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EDITED BY

Lihua Yang,
Chinese Academy of Sciences (CAS), China

REVIEWED BY

Ma Yanbo,
Chinese Academy of Sciences, China

*CORRESPONDENCE

Chao Wang
✉ 85251713@163.com
Hao Zhou
✉ 545699817@qq.com

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Traditional Chinese medicine treatment strategies for primary dysmenorrhea

Wenwen Duan¹, Dan Chen¹, Dan Li¹, Yue Zeng², Shanshan Liu²,
Zubo Huang², Chao Wang^{2*} and Hao Zhou^{2*}

¹Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ²Sichuan Clinical Research Center for Sub-Health, Sichuan Integrative Medicine Hospital, Chengdu, China

Primary dysmenorrhea is a common disease in women. China, under the influence of their philosophical wisdom, has developed unique theories of common clinical disorders and corresponding therapeutic cultural practices, including the application of unique medical wisdom to the treatment of primary dysmenorrhea. The article reviews the current Traditional Chinese medicine treatment strategies for primary dysmenorrhea, including acupuncture, moxibustion, acupoint application, diet improvement, and lifestyle adjustment. This article also analyzes the benefits and potential mechanisms of these treatments. Finally, this study highlights future directions for dysmenorrhea treatment, including ongoing research and potential new treatment modalities. This review aims to guide healthcare providers in developing the personalized treatment strategies for patients with primary dysmenorrhea and promote a more harmonious doctor-patient relationship.

KEYWORDS

primary dysmenorrhea, traditional Chinese medicine, treatment strategies, biomolecular mechanism, women's health

1 Introduction

Clinical treatments for primary dysmenorrhea are varied and cover modern drug therapy, traditional cultural therapeutic practices, physical therapy, surgical therapy, and other therapies. In modern drug therapy, non-steroidal anti-inflammatory drugs (NSAIDs) (1), acetaminophen (2, 3), opioids (Tramadol) (4), contraceptive pills (5, 6) etc. on the list of analgesics for dysmenorrhea patients. Physical treatment methods such as transcutaneous electrical nerve stimulation, cryotherapy (7), extracorporeal shock wave (8), heat therapy (9), pulse technology (10), etc. continue to open up treatment options for dysmenorrhea. In addition, exercise (11, 12), aromatherapy (13), fish oil (14), water intake (15) have also been recommended as therapies for primary dysmenorrhea. While these methods may offer some help, they are accompanied by numerous limitations. For example, non-steroidal anti-inflammatory drugs have been reported to disrupt the intestinal microbiota, induce gastrointestinal inflammation, and may compromise the immune system with long-term use (16, 17). Moreover, the efficacy

and safety of some physical therapy modalities have not been conclusively validated. Surgical treatments are not suitable for most people (18, 19). Therefore, exploring safer, more effective, and natural treatment options is the core pathway for coping with primary dysmenorrhea. With the development of globalization, the traditional treatment practice based on cultural customs has been vigorously excavated and promoted. These therapeutic cultural practices are often used in clinical practice as complementary and alternative therapies that focus on the psychological, physical, and emotional aspects of a person's health as a whole (20). Traditional therapeutic cultural practices are used in many countries and regions in the world, which are based on specific regional or national cultural knowledge, theory, belief, experience, skills, and practice summary, for the prevention, maintenance, improvement, and treatment of disease medicine (21). There are significant differences between traditional and modern medicine treatment methods. Traditional therapeutic practices pay attention to individual differences, and gives different treatment methods according to different people, and this kind of treatment means profoundly reflect personalized medicine (22). However, Western treatment practices focus on providing patients

with more immediate symptomatic relief in the short term by acting on a single target of the disease and giving specific targeted drugs (23). Traditional Chinese Medicine (TCM) has its own unique method for treating primary dysmenorrhea. TCM uses Chinese herbal medicine, acupuncture, moxibustion, massage, acupoint patches and other traditional specialties to treat primary dysmenorrhea. These treatments not only have significant analgesic effects but also have small adverse reactions (24). This review focuses on the role and application of Chinese herbs, acupuncture, moxibustion, acupoint application and massage therapies in the treatment of primary dysmenorrhea (Figure 1). These therapies, as the characteristic means of Chinese medicine, provide diversified treatment options for patients and help women's health.

