



**REVIEW ARTICLE**

**Natural Products in Treatment of Inflammatory Bowel Disease – A Review**

**Dineshkumar K. Dangar\*, Chintankumar J. Tank, Rishad R. Jivani**

*Faculty of Pharmacy, Dr. Subhash Technical Campus, Junagadh, Gujarat-362001, India.*

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**ABSTRACT**

Inflammatory bowel disease is an inflammatory chronic disease that affects the mucosa and submucosa of the colon and rectum. Various types of drug treatments are available such as aminosalicylates. Inflammatory bowel disease is a common disorder that affects thousands of individuals across worldwide. Accordingly, the main concern of the current article is to introduce a safe drug from natural products, to be used for the management of inflammatory bowel disease. A widespread search has been launched to identify new anti-ibd therapies from natural products. Herbs, medicinal plants, spices, vegetables and crude drug substances are considered to be a potential source to control various diseases including gastric ulcer and ulcerative colitis. Literature survey revealed large number of medicinal plants and their secondary metabolites with potential anti-ibd activities have been reported. Treatment with natural products produces promising results and fewer side effects. Our goal is to collect the published data in the recent years and reviews the natural products reported in the treatment of inflammatory bowel disease.

**KEYWORDS**

Inflammation, Ulcerative Colitis, Natural Plants

**INTRODUCTION**

Inflammation is the first biological response of the immune system to any foreign stimuli. Stimuli such as mechanical or physical damage, uv radiation, microbial invasion, and immune reactions are responsible for inflammation in most cases. Inflammation is characterized by redness, heat, swelling, and pain. On the bases of pathological features, there are two major forms of inflammation: acute and chronic. Chronic inflammation is characterized by persistent inflammation. In acute inflammation, it occurs over seconds, minutes, hours, and days. IBD is inflammation of the gastrointestinal (GI) tract and characterized by chronic or relapsing immune system activation.

Two forms of IBD are ulcerative colitis and Crohn's disease.<sup>1</sup> Ulcerative colitis is limited to the inner lining of the colon (large intestine) or rectum. All anti-inflammatory drugs or agents such as 5-aminosalicylic acid (5-ASA) and 6-mercaptopurine are choice of drug to treat IBD. Steroids and non-steroidal anti-inflammatory drugs can give relief from symptoms. However, it produces severe side effects and they are inadequate.<sup>2-4</sup> Therefore, with certain limitations of current drug remedies it is crucial to identify a new and safe drug for preventing or treating IBD<sup>5</sup>. Consequently, many people with ulcerative colitis prefers natural products as alternative medicine.<sup>2</sup>

A number of studies revealed that plant derived extracts or plant derivatives such as phenolic compounds and flavonoids show anti-inflammatory activity by controlling the levels of

**\*Address for Correspondence:**

**Dangar Dineshkumar K.,**

Faculty of pharmacy,

Dr. Subhash Technical Campus, Junagadh,

Gujarat-362001, India.

E-Mail Id: [dineshdangar@gmail.com](mailto:dineshdangar@gmail.com)

various inflammatory cytokines or inflammatory mediators including IL-1, IL-6, IL-10, TNF- $\alpha$ , NF- $\kappa$ B, NO, iNOS and COX-2. However, the claims of benefits of many plants or plant based medicines marketed to the general population are only supported by empirical or preliminary scientific data.<sup>6</sup> Therefore, the aim of this review is to provide an overview of the effects of natural products used worldwide for the treatment of ulcerative colitis form of inflammatory bowel disease. For this purpose, electronic databases including Pubmed, Scopus, Embase, and Google Scholar were searched for each of the natural products.

### Clinical Presentation

Inflammatory bowel disease can be presented with diarrhea, rectal bleeding, tenesmus, passage of mucus and abdominal pain with other symptoms like anorexia, nausea, vomiting, fever and weight loss.

### Diagnosis

The diagnosis of UC is made on clinical suspicion and confirmed by biopsy, stool examinations, sigmoidoscopy or colonoscopy, or barium radiographic examination. The presence of extracolonic manifestations such as arthritis, and uveitis may also aid in establishing the diagnosis.<sup>7</sup>

