MANAGEMENT OF INFLAMMATORY BOWEL DISEASE AND EXPERIMENTAL MODELS ESTABLISHED FOR EVALUATION- AN UPDATE

J. Anbu*, Ramya Krishna P.S., Ramya H.S., Vineeth Reddy, R. Sathiya and Saraswathy G.R.

Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, Karnataka, India- 560054.

ABSTRACT

Inflammatory bowel diseases (IBD) include Ulcerative colitis (UC), an inflammatory disease of the large intestine and Crohn’s disease (CD). Ulcerative colitis is ulcers form in the inner lining or mucosa of the colon or rectum, often resulting in diarrhea, blood, and pus. The use of conventional steroids, glucocorticoids TNF-α inhibitors are found highly effective in treating IBD but their use is associated with some adverse effects. Therefore, the importance of using natural products has increased, as they have interest in discovering efficient new drugs with less adverse effects. Natural drugs are desirable for the treatment of inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. However, there are limited controlled evidences indicating the efficacy of traditional Chinese medicines, such as aloe vera gel, wheat grass juice, Boswellia serrata etc., in the treatment of UC. Many experimental models such as TNBS model, hapten induced colitis etc. are established for the evaluation of drugs in IBD. This review focuses on the management of IBD by using medicinal plants, synthetic drugs and methods established for the evaluation of drugs in IBD.

KEYWORDS: Inflammatory bowel disease, Ulcerative colitis, Crohn’s disease.

INTRODUCTION

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn’s disease (CD) are debilitating and chronic disorders with unpredictable courses and
complicated treatment measures. Therefore, an efficient treatment protocol seems necessary as therapeutic prophylaxis for these disorders. Ulcerative colitis is an inflammatory disease of the large intestine. Ulcers form in the inner lining or mucosa of the colon or rectum, often resulting in diarrhea, blood and pus. Ulcerative colitis affects the colon and rectum and typically involves only the innermost lining or mucosa. Inflammatory bowel disease is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora. This aberrant response is most likely facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system. Mechanisms involved in pathogenesis of Inflammatory bowel disease are immune response and inflammatory pathways, the activation of central immune-cell response, genetic factors, histamine in pathogenesis of inflammatory bowel disease, mast cell proteases in pathogenesis of IBD, infectious factors in pathogenesis of IBD and oxidative stress.

Medicinal Plants for IBD

**Boswellia (Boswellia serrata)**

Boswellic acid is the resin of the plant derived from *Boswellia serrata* or Indian frankincense, an ayurvedic herb has been used traditionally to treat UC. It is the major constituent of Boswellia thought to contribute to most of the herbal pharmacological activities. *In vitro* studies and animal models have shown that boswellic acid could inhibit 5-lipoxygenase selectively with anti-inflammatory and antiarthritic effects. Since the inflammatory process in IBD is associated with increased function of leukotrienes, the benefits of Boswellia in the treatment of UC have proven a positive result. Moreover, it has also been found to directly inhibit intestinal motility with a mechanism involving L-type Ca\(^{2+}\) channels. In animal models of inflammation, it has been shown to be effective against Crohn's disease, UC, and ileitis.

**Aloe vera gel (Aloe barbadensis)**

*Aloe vera* is a tropical plant used in traditional medicine throughout the world. It has been studied for its ability to relieve UC. Aloe vera gel is the mucilaginous aqueous extract of the leaf pulp of *Aloe barbadensis Miller*. Aloe vera juice has anti-inflammatory activity and been used by some doctors for patients with UC. It was the single most widely used herbal therapy. There is some preliminary evidence to suggest that oral administration of aloe vera might be effective in reducing blood glucose in diabetic patients and in lowering blood lipid
levels in hyperlipidaemia. The topical application of aloe vera does not seem to prevent radiation-induced skin damage. It might be useful as a treatment for genital herpes and psoriasis. The evidence regarding wound healing is contradictory.\cite{5} A double-blind, randomized trial was undertaken to examine the effectiveness and safety of aloe vera gel for the treatment of mild-to-moderate active UC.\cite{6}

