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Review

# Therapeutic effects of traditional Chinese herbal prescriptions for primary dysmenorrhea

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ABSTRACT

Primary dysmenorrhea is a common disease among females in their reproductive age and adolescents. The main complaint is lower abdominal pain during menstruation. Females, who suffer from dysmenorrhea, widely use nonsteroidal anti-inflammatory drugs that reduce muscle spasm by inhibiting prostaglandin synthesis and vasopressin secretion. However, there are side effects when patients take them for a long time. It is therefore against this backdrop that herbal medicines are suggested as an alternative source of treatment for primary dysmenorrhea. In this paper, a review of studies demonstrating the relieving of uterine contraction and reduction in prostaglandin synthesis by alternative sources such as traditional Chinese medicines (TCM) is spelt out. TCM conceptualizes that, menstrual pain resulting from *qi* is due to stagnated and retained blood. Blood deficiency and coldness in the whole human body are two additional causes of dysmenorrhea. Therefore, based on these, the main focus of treatment is directed at relieving the above symptoms. Chinese herbal prescriptions exert their effects through these mechanisms: prostaglandin reduction, inhibition of cyclooxygenase, intracellular $Ca^{2+}$, and nitric oxide, declining malondialdehyde, and reverse increasing superoxide dismutase. Hence, Chinese herbal prescriptions, present perhaps a more beneficial efficacious alternative in the treatment of primary dysmenorrhea, more especially in the confines of complementary and alternative medicine.



**Contents**



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## 1. Introduction

Dysmenorrhea is one of the most frequently encountered gynecologic disorders (Rafique & Al-Sheikh, 2018). It refers to painful menstruation that is often accompanied by cramps and contractions in the lower abdominal region during the menstruation, and is a common gynecological complaint among adolescent girls and women of reproductive age (Unsal, Ayranci, Tozun, Arslan, & Calik, 2010). General dysmenorrhea is usually classified into two subcategories: primary dysmenorrhea (PD) and secondary dysmenorrhea (Ju, Jones, & Mishra, 2014). Primary dysmenorrhea occurs in the absence of an identifiable pathological condition (Lichten & Bombard, 1987). When the menstrual pain is associated with an organic pathology such as endometriosis, pelvic inflammatory disease, intra-uterine devices, irregular cycles or infertility problems, ovarian cysts, adenomyosis, uterine myomas or polyps, intra-uterine adhesions, cervical stenosis etc., it is defined as secondary dysmenorrhea (Proctor & Farquhar, 2006). The prevalence rates of dysmenorrhea differ by age. However, more than 50% of women in all age groups experience dysmenorrhea. The prevalence rate of dysmenorrhea worldwide is between 50.9% and 87.4% (Nur Azurah, Sanci, Moore, & Grover, 2013). Menstrual disorders are key health issues for adolescent girls because they influence not only upcoming fertility, but also mental health and quality of life (Davis & Westhoff, 2001). Associated with the pain, are headaches, nausea, vomiting, backache, general weakness, and gastrointestinal symptoms (Abdul-Razzak, Ayoub, Abu-Taleb, & Obeidat, 2010). In PD, pain begins few hours before or after the onset of menstruation and lasts for 24–48 h. The pain usually occurs in the 1st day and rarely continues to next day (Mahvash et al., 2012). Means of pharmacological therapies for dysmenorrhea contain nonsteroidal anti-inflammatory drugs (NSAIDs) (Dawood, 2006; Uysal et al., 2016) which relieve the activation of the myometrium by inhibiting prostaglandin synthesis and the excretion of vasopressin (Angelo Mieli, Adri Cezarino, Ramos Margarido, & Simões, 2013; Ryan, 2017). Although the fact that these drugs are approved in cases of dysmenorrhea, there are several conditions such as insufficient pain control, gastrointestinal discomforts, and long haul renal dysfunction (Green, 2001). In clinical settings, patients who do not respond to drugs, have surgical options being recommended, but it is not certainly an appropriate option of treatment since there are not recorded in studies with evidence of its long-term efficacy (Latthe, Proctor, Farquhar, Johnson, & Khan, 2007). These limitations of conventional treatments therefore thrusts herbal medicines as measured possible alternatives for the treatment of dysmenorrhea (Hsu, Yang, & Yang, 2006; Jenabi & Fereidoony, 2015). Herbal medicines have been in usage in Eastern countries for a long time. Recent times have seen an overwhelming global usage of herbal medicines (Nahid, Fariborz, Ataolah, & Solokian, 2009; Rashidi, Mirhashemi, Taghizadeh, & Sarkhail, 2013). Moreover, the supply and demand of complementary and alternative medicine (CAM) in many countries is increasing (Tabish, 2008). Studies reported that more than 48% of women must use of CAM for either prescriptions or enhancing the helpfulness of their prescriptions (Eisenberg et al., 1998; Lloyd & Hornsby, 2009). The side effects of CAM are less than those of NSAIDs (Gollschewski, Anderson, Skerman, & Lyons-Wall, 2004). Chinese herbal prescriptions have been recorded in history for more than 2000 years. In China, there have been more than 100 clinical trials exploring the impact of herbal prescription on female-specific diseases (Flower, Lewith, & Little, 2011).

Currently, pre-clinical and clinical-trial studies of Chinese herbal prescriptions have widely been increased and developed in female-specific diseases particularly for dysmenorrhea. In China, traditional Chinese prescriptions are already used as an alternative treatment for dysmenorrhea. This paper is scoped to review the findings of the studies on pre-clinical and clinical trials as regards the efficacy of Chinese herbal prescriptions on primary dysmenorrhea. We have analyzed the obtainable experimental outcomes regarding Chinese herbal prescriptions used for PD and the underlying fundamental mechanisms.