2 Chinese herbal medicine and its function

Herbs are the cornerstone of traditional medicine. Traditional Chinese medicine has a long history and rich experience in the

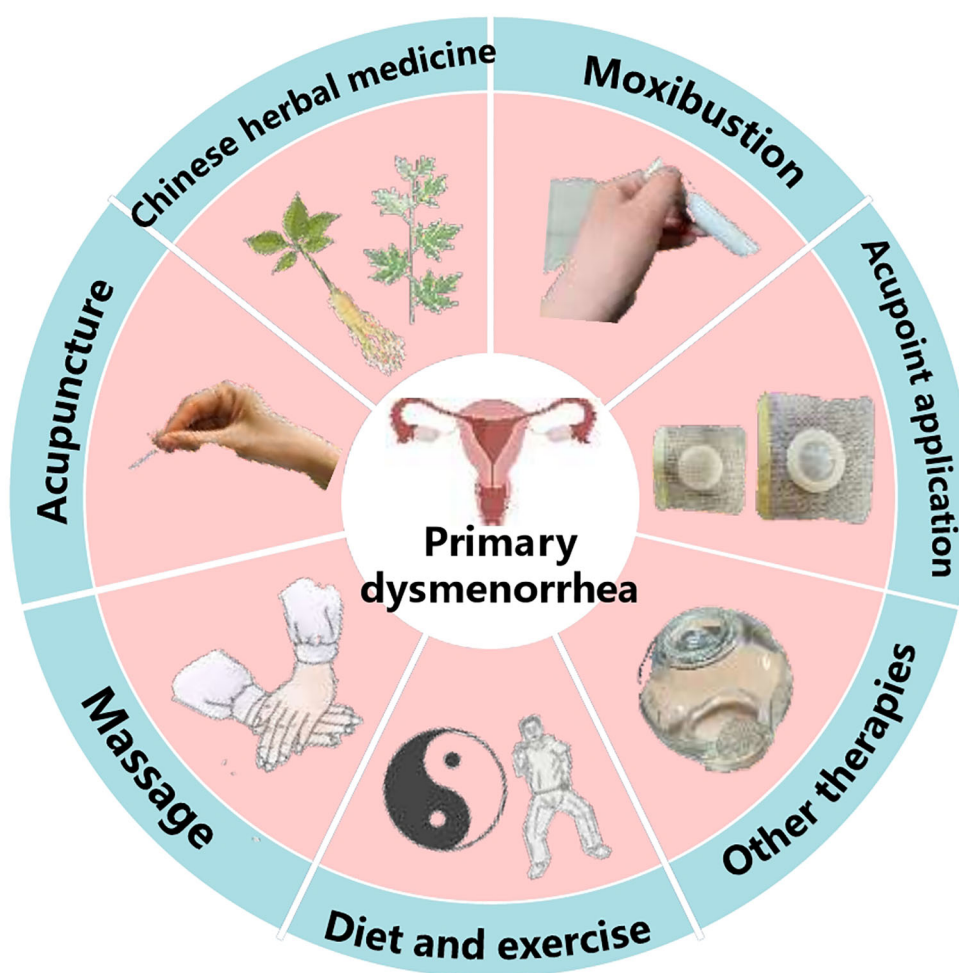


FIGURE 1
Chinese medicine treatment measures for primary dysmenorrhea.

