, and the top 10 core targets were AKT1, TP53, STAT3, SRC, MAPK1, MAPK3,

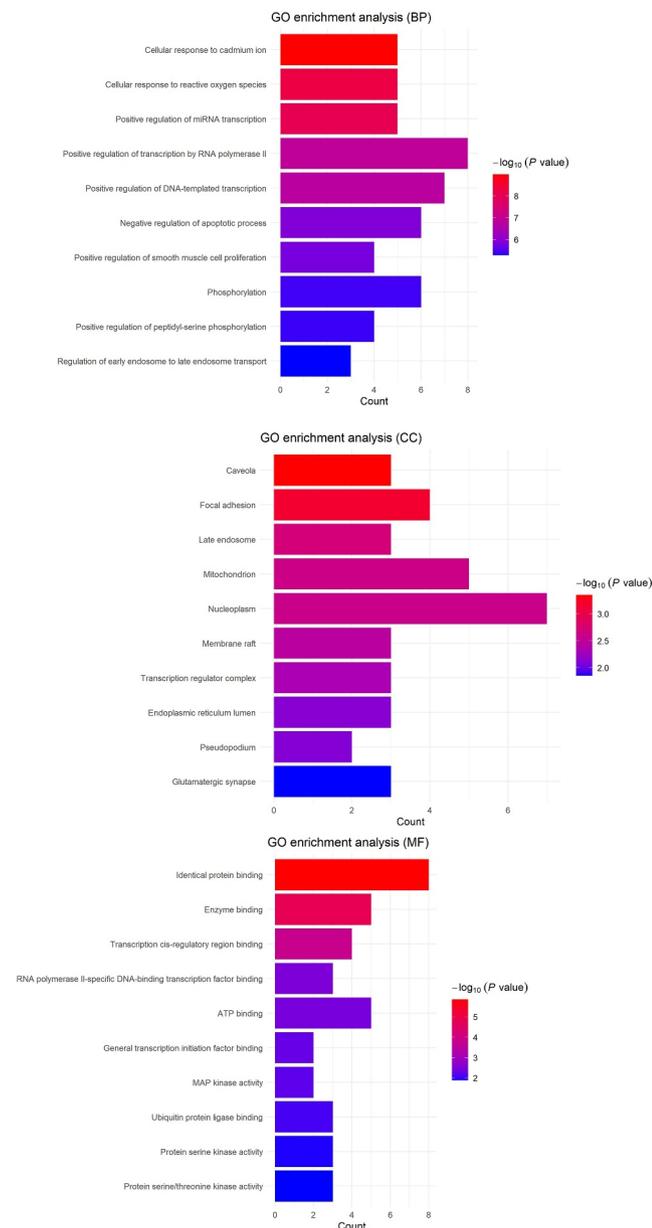


FIGURE 8 Top 10 results of gene ontology enrichment analysis for key targets.

(MAPK) signaling pathway, NOD signaling pathway, and mTOR-signaling pathway [36]; in immune cell activation and proliferation as well as immune metabolism through the TNF signaling pathway [37]; in autoimmune responses and inflammatory responses through the IL-17 signaling pathway [38]; in the regulation of CD4⁺ T cell differentiation to Th17 cells through the Th17 cell differentiation pathway [39]; in T cell development, activation, and acquired immune response through the T cell receptor signaling pathway [40]; in the activation of B cells, antibody production, and humoral immune response through the B cell receptor signaling pathway [41]; and in immune cell activation and allergic response through the FcεRI

signaling pathway [42]. According to the above results, Ciwujia can contribute to the activation and proliferation of different immune cells via a variety of intracellular signaling pathways. It can also influence different immune responses, including humoral, autoimmune, inflammatory, and acquired immune responses and ultimately play a part in immune enhancement. However, the findings of the pathway enrichment analysis require additional experimental confirmation.

It has been demonstrated that syringin can produce immunomodulatory effects by inhibiting TNF- α production and CTLL-2 cell proliferation [43], induce breast cancer cell apoptosis by regulating the PI3K/Akt/mTOR pathway [44], and enhance the immune function of mice by increasing the number of antibody-producing cells, enhancing delayed-type hypersensitivity, and improving the function of monocyte-macrophages [45]; eleutheroside E was able to counteract collagenous arthritis by inhibiting the release of inflammatory factors and by inhibiting the production of TNF- α and IL-6 in macrophages [46]; polysaccharides in Ciwujia also possessed immunomodulatory effects [47]. The molecular docking results showed that the key components of Ciwujia (syringin, eleutheroside E, and chlorogenic acid) could spontaneously bind to the core targets and bind well.

