

# Behcet's Disease

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Behcet's disease (BD) is a multisystemic inflammatory disorder characterized by a range of manifestations, such as recurrent oral ulcers, genital ulcers, arthritis, vasculitis, and skin lesions. The age of onset of BD is usually 30–40 years.

Keywords: integrative medicine ; complementary and alternative medicine ; herbal medicine ; Behcet's disease

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## 1. Introduction

The prevalence of BD is higher in the Middle East and Asia than in North America and northern Europe. In particular, its prevalence is highest in Turkey (80–370 cases per 100,000 persons) <sup>[1][2][3][4]</sup>. BD is commonly treated with steroids and immunomodulatory drugs such as corticosteroids, colchicine, and thalidomide, which often present side effects such as peripheral neuropathy, loss of appetite, nausea, diarrhea, and intestinal bleeding or perforation <sup>[5][6][7]</sup>.

Integrative medicine refers to the combination of conventional drug therapies with complementary or alternative medicine (CAM) therapies such as acupuncture and herbal medicine <sup>[8]</sup>. Integrative medicine combines the benefits of both Western medicine and CAM <sup>[9]</sup>. It has, therefore, become increasingly prevalent and popular, not only in China but also worldwide <sup>[10]</sup>. Clinical trials have revealed that a combination of herbal medicine and drug therapy is more effective than herbal medicine alone and significantly reduces the symptoms and recurrence rate of BD. This improvement is accompanied by the expression of the cytokine LI-4 <sup>[11][12]</sup>. A recent publication also reported that herbal medicine was favorable for treating BD, showing the potential of herbal medicine in complementing conventional medication <sup>[13]</sup>.

## 2. Integrative Medicine (Herbal Medicine Combined with Drug Therapy) for Behcet's Disease

Clinical manifestations vary greatly among BD patients, and conventional therapy highly depends on the severity of the disease, which often involves several body systems and organs. The main principle of BD treatment via drug therapy remains to be subduing inflammation during attacks and improving patients' quality of life by easing symptoms, increasing immunity, and reducing recurrence <sup>[14]</sup>. Although evidence supporting the use of azathioprine and cyclosporin A for ocular manifestations and interferon (IFN) $\alpha$  for mucocutaneous manifestations is available, evidence for vascular, gastrointestinal, and neurological involvement is still lacking <sup>[6]</sup>. To date, the effectiveness of drug therapy is based mostly on case reports/series and a limited number of RCTs.

Herbal medicine has been shown to have anti-inflammatory properties with favorable impacts on immune function and could play a critical role in complementing drug therapy <sup>[15]</sup>. This review showed a superior response rate with herbal medicine plus drug therapy (relative risk (RR) 1.19, 95% confidence interval (CI) 1.13 to 1.25,  $n = 1034$ ,  $p < 0.00001$ ,  $I^2 = 0\%$ , low certainty of evidence (CoE)) compared to drug therapy. Integrative medicine also lowered the recurrence rate after 2 months of follow-up (RR 0.27, 95% CI 0.09 to 0.76,  $n = 120$ ,  $p = 0.01$ ,  $I^2 = 0\%$ , low CoE). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and skin lesions were also significantly improved using integrative medicine, but equivalent effects were seen for oral ulcers, genital ulcers, and eye inflammation. Only minor adverse events were reported in both groups.

Although evidence for proving the effectiveness of herbal medicine combined with drug therapy in the treatment of BD remains weak, accumulating evidence still shows encouraging effects. Medical professionals may still cautiously recommend the use of herbal medicine combined with drug therapy to patients who present side effects and resistance to drug therapy over a long duration.

## Implications for Research

There are several concerns regarding the use of herbal medicine combined with drug therapy for the treatment of BD. First, the herbal prescriptions and drug therapies used in the included studies varied across studies. It might not have been sufficient to demonstrate the complete effects for treating BD, and a subgroup analysis was unable to be conducted due to the small number of studies included. Second, all studies had a short duration of treatment. BD is an autoimmune disease with a high rate of recurrence. It is necessary to prove the effectiveness of herbal medicine combined with drug therapy on the recurrence rate by extending the period of treatment. Third, a number of AEs were reported in the herbal medicine combined with drug therapy group, and this has raised concerns about possible herb–drug interactions, such as pharmacokinetic and pharmacodynamic (PK–PD) interactions. The integration of herbal medicines with conventional drugs may cause changes in the movement, absorption, biochemical, and physiological effects of the herbs. Herb–drug interactions due to the concurrent use of herbs with conventional drugs may also magnify the effects of drugs, plausibly leading to the effectiveness of herbal medicine combined with drug therapy in treating BD. Fourth, the herbs with the highest frequency of use across the studies were *Glycyrrhizae Radix et Rhizoma*, *Scutellariae Radix*, and *Coptidis Rhizoma*.<sup>[16][17][18]</sup> These herbs have shown great potential in the treatment of inflammation-related diseases due to their anti-inflammatory active compounds. Future studies on these herbs, as single herbs or decoctions, should be considered to validate their usage and effectiveness in treating BD. In general, well-designed RCTs in compliance with the CONSORT guidelines<sup>[19]</sup>, long-term treatment periods, large sample sizes, and data on PK–PD parameters are warranted to guide the implementation of integrative medicine in clinical practice in the near future.

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