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Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Identifying core herbal treatments for urticaria using Taiwan's nationwide prescription database

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ARTICLE INFO

Article history:

Received 13 November 2012

Received in revised form

18 April 2013

Accepted 30 April 2013

Available online 14 May 2013

Keywords:

Association rule mining

Traditional Chinese medicine

National Health Insurance Research

Database

Urticaria

Xiao Feng San

ABSTRACT

Ethnopharmacological relevance: Urticaria is a common skin disease that has a high impact on a patient's daily life. Chinese herbal medicine (CHM) has been frequently used for treatment of skin manifestations in addition to Western medicine. The aim of this study is to analyze a nationwide prescription database to explore the most commonly used CHM for urticaria.

Materials and methods: A nationwide CHM prescription database was used, and data from ambulatory visits of patients with a single diagnosis of urticaria (ICD-9 code: 708) were identified for the study. Association rule mining was applied to explore the core formula and popular combinations of CHM for urticaria.

Results: A total of 33,355 ambulatory visits made by 12,498 patients were included in this study. On average, 6.18 CHMs were used per prescription. Xiao Feng San (XFS) and *Cryptotympana pustulata* Fabricius were the most commonly used herbal formula (HF) and single herb (SH), found in 49.44% and 24.67% of all prescriptions, respectively. XFS with *Cryptotympana pustulata* Fabricius were used most frequently in a two-combination CHM (9.95%). Moreover, XFS with *Kochia scoparia* (L.) Schrad. plus *Dictamnus dasycarpus* Turcz. were the most frequent three-combination CHM (3.46%). XFS was the core formula for urticaria since it was included in nearly all combinations prescribed for the treatment of urticaria.

Conclusions: XFS is the most important core herbal treatment used for urticaria in Taiwan, and *Cryptotympana pustulata* Fabricius with XFS is the most popular combination. Further well-designed clinical trials and animal model studies for urticaria are still needed to explore the efficacy and mechanism of CHM in urticaria.

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Abbreviations: TCM, traditional Chinese medicine; XFS, Xiao Feng San; JFBDS, Jing Fang Bai Du San; HF, herbal formula; SH, single herb; CAM, complementary and alternative medicine; CHM, Chinese herbal medicine; NHI, National health insurance; NHRI, National Health Research Institute; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Disease, 9th edition, Clinical Modification; ARM, association rule mining; IRB, Institutional Review Board; MMP-9, matrix metalloproteinase-9; MAPK, mitogen activated protein kinase; NF, nuclear factor; TNF, tumor necrosis factor; IL, interleukin; IgE, immunoglobulin E.

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1. Introduction

Urticaria, characterized by recurrent pruritic wheals with central pallor, is one of the most common dermatological diseases (Bossi et al., 2011). A high life-time prevalence, about 20% of the general population for any type of urticaria, is reported, and urticaria is the fourth most prevalent allergic disease (Ferrer, 2009; Zuberbier et al., 2009). A patient's quality of life is often severely affected, and comorbidities such as depression and anxiety, are often present owing to prolonged and easily relapsed clinical courses of urticaria (Herguner et al., 2011). Consequently, urticaria places a great cost burden on medical care due to its considerable influence on a patient's physical and social abilities (DeLong et al., 2008).

Currently, the pathogenesis of urticaria is not fully understood, and, therefore, several medications have been used alone or in combination for symptom relief. Mast cell degranulation, histamine release, autoimmune activation, chronic inflammation, immunoglobulin E (IgE) and anti-thyroid peroxidase antibody production, up-regulation of adhesion molecules, hyper-responsiveness to anti-IgE cross-linking on basophils, increase in coagulation activity, and oxidative stress have been reported previously as potential mechanisms of urticaria (Cassano et al., 2006; Bossi et al., 2011; Takeda et al., 2011). Because of these diverse and complicated disease mechanisms, a combination of medications is commonly used. Antihistamines, corticosteroids, and leukotriene antagonists all have anti-inflammatory effects and thus are commonly used in the United States for treatment of urticaria. The duration of the treatment ranges from 30 to 190 days (Zazzali et al., 2012).

Nevertheless, the efficacy of treatment on symptom control remains less than optimal even when multiple medications are used. Side effects and dependence on long-term medication use have been increasingly of concern. As a result, exploration of alternative therapies with more favorable safety profiles is urgently needed (Magerl et al., 2010; Zazzali et al., 2012). Complementary and alternative medicine (CAM), as an adjuvant therapy given in addition to primary treatment, have been used and studied increasingly in the recent years. Up to 82% of US patients with dermatological complaints have used CAM, mainly herbal or dietary supplements for relief of symptoms (Kalaaji et al., 2012). In Taiwan, traditional Chinese medicine (TCM) is the most common treatment used along with Western medicine, and Chinese herbal medicine (CHM) is the most popular type of TCM. Approximately 30% of all patients in Taiwan used TCM in 2001, and about 90% of TCM users received CHM as treatments for various diseases (Chang et al., 2007, 2008). However, large-scale and extensive study of the most commonly used CHM is lacking.

