Advances in Pharmacological Effects and Clinical Application of Pulsatilla Decoction

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Keywords: Pulsatilla decoction; pharmacological action; clinical application; overview

Abstract: Pulsatilla Decoction comes from treatise on febrile diseases. Its efficacy is to clear away heat, detoxify, cool blood and stop dysentery; In recent years, studies have found that the pharmacological effects and clinical applications of Pulsatilla decoction are diverse and extensive, with anti-inflammatory, bacteriostatic, antidiarrheal, antitumor and other effects. It is mainly used in ulcerative colitis, radiation proctitis, colorectal cancer, diarrhea, bacillary dysentery, anal sinusitis, anal recess inflammation and so on. This paper expounds its progress from the pharmacological action and clinical application of Pulsatilla decoction, in order to provide some experience for the further research of Pulsatilla decoction. Pulsatilla Decoction comes from Zhongjing's "Treatise on Febrile Diseases" [1] . Among them, "Treatise on Febrile Diseases Differentiation and Treatment of Jueyin Pulse Syndrome" wrote: "Hot Li under the severe, Pulsatilla Decoction main." "Those who want to drink water because of the heat, the Pulsatilla soup is the main one. " It shows that the Pulsatilla Decoction is mainly used to treat heat and poison, and the characteristics of spleen and stomach deficiency and cold are contraindicated; This prescription is composed of four herbs, which are Pulsatilla, Huang Lian, Phellodendron, and Qinpi. The king medicine for Pulsatilla, the main effect is to clear heat and detoxify, cool blood dysentery. Huang Lian is the minister medicine, bitter cold sex taste, has the function of clearing heat and detoxifying, clearing heat and drying dampness; Phellodendron phellodendron has the effect of reducing coke and dampness and dysentery by combining with Coptis chinensis. Qinpi bitter cold astringent, strong astringent effect, often used for hemostasis. Combined with four drugs, it is a good prescription for treating heat poison blood dysentery. It is widely used in ulcerative colitis, colorectal cancer, bacillary dysentery, radiation proctitis, diarrhea caused by damp heat and other diseases. The progress of pharmacological research and clinical application of Pulsatilla Decoction on related diseases in recent five years is summarized as follows.

