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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 ≤ 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 ≤ 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

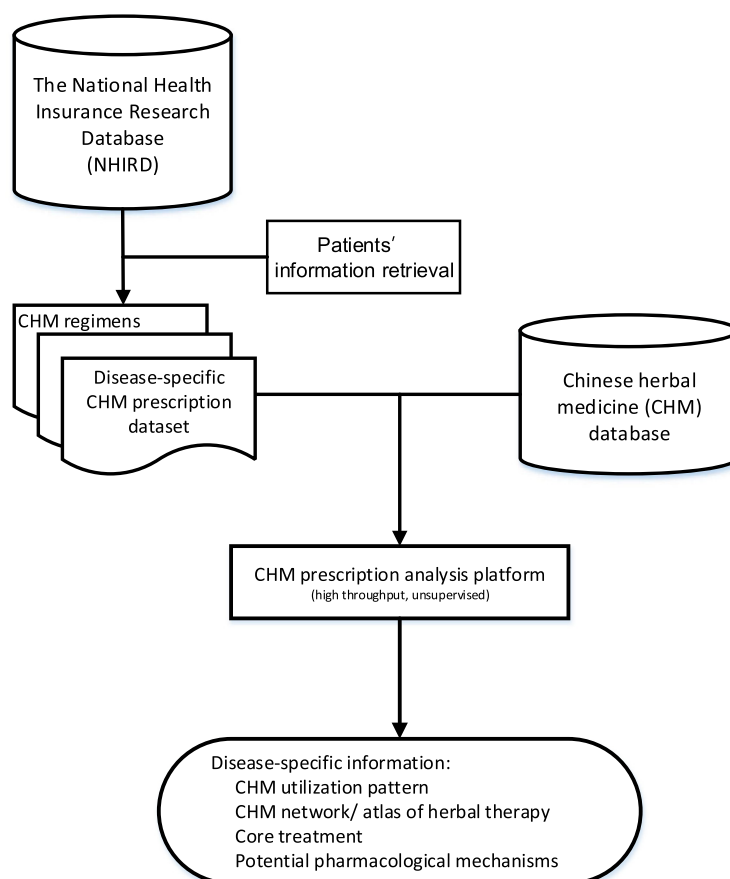


Fig. 1. Flow chart of Chinese herbal medicine (CHM) prescription analysis platform.

Chinese herbal medicine (CHM) material medica

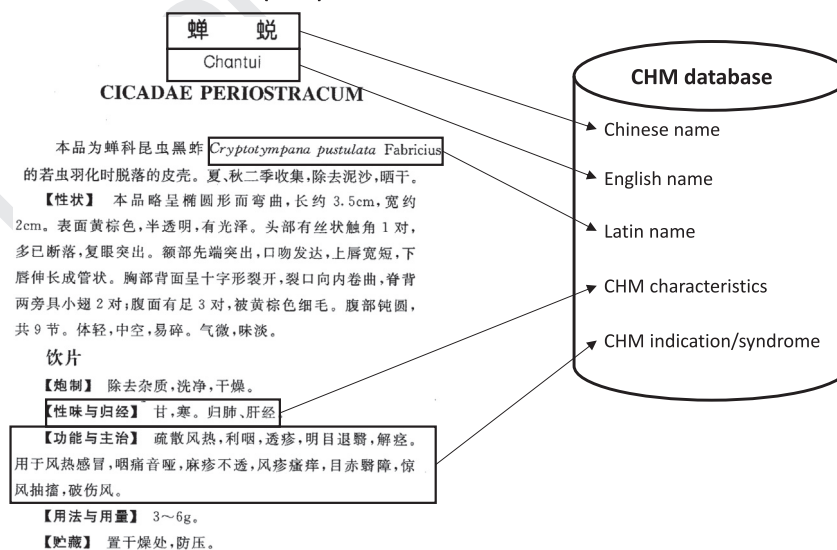


Fig. 2. Construction and examples of the Chinese herbal medicine (CHM) database (contents adopted from the Pharmacopoeia of the People's Republic of China, 2010 edition, and the Compendium of Materia Medica).

CHMs and therefore had a TCM indication that differed from other CHM clusters. These indications often corresponded to TCM syndromes and core CHMs were identifiable at the center of each cluster. Consequently, from the CHM network generated by ARM and SNA, the core CHM, important CHM combinations, and the most common TCM

syndrome for treatment were established (Chen et al., 2014a; Chen et al., 2014b).

