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## Chinese herbal medicine network and core treatments for allergic skin diseases: Implications from a nationwide database ☆

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## ABSTRACT

**Ethno-pharmacological relevance:** Chinese herbal medicine (CHM) is commonly used to treat skin diseases, but CHM prescription patterns are difficult to understand due to their complexity and inter-connections. This study aimed to demonstrate CHM core treatments and network for treatment of allergic skin diseases by analyzing a nationwide prescription database.

**Materials and methods:** All CHM prescriptions made for atopic dermatitis (with age limitation  $\leq 12$  years) and urticaria for the entire year of 2011 were included. Association rule mining (ARM) combined with social network analysis (SNA) were used to analyze CHM prescriptions and explore the CHM prescription pattern and network.

**Results:** A total of 27,350 and 97,188 prescriptions for atopic dermatitis and urticaria, respectively, were analyzed. Xiao-Feng-San (XFS) was the most commonly used CHM (32% of prescriptions for atopic dermatitis and 47.4% for urticaria) and was the core treatment for both diseases. Moreover, 42 and 82 important CHM-CHM combinations were identified to establish the CHM network, and XFS with *Dictamnus dasycarpus* Turcz was the most prevalent (6.4% for atopic dermatitis and 9.1% for urticaria). Traditional Chinese Medicine heat syndrome was most prevalent cause. Extensive anti-inflammation, anti-allergy, anti-oxidation, and anti-bacterial effects were also found among the CHMs.

**Conclusions:** Network analysis on CHM prescriptions provides graphic and comprehensive illustrations regarding CHM treatment for atopic dermatitis and urticaria. The CHM network analysis of prescriptions is essential to realize the CHM treatments and to select suitable candidates for clinical use or further studies.

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## 1. Introduction

Traditional Chinese medicine (TCM) is a treatment system that has been used for more than 2000 years and is still in commonly used

**Abbreviations:** ARM, Association rule mining; CHM, Chinese herbal medicine; HF, Herbal formula; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; SH, Single herb; SNA, Social network analysis; TCM, Traditional Chinese medicine; XFS, Xiao-Feng-San

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(Scheid, 1999; Tang et al., 2008). The cost of TCM treatment has increased rapidly in recent decades and has attracted increasing attention from researchers (Raschetti et al., 2005; Scheid, 1999; Tang et al., 2008). Large amounts of information on TCM in clinical use, including Chinese herbal medicine (CHM), acupuncture, and manual therapy, have been recorded and continues to increase (Raschetti et al., 2005). Novel study methods to analyze and summarize this body of clinical data are urgently needed to translate TCM into modern science (Feng et al., 2006).

Due to the enormous amount of prescriptions and highest use rate among all TCM modalities, CHM is the most important study target (Chen et al., 2007; Chen et al., 2012). Identifying core CHM treatments is essential for candidate selection of basic research, clinical trials, and daily practice (Chen et al., 2013; Yuan et al., 2012). Complicated CHM prescriptions may lead to high heterogeneity in choosing CHMs for

clinical trials and in choosing uncommon CHMs as study candidates in bench studies (Chen et al., 2011a; Hu et al., 2011). CHM prescriptions are often complex and composed of several CHMs in one prescription, making it difficult to analyze them by conventional statistical methods. Thus, several new methods have been developed to analyze CHM (Chen et al., 2013; Feng et al., 2006; Hao da and Xiao, 2014; Li and Zhang, 2013; Zhang et al., 2013). CHM network analysis is one of the most important methods used to demonstrate connections between CHMs and has been widely applied to explore the connections between CHMs and potential underlying pharmacological mechanisms (Chen et al., 2013; Hao da and Xiao, 2014; Lin et al., 2013; Poon et al., 2011; Yuan et al., 2012).

Urticaria and atopic dermatitis are common allergic skin diseases that are good study targets for CHM network analysis due to their complicated pathogenesis and limited treatment options from Western medicine. From the TCM viewpoint, each of these diseases may involve several TCM syndromes and numerous CHMs for treatment. This is because TCM doctors usually make up prescriptions using the idea of “syndrome differentiation and treatment” or “bian zheng lun zhi” in Chinese. In this treatment model, patients are diagnosed with one or more TCM syndromes according to their manifestations and are treated with CHM prescriptions based on their TCM syndrome (Jiang et al., 2012). A group of CHMs are then initially chosen for the major syndrome and other CHMs are added for the minor syndromes or symptoms. The TCM doctors usually treat a disease with the concept of a CHM network, “multiple targets, complex diseases”, rather than as a single drug for a disease, as in Western medicine (Li and Zhang, 2013).

This study aimed to explore the CHM network and core treatments for urticaria and atopic dermatitis by analyzing a nationwide CHM prescription database.

