



Research paper

Chinese herbal products for nasopharyngeal carcinoma: A population-based registry study

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ARTICLE INFO

Keywords:

Nasopharyngeal carcinoma
Traditional Chinese medicine
Chinese herbal products
Complementary and alternative medicine
Gan-Lu-Yin
Registry database

ABSTRACT

Introduction: The use of traditional Chinese medicine (TCM) as a complementary and alternative medicine for the treatment of nasopharyngeal carcinoma (NPC) and its treatment-related side effects has been increasing. We investigated the utilization of Chinese herbal products (CHPs) for NPC in Taiwan.

Methods: This retrospective, nationwide, population-based study was conducted and obtained data from the Registry for Catastrophic Illnesses Patient Database from 2001 through 2011 in Taiwan. The top ten most frequently prescribed formulae and single CHPs for treating NPC were assessed. Demographic characteristics, including sex and age at diagnosis of NPC, were examined, together with existing comorbidities. Descriptive statistics and multiple logistic regression analysis were employed to estimate the adjusted odds ratios (aORs) for CHP utilization.

Results: In total, 17,816 patients aged ≥ 20 years were newly diagnosed with NPC. Of these, 4749 patients used TCM outpatient services for NPC treatment. NPC patients using TCM were more likely to be women (aOR, 1.47; 95% CI, 1.37–1.58), young, and residents of central Taiwan (aOR, 1.49; 95% CI, 1.37–1.62) and southern Taiwan (aOR, 1.12; 95% CI, 1.05–1.21). The most commonly prescribed formula CHP was Gan-Lu-Yin (2.99%), followed by Xin-Yi-Qing Fei-Tang (1.52%) and Shan-Shen-Mai-Men-Dong-Tang (0.92%). The most commonly prescribed single CHP was Bai Hua She She Cao (*Hedyotis diffusa*) (3.23%), followed by Xuan Shen (*Scrophularia ningpoensis*) (2.24%) and Mai Men Dong (*Radix Ophiopogonis*) (1.84%).

Conclusions: These findings provide information regarding personalized therapies for NPC and can promote further clinical experiments and pharmacological research on CHPs for NPC treatment in Taiwan.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharynx, most commonly the posterolateral nasopharynx, pharyngeal recess, or fossa of Rosenmüller. The most common presentation is a palpable neck lump, with approximately 60% patients seeking medical attention when this occurs. Such lumps develop because of

metastatic disease in the cervical lymph nodes. In endemic regions such as China, Hong Kong, and Singapore, a Chinese adult man seen with large, bulky bilateral nodes is generally considered to have NPC or lymphoma. Although 60% patients with NPC initially present with a neck lump caused by nodal metastasis, at least 80% patients are diagnosed with positive nodes (N1, N2, or N3) [1]. Men are two to three times more likely to develop NPC than are women, and the peak age of

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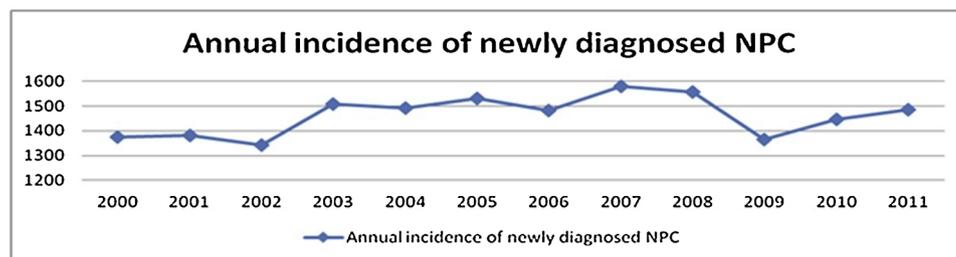
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<https://doi.org/10.1016/j.eujim.2019.100979>

Received 5 April 2019; Received in revised form 13 September 2019; Accepted 15 September 2019

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(a)



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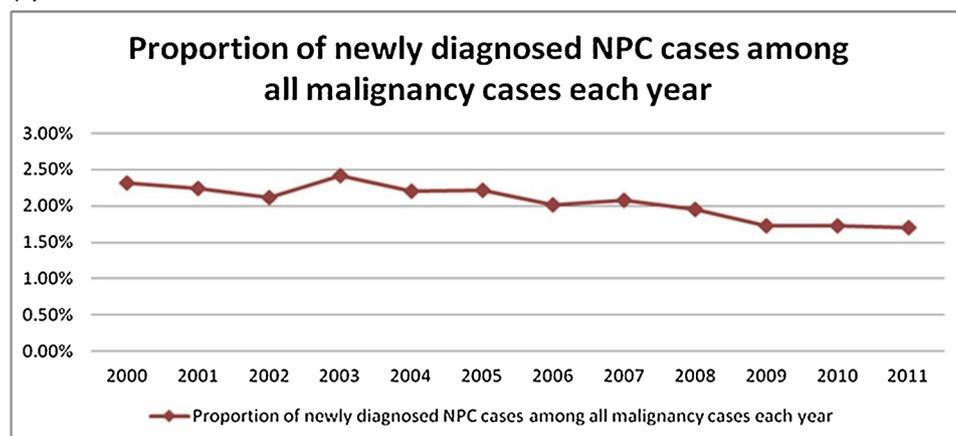


