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Research progress of three kinds of oral polyherbal formulations for primary dysmenorrhea

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Abstract. Dysmenorrhea is a worldwide problem that plagues the vast majority of women, in which about 90% are primary dysmenorrhea (PD), in recent years, how to effectively and thoroughly treat primary dysmenorrhea has attracted the attention of researchers. PD refers to the absence of organic changes in the genitals, abdominal pain, backache, lower abdominal pain and other symptoms before and after menstruation and menstruation, also known as functional dysmenorrhea. The current clinical treatment of it is mainly based on non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose oral contraceptives, but as a Western drug they have heavy toxic side effects. Traditional Chinese medicine (TCM), which has few toxic side effects and generally better curative effects, has gradually entered people's field of vision. There are many effective formulas in TCM for the treatment of primary dysmenorrhea, and this article mainly discusses the main components of three of them, and many studies have revealed the main chemical components of three of these Chinese polyherbal formulations (PHFs) and their pharmacological mechanisms, and their clinical effect is better than or not inferior to that of Western medicine. However, most of the existing studies are based on modern pharmacology and lack in-depth discussion according to TCM theories and methods. Further experimental and clinical studies are needed to address these issues for the comprehensive development and application of TCM compound preparations for the treatment of primary dysmenorrhea.

Keywords: Primary dysmenorrhea, traditional Chinese medicine, Prasaplai, Xuefu Zhuyu Decoction, Dang Gui Shao Yao San.

1. Introduction

Dysmenorrhea is a common gynecological disease that plagues women, which can be divided into primary dysmenorrhea and secondary dysmenorrhea, in which about 90% are primary dysmenorrhea (PD), PD refers to the absence of organic changes in the genitals, abdominal pain, backache, lower abdominal pain and other symptoms before and after menstruation and menstruation, also known as functional dysmenorrhea [1], which is mainly manifested as crampy pain in the lower abdomen before and after menstruation, mostly accompanied by headache, dizziness, nausea, vomiting, limb weakness and other systemic symptoms, the disease mostly occurs within two years of menarche, Young women less than 25 years old, the work, study and life of people with severe primary dysmenorrhea will be affected [2]. At present, the world's drugs for the treatment of primary dysmenorrhea are mainly NSAIDs and low-dose oral contraceptives and other Western drugs, although effective, but side effects such as allergic reactions, gastrointestinal reactions and so on are also very significant [1], so in recent years,

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people have begun to pay more and more attention to the treatment of the disease through drugs with good efficacy, small toxic side effects, and less damage to the body. Among them, traditional Chinese PHFs, as drugs that have been used to treat dysmenorrhea for thousands of years, have come into people's field of vision and have become a research hotspot. In 2022, there were two reviews of the literature [2,3] about the oral PHFs treating primary dysmenorrhea, which comprehensively summarize the traditional Chinese PHFs for the treatment of primary dysmenorrhea in recent years, including their mechanism of biological action and scientific evaluation of clinical treatment effects.

2. Risk factors

There are many risk factors for the onset of PD, and current studies have shown that the most important risk factor is age [2]. Many studies have confirmed that there is a significant correlation between age and the incidence of PD. One systematic review reported that women younger than 30 years of age had a higher risk of developing PD, while another study [3] noted that women under 20 years of age had a higher risk of developing PD. This may be due to prolonged exposure of the uterus to prostaglandins. In addition, non-childbirth [4], smoking and alcohol consumption also put women at higher risk of PD. Mood and psychology are also risk factors that play a role in contributing to PD, with a large body of literature suggesting that depression and anxiety are positively associated with the risk of PD [5]. Women with anxiety and depression have higher pain sensitivity, which makes them more sensitive to the sensation of pain during menstruation. A population-based study has shown that stress predisposes women to menstrual cramps, as stress may stimulate a neuroendocrine response that interferes with the normal process of ovulation.

3. Pathogenesis

The eventual painful sensation of primary dysmenorrhea is caused by abnormal contractions of the uterine muscles or uterine ischemia. Intrauterine muscle contractions are common during menstruation, with a normal basal contraction frequency of 3-4 times every 10 minutes in healthy women and a peak intrauterine pressure of 120 mmHg [6]. however, a significant increase in systolic frequency (4-5 beats every 10 minutes) and intrauterine pressure (usually over 150-180 mmHg) were found in women with PD.

A variety of inflammatory markers and hormones have been implicated in pelvic pain in women with PD. Hormones such as estrogen, progesterone, oxytocin, antidiuretic hormone, and follicle-stimulating hormone (FSH) are involved in the pathophysiological process of PD [2]. The plasma levels of oxytocin, antidiuretic hormone and FSH in patients with PD were significantly increased. However, the mechanism by which each hormone causes PD is not well understood. Different studies have proposed several mechanisms that suggest different hormones play different roles in PD. Patients with PD have high estrogen levels and low progesterone levels during menstruation. High estrogen levels increase the expression of oxytocin receptors (OTRs), which leads to the influx of calcium ions and the contraction of uterine smooth muscles. Low progesterone levels activate the arachidonic acid pathway, which increases prostaglandin synthesis.