### Treatment with Synthetic Drugs

Now, even single effective therapy is not reported to treat ibd. All treatment depends on reduction of the abnormal inflammation in the colon lining and thereby relieves the symptoms of ibd like diarrhea, rectal bleeding, and abdominal pain. The treatment depends on the severity of the disease, therefore treatment is adjusted for each individual. In the cases of mild to moderate ulcerative colitis, patients are treated with corticosteroids to reduce inflammation and relieve symptoms of it. Nearly one by fourth of patients with UC underwent steroids therapy and becomes steroid-dependent with short duration and virtually they may develop steroid related adverse events. Other drugs like immunomodulators that reduce inflammation by affecting the immune system

and aminosalicylates are also available to treat any form of ibd.<sup>8</sup>

### Modern Evidence for the Efficacy of Plants on Ulcerative Colitis

#### *Moringa oleifera*

Anticolitis effect of *Moringa oleifera* seeds hydro-alcoholic extract (MSHE) and its chloroform fraction (MCF) was studied on acetic acid-induced colitis in rats. Extracts with three different doses were effective to reduce weight of distal colon as a marker for inflammation and tissue edema. *Moringa oleifera* were effective to reduce ulcer severity, area, and index as well as mucosal inflammation severity and extent, crypt damage, invasion involvement, total colitis index, and MPO activity compared with controls. *Moringa oleifera* were effective to treat experimental colitis and this might be attributed to their similar major components, biophenols and flavonoids.<sup>9</sup>

#### *Ageratum conyzoids*

*Ageratum conyzoids* belonging to asteraceae family and used traditionally to treat ulcers and inflammation. *Ageratum conyzoids* evaluated with acetic acid induced colitis and indomethacin induced entero colitis in rats. Pretreatment with ethanolic extract of *Ageratum conyzoids* at different doses revealed significant anti-ibd activity. Histopathological study supports the anti-ibd effect of *Ageratum conyzoids*.<sup>10</sup>

#### *Daucus carota*

Aqueous extract of *Daucus carota* (AEDC) was evaluated with acetic acid induced experimental colitis in wistar rats. Intrarectal instillation of acetic acid resulted significant decreased in food and water intake, body weight of animals. It caused enhanced colon weight, colon width, colon weight to length ratio, spleen weight, ulcer area, ulcer index, colonic myeloperoxidase (MPO) and nitric oxide. The 7 days pretreatment with *Daucus carota* aqueous extract with different doses significantly decreased stool consistency, macroscopical score, colon weight, colon width, colon weight to length ratio, spleen weight, ulcer area, ulcer index, colonic MPO and nitric oxide.<sup>11</sup>

### **Brahmi**

Yamada *et al.* evaluated a comparative study of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi.<sup>12</sup> Ashwagandha (*Withania somnifera*) and Brahmi (*Bacopa monnieri*) are commonly found in India. Comparison of the immunostimulatory effects of Ashwagandha and Brahmi with the effect of Echinacea and observed the Brahmi diet enhance immune function by increasing the levels of IgA and IgG in the serum of male Sprague Dawley rats.

### **Gardenia jasminoides**

*Gardenia jasminoides* Ellis (GJE) is a flowering plant which belongs to the genus *Gardenia* and family Rubiaceae. It has traditionally been used as folk medicine in many Asian countries. The ethanol and water extracts from *Gardenia jasminoides* Ellis have been researched to evaluate their antioxidant activity. Both extracts showed high antioxidant activity by scavenging various radicals. The extracts showed strong reducing power, nitrite scavenging activity, linoleic acid oxidation inhibition, superoxide dismutase-like (SOD-like) activity, and catalase activity *in vitro*.<sup>13</sup> Glycoprotein isolated from *Gardenia jasminoides* Ellis (GJE) fruits suppressed MPO activity, TBARS level, and NO production and inhibited the over production of iNOS, COX-2, and NF-kappa in DSS-induced mice.<sup>14</sup>

### **Chrysanthemum indicum**

*Chrysanthemum indicum* Linn is an herb that belongs to the genus of chrysanthemum and family of Asteraceae. It is traditionally used in China and Korea and treats various immune-related disorders, hypertension and various infectious diseases including pneumonia, colitis, stomatitis and fever.<sup>15,16</sup> Butanol-soluble fraction of *Chrysanthemum indicum* inhibited on the auricle edema in mice.<sup>15</sup>

### **Avicennia marina**

*Avicennia marina* (*A. marina*) is a plant of the Acanthaceae, commonly known as grey mangrove or white mangrove. *A. marina* decreased the colonic lipid peroxides, glutathione

peroxidase, and serum nitric oxide, lesion score and wet colon weight, and increased the colonic and erythrocyte superoxide dismutase and glutathione levels compared with colitis control.<sup>17</sup>

### **Patrinia scabiosaefolia**

*Patrinia scabiosaefolia* Fisch belongs to the family Valerianaceae. In Asia, the plants are usually used to treat anti-inflammatory diseases, especially for colonic inflammations, virus infections, hepatitis, and uteritis.<sup>18</sup> The root extracts of *Patrinia scabiosaefolia* Fisch suppressed weight loss, diarrhea, gross bleeding, infiltrations of immune cells, prevented shortening of colon length and enlargement of spleen size, down regulated the abnormal secretions and mRNA expressions in mice with DSS induced colitis.<sup>19</sup> Histological study indicated that the extracts reduced edema, mucosal damage, the loss of crypts.<sup>19</sup>

