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# Investigation on Chinese herbal medicine for primary dysmenorrhea: Implication from a nationwide prescription database in Taiwan



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## KEYWORDS

Primary dysmenorrhea; Chinese herbal medicine; The National Health Insurance Research Database; Association rule mining

## Summary

**Objective:** Primary dysmenorrhea is a common gynecological condition, for which Chinese herbal medicine (CHM) has been widely used in addition to western medicine. The aim of this study is to explore CHM commonly used to treat dysmenorrhea in young Chinese women.

**Design:** Observational retrospective study.

**Setting:** The National Health Insurance Research Database in Taiwan.

**Population:** Women aged from 13 to 25 years with single diagnosis of primary dysmenorrhea.

**Methods:** CHM prescriptions made for primary dysmenorrhea women during 1998–2008 were extracted to build up CHM prescription database. Association rule mining was used to explore the prevalent CHM combination patterns in treating primary dysmenorrhea.

**Main outcome measures:** Prevalence and mechanisms of CHM combinations.

**Results:** Totally 57,315 prescriptions were analyzed and, on average, 5.3 CHM was used in one prescription. Dang-Gui-Shao-Yao-San (DGSYS) was the most commonly used herbal formula (27.2%), followed by Jia-Wei-Xiao-Yao-San (JWXYS) (20.7%) and Wen-Jing-Tang (WJT) (20.5%).

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*Corydalis yanhusuo* and *Cyperus rotundus* were the most commonly used single herb, found in 33.1% and 29.2% of all prescriptions. Additionally, *C. yanhusuo* with *C. rotundus* is the most commonly used two CHM in combination, accounting for 14.24% of all prescriptions, followed by DGSYS with *C. yanhusuo* (10.47%). Multi-target effects on primary dysmenorrhea, such as analgesia, mood modifying and hormone adjustment, were found among commonly prescribed CHM in this study.

**Conclusions:** This study discovered the potential importance of *C. yanhusuo*, *C. rotundus* and DGSYS in treating primary dysmenorrhea. Further clinical trials or bench studies are warranted based on the results.

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## Introduction

Dysmenorrhea is the most prevalent gynecological discomfort among women during reproductive age and it is also the main reason for sick leave or short-term absenteeism among school-aged girls.<sup>1,2</sup> Six-hundred million hours lost from work and two billion US dollar economic cost was reported in the mid 1980s in the United States and the cost is believed to be much higher today.<sup>3,4</sup> Primary dysmenorrhea is characterized by cramping, colicky, or dull suprapubic pain associated with menses in the absence of other gynecologic pathology such as endometriosis, uterine myoma, or malformation of genital organs; additionally, this pain usually happens few hours before or after onset of menstrual bleeding; the duration of pain may last 2–3 days.<sup>5</sup> The onset of primary dysmenorrhea is usually during mid and late adolescence after normal ovulatory patterns are established.<sup>1</sup>

The mechanisms of primary dysmenorrhea have been attributed to the high serum level of prostaglandin E2 (PGE2), prostaglandin F2- $\alpha$  (PGF2- $\alpha$ ), and leukotriene among primary dysmenorrhea women. Severe myometrial contraction, vasoconstriction, uterine ischemia, and subsequent dysmenorrheic pain are resulted from the release of these cytokines. Moreover, progesterone withdrawn before the beginning of menstrual cycle initiates the arachidonic acid release and further cytokine from degradation of arachidonic acid. Higher cytokine level contributes to higher intensity of dysmenorrhea pain and the associated symptoms.<sup>6–8</sup> Non-steroid anti-inflammatory drugs (NSAID), therefore, are the primary treatment for this condition, but are limited by inadequate pain control, gastrointestinal discomfort and impact on renal function. Combined oral contraceptives are also frequently used, but are not universally accepted perhaps due to its potential side effects on inducing endometriosis.<sup>2,9</sup> For the above reason, alternative therapies are in high demand in many countries.<sup>10</sup>

Chinese herbal medicine (CHM) is well-accepted and commonly used in Taiwan to treat various conditions, such as menopausal symptoms, gastrointestinal dysfunction and allergic diseases.<sup>11,12</sup> For primary dysmenorrhea, CHM has been shown to be more effective than other TCM interventions, such as acupuncture in previous meta-analysis, although the quality of clinical trials were generally poor.<sup>4</sup> In addition to diagnosis of a particular disease, TCM doctors focus on the sub-categories of disease, namely ‘‘syndrome’’, or ‘‘zheng’’ in Chinese; for example, cold-dampness stagnation, and blood-qi stagnation syndrome of dysmenorrhea.<sup>13,14</sup> Each TCM syndrome is judged by TCM doctor on the basis of patient’s physical condition, disease

status, and constitution,<sup>15</sup> after which CHM prescriptions for treatment are given. The combinations of CHM used to treat dysmenorrhea are heterogeneous and not well-characterized. Identifying these common combinations of CHM will enhance understanding of diseases and focus intervention trials. Therefore, the aim of this study is to determine the pattern of use of CHM to treat primary dysmenorrhea in young Chinese women by using a nationwide prescription database.

## Methods

### Chinese herbal medicine (CHM) in Taiwan

The National Health Insurance (NHI), which provides coverage for more than 98% of the population of Taiwan, includes prescription coverage for CHM. Prescriptions for CHM and western medicine (WM) are equally covered by national health insurance in Taiwan, and therefore patients are free to choose treatments. There are two types of CHM reimbursed by the NHI in Taiwan, herbal formulas (HF) and single herbs (SH). SH are single Chinese medical substances recorded in the ancient classics, and they are obtained and processed from individual plants, animals, insects or even minerals. In contrast, HF are mixtures of several SH with fixed proportions according to ancient TCM classics and have specific indications to TCM syndrome and purported therapeutic effectiveness. HF and SH are all processed into concentrated powders. Additionally, CHM in Taiwan is provided by pharmaceutical manufacturers with certificates of Good Manufacturing Practice and is closely monitored by the government.

### Chinese herbal medicine (CHM) prescription database

The national insurance claim database captures contents of every ambulatory visits, including reasons for visits, facilities visited, examinations ordered by doctors, and prescriptions. Additionally, patients’ characteristics are recorded in detail, such as gender, birth date, critical illness and identification number. All these claim data are re-compiled by the National Health Research Institutes (NHRI) to build up the National Health Insurance Research Database (NHIRD). The NHIRD becomes a nationwide database since the coverage of the national health insurance (NHI) is as high as 98.3% and keeps increasing. From the entire database, a total of two million patients were sampled randomly by the

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