**Licorice (Glycyrrhiza glabra)**

Licorice has got immune modulatory and adaptogenic property, which is required for the pathogenesis of UC. A number of active chemicals, including glycyrrhizin are thought to account for its biologic activity. Diammonium glycyrrhizinate is a substance that is extracted and purified from licorice, and may be useful in the treatment of UC.\cite{8} Evidence has also reported that diammonium glycyrrhizinate could improve intestinal mucosal inflammation in rats and importantly, reduce expression of NF-κB, TNF-α and ICAM-1 in inflamed mucosa.\cite{9} Clinical studies on licorice have also been performed in combination with other herbs and demonstrated to be effective in the management of UC.\cite{10} The antiestrogenic action documented for glycyrrhizin at high concentration has been associated with glycyrrhizin-binding estrogen receptors. However, estrogenic activity has also been reported for licorice and is attributed to its isoflavone constituents. It has been suggested that glycyrrhizin may exert its mineralocorticoid effect via an inhibition of 11β-hydroxysteroid dehydrogenase.\cite{11}

**Slippery elm (Ulmus fulva)**

Slippery elm is a supplement that is made from the powdered bark of the slippery elm tree. It has long been used by Native Americans to treat cough, diarrhea, and other GI complaints.\cite{12} Recently, slippery elm has been studied for use as a supplement for IBD. A study has confirmed the antioxidant effects of slippery elm when used in patients with IBD. The research so far has been promising, but there is not enough to warrant the widespread use of slippery elm in the treatment of IBD. \cite{13}

**Tormentil extracts (Potentilla erecta)**

*Potentilla erecta* (syn. *Tormentilla erecta*, *Potentilla laeta*, *Potentilla tormentilla*, known as the (common) tormentil or septfoil) is herbaceous perennial plant belonging to the rose family (Rosaceae). Tormentil extracts have antioxidative properties and are used as a complementary therapy for chronic IBD. In individual patients with UC positive effects have been observed. Sixteen patients with active UC received tormentil extracts in escalating doses
of 1200, 1800, 2400, and 3000 mg/day for 3 weeks each. Each treatment phase was followed by a 4-week washout phase. The outcome parameters were side effects, clinical activity index, C-reactive protein, and tannin levels in patient sera. Mild upper abdominal discomfort was experienced by 6 patients (38%), but did not require discontinuation of the medication. During therapy with 2400 mg of tormentil extracts per day, median clinical activity index and C-reactive protein improved from 8 (6 to 10.75) and 8 (3 to 17.75) mg/L at baseline to 4.5 (1.75 to 6) and 3 (3 to 6) mg/L, respectively. During therapy, the clinical activity index decreased in all patients, whereas it increased during the washout phase. Tormentil extracts appeared safe up to 3000 mg/day.\[14\]

**The wheat grass (Triticum aestivum)**

The wheat grass juice has been used for the treatment of various GI conditions. A double-blind study has demonstrated that supplementation with wheat grass juice for 1 month results in clinical improvement in 78% of people with UC, compared with 30% of those receiving a placebo. The amount of wheat grass used is 20 mL per day initially, and this is increased by 20 mL/day to a maximum of 100 mL per day (approximately 3.5 ounces). No serious side effects are noticed. Wheat grass juice appears to be effective and safe as a single or adjuvant treatment of active distal UC.\[15\]

**Curcumin (Curcuma longa)**

Curcumin is a compound in turmeric (Curcuma longa) that has been reported to have anti-inflammatory activity. It has been found to induce the flow of bile, which helps in breakdown of fats. Additionally, it could reduce the secretion of acid from the stomach and protect against injuries such as inflammation along the stomach (gastritis) or intestinal walls and ulcers from certain medications, stress, or alcohol. In a preliminary trial, 5 of 5 people with chronic ulcerative proctitis had an improvement in their disease after supplementing with curcumin. Curcumin inhibits the activation of NF-κB. NF-κB promotes the synthesis of many antioxidant enzymes. Curcumin directly binds to thioredoxin reductase and irreversibly changes its activity from an antioxidant to a strong pro-oxidant.\[16,17\]

**Germinated barley foodstuff (Hordeum vulgare)**

Two open-label Japanese trials have shown the efficacy of Germinated barley foodstuff (GBF) in the treatment of UC, consisting mainly of dietary fiber and glutamine-rich protein that function as a probiotic. In the first report, 11 patients given GBF for 4 weeks as an adjunctive treatment showed a greater decrease in clinical disease activity than 9 patients
given conventional therapy alone. In a follow-up study, 24 weeks of treatment of 21 patients with GBF together with continuing 5-aminosalicylic acid and steroid therapy reduced rectal bleeding and nocturnal diarrhea. [18,19,20,21]