The SNA was originally designed to explore communication patterns between individuals in a large population and classify similar individuals to examine the sub-structure of society (Wasserman et al.,

1994). It was also applied in research on the system biology of TCM (Yang et al., 2013b). To create a CHM network, three SNA measurements were used: modularity, degree and centrality (Memon et al., 2010; Wakita and Tsurumi, 2007). Modularity was the indicator of fitness of the clustering results, as only the cluster model with the best modularity value was included in the final result. In the final model, the most related CHMs were classified into the same cluster with the longest relationship with other clusters or CHMs. Degree indicated the number of connections to a CHM, while centrality indicated the importance of a CHM in a network. A CHM with higher degree and centrality values were more important in the network (Wakita and Tsurumi, 2007; Yang et al., 2013a). The freeware “R” were used to perform SNA for CHM in this study.

3. Results

3.1. CHM network for atopic dermatitis

In the one-year study period, 10,547 children used CHMs (98.7% of all TCM users) for atopic dermatitis and 27,350 prescriptions were made. Overall, 606 kinds of CHMs were used by TCM doctors, with an average of 5.6 kinds of CHM used per prescription. Of the top 10 most commonly used CHMs (Table 1), XFS was the most common (32% of all prescriptions, with a daily dose of 3.7 g), accounting for nearly one-third of all prescriptions, followed by *Glycyrrhiza uralensis* Fisch. (Gang Cao, 21.7% of all prescriptions, 0.9 g/day) and *Forsythia suspensa* (Thunb.) Vahl. (Lian Qiao, 15.9% of all prescriptions, 1.0 g/day). In general, SHs were used more commonly than HF, but HF were usually used at a higher daily dose (Table 2).

Using ARM and SNA, 42 important CHM combinations were identified (Table 2). The CHM network for atopic dermatitis (Fig. 3a), five clusters were found among these important CHM combinations and each cluster was mainly responsible for a certain TCM syndrome when applying the characteristics of the CHM into the network diagram (Fig. 3b). Core CHMs and important CHM combinations were

Table 1
The top 10 most commonly used Chinese herbal medicine for atopic dermatitis and urticaria.

English name	Latin name	CHM type	Dosage (g/day)	Number of prescriptions (%)
(a) Atopic dermatitis (n=27,350)				
Xiao-Feng-San (XFS) ^a		HF	3.7	8747 (32.0)
Gang Cao	<i>Glycyrrhiza uralensis</i> Fisch.	SH	0.9	5934 (21.7)
Lian Qiao	<i>Forsythia suspensa</i> (Thunb.) Vahl.	SH	1.0	4348 (15.9)
Bai Xian Pi	<i>Dictamnus dasycarpus</i> Turcz.	SH	1.1	3785 (13.8)
Chan Tui	<i>Cryptotympana pustulata</i> Fabricius	SH	1.4	3484 (12.7)
Di Fu Zi	<i>Kochia scoparia</i> (L.) Schrad.	SH	1.6	3274 (12.0)
Yi Yi Ren	<i>Coix lacryma-jobi</i> var. <i>ma-yuen</i> (Rom.Caill.) Stapf	SH	1.2	3207 (11.7)
Jing-Fang-Bai-Du-San ^b		HF	3.2	2834 (10.4)
Jin Yin Hua	<i>Lonicera japonica</i> Thunb.	SH	1.2	2821 (10.3)
Mu Dan Pi	<i>Paeonia suffruticosa</i> Andr.	SH	1.2	2658 (9.7)
(b) Urticaria (n=97,188)				
Xiao-Feng-San (XFS) ^a		HF	5.2	46,024 (47.4)
Bai Xian Pi	<i>Dictamnus dasycarpus</i> Turcz.	SH	1.4	16,542 (17.0)
Chan Tui	<i>Cryptotympana pustulata</i> Fabricius	SH	1.3	15,494 (15.9)
Mu Dan Pi	<i>Paeonia suffruticosa</i> Andr.	SH	2.0	13,414 (13.8)
Di Fu Zi	<i>Kochia scoparia</i> (L.) Schrad.	SH	1.6	13,316 (13.7)
Jing-Fang-Bai-Du-San ^b		HF	4.4	13,153 (13.5)
Lian Qiao	<i>Forsythia suspensa</i> (Thunb.) Vahl.	SH	1.4	13,077 (13.4)
Gang Cao	<i>Glycyrrhiza uralensis</i> Fisch.	SH	1.1	9722 (10.0)
Jin Yin Hua	<i>Lonicera japonica</i> Thunb.	SH	1.3	8220 (8.5)
Jing Jie	<i>Schizonepeta tenuifolia</i> (Benth.) Briq.	SH	1.5	8136 (8.4)

