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NOVEL APPROACHES IN THE MANAGEMENT OF ULCERATIVE COLITIS

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ABSTRACT
Although many types of treatments have been proposed but for the management of ulcerative colitis additional therapeutic approaches are needed as many patients dose not respond properly to the currently available options or show significant adverse effects of the prescribed medications. Therefore there is a need to develop safe and effective alternatives for the management of ulcerative colitis. From the beginning, plants have proved to play a vital role in maintaining human lifestyle and health as they are the principle source for medicines, cosmetics, etc. Herbal medicines are based on the fact that the plants contains natural substances that can promote health and alleviate illness. The use of plants as a source of medicines for use in investigation, prevention, and treatment of disease is also very promising as they lacks majority of side effects that are encountered while on chemically derived medications.

KEYWORDS: IBD, Herbal Plants, Antioxidants, Synthetic drugs.

INTRODUCTION
Inflammation is the first biological response of our immune system towards an infection or irritant. Inflammatory bowel disease is a chronic inflammatory condition of the GI Tract constituting two idiopathic conditions i.e. Ulcerative Colitis and Chron`s disease. While ulcerative colitis is limited to large intestine and the rectum, chrons disease can hit any part of the gi tract from mouth to anus (Kumar et.al., 2004).

In Ulcerative colitis chronic inflammation occurs in the inner line of colon and/or the rectum limited to the mucosal and sub mucosal layers characterized by diarrhoea with frank blood in the stools and abdominal pain. The patient has frequent bowel movement and always in an urgency to evacuate bowel. Other symptoms includes rectal pain, fever and weight loss. Extra intestinal symptoms occurs in rare cases. The symptoms depends upon the inflammatory condition of the patient, if fulminant condition occur, surgery is the only treatment (Monsen et al., 1990) (Sudha et al., 2010) (Razi et al., 2009).

The extent of inflammation can be restricted to the rectum (proctitis) or the rectum and sigmoid colon (proctosigmoiditis). Distal inflammation is more often associated with symptoms of urgency. Inflammation can also be extended to the splenic flexure (leftsided colitis), the hepatic flexure (extensive colitis) or involve the entire colon and rectum (total colitis). The seriousness of the disease is often dependent upon the extent of inflammation whereas severity is dependent upon the intensity of the inflammation. A limited but intensely inflamed section of the colorectum can be of utmost difficulty for the patient(Das, 1999).

The etiology of the disease is yet to be revealed but the pathogenesis is believed to be multifactorial.

Factors for IBD
The most accepted hypothesis currently implicates that IBD is a multifactorial disorder. Factors such as Disregulated immune system responses as caused by genetic and environmental factors, Abnormal gastrointestinal luminal factors, oxidative stresses, and defective GI mucosal barrier allowing the luminal factors to get into the mucosa **(Kucharzik et al., 2006) (Scaldaferri et al., 2007)**. But still the specific etiology of IBD is unclear **(Lim et al., 2010).**

1- Immune System
It has been reported that in IBD both the Innate and Adaptive immune system shares defective responses (Brown et al., 2007). It has been demonstrated that the properties of the cell mediating innate immunity such as neutrophils, macrophages, dendritic cells and natural killer cells are changed and impaired mucosal T-cell response as well as over expression of cytokines such as TNF-α, Interferon-$^{\gamma}$, interleukin-1β (IL-1 β), IL-6, IL-12 occour in patients with IBD. These drastic changes to the mucosal membrane of large intestine results in impairment of mucous barrier, inflammation, ulcers and

hemorrhage (Sklyarov et al., 2011) (Hosi et al., 2001) (Martin et al., 2005).

Excessive expression of TNF-α damages the epithelial barriers, initiates apoptosis and enhance chemokines secretion by colonic epithelial cells (Cho et al., 2011).

Recently certain analysis have shown the effectiveness of anti- TNF-α drugs in ulcerative colitis.

2- Oxidative Stress

In inflammation, the damaging role of oxidative stress has been well established (Parker et al., 2007) (Brody et al., 1996) (Jahanshahi et al., 2004). In ulcerative colitis, oxidative stress acts as a triggering factor which results in chronic inflammation of the intestine. Reactive oxygen species(ROS) being very unstable reacts instantly with tissue micromolecules which causes damage to the DNA and essential proteins(Beckman et al., 1997).

Various studies have found that there is a decrease in total antioxidant capacity and increase in Reactive oxygen species (ROS) in patients with IBD (Parker et al., 2007), (Brody et al., 1996), (Shiratora et al., 1989) (Buffinton et al., 1995).

