



AN UPDATE ON NOVEL APPROACHES IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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Article Received on: 28/05/12 Revised on: 19/07/12 Approved for publication: 30/07/12

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ABSTRACT

Although many types of treatment have been proposed and clinically proven, additional therapeutic approaches are needed because many patients do not satisfactorily respond to the currently available options or shows significant side effects due to their prolonged use. Therefore there is need to develop safe and effective alternative therapeutic agents for treatment of Inflammatory Bowel Disease (IBD). Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served humans well as valuable components of medicines, seasonings, beverages, cosmetics and dyes. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness. The future of higher plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is also very promising as they do not produce any significant harm to the living beings. Thus the review aimed to securitize herbal drugs effective in the management of IBD.

KEYWORDS: IBD, herbal medicines**INTRODUCTION**

Inflammatory Bowel Disease (IBD) is a term collectively assigned to Ulcerative Colitis (UC) and Crohn's disease (CD) that are immune mediated, multifactorial, chronic, relapsing and remitting gastrointestinal tract (GIT) disorders¹. IBD is characterized clinically by disruption of epithelial barrier of GIT resulting in severe rectal bleeding, diarrhea and the formation of epithelial ulceration^{2,3}. Various pathological factors are responsible for the progression of IBD like smoking, non-steroidal anti inflammatory drugs (NSAIDs) such as indomethacin, contraceptive pills⁴ along with various substances used as abrasives in toothpaste such as tricalcium phosphate, silicate, calcium pyrophosphate⁵ and large intake of fermentable but poorly absorbed short chain carbohydrates and polyols (designated as FODMAPs- Fermentable Oligo-, Di- and Mono-saccharides and Polyols)⁶.

Evidences too revealed the role of mitogen activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB) in IBD⁷. Moreover, reports indicate a severe imbalance of immune system⁸ with mast cell degranulation⁹. These findings introduced the requirement of developing and evaluating agents that can treat IBD by regulating inflammatory responses, including oxidative stress or pro-inflammatory cytokine release. A number of synthetic therapeutic interventions are available in the market for the management of IBD but they possess severe adverse drug reactions (ADRs). So, this review has been designed to explore such herbal drugs in the management of IBD that possess fewer side effects but more therapeutic efficacy. A number of medicinal plants and medicines derived from them have been found to show antioxidant and anti-inflammatory properties by virtue of their medicinal constituents in IBD.

POTENTIAL INTERVENTIONS IN THE MANAGEMENT OF IBD**a) *Aloevera barbadensis* Mill (Liliaceae)**

Aloe vera gel has a dose-dependent inhibitory effect on production of reactive oxygen metabolites, PGE2 and (at high doses) IL-8, by human colonic epithelial cells grown in tissue culture¹⁰. A randomized, double-blind, placebo-controlled trial was performed to study the efficacy and safety of aloe vera (*Aloevera barbadensis* M.) leaves gel for the treatment of mild to moderately active UC. The results offer that, oral aloe vera gel taken for 4 weeks produced a symptomatic

clinical response more frequently than did placebo; it also reduced the histological disease activity and appeared to be safe¹⁰.

b) *Boswellia serrata* (Burseraceae)

Boswellia or Indian frankincense is an ayurvedic herb that is derived from the resin of the plant, and has also been used traditionally to treat UC. Boswellic acid, the major constituent of *Boswellia*, is thought to contribute to most of the herbal pharmacologic activities. It has been documented that, it exerts its effect by inhibiting leukotriene biosynthesis in neutrophilic granulocytes by noncompetitive inhibition of 5-LOX¹¹. Clinical study was carried out on patients with IBD using *Boswellia serrata* gum resin and based this study results, mucosal injury and activation of leukocytes were recorded. Results of the study were very encouraging and showed reduced mucosal injury by inhibiting activity and adherence of activated leukocytes to intestinal mucosal cells in patients with IBD¹². In a double-blind placebo control study, *Boswellia serrata* gum resin preparation (350 mg TID for 6 weeks) was given to UC patients. Stool properties, biopsies, and various blood parameters were studied. Patients receiving sulfasalazine (1 g thrice daily) served as controls. All parameters tested improved after treatment with *Boswellia serrata* gum resin, the results being similar compared to controls: 82% out of treated patients went into remission; in case of sulfasalazine remission rate was 75%¹³.

c) *Daucus carota* (Umbelliferae)

The protective effects of powdered extract of *Daucus carota* could be explained partially by that oxidative stress and GSH (reduced glutathione) depletion which are highly associated with the pathological mechanism of UC, and the protective effects of daucus carota are closely related to the prevention of oxidative stress, which may occur during neutrophil infiltration in the pathological process of UC. This study demonstrated that powdered aqueous extract of *Daucus carota* at the dose of 200 and 400 mg/kg significantly attenuated the various macroscopical parameters, histological alterations as well as biochemical measurements in acetic acid induced UC in rats¹⁴.

d) *Glycyrrhiza glabra* L. (Fabaceae) or Licorice

Diammonium glycyrrhizinate is a substance that is extracted and purified from licorice. Evidence has reported that diammonium glycyrrhizinate could improve intestinal

mucosal inflammation in rats and more interestingly, reduced the expression of NF- κ B, TNF- α and ICAM-1 in inflamed mucosa¹⁵. Clinical studies on licorice have also been performed in combination with other herbs and demonstrated to be effective in the management of UC¹⁶.