^a Composition of XFS: *Saposhnikovia divaricata* (Turcz.) Schischk., *Atractylodes lancea* (Thunb.) DC., *Schizonepeta tenuifolia* (Benth.) Briq., *Arctium lappa* L., *Glycyrrhiza uralensis* Fisch., *Rehmannia glutinosa* (Gaertn.) DC., *Gypsum Fibrosum*, *Clematis armandii* Franch. or *Clematis montana* Buch.-Ham. ex DC., *Anemarrhena asphodeloides* Bunge., *Angelica sinensis* (Oliv.) Diels., *Cryptotympana pustulata* Fabricius, *Sesamum indicum* L., *Sophora flavescens* Aiton

^b Composition of Jing-Fang-Bai-Du-San: *Schizonepeta tenuifolia* (Benth.) Briq., *Saposhnikovia divaricata* (Turcz.) Schischk., *Notopterygium incisum* Ting. ex H. T. Chang, or *Notopterygium forbesii* Boiss., *Angelica biserrata* (Shan et Yuan) Yuan et Shan, *Bupleurum chinense* DC., *Peucedanum praeruptorum* Dunn. or *Peucedanum decursivum* Maxim., *Ligusticum chuanxiong* Hort., *Citrus aurantium* L., *Platycodon grandiflorum* (Jacq.) A. DC., *Poria cocos* (Schw.) Wolf., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Rosc., *Mentha haplocalyx* Briq.

Table 2
The top 5 Chinese herbal medicine combinations for atopic dermatitis and urticaria.

Combinations of CHM			Number of prescriptions (%)		Confidence	Lift
(a) Atopic dermatitis (n=27,350)						
Xiao-Feng-San	with	<i>Dictamnus dasycarpus</i> Turcz.	1743	(6.4)	46.06	1.44
Xiao-Feng-San	with	<i>Kochia scoparia</i> (L.) Schrad.	1502	(5.5)	29.53	1.44
<i>Dictamnus dasycarpus</i> Turcz.	with	<i>Kochia scoparia</i> (L.) Schrad.	1444	(5.3)	45.88	3.19
Xiao-Feng-San	with	<i>Cryptotympana pustulata</i> Fabricius	1270	(4.6)	44.11	1.14
<i>Forsythia suspensa</i> (Thunb.) Vahl.	with	<i>Lonicera japonica</i> Thunb.	1244	(4.6)	38.16	2.78
(b) Urticaria (n=97,188)						
Xiao-Feng-San	with	<i>Dictamnus dasycarpus</i> Turcz.	8813	(9.1)	53.28	1.13
Xiao-Feng-San	with	<i>Kochia scoparia</i> (L.) Schrad.	8233	(8.5)	61.85	1.31
Xiao-Feng-San	with	<i>Cryptotympana pustulata</i> Fabricius	7399	(7.6)	47.77	1.01
Xiao-Feng-San	with	<i>Paeonia suffruticosa</i> Andr.	5717	(5.9)	34.57	2.52
Xiao-Feng-San	with	Jing-Fang-Bai-Du-San	4742	(4.9)	61.21	1.30