Various recent investigation on herbal plants proved them to be effective in inflammation due to their antioxidant properties.

3- Microbial Effects

Potential roles of GI microbial content in pathogenesis of IBD has been reported (Marteau et al., 2004). The disease occour in the areas of gi tract with highest concentration of luminal bacteria. Massive intraction between the host mucosal immunity and interacting micro flora results in inflammation.

Normal nonpathogenic enteric bacterias can induce chronic inflammation in genitically predisposed patient with defective immunoregulation, bacterial clearance or mucosal barrier function (Rahimi R et al., 2010).

It has been demonstrated that the amount of intestinal bacterias is higher in patients with IBD as compared to normal as well as the concentration of bacterias increases with disease severity(Swidsinski A et al., 2002) (Sartor 2003) (Kruis W et al., 2004).

The modification of intestinal microbial flora by probiotics and antibacterial proved to be effective in the management of ulcerative colitis (Rahimi R et al., 2007), (Rahimi R et al., 2008).

4-Nuclear factor kappa-β

This protein family promotes the expression of more than 150 genes in humans some of them plays an important role in regulating inflammation and apoptosis (Kumar A et al., 2004).

There are clear evidences that in human inflammatory bowel disease there is an appropriate activation of nuclear factor kappa-β(Schreiber et al., 1998) (Andersen L et al., 2005). So nuclaear factor k- β can be a valid target for managing reemission and can be searched for future treatment strategy.

5- Nitric oxide

Nitric oxide is synthesized within the body from its precursor moleculles argenine and oxygen in the presence of enzyme NO Synthase. The enzyme exist in three isoforms i.e. neuronal NOS (n-NOS), endothelial NOS (e-NOS) and inducible NOS (i-NOS).

The consecutive forms of NO synthase (c-NOS) which includes e-NOS and n-NOS are important for normal physiology and inhibition of these results in cellular damage. While large amount of i-NOS results in NO overproduction which induces inflammation by combined result of nitrosation, oxidative damage and enhanced inflammatory cytokines and inhibition of the same reduces inflammation (Kanwar et al., 2009), (KUBES p et al., 2000). There are clear evidences of NO over production by i-NOS in patients with IBD (Martin et al., 2007).

6. Cyclooxygenase-2

Cyclooxygenase-2 (Cox-2) is another involved factor in IBD acting through synthesis of prostaglandins. Thus, selective Cox-2 inhibitors, such as celecoxib, are another class of drugs that have been claimed to be effective in IBD (Mahadevan U et al., 2002) (Miedany Y et al., 2006).

7. Leukotriene B4

Leukotriene B4 is a pro-inflammatory mediator with a role in several inflammatory diseases such as IBD. Inhibition of this mediator can reduce inflammation and ameliorate IBD (Sharon P 1984).

Herbal plants effective in management of IBD

Aloe vera

Aloe vera gel is acquired from aloe plant and its medicinal attributes has been listed in majority of drug literatures. Aloe vera gel has an dose dependent inhibhitory effect on the manufacturing of reactive oxygen species, prostaglandins, and IL-8 by way of human colonic epithelial cells in vitro (Langmead et.al 2004).

For the remedy of mild to mild ulcerative colitis a double blinded placebo trial was executed. Aloe vera gel given for four weeks produces a symptomatic clinical response, also it reduces histological ailment activity appeared to be secure to use. (Langmead et.al 2004).

Boswellia serrata

Boswellia serrata (indian frankincense) secrets and techniques resin which is the remoted to attain boswellic acid. this compound is thought to be chargeable for

maximum of its pharmacological interest. Boswellic acid being a non competitive inhibitor of 5-lipooxygenase inhibits leukoterine biosynthesis in neutrophillic granules (Aamon HP, 2002).

Clinical research become finished in on IBD patients the use of boswellia serrata gum resin and the end result confirmed reduced mucosal injury and decrease the activity and adherence of activated leukocytes to intestinal mucosal cells (Anthoni et.al 2001).

In an some other medical study (350mg TID) boswellia serrata gum resin guidance changed into given to a group of ulcerative colitis patients and the manipulate organization turned into handled with sulfasalazine(1g TID) for 6 weeks. consequences being quite similar eighty two% out of handled patients went into reemission even as in case of sulfasalazine it become 75% (Gupta et.al 2001).