## 2. Principal causes of primary dysmenorrhea in Western and Eastern medicines

PD is one of the most common female-specific disease conditions (Mannix, 2008). At the beginning of menstruation, the first symptom of PD is manifested by lower abdominal pain, backache, headache, and often times after menarche when the ovulatory cycles are established (Charu, Amita, Sujoy, & Thomas, 2012). The incidence of PD is 25% the number of women and 90% of adolescents globally, and nearly 15% patients have severe pain (French, 2005; Singh et al., 2008). A recent study has shown that, the 18–36 age group records the most incidence cases in Turkey (Aktaş, 2015). A Japanese study also described that the prevalence of dysmenorrhea proportion is dependent on age and thus reported 31.6% for 12-year-old, 39.5% for 13-year-old, 50.3% in 14-year-old, and 55% in 15-year-old (Kazama, Maruyama, & Nakamura, 2015). A Chinese study also showed that the incidence of dysmenorrhea was 54% female college students in the age range of 16–22 among the female students in college (Zhou, Yang, & Group, 2010). Therefore, the above studies provide an evidence of dysmenorrhea occurring much more in younger females.

The causative reason for PD is not well explained; Although, the accountable reason has been attributed to the over synthesis of prostaglandins in the endometrium (Bonney & Franks, 1987; Masoumi, Asl, Poorolajal, Panah, & Oliaei, 2016; Wu, Huang, Kapoor, Chen, & Huang, 2008). Another study defined myometrial hyperactivity symptom as the main cause of PD, which comes about due to high prostaglandins level, particularly PGF2$\alpha$ and PGF2 which have roles of increasing uterine muscle tone and high-amplitude contractions (Akerlund, 1979; Gao, Jia, Zhang, & Ma, 2017), as well as arachidonic acid is obtained from phospholipids by the phospholipase $A_2$ enzyme (Iacovides, Avidon, & Baker, 2015; Jabbour, Sales, Smith, Battersby, & Boddy, 2006; Sales & Jabbour, 2003). Particularly, cyclooxygenase (COX) acts on arachidonic acid and yields cyclic endoperoxides prostaglanding G (PGG) and prostaglanding H (PGH) that play a role to ensure rise in prostaglandins level, which generates powerful vasoconstriction and myometrial contractions (Fig. 1). PD is believed to be associated with many factors, including behavioral and psychological aspects. An age of under 20 years, nulliparity, heavy menstrual flow, smoking, high socioeconomic status, attempts to lose weight, physical activity, disruption of social networks, depression, and anxiety are risk factors of dysmenorrhea (Hailemeskel, Demissie, & Assefa, 2016).

According to theories of traditional Chinese medicine (TCM), the main cause of dysmenorrhea is *qi* stasis caused by the invasion of the six exogenous pathogenic factors (Li et al., 2015). *Qi* stasis then results in the blockage of blood flow, which further leads to blood stasis and lumps (Han, 2016; Su et al., 2013a). Menstrual pain resulting from *qi* is thus due to stagnated and retained blood. Blood deficiency and coldness in the whole human body are also two additional causes of dysmenorrhea. Thus, the causes of dysmenorrhea can be divided into *qi* stasis, blood stasis, and blood deficiency types according to different situations (Fang, Hong, Junhong, Wei, & Namei, 2013). The technique based on TCM theory for treating nonspecific disorders, such as dysmenorrhea, involves eliminating the intrinsic causes (Bai & Song, 2012). Therefore, in TCM, treatment of *qi* stasis type of dysmenorrhea, involves promoting fluid *qi* movement and also promoting *qi* and blood flow (Dang et al.,

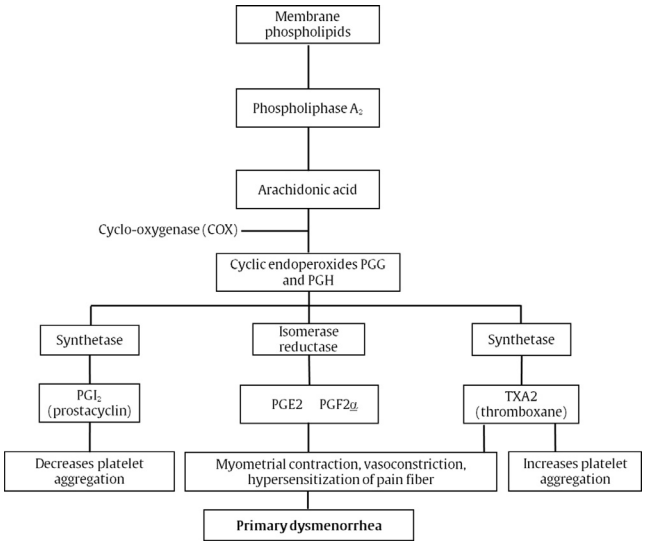


**Fig. 1.** Pathogenesis of primary dysmenorrhea (Harel, 2008; Teimoori, Ghasemi, Hoseini, and Razavi, 2016; Su et al., 2013b).

2015). In Western medicine, the main treatment trends tend to relieve prostaglandins synthesis and to suppress their production from biosynthesis (Patel, Patel, Acharya, Nakum, & Tripathi, 2015).

