J Chin Med 34(1): 77-94, 2023
DOI: 10.6940/JCM.202306_34(1).05

Original Article

Identifying the Network Pharmacology of Panax Ginseng in Digestive Diseases: Implications from the National Health Insurance Research Database

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Background: *Panax ginseng* C.A.Mey. (PG) is a widely used natural product in many diseases. However, the status of PG use based on clinical experience remains unclear. This study aims to explore the characteristics of the PG users and how PG was prescribed in Taiwan, and the results are applied for further network pharmacology analysis. **Methods:** Patients who used PG were identified using Taiwan's National Health Insurance Research Database. Descriptive statistics were used to evaluate the presenting features of PG users, and the reasons of PG use compared to other CHM users. By querying online biomedical databases, network pharmacology was used to assess the possible molecular pathways acted upon by PG in digestive diseases. **Results:** PG usage rose most in patients with immune or neoplasm-related disorders history. Digestive diseases accounted the most common reasons for PG use. PG plays an important role in peptic ulcer disease through lipid metabolism and inflammatory bowel disease via immune regulation. **Conclusion:** This study offers a general overview of the status of PG use in Taiwan, and a description of how PG acts on key diseases, which should be useful for PG researchers and clinical physicians.

Key words: Bioinfomatics; the National Health Insurance Research Database; Network pharmacology; *Panax ginseng* C.A.Mey.; Traditional Chinese medicine

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Received 7th December 2022, accepted 28th March 2023

Introduction

Panax ginseng C.A.Mey. (PG) is a widely used natural product in 35 countries worldwide, mainly Asia [1]. The use of PG remains an essential issue from pharmacology research to clinical practice [2]. For a long time, PG has been used as a traditional medicine for its curative and restorative properties. As more and more researchers recognized PG's pharmaceutical and clinical potential, the number of publications has increased dramatically in the past decades [2]. Recent studies have shown promising results in the areas of immunomodulatory [3], anti-cancer [4], anti-aging [5,6], anti-hyperglycemic [7], and gut microbiota-mediated [8] effects. Most research on PG has focused on pharmacology, plant science, and complementary integrative medicine [2]. Some meta-analyses and systematic reviews have focused solely on PG's clinical effects [9-11]. Rather than being used alone, it has been shown that, in clinical practice, PG is commonly used with other Chinese herbal medicine (CHM) [12-15]. However, the prescription pattern and the pattern of PG usage have received relatively little attention. Due to PG's therapeutic potential, information about its usage (e.g., characteristics of PG users, prescription pattern) is necessary but currently quite limited. One study which analyzed trends in PG research in 2010 reported that most of the publications about PG were bench studies [16]. The lack of real-world data on PG's clinical use pattern makes it difficult to assess its medical importance, which is crucial for clinicians, researchers, and PG trading companies.

Network pharmacology effectively reveals the regulation principles between diseases and specific molecules, and is particularly suitable for natural products due to the complexity of the compounds involved. Several network pharmacology studies on PG were conducted [17-19], focusing on the role of PG in lung cancer [19], hypoxia [17] and immunoregulation mechanisms [18]. However, the target diseases in these studies were not determined by real-world prescription frequency. There was no analysis of the relationship between PG usage and disease, which is important for drug development.

This study aims to evaluate the use pattern of PG by using a nationwide real-world clinical database. Evaluating PG utilization-including the user's characteristics, the user's chief complaints, the user's underlying disease, and the prescription pattern of herbal formulas (HF) containing PG can provide a more comprehensive viewpoint about using PG. Also, the study of PG's network pharmacology and possible molecular pathways promises to provide a clearer understanding of how PG achieves its therapeutic effects on specific diseases.

Materials and methods

1. Data source

The National Health Insurance Research Database (NHIRD), which contains medical data from National Health Insurance (NHI) records, was used as the data source for this study. Taiwan's NHI covers nearly the entire population [20], and traditional Chinese medicine (TCM) has been reimbursed under NHI since 1996 [21]. NHI covered most CHM in concentrated scientific TCM granule form prescribed by TCM doctors, including formulas containing PG. All these records were updated in the NHIRD routinely in daily practice, and therefore make the NHIRD become a great material to study the use of PG on a nationwide scale. Comprehensive information about each patient's