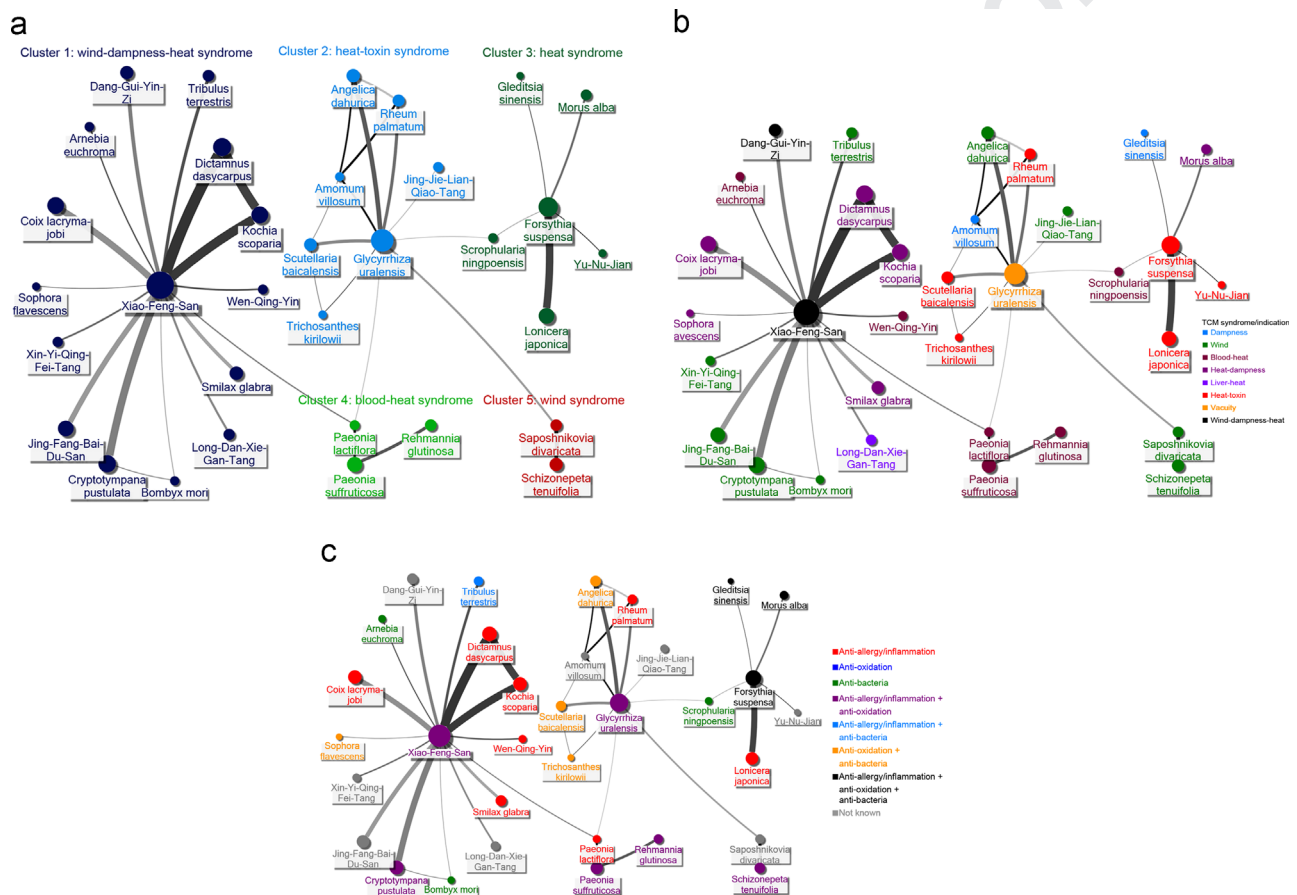


Fig. 3. (a) Chinese herbal medicine (CHM) network for treating atopic dermatitis. (b) Network with TCM syndrome mapping. (c) Network with potential pharmacological mechanisms. The width of connecting lines represents the confidence of each combination, and the depth of color represents prevalence. The connection between CHMs is more important if the connection line is thicker and darker. The size of circle represented the prevalence of each CHM and larger meant higher prevalence. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

required effectiveness (Fig. 4b). Similarly, most CHM, especially SH, had effects on inflammation, allergic reaction, oxidative stress, and infection, with strong inter-connections between CHMs (Fig. 4c).

4. Discussion

This is the first study to demonstrate the detailed CHM network for treating atopic dermatitis and urticaria, instead of brief networks as presented previously. By combining ARM and SNA, two novel computational methods are used to demonstrate complicated relationships between numerous objects such that a CHM network for a particular disease can be constructed to graphically present the

relationships among CHMs. Through these CHM network diagrams, the core CHMs, CHM clusters, and CHM interconnections can be identified. In addition, using a nationwide CHM prescription database to identify study targets, these results represent a consensus of TCM doctors in Taiwan and may be a reference for TCM doctors or researchers when choosing candidate CHMs from the enormous number of available CHMs.

A CHM network demonstrates the disease-TCM syndrome-CHM treatment relationship when characteristic and pharmacological mechanisms are incorporated into the CHM network. More importantly, such a network provides study targets of potential pharmacological mechanisms of the CHM within the same clusters. For instance, CHMs within the heat syndrome clusters may be worth studying for

