



Review

Effects and mechanisms of Shaofu-Zhuyu decoction and its major bioactive component for Cold - Stagnation and Blood – Stasis primary dysmenorrhea rats



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ABSTRACT

Ethnopharmacological relevance: Traditional Chinese medicine (TCM) is used under the guidance of the theory of traditional Chinese medical sciences in clinical application. The Chinese herbal formula, Shaofu Zhuyu decoction (SFZYD), is considered as an effective prescription for treating Cold - Stagnation and Blood – Stasis (CSBS) primary dysmenorrhea. The previous studies showed the SFZYD exhibited significant anti-inflammation and analgesic effect. In this present study the metabolomics of CSBS primary dysmenorrhea diseased rats and the cytokine transcription in PHA stimulated-PBMC were investigated to explore the effects and mechanisms.

Aim of the study: Explore a valuable insight into the effects and mechanisms of SFZYD on Cold - Stagnation and Blood – Stasis primary dysmenorrhea rats.

Materials and methods: We established CSBS primary dysmenorrhea diseased rats according the clinical symptoms. A targeted tandem mass spectrometry (MS/MS)-based metabolomic platform was used to evaluate the metabolic profiling changes and the intervention effects by SFZYD. The PBMC cell was adopted to explore the mechanisms by analyzing the signaling pathway evaluated by expression of inflammatory cytokines, *c-jun* and *c-fos* and corresponding phosphorylation levels.

Results: Estradiol, oxytocin, progesterone, endothelin, β -endorphin and $\text{PGF}_{2\alpha}$ were restored back to the normal level after the treatment of SFZYD. Total twenty-five metabolites (10 in plasma and 15 in urine), up-regulated or down-regulated, were identified. These identified biomarkers underpinning the metabolic pathway including pentose and glucuronate interconversions, steroid hormone biosynthesis, and glycerophospholipid metabolism are disturbed in model rats. Among these metabolites, twenty one potential biomarkers were regulated after SFZYD treated. The compound of paeoniflorin, a major bioactive compound in SFZYD, was proved to regulate the MAPK signaling pathway by inhibiting the expression of IL-1 β , IL-2, IL-10, IL-12, TNF α , INF γ , *c-jun* and *c-fos* in PHA stimulated-PBMC.

Conclusion: These findings indicated that SFZYD improved the metabolic profiling and biochemical indicators on CSBS primary dysmenorrhea rats. And the mechanisms were closely related with the regulation of the MAPK pathway by reduction in phosphorylated forms of the three MAPK (ERK1/2, p38 and JNK) and down regulation of *c-jun* and *c-fos* by paeoniflorin. The data could be provided the guidance for further research and new drug discovery.

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Contents

1. Introduction.....	235
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Abbreviations: TCM, (Traditional Chinese medicine); SFZYD, (Shaofu Zhuyu decoction); CSBS, (Cold - Stagnation and Blood – Stasis); PBMC, (peripheral blood mononuclear cells); PD, (primary dysmenorrhea); MAPK, (mitogen-activated protein kinases); NSAIDs, (Non-steroidal anti-inflammatory drugs); PCR, (Polymerase Chain Reaction); UPLC, (Ultra High Performance Liquid Chromatography)

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2. Materials and methods	236
2.1. SFZYD preparation	236
2.2. Animal handling and grouping	236
2.3. Animal plasma and urine samples	236
2.4. Biochemical indicators measurements	236
2.5. Chromatography and mass spectrometry conditions	236
2.6. Pattern recognition analysis and data processing	236
2.7. Biomarkers identification and construction of metabolic pathway	237
2.8. Isolation of peripheral blood mononuclear cells (PBMC)	237
2.9. Real-time quantitative PCR	237
2.10. Western blot analyses	237
2.11. Compliance with ethical requirements	237
3. Results	237
3.1. Biochemical indicators analysis	237
3.2. LC-MS Analysis of metabolic profiling	237
3.3. Identification of potential biomarkers and metabolic pathway function analysis	237
3.4. Intervention effects of SFZYD	238
3.5. Correlation analysis between biomarkers and biochemistry indicators	238
3.6. Effect of paeoniflorin on cytokine transcription in phytohaemagglutinin (PHA) stimulated-PBMC	240
3.7. Response of MAPK on treatment with Paeoniflorin	240
3.8. Down regulation of <i>c-jun</i> and <i>c-fos</i>	241
4. Discussion	241
5. Conclusion	242
Author contributions	242
Acknowledgments	243
References	243