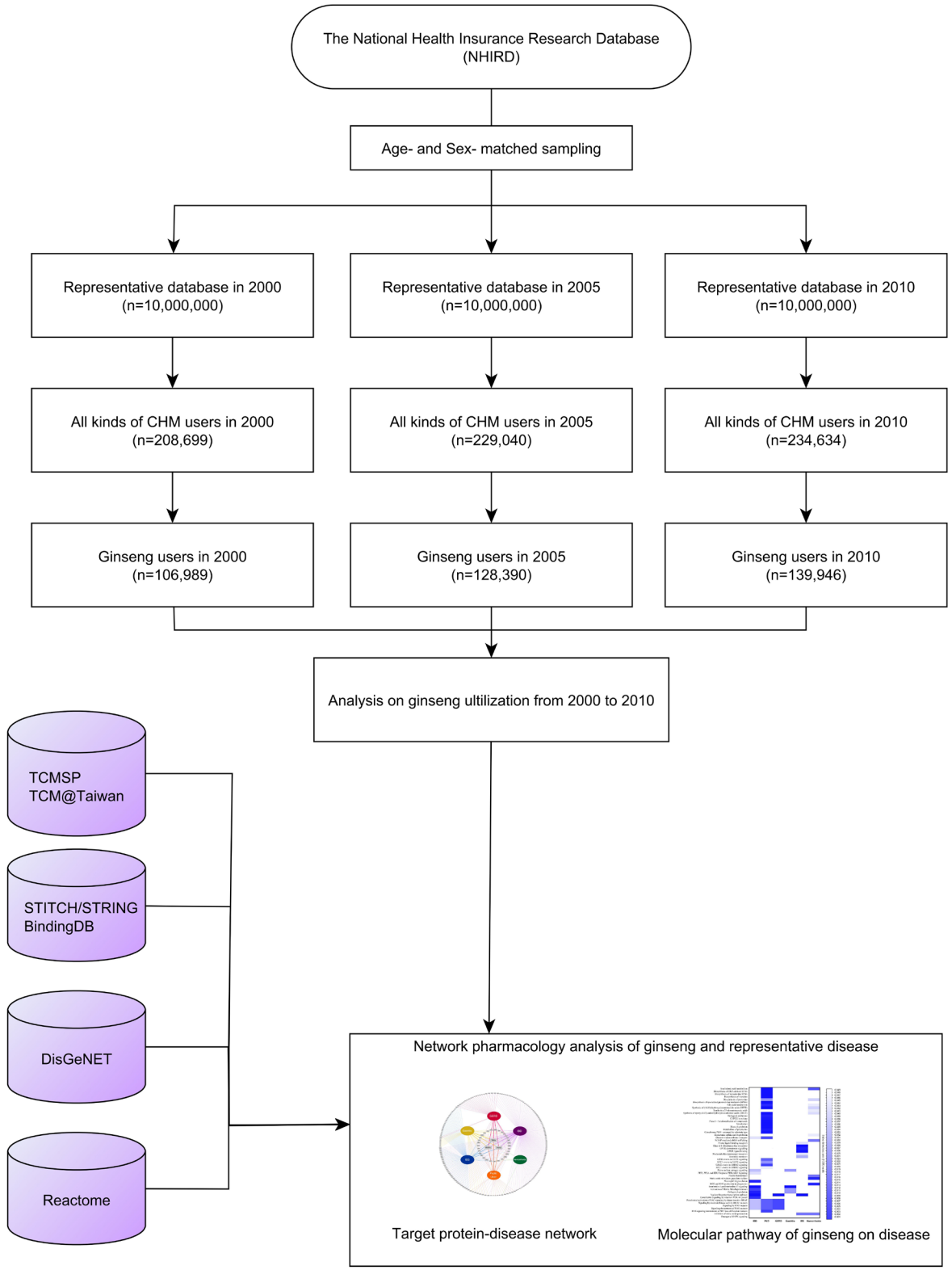

Figure 1. Flow diagram of this study.

use of TCM, demographics, gender, age, underlying conditions, living situation, medical costs, chief complaint, and level of insurance was included in the NHIRD. The database also contains almost all interventions made by licensed physicians, including Western Medicine and TCM doctors. In Taiwan, TCM administered in ambulatory clinics is reimbursed, while inpatient TCM is not. For this study, all TCM use data was extracted from one million random beneficiaries in 2000, 2005, and 2010, respectively from the original NHIRD as the basis for this analysis.

2. Study design

A flow diagram of this study is shown in Figure 1. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to identify patients' underlying medical conditions and the reason for PG use (as shown in Supplementary Table S1-2). CHM and PG prescriptions were evaluated for all eligible subjects. One or more uses of CHM qualified a patient as a CHM user. PG users were

Table 1. Characteristics of ginseng users in Taiwan, 2000-2010

	2000 (n=106,989)		2005 (n=128,390)		2010 (n=139,946)		*P*
Gender (n, %)							<0.001
Female	63,623	59.5	79,915	62.2	89,744	64.1	
Male	43,366	40.5	48,475	37.8	50,202	35.9	
Age (years, (n, %))							<0.001
-20	22,296	20.8	23,336	18.2	22,986	16.4	
21-40	40,600	38.0	45,923	32.3	49,159	35.1	
41-60	30,215	28.2	41,450	35.8	47,287	33.8	
61-	13,818	12.9	17,681	13.8	20,514	14.7	
Insured level ($NTD/month, (n, %))							<0.001
-20,000	86,354	80.7	90,012	70.1	70,184	50.2	
20,001-40,000	15,218	14.2	25,002	19.5	49,993	35.7	
40,001-	5,417	4.1	13,376	10.4	19,769	14.1	
Geolocation (n, %)							<0.001
1+2 (more urban)	62,107	58.0	76,876	59.9	86,014	61.5	
3+4	35,538	33.2	40,868	31.8	43,362	31.0	
Others (more rural)	9,344	8.7	10,646	8.3	10,570	7.6	

Table 1. Characteristics of ginseng users in Taiwan, 2000-2010 (continued)