treatment of dysmenorrhea. This natural therapy distinguishes the overall pathological changes of dysmenorrhea in a certain period by collecting the etiology and pathogenesis of patients and using a single drug or a combination of multiple drugs to form a prescription to treat the illness (25), which plays a role in reconciling human qi and blood, promoting blood circulation and removing blood stasis, warming meridians and dispelling cold, and dredging meridians and relieving pain. Some decoctions such as Xuefu Zhuyu Decoction (26) and Danggui Sini Decoction (27) showed strong analgesic effects, and no adverse reactions were reported. The drugs in these decoctions are derived from natural products, the cost of treatment is not expensive, and the effective biological activity in natural products acts as the target of disease (28). A study found that Chinese herbal medicine has a significant relief effect on the pain of primary dysmenorrhea (29). This is closely related to the anti-inflammatory and analgesic effects of Chinese herbal medicine (30, 31). For example, Akebiae Fructus regulates the expression of these genes (Plpp3, Sgpp2, Arg1, Adcy8, Ak5) by inhibiting the concentration of $PGF_{2\alpha}$ to regulate the enzymes in sphingolipid, glycerophospholipid, arginine, proline metabolism, and purine metabolism, reduce the intensity of uterine contraction and relieve dysmenorrhea (32). Cinnamon and fennel can shorten the duration of dysmenorrhea pain (33). Jasmine plays an anti-inflammatory role and relieves dysmenorrhea by acting on three core pathways, including PTGS2, OPRD1, and NOS3 (34). The decoction is another form of clinical application of herbal medicine in the treatment of primary dysmenorrhea. Gegen decoction is a traditional Chinese medicine prescription mainly used for the treatment of reproductive system diseases in China (35). According to the theory of traditional Chinese medicine, primary dysmenorrhea can be caused by the cold generated inside or outside the body, which stays in the uterus, and the cold belongs to a kind of evil qi, which has the effect of astringency so that the uterus has a problem in blood drainage and produces pain. The traditional Chinese medicine in Gegen Decoction can be used to treat dysmenorrhea caused by cold evil. Modern research (35) has found that Gegen Decoction acts on the key targets arginine vasopressin (AVP) and estrogen. Siwu decoction has been proven to be safe and effective in the treatment of primary dysmenorrhea. Siwu Decoction is the first prescription for the treatment of female diseases, which contains four Chinese herbal medicines (36). The precise compatibility of these four drugs can relax the uterine smooth muscle by acting on the hormone regulation pathway, thereby relieving pain (37). Danggui Sini Decoction is a classic prescription created by Zhongjing Zhang, a famous Chinese doctor in the Han Dynasty (38). The results of KEGG pathway analysis showed that the active components in this prescription can exert analgesic effects by acting on the mitogen-activated protein kinase (MAPK) signaling pathway and arachidonic acid metabolism signaling pathway (38). Shaofu-Zhuyu decoction can also regulate the balance of downstream pro-inflammatory cytokines and anti-inflammatory cytokines by regulating the MAPK signaling pathway (39). This review systematically sorts out four commonly used compounds for the treatment of primary dysmenorrhea (Gegen Decoction, Shaofu-Zhuyu Decoction, Danggui Sini Decoction and

Siwu Decoction) and analyzes the high-frequency drugs (Jujubae Fructus, Ginger, Radix Paeonia Rubra, Ramulus Cinnamomi, Chuanxiong, Rehmannia Radix, Angelica). Through the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database and Swiss Target Prediction database, the active components and their targets of the above traditional Chinese medicines were extracted, and the disease targets related to primary dysmenorrhea were screened out by combining online mendelian inheritance in man (OMIM), DisGeNET, and Drugbank databases. Finally, a total of 73 chemical components and 237 cross-targets were screened out. The traditional Chinese medicine-component-target-disease network diagram (Figure 2) was constructed by Cytoscape 3.7.2 software, and the protein-protein interaction (PPI) network analysis was carried out to further explore the core targets. (Figure 3). These core targets are STAT3, AKT1 SRC, EGFR, ESR1, BCL2, CASP3, JUN. The results suggest that the above herbs may exert their therapeutic effects on primary dysmenorrhea by acting on key action targets such as STAT3, ESR1 and AKT1 through active ingredients such as beta-sitosterol, kaempferol and baicalein. In addition, through network pharmacology analysis, we found that the main compound category in the above core Chinese herbal medicines was phytosterol. Based on the existing research, it is speculated that it may play an anti-inflammatory effect by inhibiting the inflammatory response pathway (40), thus having a potential therapeutic effect on primary dysmenorrhea.

It is worth noting that due to the lack of standardized processing, quality of quality of Chinese herbal medicine, and potential drug interactions, some Chinese herbal preparations may have efficacy and safety issues (41). These problems can be avoided. From the perspective of patients, it is recommended that patients seek professionally qualified Chinese medicine practitioners to implement the diagnosis and treatment process of Chinese herbal medicine. Professional Chinese medicine practitioners can provide accurate and personalized Chinese herbal medicine treatment programs according to the patient's specific condition, constitution, and symptoms to ensure the safety, and effectiveness of the treatment. From the perspective of the development of traditional Chinese medicine, the cooperation of various aspects is very important. On the one hand, Chinese medicine practitioners should continue to accumulate experience through the in-depth study of the basic theory of traditional Chinese medicine and combined with clinical practice to accurately understand the nature, taste, efficacy, indications, compatibility rules, and contraindications of Chinese herbal medicines to formulate safe, effective and personalized treatment plans for patients. On the other hand, we should strengthen the supervision of the quality of Chinese herbal medicines, strictly regulate the planting, collection, and processing of Chinese herbal medicines, and ensure the safety and efficacy of Chinese herbal medicines (42).