1. Introduction

Traditional Chinese Medicine (TCM), which has been proved to be effective and safe in clinical applications for thousands of years, is considered as a feasible alternative treatment for PD (Hsu et al., 2006). Shao-Fu-Zhu-Yu Decoction (SFZYD) is considered as an effective prescription for treating PD. This prescription originally came from “Correction of Errors in Medical Classics” compiled by Qing-ren Wang in Qing dynasty (A.D. 1830). The formula includes the following ten herbs: Angelicae sinensis Radix, Chuanxiong Rhizoma, Corydalis Rhizoma, Foeniculi Fructus, Zingiberis Rhizoma, Myrrha, Trogopteri Feces, Typhae Pollen, Paeoniae Radix Rubra, and Cinnamomi Cortex, respectively. It has been used in clinic to treat blood stasis syndrome of gynecology diseases such as dysmenorrhea for about 200 years (Fan et al., 2011; Cheng et al., 2011). Our previous researches also indicated that SFZYD showed an inhibition of uterine smooth muscle constriction and manifested an anti-inflammatory activity (Su et al., 2010a). Recent study showed that SFZYD could significantly improve the outer membrane of uterus microcirculation and blood coagulation function of rat with blood stasis (Su et al., 2010b). Furthermore, the metabolomics study in patients affected by PD has given clinical evidence that SFZYD prevents and benefits many disorders throughout the body (Su et al., 2013). However, the therapeutic mechanisms of SFZYD still need comprehensive investigation.

PD is one of the most common gynaecological disorders in young women (Doubova et al., 2007; Wolf et al., 1999). With symptoms becoming severe, it will lead to a lot of problems (French et al., 2005; Davis et al., 2005). Traditional Chinese physicians treat PD based on an overall analysis of the illness and the patient's condition, and the type of syndrome for PD is considered the most important.

The pathogenesis of PD is not precisely understood. However, theories proposed by available data mostly congregate on the excessive secretion of uterine prostaglandins (PGs) for the underlying cause of PD (Chan et al., 1980). Therefore, some medications specific to decrease the production of PGs are applied to relieve the symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs)

are the most common pharmacologic treatments for PD. Moreover, PD has also been suggested to be a sex-hormone and ovarian steroids related disorder (Ostad et al., 2001). So some other methods such as oral contraceptive pills and Mirena were applied for treating PD. The efficacy of these drugs is obvious and rapid, but a certain number of women affected by PD do not respond to these medicines and be allergic to these medications. Furthermore, they are intolerable and have plenty of side effects that affect gastrointestinal, hepatic, renal, and even cardiac systems (Zahradnik et al., 2010; Davis et al., 2005; Proctor et al., 2001).

PD is associated with inflammation, and when inflammation occurs, some cytokines, chemokines, growth factors, and other mediators are produced and the leukocytes are recruited to the area of injury or infection (Kracht et al., 2002; White et al., 2005; Moss et al., 2005). Thus, the cytokine antagonists may have significant therapeutic efficacy in several areas of cancer therapy and inflammatory diseases (Balkwill et al., 2001). Some chemical compound block TNF signaling and synthesis such as the inhibitors of p38 MAPK is under clinical evaluation (Yan et al., 2006). Furthermore, anti-pro-inflammatory cytokine therapy has been regarded as a potential anti-inflammatory treatment (Baggio et al., 2005; Hougee et al., 2005).

Metabolomics is very useful for diagnosing and monitoring disease progression. However, there are few reports of metabolic profiling or biomarkers researches on PD, except Su et al. (2013) and Liu et al. (2013). Metabolomics has been used for the analysis of low molecular weight compounds to systematic investigation of metabolic responses in biological systems to genetic or environmental stimuli (Nicholson et al., 2012).

In this paper, the metabolic profiling changes were investigated based on UPLC-QTOF/MS/MS in order to discover the potential biomarkers for Cold - Stagnation and Blood - Stasis primary dysmenorrhea rats and explore the action mechanisms of SFZYD. Furthermore, we explored the effects of paeoniflorin (a major bioactive compound in SFZYD) on IL-1 β , IL-2, IL-10, IL-12, TNF α , INF γ , *c-jun* and *c-fos* expression in PHA stimulated-PBMC (peripheral blood mononuclear cell) and to explore the regulation of possible signaling pathways.

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