	2000 (n=106,989)		2005 (n=128,390)		2010 (n=139,946)		*P*
Underlying conditions (n, %)							
Infectious and parasitic diseases	7,434	6.9	6,366	5.0	6,433	4.6	<0.001
Neoplasms	1,500	1.4	6,193	4.8	7,742	5.5	<0.001
Endocrine, nutritional and metabolic diseases, and immunity disorders	3,099	2.9	12,877	10.0	16,339	11.7	<0.001
Diseases of the blood and blood-forming organs	457	0.4	1,698	1.3	1,996	1.4	<0.001
Mental disorders	2,920	2.7	10,286	8.0	11,154	8.0	<0.001
Diseases of the nervous and sensory system	21,352	20.0	31,672	24.7	34,971	25.0	<0.001
Diseases of the circulatory system	5,580	5.2	16,732	13.0	20,525	14.7	<0.001
Diseases of the respiratory system	51,160	47.8	59,010	46.0	66,365	47.4	<0.001
Diseases of the digestive system	20,133	18.8	55,352	43.1	61,836	44.2	<0.001
Diseases of the genitourinary system	14,774	13.8	22,969	17.9	24,107	17.2	<0.001
Complications of pregnancy, childbirth, and the puerperium	1,130	1.1	1,372	1.1	1,495	1.1	0.947
Diseases of the skin and subcutaneous tissue	15,919	14.9	26,617	20.7	29,535	21.1	<0.001
Diseases of the musculoskeletal system and connective tissue	12,393	11.6	25,564	19.9	27,598	19.7	<0.001
Congenital anomalies	32	0	641	0.5	780	0.6	<0.001
Certain conditions originating in the perinatal period	75	0.1	404	0.3	475	0.3	<0.001
Symptoms, signs, and ill-defined conditions	9,063	8.5	32,763	25.5	40,148	28.7	<0.001
Injury and poisoning	7,691	7.2	21,226	16.5	23,527	16.8	<0.001

1) Abbreviations: NTD, new Taiwan dollar

2) The P-value is calculated from Chi-square test.

Table 2. The common reasons to use ginseng and other CHM.

	Ginseng users (n=378,171)	Other CHM users (n=294,202)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
Infectious and parasitic diseases	268 (0.1%)	364 (0.1%)	<0.001	0.86 (0.81, 0.90)	<0.001	0.95 (0.88, 1.01)	0.106
Neoplasms	2,061 (0.5%)	834 (0.3%)	<0.001	1.10 (1.09, 1.12)	<0.001	1.03 (1.01, 1.04)	0.004
Endocrine, nutritional, and metabolic diseases, and immunity disorders	8,134 (2.2%)	4,081 (1.4%)	<0.001	1.09 (1.08, 1.10)	<0.001	1.02 (1.00, 1.03)	0.004
Diseases of the blood and blood-forming organs	2,506 (0.7%)	516 (0.2%)	<0.001	1.48 (1.42, 1.54)	<0.001	1.02 (0.98, 1.05)	0.324
Mental disorders	5,144 (1.4%)	1,630 (0.6%)	<0.001	1.27 (1.24, 1.29)	<0.001	1.04 (1.02, 1.06)	<0.001
Diseases of the nervous and sensory system	17,076 (4.5%)	7,928 (2.7%)	<0.001	1.17 (1.15, 1.18)	<0.001	1.04 (1.03, 1.05)	<0.001
Diseases of the circulatory system	11,021 (2.9%)	4,628 (1.6%)	<0.001	1.14 (1.13, 1.15)	<0.001	1.02 (1.01, 1.03)	<0.001
Diseases of the respiratory system	80,372 (21.3%)	78,253 (26.6%)	<0.001	0.95 (0.95, 0.95)	<0.001	0.98 (0.97, 0.98)	<0.001
Diseases of the digestive system	81,769 (21.6%)	33,254 (11.3%)	<0.001	1.20 (1.19, 1.20)	<0.001	1.03 (1.03, 1.04)	<0.001
Diseases of the genitourinary system	43,742 (11.6%)	21,626 (7.4%)	<0.001	1.13 (1.12, 1.14)	<0.001	1.04 (1.03, 1.04)	<0.001
Complications of pregnancy, childbirth, and the puerperium	1,501 (0.4%)	416 (0.1%)	<0.001	1.40 (1.33, 1.48)	<0.001	1.02 (0.97, 1.07)	0.402
Diseases of the skin and subcutaneous tissue	14,186 (3.8%)	20,354 (6.9%)	<0.001	0.88 (0.88, 0.89)	<0.001	0.98 (0.97, 0.98)	<0.001
Diseases of the musculoskeletal system and connective tissue	51,573 (13.6%)	38,011 (12.9%)	<0.001	1.07 (1.07, 1.08)	<0.001	1.08 (1.08, 1.09)	<0.001
Congenital anomalies	652 (0.2%)	286 (0.1%)	<0.001	1.16 (1.11, 1.21)	<0.001	1.03 (0.98, 1.09)	0.205
Certain conditions originating in the perinatal period	33 (0.0%)	20 (0.0%)	0.38	1.49 (1.02, 2.18)	0.039	1.5e+06 (0.00, .)	0.972
Symptoms, signs, and ill-defined conditions	127,262 (33.7%)	61,439 (20.9%)	<0.001	1.22 (1.22, 1.23)	<0.001	1.09 (1.09, 1.10)	<0.001
Injury and poisoning	24,922 (6.6%)	37,321 (12.7%)	<0.001	0.74 (0.73, 0.75)	<0.001	1.05 (1.04, 1.07)	<0.001