Fig. 1. Annual incidence and proportion of newly diagnosed nasopharyngeal carcinoma (NPC) from 2001 through 2011 in Taiwan. (a) The graph shows that approximately 1300–1600 individuals were diagnosed with NPC each year. (b) The graph shows that newly diagnosed cases of NPC accounted for approximately 2% of all malignancy cases each year [6].

occurrence is between 50 and 60 years [2].

The incidence of NPC is reportedly less than 1 per 100,000 for both men and women in most countries; however, it is 20–30 per 100,000 men and 15–20 per 100,000 women in Hong Kong [3]. NPC is an infection-related cancer that is strongly driven by the Epstein–Barr virus. The occurrence of this infection is strongly associated with genetics, particularly in South China, Hong Kong, and Taiwan [4,5]. From 2001 through 2011, approximately 1300–1600 individuals were newly diagnosed with NPC in Taiwan (Fig. 1a), with NPC accounting for approximately 2% of all cases of malignancies (Fig. 1b) during this period [6]. In fact, NPC is the twelfth most common cancer among men in Taiwan [7].

Interest in complementary and alternative medicine (CAM) is increasing among not only patients looking for help but also healthcare providers studying the effectiveness of various therapies and management techniques. Up to 52% cancer patients use one or more CAM treatments, and over 80% patients use CAM concurrently with chemotherapeutic agents during the initial phases of cancer treatment [8–10]. Traditional Chinese medicine (TCM) is the most common CAM in our clinical practice. Considering that different stages of NPC are characterized by various clinical features and complications before and after conventional treatments, TCM doctors typically provide treatment using different combinations of Chinese herbs.

In Taiwan, Chinese herbal products (CHPs) have been listed under the National Health Insurance (NHI) program since 1995. NHI covers 99.6% of Taiwan's residents. However, there is a lack of large-scale statistical data on the clinical usage of TCM in NPC. Therefore, we aimed to investigate the utilization of CHPs for NPC from 2001 through 2011 in Taiwan by exploring the demographic characteristics of patients and the patterns of CHP prescriptions. While demographic data can provide relevant information for clinical pharmaceutical and epidemiological studies, data regarding prescription patterns can provide information regarding the monitoring, evaluation, and modification of medical services and facilitate the establishment of reference data concerning individualized therapies for NPC. The data file we used was provided by Taiwan NHRI, which had been authorized by the Ministry

of Health and Welfare to manage the claims data of the NHI. This is the most current data available and further update databases by NHRI are not yet available.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program of Taiwan is a universal insurance program established in 1995, reforming from 13 insurance-related systems and providing coverage for 99.9% Taiwanese citizens by the end of 2014. The NHI Research Database (NHIRD) has been managed, maintained, and released by the National Health Research Institute (NHRI) in Taiwan. In this population-based study, we obtained data from the Registry for Catastrophic Illnesses Patient Database (RCIPD), which is a part of NHIRD. RCIPD contains claims data from insurers diagnosed with one of 30 categories of major diseases (cancer, chronic mental illness, end-stage renal disease, several autoimmune diseases, etc.) who require long-term care and are exempted from co-payment. Registered data include demographic data, the date of visit or hospitalization, drug prescriptions, and diagnoses coded in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). For the protection of insurer privacy, all potentially identifying information was encrypted. The study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115).

