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Efficacy Analysis of Guizhi Fuling Wan in the Treatment of Primary Dysmenorrhea

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Abstract:

Primary dysmenorrhea is a highly prevalent benign gynecological disorder among women of childbearing age. Its core pathogenesis lies in the excessive synthesis and release of endometrial prostaglandin F2α(PGF2α). Guizhi Fuling Wan(GZFLW), a classic prescription in traditional Chinese medicine (TCM) for promoting blood circulation and resolving blood stasis, has been widely used in the clinical treatment of this disease. This paper systematically reviews the molecular mechanisms and clinical evidence of GZFLW in the treatment of primary dysmenorrhea. It can alleviate uterine smooth muscle spasm and pain through effecting the Nuclear Factor-κB (NF-κB)/Cyclooxygenase-2 (COX-2)/PGF2α Signaling Pathway, downregulating Oxytocin Receptor (OTR) Protein Expression and regulating small molecules in uterine tissues, with synergetic therapeutic efficacy with Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and a favorable safety profile. In view of the limitations of existing studies, which are mostly focused on combination medication and lack comparative studies with other TCM preparations. Monotherapy research can be explored in the future to improve the relevant evidence-based foundation.

Keywords: Guizhi Fuling Wan, Primary Dysmenorrhea, Molecular Mechanism.

1. Introduction

The definition of Dysmenorrhea is the menstrual-associated cramping pain in the uterus and represents the most frequ1 gynecological symptom among females of reproductive age [1, 2]. It is clinically classified into two categories: primary and secondary. Primary dysmenorrhea refers to menstrual pain without underlying pelvic organic pathology, characterized pathologically by excessive contraction of uterine smooth muscle and spastic ischemia, accounting for more than 90% of all dysmenorrhea cases. Secondary dysmenorrhea arises because of pelvic organic diseases such as endometriosis, chronic pelvic inflammatory disease, and adenomyosis [1]. The prevalence of primary dysmenorrhea is notably high, affecting 50% to 90% of adolescent girls and women of reproductive age worldwide, making it the most frequent cause of diminished quality of life during menstruation as well as absenteeism from school and work [2,

3]. Chronic and recurrent dysmenorrhea not only induces significant physical discomfort but also increases the risk of suffering from emotional disorders such as anxiety and depression [3, 4]. The current research mainly focuses on the pathogenesis and effective treatments of primary dysmenorrhea. Regarding the pathogenesis, researchers have shifted from exploring a traditional single pathological mechanism to conducting multi-system integrated mechanism studies, concentrating on core molecular pathways, inflammatory immunity and endocrine metabolism in the development of dysmenorrhea [5]. In terms of effective treatments, the research is divided into drug and non-drug interventions. Through the evaluation of the effectiveness and safety of various therapies, the treatment plan for primary dysmenorrhea is optimized. It has thus emerged as a prominent issue in female reproductive health, and the development of safe and effective treatment regimens remains a research emphasis in the domain of gynecology.

This article systematically reviews the multi-target action pathways of Guizhi Fuling Wan (GZFLW) in the clinical application of treating primary dysmenorrhea, clarifies the molecular mechanisms of its regulation of the main disease signal pathways, and synthesizes clinical research datasets to appraise the therapeutic efficacy and safety profile of GZFLW for primary dysmenorrhea, and identify its clinical advantages. This article supplements the evidence-based basis for the clinical application of GZFLW, which can provide ideas for the integrated traditional Chinese medicine (TCM) and Western medicine (WM) treatment of primary dysmenorrhea and offer theoretical support for the modern research and clinical transformation of TCM prescriptions.

2. Bioactive Component of GZFLW

GZFLW is a classic ancient prescription that derives from Synopsis of the Golden Chamber, written by the famous Eastern Han Dynasty physician Zhang Zhongjing. It is composed of five TCMs: Guizhi (Cinnamon Twig), Fuling (Poria), Mudanpi (Peony Bark), Baishao (White Peony Root), and Taoren (Apricot Kernel).

GZFLW is characterized by complex chemical composition and synergistic effects of multiple components. Existing studies have successfully isolated and identified 219 monomeric compounds from GZFLW, using high-performance liquid chromatography (HPLC), gas chromatography (GC) and various high-resolution coupled mass spectrometry techniques (such as UPLC-Q-TOF-MS, UPLC-QQQ-MS/MS, GC-MS, etc.). These compounds can be systematically divided into six structural categories: phenylpropanoids (14 species), terpenoids (87 species, including 40 monoterpenes, 19 sesquiterpenes, 1 diterpene and 27 triterpenes), tannins (16 species), acetophenones (13 species), flavonoids (9 species) and others (70 species, covering phenolic acids, sterols, fatty acids, saccharides, amino acids, etc.). Among the identified compounds, eight core active ingredients, namely paeoniflorin, paeonol, prunasin, gallic acid, albiflorin, amygdalin, cinnamaldehyde and cinnamic acid, have been confirmed by multiple in vivo and in vitro animal experiments and network pharmacological studies to be directly related to the therapeutic effect of GZFLW on PD [6]. The GZFLW is mainly used to treat gynecological diseases such as uterine fibroids, pelvic inflammatory disease, dysmenorrhea, endometriosis, and ovarian cysts. Modern pharmacological research has found that it plays a significant role in multiple fields, including anti-atherosclerosis, alleviating kidney damage, and peripheral neuropathy [7, 8].