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio

OR and aOR were estimated by comparing the characteristics of ginseng users to other CHM users.

defined as anyone who used either an HF containing PG or the single herb (SH) PG at least once. All diagnosis coded in medical records in the previous year before PG use is regarded as underlying disease, and the main diagnosis when using PG is regarded as the main reason for medical treatment. The protocol for this study was approved by the institutional review board of the Chang Gung Memorial Foundation. (IRB number：202001922B1)

3. PG prescription database

CHM is generally prescribed as either SH or HF; both are present in the CHM prescription database. SH is an extract of an individual herb or other natural ingredients. HF is a combination of more than one SH in fixed proportions according to TCM pharmacopeia. Both are concentrated into powder in pharmaceutical facilities prior to distribution. Dosage, measured in grams, was the sum of PG dosage in SH and PG-containing HF during a given year. The definition of PG-containing HF was based on TCM preparation license approved by Food and Drug Administration, Ministry of Health and Welfare in Taiwan. PG dosage in HF was calculated by adding together the total weight of PG, according to the proportion of PG in each HF.

4. Statistical analysis

Descriptive statistics were used to identify the common features of PG users. Mean with standard deviation was used to present continuous variables, while counts and proportion in percentage were used to present categorical data. The commercial statistical software STATA (Release 16. College Station, TX) was used to perform the descriptive statistical analysis, which was used for presenting baseline features of PG users, such as age, gender, insured level, geolocation, and co-morbidities, underlying disease, as well as the reasons for PG use. We used logistic regression analysis to differentiate the most common reasons between those who did and did not use PG in CHM users, and adjusted odds ratios (aORs) to estimate the OR under consideration of all accessible covariates, including age, gender, socio-economic status, and co-morbidities. To save the computation time and make the comprehensive summary of PG use, we combined three cohorts before examining the aORs. Whoever being recognized as the PG user in any cohort would be marked as the PG user in the combined dataset. Additionally, the diagnosis code one year before PG use in these three cohorts would be combined and recognized as the underlying diseases when using PG. The freeware KNIME (version 3.4) was used to deal with the databases. Statistics with a p-value ≤ 0.05 represented significant results.

5. Pharmacology network analysis

The detailed data processing of pharmacology network analysis was demonstrated in our previously published article [22,23]. Briefly, the potential active components of PG were obtained via querying the online databases: TCM database@Taiwan and The traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) [24,25]. Furthermore, the target proteins of PG components were acquired from the following two biomedical databases: the Search Tool for Interacting Chemicals (STITCH) [26] and the BindingDB [27] via an application programming interface (API) to keep up with the latest information on the relationship between components and target proteins (last assessed date: 2021/12/31). Moreover, DisGeNET was used to identify the potential connections between PG acting proteins and representative diseases analyzed from NHIRD [28]. The freeware Cytoscape (version

3.8) was used to illustrate and analyze the network of component-target proteins and diseases. Finally, the Reactome molecular database was utilized to perform overrepresentation tests and identify potential molecular pathways acted upon by PG in these diseases [29].

Results

1. Characteristics of PG users

In 2010, 139,946 patients were PG users, out of 1,000,000 randomly sampled patients, accounting for 14% of the patient population, while there were 106,989 (10.7%) in 2000 and 128,390 (12.8%) in 2005. All of these users were included in the characteristic analysis. Table 1 summarized the characteristics of PG users, which were more frequently female, adult (21-40 years), and had lower insured levels (0-20,000, $NTD/month) and lived in more urban area. There was a prominent increase of PG utilization rate of female (from 59.5% to 64.1%, $P < 0.001$) and urban patients (from 58.1% to 61.5%, $P < 0.001$) across the 10 years. People with higher insured levels (20,001-, $NTD/month) or older than 41 accounted for relatively smaller percentage in PG users, but had a larger utilization rate increase, which is 31.5% (from 18.3% to 49.8%, $P < 0.001$) and 7.4% (from 41.1% to 48.5%, $P < 0.001$) respectively.

Trends of medical conditions of PG users were also analyzed. Most of the underlying conditions showed an increasing trend from 2000 to 2010, particularly "diseases of the digestive system" (Table 1). Compared with other underlying conditions, the only disease that showed a decreasing trend from 2000 to 2010 was "infectious and parasitic diseases." The only disease without a statistically significant difference was "complications of pregnancy, childbirth, and the puerperium". Interestingly, compared to 2000, the data showed a dramatic increase in the PG utilization rate of patients who had the underlying disease of "endocrine, nutritional and metabolic diseases, and immunity disorders" and "neoplasm," which is 4.03 times (from 2.9% to 11.7%, $P < 0.001$) and 3.92 times (from 1.4% to 5.5%, $P < 0.001$) in 2010, respectively.

Table 2 sums up the common reasons to use PG and other non-PG CHM in 10 years. Except for the unspecific diagnosis (Symptoms, signs, and ill-defined conditions), we reported that diseases of the respiratory system (80,372, 21.3%) and the digestive system (81,769, 21.6%) accounted for the highest proportion. Patients whose main diagnosis is diseases of the digestive system had a higher aOR (1.03) of using PG, indicating the critical role of PG in digestive disorders.