2.2. Study population

We identified 30294 patients with newly diagnosed NPC (ICD-9-CM 147) from RCIPD. Patients with missing information on age or sex ($n = 14$), those diagnosed with NPC before the end of 1999 ($n = 12302$), and those aged < 20 years ($n = 162$) were excluded. Eventually, 17816 patients were included in the study and further divided into TCM users ($n = 9577$, including CHPs, acupuncture and Chinese traumatology users) and TCM nonusers ($n = 8239$; Fig. 2). The

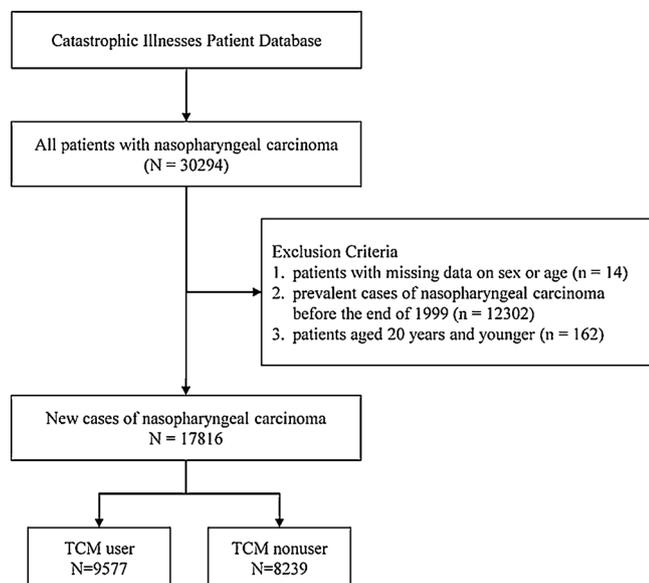


Fig. 2. Flowchart shows the process of subject recruitment from the Catastrophic Illnesses Patient Database in Taiwan. All patients newly diagnosed with nasopharyngeal carcinoma from 2001 through 2011 were identified and screened.

TCM, traditional Chinese medicine.

former were defined as individuals who used TCM outpatient services at least once during the study period, while the latter were defined as individuals who never visited TCM clinics after the first NPC diagnosis.

Evaluated demographic factors included sex, age (20–29, 30–39, 40–49, 50–59, and ≥ 60 years), occupational status [white collar (performing professional, managerial, or administrative work), blue collar (requiring manual labor), and others], and residential areas area (northern Taiwan, central Taiwan, southern Taiwan, and eastern Taiwan and offshore islands).

2.3. Statistical analysis

Descriptive statistics for the TCM users and TCM nonusers are presented as means and standard deviations (SD) for continuous variables and numbers and percentages for categorical variables. Differences in the distribution of these statistics between the two groups were assessed using Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. Multiple logistic regression analysis was performed to determine the correlation between demographic data (sex, age, occupational status, and residential area) and TCM use. The logistic regression model produced odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Adjusted ORs (aORs) were used to predict patients with higher odds of using TCM. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). All P-values were derived from two-sided tests, with the significance level set at 0.05.

3. Results

The patient recruitment flowchart is presented in Fig. 2. Table 1 showed demographic characteristics and results of multiple logistic regression analysis of the NPC patients in the TCM and non-TCM users. In total, 17,816 patients aged ≥ 20 years were newly diagnosed with NPC from 2001 through 2011. Among them, 9577 (53.8%) NPC patients used TCM outpatient services at least once. Among all TCM users, 49.6% ($n = 4749$) used TCM for NPC treatment. The percentages of men and women among TCM users were 71.3% and 28.7%, respectively. The mean ages were 52.9 years and 49.0 years for the non-TCM

and TCM users, respectively. After adjusting for sex, age, occupational status, and living area, women (aOR, 1.47; 95% CI, 1.37–1.58); patients aged 20–29 (aOR, 2.33; 95% CI, 1.96–2.77), 30–39 (aOR, 2.15; 95% CI, 1.95–2.37), 40–49 (aOR, 1.80; 95% CI, 1.65–1.95), or 50–59 (aOR, 1.52; 95% CI, 1.39–1.65) years; and residents of central (aOR, 1.49; 95% CI, 1.37–1.62) and southern (aOR, 1.12; 95% CI, 1.05–1.21) Taiwan were more likely to utilize TCM services, whereas blue-collar workers (aOR, 0.88; 95% CI, 0.83–0.94) and residents of eastern Taiwan and offshore islands (aOR, 0.80; 95% CI, 0.70–0.91) were less likely to use TCM services.

The average number of CHPs in a single prescription for TCM users was 6.56 (Fig. 3), with the majority of prescriptions containing six herbs, followed by seven and five.

Gan-Lu-Yin was the most frequently prescribed formula CHP, followed by Xin-Yi-Qing-Fei-Tang, Sha-Shen-Mai-Men-Dong-Tang, Zhi-Bai-Di-Huang-Wan, and Shan-Zhong-Kui-Jain-Tang. The most commonly prescribed single herb was Bai-Hua-She-She-Cao (*Hedyotis diffusa*), followed by Xuan Shen (*Scrophularia ningpoensis*), Mai-Men-Dong (*Radix Ophiopogonis*), Dan Shen (*Salvia miltiorrhiza*), and Ban-Zhi-Lian (*Scutellariae Barbatae*) (Table 2).