**Bromelain (Ananas comosus)**

Bromelain is an anti-inflammatory and has been used as a digestive aid and a blood thinner as well as to treat sports injuries, sinusitis, arthritis and swelling. Bromelain has been studied for use as a supplement for IBD, especially UC. Emerging research on pineapple suggests that pineapple's active component, “bromelain” may help to relieve the inflammation associated with UC. The mechanisms that are primarily responsible for its anti-inflammatory effects are still unclear. However, proteolytic activity is required for the anti-inflammatory effect of bromelain on T-cell activation and cytokine secretion in vitro and in murine models of IBD *in vivo*. The major mechanism of action of bromelain appears to be proteolytic in nature, although evidence also suggests an immunomodulatory and hormone-like activity acting via intracellular signaling pathways. Bromelain has been shown to reduce cell surface receptors, such as hyaluronan receptor CD44, which is associated with leukocyte migration and induction of pro-inflammatory mediators. Additionally, bromelain is also reported to significantly reduce CD4+ T-cell infiltrations, which are primary effectors in animal models of inflammation in the gut. [22,23]

**Guggulsterone (Commiphora wightii)**

Guggulsterone is a plant steroid found in the resin of the guggul plant, is an anti-inflammatory compound with the capacity to prevent and ameliorate T-cell–induced colitis. These data ground the use of Guggulsterone, a natural cholesterol-lowering agent, in the treatment of chronic inflammatory diseases. [24] Guggulsterone inhibits LPS- or IL-1b-induced ICAM-1 gene expression, NF-κB transcriptional activity, IkB phosphorylation/degradation, and NF-κB DNA-binding activity in IEC and strongly blocked IKK activity. Guggulsterone significantly reduced the severity of DSS-induced murine colitis as assessed by clinical disease activity score, colon length, and histology. Furthermore, tissue upregulation of IkB and IKK phosphorylation induced by DSS was attenuated in guggulsterone-treated mice. [25] 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 IBD. [26]
Chamomile (*Matricaria chamomilla*)

Chamomile is the common name for several daisy-like plants of the family Asteraceae that are commonly used to make herb infusion that can help to induce sleep. Chamomile has been used for inflammation associated with hemorrhoids when topically applied.\(^{27}\) There is Level B evidence to support the claim that chamomile possesses anxiolytic (anti-anxiety) properties and may have clinical applications in the treatment of stress and insomnia.\(^{28}\) Chemical components of chamomile extract have demonstrated anti-inflammatory,\(^{29}\) antigenotoxic,\(^{30}\) and anticancer\(^{31}\) properties when examined in vitro and in vivo studies.

Psyllium or Ispaghula (*Plantago ovata*)

Psyllium, or Ispaghula, is the common name used for several members of the plant genus *Plantago* whose seeds are used commercially for the production of mucilage. Several studies point to a cholesterol reduction attributed to a diet that includes dietary fiber such as psyllium. Research concludes that the use of soluble-fiber cereals is an effective and well-tolerated part of a prudent diet for the treatment of mild to moderate hypercholesterolemia. Although the cholesterol-reducing and glycemic-response properties of psyllium-containing foods are fairly well documented, the effect of long-term inclusion of psyllium in the diet has not been determined. Choking is a hazard if psyllium is taken without adequate water as it thickens in the throat.\(^{32}\) Cases of allergic reaction to psyllium-containing cereal have also been documented.\(^{33}\) Psyllium is mainly used as a dietary fiber, which is not absorbed by the small intestine. The purely mechanical action of psyllium mucilage absorbs excess water while stimulating normal bowel elimination. Although its main use has been as a laxative, it is more appropriately termed a true dietary fiber and as such can help reduce the symptoms of both constipation and mild diarrhea. The laxative properties of psyllium are attributed to the fiber absorbing water and subsequently softening the stool. It is also one of the few laxatives not to promote flatulence.\(^{34}\)

Hibiscus (*Hibiscus rosa-sinensis*)

