NATURAL AGENTS FOR INFLAMMATORY BOWEL DISEASE

Darji Vinay Chhanalal¹*, Bariya Aditi Hemrajbhai², Deshpande Shrikalp Shrikant³

¹Department of Pharmacology, Sharda School of Pharmacy, Pethapur, Gandhinagar - 382610, Gujarat, India
²Department of Pharmacology, Kalol Institute of Pharmacy, Kalol, Gandhinagar - 382721, Gujarat, India
³Department of Pharmacology, K.B. Institute of Pharmaceutical Education & Research, Gandhinagar - 382023, Gujarat, India

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of gastrointestinal tract. It comprises the two conditions, Crohn’s disease and ulcerative colitis, characterized by chronic recurrent ulceration of the bowel. Conventional drugs for colitis treatment include aminosalicylate, corticosteroids, antibiotics & immunomodulators. 5-Amino salicylic acid having side effects in 30% of the patients. Systemic corticosteroids producing incidence of complication is 4.3%. Antibiotic therapy is beneficial in 70% of the patients & Immunomodulators having 50 to 70% beneficial effects. This report shows that there is no any appropriate treatment available to treat IBD without side effects. A natural agent with reduced or no toxicity is therefore essential. In nature there are so many types of natural agents which are used as protective agents in IBD. This article emphasizes many natural products obtained from plant & other sources, which possess potent activity against experimentally induced IBD.

KEYWORDS: Natural agents, Inflammatory bowel disease (IBD), Ulcerative colitis.

*Corresponding author
Darji Vinay Chhanalal, Department of Pharmacology, Sharda School of Pharmacy, Pethapur, Gandhinagar-382610, Gujarat, India E-mail: vinay_pharma05@yahoo.com

INTRODUCTION

Inflammatory bowel disease is a chronic inflammatory disease of gastrointestinal tract. Inflammatory bowel disease comprises the two conditions, Crohn's disease and ulcerative colitis, characterized by chronic recurrent ulceration of the bowel and of unknown etiology. The pathogenesis likely involves genetic, environmental, and immunologic factors.¹

Although the incidence and prevalence of ulcerative colitis and Crohn's disease are beginning to stabilize in high-incidence areas such as northern Europe and North America, they continue to rise in low-incidence areas such as southern Europe, Asia, and much of the developing world. As many as 1.4 million persons in the United States and 2.2 million persons in Europe suffer from these diseases. In India, ulcerative colitis was first reported in 1964 and Crohn's disease was considered almost nonexistent till 1986. During the last 10 years, Crohn's disease is being reported more frequently from different parts of India, especially southern India.² Accordingly, a number of animal models with defined knockouts of inflammatory factors such as IL-2, IL-10, and the T cell receptor, as well as seemingly unrelated molecules, such as the multidrug resistance protein appear to result in bowel inflammation.³ Several cytokines including TNF-α and IL-1β, have been shown to be upregulated in inflammatory bowel disease and serve to amplify and perpetuate tissue damage. Furthermore, chemokines are also upregulated, thus providing a continuous signal for the influx of leukocytes.⁴ There is greatly increased production rates of nitric oxide (NO) into the colonic lumen of patients with inflammatory bowel disease and provided evidence for the hypothesis that the enzyme, inducible NO synthase (iNOS), is the source of excess NO production.⁵ Management of inflammatory bowel disease involves the use of 5-aminosalicylic acid and immunosuppressive agents such as corticosteroids and 6-mercaptopurine as well as its precursor azathioprine.⁶ Long term use of glucocorticoids is associated with high rates of relapse and unacceptable toxicity as well as a significant number of patients are resistant or intolerant to thiopurines. Novel agents such as monoclonal antibodies against TNF-α have been developed and demonstrate clinical
efficacy. However, these agents are expensive and not without side effects. Consequently, there is a need for alternative agents that may be equally or more effective as well as being cheaper. Therefore a natural agent with reduced or no toxicity is essential. Numerous plant products are now used for the remedy of IBD. Some medicinal plants and their products, including vegetables, fruits and crops may prevent from IBD (Table 1). Most of these plants possess the activity against IBD by their Anti-oxidant mechanism.

**Natural agents useful in IBD**

*Punica granatum*  
*Punica granatum* Linn is a native of Afghanistan, Baluchistan and Persia, apparently wild in warm valleys in outer parts of Western Himalaya, hilly tracts. It belongs to family Punicaceae (Figure 1). It posses the various activities like Antidiarrhoeal, Anthelmintic, Antibacterial, Antifungal, Antifertility, Spasmogonic, Antioxidant, Analgesic & Antidiabetic. *Punica granatum* was tested for 2, 4-dinitro benzene sulfonic acid (DNBS) induced colitis, and antioxidant activity was evaluated to clarify its possible mode of action. Experimental colitis was induced by DNBS (120 mg/kg) intrarectally. *Punica granatum* fruit juice (4 ml/kg) orally was given as a treatment for a 18 days & it was found that *Punica granatum* fruit juice (4ml/kg) was significantly effective against experimentally induce IBD.