CHM use is unique in Taiwan because it is fully reimbursed by the National Health Insurance (NHI) as is Western medicine, and, therefore, people are able to freely choose this type medical of therapy. All CHM are prescribed electronically, and the information is stored in a computer database by the National Health Research Institute (NHRI) to form the National Health Insurance Research Database (NHIRD). Due to the high coverage by the NHI in Taiwan, including up to 98.3% of individuals by the end of 2006 and increasing substantially (Chen et al., 2012b), nearly all CHM prescriptions for urticaria are included in the NHIRD, making it feasible to conduct a nationwide analysis on the management of urticaria using this database.

The aim of this study was to explore the most commonly used CHMs for urticaria by analyzing the prescriptions from the nationwide database in Taiwan. To explore the effective CHM combinations for treating urticaria, association rule mining (ARM) was used. ARM is a recent technique that is widely applied to medical research on large-scale database, such as an analysis on CHM prescription patterns or comorbidities of diseases (Tai and Chiu, 2009; Chen et al., 2011). The results of this study can be used as a practical reference for further clinical trials or pharmacological experiments.

2. Material and methods

2.1. Data source

Information on CHM prescriptions extracted from the NHIRD was used in this study. Data from 2 million patients were randomly sampled from the entire NHIRD, and this sample database fully

reflected the entire NHIRD since patient characteristics were the same. From the sample database, each visits for TCM during 1998 and 2008 were used to compose the CHM prescription database. Since 1995, the year the NHI program start, all ambulatory visits were recorded in the NHIRD, including the visit date, patient identification numbers, patient sex, medical services facilities, diagnosis, interventions, and any TCM or Western medicine prescriptions. Patient identification numbers were encrypted, and written informed consent was exempted. The International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) was used for the diagnosis of every visit. TCM physicians may use up to three diagnoses for one ambulatory visit, and the first diagnosis must be the main reason for each visit.

2.2. Inclusion and exclusion criteria of studying subjects

To identify urticaria patients, TCM users with a primary diagnosis labeled ICD-9 code 708 were included. Visits for other TCM therapies, such as acupuncture and massage, were excluded to reduce the potential for confounding of prescribed medications. Additionally, visits with a second diagnosis were excluded to eliminate the considerable influence from comorbidities.

2.3. Chinese herbal medicine in Taiwan

Two kinds of CHM, herbal formula (HF) and single herb (SH), were reimbursed by the NHI. Every HF was a preformed powder mixture of several SH with a fixed proportion according to TCM classes and could be used as a single drug. In daily practice, HF was given mainly for a specific disease condition, and SH was usually used to strengthen the therapeutic effects of HF on the basis of patient's condition. As a result, multiple HF or SH were commonly used to make up prescriptions for different presentations of a specific disease. Essentially, analysis of the associations between CHM in all prescriptions made for urticaria would identify the main HF for a disease, namely the core formula, important HF/SH combinations and the main TCM concept for treatment of a disease (Kung et al., 2006; Chen et al., 2008, 2011).

2.4. Statistical analysis of the prescription database

Descriptive statistics were used for variables such as age and sex of TCM users in addition to prescribing patterns. Furthermore, ARM was applied to explore the possible combinations of CHM. Two decisive factors were needed in ARM for the effective exploration of meaningful combinations: support and confidence factors. The support factor was the frequency of all possible combinations among all prescriptions, which is similar to the concept of prevalence in epidemiology. Combinations were thought to be used frequently enough in daily practice only when the frequency was higher than the value of the support factor. The second factor, the confidence factor, was equal to the conditional probability of two CHM (A and B) over a single CHM (A), and higher confidence factor level represented closer association between CHM (A) and CHM (B).

The decision threshold for these two factors was the result of repeated scanning and examining processes. Consequently, under the supervision of experienced TCM physicians, the minimum support and confidence factors in this study were set to 1% and 30%, respectively; both values were similar those used in previous works (Hsieh et al., 2008; Chen et al., 2011). Only the CHM combinations with prevalence higher than 1% were kept, and only the significantly associated combinations (with a probability higher than 30%) were thought to be meaningful CHM combinations. The freeware "R", version 2.15.1, with package "arules" was

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