3 Acupuncture therapy and its effect

Acupuncture originated in China and has a history of more than 3,000 years (43). It is an important part of traditional Chinese

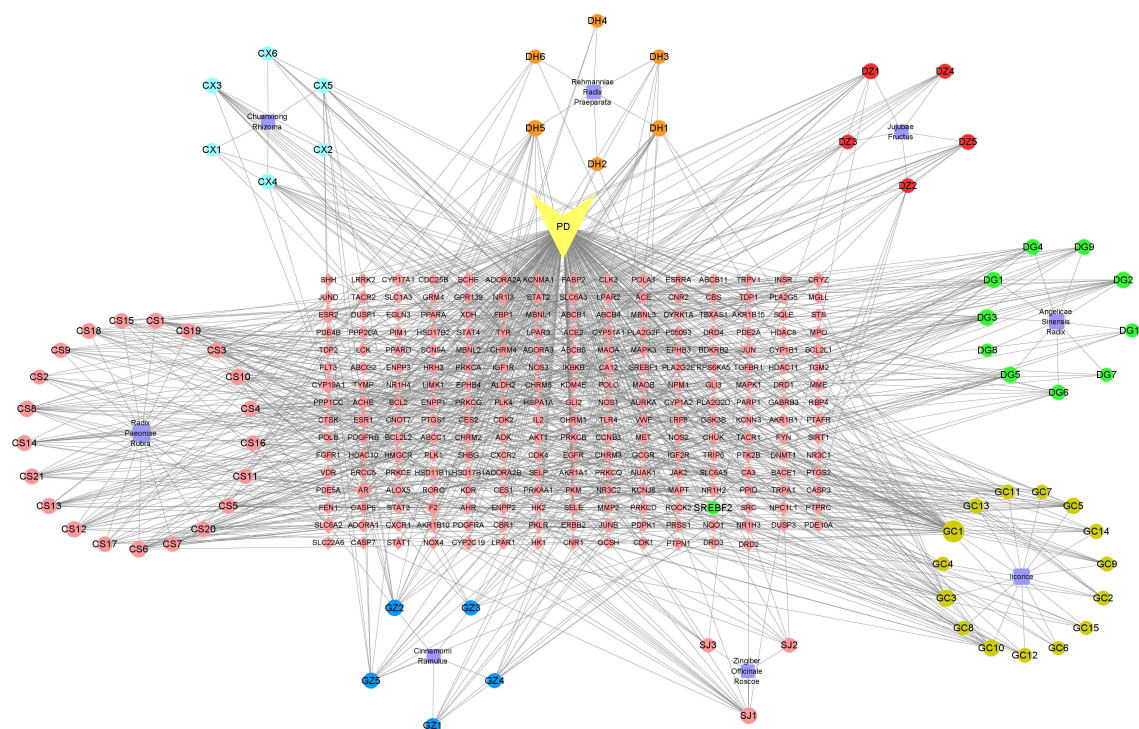


FIGURE 2

The core Chinese herbal medicine-component-target-disease network diagram of four common compounds of Gegen Decoction, Siwu Decoction, Danggui Sini Decoction and Shaofu Zhuwu Decoction.

medicine. Acupuncture, as an ancient therapy, is simple to operate and has significant efficacy (44). Acupuncture can restore the balance of yin and yang in the body, realize the treatments of the disease by stimulating specific acupoints, regulate qi and blood circulation, and activate meridian function (45). At present, more and more scientists are working to confirm the true efficacy of acupuncture and to explore the physiological and biological mechanisms of acupuncture (43). Acupuncture may regulate hormone levels by affecting the hypothalamic-pituitary-adrenal axis (HPA axis), regulate specific neurotransmitters, and affect the immune system by modulating immune cell function and release of inflammatory factors, which are mechanisms that work together to mediate the analgesic and anti-inflammatory therapeutic effects of acupuncture by acting on acupoint-specific structures (46–49). (Figure 4)

From 2020 to 2022, a large number of articles proving the effectiveness of acupuncture in the treatment of primary dysmenorrhea were been published (50–53). These studies found that acupuncture plays a role in the treatment of dysmenorrhea by regulating a variety of inflammatory factors and cytokines. An animal study confirmed that acupuncture can improve the degree of pain in rats with primary dysmenorrhea by reducing the level of uterine $\text{PGF}_{2\alpha}$ and down-regulating the phosphatidylinositol-3-kinase (PI3K)/protein kinase B(Akt)/mammalian target of rapamycin(mTOR) signaling pathway (54). Another animal study found that electroacupuncture may reduce the inflammatory response in primary dysmenorrheal rats by decreasing the expression of Toll-like receptor 4(TLR4), inhibiting the activation of NF-kappa B(NF- κ B), and decreasing the levels of

inflammatory factors such as interleukin-1 β (IL-1 β) and IL-18 (55). The analgesic and anti-inflammatory effects of acupuncture promote the application and development of acupuncture in gynecological diseases (56). In conclusion, acupuncture is effective in relieving dysmenorrhea symptoms through mechanisms such as modulating multiple signaling pathways.