With the continued discovery of new components and targets of Ciwujia, there is an urgent need to expand the scope of data analysis and further improve the accuracy of computational methods in order to more comprehensively understand its pharmacological activity and its potential effects on immunity. More sophisticated statistical methods and algorithms should be used in future studies to integrate data from different studies to obtain a broader perspective of information. Given the broad scope of the concept of immunity, the current study was inadequate in terms of data aggregation and used a limited sample size. Therefore, more refined experiments should be designed in future studies to explore in greater depth the specific effects of Ciwujia on the immune system.

CONCLUSION

The study examined the effectiveness and usage patterns of different kinds of TCMS, their categorization into four qi and five tastes, the characteristics of herbs, the design of dosage forms, the frequency of the used raw material combinations etc. In the meantime, the study initially revealed how the active ingredients in Ciwujia regulate and enhance the immune response through specific biological pathways. In addition, molecular docking technology further confirmed the interaction patterns of these components with immune-related targets.

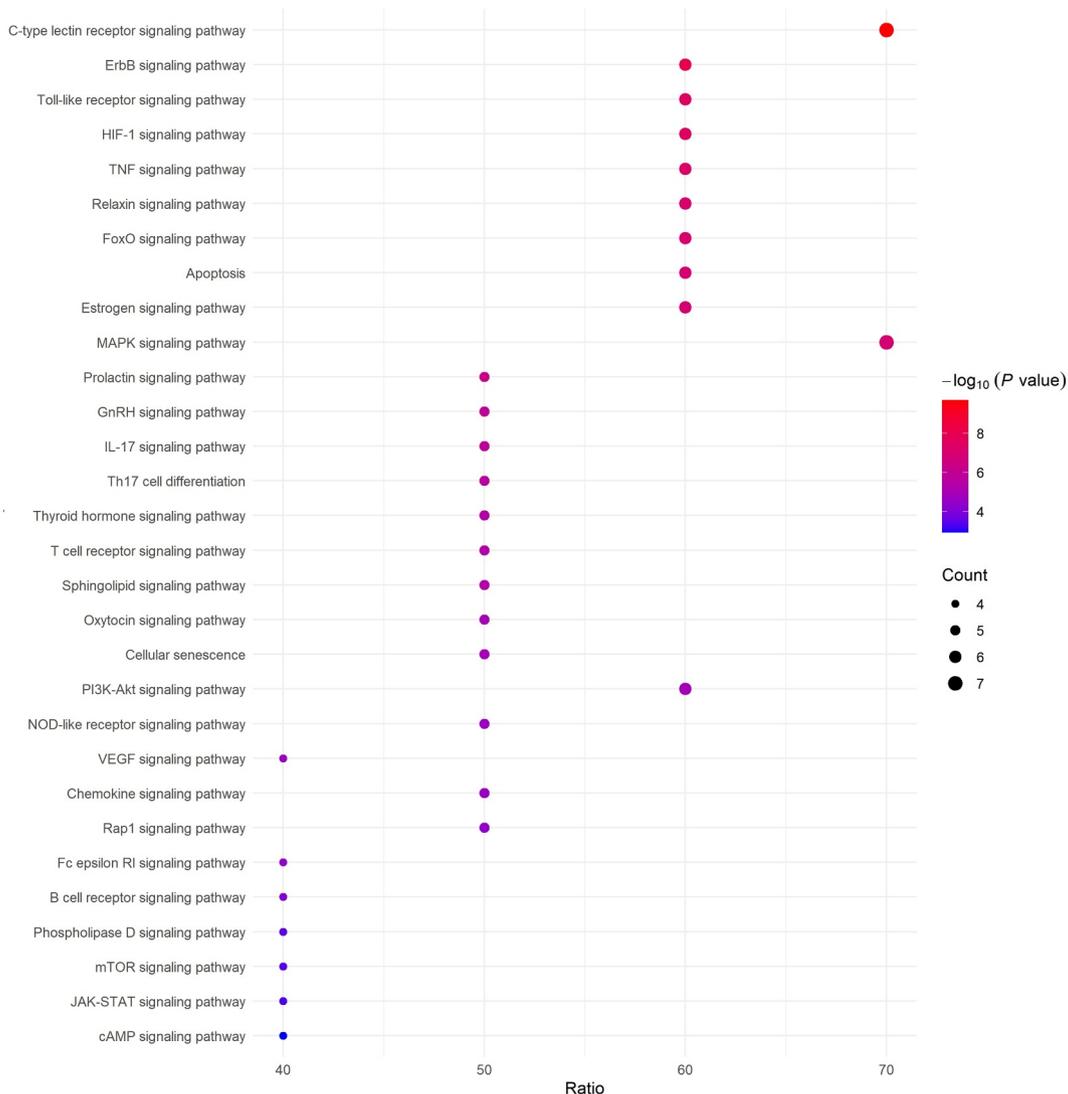


FIGURE 9 Top 30 results of Kyoto encyclopedia of genes and genomes pathway enrichment analysis for key targets.