The top five common combinations comprising two formula CHPs and those comprising two single CHPs are shown in Table 3, while the top five combinations comprising three formula CHPs are shown in Table 4.

4. Discussion

In this nationwide study of CHP use for NPC treatment from 2001 through 2011 in Taiwan, we observed that women with NPC were more likely to use TCM than were men, though men are more likely to develop NPC. Moreover, TCM users were younger than nonusers, probably because younger patients readily accept a variety of treatments. Patients in central Taiwan had a 1.4 fold higher adjusted OR for TCM use than did those in northern Taiwan, possibly because central Taiwan has the highest density of TCM clinics in Taiwan [11]. Therefore, TCM services are easily available for residents of central Taiwan. The allocation of TCM services could have affected the TCM-seeking behavior of patients. Our study results also showed that white-collar workers were more likely to use TCM. White-collar workers are generally richer than blue-collar workers, so they are able to afford additional treatments. Our results were in accordance with a previous study of TCM use by adult patients with cancer [12]. The demographic characteristics of NPC patients reported in this study may help public health policymakers and clinicians in making informed decisions regarding the distribution of TCM supplements in the different regions in Taiwan.

Conventional treatments for NPC include surgery, radiation therapy (RT), and chemotherapy or target therapy. Currently, RT is the mainstay of treatment for NPC because the primary tumor is not easily amenable to surgical resection in most cases [13]. Our data from NHI (shown in Fig. 4) also showed that RT was the most common treatment strategy used for patients with NPC from 2001 through 2011 in Taiwan. However, RT often causes several side effects such as mucositis, xerostomia, dysphagia, dermatitis, weight loss, and malnutrition. Among these, xerostomia is one of the most common acute and long-term side effects that is primarily induced by RT and is dependent on the cumulative radiation doses to the head and neck region [1]. In recent years, the use of TCM in combination with conventional cancer therapy has become more widespread. NPC patients receiving conventional anticancer therapies combined with TCM treatment reportedly exhibited increased survival rates, enhanced tumor responses, an improved Karnofsky performance status, lower side effect rates, and better immunostimulation [14]. Because NPC and its treatment can cause many complications, the goal of TCM is to not only try and cure the cancer but also prevent unwanted complications during conventional treatments.