*Vaccinium ashei*  
*Vaccinium ashei* commonly known as Blueberry (Figure 2) is native to the southeastern U.S. where they occur in mixed woods, on high banks along streams or rivers, and in pine flatwoods communities. It belongs to family Ericaceae. Many of the heath-promoting properties of blueberries are thought to be attributable to anthocyanins that structurally belong to the natural products of flavonoids. Anthocyanins from blueberries are also used as anti-inflammatory, antimutagenic and rhodophylactic agents and the principal therapeutic benefits attributable to anthocyanins include antioxidant protection and maintenance of DNA integrity. Anthocyanins extract of blueberry was tested against trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease (IBD) model of mice. Colitis was induced by intracolonic injection of 0.5 mg of TNBS dissolved in 50% ethanol-phosphate buffered solution. Anthocyanins extract of blueberry rendered strong protection against TNBS-induced colonic damage at a dosage of 40 mg/kg.

*Emblica officinalis*  
*Emblica officinalis* (family: Euphorbiaceae) is an herbal plant widely used in many of the indigenous medical preparations against variety of the diseases (Figure 3). It is commonly known as Aamla & found throughout India till the height of 4500 feet. It has potent antimicrobial, anti-diabetic, antitussive, adaptogenic, antioxidiant, antitumour, radioprotective, antiulcerogenic, analgesic, anti-pyretic and anti-inflammatory activities of. Protective effect of methanolic fruit extract of *Emblica officinalis* (MEO 200 mg/kg) on acetic acid induced ulcerative colitis was evaluated in male Wistar rats. Colitis was induced by intracolonic instillation of 2 ml of 4% v/v acetic acid solution. The effect was assessed on the basis of macroscopic score, wet weight/length ratio of colonic tissue, biochemical changes and histopathological studies. Induction of colitis by acetic acid produced severe ulceration, edema and inflammatory cells infiltration in colonic tissues and increased levels of serum marker enzyme lactate dehydrogenase (LDH). Pretreatment with MEO (200 mg/kg) decreased serum LDH and restored histopathological changes near to normal. Result indicates that MEO can protect against acetic acid induced ulcerative colitis and may be beneficial in patients with inflammatory bowel disease. This protective effect may, at least in part, be due to their anti-inflammatory and/or antioxidant actions.

*Crocus sativus*  
*Crocus sativus* (Common name: Saffron) is a native of south Europe and is cultivated in Spain, France, Italy, Greece, India and China (Figure 4). Cultivation in India is mostly confined to the table-land of Pampur (5,300 ft. above sea level) in Kashmir and Kishtwar in Jammu. It belongs to family Iridaceae & main chemical constituent of *Crocus sativus* is Crocetin. Extensive research has been conducted on Crocetin, and it has been shown that it can inhibit tumor promotion, has hepatoprotective activity, is antidiabetic, has antioxidative & anti-inflammatory activities, is useful in cardiac diseases and have antiapoptic activities. Protective effect of crocetin was evaluated in 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) induced inflammatory bowel disease (IBD) in mice model. Treatment of TNBS induced (60 mg/ml in 30% ethanol) mice with crocetin (50 mg/kg/day) for 8 days significantly reduced the symptoms of IBD & regulates the various biochemical levels. Crocetin showed its protective effect in TNBS induced colitis by down regulation of NFkB.

*Curtcuma longa*  
Turmeric the common name for *Curtcuma longa* (Figure 5) is an Indian spice derived from the rhizome of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. *Curtcuma longa* is a perennial member of the
Thymol exhibits multiple biological activities. It is a natural terpenoid thymol. Thymol exhibits multiple biological activities including anti-inflammatory, immunomodulating, antioxidant, antibacterial, antifungal, and free radical scavenging properties. Oregano is recognized for its potential therapeutic role because of its diaphoretic, carminative, antispasmodic, antiseptic, and tonic properties. Oregano oil is known to possess antimicrobial, antifungal, and antioxidant activities. Combination of thyme and oregano oil is known to possess antimicrobial, antifungal, and antioxidant activities. Oregano essential oil is obtained by steam distillation of *O. vulgare* and its major compounds are carvacrol and thymol. Oregano essential oil is known to possess antimicrobial, antifungal, and antioxidant activities. Combination of thyme and oregano essential oil (0.2% thyme and 0.1% oregano oils) significantly decreases the level of IB in TNBS-induced colitis in mice. Administration of thyme oil in combination with oregano oil could be more effective in improvement of trinitrobenzenesulphonic acid (TNBS)-induced colitis than the separate administration of these essential oils.16

**Aegle marmelos**

*Aegle marmelos* (Syn: Bilva, Family: Rutaceae) is distributed throughout the deciduous forests of India, ascending to an altitude up to 1200 m in the western Himalaya and also in Andaman Islands. Because of its use in worship, it has been cultivated all over, particularly in the vicinity of Shiva temples (Figure 9). It posses the various activities like hypoglycemic, spasmodic, antiviral, cardiac stimulant, antiemetic, antiinflammatory, immunomodulating, antioxidant, antifungal, and free radical scavenging properties. Oregano essential oil is obtained by steam distillation of *O. vulgare* and its major compounds are carvacrol and thymol. Oregano essential oil is known to possess antimicrobial, antifungal, and antioxidant activities. Combination of thyme and oregano essential oil (0.2% thyme and 0.1% oregano oils) significantly decreases the level of IB in TNBS-induced colitis in mice. Administration of thyme oil in combination with oregano oil could be more effective in improvement of trinitrobenzenesulphonic acid (TNBS)-induced colitis than the separate administration of these essential oils.16

