ABSTRACT
Dysmenorrhea is one of the most common gynecologic complain, especially among young women. It influences daily activities, and lowers life quality. In clinical practice, non-steroidal anti-inflammatory drugs (NSAIDs) are used as the first-line treatment for dysmenorrhea. However, long-term use of these medications is associated with side effects. Some Chinese herbal medicines (CHMs) were reported to be effective and safe for dysmenorrhea. However, it is not easy to know well with the treatment principles of dysmenorrhea. This study is aimed to explore the basic treatment principles of dysmenorrhea with text mining technology by mining syndromes and CHMs prescriptions of dysmenorrhea and the connections between them under the framework of traditional Chinese medicine (TCM). The text mining results show that blood stasis due to cold, deficiency of qi and blood, stagnation of cold-dampness, stagnation of liver-qi, blood stasis, deficiency of liver and kidney, yin deficiency of kidney, yin deficiency of liver and kidney, and qi stagnation due to cold are the top 10 syndromes in dysmenorrhea. And from these syndromes, we can extract that blood stasis, qi stagnation, cold coagulation, cold-dampness, and deficiency of vital qi are the main pathologic factors of dysmenorrhea, and blood stasis is the most important one among them. Radix Angelicae Sinensis, Rhizoma Corydalis, Radix Paeoniae Alba, Ramulus Cinnamomi, Rhizoma Chuanxiong, Poria, Rhizoma Cyperi, Radix Salviae Miltiorrhizae, Flos Carthami, and Radix Glycyrrhizae are the top 10 CHMs used for dysmenorrhea. And drugs of relieving pain by activating blood flow and dissolving blood stasis such as Radix Angelicae Sinensis, Rhizoma Corydaldis and Rhizoma Chuanxiong are most often prescribed. From these results, we can draw a conclusion that relieving pain by activating blood circulation and resolving blood stasis is a basic treatment principle for dysmenorrhea.
1. INTRODUCTION
Dysmenorrhea is a kind of periodic gynecopathy, which happens on lower abdominal pain, or lumbosacral dragging pain, even syncope due to megalgia during menstruation and before or after of it. Western dysmenorrhea divides it into primary dysmenorrhea (menstrual pain without pelvic abnormality) and secondary dysmenorrhea (menstrual pain with pelvic abnormality). The former is often associated with some symptoms including lethargy, tiredness, depression, inability to concentrate in work [1]. The latter is secondary to certain pelvic abnormality (i.e. endometriosis, adenomyosis, chronic pelvic inflammation, gynecological tumor, etc.), and it is usually accompanied some gynecologic symptoms including dysuria, abnormal uterine bleeding, chronic pelvic pain, uterine fibroids and infertility [2, 3]. Dysmenorrhea is a very common health problem in gynecology [4-6], especially among young women. A study showed that among 3,340 girls, 86.6% suffered from dysmenorrhea-related symptoms: 12.4% described having severe dysmenorrhea and 74.2% moderate dysmenorrhea [7]. Dysmenorrhea has negative effects on daily activities, academic activities, and quality of life [1, 4, 7-10].

Modern medicine considers that primary dysmenorrhea is related with excessive production and release of endometrial prostaglandin (PG) during menstruation. A content increase of PGF2 is a major cause of dysmenorrhea. Menstrual pain gets worse as PGF2 increases and PGE2 decreases because the former causes contraction and the latter relaxation of the uterine smooth muscle. In west medicine, secondary dysmenorrhea is treated differing from disease to disease, primary dysmenorrhea is commonly treated with non-steroidal anti-inflammatory drugs (NSAIDs), and anti-spasmodic drugs [7, 11, 12]. NSAIDs are considered the first-line of treatment for dysmenorrhea [7]. Although their effect is useful and rapid, however, these drugs exert side effects when administered over a long period of time and alternatives must be available [11].

Chinese medicinal therapy is considered as a feasible alternative medicine [13]. Traditional Chinese medicine (TCM) holds that the major pathogenesis of dysmenorrhea lies in pathogenic factors lurking in interior or deficiency of essence and blood meet with the rapid physiological change of qi and blood of the both Chong and Ren meridians during menstruation and before or after of it, which results in disharmony of qi and blood of uterus or malnutrition of the uterine. Many Chinese herbal medicines (CHMs) are aimed to regulate the flow of qi and blood and to return the body to a harmonious [14]. And they are effective for dysmenorrhea [15-17], some of them with fewer side effects [15].