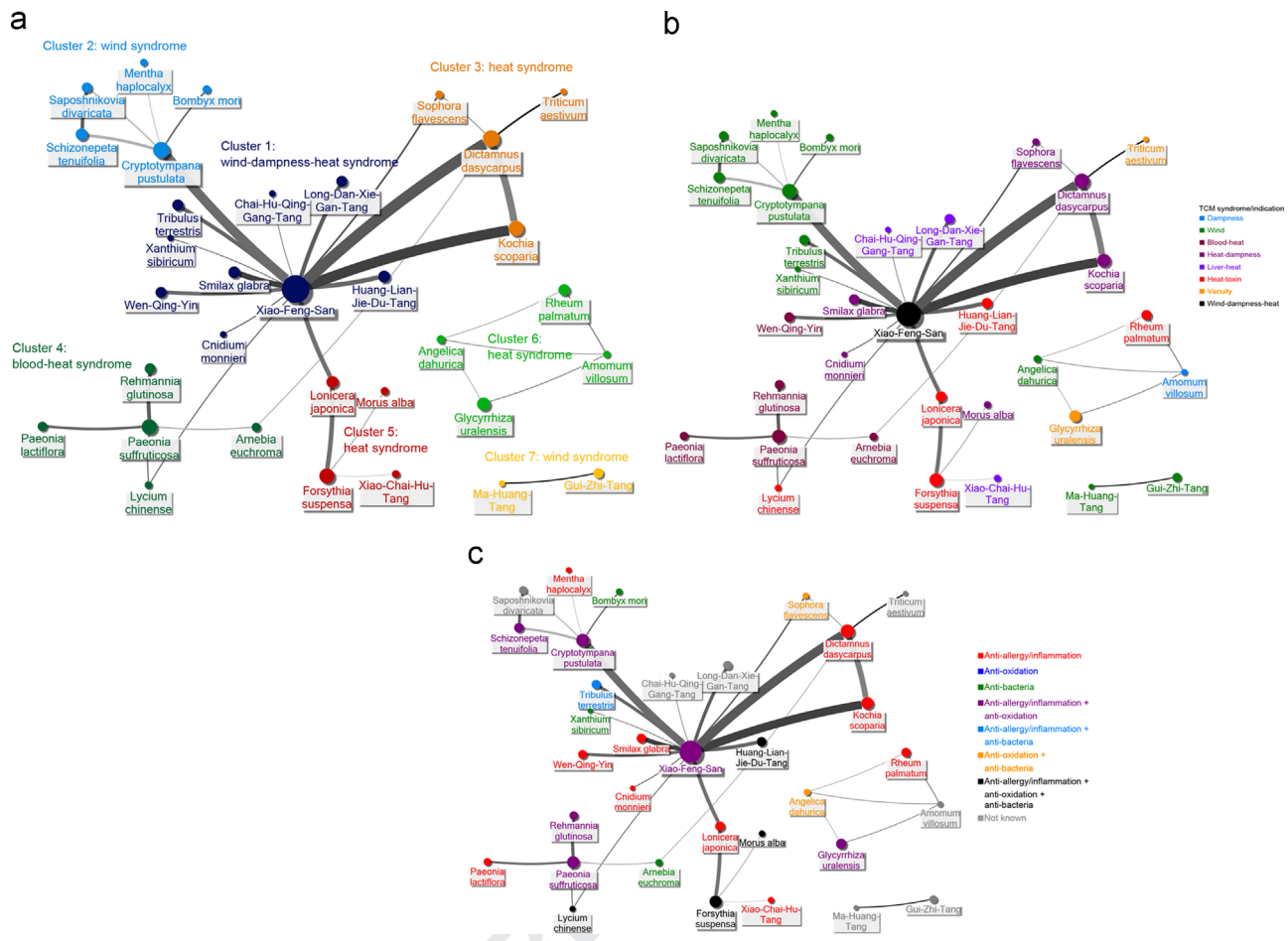


Fig. 4. (a) Chinese herbal medicine network for treating urticaria. (b) Network with Traditional Chinese Medicine syndrome mapping. (c) Network with potential pharmacologic mechanisms.

their effects on innate immunity against bacterial infection and inflammation. The mechanisms of action may be similar.

Extensive existing anti-bacterial effect among the CHM network of atopic dermatitis is an interesting and important finding. The importance of bacterial infection has been known for years, but the routine use of oral or topical antibiotics is not recommended by current guidelines due to possible drug resistance (Berke et al., 2012; Huang et al., 2009; Ong et al., 2002). Aside from direct bactericidal effect from conventional antibiotics, CHMs may strengthen the body's innate immunity against bacterial infections, which may provide an alternative therapy for control of atopic dermatitis.

Coix lacryma-jobi var. *ma-yuen* (Rom.Caill.) Stapf has been reported to enhance innate and adaptive immunity via increasing the amount of cytotoxic-T cells and NK cells, while various CHMs such as *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., and *Viola prionantha* Bunge are reported to possess a wide coverage of action against bacterial infections (Hidaka et al., 1992; Muluye et al., 2014; Xie et al., 2004). With these anti-bacterial effects, CHM may be an effective complementary therapy to conventional treatments for atopic dermatitis.