4 Moxibustion and its effects

Moxibustion is also used to treat primary dysmenorrhea as a therapeutic cultural practice. Moxibustion has the characteristics of simplicity and convenience. In addition to being used in China, moxibustion is favored by Japan, the United States, and other regions (57). Moxibustion can treat primary dysmenorrhea by regulating endocrine, immune function, nerve factors, and uterine microcirculation (58). The Evidence-Based Clinical Practice Guidelines for the Treatment of Primary Dysmenorrhea published by Nie Rongrong et al. in 2021 affirmed the therapeutic effects of moxibustion, and also documented that moxibustion may be associated with adverse effects including burns, skin irritation, skin blisters, and pain; however, moxibustion does not cause damage to internal organs, and therefore it is a recommended therapy (59).

An animal study confirmed that rats with primary dysmenorrhea had a significant reduction in pain after receiving an intervention with moxibustion (60). Another study found that moxibustion analgesia may be induced by altering functional brain

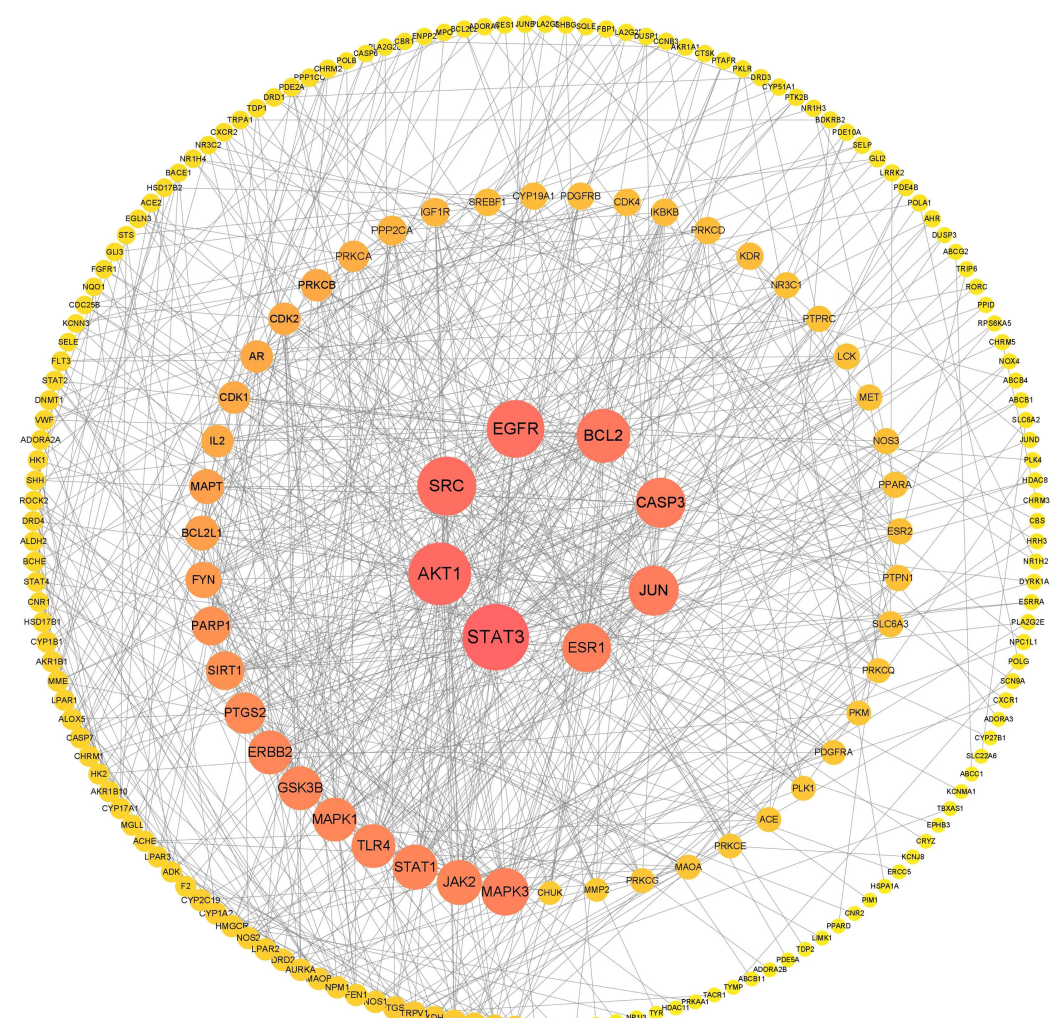


FIGURE 3
Protein-protein interaction network diagram.