## 3. Studies of Chinese herbal prescriptions on PD in pre-clinic and clinical-trial

Studies focused on inhibition of uterine contraction and their potential effects were described by several results such as analgesia, anti-inflammation, vasorelaxation, and anti-oxidation. The limitation of this review stems from the fact that, only PD symptoms were studied or focused on. Accompanying complains such as nausea, vomiting, diarrhea, fatigue, and anxiety, were not factored in surveys and the further studies must possibly provide requisites to investigate the effects of herbal prescriptions on related mood disorders. Studies were summarized in Tables 1-3). Frequently investigated studies were on Shaofu Zhuyu Decoction (Lesser Abdomen Stasis-Expelling Decoction) and Siwu Decoction among Chinese herbal prescriptions.

## 4. Potential of herbs in Chinese herbal prescriptions in treating PD

According to the theories of TCM, the concept of PD is directly linked to *qi* stasis, blood stasis and blood deficiency types (Li et al., 2007). The principle of the TCM and its philosophy is centered on eliminating the fundamental causes. According to ancient books, medicinal herbs were used to invigorate blood and *qi* and promote blood movement (Cen et al., 2017). Approximately 136 Chinese medicinal herbs have been approved for the TCM treatment of dysmenorrhea (Jia, Wang, Xu, Zhao, & Zhang, 2006). In this review, descriptions of the most frequently used herbs and main bioactive ingredients in Chinese herbal prescriptions have been outlined in Tables 4 and 5. Further investigations are needed to study individual herbs in the traditional prescriptions and potential to treat PD.

## 5. Possible mechanisms of Chinese herbal prescriptions and herbals in treating PD

Recent surveys showed that traditional Chinese herbal prescriptions and their components ensure their curative effects through numerous mechanisms including: modulation of prostaglandins (PGs) levels, nitric oxide reduction, inhibition of calcium channel and cyclooxygenase-2 (COX-2), microcirculation, declining levels of malondialdehyde (MDA), and reverse rising superoxide (SOD). A combination of herbal formulas is thus expected to integrate several mechanisms to relieve symptoms of PD. The potential approach frequently employed by herbal prescriptions in the treatment of dysmenorrhea is outlined in long history. The mechanism of action of Chinese herbal prescriptions was as below (Fig. 2).

**Table 1**
Studies of traditional Chinese herbal prescriptions on primary dysmenorrhea model in pre-clinic.

| Chinese herbal prescriptions | Studies | Dosages | Outcomes |
|---|---|---|---|
| Jingqian Zhitong Formula | *In vivo* | 0.218 g/kg | It reduced uterine contraction induced by oxytocin, analgesia via decreasing prostaglandin PGF2$\alpha$ level and intracellular $Ca^{2+}$ (Pu, Fang, Gao, Liu, & Li, 2015). |
| Gegen (*Puerariae Lobatae Radix*) Decoction | *In vivo* | 3.5, 7 and 14 g/kg | It reduced uterine contraction induced by oxytocin, intracellular $Ca^{2+}$ and PGF2$\alpha$ and blood flow velocity (reduced by oxytocin) enhanced (Yang, Wang, Zhang, Wang, & Zhou, 2016). |
| Siwu Decoction (Four Ingredients Decoction) | *In vivo* | 3.78 mg crude herbs/g/kg | Blood flow rate was increased in PD syndrome (Liu et al., 2014). |
| | *In vitro* | 0.01 mg/mL or 0.001 mg/mL | Uterine contraction was reduced by induced-oxytocin and suppressed intracellular $Ca^{2+}$ (Liu et al., 2011). |
| | *In vivo* | 54.60 mg/g, 27.30 mg/g, and 5.46 mg/g | |
| Shaofu Zhuyu Decoction (Lesser Abdomen Stasis-Expelling Decoction) | *In vivo* | – | The rate of estradiol, oxytocin, and PGF2$\alpha$ were reduced and progesterone was increased (Huang et al., 2016). |
| | | 0.92, 1.84, and 3.68 g/kg | Abdominal contraction was relieved induced by acidic-acid, decreased uterine contraction induced by oxytocin and intracellular $Ca^{2+}$ (Ma et al., 2011). |
| | *In vitro* | 6.25, 12.5, 25, 50, 100, and 200 μg/mL | Uterine contraction induced by oxytocin level was decreased (Su et al., 2010). |
| Bak Foong Pills | *In vitro* | –4.5–2.5 log mg/mL | It inhibited intracellular $Ca^{2+}$ and the level of uterine contraction induced by oxytocin was decreased (Rowlands, Cui, Wong, Gou, & Chan, 2009). |
| Yuanhu Painkillers | *In vivo* | 0.698 g/kg | Nitric oxide, its synthase (iNOS) and intracellular malondialdehyde synthases were degraded and reverse superoxide dismutase. The writhing score of rats induced by oxytocin was decreased (Chen et al., 2013). |
| Guizhi Fuling Pills | *In vivo* | 0.54, 1.08 g/kg | It inhibited the oxytocin-induced writhing, intracellular $Ca^{2+}$ and reduced PGF2$\alpha$ level, COX-2 and uterine contraction induced by $PGF_{2\alpha}$ (Sun et al., 2016). |
| | *In vitro* | 25 μg/mL for 15 min | |
| Danggui Shaoyao Powder | *In vitro* | 1,10, and 100 μg/mL | It inhibited oxytocin-induced $PGF2\alpha_{2\alpha}$ production and suppressed COX-2 and its mRNA expression (Hua et al., 2008). |
| Dachuanxiong Oral Liquid | *In vitro* | 125, 250, 500, and 1000 μg/mL | It suppressed LPS-induced nitric oxide production and released PGE2 production level, and inhibited iNOS and cyclooxygenase-2 mRNA expression (Liu et al., 2017). |