We found that the most commonly prescribed formula CHP for NPC

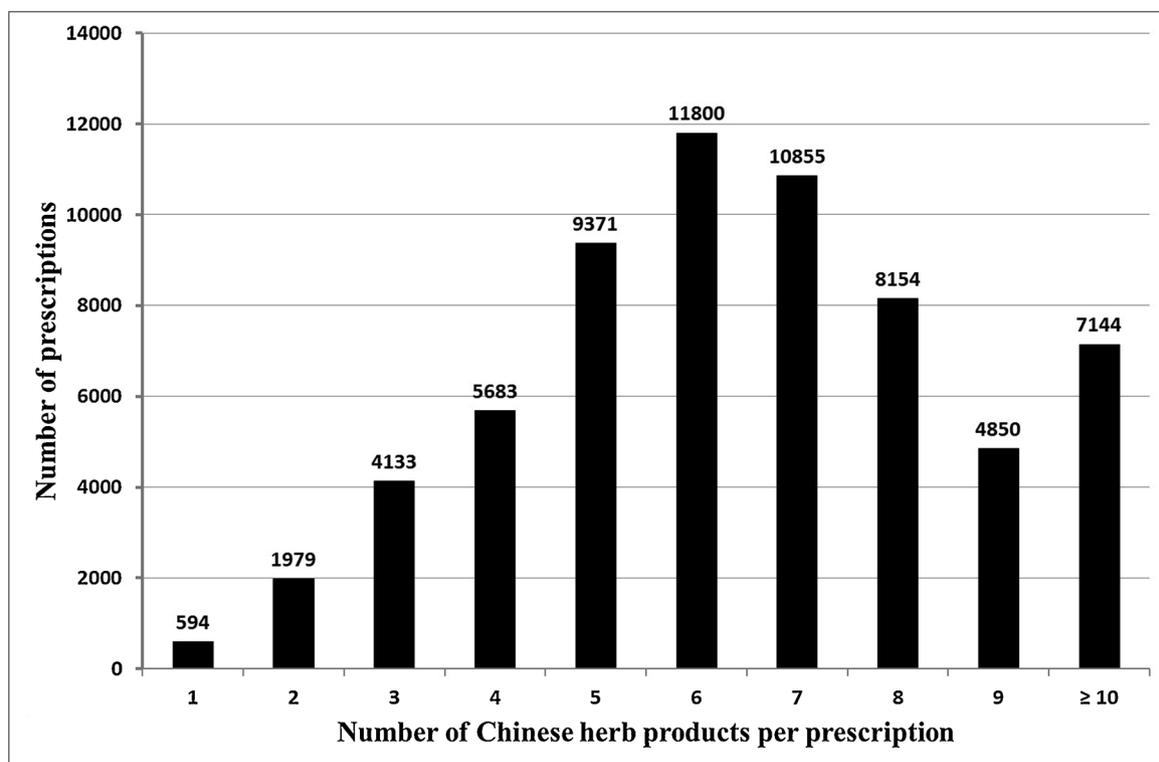
Table 1

Demographic characteristics and results of multiple logistic regression analysis for patients newly diagnosed with nasopharyngeal carcinoma from 2000 through 2011 in Taiwan.

Characteristics	TCM nonusers		TCM users		p-value	OR (95% CI)	
	N	%	N	%		Crude	Adjusted [†]
No. of patients	8239		9577				
TCM for nasopharyngeal carcinoma			4749				
Sex					< 0.001		
Women	1785	21.7	2749	28.7		1.46 (1.36–1.56)***	1.47 (1.37–1.58)***
Men	6454	78.3	6828	71.3		1.00	1.00
Age at diagnosis of nasopharyngeal carcinoma, years					< 0.001		
20–29	238	2.89	423	4.42		2.40 (2.03–2.85)***	2.33 (1.96–2.77)***
30–39	1128	13.7	1817	19.0		2.18 (1.98–2.40)***	2.15 (1.95–2.37)***
40–49	2387	29.0	3191	33.3		1.81 (1.66–1.96)***	1.80 (1.65–1.95)***
50–59	2175	26.4	2436	25.4		1.51 (1.39–1.65)***	1.52 (1.39–1.65)***
≥ 60	2311	28.1	1710	17.9		1.00	1.00
Mean (SD)	52.9	(13.4)	49.0	(12.1)	< 0.001		
Occupational status					< 0.001		
White collar	3943	47.9	5119	53.5		1.00	1.00
Blue collar	3171	38.5	3409	35.6		0.83 (0.78–0.88)***	0.88 (0.83–0.94)***
Others	1125	13.7	1049	11.0		0.72 (0.65–0.80)***	0.74 (0.67–0.81)***
Residential areas					< 0.001		
Northern area	3667	44.5	3989	41.7		1.00	1.00
Central area	1363	16.5	2105	22.0		1.42 (1.31–1.54)***	1.49 (1.37–1.62)***
Southern area	2628	31.9	3022	31.6		1.06 (0.99–1.13)	1.12 (1.05–1.21)**
Eastern area and offshore islands	581	7.05	461	4.81		0.73 (0.64–0.83)***	0.80 (0.70–0.91)***

TCM, traditional Chinese medicine; SD, standard deviation; OR, odds ratio; CI, confidence interval.

* p < 0.05, ** p < 0.01, *** p < 0.001.

[†] Model adjusted for sex, age (categorical), occupational status, and area.**Fig. 3.** Average number of Chinese herbal products (CHPs) per prescription for nasopharyngeal carcinoma in Taiwan (2001 through 2011).

treatment was Gan-Lu-Yin, followed by Xin-Yi-Qing-Fei-Tang and Shan-Shen-Mai-Men-Dong-Tang. The prescription pattern indicated that TCM physicians usually formulated personalized therapies according to the presenting symptoms and signs.

Gan-Lu-Yin is used to nourish yin and clear heat [15]. It is clinically used to treat gingivitis, conjunctivitis, mucositis, and stomatitis. A previous study showed that modified Gan-Lu-Yin, alone or in

combination with other TCM formulae, could reduce the symptoms of dry mouth and treat acute mucositis caused by RT [16]. Several studies reported that some single herbs within Gan-Lu-Yin had antitumor activities via the inhibition of cell proliferation, inflammation and angiogenesis [17–20]. *Scutellaria baicalensis* Georg (Huang Chin) was reported to have anticancer effects in several malignancies. It can induce cell cycle arrest as well as suppress cancer cell colony formation and

Table 2

Top ten formula and single CHPs prescribed by TCM physicians for the treatment of nasopharyngeal carcinoma in Taiwan (2001 through 2011; total number of CHPs, n = 423545).