XFS is the core treatment for these three allergic diseases as seen by its highest prevalence, its central role in the largest cluster, and its multiple connections to other clusters of CHM (Figs. 3 and 4). TCM doctors often combine XFS with other CHMs when treating allergic skin diseases. It has extensive effects on alleviating inflammation, allergy, and oxidation reactions in allergic skin diseases, which may be the reason for its effectiveness and common use (Chen et al., 2014c; Cheng et al., 2011; Sheehan and Atherton, 1992). The anti-allergy effect of XFS is by inhibiting IgE release from mast cells derived from

mouse bone marrow cells (Shichijo and Saito, 1997). Furthermore, the imbalance between Th1 and Th2 cells is corrected via decreasing the serum levels of IL-4 and interferon-gamma by treating mite antigen-induced allergic dermatitis in mice with XFS (Gao et al., 2005). Such effects cover the common pathway of urticaria and atopic dermatitis, but, like Western medicine treatments, additional CHMs are still needed. For example, bacterial infection and skin barrier defects are two pathologic features of atopic dermatitis, as distinguished from urticaria, and thus, more CHM with effects on these two effects are needed.

Aside from core treatments, the additive effects between CHMs and clusters can be clearly illustrated by the CHM network. For example, for treating urticaria, XFS-based CHM prescriptions are usually connected to *C. pustulata* Fabricius (center of wind syndrome, cluster 2), *Dictamnus dasycarpus* Turcz. and *Kochia scoparia* (L.) Schrad. (center of heat syndrome, cluster 6), *Paeonia suffruticosa* Andr. (center of blood-heat syndrome, cluster 5), and *Lonicera japonica* Thunb. (heat syndrome, cluster 3) (Fig. 4a–c).

The anti-oxidation and anti-inflammation effects of XFS cluster may be strengthened by two N-acetyldopamine dimers extracted from *C. pustulata* Fabricius (Xu et al., 2006). Moreover, urticaria-related insomnia may be relieved by an additional dose of *C. pustulata* Fabricius, which may increase serotonergic activity and decrease locomotor activity in the brain (Hsieh et al., 1991). Furthermore, the anti-inflammation and anti-allergy effects of XFS can be strengthened by combining it with *L. japonica* Thunb., *D. dasycarpus* Turcz., and *K. scoparia* (L.) Schrad., as *L. japonica* Thunb. and *D. dasycarpus* Turcz. can both inhibit histamine release from mast cells *in vitro* (Chan et al., 2008; Jiang et al., 2008).

The CHM networks are also useful when investigating novel drugs. Heat-blood clearing CHMs may be valuable alternative treatments for atopic dermatitis via increasing the expression of filaggrin. Filaggrin deficiency is considered as one of the most important pathogenic factors for dry skin and relapsed itching among patients with atopic dermatitis such that a 5–10% increase in filaggrin is useful for controlling symptoms (McGrath, 2012). Ursolic acid and oleanolic acid supplements are reported to be effective in increasing filaggrin expression and these two compounds are abundantly found in CHMs (Lim et al., 2007). *P. lactiflora* Pall., which is used in CHM for atopic dermatitis (Fig. 3a and b), is an alternative source of ursolic acid and oleanolic acid (Zhou et al., 2011) and is often used by TCM doctors.

From a TCM viewpoint, *P. lactiflora* Pall. is used to clear blood heat in the body, which may be characterized by dry skin, lichenification, and itchiness that worsens in the evening. These symptoms closely resemble atopic dermatitis. Thus, aside from *P. lactiflora* Pall, CHMs like *P. suffruticosa* Andr. and *Rehmannia glutinosa* (Gaertn.) Libosch. in the same cluster for blood heat syndrome are novel sources with enormous potential of supplement filaggrin.

A part from candidates for studies on the efficacy and mechanism of action, targets of safety issues may arise from a CHM network. *G. uralensis* Fisch., or licorice, has been commonly used for atopic dermatitis (Table 1), alone or in combination with other CHMs, especially among children (Fig. 3). From a TCM viewpoint, *G. uralensis* Fisch. has the ability to remedy deficiency and detoxify other CHMs and to protect the gastrointestinal system. Moreover, *G. uralensis* Fisch. has been shown to have anti-inflammatory and anti-oxidant effects, which are important in treating allergic skin diseases (Kim et al., 2008; Lee et al., 2009; Li et al., 2010; Li et al., 2011; Yang et al., 2013c). Nonetheless, the safety issues should be carefully considered, especially when treating atopic dermatitis in children. Over-use of *G. uralensis* Fisch. may cause hypokalemia, sodium retention, edema, and even congestive heart failure due to its aldosterone-like effect (Francini-Pesenti et al., 2008; Yasue et al., 2007).

Similarly, *L. japonica* Thunb. and *D. dasycarpus* Turcz. should be used carefully, especially since both are commonly used and frequently combined with core CHMs (Fig. 3a and b). Misuse of the aerial part rather than the root bark part of *D. dasycarpus* Turcz. may lead to liver injury (Saw, 1996; Vautier and Spiller, 1995). On the other hand, cadmium contamination may occur in *L. japonica* Thunb. due to its high resistance to cadmium accumulation (Liu et al., 2009). Therefore, these CHMs should be used with caution in terms of duration and dose.