2. Prescription trends of CHM containing PG

Different CHM contained PG were used in Taiwan, and each year's ranking of prescription frequency was demonstrated in Table 3. All CHM mentioned in the table were HF, suggested a prescription preference for HF over SH when using PG in Taiwan. All of them, except Xiao-Chai-Hu-Tang can be divided into five major indication categories (Table 3). Overviewing the change of 10 most commonly used CHM containing PG from 2000 to 2010, CHM for the digestive system had always remained the most important position, and Ban-Xia-Xie-Xin-Tang was constantly the dominant CHM in the category. The ranking of CHM for the musculoskeletal system and respiratory system gradually declined over the years, but Du-Huo-Ji-Sheng-Tang was still a widely used choice. Another noteworthy difference was the growing importance of PG use in the cardiovascular system and

Table 3. The top 10 most commonly used CHM containing ginseng and five major indication categories, statistics presented as the percentage of all ginseng users per year.

Rank	2000		2005		2010	
1	Du-Huo-Ji-Sheng-Tang	15.3%	Ban-Xia-Xie-Xin-Tang	13.4%	Ban-Xia-Xie-Xin-Tang	15.2%
2	Xiao-Chai-Hu-Tang	13.1%	Xiao-Chai-Hu-Tang	13.3%	Xiao-Chai-Hu-Tang	14.5%
3	Ban-Xia-Xie-Xin-Tang	12.4%	Xiang-Sha-Liu-Jun-Zi-Tang	12%	Xiang-Sha-Liu-Jun-Zi-Tang	11.9%
4	Mai-Men-Dong-Tang	11.4%	Du-Huo-Ji-Sheng-Tang	11.6%	Du-Huo-Ji-Sheng-Tang	10.9%
5	Xiang-Sha-Liu-Jun-Zi-Tang	10.4%	Mai-Men-Dong-Tang	10.7%	Bu-Zhong-Yi-Qi-Tang	10.1%
6	Bu-Zhong-Yi-Qi-Tang	9.7%	Bu-Zhong-Yi-Qi-Tang	10.1%	Tian-Wang-Bu-Xin-Dan	9.2%
7	Dang-Gui-Nian-Tong-Tang	7.3%	Tian-Wang-Bu-Xin-Dan	8.9%	Mai-Men-Dong-Tang	9.2%
8	Qing-Zao-Jiu-Fei-Tang	6.1%	Gui-Pi-Tang	7.4%	Zhi-Gan-Cao-Tang	7.9%
9	Shen-Ling-Bai-Zhu-San	5.9%	Zhi-Gan-Cao-Tang	7.1%	Sheng-Mai-San	7.7%
10	Gui-Pi-Tang	5.9%	Dang-Gui-Nian-Tong-Tang	6.4%	Chai-Hu-Jia-Long-Gu-Mu-Li-Tang	7.6%

Indication categories	Chinese Herbal Medicine
Digestive system	Ban-Xia-Xie-Xin-Tang Xiang-Sha-Liu-Jun-Zi-Tang Bu-Zhong-Yi-Qi-Tang Shen-Ling-Bai-Zhu-San
Respiratory system	Mai-Men-Dong-Tang Qing-Zao-Jiu-Fei-Tang
Musculoskeletal system	Du-Huo-Ji-Sheng-Tang Dang-Gui-Nian-Tong-Tang
Cardiovascular system	Zhi-Gan-Cao-Tang Sheng-Mai-San
Sleep disorder	Gui-Pi-Tang Tian-Wang-Bu-Xin-Dan Chai-Hu-Jia-Long-Gu-Mu-Li-Tang

sleep disorder.

3. Network pharmacology analysis of PG in digestive diseases

Figure 2 depicts the network pharmacology between six representative digestive diseases and proteins regulated by PG. 248 proteins were noted and several proteins showed relatively higher importance than others. VEGFA, TNFA, and PGH2 are linked to all digestive diseases except hemorrhoids. RASK, EGFR, CP3A4, NOD2, and TLR2 are linked to four kinds of digestive diseases. Inflammatory bowel disease (IBD) was relevant to the most proteins (183 proteins) in the network, while hemorrhoids had the fewest connections (4 proteins).