*Hibiscus rosa-sinensis*, known colloquially as rose mallow, Chinese hibiscus, China rose and shoe flower, is a species of flowering plant in the family Malvaceae, native to East Asia. The flower is additionally used in hair care as a preparation. An extract from the flowers of *Hibiscus rosa-sinensis* has been shown to function as an anti-solar agent by absorbing ultraviolet radiation.\(^{35}\) An investigation demonstrates *Hibiscus rosa-sinensis* is of potent therapeutic value in the amelioration of experimental colitis in laboratory animals by
inhibiting the proinflammatory mediator like NO and TNF-alpha. *Hibiscus rosa sinensis* leaves significantly reduced the severity of TNBS-induced murine colitis as assessed by clinical disease activity score, colon length, and histology.\[^{36}\]

*Teucrium polium*

It is a sub-shrub and herb native to the Mediterranean region and the Middle East. It has also shown some promise in the treatment of visceral pain. In traditional Persian medicine, *T. polium* (locally called 'kalpooreh') is used as an anti-hypertensive, anti-bacterial, carminative, anti-nociceptive, anti-inflammatory, anti-diarrhea, anti-diabetes and anti-convulsant agent. A scientific study found that it does have anti-nociceptive and anti-spasmodic effects. *Teucrium polium* has shown hypoglycemic effect in type 1 diabetes induced by single high dose of the cytotoxic agent streptozotocin (STZ) in rats and it also may be considered as a treatment of choice in acetic acid induced ulcerative colitis in the dogs.\[^{37}\]

*Aamla (Emblica officinalis)*

*Phyllanthus emblica* (syn. *Emblica officinalis*), the Indian gooseberry, or Dhatrik (in Maithili), or amla from Sanskrit amalika. Tamil nellika, Hindi avala, is a deciduous tree of the family Phyllanthaceae. In traditional Indian medicine, dried and fresh fruits of the plant are used.\[^{38}\] According to Ayurveda, aamla fruit is sour (amla) and astringent (kashaya) in taste (rasa), with sweet (madhura), bitter (tikta) and pungent (katu) secondary tastes (anurasas). Its qualities (gunas) are light (laghu) and dry (ruksha), the postdigestive effect (vipaka) is sweet (madhura), and its energy (virya) is cooling (shita). In Ayurvedic polyherbal formulations, Indian gooseberry is a common constituent, and most notably is the primary ingredient in an ancient herbal rasayana called Chyawanprash. This formula, which contains 43 herbal ingredients as well as clarified butter, sesame oil, sugar cane juice, and honey, was first mentioned in the Charaka Samhita as a premier rejuvenative compound.\[^{39}\] In Chinese traditional therapy, this fruit is called yuganzi, which is used to cure throat inflammation. Emblica officinalis tea may ameliorate diabetic neuropathy due to aldose reductase inhibition.\[^{40}\] In rats it significantly reduced blood glucose, food intake, water intake and urine output in diabetic rats compared with the non-diabetic control group.\[^{41}\] The present data suggest that the Emblica officinalis can protect acetic acid-induced colitis in rats and may be beneficial in patients with inflammatory bowel diseases. This protective effect may, at least in part, be due to their anti-inflammatory and/or antioxidant actions.\[^{42}\]
Indian licorice (*Abrus precatorius*)

Known commonly as jequirity, Crab's eye, rosary pea, precatory pea or bean, John Crow Bead, Indian licorice, Akar Saga, gidee gidee or Jumbie bead. A variety of pharmacological effects have been observed in rodents, but have not been demonstrated clinically in humans, such as antioxidant, anti-inflammatory and analgesic potential in rodents.\[^{43}\] A methanolic extract of *A. precatorius* seeds causes reversible alterations in the estrous cycle pattern and completely blocked ovulation in Sprague-Dawley rats.\[^{44}\] The methanolic extract also produces dose-dependent bronchodilator activity in a guinea pig model.\[^{45}\] An aqueous extract of leaf of *Abrus precatorius* possesses potent activity in inflammatory bowel disease. *Abrus precatorius* was reported as the contents of glycyrrizinic acid which has strong anti-inflammatory and antiulcer activity.\[^{46}\] In Siddha system, the white variety is used to prepare oil that is claimed to be an aphrodisiac.\[^{47}\] A tea is made from the leaves and used to treat fevers, coughs and colds. Seeds are poisonous and therefore are used after mitigation.\[^{48}\]

Cucumber (*Cucumis sativus*)

