Cordyceps pruinosa for the treatment of inflammatory bowel disease

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Abstract

To date, there have been no curative drugs for inflammatory bowel disease (IBD). Conventional drugs and biologic agents are not always effective and may cause serious side effects. Therefore, it is still challenging to develop effective and safe novel drugs for IBD. Although the exact etiology of IBD remains elusive, it is generally accepted that the immune system of the gut plays a central role in the pathogenesis of IBD. Recently, the nuclear transcription factor kappa B (NF-κB) has been identified as the pivotal elements in the regulation of the increased inflammatory activity. Moreover, recent studies have shown that Cordyceps pruinosa extract is a inhibitor of NF-κB activation and can enhance weak immune functions. Based on these facts, I hypothesize that Cordyceps pruinosa extract may thus exert its therapeutic effect on IBD by regulating NF-kB activity and improving impaired immune functions.

Keywords
Inflammatory bowel disease, Nuclear factor-kappa B, Cordyceps pruinosa

Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is a non-specific chronic relapsing inflammatory disease of the gastrointestinal tract. Although great advances have been made in the management of the disorder, no curative drugs until now are available for this disease because the exact causes of it are poorly understood (1-3).

Conventional therapy, including corticosteroids, 5-aminosalicylic acid and immunosuppressive agents, is aimed at control of inflammation but does not change the natural course of IBD. Moreover, many patients with IBD become refractory to conventional therapies during the course of disease and experience drug-related toxicity (4).

Although total colectomy is curative for ulcerative colitis, early colectomy is limited due to reducing patients’ quality of life. However, the endoscopic recurrence rate had increased to 85% and symptomatic recurrence occurred in 34% at three years after surgery for Crohn’s dis-
ease, surgery is thus not curative for Crohn’s disease(5).

Recently, some expensive biologic agents, antitumor necrosis factor alpha antibody, such as infliximab and adalimumab, have been shown to be effective in clinical application. However, they can inflict serious side effects, such as infection (6), infusion reactions (7), autoimmunity reaction (8) and mutagenesis (9). Therefore, it is still challenging to develop novel specific drugs for IBD so as to maximize efficacy while balancing risk and cost.

Hypothesis

Although the exact cause of IBD remains unknown, it has been generally accepted that the immune system of the gut plays a critical role in the pathogenesis of IBD. The high levels of pro-inflammatory cytokines in the intestinal mucosa are considered to be an important factor in the pathophysiology of enteric inflammation in IBD. Recently, the nuclear transcription factor kappa B (NF-κB) which consists of p65, c-Rel, RelB, p50 and p52, has been identified as the pivotal elements in the regulation of the increased inflammatory activity (10). Therefore, carefully targeting specific NF-κB subunits or signalling components probably represents a promising tool for future therapy of IBD (11).

Cordyceps pruinosa which is a fungal parasite on larvae of Lepidoptera, may regulate the production of inflammatory mediators just like cordycepin (12). Recently, a study has shown that methanol extract of Cordyceps pruinosa is an inhibitor of NF-κB activation and can suppress the expression of proinflammatory cytokine (13). This result is of great interest and, based on this finding, it could be speculated that Cordyceps pruinosa is useful in the treatment of patients with IBD. However, there have been no reports so far of the possible therapeutic role of Cordyceps pruinosa in the treatment of IBD. Therefore, I hypothesize that Cordyceps pruinosa can exert its anti-inflammatory effect on IBD by suppressing the activation of NF-κB signaling pathway.

Evaluation of the hypothesis

To test this hypothesis I offer following methods:

1. Macrophages or lamina propria mononuclear cells, which can be isolated from intestinal mucosal biopsy specimens from patients with IBD, are cultured with or without methanol extract of Cordyceps pruinosa and dexamethasone. NF-κB p65, c-Rel, RelB expression are measured by Western blot analysis. Cytokine levels are determined by enzyme-linked immunosorbent assay. The expression of cytokines mRNA are detected by reverse transcription-polymerase chain reaction.

2. BALB/c mice will be randomized into three groups. The first group, designated as normal control (n=12), receive tap water for 14 days. The second group, designated as control (n=12), receive 2,4,6-trinitrobenzensulfonic acid for 14 days. The third group, designated as experimental group (n=12), receive 2,4,6-trinitrobenzensulfonic acid given orally by gavage for 7 days and the extract of Cordyceps pruinosa orally by gavage on day 7 and continue for an additional 7 days. BALB/c mice will be obtained from the Experimental Animal Center of Sichuan University, China. The study will be approved by the Animal Ethics Committee of West China Hospital of Sichuan University. The histological score and disease activity index are observed. The expression of tumor necrosis factor–α (TNF-α), interleukin (IL)-1β, IL-6 and interferon-γ are studied by reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay. NF-κB DNA binding activity is monitored by electrophoretic mobility shift assay. Safety evaluation will be conducted.