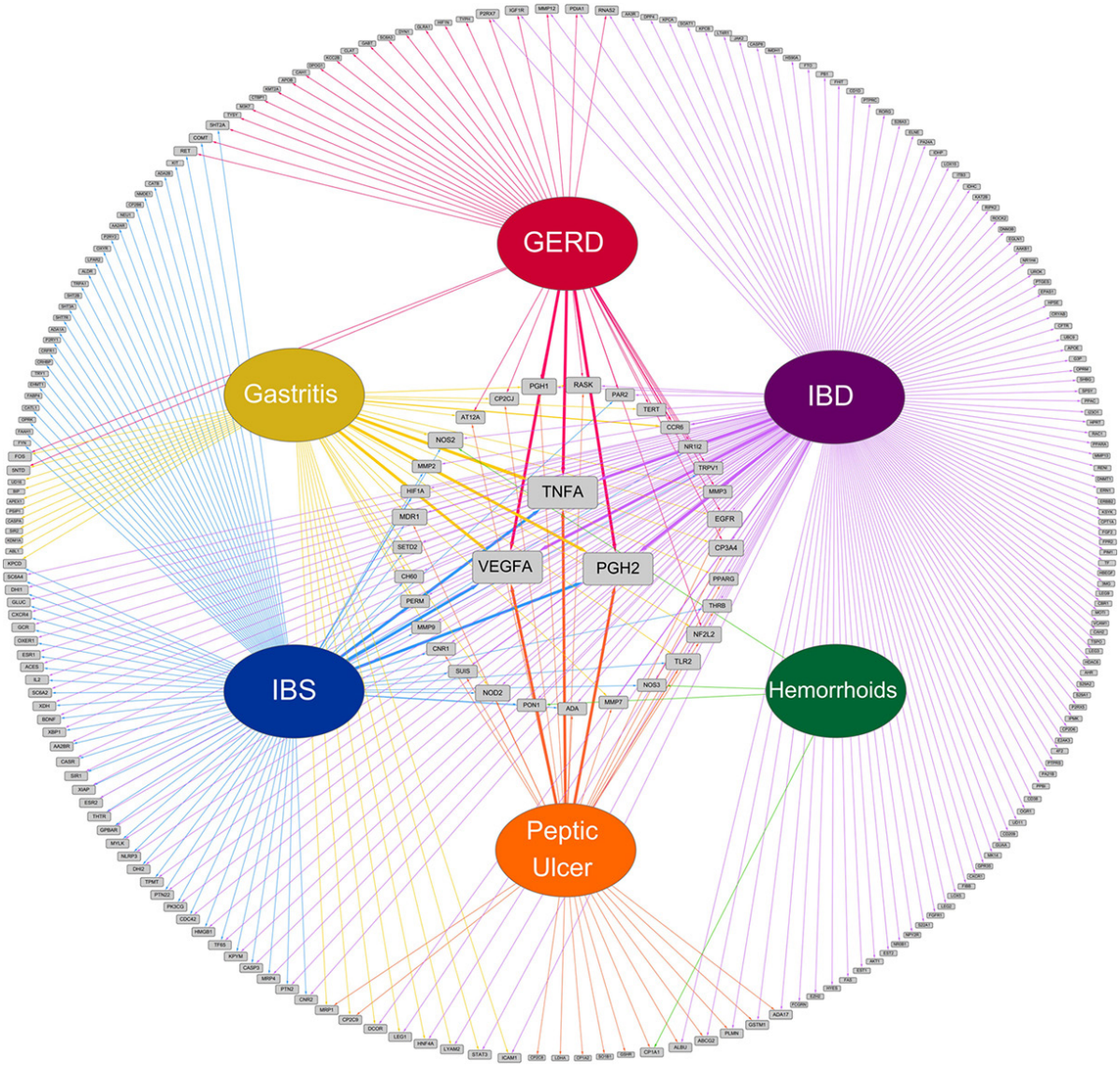

Figure 2. Target-disease interaction network of ginseng in digestive diseases. Nodes with a higher degree of centrality, depicted as bigger ones, represented a more total number of connections linking to them, and may have higher importance among all proteins.

Figure 3 summarizes possible molecular pathways regulated by PG in digestive disease mechanisms. Overall, PG was involved in a total of 49 molecular pathways in six representative digestive diseases. Among all the diseases, PG participated in the most pathways in peptic ulcer disease (PUD) and IBD (27 and 13 pathways respectively). Also, pathways that had a strong correlation with PG (bluer ones) mostly belong to PUD and IBD. The most important category of pathway was “Metabolism of lipids”, which was highly connected to PUD. Mechanisms associated with the immune system had a stronger connection with IBD.

