Identifying Chinese herbal medicine network for treating acne: Implications from a nationwide database

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ABSTRACT

Ethno-pharmacological relevance: Acne is a highly prevalent inflammatory skin disease which causes patients great psychological stress, especially teenagers. Chinese herbal medicine (CHM) is commonly used to treat acne with personalized but complicated prescriptions. The aim of this study is to determine a CHM network and core CHM treatments for acne by analyzing a nationwide database.
Materials and methods: From January 1st to December 31st, 2011, all CHM prescriptions made for acne (ICD-9-CM code: 706.0 or 706.1) were included in this study. Visits with acupuncture, manual therapy or other treatment modalities were excluded, and CHM visits with other diagnoses were also excluded in final analysis. Association rule mining (ARM) and social network analysis (SNA) were used to explore and demonstrate a CHM network.
Results: A total of 91,129 patients used traditional Chinese medicine, and 99% of them chose CHM for acne treatment. Most CHM users were teenagers, and there were twice as many female patients as male patients. A total of 279,823 CHM prescriptions were made for acne in 2011. Qing-Shang-Fang-Feng-Tang was the most commonly used CHM (31.2% of all prescriptions), and Zhen-Ren-Huo-Ming-Yin combined with *Forsythia suspensa* (Thunb.) Vahl. (Lian Qiao) was the most commonly used CHM-CHM combination. Thirty-one important CHM-CHM combinations were identified, and the CHM network could be built. Extensive coverage of the known pathogenesis of acne could be found in the CHM network when incorporating CHM pharmacological mechanisms into the network. Anti-inflammatory and anti-bacterial effects were commonly found in the CHM network, and CHMs with anti-androgen, anti-depressive and skin whitening effects were frequently used in combination.
Conclusions: The CHM combination patterns and core treatments for acne were disclosed in this study by applying network analysis to a CHM prescription database. These results may be beneficial for further bench or clinical studies when choosing target CHM.

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1. Introduction

Acne is the one of the most prevalent chronic inflammatory cutaneous disorders, and more than 70% of people report having acne during and after their teenage years, most of whom are women (Collier et al., 2008). Although acne rarely causes death directly, psychological stress due to scars and pustule lesions on the face can have a high emotional impact on a patient's life, especially when up to 20% of teenagers may have lifelong scars due to acne (Misery, 2011; Williams et al., 2012). Multiple factors are associated with the pathogenesis of acne, including follicular hyperkeratinization, androgen-induced sebum hyper-production, follicles infected with *Propionibacterium acnes* and inflammation (Kurokawa et al., 2009). Multiple treatments including antibiotics, topical retinoid, oral isotretinoin, benzoyl peroxide, azelaic acid, salicylic acid, and hormone therapy are often used alone or in combination to control symptoms; nevertheless, there are still limitations with these treatments. In addition to potential gastrointestinal upset, the emergence of antimicrobial resistance in

the community should be considered after the extended use of oral antibiotics (Williams et al., 2012). Oral isotretinoin is currently the only acne treatment that can alter the natural course of the disease; however, it is associated with teratogenicity, cheilitis, skin and mucosal dryness, eczema, liver toxicity, tiredness, epistaxis, desquamation, photosensitivity, and even inflammatory bowel disease (Etminan et al., 2013; Rademaker, 2010).

Traditional Chinese medicine (TCM) is one of the most commonly used alternative medicines in Taiwan due to easy accessibility with full national health insurance coverage (Chen et al., 2007; Chen et al., 2012). Several modalities such as Chinese herbal medicine (CHM), acupuncture and cupping therapy are used, with CHM being the most common (Cao et al., 2015). CHM is often used to alleviate the severity of acne by clearing heat toxins and dampness, which are regarded as the main causes of acne from a TCM viewpoints (Cao et al., 2015). Nevertheless, the considerable complexity of CHM prescriptions makes it difficult to gain insights into CHM with regards to the mechanisms and application into clinical practice, since TCM doctors usually use several CHMs in combination to treat a disease. This may cause high heterogeneity when performing a meta-analysis on the efficacy of CHM, and may also account for substantial discrepancies between the CHM used in real clinical practice and research targets in bench studies (Hu et al., 2011). Moreover, this discrepancy may become greater if the study target is selected from a textbook or TCM classics due to the considerable differences in prescribing CHMs between practice and literature (Scheid et al., 2010).