1. Advances in research on pharmacological effects

1.1 Inflammation related

1.1.1 Ulcerative colitis

At present, there are many reports on the mechanism of Pulsatilla Decoction on ulcerative colitis, and related studies have been conducted from different perspectives. Most studies have found that Pulsatilla Decoction mainly regulates the level of inflammatory factors, regulates immune function and alleviates symptoms. For example, Li Jing^[2] et al. found that Pulsatilla Decoction combined with colonic dialysis could relieve the symptoms of ulcerative colitis by reducing serum levels of IL-23. IL-17 and TNF-α. Hu Xiaoli^[3] et al. randomly divided 96 healthy male C57BL/6 mice into 8 groups and gave them free access to 3% glucan sodium sulfate (DSS) to establish a mouse model of acute ulcerative colitis. To observe the intervention effect of Pulsatilla Decoction on it, the results showed that, Pulsatilla Decoction can decrease the levels of IL-1β and TNF-α in serum and colon tissue, decrease the levels of IL-17, and increase the levels of IL-10 in serum and colon tissue. Alleviating the release of anti-inflammatory cytokines and inhibiting the expression of inflammatory factors had therapeutic effects on ulcerative colitis, but had no effect on normal mice. Li Panpan [4] et al. also found that Pulsatilla Decoction could reduce the level of IL-17A and increase the level of IL-10, thus achieving the effect of inhibiting inflammation. Xu Jiaping^[5] et al. randomly divided 124 patients with ulcerative colitis into the control group and the observation group. Through observation, CD3+ and CD8+ in peripheral blood of patients taking Pulsatilla Decoction decreased, while CD4+ and CD4+/CD8+ increased, which confirmed that Pulsatilla Decoction could also regulate the immune function of patients. At the same time, Wang Tong [6] et al. also confirmed that Pulsatilla Decoction may achieve the purpose of treating ulcerative colitis by regulating some immune functions through experiments on mice. It has also been found that the mechanism of Pulsatilla Decoction regulating ulcerative colitis may be related to the activity level of transcription factor NF-κB. For example, Zhong Yu [7] et al. found in mouse experiments that Pulsatilla Decoction may inhibit the TLR4/NFκB signaling pathway, down-regulate the levels of P-selectin, MPO, MIF and TXB2, promote intestinal mucosal repair and reduce inflammation. Shi Pinghui [8] et al. also found that Pulsatilla Decoction can reduce the production and release of pro-inflammatory factors and IL-8 by reducing the expression of NF-kB m RNA in patients' mucosal tissues, thus inhibiting the inflammatory response. Xie Ziwei [9] et al. believed that the treatment of ulcerative colitis by Pulsatilla Decoction might be related to the regulation of cytokines. Mucin MUC2 is the secretion of goblet cells of intestinal mucosa, and studies have confirmed that it plays an important role in maintaining the stability of intestinal microenvironment and the normal function of intestinal epithelial cells [10]. Zhang Ruifang [11] et al. found that Pulsatilla Decoction could play an anti-inflammatory role by upregulating the expression of MUC2 in addition to reducing the expression of IL-6 and increasing the expression of IL-10. Studies have found [12] that the balance of helper T cells 17(Th17) and regulatory T cells (Treg) is closely related to intestinal immunity. Zhiwei Miao^[13] et al. found that Pulsatilla Decoction can prevent colitis induced by sodium glucan sulfate (DSS) in mice, and the mechanism may be partly attributed to regulating Th17 / Treg cell balance and restoring intestinal epithelial barrier. The p38 MAPK pathway is a signaling pathway in mammals, which is involved in immune and inflammatory responses [14]. Studies have shown that [15] enhanced Pulsatilla Decoction can promote the mechanical barrier repair of intestinal mucosa and reduce the permeability of intestinal mucosa by inhibiting the activation of p38 MAPK/MLCK pathway. At the same time, studies have shown that the treatment of ulcerative colitis by Pulsatilla Decoction may be related to the regulation of intestinal flora [16-18], which is worthy of further study. In conclusion, it can be found that Pulsatilla Decoction can improve ulcerative colitis by inhibiting inflammatory factors, regulating immune function, inhibiting signaling pathway and regulating intestinal flora, and has definite curative effect. However, TCM compounds are composed of various traditional Chinese medicines, and their chemical components are complex and interact with each other. Therefore, it is difficult to define the specific mechanism of action of TCM compounds in the treatment of diseases, which can be further studied in the future.

1.1.2 Radiation proctitis

The mechanism of radiation proctitis is not well studied. Zhao Yang ^[19] proved through experiments that Huaihua SAN combined with Pulsatilla Decoction could reduce the expression of NF-κB, ICAM-1 and VCAM-1, and improve the symptoms and rectal mucosal injury of rats with radiation proctitis. Jiang Weidong^[20] et al. found that Pulsatilla Decoction may reduce the inflammation, congestion, edema and collagen fiber hyperplasia of rat rectal mucosa by down-regulating the expressions of fibrosis related factors CollagenI, TGF-β-1 and Smad3.

1.1.3 Other

Through literature retrieval in the past five years, it was found that Pulsatilla Decoction can also treat anally sinusitis and anal cryptitis, etc. but most of the literature focused on the efficacy observation of Pulsatilla Decoction in the treatment of related diseases, and there were few studies on the related mechanism. It can be used as a research direction for further exploration in the future.

1.2 Tumor suppression

1.2.1 Colorectal cancer

5-fluorouracil (5-FU) is an anti-metabolic chemotherapy drug, which can significantly reduce the mortality of colorectal cancer patients with positive lymph nodes [21]. Yanghua Jie[22] et al. found through experiments that Pulsatilla Decoction enhanced 5-FU-induced immunogenic cell death and anti-tumor effects in colorectal cancer by inactivating signal sensors and transcription-3 activators. The combination of 5-FU and Pulsatilla Decoction can significantly improve the antitumor activity of 5-FU in colorectal cancer. Jie Yanghua^[23] et al. found that Pulsatilla Decoction could effectively improve the inflammatory microenvironment of colorectal cancer mice, and speculated that its mechanism might be related to the downregulation of Ccr1, Cxcl1, Cxcl5 and Spp1 mRNA expression, inhibition of interleukin (IL-17), IL-23, tumor necrosis factor (TNF-α) release and blocking of JAK2/STAT3 pathway transduction. Wu Jinlin [24] et al. explored the mechanism of action of Pulsatilla Decoction in the treatment of colorectal cancer by using the method of network pharmacology, and found that Pulsatilla Decoction may have 10 signaling pathways related to colorectal cancer, such as tumor metabolic pathway and angiogenesis pathway, and at the same time may treat colorectal cancer through multiple biological processes such as affecting tumor pathway and inflammatory factors. It was further confirmed that Pulsatilla Decoction could treat colorectal cancer through multiple channels, multiple targets and multiple angles.