*Cucumis sativus* belongs to the family Cucurbitaceae. It possesses potent activity against various pathological changes caused by administration of acetic acid. *C. sativus* was found to be effective in both post treatment and pretreatment given in acetic acid models. It could be hypothesized that the drug may form a layer over the colonic mucosa and also reduce localize inflammatory processes. The drug possesses free radical scavenging profile. Hence, it was able to reverse the localized inflammatory response and heal the hemorrhagic lesions which were caused by the administration of acetic acid.\[^{49}\]

Vitex negundo

It is a large aromatic shrub, widely used in folk medicine, particularly in South and Southeast Asia. It is known under a variety of names in different languages: Tamil: nochhi; Hindi: nirgundi; Sanskrit: ,sindhuvara; Telugu : Sindhuvara; Filipino: lagundî; Sinhala: nika; and Bengali: Nishinda, Nepali: Simali and nirgudi in marathi. Roots and leaves used in eczema, ringworm and other skin diseases, liver disorders, spleen enlargement, rheumatic pain, gout, abscess, backache. *In vitro* and animal studies have shown that chemicals isolated from the plant, *vitex negundo* have potentialanti-inflammatory,\[^{50}\] antibacterial,\[^{51}\] antifungal \[^{52,53}\] and analgesic\[^{54}\] activities.
Synthetic Drugs in IBD[55]

5-Aminosalicylic Acid Derivatives
The 5-aminosalicylic acid derivatives are effective in reducing inflammatory reactions. All of the aminosalicylates are useful for treating flares of mild to moderate ulcerative colitis and occasionally Crohn colitis and for maintaining remission.

Sulfasalazine (Azulfidine, Azulfidine EN-tabs)
Sulfasalazine is considered best for colonic disease, although it is also considered first-line therapy for Crohn’s disease. This agent is used for acute disease and for maintenance of remission.

Mesalamine (Asacol, Pentasa, Canasa, Rowasa, Lialda, Apriso)
Mesalamine is a 5-ASA that acts systemically and also has activity as a topical anti-inflammatory.

Balsalazide (Colazal)
Balsalazide is a prodrug 5-ASA connected to a 4-aminobenzoyl-(beta)-alanine carrier by an azo bond; colonic bacteria break the azo bond, releasing the active 5-ASA. Metabolites of the drug may decrease inflammation by blocking the production of arachidonic acid metabolites in colonic mucosa.

Olsalazine (Dipentum)
Olsalazine is useful for active disease and maintenance of remission in ulcerative colitis. Dipentum is a 5-ASA connected to a 5-ASA by an azo bond; colonic bacteria break the azo bond, releasing the active 5-ASA. An adverse event of high ileal secretion of chloride creates a different type of diarrhea, which lessens its acceptability.

Butyrate
Butyrate is an important energy source for intestinal epithelial cells and plays a role in the maintenance of colonic homeostasis. Butyrate enemas have been studied for use in treating UC. Some studies have shown that the topical use of butyrate may help decrease the inflammation in the colon.[7]

Metronidazole (Flagyl)
Metronidazole is a widely available, inexpensive antibiotic and antiprotozoal agent. This agent inhibits protein synthesis and causes cell death in susceptible organisms by diffusing
into the organism and causing a loss of helical DNA structure and strand breakage. Metronidazole's adverse-event profile includes headache, dysgeusia, and neuropathy.

**Ciprofloxacin (Cipro)**

Ciprofloxacin is a fluoroquinolone antibiotic commonly used for the treatment of urinary, skin, and respiratory tract infections. This agent inhibits bacterial DNA synthesis and, consequently, growth by inhibiting DNA gyrase and topoisomerases, which are required for replication, transcription, and translation of genetic material. Caution is advised with the use of ciprofloxacin regarding tendon rupture.

**Rifaximin (Xifaxan)**

Rifaximin is a nonabsorbed (< 0.4%), broad-spectrum antibiotic specific for enteric pathogens of the gastrointestinal tract (ie, gram-positive, gram-negative, aerobic, anaerobic). It is a rifampin structural analog and it binds to the beta-subunit of bacterial DNA-dependent RNA polymerase, thereby inhibiting RNA synthesis.

**Corticosteroids**

Corticosteroid agents are the treatments of choice for an acute inflammatory bowel disease (IBD) attack; administer intravenously in severe disease. Administer increased or stress doses to patients already on steroids. Do not use steroids for maintaining IBD remission, because of their lack of efficacy and potential complications, including avascular necrosis, osteoporosis, cataracts, emotional lability, hypertension, diabetes mellitus, cushingoid features, acne, and facial hair. Cortenema, Cortifoam, and Anusol-HC suppositories are useful in treating distal disease (proctitis and proctosigmoiditis).

