

Study on the Mechanism of Leonurus Japonicus in Treating Primary Dysmenorrhea

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Abstract. Primary dysmenorrhea (PD) refers to spasmodic lower abdominal pain occurring during menstruation or around the time of menstrual onset in the absence of pelvic organic pathology, significantly impairing women's daily work, study, and quality of life. The pathogenesis of PD is complex, primarily involving abnormal prostaglandin secretion leading to elevated prostaglandin levels, inflammatory responses and oxidative stress, psychological factors, and the synergistic involvement of various vascular and neural mediators such as vasopressin and leukotrienes. *Leonurus japonicus* Houtt. (Yimucao), a traditional key herb in gynecology, demonstrates significant efficacy in alleviating dysmenorrhea. Studies indicate that *L. japonicus* and its active constituents exert therapeutic effects through multiple pathways, including anti-inflammatory and analgesic actions, regulation of uterine smooth muscle contraction, and antioxidant activities. These bioactive compounds modulate the expression of prostaglandin F₂ α (PGF₂ α), bidirectionally regulate uterine smooth muscle tone, and interrupt oxidative stress-mediated inflammatory cascades, thereby intervening in PD via a multi-target and multi-pathway mechanism.

Keywords: Primary Dysmenorrhea, *Leonurus Japonicus*, Leonurine, Oxidative Stress

1. Introduction

Primary dysmenorrhea (PD) is menstrual pain occurring in the absence of pelvic organic pathology. It typically emerges 6-24 months after menarche, presenting primarily as midline, cramping lower abdominal pain, often accompanied by nausea, diarrhea, and fatigue. Symptoms generally subside on the second or third day of menstruation but can significantly impair learning, work performance, and quality of life. Currently, nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen) and hormonal contraceptives are first-line clinical treatments for PD. NSAIDs effectively alleviate dysmenorrhea by inhibiting cyclooxygenase-mediated prostaglandin synthesis; however, long-term use is associated with adverse effects such as gastrointestinal mucosal injury and endocrine disruption. Combined oral contraceptives (COCs) relieve dysmenorrhea by suppressing ovulation and endometrial proliferation, thereby reducing prostaglandin production. Nevertheless, they may cause adverse reactions including irregular bleeding, headache, and nausea, and carry a risk of venous thromboembolism. As a traditional Chinese herb commonly used in gynecology, *Leonurus heterophyllus* (Yimucao) is indicated for regulating menstruation and treating dysmenorrhea. Due to its significant efficacy and mild regulatory properties, it has garnered increasing attention in recent

years. This article systematically elucidates the mechanisms of *Leonurus heterophyllus* in treating PD through three dimensions: anti-inflammatory analgesia, regulation of uterine smooth muscle contraction, and antioxidant activity, based on an integration of existing literature. The aim is to provide scientific evidence for the use of herbal medicines as alternative or adjunctive therapies for primary dysmenorrhea [1].

2. Pathogenesis of primary dysmenorrhea

2.1. Prostaglandin theory

The currently accepted core pathogenic mechanism of PD is the prostaglandin theory. During menstruation, the abrupt decline in estrogen and progesterone levels stimulates a massive release of phospholipase A₂ from endometrial lysosomes, accelerating the generation of free arachidonic acid. Under the catalysis of cyclooxygenase-2 (COX-2), arachidonic acid is converted into large amounts of prostaglandins, particularly leading to abnormally elevated levels of PGF₂α. High concentrations of PGF₂α act on the uterus, inducing uncoordinated contractions or even spasms of uterine smooth muscle, which results in local tissue ischemia and hypoxia. Simultaneously, it increases the sensitivity of peripheral nociceptive nerve endings, ultimately triggering severe pain [2, 3].