**Ficus bengalensis**

*Ficus bengalensis* (Banyan tree), is a large tree with aerial Roots & it belongs to family Moraceae (Figure 10). It grows wild in lower Himalayas and is found all over India. Different parts of the tree have been found to possess medicinal properties: leaves are good for ulcers, aerial roots are useful in treating gonorrhea, seeds and fruits are used as cooling agent and tonic as well. The water extract of FB bark has been reported to possess hypocholesterolaemic and hypolipidaemic effects.18 Effects of ethanol extract of *Ficus bengalensis* bark (AEFB) were studied on 2,4,6-dinitrobenzenesulfonic acid (TNBS, 0.25 ml 120 mg/ml in 50% ethanol
intrarectally, on first day only) induced IBD in rats. The effects of co-administration of prednisolone (2 mg/kg) and AEFB (250, 500 mg/kg) for 21 days were evaluated. Animals sacrificed at end of the experiment and various histopathological parameters like colon mucosal damage index (CMDI) and disease activity index (DAI) were assessed. In the colon homogenate malondialdehyde (MDA), myeloperoxidase (MPO), superoxide dismutase (SOD), and nitric oxide (NO) levels and in mesentery % mast cell protection was also measured. Rats treated with only TNBS showed more score of CMDI and DAI, higher MDA, NO, MPO, and lower SOD activity as compared to the control group. Treatment with AEFB significantly declined both indices scores and decreased the MPO, MDA, NO, and increased the SOD activity. AEFB also increased the % mast cell protection compared to alone TNBS-treated animals. AEFB has a significant protective effect in the IBD in rats that is comparable to that of prednisolone and may be because of the presence of flavonoids, terpenoids, and phenolic compounds.\(^\text{19}\)

**Brassica oleracea & Carica papaya**

*Brassica oleracea* (Kale) var. gongylodes (Brassicaceae) commonly known as Knol-Khol (Figure 11), kale is rich in the antioxidant vitamins C, E and carotene and are good sources of dietary fiber. They also contain sulforaphanes and other isothiocyanates, which are believed to stimulate the production of protective enzymes in the body. *Brassica oleracea* is reported as antihyperglycaemic & antioxidant agent.\(^\text{20}\) *Carica papaya* (Papaya) is a plant belongs to family of Caricaceae (Figure 12). The use of Carica papaya L. in traditional medicine relies on Papain. The active principle exerts an ulcer protective effect. The *Carica papaya* possesses antioxidant, antimicrobial & anti-inflammatory activities.\(^\text{21}\) Rats received, orally, 500 mg/kg of rat weight of three treatments of dried vegetables: papaya, kale and the mixture of both vegetables (60% of kale plus 40% of papaya) in TNBS-induced colitis study. In the prebiotic study, after two weeks of treatment, bacteria counts were determined. In the anti-inflammatory study, after the two weeks of treatment, colitis was induced by intracolonic administration of TNBS, and one week after, damage score and biochemical parameters were evaluated. Only the administration of the mixture was able to modulate the bacterial flora in healthy rats, as well as in rats with colitis induced by TNBS. In addition, the mixture showed intestinal antiinflammatory effect in the colitic rats. This effect was evidenced by a reduction in damage score, by the colonic iNOS expression downregulated, by the decrease in the production of the TNF\(\alpha\) and IL-1\(\beta\) and by the decrease in the MPO activity. The combination of both vegetables showed prebiotic and anti-inflammatory effects in the TNBS model of rat colitis, when compared to each single vegetable alone.\(^\text{22}\)

**Glycyrrhiza glabra**

*Glycyrrhiza glabra* Linn. of the family Leguminosae (Figure 13), is a genus of perennial herbs and under shrubs distributed in the subtropical and warm temperate regions of the world, chiefly in the Mediterranean countries and China. The dried, peeled or unpeeled underground stems and roots constitute the drug known in the trade as liquorice. The roots and rhizomes possess demulcent, antiinflammatory, antistress, anti depressive and expectorant property and useful in the treatment of peptic ulcer.\(^\text{23}\) Diammonium Glycyrrhizinate (DG) is a one of the important constituent extracted and purified from *Glycyrrhiza glabra*. Diammonium Glycyrrhizinate Significantly (P < 0.01) reduces the inflammatory injury in acetic acid induced colitis in rats. This may occur via suppression of NF-\(\kappa\)B, TNF-\(\alpha\) and ICAM-1 in colonic mucosa.\(^\text{24}\)

**REFERENCES**

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Table 1: Natural agents proved in IBD

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Name of the plant</th>
<th>Common Name</th>
<th>Family</th>
<th>Part Used</th>
<th>Imp. Chemical Const.</th>
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<td>Euphorbiaceae</td>
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