Formula CHPs	Number (%)	Single CHPs	Number (%)
Gan-Lu-Yin	12651 (2.99)	<i>Hedyotis diffusa</i>	13666 (3.23)
Xin-Yi-Qing-Fei-Tang	6428 (1.52)	<i>Radix Scrophulariae</i>	9469 (2.24)
Shan-Shen-Mai-Men-Dong-Tang	3912 (0.92)	<i>Radix Ophiopogonis</i>	7773 (1.84)
Zhi-Bai-Di-Hung-Wan	3858 (0.91)	<i>Salvia miltiorrhiza</i>	7031 (1.66)
Shan-Zhong-Kui-Jain-Tang	2891 (0.68)	<i>Scutellariae Barbatae</i>	6062 (1.43)
Mai-Men-Dong-Tang	2845 (0.67)	<i>Herba Dendrobii</i>	5831 (1.38)
Chang-Er-Zi-San	2786 (0.66)	<i>Bulbus Fritillariae</i>	5120 (1.21)
Jia-Wei-Xiao-Yao-San	2719 (0.64)	<i>Radix Trichosanthis</i>	4954 (1.17)
Yi-Guan-Jian	2620 (0.62)	<i>Radix Puerariae</i>	4752 (1.12)
Bu-Zhong-Yi-Qi-Tang	2539 (0.60)	<i>Radix Rehmanniae</i>	4621 (1.069)

TCM, traditional Chinese medicine; CHPs, Chinese herbal products.

Table 3

Top five combinations comprising two combination CHPs or two single CHPs prescribed for nasopharyngeal carcinoma in Taiwan (2000 through 2011; total number of CHPs, n = 423545).

Two combination CHPs	Number (%)
Gan-Lun-Yin and Zhi-Bai-Di-Huang-Wan	1147 (0.27)
Gan-Lun-Yin and Xin-Yi-Qing-Fei-Tang	894 (0.21)
Jia-Wei-Xia-Yao-San and Gan-Lun-Yin	617 (0.15)
Gan-Lun-Yin and Ma-Zi-Ren-Wan	564 (0.13)
Gan-Lun-Yin and Cang-Er-Zi-San	514 (0.12)
Two single CHPs	Number (%)
<i>Scutellariae Barbatae</i> and <i>Hedyotis diffusa</i>	5003 (1.18)
<i>Radix Scrophulariae</i> and <i>Radix Ophiopogonis</i>	2900 (0.68)
<i>Salvia miltiorrhiza</i> and <i>Hedyotis diffusa</i>	2325 (0.55)
<i>Scrophularia ningpoensis</i> and <i>Radix Rehmanniae</i>	2224 (0.53)
<i>Radix Rehmanniae</i> and <i>Radix Ophiopogonis</i>	1906 (0.45)

CHPs, Chinese herbal products.

migration. *Scutellaria baicalensis* Georg has lots of ingredients, including baicalin. Baicalin was found to have anticancer effect for nasopharyngeal carcinoma by affecting genome instability and splicing [21–26]. In summary, Gan-Lu-Yin can be used as an adjuvant treatment to not only reduce RT-related side effects but also cure the cancer.

Xin-Yi-Qing-Fei-Tang, the second most commonly prescribed formula CHP in our study, clears heat from the lungs and stomach and unblocks the nasal orifices. In TCM practice, Xin-Yi-Qing-Fei-Tang is often appropriate for patients with yellow sputum; a stuffy nose; and thick, sticky, and yellow nasal discharge due to upper respiratory tract infection or allergies [27]. It is also the most common herbal formula used for children with allergic rhinitis and adults with chronic rhinosinusitis [27,28]. NPC patients often exhibit yellow, thick, and sticky mucus due to upper respiratory tract infection or inflammation while receiving anticancer treatment. This could be the reason why Xin-Yi-Qing-Fei-Tang was such a commonly prescribed combination in our

study.

Shan-Shen-Mai-Men-Dong-Tang is used to clear and nourish the lungs and stomach, engender fluid, repair damaged cells, and control the symptoms of dryness associated with cancer treatment [29]. One study by Sung and Dong (2001) in China also showed that Shan-Shen-Mai-Men-Dong-Tang could improve oral dryness and resolve difficulties in chewing and swallowing in patients with head and neck cancer who received chemoradiotherapy [30]. In addition, Shan-Shen-Mai-Men-Dong-Tang, the third most common formula CHP in our study, may strengthen the patient's immune system, because it was found to significantly increase the Zn levels in urine samples from patients with head and neck cancer [29]. It has been previously shown that Zn plays a significant role in the metabolic response to injury and wound healing [31], and increasing the Zn levels may enhance the healing process for patients with RT-induced mucositis and dermatitis.