1.2.2 Adenocarcinoma of lung

Jin Shenyi^[25] et al. took human lung adenocarcinoma cell lines A549 and H1975 as research objects, and observed the results after the intervention of Pulsatilla Decoction with different concentrations. It was found that different concentrations of Pulsatilla Decoction inhibited cell proliferation and cell cloning formation of A549 and H1975 cells, and significantly reduced the expressions of CDK1, CyclinB1 and Caspase8, 9, 3, PARP and Bcl2 proteins, which confirmed that

Pulsatilla Decoction may reduce the expression of proteins related to cell cycle and apoptosis. Thus promoting the apoptosis of human lung adenocarcinoma cells.

1.2.3 Breast cancer

Through experiments, Shi Shanshan^[26]explored the effect and mechanism of Chinese herbal medicine Radix craggifolium extract (Radix craggifolium saponin B4) on human breast cancer MCF-7 and MDA-MB-231 cells. It was found that the saponin B4 can reduce the cell activity, and its mechanism may be related to the increased expression levels of FAS, FASL and Caspase-3 proteins.

1.3 Bacteriostatic effect

1.3.1 Bacillus dysentery

Wang Li ^[27] et al. found through experiments that Pulsatilla Decoction could inhibit the growth of bacillary dysentery by destroying the cell membrane and cell wall. Wang Xiaoxian ^[28] et al. found that Pulsatilla Decoction had a good inhibitory effect on intestinal bacteria such as Typhoid bacillus and dysentery bacillus. At present, the research on the inhibition of bacillary dysentery by Pulsatilla Decoction is still in a relatively shallow stage. Most of the studies have found that Pulsatilla Decoction has antibacterial effect through clinical observation, but the mechanism is rarely discussed. Further experimental studies are needed to discover the potential mechanism of action.

1.3.2 Vulvovaginal candida

Studies have shown that Pulsatilla Decoction can inhibit vulvovaginal candida by blocking neutrophil recruitment ^[29-30], regulating pH signaling pathway^[31], downregulating cytokines ^[32], remodeling vaginal mucosal epithelial barrier and other aspects ^[33]. At the same time, Lilin Yang^[34] et al. confirmed that Pulsatilla Decoction had an inhibitory effect on the proliferation, adhesion and inflammation of Candida albicans through mouse experiments. Yunxia Wang^[35] et al. further found that n-butanol extract of Pulsatilla Decoction could inhibit the adhesion of Candida albicans to a certain extent under acidic conditions.

1.3.3 Other

At the same time, previous studies have found [36] that different extracts and components of grainhead have inhibitory effects on Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and paratyphoid, among which prograinhead has the most significant effect.

1.4 Antidiarrheal

Yong-Li Hua^[37] et al. proved through mouse experiments that Pulsatilla Decoction played an important role in the treatment of damp-heat induced diarrhea by regulating the disorder of energy metabolism, glycerol phospholipid metabolism and glycerol metabolism, and promoting lysoPC production to restore intestinal function. Earlier studies^[38] found that Pulsatilla Decoction had a good effect on small intestinal diarrhea induced by castor oil in mice, which was significantly better than any single drug. The effect on mice colic diarrhea caused by senna leaf was significant and long-lasting.