Because of the complication of TCM theory, the principles of treatment of dysmenorrhea are not easy to manage. This study is with the purpose of exploring the basic treatment principles of dysmenorrhea with a text mining technology through mining syndromes and CHMs prescriptions of dysmenorrhea and the correlations between them under the framework of TCM theory.

2. MATERIAL AND METHODS
2.1 Data Collection
The dataset were downloaded from SinoMed (http://sinomed.cintcm.ac.cn/index.jsp) on the default query strategy with the query term of “dysmenorrhea” on Oct. 24, 2012. This dataset contains 7,952 records of literatures on clinical practices or theoretical research on dysmenorrhea. In this dataset, each record/paper is tagged with a unique ID. These records contain the title, keywords, and abstract of published papers [18].

2.2 Data Filtering
With the data set on dysmenorrhea was downloaded from SinoMed database. The regularities of TCM patterns and CHMs on dysmenorrhea were mined by data slicing algorithm [18].

Pattern (also called as Syndrome, or Zheng) differentiation is regarded as the key role in the clinical practice of TCM [19]. Usually, pattern identification is the basis of the prescription of herb
formulæ, CHMs, or other TCM therapies. Thus it is natural and intuitive to filter out the pattern and then try to find the association regularities between pattern and CHMs.

Based on the keyword list of CHMs (both legal names and other popular names are included for calculation), we filtered the CHMs in the plain text format, and then converted all popular names into legal names. All the CHMs were tagged with their unique paper ID. Based on the unique paper ID, we could construct the pairs of CHMs co-existed in literature. For example, in one paper, CHMs of Radix Angelicae Sinensis, Rhizoma Cyperi, and Rhizoma Chuanxiong are mentioned. Then, the pairs of co-existed CHMs of “Radix Angelicae Sinensis - Rhizoma Cyperi”, “Radix Angelicae Sinensis - Rhizoma Chuanxiong”, and “Rhizoma Cyperi - Rhizoma Chuanxiong” are constructed.

With these pairs of patterns or CHMs, the networks of patterns and CHMs in dysmenorrhea treatment can be showed visually with Cytoscape 2.8 software, respectively. By checking these two networks, the correlation between TCM patterns and CHMs can be analyzed and explored.

3. RESULTS

In this paper, focused on dysmenorrhea, we explored the principles of pattern differentiation and CHMs prescriptions and the association between the two aspects under the framework of TCM theory from 7,952 literatures. The network construction is based on the analysis of networks of pattern and CHM correlated with dysmenorrhea in literature. The correlations among these networks are built-up under the professional knowledge of TCM.

3.1 Major TCM Patterns in Dysmenorrhea

As a result, a total of 116 TCM patterns are detected to be related with dysmenorrhea, and the top 10 TCM patterns are presented in Figure 1. The top 10 patterns are blood stasis due to stagnation of qi, blood stasis due to cold, and deficiency of qi and blood in dysmenorrhea, stagnation of cold-dampness, stagnation of liver-qi, blood stasis, deficiency of liver and kidney, yin deficiency of kidney, yin deficiency of liver and kidney, qi stagnation due to cold. As can be seen in Figure 1, the toppest pattern is blood stasis due to stagnation of qi, and the next one is blood stasis due to cold.

3.2 Most Frequently Prescribed CHMs in Dysmenorrhea Treatment

Altogether 208 CHMs are mined from the literature in treatment of dysmenorrhea. The top 10 frequently prescribed CHMs are shown in Fig. 2. It demonstrates that Radix Angelicae Sinensis is most frequently prescribed in dysmenorrhea management, which is used for enriching blood and promoting blood flow, and regulating of painful menstruation. As to others, i.e., Rhizoma Corydalis, Rhizoma Chuanxiong, Radix Salviae Miltiorrhizae, and Flos Carthami are used for promoting blood circulation to remove blood stasis, regulating menstruation and relieving pain; and additionally Rhizoma Corydalis, Rhizoma Chuanxiong can promoting qi circulation; Ramulus Cinnamomum is used for warming and clearing meridians; Poria is used for removing dampness by promoting diuresis; Rhizoma Cyperi is used for soothing liver, regulating qi, regulating menstruation and relieving pain; Radix Paeoniae Alba is used for nourishing blood for regulating menstruation, calming liver and relieving pain; Radix Glycyrrhizae is used for supplement qi. And among these CHMs, drugs of relieving pain by activating blood circulation are most often used.