**Table 2**
Chinese herbal prescriptions on primary dysmenorrhea using different models of study.

| Chinese herbal prescriptions | Models | Outcomes |
|---|---|---|
| Shaofu Zhuyu Decoction (active fraction) | Vascular smooth muscle cells (VSMCs) | MAD was decreased and SOD was increased (Liu et al., 2010). |
| Danggui Shaoyao Powder | Endometrial epithelial cells | It inhibited oxytocin-induced PGF2$\alpha$ production and COX-2 mRNA expression (Hua et al., 2008). |
| Dachuanxiong Formula | Murine macrophage RAW 264.7 cell line | It suppressed LPS-induced NO production<br>It reduced PGE2 production.<br>It inhibited iNOS and COX-2 mRNA expression. |
| Bak Foong Pills | Vascular endothelial cells | It reduced uterine contraction induced by oxytocin and inhibited intracellular $Ca^{2+}$ channel (Rowlands et al., 2009). |
| Yuanhu Painkillers | Vascular endothelial cells | The synthesis of NO and iNOS, and writhing response induce by oxytocin injection were reduced. Nuclear factor-kappa B (NF-kB) was decreased. SOD was increased and MDA was decreased (Chen et al., 2013). |
| Shaofu Zhuyu Decoction | Cold coagulation blood stasis model in rats | It prolonged TT and PT significantly (Su et al., 2013b).<br>Progesterone, inflammatory factors levels of PGF2$\alpha$ and endothelin were inhibited significantly (Huang et al., 2016). |
| Gegen Decoction | Dysmenorrhea model (induced by estradiol benzoate) in rats | It reduced uterine contraction (induced by oxytocin), $Ca^{2+}$, and PGF2$\alpha$.<br>Blood flow velocity was increased (Yang et al., 2016). |

**Table 3**
Studies of traditional Chinese herbal prescriptions on primary dysmenorrhea in clinic.

| Herbal prescriptions | Participants | Dosages | Outcomes |
|---|---|---|---|
| Siwu Decoction | Female patients (20–30 years of age) | 15 g/kg in total taken in three divided doses of 5 g each | It significantly reduced the menstrual pain measured by VAS score compared with diclofenac sodium (Cheng, Lu, Su, Chiang, & Wang, 2008). |
| | Female patients (average age 23.3) | 7.5 g/kg for 5 d | The pain intensity was decreased in Siwu Decoction group and increased in the placebo group (ibuprofen) and pain was scored by VAS criteria (Yeh et al., 2007). |
| | Female patients (average age 23.3) | – | VAS was negative in Siwu Decoction group and positive in the placebo group. Pulsatility Index values were significantly decreased in Siwu Decoction (Yeh et al., 2009). |
| Danggui Shaoyao Powder | Female patients (14–45 years of age) | 7.5 g/kg in total taken in three divided doses of 2.5 g each | It obviously decreased the menstrual pain (measured by VAS score) compared with diclofenac sodium (Kotani et al., 1997). |
| Shaofu Zhuyu Decoction | Female patients (18–40 years of age) | In the first menstrual period, twice daily (200 mL each time) for 5 d. In the second and third menstrual cycles, the same dosage for 10 d (5 d before the menstruation). | The biomarker PGF2$\alpha$, endothelin-1, and oxytocin were significantly decreased, and progesterone was increased in blood (Su et al., 2013a). |

### 5.1. Reduction of prostaglandin

The pathophysiology of PD lies with the imbalance and the abnormal uterine activity due to increasing and decreasing prostaglandins (Dawood, 1985). Prostaglandins therefore contribute to the associated pain factor with PD (Blesson & Sahlin, 2014; Lumsden, Kelly, & Baird, 1983). As the PGF2$\alpha$ and its relating receptors establish uterine contractility, ischemic pain is induced (Coco, 1999; Ylikorkala & Dawood, 1978). Accompanying contraction is the possible constriction of the blood vessels and myometrium resource blood circulation to the endometrium in short time (Ricciotti & FitzGerald, 2011; Robinson, 1983). A previous study showed that PGF2$\alpha$/PGE2 in the endometrium was higher in females with dysmenorrhea (Thabet, Elsodany, Battecha, Alshehri, & Refaat, 2017). Studies have reported that Chinese herbs can reduce prostaglandins level, particularly PGF2$\alpha$ as stated in formulas such as Jingqian Zhitong Formula, Gegen Decoction, Danggui Shaoyao Powder, Shaofu Zhuyu Decoction. Guizhi Fuling Pills, and increase blood flow rate in of Gegen and Siwu prescriptions studies.

### 5.2. Regulation of cyclooxygenase synthesis

Cyclooxygenase synthesis plays an important role in PD and also the inflammation process. It's reported that cyclooxygenase acts on arachidonic acid to produce prostanoids by means of the cyclooxygenase pathway (Sordelli, Beltrame, Cella, Franchi, & Ribeiro, 2012). There are two forms of cyclooxygenase, COX-1 and COX-2. COX-1 is concealed basally while COX-2 is secreted in response to a variety of cytokines and growth factors and is used in signaling pain and inflammation. NSAIDs can inhibit both COX-1 and COX-2 in dysmenorrhea (Harel, 2012). The inhibition of COX-2 by NSAIDs can relieve contraction due to the inhibition of the production of prostaglandins such as PGF2$\alpha$ (Chen et al., 2012). Therefore, when the level of COX-2 expression is increased, prostaglandin level is enhanced and that is the main mechanism of dysmenorrhea (Sales & Jabbour, 2003; Stack & DuBois, 2001). Several herbal prescriptions have been proven to obviously inhibit COX-2 expression including Guizhi Fuling, Danggui Shaoyao Power, and Dachuanxiong prescriptions.