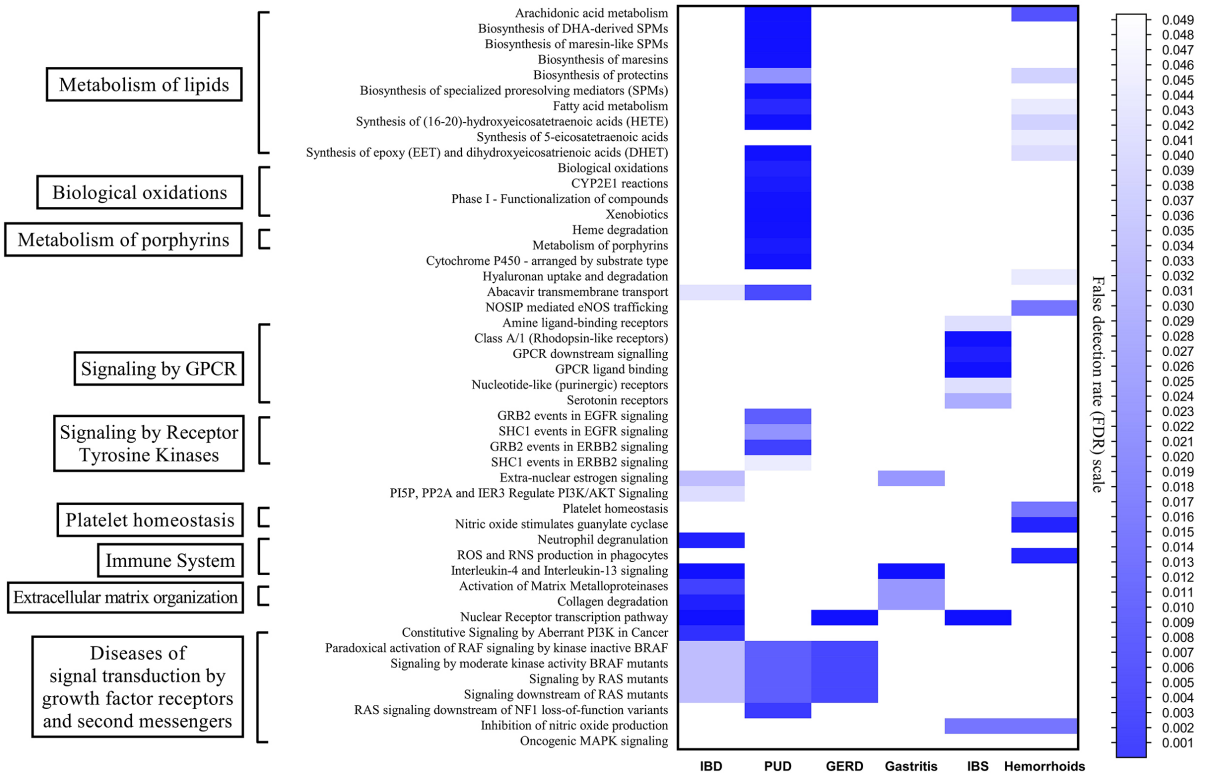

Figure 3. The molecular pathways covered by ginseng in digestive diseases.

Discussion

Although there have been few papers about the commonalities and medical conditions of PG users, our data showed that PG users shared similar characteristics with CHM users in general, which had been demonstrated in previous articles [21,30,31]. According to Table 2, patients who were female and young adults (21-40 years) visited CHM clinics more. Chen FP et al. and Yeh YH et al. both found that females tended to use CHM more than males did [21,30]. Research in Germany found that younger people had a more positive attitude towards complementary and alternative medicine [31]. The population of people older than 41 had a larger increase in PG user’s number throughout the years. The PG

users after middle age may benefit from PG's anti-aging effects and it may make physicians more willing to prescribe PG-containing formulas. People with higher insured levels also had a larger increasing rate. Though more than 99% of residents in Taiwan can afford TCM treatment under NHI, it is usually seen as an adjuvant therapy to western medicine and is usually considered to have a longer course of treatment, which makes it more accessible for patients with more financial means. The wellness-promoting effects of PG and CHM also appeal more to this group.

Among the common reasons to use PG and other CHM, diseases of the respiratory system and the digestive system were the top two (Table 2). Patients with diseases of the digestive system used PG much more than other CHM (OR=1.20), indicating the importance of PG in digestive diseases. A systematic review of PG concluded that it showed promising results for improving chronic respiratory conditions [32]. Other research showed possible benefits of PG for the digestive system as well. In the animal model, Sun Y et al. reported that PG extracts improve the gut metabolism and microbiota [33], and Li S et al. reported PG polysaccharides could improve antibiotic-associated diarrhea [34]. Also, saponins regulate intestinal inflammation in colon cancer and IBD [35]. Other than PG's pharmaceutical and clinical effects mentioned above, PG users' disease distribution possibly correlates to that of CHM users as well, since PG is one of the most popular herbs in CHM. The most common reasons for TCM visits were diseases of the respiratory system, and diseases of the digestive system ranked fifth [21]. In another study of children, diseases of the respiratory system ranked first, and digestive diseases ranked third [36].

CHM related to the digestive system accounted for the most crucial role in all three years (Table 3), which may be associated with the pharmacology effects on the digestive system, as mentioned above. Ban-Xia-Xie-Xin-Tang was always the most used one in the category. In a previous study, the mechanisms of Ban-Xia-Xie-Xin-Tang was found positively correlated to three representative digestive diseases: colitis, diabetes mellitus, and gastric cancer. PG was measured as the second-most relevant herb between colitis genes and herb targets in Ban-Xia-Xie-Xin-Tang, and therefore proved its dominant role in the clinical effects of Ban-Xia-Xie-Xin-Tang [37].

Since CHM for the digestive system accounted for the highest proportion among all prescriptions containing PG, it is likely that PG is involved in digestive disease-related regulation mechanisms. Six representative digestive diseases were chosen and network pharmacology analysis was done to investigate how PG acts on digestive diseases (Figure 2, Figure 3). Of all proteins identified in Figure 2, VEGFA, TNFA, and PGH2 showed the most significant correlation with illness, linked to all digestive diseases except hemorrhoids. Several studies posit that ginsenosides may offer protection against drug-induced gastrointestinal injury by increasing VEGFA expression [38,39] and therefore enhancing wound healing and angiogenesis [40]. Research in animal models has suggested that ginsenoside’s anti-ulcer effects may be accomplished by reducing TNFA and increasing PGE2 (which can be converted from PGH2) [39,41,42]. It may also be associated with the proliferative and antiapoptotic effects of PGE2 on epithelial cells in gastrointestinal injury [43].

Figure 3 offers a broader explanation of the interaction between digestive diseases and PG, from proteins to molecular pathways. The most important

category of pathway was “Metabolism of lipids”, which was highly connected to PUD. Metabolites of lipids have long been proven to have a vital role in protection and anti-inflammation of gastrointestinal tract [44,45]. In addition, specialized pro-resolving mediators (SPMs) derived from omega-3 essential fatty acids, including resolvins, protectins, and maresins, serve as important regulators of inflammation regulation [46]. Another study reported that ginsenosides are effective in mitigating aspirin-induced gastric mucosal injury by modulating gastric arachidonic acid metabolism [42]. Figure 3 shows that the synthesis of all the lipids mentioned above can be regulated by PG. Apart from lipid metabolites, mechanisms associated with the immune system also had a strong correlation with PG, and had higher relation with IBD. Previous studies found that ginsenosides improved IBD by regulating inflammatory signaling pathways, and also engaging in innate immune response [18,47,48].

