



Pulsatilla decoction inhibits *Candida albicans* proliferation and adhesion in a mouse model of vulvovaginal candidiasis via the Dectin-1 signaling pathway



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ABSTRACT

Ethnopharmacological relevance: *Pulsatilla decoction* (PD) is a classical prescription in Traditional Chinese Medicine (TCM) and has been reported to have inhibitory effects on *Candida albicans* proliferation.

Study aim: To investigate the therapeutic effects of PD in the treatment of Vulvovaginal candidiasis (VVC) and elucidate the potential mechanism.

Materials and methods: Female BALB/c mice (N = 90) were randomized to six treatment groups, including the Control group, Model group, three PD groups and Fluconazole group which served as a positive control (20 mg/kg weekly). The three PD groups (low dose group, medium dose group and high dose group) were given a daily intragastric gavage of PD at doses of 5, 10 and 20 g/kg, respectively. Five animals from each group were euthanized on Day 4, Day 7 and Day 14 after treatment. Colony forming unit (CFU) was measured by the serial dilution method. The degree of infection was assessed by Gram staining, Periodic acid schiff (PAS) staining, Hematoxylin and eosin (H&E) staining and Scanning electron microscopy (SEM). The serum inflammation levels were determined by a Luminex assay. Gene and protein expression levels of components of the Dectin-1 signaling pathway were determined by Real-time PCR, Western-blot and immunohistochemistry, respectively.

Results: The administration of PD significantly decreased the fungal load from Day 7 post-infection onwards and decreased the number of visible microorganisms based on findings from Gram staining, PAS staining and SEM. H&E staining indicated that the impaired histological profiles were improved in all three PD groups. PD led to a significantly lower level of IL-23 in the serum; the levels of IL-10 and TNF- α were also decreased, although the differences were not significant. Furthermore, a substantial downregulation of Dectin-1, CARD9 and NF- κ B mRNA levels and Dectin-1, Syk, CARD9 and NF- κ B protein levels was observed after the administration of PD.

Conclusion: This study suggests that PD exerts inhibitory effects on *C. albicans* proliferation, adhesion and inflammation and simultaneously downregulates the expression levels of important genes and proteins associated with the Dectin-1 pathway, highlighting the potential application of PD to improve the clinical management of VVC.

1. Introduction

Vulvovaginal candidiasis (VVC) is one of the most common types of vaginitis and affecting 70–75% of women at least once in their lifetime, with 40–45% of women experiencing recurrence (Workowski and

Berman, 2006). VVC is caused by *Candida* in its hyphal phase, and the clinical symptoms of VVC include obvious pruritus and burning pain in the vulvae. In some severe cases, the patients may experience extreme pinching and piercing pain. VVC is also closely associated with dyspareunia, dysuria and frequency of urination. As a result, VVC can

Abbreviations: PD, *Pulsatilla decoction*; TCM, Traditional Chinese Medicine; VVC, Vulvovaginal candidiasis; HPLC, High performance liquid chromatography; CFU, Colony forming unit; PAS, Periodic acid schiff; H&E, Hematoxylin and eosin; SEM, Scanning electron microscopy; CLR, C-type lectin receptor; PRR, Pattern recognition receptor; PAMP, Pathogen-associated molecular pattern; ITAM, Immunoreceptor tyrosine activation motif; Syk, Spleen tyrosine kinase; CARD9, Caspase recruitment domain-9; SDA, Sabouraud dextrose agar; ATCC, American Type Culture Collection; PBS, Phosphate buffered saline; RT-PCR, Real-time polymerase chain reaction; SDS-PAGE, Sodium dodecyl sulfate-polyacrylamide gel electrophoresis; PVDF, Polyvinylidene difluoride; EDTA, Ethylenediamine tetraacetic acid