### 5.3. Effects of intracellular $Ca^{2+}$ on PD

The regulation of $Ca^{2+}$ channel has an effect on uterine contraction and is associated with dysmenorrhea (Ausina, Savineau, Pinto, Martin, & Candenas, 1996; Fenakel & Lurie, 1990). Contraction of smooth muscles including the contraction of myometrium is dependent on the increase of $Ca^{2+}$ and this can be achieved through $Ca^{2+}$ influx pathways from the extracellular region to intracellular region. When the intracellular $Ca^{2+}$ proportion is increased

**Table 4**
Commonly used herbs in Chinese herbal prescriptions for primary dysmenorrhea.

| Scientific names | Chinese herbal prescriptions | Efficiency of CMM | Modern approaching studies |
|---|---|---|---|
| *Paeonia lactiflora* | Shaofu Zhuyu Decoction, Jingqian Zhitong Formula, Xiangfu Siwu Decoction, Gegen Decoction, Bak Foong Pills, Guizhi Fuling Pills, Danggui Shaoyao Powder | Nourishing the blood | It inhibited nitric oxide and cyclooxygenase-2 (Lee, Lee, & Mar, 2003). |
| | | Blood deficiency in uterus | It enhanced prostaglandin $E_2$ (Afroz et al., 2018). |
| | | Relieving pain, irregular menstruation with pain | It decreased the levels of TNF-$\alpha$ and nuclear factor-$\kappa$B (Zhou et al., 2017).<br>It suppressed synthesis of inducible nitric oxide synthase (iNOS) (Shao et al., 2016). |
| *Ligusticum chuanxiong* | Shaofu Zhuyu Decoction, Jingqian Zhitong Formula, Siwu Decoction, Bak Foong Pills, Danggui Shaoyao Powder, Dachuanxiong Oral Liquid | Active blood, move *qi*, alleviate pain | It inhibited nitric oxide production, anti-inflammatory effect in LPS-treated RAW264.7 macrophages (Huang et al., 2013).<br>It reduced abdominal muscle contraction induced by acetic acid and relieved dysmenorrhea caused by oxytocin (Gao & Xi, 2010).<br>It exerted significantly suppressive effects on TNF-$\alpha$ (Liu et al., 2005).<br>It inhibited cyclooxygenase-2 (Sue et al., 2009). |
| *Angelicae sinensis* | Shaofu Zhuyu Decoction, Jingqian Zhitong Formula, Siwu Decoction, Bak Foong Pills | Tonify blood, promote *qi*, relieve pain, irregular menstruation | It suppressed TNF-$\alpha$ and the release of prostaglandin $E_2$ (Zhong et al., 2016).<br>It decreased the level of nitric oxide, iNO S, prostaglandin $E_2$, TNF-$\alpha$, inhibited cyclooxygenase-2 (Li et al., 2016).<br>It prolonged the prothrombin time (PT), activated partial thromboplastin time (APTT), and reduced the fibrinogen (FIB) (Li, Tang, & Guo, 2012). |
| *Cinnamomum cassia* | Shaofu Zhuyu Decoction, Gegen Decoction, Guizhi Fuling Pills | Blood stasis, *qi* stagnation, cold pain | It reduced the level of oxytocin, prostaglandin $F_{2\alpha}$, and cyclooxygenase-2 (Sun et al., 2017).<br>It reduced abdominal contraction induced by oxytocin, prostaglandin $E_2$ level, the nitric oxide and its iNOS expression, and TNF-$\alpha$, suppressed cyclooxygenase-2 (Sun et al., 2016) and uterine contraction (induced by oxytocin), reduced intracellular $Ca^{2+}$ (Alotaibi, 2015). |
| *Corydalis yanhusuo* | Shaofu Zhuyu Decoction, Siwu Decoction, Yuanhu Painkillers | Blood and *qi* stagnation, relieve pain | It significantly inhibited the intracellular $Ca^{2+}$ levels (Li, Chen, & Zhang, 2017) . |
| *Zingiber officinale* | Shaofu Zhuyu Decoction, Gegen Decoction | Lowering abdominal disorders, alleviate pain, cold syndrome | It significantly decreased the inflammatory mediators nitric oxide, prostaglandin $E_2$ (Montserrat-de La Paz et al., 2018), nitric oxide, and prostaglandin $E_2$ levels (Kim, Kim, & Kim, 2017), and reduced he level of malondialdehyde (Cui et al., 2018). |
| *Rehmannia glutinosa* | Siwu Decoction, Bak Foong Pills | Nourishing blood, replenish essence and marrow | It elevated superoxide dismutase and reversed degraded TNF-$\alpha$, malondialdehyde (Zhou et al., 2015) and reduced tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and iNOS (Choi et al., 2013), and inhibited cyclooxygenase-2 (Zhu et al., 2017). |
| *Cyperus rotundus* | Siwu Decoction, Bak Foong Pills | Regulating *qi* and menstruation, relieve pain | It significantly inhibited lipopolysaccharide (LPS)-induced production of nitrite oxide (NO), iNOS, and prostaglandin $E_2$ as well as cyclooxygenase-2 (Seo et al., 2016). |
| *Glycyrrhizae uralensis* | Gegen Decoction, Bak Foong Pills | Replenishing *qi*, relieve spasm and pain | It reduced intracellular $Ca^{2+}$ and relaxing vascular with phenylephrine (Tan et al., 2017), uterine contraction induced by oxytocin (Jia et al., 2013). |
| *Angelica dahurica* | Yuanhu Painkillers, Danggui Shaoyao Powder | Stop pain, regulate *qi*, | It decreased LPS-induced boost of cyclooxygenase-2 and iNOS protein stages (Lee et al., 2017) and reduced nitric oxide and prostaglandin $E_2$ levels (Kim et al., 2015). |
| *Poria cocos* | Guizhi Fuling Pills, Danggui Shaoyao Powder | *Qi* deficiency, promote diuresis, invigorate blood | It inhibited cyclooxygenase-1,5-lipoxygenase, phospholipase $A_2$ (Prieto et al., 2003).<br>It decreased expression of iNOS, cyclooxygenase-2 and prostaglandin $E_2$ (Jeong et al., 2014). |