connectivity in women with primary dysmenorrhea (61). In addition, the timing of the moxibustion treatment also has a certain effect on the duration of pain, especially moxibustion before menstruation is more effective in analgesia (62). In conclusion, the analgesic effect of moxibustion on dysmenorrhea is remarkable (63).

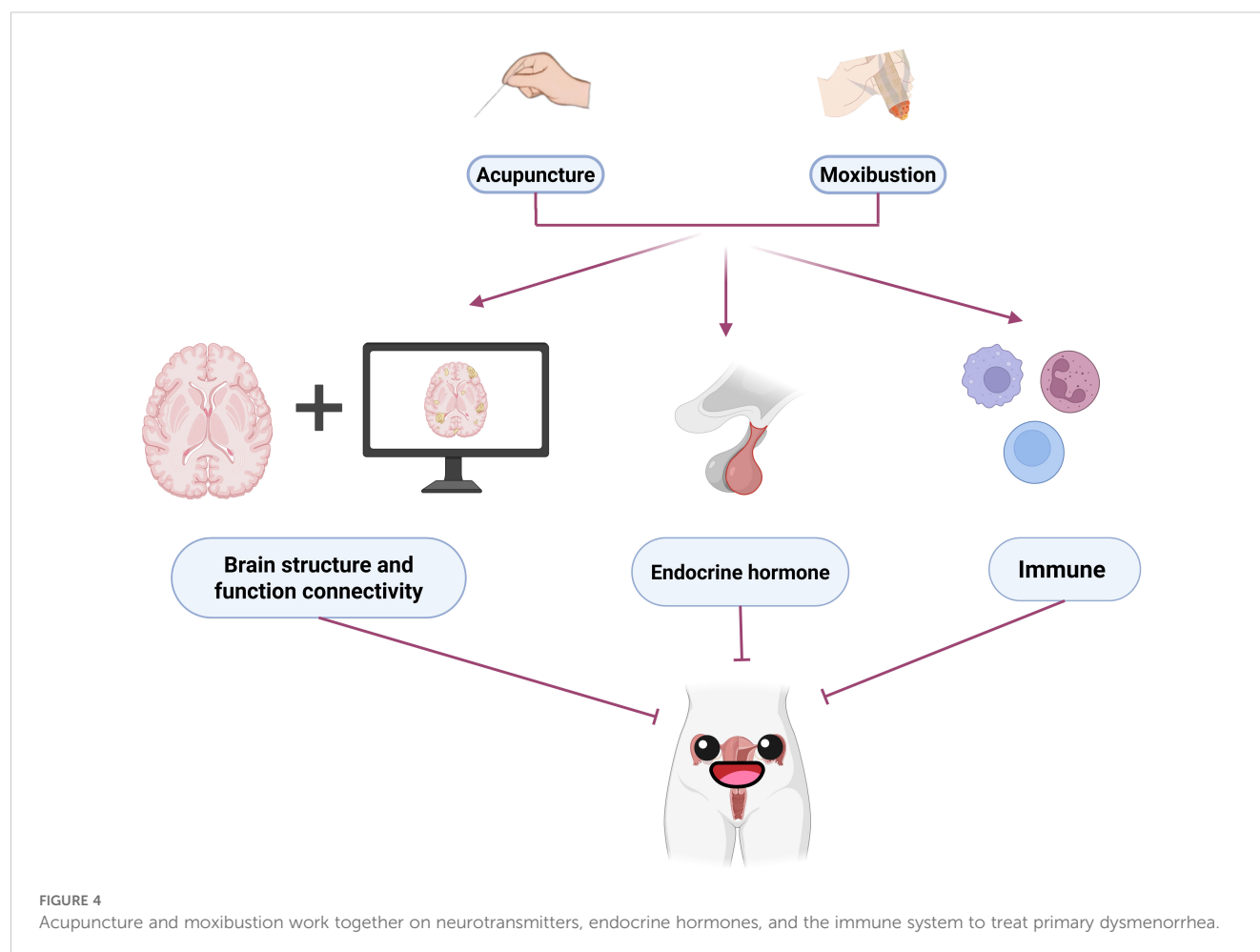
5 Acupoint application therapy and its effect