3. Etiology of Primary Dysmenorrhea

The understanding of dysmenorrhea etiology in TCM has a long history. In the Qing Dynasty, Tang Zonghai's Theory of Blood Syndromes put forward that "If there is no blood stasis, the menstrual flow will be smooth and the person will be healthy", clarifying blood stasis as the core pathogenesis of dysmenorrhea. In the Ming Dynasty, Zhang Jiebin's Jingyue Quanshu further s classified cold coagulation, blood stasis, qi stagnation and heat stagnation as the four main pathogenic factors, covering both exogenous and endogenous pathways [9]. Modern medicine holds that the excessive synthesis and release of prostaglandin F2α is the main cause of primary dysmenorrhea. It is secreted by the ovaries and the endometrium, with arachidonic acid as its precursor. Prostaglandin F2α causes uterine smooth muscle contractions and vasoconstriction, putting the uterus in a state of ischemia and hypoxia, thereby causing pain. The synthesis of prostaglandin F2α is influenced by the key transcription factor Nuclear Factor-κB (NF-κB) and the main rate-limiting enzyme Cyclooxygenase-2 (COX-2). An increase in the expression of the transcription factor and an enhancement in the enzymatic activity of the rate-limiting enzyme both lead to an increase in the synthesis of prostaglandin F2α [10].

4. Molecular Mechanisms of GZFLW in the Treatment of Primary Dysmenorrhea

4.1 Effect on the NF-κB/COX-2/PGF2α Signaling Pathway in Uterine Tissues

The core mechanisms by which GZFLW exerts its analge-

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sic effect is inhibiting the activation of NF-κB transcription factor and downregulating the expression of COX-2, thereby fundamentally blocking the synthesis of prostaglandins, the key algogenic mediators. NF-κB is a pivotal transcription factor that regulates inflammatory responses and serves as the upstream switch for the induction of COX-2 synthesis.

The in vivo animal experimental study conducted by Liu et al. has provided direct experimental evidence supporting the above-mentioned mechanism of action. In an earlier investigation, researchers developed a primary dysmenorrhea rat model, with three groups designed: normal control, model control, and GZFLW intervention. The pathological alterations of rat uterine tissues were assessed across all groups, and the expression levels of PGF2α, COX-2, total NF-κB and phosphorylated NF-κB in uterine tissues were quantified. The results showed that compared with the model control group, the levels of PGF2α, COX-2, and p-NF-κB in the uterine tissues of the GZFLW intervention group were significantly decreased, while no significant change was observed in total NF-κB level [11]. This finding suggests that GZFLW can reduce the activation level of NF-κB by inhibiting its phosphorylation modification, thereby blocking the downstream cascade reaction. Presently, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line medications used clinically to treat primary dysmenorrhea. These drugs mainly reduce prostaglandin production by directly inhibiting the enzymatic activity of COX-2. In contrast, GZFLW can target the upstream link of the NF-κB/COX-2 signaling pathway, downregulate COX-2 expression at the transcriptional level, and achieve fundamental blockade of the synthesis of algogenic mediators.

4.2 Regulation of Oxytocin Receptor (OTR) Protein Expression

GZFLW can also directly inhibit excessive spasmodic contraction of uterine smooth muscle and alleviate the symptoms of primary dysmenorrhea by downregulating the protein expression of OTR in uterine tissues. OTR is a key membrane receptor that mediates uterine smooth muscle contraction, and the specific binding of oxytocin to OTR on the membrane of uterine smooth muscle cells is the core signal triggering uterine contraction. In vivo animal experiments have provided direct experimental evidence for this mechanism of action. Five groups were designed for one previous research: normal control group, primary dysmenorrhea model control group, positive control group, and low- and high-dose GZFLW intervention groups. After measuring the OTR expression levels in the uterine tissues of all groups, the findings indicated that, relative to the model control group, GZFLW preparation could significantly downregulate OTR protein expression in uterine tissues, with inhibition rates of 60% and 65% in the low- and high-dose groups, respectively, which could effectively block the activation of the OTR signaling pathway [12]. The above results confirm that GZFLW can reduce the binding of oxytocin to its receptor by inhibiting OTR expression, thereby suppressing Ca^{2+} release from smooth muscle cells and alleviating excessive uterine contraction.