Furthermore, comparisons of the CHM network for atopic dermatitis and urticaria leads to a greater understanding of the CHM treatment model, “bian-zheng-lun-zhi”, which means treatment decision based on identification of the TCM syndrome. Several TCM syndromes may be identified for one disease due to the variety of skin manifestations and the patients' constitution, and one syndrome may be found in all allergic diseases. For example, XFS, indicated for wind-dampness-heat syndrome, is the most important CHM for these diseases even if the pathogenesis of these diseases varies.

On the other hand, every disease has its own CHM network with different CHM and syndrome distributions. This is because the choice of CHM depends on both on the disease and TCM syndrome rather than on the disease alone, as in a Western medicine. Consequently, prescriptions of CHMs are much more complicated than Western medicine prescriptions and a network is needed to demonstrate the CHM treatment model, as the slogan “multiple target, complex disease” (Li, 2009).

5. Conclusions

Network analysis, composed of ARM and SNA, on CHM prescriptions is beneficial to realize combinations of CHM and core CHM in

treating specific diseases. This is helpful in understanding the art of prescribing CHMs and in choosing study candidates, especially when incorporating individual CHM characteristics and pharmacologic mechanisms into the network.

Conflict of interest

None.

Financial disclosure

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jep.2015.04.002>.

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Appendix 1. Potential pharmacologic mechanisms of Chinese herbal medicine (CHM) for allergic

dermatologic diseases

CHM	Ingredients	Possible pharmacological effects on urticarial
Single herb (SH)		
<i>Arnebia euchroma</i>	Hexane extract	Anti-microbial effect (Damianakos et al., 2012)
<i>Angelica dahurica</i>	Ethanol extract	Inhibitory effect on NO, TARC and MDC production; decreasing serum IgE and histamine in atopic dermatitis NC/Nga mice model(Lee et al., 2012)
	Isoimperatorin	Anti-inflammation via inhibiting cyclooxygenase-2/5-lipoxygenase activity in bone marrow-derived mast cells(Moon et al., 2008)
	Hexane extract	Anti-microbial effect for <i>Staphylococcus aureus</i> (Lechner et al., 2004)
<i>Bombyx mori</i>	Vitellogenin	Anti-microbial effect(Singh et al., 2013)
<i>Coptis chinensis</i>	Ethanol extract	Anti-oxidation effect(Ban et al., 2011)
	Water extract	Anti-inflammation effect(Choi et al., 2013)
		Anti-microbial effect(Nagajyothi et al., 2014)
<i>Cryptotympana pustulata</i>	N-acetyldopamine	Anti-inflammation, by inhibiting of IL-6, TNF- α (Xu et al., 2006)
<i>Coix lacryma-jobi</i>	Ethanol extract	Anti-inflammation, anti-allergic effects, reduction of histamine release in RBL-2H3 cells (Chen et al., 2012)
<i>Dictamnus dasycarpus</i>	Methanol extract	Improving allergic skin diseases in animal model; anti-inflammation, reduction of histamine release via p38 MAPK pathway in RBL-2H3 cells(Kim et al., 2013)
	Ethanol extract	Decrease histamine release from mast cells and vascular permeability in allergic animal model and in vitro(Jiang et al., 2008)
<i>Forsythia suspensa</i>	Isoforsythiaside	Anti-oxidation and anti-bacterial effect in vitro(Qu et al., 2012)
	Alkaloids	Anti-inflammation in vitro(Dai et al., 2009)
	Methanol extract	Reducing mast cell degranulation in allergic animal model induced by soybean(Hao et al., 2010)
	Forsythiaside	Anti-oxidation and anti-bacterial effect in vitro(Qu et al., 2008)