**Table 5**
Efficacy of several bioactive components of Chinese herbal prescriptions.

| Bioactive components | Chinese herbal prescriptions | Studies | Dosages | Outcomes |
|---|---|---|---|---|
| Vanillic acid<br>Ferulic acid<br>Typhaneoside | Shaofu Zhuyu Decoction | *In vitro* | 57.6 μg/mL ($ED_{50}$)<br>63.0 μg/mL ($ED_{50}$)<br>109.7 μg/mL ($ED_{50}$) | At 5 μg/L oxytocin-induced uterine contraction, inhibitory activities (Su et al., 2010). |
| Core licorice aqueous extract | Gegen Decoction, Bak Foong Pills | *In vitro* | 0.025, 0.05 and 0.1 mg/mL | Uterine contraction (induced by KCl, ACh, CCh, OT, bradykinin, propranolol) was reduced (Jia et al., 2013). |
| Quercetin, | (A main flavonoid in onion) | *In vitro* | 10, 25, 50 and 100 μg/mL | Uterine contraction (induced by PGE2, KCl, and oxytocin) was reduced. |
| | | *In vivo* | 10, 25, or 50 mg/kg | Intracellular $Ca^{2+}$ was degraded (Wu, Shieh, Wang, Huang, & Hsia, 2015). |
| SF-7 active fraction | Shaofu Zhuyu Decoction | *In vitro* | 0.05, 0.1, 0.2 0.4, and 0.8 mg/mL | Cell apoptosis induced by $H_2O_2$ was decreased.<br>It inhibited $H_2O_2$-induced intracellular accumulation of reactive oxygen species (ROS).<br>It reduced the intracellular $Ca^{2+}$ concentration in $H_2O_2$-injured VSMCs (Liu et al., 2010). |
| Tetrahydrocolumbamine<br>Protopine<br>Corydaline<br>Tetrahydropalmatine<br>Tetrahydrocoptisine<br>Berberine | Siwu Decoction | *In vitro* | 0.99 μg/mL<br>0.82 μg/mL<br>0.75 μg/mL<br>1.02 μg/mL<br>0.63 μg/mL<br>0.29 μg/mL | It possessed high inhibitory actions on uterine contraction induced by oxytocin (Liu et al., 2011). |

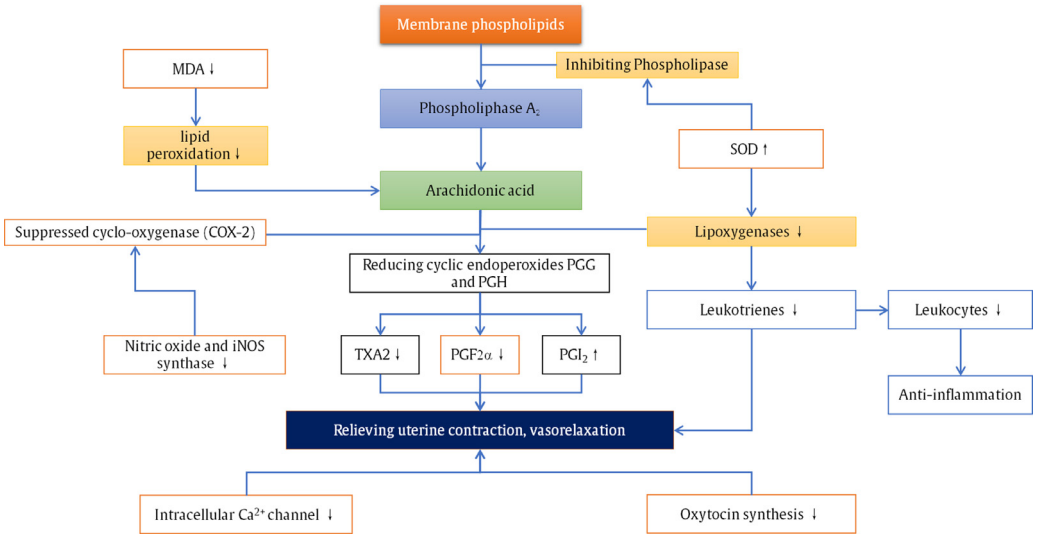


**Fig. 2.** Mechanism of Chinese herbals prescriptions on primary dysmenorrhea.

in the smooth muscles, the transient rise in $Ca^{2+}$ concentration is achieved, which is marked by uterine contraction (Matsuo, Gokita, Karibe, & Uchida, 1989; Wrayzx et al., 2003). Therefore, the method of treatment is targeted at blocking $Ca^{2+}$ channels to reduce intracellular $Ca^{2+}$ levels in dysmenorrhea (Braileanu, Simasko, Uzumcu & Mirando, 1999; Chen & Khalil, 2008; Shih & Yang, 2012). This review has shown that Chinese herbal prescriptions such as Xiangfu Siwu Decoction, Shaofu-Zhuyu Decoction, Jingqian Zhitong Fang, etc., have the effects to reduce intracellular $Ca^{2+}$ levels thus making them potent alternatives for the treatment of dysmenorrhea.