**Hydrocortisone (Solu-Cortef, Cortef )**

Prednisone acts as a potent inhibitor of inflammation. It may cause profound and varied metabolic effects, particularly in relation to salt, water, and glucose tolerance, in addition to their modification of the immune response of the body. Alternative corticosteroids may be used in equivalent dosage.

**Methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol)**

Adrenocortical steroids act as potent inhibitors of inflammation and may cause profound and varied metabolic effects, particularly in relation to salt, water, and glucose tolerance, in
addition to modification of the immune response. Alternative adrenocortical steroids may be used in equivalent dosage. Methylprednisolone has a greater saltwater-retention side effect.

**Prednisolone** (Orapred, Pediapred, Millipred)
Corticosteroids act as potent inhibitors of inflammation. They may cause profound and varied metabolic effects, particularly in relation to salt, water, and glucose tolerance, in addition to modification of the immune response. Alternative corticosteroids may be used in equivalent dosage.

**Budesonide** (Entocort)
Budesonide alters the level of inflammation in tissues by inhibiting multiple types of inflammatory cells and decreasing the production of cytokines and other mediators involved in inflammatory reactions. Only 10% is bioavailable because of first-pass metabolism.

**Dexamethasone** (Baycadron)
Dexamethasone has many pharmacologic benefits, but there are also significant adverse effects. It stabilizes cell and lysosomal membranes, increases surfactant synthesis, increases serum vitamin A concentrations, and inhibits prostaglandin and proinflammatory cytokines.

**Immunosuppressants**
Immunosuppresant agents are useful as steroid-sparing agents, in healing fistulas, or when the patient has serious contraindications to surgery. They are used in patients who are refractory to or unable to tolerate steroids and in patients in whom remission is difficult to maintain with the aminosalicylates alone. Azathioprine and its metabolite, 6-mercaptopurine, have been useful in Crohn disease complicated by recurrent rectal fistulas or perianal disease; however, the clinical response can take up to 6 months. Methotrexate has also been tried.

**Azathioprine** (Imuran, Azasan)
Azathioprine inhibits mitosis and cellular metabolism by antagonizing purine metabolism and inhibiting synthesis of DNA, RNA, and proteins; these effects may decrease proliferation of immune cells and result in lower autoimmune activity.

**6-Mercaptopurine** (Purinethol)
6-Mercaptopurine is a purine analog that inhibits DNA and RNA synthesis, causing cell proliferation to arrest.
Methotrexate (Rheumatrex, Trexall)
Methotrexate impairs DNA synthesis and induces the apoptosis and reduction in interleukin (IL)-1 production. It is indicated for moderate to severe disease and maintenance of remission. The onset of action is delayed.

Cyclosporine (Sandimmune, Neoral)
Intravenous cyclosporine is effective for avoiding surgery in patients with ulcerative colitis who have failed to respond to 7-10 days of high-dose oral or parenteral corticosteroids. Concomitant administration of IV corticosteroids is recommended in these cases. Cyclosporine is a cyclic polypeptide that suppresses some humoral immunity and, to a greater extent, cell-mediated immune reactions, such as delayed hypersensitivity, allograft rejection, experimental allergic encephalomyelitis, and graft-versus-host disease.

TNF Inhibitors
Monoclonal antibodies targeted against tumor necrosis factor alpha (TNFα) interrupt endogenous TNF. Increased TNFα levels have been observed in Crohn disease and ulcerative colitis and are thought to be part of the pathogenesis of IBD. TNFα induces proinflammatory cytokines (eg, interleukins), enhance leukocyte migration, activate neutrophils and eosinophils, and induces enzymatic degradation. This class includes adalimumab, certolizumab, golimumab, and infliximab. Infliximab and adalimumab are FDA approved for both Crohn disease and ulcerative colitis, whereas certolizumab is FDA approved only for Crohn disease and golimumab only for ulcerative colitis.