<i>Gardenia jasminoides</i>	Ethyl acetate fraction	Anti-allergic effect(Sung et al., 2014)
<i>Gleditsia sinensis</i>	Ethanol extract	Anti-allergy and anti-inflammation effect(Dai et al., 2002)
	Phenolic compounds	
<i>Glycyrrhiza uralensis</i>	Glycerol	Anti-microbial effect(Zhou et al., 2007)
		Immunosuppressive activity via inhibition of calcineurin activity in lymphocyte cell line(Li et al., 2010)
	Isoliquiritigenin	Inhibits iNOS and COX-2 expression via NF-kappa B pathway in macrophage cell line(Kim et al., 2008)
	Flavonoids	Anti-oxidation effect(Li et al., 2011)
		Inhibit memory Th2 response(Yang et al., 2013)
	Methanol	Anti-microbial effect for <i>Staphylococcus aureus</i> (Lee et al., 2009)
<i>Kochia scoparia</i>	Oleanane saponin	Anti-allergy effect via inhibiting of humoral immunity(Matsuda et al., 1997)
<i>Lonicera japonica</i>	Luteolin	Regulatory effect on mast cell-mediated inflammation (Kang et al., 2010)
	di-O-caffeoylquinic acids	Anti-bacterial effect(Han et al., 2014)
	Water extract	Anti-inflammation effect via inhibiting COX isoenzyme(Xu et al., 2007)
		Suppress histamine release from mast cell (Chan et al., 2008b)
<i>Lycium chinense or Lycium barbarum</i>	Hydrolysis	Anti-inflammation effect(Song et al., 2014)
	Ethyl acetate extract	Anti-oxidation effect(Jiang, 2014)
		Anti-microbial effect for <i>Staphylococcus aureus</i> (Lee et al., 2005)
<i>Mentha haplocalyx</i>	Water extract	Anti-inflammation and anti-allergic effect(Chan et al., 2008a)
<i>Morus alba</i>	Oxyresveratrol	Anti-inflammation via inhibition of MEK/ERK pathway(Chen et al., 2013)
	Ethanol extract	Anti-oxidation and anti-microbial effect(Wang et al., 2012b)
<i>Paeonia lactiflora</i>		Anti-allergic effect(Lee et al., 2008)
<i>Paeonia suffruticosa</i>	Water extract	Suppress histamine release (Chan et al., 2008b)
		Inhibit eosinophil migration from mast cell and inhibit the productions of IL-6, TNF-alpha (Kim et al., 2007)

<i>Prunus armeniaca</i>	Methanol and water extract	Anti-oxidation and anti-microbial effect(Yigit et al., 2009)
<i>Rehmannia glutinosa</i>	Water extract	Anti-allergic effect(Sung et al., 2011)
	Water extract	Anti-inflammation effect(Liu et al., 2012)
<i>Rheum palmatum</i> or <i>Rheum tanguticum</i> or <i>Rheum officinale</i>	Water extract	Regulation of immediate type allergic reaction (Kim et al., 1998)
	Ethanol extract	Anti-inflammation/anti-allergic effect via inhibiting 5-lipoxygenase catalyzed leukotriene production(Jin et al., 2011)
<i>Scutellaria baicalensis</i>	Ethanol extract	Anti-inflammation and anti-allergic effect via restoring IL-18 and TNF-alpha expression and inhibiting MAPK expression(Jung et al., 2012)
<i>Smilax glabra</i>	Water extract	Anti-inflammation effect(Jiang et al., 1997)
<i>Sophora flavescens</i>	Methanol extract	Anti-inflammation and anti-microbial effect(Han and Guo, 2012)
	Methanol extract	Anti-allergic effect(Kim et al., 2012)
<i>Taraxacum mongolicum</i>	Methanol extract	Anti-oxidation effect(Shi et al., 2008)
<i>Tribulus terrestris</i>	Water extract	Anti-oxidation effect(Kamboj et al., 2011)
	Water extract	Anti-microbial effect(Gopinath et al., 2012)
<i>Trichosanthes kirilowii</i>		Anti-inflammation effect(Akihisa et al., 1994)
<i>Schizonepeta tenuifolia</i>	Water extract	Anti-oxidation and anti-inflammation effect(Wang et al., 2012a)
	Ethanol extract	Anti-inflammation effect(Byun, 2014)
<i>Scrophularia ningpoensis</i>		Anti-microbial effect(Li et al., 2009)
<i>Viola prionantha</i>	Ethyl acetate extracts	Anti-microbial effect(Xie et al., 2004)
<i>Xanthium sibiricum</i>	Xanthanolide	Anti-microbial effect for <i>Staphylococcus aureus</i> (Sato et al., 1997)
Herbal formula (HF)		
Xiao-Feng-San		Inhibit IgE-dependent histamine release from mast cells (Shichijo and Saito, 1997)
		Anti-inflammation and anti-oxidation (Akamatsu et al., 1998)
		Reduce delayed-type hypersensitivity (Nose et al., 1999)
		Immuno-modulation of Th1 and Th2 cells(Gao et al., 2005)
Long-Dan-Xie-Gan-Tang		Immunomodulatory effects on CD4 ⁺ CD25 ⁺ T cells (Lee and Chang, 2010)

Huang-Lian-Jie-Du-Tang	Anti-inflammation, decrease cellular adhesion molecule expression (Wu et al., 2012) Immuno-modulation of Th1/Th2 in animal model(Gao et al., 2005)
Wen-Qing-Yin	Anti-allergic effect(Koda et al., 1987)

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