### 5.4. Effects of nitric oxide and its synthase on PD

Nitric oxide (NO), well-known present in the blood vessel, is a relaxing agent in endothelium (Wallace, 2005). NO is biosynthesized endogenously from oxygen and NADPH (Sharma, Al-Omran, & Parvathy, 2007). NO has relaxing effects on the endothelium of blood vessels, so it produces an effect of vasodilation of the vessels enhancing the flow of blood in organisms (Webb et al., 2008). NO activity has effects on the severity of dysmenorrhea symptoms and affects the homocysteine metabolic pathway in dysmenorrhea symptoms (Galley, Coomansingh, Webster, & Brunt, 1998). In contrast, homocysteine has a role in inflammation in the blood vessels, which may be manifested as damaging influence in endothelial cells, increasing coagulation and proliferation of smooth muscle cells (Yang, Chai et al., 2016). Hence, decreasing NO level in serum causes more repeated muscular and vessels contractibility of the uterus (Wang, Hsu, Chien, Kao, & Liu, 2009). NO release is elaborate in the synthesis of prostaglandins, particularly PGE2 (Siemieniuch, Woclawek-Potocka, Deptula, Okuda, & Skarzynski, 2009). The induction of nitric oxide synthase which is iNOS, with the consequent release of NO seems to increase the production of PGE2 through activation of cyclooxygenase in the inflammation processes (Shi et al., 2012). NO has been shown to stimulate the activity of COX-2 in many tissues (Salvemini, 1997; Shinmura et al., 2002). Decreasing of NO could promote nociceptive communication and pain, as enhancing of NO may suppress analgesia (Liao, Ho, & Lin, 2005). On the other hand, several studies have shown that NO is linked to several central nervous system disorders and also has roles in the pathophysiology of primary type of headaches (Olesen, 2008; Steinberg & Nilsson Remahl, 2012). On the onset of inflammatory processes in organism, the macrophages are at the fore front of the ensuing plethora of complaints, making use of generating factors for example TNF-$\alpha$, and inflammatory mediators with NO (Ghasemzadeh, Amin, Mehri, Mirnajafi-Zadeh, & Hosseinzadeh, 2016; Turini & DuBois, 2002). Therefore, the concept of treatment lies on the inhibition of inflammatory response in macrophages via the regulation of NO (Son et al., 2006). Yuanhu Painkillers, Shaofu Zhuyu Decoction, and Dachuanxiong prescriptions have shown to have this ability as shown in this review.

### 5.5. Relation of superoxide dismutase and malondialdehyde enzymes to PD

Superoxide dismutase (SOD) has a potent anti-inflammatory activity and accordingly thus has a role in inflammatory diseases (Fukai & Ushio-Fukai, 2011). Treatment with superoxide decreases reactive oxygen species generation and oxidative stress, including inflammation factors such as lipoxygenases and phospholipases which inhibit endothelial stimulation (Brady, Texel, Kishimoto, Koehler, & Sapirstein, 2006). Such antioxidants therefore may be important as regard new therapies for the treatment of even inflammatory bowel disorders (Seguí et al., 2004). During PD, SOD activity is degraded and reverses the level of malondialdehyde (MDA) in rat uterus (Dikensoy et al., 2008). Again, superoxide is one of the most important biological antioxidant that can act against free radicals that prevent subsequent lipid peroxidation (Seyhan & Canseven, 2006), producing high levels of MDA which is directed toward cells and their membranes (Yeh, Chen, So, & Liu, 2004). The high levels of MDA in serum indicate the unit of lipid peroxidation (Davey, Stals, Panis, Keulemans, & Swennen, 2005; Ilhan, Halifeoglu, Ozercan, & Ilhan, 2001). MDA noticeably has roles in thromboxane A2 synthesis, where in COX-1/COX-2 processes arachidonic acid gives prostaglandin H2 using platelets and a wide selection of additional cell types (Farmer & Davoine, 2007; Pryor & Stanley, 1975). Thromboxane synthase plays role in thromboxane A2 and MDA (Marnett, 1999). In this review, Yuanhu Painkillers have shown to reduce MDA and increase superoxide, thus antioxidant effect of herbal medicines provides an alternate window in the alleviation of PD.

Chinese herbal medicines have great advantages, such as the complex effectiveness of treatment and very few adverse effects, for the treatment for PD on the long haul. However, there is the

lack of objective and uniform criteria for diagnosis and treatment, which affects the judgment and comparability of clinical real efficacy, especially for long-term efficacy and prevention of adverse recurrences. For the long-term treatment of PD, the traditional Chinese herbal prescriptions may have some safety problems, so in-depth safety studies are needed to reduce the incidence of the few probable adverse reactions.

Most studies on the treatment of PD are those of oral administration. Therefore, comparison between new dosage forms such as the oral nanocrystal, suppository, and injection will be a great addition. New dosage forms can be developed based on traditional Chinese herbal prescriptions, ensuring that they have the characteristics of stable composition, accurate compatibility and easy administration.