With regard to single CHPs, the most common one in our study was *Hedyotis diffusa*, followed by *Radix Scrophulariae* and *Radix Ophiopogonis*. Our findings were consistent with those of a previous NHI survey, where *Hedyotis diffusa* was the most commonly prescribed single herb for patients with cancer [32]. This CHP is used to clear heat, strongly relieve fire toxins, and abscesses. It exhibits several biological activities such as anticancer, antioxidative, anti-inflammatory, and neuroprotective effects [33,34]. *Hedyotis diffusa* also showed suppressive effects on the aggressive phenotypes of laryngeal squamous carcinoma cells, induced cell cycle arrest and apoptosis, and inhibited cancer cell invasion via inhibition of B-cell lymphoma 2 (Bcl-2), MMP-2, and μ PA, which are involved in cell growth, survival, and invasion [34,35]. In addition, it inhibited inducible nitric oxide synthase and interleukin-1 β expression in a concentration-dependent manner while promoting the expression of inducible hemoxygenase and peroxisome proliferator-activated receptor gamma (PPAR- γ). The anti-inflammatory effects of *Hedyotis diffusa* are most likely facilitated by its inhibitory effects on the c-Jun N-terminal kinase (JNK) signaling pathway [36].

Radix Scrophulariae (Xuan Shen) is used to clear heat and cool the blood, nourish yin, and relieve toxicity. It is often used for the treatment of fever, swelling, neuritis, laryngitis, constipation, and inflammatory diseases [37]. The constituents of *Radix Scrophulariae* were reported to show antioxidant, antibacterial, anti-inflammatory, neuroprotective, antidiabetic, cytotoxic, and antimicrobial activities [38,39]. In addition, the anti-inflammatory effects of this drug were associated with the NF- κ B signaling pathway [40]. In another study, *Radix Scrophulariae* combined with *Vitiscis Fructus* was shown to decrease cell adhesion, alter the cell morphology to a round shape, and induce cell death in cancer cells [41].

Radix Ophiopogonis is capable of tonifying yin, engendering fluid, moistening the lungs, and clearing the heart; accordingly, it is often used for the treatment of dry cough, dry mouth, throat impediment and pain, vexation and insomnia, and constipation [42]. It has been shown to exert cardiovascular protection and anti-inflammatory, antidiabetic, anticancer, antioxidative, and immunomodulatory activities in previous studies [43,44]. The anti-inflammatory activity could be attributed to a decrease in IL-6 production [45]. In addition, this herb was found to induce apoptosis of prostate cancer cells via a receptor interacting

Table 4

Top five combinations comprising three combination CHPs prescribed for nasopharyngeal carcinoma in Taiwan (2000 through 2011; total number of CHPs, n = 423545).

Three combination CHPs	Number (%)
Ma-Zi-Ren-Wan, Zhu-Ling-Tang, and Long-Dan-Xie-Gan-Tang	144 (0.03)
Shu-Jing-Huo-Xue-Tang, Dang-Gui-Nian-Tong-Tang, and Du-Huo-Ji-Sheng-Tang	103 (0.02)
Chai-Ge-Jie-Ji-Tang, Shu-Jing-Huo-Xue-Tang, and Dang-Gui-Nian-Tong-Tang	73 (0.02)
Liu-Wei-Di-Huang-Wan, Tian-Wang-Bu-Xin-Dan, and Suan-Zao-Ren-Tang	72 (0.02)
Chai-Ge-Jie-Ji-Tang, Shu-Jing-Huo-Xue-Tang, and Du-Huo-Ji-Sheng-Tang	72 (0.02)

CHPs, Chinese herbal products.