4. Three kinds of PHFs used for the treatment of primary dysmenorrhea

Based on the experience of TCM and research through modern methods, PHF has greater advantages in treating diseases than a single herb. The combination of several herbs in one formula creates a synergistic effect and minimizes its toxic effects. The synergistic effect of the herbs in PHF makes them have a better therapeutic effect. PHF has a wider therapeutic window than a single herb and can be used safely at high doses. Globally, there are 11 PHFs which are effective and commonly used for the treatment of PD [1,2]. This paper will select prasaplai, xuefu zhuyu decoction (XZD), dang gui shao yao san(DGSYS) and compare and comprehensively discuss them from the dimensions of their mechanism of action, active ingredients and application status.

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4.1. Prasaplai

Prasaplai is a Thai traditional preparation originated 100 years ago, which is used for the management of PD. The main active ingredients of prasaplai include Acorus calamus, Allium sativum, Citrus hystrix, Curcuma zedoaria, Eleutherine palmifolia, Nigella sativa, Piper retrofractum, Piper nigrum, Zingiber cassumunar, Zingiber officinale, sodium chloride, camphor. Current studies have shown that it exerts its effect in the treatment of PD mainly through the inhibition of COX-1 and COX-2 [7]. In addition to this, it can also reduce the release of PGE2, oxytocin and acetylcholine.

In this formula, Zingiber officinale as the king medicine and main ingredient (50%), plays a major anti-inflammatory role by inhibiting the expression of COX-2 and PGE2, and Zingiber cassumunar, Nigella sativa, Acorus calamus, Allium sativum, Curcuma zedoaria are all minister drugs, by inhibiting COX-1 and COX-2 and reducing the release of oxytocin and acetylcholine to help enhance the effect of the formula. The assistant and guide medicine in the formula are Citrus hystrix, Eleutherine palmifolia, Piper retrofractum, Piper nigrum, in which Piper retrofractum, Piper nigrum has a strong anti-inflammatory activity, The piperine in it can improve the bioavailability of compounds in drugs, and can enhance the activity of the king medicine and the minister medicine.

To date, there have been studies that have conducted clinical trials on Prasaplai to evaluate its safety and efficacy. A phase II clinical trial has confirmed the effectiveness of Prasaplai, with patients receiving Prasaplai experiencing less pain and side effects compared to those receiving mefenamic acid at 3 months of follow-up [8]. In a six-month study in a phase III clinical trial, Prasaplai was also shown to be as effective as mefenamic acid in the treatment of PD without hepatic or renal complications [9]. A short-term randomized trial showed that although Prasaplai was useful in pain relief, there was no significant difference in its clinical efficacy compared to placebo. However, two components of Prasaplai (Zingiber officinale and Nigella sativa) have an antiemetic effect that reduces nausea and vomiting after used to treat PD. Although three clinical studies reported multiple beneficial effects, three studies used doses that differed from the standardised doses recommended by the National List of Herbal Medicines. Future studies can compare the therapeutic effects of Prasaplai and nonsteroidal anti-inflammatory drugs (NSAIDs) for treating primary dysmenorrhea at standard doses (1000 mg, three times daily) for more reliable results.

4.2. Xuefu Zhuyu Decoction (XZD)

The main ingredients of XZD include Prunus persica, Angelicae sinensis, Ligusticum striatum, Carthamus tinctorius, Paeoniae lactiflora, Rehmanniae glutinosa, Citrus aurantium, Bupleuri chinese, Platycodon grandiflorus, Achyranthes

bidentatae, Glycyrrhizae uralensis. Current studies have shown that it exerts its effect in the treatment of PD mainly through reducing the level of arachidonic acid [10].

XZD treats PD by relieving pain, promoting blood circulation and removing stasis. In XZD, Carthamus tinctorius and Prunus persica are the king medicines, which have the effects of promoting blood circulation, removing stasis, and breaking blood stagnation; Paeoniae lactiflora and Ligusticum striatum are the minister medicines that help the king medicines, and the Achyranthes

bidentatae are also the minister medicines, which have the effects of invigorating blood, passing menstruation and removing stasis; The Rehmanniae glutinosa, and Angelicae sinensis, that nourish and invigorate the blood, the Citrus aurantium and Platycodon grandiflorus that widens chest and promotes qi, and the Bupleuri chinese that soothes the liver and relieves depression are all assistant medicines; The Platycodon grandiflorus which is used as a guide medicine carries medicine upward, and Glycyrrhizae uralensis blends medicines [10].