3. The components of methanol extract of Cordyceps pruinosa are analysed using size-exclusion chromatography and mass spectrometry.

Discussion

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease of the gastrointestinal tract. Ulcerative colitis and Crohn’s disease are the two major types of IBD. Although IBD has been described as a clinical entity for over 100 years, its exact etiology has not been defined. However, it has been generally accepted that the immune system of the gut plays a critical role in the pathogenesis of IBD. Recently, an important conceptual development in the understanding of IBD pathogenesis has been the more focused appreciation of the nature of the microbial–innate-immune-response interaction which may depend on the competence of the host response rather than the intrinsic invasiveness of the bacteria per se during the transition from physiological to pathological intestinal inflammation. Moreover, epithelial-cell-specific NF-κB activation or suppression seems to be a nodal point in the suppression and/or recruitment of immune responses in IBD (14,15). Therefore, both selectively targeting specific NF-κB subunits, IκB proteins, or kinases which have a degree of tissue specificity, and boosting weak immune functions probably represents a promising tool for future therapy of IBD.
Cordyceps pruinosa, a major entomogenous fungus, which belongs to the Ascomycota, Pyrenomycetes, Sphaeriales, Clavicipitaceae, and parasites on the larvae of Lepidoptera, has been received special attention for medicinal purpose due to its various bioactive ingredients such as N6-(2-hydroxyethyl)adenosine, and Cordyceps pruinosa polysaccharide. (16,17). Recently, there is convincing evidence that Cordyceps pruinosa methanol extract inhibits the production of NO, PGE2, IL-1β, and TNF-α in LPS-stimulated macrophages and LPS-administer mice. This anti-inflammatory effect occurs by down-regulation of iNOS, COX-2, IL-1β, and TNF-α gene expression via the suppression of NF-κB activation (13). In addition, Cordyceps pruinosa polysaccharide has been shown to enhance cellular immune function (18). Although it is unlikely that high molecular weight polysaccharides could be absorbed after oral administration, it is possible that it could exert a therapeutic effect by direct interaction with the intestinal mucosal immune system and microflora of the gastrointestinal tract. Therefore, the extract of Cordyceps pruinosa may exert its therapeutic effect on IBD by inhibiting pathological activation of NF-κB. The NF-κB subunits selectively targeted by Cordyceps pruinosa are not clear. In addition, it may boost weak immune functions under physiological circumstances.

The traditional Chinese medicines, Cordyceps, which is considered as a safe, cheap and effective agent, is widely used to treat various diseases, such as stomach diseases and inflammatory disorders (19,20). These evidences suggest that Cordyceps pruinosa which belongs to Cordyceps, is probably effective, cheap and safe for the treatment of IBD.

It is undeniable that cytokine level and cell culture of the above-mentioned cannot directly being related to the clinical aspects of the IBD. Moreover, the experimental disease in an animal may not exactly replicate its human analogs experimental results and must ultimately be tested on human subjects.

herb can exert its effect on IBD by regulating immune system, antagonizing oxidant activity, inhibiting leukotriene B4 or nuclear factor-kappa B and antagonizing platelet activity (21). Moreover, oxidative stress may have an etiologic role in IBD (22). Thus, further research and clinical trials are needed to evaluate the action mechanisms of the Cordyceps pruinosa which belongs to herb.

The theoretical framework of Chinese medicine is based on the Chinese cultural fabrics and clinical experience, while modern western medicine has been established on the basis of laboratory and clinical investigations (23). Therefore, further research is needed to identify the active ingredients in Cordyceps pruinosa.

**Conclusion**

In summary, Cordyceps pruinosa extract has anti-inflammatory and immunomodulating properties. It can exert its therapeutic effect on IBD by regulating the activation of NF-κB signaling pathway and boosting weak immune functions. Moreover, Cordyceps pruinosa extract is probably considered as a safe and cheap agent. Therefore, Cordyceps pruinosa extract may be a promising drug for future therapy of IBD.

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**Overview Box**

What do we already know about the subject? In the treatment of inflammatory bowel disease (IBD), there has been no curative drug and there has been no report of the possible therapeutic role of Cordyceps pruinosa so far.

What does your proposed theory add to the current knowledge available, and what benefits does it have? The proposed theory brings novel Cordyceps pruinosa extract that can exert its therapeutic effect on IBD. The extract of Cordyceps pruinosa may be effective, safe and cheap for the treatment of IBD.

Among numerous available studies, what special further study do you propose for testing the idea? Methanol extract of Cordyceps pruinosa is administered in experimental colitis and macrophages or lamina propria mononuclear cells culture media. The histological score, disease activity index, NF-κB p65, c-Rel, RelB, TNF-α, IL-1β, IL-6, INF-γ and NF-κB DNA binding activity should be observed to confirm the idea. Safety evaluation ought to be conducted.
References