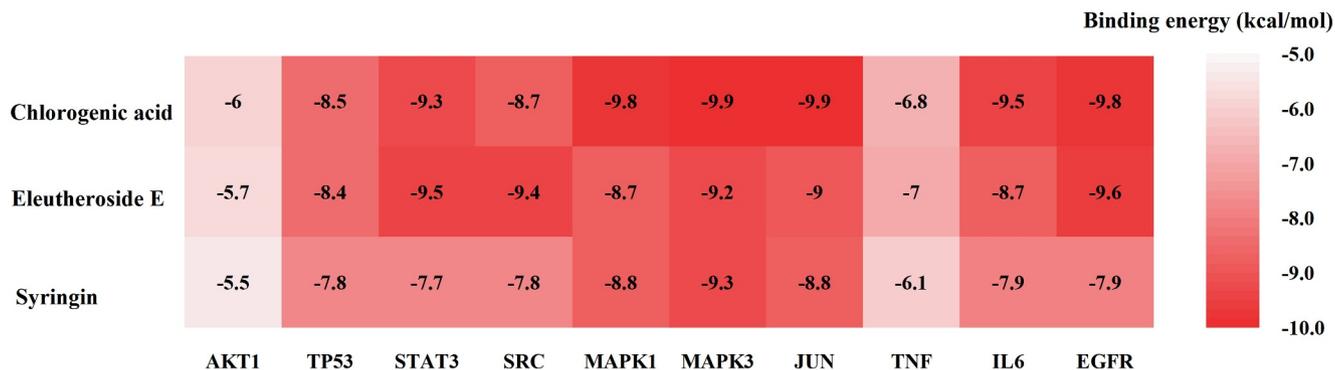


FIGURE 10 Molecular docking heat map of key components of Ciwujia with core target points. AKT1, AKT serine/threonine kinase 1/RAC-alpha serine/threonine-protein kinase; EGFR, epidermal growth factor receptor; IL6, interleukin-6; JUN, jun proto-oncogene; MAPK1, mitogen-activated protein kinase 1; MAPK3, mitogen-activated protein kinase 3; SRC, src proto-oncogene, nonreceptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; TP53, tumor protein p53.

TABLE 8 Binding energy between key components of Ciwujia and core target points.

Key components	CAS no.	Binding energy (kcal/mol)									
		AKT1	TP53	STAT3	SRC	MAPK1	MAPK3	JUN	TNF	IL6	EGFR
Syringin	118-34-3	-5.5	-7.8	-7.7	-7.8	-8.8	-9.3	-8.8	-6.1	-7.9	-7.9
Eleutheroside E	39432-56-9	-5.7	-8.4	-9.5	-9.4	-8.7	-9.2	-9.0	-7.0	-8.7	-9.6
Chlorogenic acid	327-97-9	-6.0	-8.5	-9.3	-8.7	-9.8	-9.9	-9.9	-6.8	-9.5	-9.8

Abbreviations: AKT1, AKT serine/threonine kinase 1/RAC-alpha serine/threonine-protein kinase; EGFR, epidermal growth factor receptor; IL6, interleukin-6; JUN, jun proto-oncogene; MAPK1, mitogen-activated protein kinase 1; MAPK3, mitogen-activated protein kinase 3; SRC, src proto-oncogene, non-receptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; TP53, tumor protein p53.

In conclusion, this will help to develop more effective Ciwujia-containing health food products with targeted health-care functions in the future to meet the growing market demand for improving the function of the immune system.

AUTHOR CONTRIBUTIONS

Meiyue Li: Data curation; formal analysis; investigation; methodology; validation; visualization. **Pei Ma:** Conceptualization; funding acquisition; methodology; visualization; writing—review and editing. **Xue Li:** Data curation; investigation; validation; visualization. **Lijia Xu:** Conceptualization; project administration; resources; supervision. **Lifeng Yue:** Conceptualization; supervision; writing—review and editing.

ACKNOWLEDGMENTS

This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS 2021-I2M-1-031), the Key Project at Central Government Level: the ability establishment of sustainable use for valuable Chinese medicine resources (2060302), and the National Natural Science Foundation of China (82174046).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENTS

The data underpinning this network pharmacology analysis are derived from previously reported studies and databases, all of which have been duly cited. Upon reasonable request, the data that support the findings of this study can be acquired from the corresponding author.

ETHICS STATEMENT

Since the data employed for bioinformatics analysis were obtained from publicly accessible databases, and our research did not involve the use of human or animal samples, nor any experiments related to biosafety, no ethical approval was required. Moreover, all the data sourced from these public databases have been previously published and can be openly cited.

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How to cite this article: Li M, Ma P, Li X, Xu L, Yue L. Utilizing data mining and network pharmacology to analyze the formulation rule and function of enhancing immunity of *Acanthopanax Radix* et *Rhizoma*-containing health products. *Adv Chin Med.* 2025;2(1):30-44. <https://doi.org/10.1002/acm4.31>