Scientists have conducted numerous clinical trials to evaluate the effectiveness of XZD in alleviating PD. Currently, all studies are published in Chinese. A meta-analysis has analyzed published studies. Of the eight studies analyzed, most of the studies favored XZD in combination with Western medicine or XZD alone for pain relief in PD. The potential mechanism of biological action of XZD has not been fully elucidated. What is currently known is that XZD exerts anti-inflammatory effects by reducing arachidonic acid levels in the brain. Since arachidonic acid is a precursor to prostaglandins, reducing the

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release of arachidonic acid may relieve the pain of PD. However, no studies have evaluated the effect of XZD on key inflammatory mediators of PD (PGE2, PGF2α, etc.), therefore, subsequent studies can evaluate the effect of XZD on key inflammatory mediators of PD by establishing mouse models of inflammation for clinical trials.

Add or subtract medicines: This depends on different kinds and situations of PD, If the mouth is bitter and the fur is yellow, the menstrual period is prolonged and the color is purple and dark, it is a sign of liver stasis and heat, add: Cape jasmine, Prunella vulgaris; Those who urethra and anus swell should add Cimicifuga foetida; Those who eat less and have a lot of stuffiness should add Gaultheria leucocarpa, Poria cocos, and Citri Reticulatae Pericarpium to strengthen and harmony reduction and inversion of the spleen and stomach: Those with cold coagulation and blood stasis add Aconitum carmichaeli Debx, Zingiberis Rhizoma, Cinnamomum cassia Presl. And those with qi deficiency and stasis reduce blood invigorating drugs, and add tonic medicines such as Codonopsis pilosula, Astragalus zacharensis Bunge, and Gaultheria leucocarpa [11].

4.3. Dang Gui Shao Yao San (DGSYS)

The main ingredients of DGSYS include Poria cocos, Paeonia lactiflora, Atractylodes macrocephala, Ligusticum striatum, Alisma orientale, Angelica sinensis. Its biological mechanism of action is to alleviate PD symptoms by inhibiting the uterine contractions caused by the drug action of PGF2, acetylcholine, and oxytocin [12].

In this formula, Paeonia lactiflora has an acidic and cold taste, returns to the liver and spleen meridians, and has the effect of nourishing blood and softening the liver, relieving pain and urgency, and is the king medicine. Angelica sinensis tastes bitter and cold, returns to the liver, stomach and large intestine meridians, and has the effect of nourishing blood and nourishing the liver; Ligusticum striatum is warm, with the effect of invigorating blood and forming qi, dispelling wind and relieving pain. Angelica sinensis in the recipe helps Paeonia lactiflora to add and nourish the blood in liver, and Ligusticum striatum pushes stagnated qi in the blood. Angelica sinensis and Ligusticum striatum are both minister medicines. Atractylodes macrocephala is bitter, sweet and warm, and has the effect of tonifying the spleen and dampness; Poria cocos is flat and sweet and light, and has the effects of diluting water and dampness, strengthening the spleen and tonifying the middle, and calming the nerves; Alisma orientale is sweet and cold, and has the effect of diluting water and reducing swelling. Poria cocos and Atractylodes macrocephalus in the formula strengthen the spleen and soothe the liver, and the three are used as assistant medicines to make the spleen healthy, and the qi and blood are smooth. The combination of the six medicines plays a role in invigorating blood, nourishing blood and regulating the liver, relieving pain, strengthening the spleen and relieving dampness [12].

Meta-analyses evaluated the effectiveness of DGSYS versus NSAIDs in the treatment of PD. Clinical trials with sample sizes ranging from 40 to 203 compared to NSAIDs have shown good results with DGSYS in the treatment of PD. However, the evaluation of the side effects of DGSYS has not been widely reported. In recent years, only one clinical trial reported side effects (nausea and abdominal pain) in the NSAID group. Although TCM has been "safely" used in society for thousands of years, the side effects of the formula have not been fully elucidated, as robust clinical trial studies have not been conducted and reported.

Add or subtract medicines: If there is less cold pain in the alvine, add Cinnamomum cassia Presl and Zingiberis Rhizoma. Alvine tingling plus Prunus persica, Carthamus tinctorius. Alvine distension and pain, plus Curcuma aromatica Salisb, Cyperi Rhizoma. Alvine dull pain plus Astragalus zacharensis Bunge, and Codonopsis pilosula [13].

5. Conclusion

PHF is a kind of powerful drug for the treatment of primary dysmenorrhea. At present, many researchers have studied and reported on the three Chinese medicine compounds in this article, clarified the pharmacological mechanism of their main components, and proved that their clinical treatment effect is not inferior or even better than that of Western medicine, but most of the research on ,PHF were based

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on the principles and methods of modern pharmacology, and few studies would conduct in-depth research and development of traditional Chinese ,PHFs for the treatment of PD according to the theories and methods of TCM. In addition, there are few studies on the mechanism of interaction between various components in the formula and the clinical safety evaluation of the formula. All of the above questions are subject to further clinical trials and studies.

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