The aim of this study was to identify a CHM network for treating acne by analyzing a nationwide prescription database. It is difficult to analyze multiple CHMs used in a huge prescription database using conventional statistical methods. CHM network analysis, based on the most commonly used single CHM and CHM combinations, is crucial to understand what and why certain CHMs are prescribed and how TCM doctors treat a disease (Chen et al., 2015b; Poon, 2014).

2. Material and methods

2.1. Data source

The National Health Insurance Research Database (NHIRD), which includes more than 99% of all medical records in Taiwan, was used as the prescription data source in this study. The NHIRD includes all medical information required by the National Health Insurance (NHI) program since 1995, and it is updated on a regular basis. Due to the high coverage, prescription analysis can be regarded as a form of consensus from all clinicians in Taiwan (Chen et al., 2012). Patient information including gender, birth date, place of residence, reasons for medical visits, medications, interventions, examinations, hospitalization and medical expenses are all digitized and stored in the database. The NHIRD is provided publicly for researchers, and the identification of each patient is encrypted to protect their privacy. The protocol of this study was approved by the Institutional Review Board of Chang Gung Memorial Foundation (No.: 104-4077B).

2.2. Study design and subjects

Acne patients who had used at least one TCM from January 1 to December 31, 2011 were defined as TCM users. All medical care records with a single diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 706.0 or 706.1 were included in this study. Acne is diagnosed mainly by skin manifestations, including open or closed comedones, inflammatory follicles, post-inflammatory scarring and hyperpigmentation (Eichenfield et al., 2013). The accuracy and reliability of using ICD-9-CM codes as reasons for visits has been well validated in previous studies (Chen et al., 2010; Cheng et al., 2011). Visits for reasons other than CHM treatment, such as acupuncture and manual therapy were excluded.

2.3. CHM prescription dataset

CHM prescriptions were extracted from all eligible visits for acne, and a new CHM prescription dataset was generated by integrating CHM prescriptions with CHM users' information. A herbal formula (HF) and single herb (SH) are the only two kinds of CHM reimbursed by the NHI in Taiwan. A HF is made from a mixture of SHs with fixed a composition according to CHM classics, while a SH includes herbs, animals, insects, and minerals. According to CHM classics, every HF and SH has its own indications, which are usually aimed at treating certain TCM syndromes. All HFs and SHs are made into concentrated powder by the Good Manufacturing Pharmacy in Taiwan with strict regulation of heavy metals, insecticides and other possibly poisonous materials.

2.4. Bias assessment

This dataset is unique and particularly suitable for CHM prescription analysis due to its high coverage of the general population in Taiwan and unbiased selection of CHM as a treatment option (Chen et al., 2015b). In addition, by using a nationwide database, potential selection bias and referral bias can be avoided as much as possible compared to the use of a hospital-based database (Pan et al., 2014). Although the use of a single diagnosis of acne to extract medical records may markedly decrease the number of cases, this may avoid possible confounding bias caused by other co-morbidities. In addition, the exclusion of visits for acupuncture, moxibustion, or manual therapy is helpful to avoid confounding bias with a possible influence on CHM prescriptions.

2.5. Statistical analysis

Descriptive statistics were used to present the features of CHM users and prevalence of CHMs. Association rule mining (ARM) and social network analysis (SNA) were used to analyze and graphically demonstrate the combinations of CHMs. ARM is a novel data mining technique which has been widely used to explore important connections between subjects in a big database such as co-morbidities, combination patterns of CHMs, relationships between TCM syndromes for allergic rhinitis, and DNA-protein binding patterns (Chen et al., 2015b; Feng et al., 2006; Leung et al., 2010; Lin et al., 2013; Tai and Chiu, 2009; Yang et al., 2012). Every possible CHM combination was evaluated using three parameters: support, confidence and lift. Support is similar to the prevalence of a certain CHM or CHM combination, while confidence and lift factors are used to evaluate the strength of connections between the CHM with a concept similar to conditional probability (Agrawal et al., 1993; Chen et al., 2014b; Yang et al., 2013a). Significant CHM combinations were identified from the entire CHM dataset only when the value of these three parameters was higher than a preset, and this was an iterative process to reveal the most significant CHM combinations. Furthermore, SNA was used to analyze the relationships between every CHM within all important CHM combinations with a graphical demonstration of the relationships and clusters of all CHMs. The detailed algorithm has been described in previous studies, and "R" and "NodelXL" software were used to perform ARM and SNA (Chen et al., 2015b; Wakita and Tsurumi, 2007; Yang et al., 2013b).