## 2. Material and methods

### 2.1. Data source

The National Health Insurance Research Database (NHIRD) contains information from the National Health Insurance (NHI) program, established in Taiwan in 1995, and provides medical care for 23 million people or more than 99% of the population. The results and conclusions drawn from the NHIRD may be regarded as a consensus of all clinicians in Taiwan due to the high coverage of the NHI program (Chen et al., 2011b). Demographic data, reasons for medical care, interventions, medical costs, and examinations were all stored in a digital format. To identify diseases, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are used, with the first diagnosis code as the main reason for the visit. For privacy and ethical considerations, the identification numbers of all patients are encrypted. Under the supervision of an Institutional Review Board, this database is made public for researchers in Taiwan (Chen et al., 2011b).

### 2.2. Study subjects

Two major types of allergic dermatitis were analyzed: atopic dermatitis and urticaria. All subjects with a single diagnosis of urticaria (ICD-9-CM code: 708) and atopic dermatitis (ICD-9-CM code: 691.8 and 692.x with age limitation of  $\leq 12$  years) between January 1 and December 31, 2011 were included in this study. In Taiwan, the diagnoses of these skin diseases were mainly made according to clinical manifestations and criteria (Williams, 2005; Zuberbier et al., 2009).

Age was limited because most atopic dermatitis patients may improve gradually after puberty. Visits with acupuncture and massage were excluded to avoid possible influences on the choice of CHMs for

prescription and to minimize confounding bias. Visits with missing value were also excluded as well.

### 2.3. Chinese herbal medicine prescription dataset

A nationwide CHM prescription database was used as the data source for CHM prescription analysis. This database contained all CHM prescriptions extracted from the NHIRD. The use of CHMs and other TCM treatment modalities were fully and equally reimbursed by the NHI program, thereby reducing bias in choosing TCM or Western medicine treatments. Using this nationwide database also prevented referral and selection bias (Tien et al., 2014). Diagnoses and management decisions in this database were made by doctors in their daily practice. The reference value was much higher than results obtained from text books or ancient classics since the CHM prescriptions used in modern times were very different (Scheid et al., 2010).

Only two kinds of CHM were reimbursed by the NHI in Taiwan: a single herb (SH) and herbal formula (HF). A HF was used as the main part of the prescription and composed of several SHs with fixed proportions as recorded in text books or ancient TCM classics. SHs included herbs and parts of animals and minerals. Both SH and HF were made into a concentrated powder by the Good Manufacturing Production pharmacy under strict supervision for heavy metals and pesticides.

Every HF and SH had a specific TCM indication usually aimed at a specific TCM syndrome, although TCM doctors might combine a SH and HF according to the clinical implications. For example, Xiao-Feng-San (XFS; a HF with 13 SH) was commonly combined *Cryptotympana pustulata* Fabricius for urticaria (Lin et al., 2013). In this case, XFS was used for wind-heat-dampness syndrome as a single CHM that had an effect through the interactions of 13 kinds of SH, rather than the effects of individual SHs.

### 2.4. Network analysis of CHM prescriptions

The CHM network analysis was beneficial in providing detailed information on CHM prescriptions and in identifying core CHMs for a specific disease (Chen et al., 2014a; Chen et al., 2014b; Li, 2009; Lin et al., 2013). The data processing platform (Fig. 1) and the content of the CHM database (Fig. 2) included the name, characteristics, and indication of every CHM.

The commonly used CHM–CHM combinations, or herbal pairs, were the basic elements of a CHM network. A sophisticated network was created based on CHM combinations (Chen et al., 2013; Li and Zhang, 2013; Wang et al., 2012). Important CHM combinations were discovered by association rule mining (ARM), one of the most well-known data mining techniques extensively applied to explore relationships between objects in large scale databases (Agrawal et al., 1993), including CHM co-prescription patterns, TCM syndrome analysis, co-morbidities of a disease, and patterns of DNA-protein binding sequences (Chen et al., 2014a; Chen et al., 2014b; Chen et al., 2013; Leung et al., 2010; Lin et al., 2013; Tai and Chiu, 2009; Yang et al., 2012). To identify commonly used CHM–CHM combinations among the enormous number of CHM prescriptions, three factors were used: support, confidence and lift factors. Support was similar to the prevalence of a certain CHM or CHM combination, while confidence and lift factors were used to evaluate the strength of connections between CHMs (Chen et al., 2014b; Yang et al., 2013a). Only CHM combinations containing these three factors with a higher than preset threshold values were considered statistically significant, based on a previously detailed algorithm (Agrawal et al., 1993; Chen et al., 2014b; Yang et al., 2013a).

After identifying important CHM–CHM combinations, social network analysis (SNA) was used to demonstrate relationships between each CHM by clustering CHM hierarchically (Chen et al., 2014b; Yang et al., 2013a). Each cluster contained a group of highly interconnected

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