Acupoint application is a traditional external treatment that combines the basic theory of traditional Chinese medicine and the theory of meridians. Acupoint application has the advantages of simple operation, high safety, and good curative effect (64). In China, acupoint application has been widely used in internal medicine, pediatrics, gynecology, surgery, etc (65). The medicine is applied to acupoints on the surface of the body, and the medicine

is directly absorbed through the skin, coupled with the stimulation of the meridian to treat the disease (66). A study reported that acupoint application can treat dysmenorrhea by reducing the production of arachidonic acid (AA), reducing the secretion of prostaglandin ($\text{PGF}_{2\alpha}$), and promoting the production of PGE_2 (67). Therefore, acupoint application is an external treatment method that is worth recommending internationally for the treatment of primary dysmenorrhea.

6 Massage and its effect

Massage is another therapeutic practice. Massage treatment of primary dysmenorrhea shows an encouraging therapeutic effect (68). A systematic review (69) summarized the massage techniques for the treatment of primary dysmenorrhea, including viscera Tuina, aromatherapy massage, spinal Tuina, rhythmical massage therapy, and acupressure therapy. Modern research has found that



massage can improve uterine blood flow microcirculation and regulate prostaglandin levels in women with dysmenorrhea (70). In addition, massage shows its great potential as a dysmenorrhea intervention method due to its diversity and safe operation. For example, acupressure is not only easy to operate, but also easy to be accepted by patients, and can effectively reduce the degree of pain and pain duration (71). It is an external treatment worthy of recommendation in clinical practice.

7 Other therapeutic cultural practices in TCM

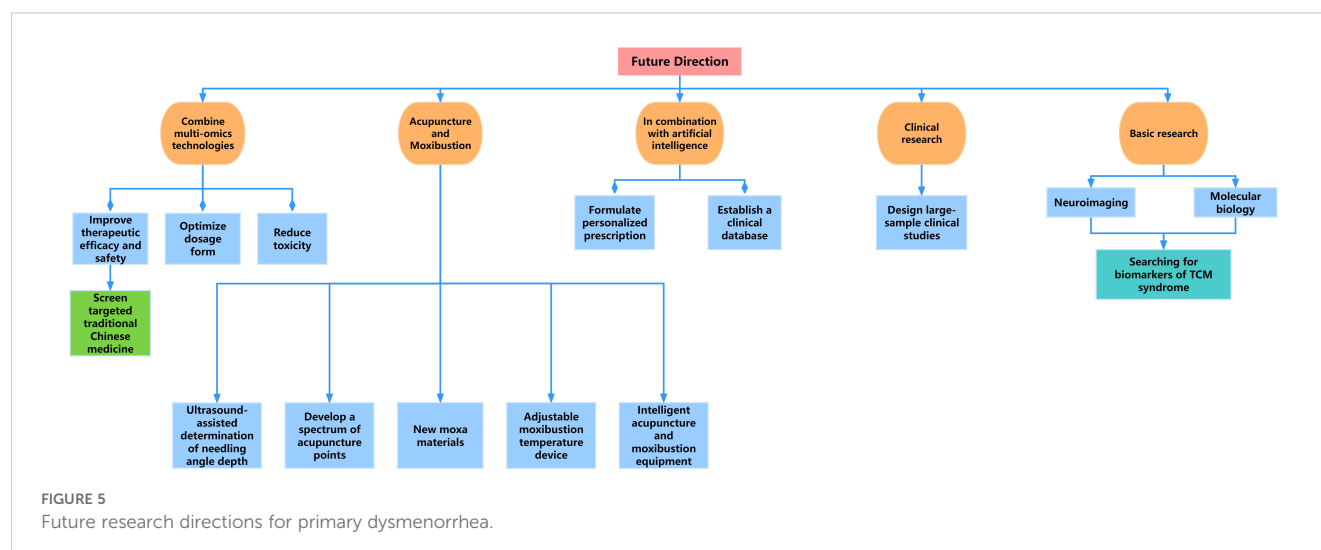
Cupping therapy is another therapeutic practice in TCM (72). A study found that static cupping reduced pain levels and accompanying pain in the lower back area in patients with primary dysmenorrhea (73). It should be noted that complications such as burns and skin infections may occur during cupping, however, with the correct cupping method and reasonable time for the tank to stay on the patient's body surface, cupping therapy is very safe and has a good analgesic effect on relieving clinical pain (74).