e) *Commiphora mukul* (Bursaceae)

Guggulsterone (GS) is a plant steroid found in the resin of the *Commiphora mukul* (guggul) plant. It is an anti-inflammatory compound with the capacity to prevent and ameliorate T-cell-induced colitis. These data reported the use of GS, a natural cholesterol-lowering agent, in the treatment of chronic inflammatory diseases¹⁷. GS significantly reduced the severity of DSS-induced murine colitis as assessed by clinical disease activity score, colon length, and histology. Furthermore, tissue upregulation of I κ B and IKK phosphorylation induced by DSS was attenuated in guggulsterone-treated mice¹⁸. The guggulsterone derivative GG-52 has both protective and therapeutic effects on inflammation in the colon, indicating that it has a potential clinical value for the treatment of IBD¹⁹.

f) *Withania somnifera* (Solanaceae)

The medicinal plant *Withania somnifera*, also known as Ashwagandha, is widely known for its anti-inflammatory, cardioactive and CNS effects. The aqueous extract of *Withania somnifera* roots has been found to produce significant mucostorative efficacy in the TNBS induce IBD in rats. The pluronic rectal gel formulation impregnated with *Withania somnifera* root extract is in liquid form that is easy to apply as enema. At body temperature, it turns into a gel, which covers the rectum surface. Histopathology examination of *W. somnifera* extract treated group revealed less damage compared to healthy animals. Mesalamine treatment compared to *W. somnifera* formulation has shown significant and comparable protection in the rats as revealed by the decreased colon weight and better gain in body weight²⁰.

g) *Emblica officinalis* (Euphorbeaceae)

The fruit pulp of *Emblica officinalis* (EO) is an important drug used in Indian systems of medicine for several diseases and as a tonic. In view of its multifarious uses, the aqueous plant extract was tested for its anti-inflammatory and antioxidant properties in acetic acid induced UC in male wistar rats. The dose of fruit pulp extract found to be most effective is 200 mg/kg. This study demonstrated that methanolic extract of *Emblica officinalis* treated group showed a decrease in the ratio of colon weight/length and macroscopic scores for the inflammation. Histopathological examination of *Emblica officinalis* extract treated group revealed less damage and reduced LDH level compared to colitis induced group²¹.

h) *Bombax malabaricum* (Malvaceae)

Recent studies have shown that aqueous extract of the *Bombax malabaricum* (AEBM), also known as Shalmali, significantly inhibits the edematous growth in indomethacin, acetic acid and iodoacetamide induced IBD in animal models. The results of this study have shown that AEBM at the dose of 270 mg/kg reduces the macroscopic score, MPO level in indomethacin and iodoacetamide induced colitis in rats, whereas it exhibit the same response at the dose of 500 mg/kg in acetic acid induced colitis in mice. AEBM significantly reduced the colonic and serum levels of TNF- α when compared with the positive control in acetic acid induced colitis model²².

i) *Garcinia cambogia* Desr. (Clusiaceae)

The extract of *Garcinia cambogia* has attracted interest due to its pharmacological properties, including gastroprotective

effects. The anti-inflammatory activity of the alcohol extract in TNBS-induced colitis rats was investigated. The results obtained revealed that garcinia administration to colitic rats significantly improved the macroscopic damage and caused substantial reductions in increases in MPO activity, COX-2 and iNOS expression. In addition, garcinia extract treatment was able to reduce PGE₂ and IL-1 β colonic levels. These anti-inflammatory actions could be related to a reduction in DNA damage in isolated colonocytes, observed with the comet assay²³.

j) *Ageratum conyzoides* (Asteraceae)

The studies conducted to evaluate the efficacy of *Ageratum conyzoides* in the treatment of IBD have demonstrated significant effect in favour of ethanolic extract of *Ageratum conyzoides* on the acetic acid and indomethacin induced IBD in rats. The results indicated that ethanolic extract of *Ageratum conyzoides* at the dose level of 500 and 700 mg/kg, *p.o.* significantly attenuated the macroscopic scoring, histopathological manifestations and raised levels of lipid peroxides and MPO. Thus, this study supports the protective and regenerative effect of *Ageratum conyzoides* pretreatment on colonic cells²⁴.

k) *Turnera ulmifolia* L. (Turneraceae)

Lyophilized infusion of *Turnera ulmifolia* ameliorates the colonic insult induced after intracolonic administration of TNBS to rats²⁵. Its phenolic components exhibit antioxidant effect by inhibiting the oxidation of the β -carotene/linoleic acid system and lipid peroxidation²⁶.

CONCLUSION

This review open vista for the treatment of IBD by the aid of herbal drugs and their signaling pathways can be targeted for effective benefits.

ACKNOWLEDGEMENT

We express sincere regards to S. Nirmal Singh Rayat, Chairman; S. Gurwinder Singh Bahra, Vice-Chairman and Dr. A.C. Rana, Director, Rayat Institute of Pharmacy, for their continual encouragement, co-operation and providing us scientific facilities.

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Source of support: Nil, Conflict of interest: None Declared