Traditional Chinese herbal prescriptions have a variety of chemical composition. It is therefore behooving to evaluate further effects to find correlation among the chemical composition, the biological effects, and biomarkers. Those may point to the profile of the metabolomics as regard biological and clinical efficacy for diagnosis and valuation of healings in clinic, thus establishing a suitable model to reasonably affect PD syndrome. Also, research on the molecular mechanism of traditional Chinese herbal prescriptions ought to be further studied. Therefore, investigators must delve into to the concepts of TCM chemistry, TCM genomics and proteomics, make use biochips and bioinformatics technology and then, combine with modern molecular biology research methods to search for composite targets.

To evaluate biological effects of the traditional Chinese herbal prescriptions, this review recommends the establishment of a cold coagulation and blood stasis rat model, vascular endothelial cell model or ovarian cell model to investigate the blood rheology and endocrine hormone in model of PD.

## 6. Way forward

Dysmenorrhea is one of the most common gynecological disorders that directly influence the quality of life of women. Medicines often used to reduce the symptoms of dysmenorrhea clinically, are NSAIDs. However, long-term use of NSAID is associated with severe side effects on the patients. Fortunately, many Chinese herbal prescriptions have great therapeutic effects on PD with fewer side effects. Herbal prescriptions therefore, match other agents, if not more regarding female-specific diseases particularly, PD. Hence, Chinese herbal prescriptions provide another therapeutic option for the treatment of PD. In light of this, advanced research should be undertaken on Chinese herbal prescriptions to elucidate and pinpoint the main compounds which are more efficacious in the treatment of PD. Detailed pharmacokinetic studies should be done to elucidate the compounds that actually work in Chinese herbal prescriptions and explain clearly the chemical changes that occur in the whole process of absorption, distribution, metabolism, and excretion of active ingredients in the organism. These will contribute to the safety and rationality of clinical medication. The insufficient study on the above aspects therefore, raises the need for further investigations (Fig. 3).

In order to investigate the safety and rationality regarding the clinical usage of Chinese herbal prescriptions, investigations into the pharmacokinetics of these Chinese herbal prescriptions should be done. Importantly, analysis of the individual components in Chinese herbal prescription and the isolation of the bioactive components need to be done to ensure effective treatment of PD. A reasonable scientific model in tune with real biological similarities needed to be established, for example, the cold coagulation-blood stasis model in animal study as suggested above. Also, toxicological studies on organs, particularly the liver and kidney should be keenly monitored. Finally, clinical trial survey should be rolled out to test it efficacy, compatibility as well as any other pharmacological parameter needed to ensure total safety of the drug.

Moreover, other studies which utilized different models to study the efficacy of TCM on treating PD yielded great results. Therefore, the available alternative source of TCM therapeutic option might be resolved PD which is the present menace of women worldwide.

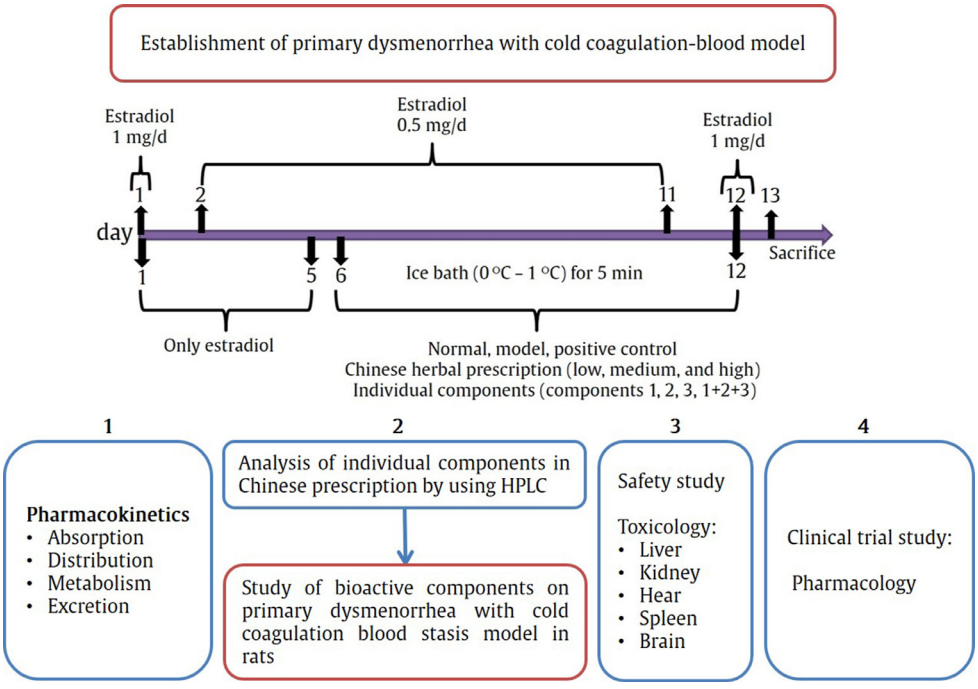


**Fig. 3.** Protocol for further investigation on PD.

## 7. Conclusion

Chinese herbal prescriptions possess great therapeutic effects on PD syndrome through many mechanistic ways such as reducing the level and synthesis of prostaglandins, relieving vasoconstriction and myometrial hyperactivity leading to the alleviation of pain as well as the effect of anti-inflammation activity. This review clearly shows that Chinese herbal prescriptions have potent beneficial actions on the treatment of PD and therefore duly provide an alternative therapeutic option regarding the treatment of PD in clinic.

## Conflict of interest

The authors express that there is no conflict of interest.

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