8 Featured TCM diet and exercise

In the traditional Chinese therapeutic practice, the adjustment of diet and exercise plays an important role in the treatment of primary dysmenorrhea. The Chinese classical medical book “Huangdi Neijing” writes that the key method of maintaining life is to eat and drink regularly, live regularly, and work and rest moderately. In many studies (11, 12, 75, 76), regular exercise is related to the improvement of overall menstrual health, possibly because it affects female hormone levels. Traditional health methods such as Baduanjin (77), which combine physical activity with wellness concepts, have much to offer in relieving menstrual cramps symptoms. In the long run, the benefits of exercise for exercisers go beyond pain relief and are broader than just overall health benefits (78).

In the diet of Chinese medicine, dietary advice for dysmenorrhea usually focuses on the significance of regulating the body's yin and yang balance and improving overall menstrual health (79). TCM practitioners will recommend specific foods or dietary regimens based on different people's constitutions and symptoms (80).

In terms of Chinese medicine exercise, patients who adopt the traditional Chinese medicine characteristic exercise method need to invest more time to achieve obvious results. This is because a study found that different types of exercise were effective in relieving the



pain of primary dysmenorrhea after 8 weeks of adherence (81). Patients who consider alleviating dysmenorrhea by participating in traditional Chinese medicine special health exercise styles can have a variety of exercise options, such as Baduanjin, Yijinjing (82), etc. The research on the improvement of dysmenorrhea by sports is currently presented in low-quality data (83). Therefore, the diet and characteristic exercise methods of traditional Chinese medicine need more evidence to confirm their scientificity.

9 Limitations

Traditional Chinese medicine has shown remarkable efficacy in the treatment of primary dysmenorrhea, but its development still faces many challenges. Because the therapeutic effect is closely related to the clinical experience of doctors, it is difficult for the Chinese medicine industry to determine a standardized development model. In addition, the uneven quality of Chinese herbal medicines further affects the reliability and safety of treatment. It is more concerned that the lack of high-quality clinical research in the field of primary dysmenorrhea in the field of traditional Chinese medicine has limited our comprehensive understanding and promotion of this treatment.

10 Conclusion and outlook

With the increasing intermingling of cultures across the globe, Traditional therapeutic practices have been promoted and applied in clinical practice due to their unique advantages. These practices can alleviate the pain level of primary dysmenorrhea to some extent and bring health benefits to women. However, there is a general lack of scientific evidence for traditional cultural medical practices.

Therefore, more scientific evidence is needed to confirm the effectiveness as well as safety of TCM in the future.

In the future, Traditional Chinese medicine can be combined with modern proteomics, metabolomics technology (84) and other multi-omics technologies (85) to seek evidence-based basis for the treatment of primary dysmenorrhea with traditional Chinese medicine. In the aspect of Chinese herbal medicine, modern drug extraction technology and modern pharmaceutical packaging technology can be used to improve the efficacy and safety of Chinese herbal medicine and optimize the dosage form to facilitate the use of patients. For some toxic drugs, future research can focus on whether the side effects of toxic drugs can be reduced by modern technology. Regarding the lack of standardization of traditional Chinese medicine prescriptions, modern artificial intelligence technology can be combined to develop personalized traditional Chinese medicine prescriptions for patients (86).

In terms of acupuncture, ultrasound can be used to determine the depth of acupuncture, accurately penetrate acupoints, quantify the depth of acupuncture, and improve the efficacy (87). In terms of moxibustion, moxibustion materials and moxibustion operation methods can be improved. Since each person's perception of temperature during moxibustion is inconsistent, moxibustion that is able to regulate temperature may be a potential future research direction. Traditional acupuncture and moxibustion rely on human labor, and the development of intelligent needling or moxibustion equipment can help free human hands (88). In addition, the clinical research design of traditional Chinese medicine intervention in primary dysmenorrhea needs to be designed in more detail and the sample size is larger (89). Animal studies need to find more pathways and targets to verify. Through clinical research and animal research, we can find more targets for traditional Chinese medicine to intervene in primary dysmenorrhea, and find out the specific biological indicators of TCM syndromes (Figure 5).

Author contributions

WD: Writing – original draft. DC: Conceptualization, Supervision, Writing – review & editing. DL: Supervision, Writing – review & editing. YZ: Conceptualization, Supervision, Writing – review & editing. SL: Conceptualization, Supervision, Writing – review & editing. ZH: Conceptualization, Writing – review & editing. CW: Writing – original draft, Writing – review & editing. HZ: Writing – original draft, Writing – review & editing.

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Conflict of interest

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