3.3 Networks of the Pattern and CHMs in Dysmenorrhea

A total of 375 co-existed TCM pattern pairs and 1,975 co-existed CHMs pairs are mined out, respectively. We construct the networks of these pairs with Cytoscape 2.8 software. In order to achieve better visualization, we choose TCM pattern pairs with threshold ≥10 and CHMs pairs with threshold ≥20 to construct the networks of patterns and CHMs in dysmenorrhea. The networks of Syndrome and CHMs with their correlations on dysmenorrhea are demonstrated in Fig. 3. The major correlations between TCM patterns and CHMs are demonstrated with arrows. Network of syndrome is shown in the lower part, network of CHMs in upper part. Bigger shape represents higher frequencies. The lines between the shapes represent the correlations between the two patterns/CHMs. Arrows represent the correlations between TCM patterns and CHMs. By checking these two
networks, the correlations between TCM patterns and CHMs can be analyzed and explored.

4. CONCLUSION AND DISCUSSION

Based on the text mining technology, it is naturally come to a point that TCM treatment principles of a disease could be mined out. From the dataset downloaded from SinoMed, we conducted a study to explore the basic treatment principles on dysmenorrhea and some conclusions can be found out as followings.

4.1 Major TCM Patterns in Dysmenorrhea can be Mined out

Pattern identification is regarded as the first step during TCM clinical practice procedure. After the pattern is approved, the treatment principle can be determined. For example, when the pattern of blood stasis due to stagnation of qi is approved, then the treatment principle of promoting blood flow and qi circulation is determined. Fig. 1 and the lower part of Fig. 3 show all the main patterns in dysmenorrhea. The major TCM organs (different from modern medical concept) involved in dysmenorrhea development are liver, and kidney. Excess and deficiency syndromes are usually coexisted in the pathogenesis of dysmenorrhea. From these syndromes, we can extract that the related pathologic factors of sthenic syndrome in dysmenorrhea include blood stasis, qi stagnation, cold coagulation, cold-dampness. Factors of asthenic syndrome generally include deficiency of qi, blood, yin. And blood stasis is the most important one among these factors. Thus, a basic treatment principle of promoting blood circulation and resolving blood stasis for dysmenorrhea can be considered.

4.2 Most often Prescribed CHMs in Dysmenorrhea Treatment can be Figured out

As herbal formulae are composed by the CHMs, the list of most frequently used CHMs can certainly provide the information of TCM treatment principles effectively due to the stability and uniqueness of each CHMs. Fig. 2 And the upper part of Fig. 3 show that these CHMs can be grouped into two major classes, one group is responsible for dispelling excess including clearing away blood stasis, qi stagnation, cold coagulation and cold-dampness. The other one focuses on strengthening vital qi. Among these CHMs, drugs with the function of relieving pain by activating blood circulation such as Radix Angelicae Sinensis, Rhizoma Corydalis, Rhizoma Chuanxiong are most often prescribed and they are also frequently used together with others. These results are corresponding with patterns.

4.3 The Basic Treatment Principles of Dysmenorrhea can Be Drawn out

In this study, through mass calculation on dataset on dysmenorrhea, the internal connections between TCM patterns and CHMs can also found among TCM networks. These internal connections can be grouped into two major hierarchical clusters. Each cluster of CHMs is associated with one major kind of patterns. The major treatment principles of TCM treatment of dysmenorrhea can be explored by text mining method and summarized in a succinct figure. From these connections, we found blood stasis is the most important pathologic factors in dysmenorrhea and drugs of relieving pain by activating blood and dissolving stasis are most often used. From these results, we can draw a conclusion that relieving pain by promoting blood circulation and resolving blood stasis is a major treatment principle for dysmenorrhea. These results indicate that text mining technology provides a novel method in exploring the regularity of treatment principles in dysmenorrhea.

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6. REFERENCES

Figure 1. Top 10 TCM patterns in Dysmenorrhea

Blood stasis due to stagnation of qi
Blood stasis due to cold
Deficiency of qi and blood
Stagnation of cold-dampness
Stagnation of liver-qi
Blood stasis
Deficiency of liver and kidney
Yin deficiency of kidney
Yin deficiency of liver and kidney
Qi stagnation due to cold

Figure 2. Top 10 frequently prescribed CHMs in treatment of dysmenorrhea

Radix Angelicae Sinensis
Rhizoma Coptidis
Radix Paeoniae Alba
Ramulus Cinnamomi
Rhizoma Chuanxiong
Poria
Rhizoma Cyperi
Radix Salviae Miltiorrhizae
Flos Carthami
Radix Glycyrrhizae
Figure 1. Networks of TCM patterns and CHMs in treatment of dysmenorrhea