Inonotus obliquus

Inonotus obliquus (IO) is a mushroom which belongs to the inonotus genus and own family Hymenochaetaceae which founds dwelling as a parasite on birches. The aquous extracts of Inonotus obliquus has been proven to suppress the expression of TNF-α, IL-4 and STAT1&6 and also the severity of ulcerative colitis in DSS prompted male BALB/c mice. It is likewise proven in vitro to inhibit LPS precipitated STAT1, pSTAT1, STAT6, pSTAT6 and TNF- α manufacturing in RAW264.7 cells (Debnath et.al. 2011). Ethanolic extracts of IO grown on germinated brown rice (IOGBR) shown to have strong pastime on ulcerative colitis in mice. IOGBR reduces the expression of proinflammatory mediators including cyclooxygenase (Cox)-2, tumor necrosis element (TNF)-α, interleukin (IL)-4, interferon (IFN)-γ. also IOGBR extracts suppress the expression of IgE and IgA in the spleen and mesenteric lymph node (MLN) as compared to the ones of the DSS-brought about colitis organization(Choi et.al. 2010). The extracts also inhibits pathological shortening of colon DSS-induced colonic tissue harm in rats (Debnath et.al. 2012).

Foeniculum vulgare

The aqueous extract from F. vulgare seeds proven to have big antibacterial pastime in vitro compared to a few trendy antibiotics (Lim et.al. 2006). In Vitro analysis of Butanol and aqueous fractions of F. vulgare fruit showed intermediate free radical scavenging hobby (Cheng et.al 2005). a group of rat pretreated with aqueous extract of F. vul-gare proven to have suppressed ethanol-brought on gastric lesions. additionally, this extract appreciably decreased lipid peroxidation and expanded antioxidant hobby(Huang et.al. 2012). management of methanolic extract of F. vulgare fruit orally to mice has been proven to suppress type four allergic reactions as well as acute and subacute inflammatory responses and also shown slight centeral analgesic impact. further, it appreciably decorate plasma antioxidant status even as suppressing lipid peroxidation chain reactions (Rosillo et.al. 2012). some initial research additionally revealed that aquous extract of F. Vulgare fruit has great NO free radical scavenging hobby in vitro (Yang et.al. 2005s).

Solanum nigrum

A glycoprotein isolated from this fruit[Solanum nigrum L. (SNL) glycoprotein has proven a dose-de-pendent lower in NO manufacturing and free radi-cal formation in DSS-brought on colitis in mice. also, it exhibited a suppressive effect on the activities of NF-κB and controlled the expression of iNOS and Cox-2 (Joo et.al. 2009). S. nigrum end result showed ef-fective unfastened radical scavenging activities in the 1,1-diphenyl- 2-picrylhydrazyl (DPPH) assay in vitro (Al- Fatimi et.al. 2007). The SNL glycoprotein has high-quality scavenging effects on each the superoxide anion and hydroxyl radical, but exhibited barely better scavenging consequences on the superoxide anion (Heo et.al. 2004). treatment with S. nigrum extract drastically inhibited the gastric lesions induced with the aid of cold restraint stress (seventy six.6%), indomethacin (seventy three.8%), pyloric ligation (eighty.1%) and ethanol (70.6%) in experimental ulcer models. It additionally showed concomitant at-tenuation of gastric secretory extent, acidity and pepsin secretion in ulcerated rats. in addition, it accelerated the healing of acetic acid-induced ulcers after 7 d of remedy. moreover, it considerably inhibited H+k+ATPase hobby and reduced gastrin secretion inside the ethanol-triggered ulcer version.(Jainu et.al. 2006) (Akhtar et.al.1989).

Gardenia jasminoides

Gardenia jasminoides Ellis (GJE) is a flowering plant belonging to the circle of relatives Rubiaceae. The ethanol and aquous extracts from Gardenia jasminoides showed high antioxidant hobby by way of scavenging various free radicals. The extracts showed strong lowering electricity, nitrite scavenging interest, linoleic acid oxidation inhibition, superoxide dismutase-like (SOD-like) pastime, and catalase activity in vitro (Debnath et.al. 2011). Glycoprotein isolated from Gardenia jasminoides end result suppressed MPO hobby, TBARS degree and NO manufacturing and inhibited the over manufacturing of COX-2 iNOS and NF-kappa-β in DSS-caused mice (Lim et.al. 2006).

Ficus bengalensis

Ficus bengalensis Linn. from the own family Moraceae is a reputed plant in Ayurvedic remedy. In Ayurvedic literature, it's far referred to 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 whilst 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 improved the SOD pastime within the colons of rats with IBD (Patel et.al. 2010).