### **Ginger (Zingiber officinale)**

Ginger, belongs to the family Zingiberaceae, and its component zingerone were investigated to determine its anti-inflammatory activity in mice colitis induced by TNBS. They ameliorated TNBS-induced colonic injury in a dose-dependent manner. Their pathway investigation on gene expression profiles has been found to control cytokine-related pathways significantly. They suppressed TNBS-induced NF-κB activation and IL-1β protein level in the colon.<sup>20</sup>

### **Withania somnifera**

*Withania somnifera* (Dunal), belongs to the family Solanaceae, is used as a medicine since 2500 years in Indian medicinal classic "Ayurveda". Aqueous extract of its the root showed anti-oxidant activity by reducing H<sub>2</sub>O<sub>2</sub> and NO. It has lipid peroxidation inhibition activity. The extracts scored positively on histopathological parameters like necrosis, edema, and neutrophil infiltration in TNBS-induced IBD rat model.<sup>21</sup>

### **Ficus bengalensis**

*Ficus bengalensis* Linn. from the family Moraceae is a reputed plant in Ayurvedic

medicine. In Ayurvedic literature, it is known as “banayan tree.” The milky juice from the stem, seeds, or fruit of this plant is used externally for rheumatism and on the soles of feet when inflamed. It is also used for the treatment of dysentery and diarrhea. The ethanol extracts from the bark of this tree declined colon mucosal damage index and disease activity index and decreased the MPO, MDA, NO, and increased the SOD activity in the colons of rats with IBD.<sup>22</sup>

Table 1: Natural Plants with Anti IBD Activity

Plant	Results
<i>Inonotus obliquus</i> <sup>1</sup>	Reduced level of Cox-2, TNF- $\alpha$ , IFN- $\gamma$ , IL-4 and IgE Increased level of IgA
<i>Patrinia scabiosaefolia</i> <sup>2</sup>	Reduced Weight loss, diarrhea, gross bleeding, and infiltrations of immune cells with reduction in TNF- $\alpha$ , IL-1 $\beta$ and IL-6.
<i>Coriolus versicolor</i> <sup>23</sup>	Reduced level of IL-1 $\beta$ , IL-6, IFN- $\gamma$ , TNF- $\alpha$ , IL-4, IgE Increased level of IgA
<i>Prunus mume</i> <sup>24</sup>	Reduced level of TNF- $\alpha$ , Cox-2, IFN- $\gamma$ , IL-4 and IgE Increased level of IgA
<i>Bacopa monnieri</i> <sup>12</sup>	Decreased level of IgA and IgG in the serum
<i>Cordyceps sinensis</i> <sup>25</sup>	Reduced level of IgE
<i>Cordyceps militaris</i> <sup>26</sup>	Inhibited colon shortening and crypt length and epithelial damage.
<i>Mume Fructus</i> <sup>27</sup>	Reduced frequency of diarrhea, colonic accretion, ulceration. reduction in level of IFN- $\gamma$ , IL-4
<i>Avicennia marina</i> <sup>17</sup>	Reduced level of colonic lipid peroxides and serum nitric oxide. increased SOD and

	glutathione levels
<i>Ficus bengalensis</i> <sup>22</sup>	Reduced MPO, MDA, NO and SOD
<i>Zingiber officinale</i> <sup>20</sup>	Reduced NF- $\kappa$ B activity and IL-1 $\beta$ signalling pathway
<i>Withania somnifera</i> <sup>21</sup>	Reduced SOD
<i>Punica granatum</i> <sup>28</sup>	Reduced iNOS, COX-2, p38, JNK, pERK1/2, I $\kappa$ B $\alpha$ and NF- $\kappa$ B
<i>Bombax malabaricum</i> <sup>29</sup>	Reduced Ulcer score and MPO activity with marked decrease in TNF- $\alpha$ level
<i>Garcinia kola</i> <sup>30</sup>	Reduced colonic damage with increase in antioxidant enzymes

## CONCLUSION

A great number of evidence suggests that chronic inflammation promotes development of numerous human diseases, including IBD. Various herbal products have been used for the treatment of IBD. With this review we found that these natural products have shown their usefulness in IBD by different mechanisms of action such as inhibiting the production of NO, Cox-2, immunomodulatory properties, antimicrobial activities, antioxidant activities, and antiulcer properties which are summarized in detail in Table. Considering the devices of action of these plants, the mixture or combination of some of them may be beneficial due the numerous mechanisms involved in IBD. However, the exact mechanisms behind the anti-IBD effects of some of these natural products are still unclear. Therefore, additional research will be needed to determine their effects and to find which specific factors are involved in improving IBD in humans.

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