1.5 Other

Chen Tiantian [39] studied the effect of alcohol extract of grangeolum on the growth of CEM cells

in leukemia through in vitro experiments, and found that alcohol extract of grangeolum could inhibit the growth of CEM cells in leukemia by inducing apoptosis, which might be caused by down-regulating Bcl-2 protein and up-regulating Bax protein, thus reducing the ratio of Bcl-2/Bax. At the same time, the expression of p53 protein was up-regulated, the expression of downstream Bax protein was activated, and the expression of Bcl-2 protein was inhibited, thus promoting cell apoptosis. The experiment provides a new direction and foundation for the treatment of leukemia. Fu Yer Liu^[40] and others observed the therapeutic effect of Pulsatilla Decoction on the liver injury of type I diabetes mice induced by streptozotocin through experiments on mice. It was found that Pulsatilla Decoction can effectively improve streptozotocin induced diabetic liver injury, and the mechanism may be related to reducing lipid peroxidation, enhancing free radical scavenging ability of the body and anti-inflammatory effect.

2. Research progress in clinical application

2.1 Ulcerative colitis

Through observation, it was found that Pulsatilla Decoction was effective in the treatment of ulcerative colitis. When treating damp-heat ulcerative colitis, Wang Meng [41] et al.gave Pulsatilla Decoction retention enema combined with acupuncture in the observation group, and oral mesalazine in the control group. After observing the efficacy, they found that the effective rate was 95.6% in the observation group and 84.4% in the control group (P<0.05), and the improvement in the observation group was significantly higher than that in the control group (P<0.05). Ma Yuexiang^[42] et al. randomly divided 140 cases of ulcerative colitis with damp heat into control group (mesalazine) and treatment group (white head soup combined with mesalazine). The total effective rate of the treatment group was 91.43%, significantly higher than that of the control group (72.86%, P < 0.05). It is suggested that Pulsatilla Decoction is effective in treating ulcerative colitis. Fan Yongqiang^[43] et al. randomly divided 120 cases of ulcerative colitis with damp-heat colitis into control group (Kangfuxin solution) and treatment group (self-designed Pulsatilla Decoction plus or without traditional Chinese medicine decoction enema). Both groups took mesalazine enteric-coated tablets on their own basis, and observed the efficacy, finding that the total effective rate was 90.00% in the treatment group and 81.67% in the control group. The clinical observation data of Pulsatilla Decoction on damp-heat ulcerative colitis are abundant and the curative effect is exact. Due to space limitation, I will not give examples here. In addition to the damp-heat syndrome type, Ma Ganzhang^[44]et al. found that Pulsatilla Decoction combined with mesalazine had a significant effect on the treatment of heat toxic incandescent-type ulcerative colitis, indicating that Pulsatilla Decoction had a definite effect on ulcerative colitis. Through meta-analysis, Wang Hanying^[45]et al. found that Pulsatilla Decoction combined with mesalazine had better clinical efficacy in the treatment of ulcerative colitis than mesalazine alone, and could improve the ratio of optimal clinical indicators. Chen Hongfei^[46] et al. also confirmed through meta-analysis that Pulsatilla Decoction combined with oral Western medicine could better reduce intestinal inflammation in the treatment of ulcerative colitis than oral Western medicine alone, and achieved significant therapeutic effect. There are abundant literatures on the clinical efficacy of Pulsatilla Decoction in the treatment of ulcerative colitis, which fully confirms the clinical significance of Pulsatilla Decoction in the treatment of ulcerative colitis, and can play a guiding role in clinical application.

2.2 Radiation proctitis

Pulsatilla Decoction also has significant curative effect on damp-heat radiation proctitis. Ma Huiqun^[47] randomly divided 60 patients with damp-heat radiation proctitis into observation group