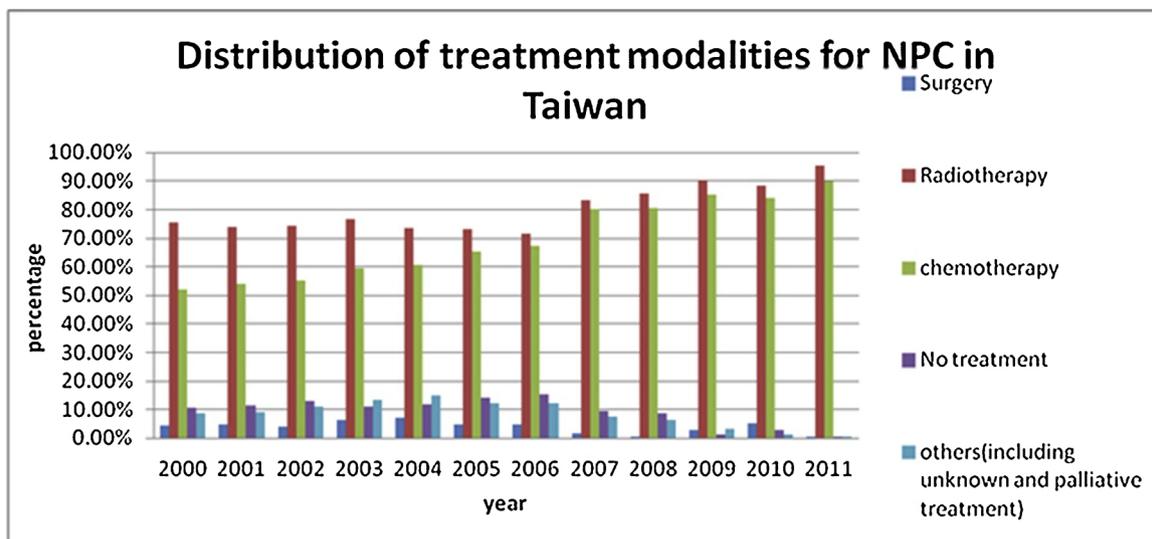


Fig. 4. Distribution of treatment modalities for nasopharyngeal carcinoma (NPC) from 2001 through 2011 in Taiwan [6].

serine/threonine kinase 1 (RIPK1)-related pathway both in vitro and in vivo [46].

We found that Gan-Lun-Yin and Zhi-Bai-Di-Huang-Wan were most commonly prescribed together, with Gan-Lun-Yin expected to nourish yin and clear heat and Zhi-Bai-Di-Huang-Wan expected to nourish the kidney and liver yin and clear heat [47,48]. Both these CHPs clear heat and nourish yin, thus reducing the side effects of RT. The second most common combination was Gan-Lun-Yin and Xin-Yi-Qing-Fei-Tang; the former clears heat while the latter treats upper airway symptoms. With regard to single CHPs, *Scutellariae Barbatae* and *Hedyotis diffusa* were most commonly prescribed in combination. Both herbs can clear heat and show anticancer activities. The second most common combination was *Radix Scrophulariae* and *Radix Ophiopogonis*, both of which strengthen yin and reduce the side effects of RT. In summary, all these CHPs are generally prescribed in combination to enhance their efficacy, minimize toxicity, and tailor the treatment according to individual needs [49].

The top three formula CHPs and single CHPs in the present study share a common function of clearing heat, and most of them can nourish yin. The main treatment for NPC is RT, the side effects of which include mucositis, xerostomia, dysphagia, and dermatitis. All these side effects are a part of the heat syndrome as per TCM theory. Therefore, herbs that can clear heat and nourish yin are generally used to minimize RT-associated side effects. Although our findings were in accordance with TCM theory, well-designed clinical trials are required to further clarify our findings. At present, there is one prospective pilot study demonstrating that Gan-Lu-Yin can be used to treat dry mouth during RT for head and neck cancer, consistent with our findings [50]. An observational study reported that Gan-Lu-Yin and Sha-Shen-Mai-Dong-Tang could improve xerostomia and quality of life in patients with head and neck cancer post-radiotherapy in Malaysia [51].

This study has several limitations. First, we did not evaluate the efficacy and adverse effects of the CHPs. Although NHIRD has extensive prescription data, we did not have access to other chart-level records such as laboratory data and physician notes. Therefore, the usefulness of the treatments could not be assessed [49,52]. Second, TCM is not fully covered by the NHI program in Taiwan. Moreover, visits to clinics not contracted with the NHI program were not included in the present study. In Taiwan, approximately 5% TCM clinics are not contracted with the NHI program; therefore, TCM use may have been underestimated [15]. Third, patients with NPC show several different symptoms, and those in different stages and receiving different treatments develop variable complications [53]. Typically, TCM physicians

prescribe one or two formulae combined with several single herbs in one prescription based on the patient's symptoms. In the present study, however, we were unable to confirm the stage of cancer and treatments during CHP use. Therefore, further studies should evaluate the pattern of utilization of CHPs during different stages and treatments for cancer.

5. Conclusions

In conclusion, our findings suggest that CHPs are widely used for the management of NPC and its treatment-related side effects in Taiwan. Patients with NPC using TCM treatment are more likely to be women, younger individuals, white-collar workers, and residents of central Taiwan. The most frequently prescribed CHPs for NPC are Gan-Lu-Yin and Bai Hua She She Cao (*Hedyotis diffusa*). These findings provide information regarding personalized therapies and can promote further clinical experiments and pharmacological research on CHPs for NPC treatment in Taiwan. Further well-designed, randomized, double-blind, placebo-controlled studies and basic mechanistic studies and clinical trials are needed to assess the safety and effectiveness of the prominent CHPs used for NPC management in Taiwan.

Declaration of Competing Interest

The authors declare they have no conflicts of interest.

Acknowledgements

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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