Infliximab (Remicade)
Infliximab was the first of this class for use in inflammatory bowel disease. Infliximab is more effective against Crohn disease than ulcerative colitis. This drug promotes mucosal healing; heals perianal and enterocutaneous fistulas; and has been shown to reduce signs and symptoms, achieve clinical remission and mucosal healing, and eliminate corticosteroid use. Infliximab is indicated for patients who have experienced inadequate response to conventional therapy. Infliximab neutralizes cytokine TNF-alpha and inhibits its binding to the TNF-alpha receptor. It is mixed in 250 mL of normal saline and infused IV over 2 hours. It is indicated for both ulcerative colitis and Crohn disease.

Adalimumab (Humira)
Adalimumab is a TNF blocking agent that has been FDA approved for both Crohn disease and ulcerative colitis. It is administered by subcutaneous injection. Adalimumab is
recombinant human immunoglobulin (Ig) G1 monoclonal antibody specific for human TNF. It binds specifically to TNF-alpha and blocks the interaction with p55 and p75 cell-surface TNF receptors.

**Certolizumab pegol** (Cimzia)
Certolizumab is a TNF blocking agent that has been FDA approved for the treatment of Crohn disease but not for ulcerative colitis. It is administered by subcutaneous injection. Certolizumab pegol is a pegylated antitumor necrosis factor (TNF)–alpha blocker, which results in disruption of the inflammatory process. It is indicated for moderate to severe Crohn disease in individuals whose condition has not responded to conventional therapies.

**Golimumab** (Simponi)
Human anti-TNF-alpha monoclonal antibody. Indicated for ulcerative colitis but not Crohn disease. It is administered by SC injection.

**Alpha 4 Integrin Inhibitors**
Integrin inhibitors are emerging as options for moderate-to-severe active IBD in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

**Natalizumab** (Tysabri)
Natalizumab is a recombinant humanized IgG4-1C monoclonal antibody produced in murine myeloma cells. It binds to alpha-4 subunits of α4β1 and α4β7 integrins expressed on the leukocyte surface, which inhibits α4-mediated leukocyte adhesion to their receptors. In Crohn disease, the interaction of the α4β7 integrin with the endothelial receptor MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease.

**Vedolizumab** (Entyvio)
Vedolizumab is a recombinant humanized monoclonal antibody that binds specifically to α4β7 integrin. It blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. It is indicated for both ulcerative colitis and Crohn disease.
Synbiotics
When probiotics and prebiotics are administered simultaneously, the combination is termed Synbiotics. The prebiotic in the synbiotic mixture improves the survival of the probiotic bacteria and stimulates the activity of the host’s endogenous bacteria. One of the study demonstrated the ability of probiotics to exert anti-inflammatory effects and shows some anti-proliferative characteristics for a specific synbiotics. The link between intestinal microflora and IBD is now well established, and altering the composition of the microflora using probiotics and prebiotics holds promise as a therapeutic strategy for ameliorating chronic intestinal inflammation.

Probiotics
Probiotics are defined as selected, viable micro bialdietary supplements that, when introduced in sufficient quantities, beneficially affect human organism through their effects in the intestinal tract. The majority of bacteria belonging to the Lactobacillus and Bifidobacterium genera are recognized as safety. The physiological effects related to probiotic bacteria include the reduction of gut pH, production of some digestive enzymes and vitamins, production of antibacterial substances. Probiotics are defined as ‘mono- or mixed cultures of live microorganisms which, when applied to animal or man, beneficially affect the host by improving the properties of the indigenous microflora’. Both Lactobacilli spp. and Bifidobacterium spp. are frequently applied as probiotics. Data from basic and clinical research suggest that probiotics may have the potential to influence different IBS disease mechanisms by modulating immune-responses, changing the intraluminal milieu or influence visceral sensory and motor functions. In the future, the definition of a probiotic may require modification, as there is experimental evidence that dead bacteria, bacterial components and substances secreted by bacteria (e.g. bacteriocins, conjugated linoleic acid) have physiologically relevant effects. The more inclusive term 'pharmabiotic' has also been proposed to encompass entities that exert this potentially important effects.