(Pulsatilla Decoction group) and control group (montmorillonite powder + dexamethasone group) to observe the efficacy. It was found that both the observation group and the control group were effective in the treatment of radiation proctitis, while the observation group had better efficacy than the control group in ESR, C-reactive protein level, rectal mucosal damage, intestinal reaction and other aspects. Lei Dongmei^[48] randomly divided 74 cases of patients with damp-heat fire-toxic acute radiation rectitis into the traditional Chinese medicine group (Pulsatilla Decoction plus minus formula retention enema) and the control group (dexamethasone sodium phosphate injection + montmorillonite powder mixture retention enema). It was found that the therapeutic effect of the TCM group was better than that of the control group in the treatment of acute radiation proctitis of damp-heat and fire-toxic type, which was mainly reflected in improving the effective rate, alleviating the clinical symptoms, improving the damage of intestinal mucosa, and improving the quality of life of the patients, and no obvious toxic reaction was found. In addition, Wang Xiuhong^[49] et al. found through clinical observation that Shaoyao Decoction combined with Pulsatilla Decoction in the treatment of dampheat accumulated radioactive proctitis could significantly relieve clinical symptoms and improve the quality of life of patients, with a good effect. Chen Shixi^[50] et al. used Pulsatilla Decoction retention enema combined with rhGM-CSF to explore the efficacy of Pulsatilla Decoction retention enema combined with RHGM-CSF to explore the effect of Pulsatilla Decoction retention enema on patients with acute radiation rectitis caused by pelvic radiotherapy for stage II ~ III cervical cancer and the effect on inflammatory response. Through observation, it was confirmed that Pulsatilla Decoction retention enema can inhibit intestinal mucosal damage and inflammatory response. However, Du Rui^[51]et al. found that in the treatment of indeterminate enteritis, the addition and reduction of Pulsatilla Decoction can improve patients' condition, relieve clinical symptoms and improve quality of life, and the efficacy is higher than that of sulfasopyridine. However, there is no significant difference between paigeonium decoction and sulfasopyridine in colonoscopy.

2.3 Anal sinusitis

Wang Xueli^[52] randomly divided 60 patients with damp-heat type anosinusitis into a treatment group (Pulsatilla Decoction retention enema) and a control group (compound keratate supposit anal therapy) to observe its efficacy. It was found that the comprehensive efficacy of Pulsatilla Decoction retention enema method was better than that of compound keralate suppot-therapy method, and it could significantly reduce the symptoms of anal swelling, pruritus, pain, and anal sinus congestion and edema of patients, effectively control the inflammatory reaction, with good long-term efficacy and no obvious adverse reactions, so it is worth further promotion and use in clinical practice.

Through clinical observation, Wu Yunxiang^[53]et al. found that compared with levofloxacin alone combined with anorectal endorectal therapy instrument, Pulsatilla Decoction with flavor combined with anorectal endorectal therapy instrument, it has significant curative effect and can improve the levels of various inflammatory factors with high safety. Sun Feng^[54] randomly divided 68 patients with ansu-sinusitis into control group and study group. The control group was treated with Jiuhua ointment for anus, and the study group was treated with Pulsatilla Decoction combined with flavor treatment. Finally, it was found that in the clinical treatment of patients with ansu-sinusitis, the application of Pulsatilla Decoction combined with Jiuhua ointment for anal treatment can significantly alleviate the symptoms of patients, and the effect is significant. In addition, through clinical observation, Sun Chengyu [55] found that retention enema of concentrated Pulsatilla Decoction combined with microwave has significant effect on anal cryptitis, which can improve the symptoms and signs of traditional Chinese medicine and relieve the degree of pain, and is relatively safe, which is worthy of further clinical exploration.

2.4 Colorectal cancer

Xiong Lifeng ^[56]et al. randomly divided the patients with damp-heat advanced colorectal cancer into two groups. The control group was treated with m FOLFOX6 combined with chemotherapy, and the treatment group was treated with Pulsatilla Decoction on the basis of the control group to observe its efficacy. The final results showed that the median survival time and 1-year survival rate in the treatment group were higher than those in the control group (P<0.05), although the short-term response rate showed better efficacy in the m FOLFOX6 group alone. The clinical symptoms and quality of life were significantly higher than those in the control group (P<0.05). It is worthy of further clinical observation and research.

2.5 Bacterial dysentery

Wang Jinhua^[57] et al. randomly divided 60 cases of bacillary dysentery patients into the observation group (Pulsatilla Decoction and Shaoyao Decoction combined with levofloxacin) and the control group (levofloxacin), and observed the efficacy, and found that the observation group could promote the rapid recovery of patients by removing the pathogenic bacteria in the patients, and the patients had no obvious adverse reactions, which was safe and reliable, and the efficacy was more significant than the control group. It is worthy of clinical promotion and application. Zhang Dahong^[58] et al. also used clinical observation and found that the combination of Pulsatilla Decoction and Shaoyao Decoction had exact curative effect on bacillary dysentery. Zhu Kai ^[59] et al. randomly divided 160 patients with acute bacillary dysenteria into a control group and a study group. The control group was given levofloxacin hydrochloride, and the study group was given Pulsatilla Decoction on the basis of the control group. The total effective rate of control group was 81.3%. The efficacy of the study group was confirmed. In addition, Zhang Guo-en^[60] found through clinical observation that the combined treatment of cefdinir and Pulsatilla Decoction could improve the negative rate of Shigella in patients with acute bacillary dysentery and reduce the inflammatory response of the body, without significant side effects.