2.2. Synergistic effects of multiple mediators

In the regulatory network of inflammatory lipid mediators, in addition to prostaglandins, leukotrienes and vasopressin can also stimulate abnormal contractions of uterine smooth muscle, mediate peripheral and central sensitization, and exacerbate menstrual pain. Leukotrienes are primarily derived from arachidonic acid via the 5-lipoxygenase pathway, with representative products including LTC₄, LTD₄, LTE₄, and LTB₄. These mediators not only induce potent vasoconstriction and smooth muscle contraction but also amplify the inflammatory cascade. Although the specific mechanisms remain to be fully elucidated, current evidence indicates that leukotrienes play a significant role in PD [4].

Arginine vasopressin (AVP), a polypeptide hormone synthesized in the hypothalamus and released from the posterior pituitary, can bind to V₁a receptors on uterine smooth muscle and uterine arteries, inducing excessive uterine contractions and intense vasoconstriction, thereby exacerbating ischemia and hypoxia. Additionally, AVP can promote the synthesis of prostaglandins in the endometrium, acting synergistically with PGF₂α to enhance pain. However, the universality of AVP's role in primary dysmenorrhea remains controversial, as some studies have not observed stable clinical efficacy from V₁a receptor antagonists [5, 6].

2.3. Inflammation-oxidative stress amplification hypothesis

Reactive oxygen species (ROS) are oxygen-containing free radicals generated during aerobic metabolism in the body. Approximately 2% of the total oxygen utilized in energy production is redirected to mitochondrial complexes I and III to generate reactive oxygen species. Lacerda-Júnior et al. confirmed this by detecting malondialdehyde (MDA) and total antioxidant capacity (TAC) levels in uterine tissue, demonstrating that ischemia-hypoxia in model rats leads to significant accumulation of ROS in the uterus. This triggers lipid peroxidation, resulting in elevated MDA levels, while simultaneously depleting antioxidant substances such as glutathione (GSH), thereby disrupting oxidative balance and exacerbating uterine tissue injury [7]. Furthermore, a close

association exists between oxidative stress and chronic inflammation. High levels of ROS play a critical role in regulating the activity of the transcription factor nuclear factor kappa B (NF- κ B), which initiates the expression of genes encoding various pro-inflammatory cytokines and COX-2. Overexpression of COX-2 catalyzes the metabolic synthesis of large amounts of prostaglandins from arachidonic acid, inducing excessive spasmodic contraction of uterine smooth muscle. This causes constriction of spiral arteries, local tissue ischemia-hypoxia, and ultimately precipitates primary dysmenorrhea [8].

2.4. Psychological factors

Multiple clinical controlled studies have confirmed that psychological cognition and emotional factors are key non-physiological mechanisms regulating pain perception in primary dysmenorrhea. Women with severe dysmenorrhea exhibit stronger pain anticipation during the premenstrual phase, accompanied by negative emotions such as anticipatory anxiety, stress, worry, and anger, resulting in a hyperalgesic phenomenon similar to the nocebo effect. Excessive premenstrual pain prediction further amplifies actual menstrual pain perception, while intensified pain experiences reciprocally reinforce negative expectations for subsequent cycles, establishing a continuous psychosomatic negative feedback loop. Even when physiological baselines such as prostaglandin levels and uterine smooth muscle contractions are comparable, long-term adverse emotions and negative pain cognitions can enhance visceral pain sensitivity via central sensitization pathways. This effect, compounded by alterations in the hypothalamic-pituitary-adrenal (HPA) axis related to emotional stress, exacerbates both the severity of dysmenorrheal pain and functional impairment [9].

3. Mechanisms of motherwort in the treatment of primary dysmenorrhea

3.1. Anti-inflammatory and analgesic effects

Leonurine is the core active component responsible for the pharmacological effects of *Leonurus japonicus* (Motherwort). In primary dysmenorrhea mouse models, leonurine significantly reduced the number of writhing responses and prolonged the latency period, demonstrating analgesic efficacy comparable to that of ibuprofen. Furthermore, leonurine markedly downregulated serum PGF2 α levels while upregulating β -endorphin (β -EP), an endogenous peptide with analgesic properties. Its underlying mechanism is closely associated with the inhibition of phosphorylation in the JNK/p38 MAPK signaling pathway [10].