4.3 Regulatory Effect on Other Small Molecules in Uterine Tissues

GZFLW also exerts an analgesic effect to alleviate primary dysmenorrhea by upregulating the expression level of nitric oxide (NO) and reducing calcium ion (Ca^{2+}) concentration in uterine tissues, thereby directly inhibiting the spasmodic contraction of uterine smooth muscle. NO is an endogenous uterine smooth muscle relaxing factor and a key messenger molecule regulating uterine contractile function. Meanwhile, calcium signaling plays a pivotal role in the modulation of myometrial contraction, and elevated intracellular Ca^{2+} levels in uterine cells are the trigger for uterine smooth muscle contraction. Both in vivo animal experiments and in vitro cell experiments have provided sufficient experimental evidence for this mechanism of action. In this study based on the primary dysmenorrhea model, a normal control group, a model control group, as well as low and high dosage Guizhi Fuling Wan intervention groups were established. The test results showed that compared with the model control group, the NO level in the uterine tissues of rats in the GZFLW intervention groups was significantly increased. GZFLW exerted a dose-dependent regulatory effect on Ca^{2+} levels; the Ca^{2+} content in uterine tissues reached 0.33 mmol/g in the model control group, while the low- and high-dose GZFLW groups decreased to 0.19 mmol/g and 0.24 mmol/g, respectively [12]. The above experimental results confirm that GZFLW can directly relax uterine smooth muscle through the synergistic pathway of upregulating NO expression and reducing Ca^{2+} levels, thereby alleviating primary dysmenorrhea.

5. Clinical Evidence

5.1 Clinical Therapeutic Effect of GZFLW

Clinical studies have shown that GZFLW can significantly alleviate the pain intensity of patients with primary dysmenorrhea. An early randomized controlled trial used random allocation to separate participants into GZFLW

and placebo groups and received the medication for three menstrual cycles, followed by a three-month follow-up. The results showed GZFLW can significantly reduce the severity of dysmenorrhea in patients with primary dysmenorrhea. The 3-month GFW intervention can reduce the Visual Analogue Scale score of patients from the baseline of 7.2 points to 3.7 points at the 6-month follow-up, and the Cox-Menstrual Symptom Scale score of menstrual symptoms from the baseline of 29.5 points to 18.0 points at the 6-month mark. Both core indicators showed a significantly greater decrease compared to the placebo group (all $P < 0.01$); and the therapeutic effect peaks at 3 months of intervention and can be stably maintained until the end of the follow-up, providing a evidence-based basis for the clinical therapy of primary dysmenorrhea [13].

5.2 Comparison of Therapeutic Efficacy Between GZFLW and NSAIDs

According to the research conducted by Zhang Bo and others, it was found that Guizhi Fuling Capsule and ibuprofen exhibit synergistic therapeutic effects. The study selected 60 patients with primary dysmenorrhea and randomly divided them into a control group and an observation group. The control group received ibuprofen sustained-release capsules, whereas the observation group was given combined therapy with ibuprofen sustained-release capsules and Guizhi Fuling Capsules. The experimental results showed that the baseline levels of TNF-α, IL-6 and IL-10 were comparable between the two groups (all $P>0.05$), while the levels of these inflammatory factors were significantly decreased in both groups after treatment. The observation group achieved a significantly better improvement in inflammatory indicators, with post-treatment levels of TNF-α, IL-6 and IL-10 reaching 10.58±3.93, 5.73±2.91 and 8.36±2.52 respectively, which were markedly lower than 14.85±3.80, 8.17±2.07 and 10.34±2.64 in the control group [14]. Clinical evidence indicates that the combination of TCM and WM significantly ameliorates inflammatory factor levels in patients with primary dysmenorrhea, with superior efficacy compared to Western medication alone.

6. Conclusion

GZFLW, as a classic formula in Synopsis of the Golden Chamber for promoting blood circulation and resolving stasis, aligns with the core TCM pathogenesis of primary dysmenorrhea, which is characterized by stagnation of blood blocking the flow and causing pain. Currently, it has become a commonly used prescription for blood-stagnation-related pain disorders in gynecology. This article systematically summarizes the current research status of GZFLW in the treatment of primary dysmenorrhea, reviews the current mainstream pharmacological mechanisms, and based on the research, GZFLW mainly exerts a synergistic effect through four ways: restricting the NF-kB/COX-2/PGF2α pathway, reducing the expression of OTR protein, increasing the NO level in uterine tissue, and lowering the intracellular Ca^{2+} level in uterine muscle cells, to alleviate excessive uterine contractions and thereby treat primary dysmenorrhea. Clinical studies also indicate that GZFLW has definite efficacy for primary dysmenorrhea. Compared with NSAIDs, GZFLW has no obvious side effects and better therapeutic effects, especially suitable for patient's intolerant to NSAIDs.

Although GZFLW is widely used in gynecological diseases with blood stasis syndrome, existing clinical studies have obvious shortcomings and severely insufficient evidence quality. At present, the vast majority of studies adopt intervention regimens of GZFLW combined with western medicine or other Chinese patent medicines. Randomized controlled trials focusing on its single use are extremely scarce, making it impossible to independently and objectively evaluate its own efficacy and safety, and difficult to form high-level evidence-based evidence. Meanwhile, existing studies have rarely conducted head-to-head comparisons between GZFLW and similar classic formulas, failing to clarify its relative advantages and applicable populations among similar Chinese medicines, which restricts precise clinical medication. Further exploration can be conducted on its combined use with TCM therapies such as acupuncture and acupoint patches, to leverage their synergistic advantages.

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