2.6 Diarrhea

Yu Jian Kan^[61] have proved that compound Pulsatilla Decoction has significant therapeutic effect on mice with diarrhea and can improve their concurrent symptoms. In addition, white head soup has been shown to be useful for pediatric diarrhea. Ma Wujie^[62] et al. randomly divided 40 children with infectious diarrhea into a treatment group and a control group. The control group was given conventional Western medicine treatment, and the treatment group was treated with Pulsatilla Decoction and Gegenqinlian Decoction plus enema on the basis of the control group. It was found that the total effective rate was 95.00% in the treatment group and 80.00% in the control group, and the difference was statistically significant (P < 0.05). Duan Jufeng^[63] et al. also used clinical observation to find that self-prepared Pulsatilla Decoction plus reduced retention enema in the treatment of pediatric autumn and winter diarrhea has significant efficacy compared with conventional Western medicine treatment, and is easily accepted by patients, which is worthy of further clinical exploration and promotion and application.

2.7 Other

In addition to the above common diseases, Wang Meng^[64] et al. also found that Pulsatilla Decoction with added flavor retention enema could prevent postoperative bleeding from damp-heat cyclic mixed hemorrhoids, and Lu Jie ^[65]et al. found that Pulsatilla Decoction had a good effect on

type III chronic prostatitis.

3. Conclusions

As a classic prescription, Pulsatilla Decoction has the function of clearing heat and detoxifying, cooling blood and stopping dysentery. It has anti-inflammatory, tumor inhibition, bacteriostasis, diarrhea and other pharmacological effects. Clinically, it is mainly used for the treatment of dampheat ulcerative colitis, damp-heat radiation proctitis, damp-heat anal sinusitis, diarrhea, dysentery and so on, which reflects the idea of treating different diseases in Chinese medicine together.

Through combing, it is found that there are still several deficiencies in the study of pharmacological effects of Pulsatilla Decoction g: (1) Lack of unified standards for the establishment of animal models of related diseases, and most of them are western medicine intervention, so TCM dialectical treatment is limited. Therefore, it is necessary to further unify the modeling standards in the future to make the experimental demonstration more accurate. (2) At present, most studies focus on studying its mechanism through mouse experiments, and there is a lack of in-depth in vivo studies. Most studies using network pharmacology only focus on the description of pathways or receptors related to pharmacological effects, and no in-depth studies have been conducted. In the future, we can further study the mechanism in vivo through cell biology and molecular biology. (3) There is a lack of toxicological studies on Pulsatilla Decoction. Therefore, future toxicological studies on the treatment of related diseases need to be improved to clarify its safety.

Meanwhile, in terms of clinical efficacy application, there is a lack of large sample, multi-center, randomized, controlled, double-blind research data, and most of them are the combination of Chinese and western treatment schemes, and the lack of clinical application of Pulsatilla Decoction for unilateral intervention of diseases. Although the efficacy is significant, it cannot reflect the key role of TCM syndrome differentiation and overall concept. And can not better show the therapeutic effect of Pulsatilla Decoction, in the future can be more single application to compare with other treatment programs, so as to provide more scientific data reference. At the same time, most of the clinical efficacy studies focused on the damp-heat ulcerative colitis, dysentery, diarrhea and other intestinal diseases. After sorting, it was found that, in addition, Pulsatilla Decoction also has curative effects on leukemia, diabetic liver injury, breast cancer, lung adenocarcinoma, vulvovaginal candidiasis, chronic prostagitis, etc., but the research on it is still in a relatively shallow stage, indicating that Pulsatilla Decoction still has huge research potential in the treatment of enteric diseases. With the accumulation of clinical evidence on the treatment of other diseases by Pulsatilla Decoction, the law of action of Pulsatilla Decoction should be studied deeply and in multiple ways in combination with modern advanced medical technology, in order to better serve the clinic.

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