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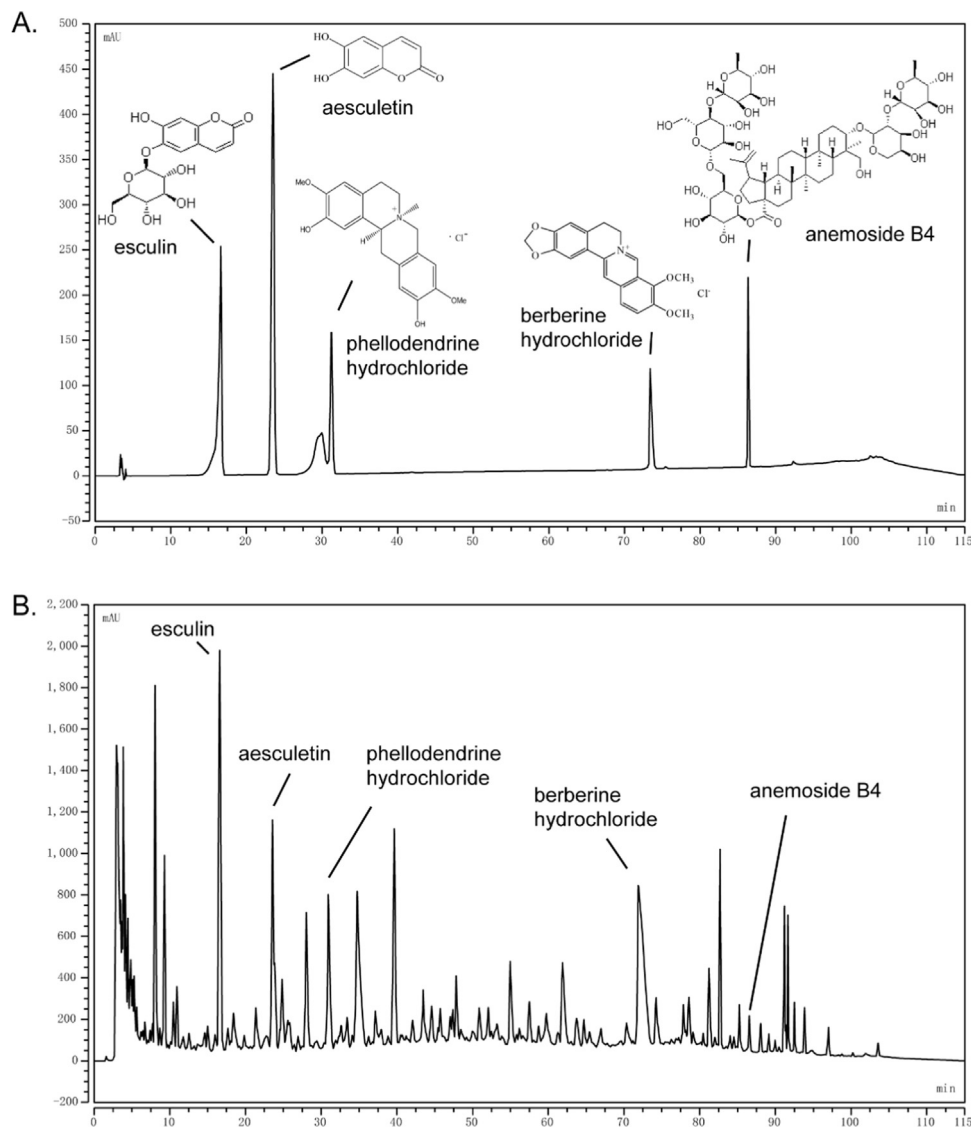


Fig. 1. HPLC analysis of the PD decoction extract. A. HPLC of the standard compounds. B. HPLC of the test solution.

markedly compromise quality of life in affected females (Cassone and Sobel, 2016).

Dectin-1 is a transmembrane protein and a member of the C-type lectin receptor (CLR) family. Accumulating evidence indicates that Dectin-1 serves as a pattern recognition receptor (PRR) and plays an essential role in defense against fungal infection (Drummond and Brown, 2011; Kerrigan and Brown, 2010). The pathogen-associated molecular pattern (PAMP) identified for Dectin-1 is β -glucan, a component of the fungal cell wall (Reid et al., 2009). At the onset of *Candida* invasion, the PRR (Dectin-1) recognizes β -glucan and triggers intracellular signaling, with phosphorylation of immunoreceptor tyrosine activation motif (ITAM). This phosphorylation provides a docking site for spleen tyrosine kinase (Syk), which plays a pivotal role in mediating the downstream cellular response (Reid et al., 2009). Syk recruits caspase recruitment domain-9 (CARD9) to activate downstream signaling components. Subsequently, CARD9 activates the canonical NF- κ B signaling pathway, resulting in the production of inflammatory cytokines and chemokines (Li et al., 2009).

Currently, azole antifungal agents are the most commonly used therapeutic regimens for VVC. However, drug resistance emerges for conventional therapies due to overprescription (Coleman et al., 2015). In addition, adverse effects related to antifungal drugs such as gastrointestinal discomfort, rash and hepatotoxicity remain barriers for wider

application. Hence, novel therapeutic approaches for VVC are needed for improved clinical management.

Over centuries of empirical clinical practice, compounds derived from Traditional Chinese Medicine (TCM) have been demonstrated to exert therapeutic effects by combining multiple components rather than targeting a single molecule (Sucher, 2013). An increasing number of studies suggested that TCM can serve as a rich resource of novel therapies. *Pulsatilla decoction* (PD), was first prescribed by Zhang Zhongjing in “Shang Han Lun”, approximately 1800 years ago. It is composed of 4 commonly used plants: *Radix pulsatilla* (Bai Tou Weng), *Cortex phellodendri* (Huang Bai), *Rhizoma coptidis* (Huang Lian) and *Cortex fraxini* (Qin Pi). The active ingredients from three of these four herbal plants (Bai Tou Weng, Huang Bai and Qin Pi) have been shown to exert anti-fungi effects *in vitro* (Liu et al., 2012; Yang et al., 2015). TCM theorizes that VVC is mainly caused by excess of damp-heat and PD is effective in correcting the dysregulation of heat and dampness. Therefore, PD is widely used in China to treat VVC and has shown satisfactory effects in clinical practice (Zhang and Zhang, 2012). While *in vitro*, studies indicated that PD has significant anti-*C. albicans* activity (Zhang et al., 2015a, 2015b), only few studies addressed the therapeutic effects of PD against *C. albicans in vivo*. In this study, we investigated the anti-*C. albicans* activity effects of PD at different doses in a mouse model of VVC. We further correlated the therapeutic effects of

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