Additionally, *in vitro* experiments have confirmed that leonurine possesses direct peripheral analgesic activity. Calcium imaging and whole-cell patch-clamp studies indicate that leonurine exhibits high selectivity for TRPA1 and TRPV4 channels. In cell lines expressing human or murine TRPA1/TRPV4, as well as in dorsal root ganglion (DRG) neurons of mice, leonurine induced a concentration-dependent increase in intracellular calcium ion concentrations, thereby causing desensitization of TRPA1- and TRPV4-mediated currents. Concurrently, this compound showed no activating effect on TRPV1 channels, further confirming the specificity of its target engagement. This mechanism of pain relief via receptor desensitization has been corroborated in other peripheral neuropathy models; for instance, in thalidomide-induced chemotherapy-induced peripheral neuropathy (CIPN) mouse models, leonurine demonstrated significant channel-dependent analgesic effects [11], providing robust theoretical support for the peripheral neural mechanisms by which Motherwort alleviates dysmenorrhea.

3.2. Regulation of uterine smooth muscle contraction

Coumarin compounds in *Leonurus* exhibit a bidirectional regulatory effect on uterine smooth muscle contraction, with the specific outcome largely determined by their chemical structures and mechanisms of action on calcium ion channels. On one hand, components such as bergapten can activate calcium channels and α -receptors, promoting extracellular calcium influx and thereby moderately enhancing uterine contractions to facilitate menstrual flow. On the other hand, coumarins like osthole primarily exert an antagonistic effect on α -receptors, inhibiting calcium influx and reducing uterine smooth muscle tone, which effectively alleviates abnormal spasms associated with dysmenorrhea. This capacity for bidirectional regulation of calcium ion homeostasis underscores the pharmacological basis for the use of *Leonurus* in providing rapid pain relief in gynecological clinical practice [12].

3.3. Antioxidant effects

Targeting the "inflammation-oxidative stress" loop in primary dysmenorrhea, leonurine demonstrates superior antioxidant activity. It specifically downregulates the expression of NADPH oxidase 4 (NOX4), thereby reducing ROS generation at the source, and directly scavenges free radicals within the body. This effectively blocks ROS-mediated downstream inflammatory cascades and improves the local uterine microenvironment. Meanwhile, flavonoids and chlorogenic acid, natural antioxidants abundant in *Leonurus japonicus* extracts, play a significant synergistic role in the systemic antioxidant stress response [10-13].

4. Conclusion

Primary dysmenorrhea, a prevalent gynecological condition among women, is not regulated by a single pathway but rather by a complex regulatory network involving the abnormal synthesis of prostaglandins, inflammatory responses, oxidative stress, multiple mediators, and psychological factors. COX-2-mediated excessive production of prostaglandins, along with vasopressin and leukotrienes inducing uterine hypercontractility, contributes to the pathology. Accumulation of ROS activates the NF- κ B inflammatory pathway, while psychological factors can trigger central sensitization of pain, collectively amplifying the pain response. As a traditional Chinese herbal medicine for gynecology, *Leonurus japonicus* (Motherwort) exerts therapeutic effects through various active components, demonstrating multi-target and multi-pathway characteristics: it alleviates inflammation and inhibits prostaglandin synthesis by suppressing signaling pathways such as MAPK and NF- κ B; reduces peripheral nociceptive sensitivity by inducing desensitization of nociceptors including TRPA1 and TRPV4; improves the uterine microenvironment by downregulating oxidative stress pathways; and bidirectionally regulates uterine smooth muscle tone via coumarin components. Future research should focus on large-scale, multi-center clinical trials and in-depth molecular mechanism studies to continuously strengthen the evidence base for *Leonurus japonicus* in PD management, thereby providing a solid scientific foundation for its further clinical development and standardized application.

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