Prebiotics
Prebiotics are an alternative for probiotics or their cofactors. They are defined as non-digestible or low-digestible food ingredients that benefit the host organism by selectively stimulating the growth or activity of one or a limited number of probiotic bacteria in the colon. The most common oligosaccharides are inulin and its hydrolysates and oligofructans. They can be found in chicory, topinambuco, onion, garlic, asparagus, artichoke, leek,
bananas, tomatoes and many other plants. The link between intestinal microflora and IBD is now well established, and altering the composition of the microflora using probiotics and prebiotics holds promise as a therapeutic strategy for ameliorating chronic intestinal inflammation.[67]

**Experimental models for the evaluation of drugs in IBD**

**TNBS model**
The model employs the use of 2,4,6-trinitrobenzenesulfonic acid (TNBS), which induces severe colonic inflammation when administered intrarectally in SJL/J mice. The colitis which results from this procedure presents clinical and histopathological findings that resemble those seen in Crohn's disease. The unit describes the critical parameters needed for successful induction of TNBS-colitis as well methods for monitoring and grading disease levels. A support protocol for isolating lamina propria mononuclear cells from mouse colons is also included.[56] Intestinal inflammation in TNBS sensitized rats as a model of chronic inflammatory bowel disease.[57] The female C57BL/6 mice can also be employed, and colitis can be induced by intracolonic injection of 0.5mg of TNBS dissolved in 50% ethanol–phosphate buffered solution.[58]

**Interleukin-4 gene transfer in experimental inflammatory bowel disease**
IBD is characterized by altered immunoregulation and augmented intestinal synthesis of nitric oxide. This is to determine the effects of exogenous IL-4, introduced by a recombinant human type 5 adenovirus (Ad5) vector, on the tissue injury associated with an experimental model of colonic immune activation and inflammation.[59]

**Selected iron chelators and anti-oxidants**
Iron chelators, such as maltol and kojic acid, have antioxidant and anti-inflammatory properties. They may have beneficial effects because iron can develop and aggravate inflammation in IBD.[60]

**Mycobacterium avium subsp. paratuberculosis lipophilic antigen model**
The 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced murine colitis model was developed to investigate the pathogenesis and to evaluate a method of treating human Crohn’s disease. This experimental model rapidly induces colitis similar to human Crohn’s disease lesion in a reproducible manner. However, natural exposure of the human digestive tract to TNBS is unrealistic.[61]
Anti-inflammatory properties of the μ opioid receptor support and its use in the treatment of colon inflammation

The physiologic role of the μ opioid receptor (MOR) in gut nociception, motility and secretion is well established. To evaluate whether MOR may also be involved in controlling gut inflammation, they first showed that subcutaneous administration of selective peripheral MOR agonists, named DALDA and DAMGO, significantly reduces inflammation in two experimental models of colitis induced by administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) or peripheral expansion of CD4+ T cells in mice.162

Hapten-induced colitis is Associated with Colonic Patch Hypertrophy and T Helper Cell 2–type responses

To investigate the potential involvement of T helper (Th)2-type responses in murine models of intestinal inflammation, the trinitrobenzene sulfonic acid (TNBS)–hapten is used to induce inflammatory bowel disease in situations where Th1-type responses with interferon (IFN)-γ synthesis are either diminished or do not occur. Intracolonic administration of TNBS to either normal (IFN-γ+/+) or Th1-deficient IFN-γ knockout (IFN-γ−/−) BALB/c mice resulted in significant colitis.63

CONCLUSION

It is concluded that, synthetic drugs such as 5-aminosalicylic acid derivatives, corticosteroids, immunosuppressants, TNF Inhibitors and Alpha 4 Integrin Inhibitors established to be beneficial for the treatment of IBD but they are associated with some adverse effects. Evaluation of some medicinal plants and nutraceuticals in the management of IBD also found more efficacious than synthetic drugs as they are associated with less/no adverse effects. Apart from this, Lactobacillus spp and Bifidobacterium spp, frequently applied as probiotics have the potential to influence different IBS disease mechanisms by modulating immune-responses, changing the intraluminal milieu or influence visceral sensory and motor functions.

Many experimental models have been established for the evaluation of IBD but, TNBS (2,4,6-trinitrobenzenesulfonic acid) model found to be the more efficient model to induce severe colonic inflammation when administered intrarectally in SJL/J mice.
REFERENCES


36. Amit D Kandhare, Kiran S Raygude, Pinaki Ghosh, Arvindkumar E Ghule, Tejas P Gosavi, Sachin L Badole, Subhash L Bodhankar. (Effect of hydroalcoholic extract...


55. William A Rowe, MD, BS Anand, MD, Gary R Lichtenstein, MD. (Inflammatory Bowel Disease Medication). Medscape Salary Employment, Updated: Jan 7, 2015.