Our study had several limitations. First, this study did not include TCM therapies that were not covered by NHI, such as herbal decoctions or CHM purchased directly from TCM herbal pharmacies. In these situations, patients need to pay entirely out-of-pocket. Thus, the use of PG might have been underestimated in this study. However, CHM is highly subsidized by NHI, which reduces the incentive for out-of-pocket payments. Second, NHIRD did not provide the full complement of lab data so we were unable to confirm each patient’s health status and disease progression in detail. Nevertheless, because physicians are asked to use a primary diagnosis code to identify the main purpose of outpatient visits using ICD-9-CM, this information provided a useful level of precision for our study. Third, only three datasets of one million random beneficiaries were applied in this study. However, since PG is a well-known drug that has been widely used for decades, analyzing the past trends is sufficient to represent clinical usage of PG, and can be helpful for developing instructions of PG use in the future.

4. Conclusion

This is the first study to demonstrate the characteristics and trends of PG usage and provide novel insight relative to the existing literature. In this nationwide population-based study, we found that higher economic status and more advanced age were correlated with greater utilization rate increase, compared with other variables examined. Patients using PG often had immunity or neoplasm-related history. People who were prescribed PG often sought help for digestive diseases. PG played an important role in digestive diseases, whether in protein-disease network pharmacology or molecular pathway analysis. This study provides a more comprehensive viewpoint about PG usage and a clearer understanding of how PG achieves its therapeutic effects on specific diseases.

Acknowledgements

This study was partially supported by the Chang Gung Memorial Foundation (grant No.: [CMRPG3J0173], and [CMRPG1J0023]), and the Ministry of Science and Technology in Taiwan (grant No.: [104-2320-B-182A-013] and [108-2320-B-182A-009-MY3]).

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Table S1. Underlying conditions and ICD-9-CM

Underlying conditions (n, %)	ICD-9-CM range
infectious and parasitic diseases	(001–139)
neoplasms	(140–239)
endocrine, nutritional and metabolic diseases, and immunity disorders	(240–279)
diseases of the blood and blood-forming organs	(280–289)
mental disorders	(290–319)
diseases of the nervous and sensory system	(320–389)
diseases of the circulatory system	(390–459)

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DOI: 10.6940/JCM.202306_34(1).05

Table S1. Underlying conditions and ICD-9-CM (continued)

Underlying conditions (n, %)	ICD-9-CM range
diseases of the respiratory system	(460–519)
diseases of the digestive system	(520–579)
diseases of the genitourinary system	(580–629)
complications of pregnancy, childbirth, and the puerperium	(630–676)
diseases of the skin and subcutaneous tissue	(680–709)
diseases of the musculoskeletal system and connective tissue	(710–739)
congenital anomalies	(740-759)
certain conditions originating in the perinatal period	(760–779)
symptoms, signs, and ill-defined conditions	(800–999)
injury and poisoning	(800–999)

1)Abbreviations: NTD, new Taiwan dollar

Table S2. Common reasons and ICD-9-CM

Common reason	ICD-9-CM
Gastritis	(535.5)
Back Problem	(724.5)
COPD	(491.22)
Constipation	(564.00)
Diarrhea	(787.91)
Anal/rectal diseases	(569.49)
Allergic Rhinitis	(477.9)
Asthma	(493.00 – 493.99)
Menstrual disorder	(626.8)
Cough	(786.2)
Dysrhythmia	(427.9)
Headache	(784.0)
Sprain	(848.9)

1)Abbreviations: COPD, chronic obstructive pulmonary disease

J Chin Med 34(1): 77-94, 2023
DOI: 10.6940/JCM.202306_34(1).05

原始論文

人參在消化系統疾病的網絡藥理學：健保資料庫的應用

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研究背景與動機：人參被廣為使用在各種疾病上，然而，目前尚未有研究針對人參在臨床上的使用狀況進行探討，本研究試圖探索在台灣人參使用者的特徵及人參的臨床使用情形，並將此結果進一步應用於網絡藥理學分析。**材料與方法：**從 2000,2005,2010 三個年度的健保資料庫百萬人承保抽樣歸人檔中，選取曾使用人參的患者，分析人參使用族群的特徵，以及使用人參的主要理由，並利用線上生物醫學資料庫進行網絡藥理學分析，評估人參在代表性疾病上的作用機制。**結果：**人參的使用量在有免疫或腫瘤病史的患者上升最多，消化系統疾病則是醫師開立含人參處方的主要原因，人參可能透過脂質代謝改善胃潰瘍、透過免疫調節改善發炎性腸道疾病。**結論：**由此研究可得知人參在台灣患者的臨床使用情形，以及人參如何作用在關鍵疾病上，可作為人參研究者及臨床醫師的重要資訊。

關鍵字：生物資訊、健保資料庫、網絡藥理學、人參、中醫藥

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111 年 12 月 7 日受理，112 年 3 月 28 日接受刊載