Ginger (Zingiber officinale)
Ginger, belongs to the circle of relatives Zingiberaceae, and its aspect zingerone were investigated to determine its anti-inflammatory activity in mice colitis triggered by means of TNBS. They ameliorated TNBS-brought on colonic injury in a dose-structured way. Their pathway research on gene expression profiles has been determined to manipulate cytokine-related pathways significantly. They suppressed TNBS-induced NF-κB activation and IL-1β protein level within the colon (Hsiang et.al. 2013).

Withania somnifera
Withania somnifera (Dunal), belongs to the circle of relatives Solanaceae, is used as a remedy when you consider that 2500 years in Indian medicinal traditional "Ayurveda". Aqueous extract of its the root confirmed anti-oxidant hobby by using reducing H2O2 and NO. It has lipid peroxidation inhibition activity. The extracts scored undoubtedly on histopathological parameters like necrosis, edema, neutrophil infiltration in TNBS-brought about IBD rat version (Pawar et.al. 2011).

Bromelain (Ananas comosus)
Bromelain is an anti-inflammatory and has been used as a digestive resource and a blood thinner as well as to deal with sports injuries, sinusitis, arthritis and swelling. Bromelain has been studied to be used as a supplement for IBD, particularly UC. emerging research on pineapple indicates that pineapple's active element, "bromelain" can also help to relieve the infection related to UC. The mechanisms which can be basically chargeable for its anti-inflammatory outcomes are nonetheless doubtful. however, proteolytic pastime is needed for the anti inflammatory impact of bromelain on T-mobile activation and cytokine secretion in vitro and in murine models of IBD in vivo. The important mechanism of movement of bromelain appears to be proteolytic in nature, even though proof also shows an immunomodulatory and hormone-like pastime performing via intracellular signaling pathways. Bromelain has been proven to lessen mobile surface receptors, together with hyaluronan receptor CD44, which is related to leukocyte migration and induction of pro-inflammatory mediators. additionally, bromelain is also stated to noticeably lessen CD4+ T-mobile infiltrations, which are primary effectors in animal models of infection inside the intestine. (Mynoot et.al. 2002) (Hale et.al. 2002).

Tormentil extracts (Potentilla erecta)
Potentilla erecta (syn. Tormentilla erecta, Potentilla laeta, Potentilla tormentilla, called the (common) tormentil or septfoil) is herbaceous perennial plant belonging to the rose own family (Rosaceae). Tormentil extracts have antioxidative properties and are used as a complementary remedy for persistent IBD. In man or woman sufferers with UC superb outcomes have been discovered. 16 sufferers with lively UC obtained tormentil extracts in escalating doses of 1200, 1800, 2400 and 3000 mg/day for three weeks each. each treatment segment became accompanied by means of a 4-week washout segment. The final results parameters had been side results, medical activity index, C-reactive protein, and tannin stages in affected person sera. slight higher abdominal pain became skilled by 6 sufferers (38%), but did now not require discontinuation of the drugs.

all through remedy with 2400 mg of tormentil extracts consistent with day, median medical hobby index and C-reactive protein stepped forward from eight (6 to ten.seventy five) and 8 (three to 17.seventy five) mg/L at baseline to four.5 (1.seventy five to 6) and 3 (three to six) mg/L, respectively. all through therapy, the clinical activity index decreased in all sufferers, whereas it improved throughout the washout section. Tormentil extracts appeared safe up to 3000 mg/day. (Ditfurth et.al. 2002)

Psyllium or Ispaghula (Plantago ovata)
Psyllium, or Ispaghula, is the commonplace name used for several individuals of the plant genus Plantago whose seeds are used commercially for the manufacturing of mucilage. P. ovate seeds enhance and meliorate the improvement of colonic infection in transgenic rats as evidenced through an development of intestinal cyto structure, enormous lower in a number of the pro-inflammatory mediators which includes cyclooxygenase (Cox)-2, tumor necrosis aspect (TNF)-α, interleukin (IL)-four, interferon (IFN)-γ and higher manufacturing of short-chain fatty acids(Rodri´ guez-Cabezas et al., 2003). An open label, parallel-institution, multicenter, randomized medical trial in sufferers with ulcerative colitis concluded that Plantago ovataseeds (nutritional fiber) might be as powerful as mesalamine to preserve remission inulcerative colitis (Ferna´ndez-Ban˜ ares et al., 1999). in addition, P. Ovata has been well documented for its laxative and cholesterol-lowering movements.

Commiphora mukul
Guggulsterone (GS), a steroid isolated from the gum resin of C. mukul has been shown to protect mice in opposition to the improvement of signs and symptoms and signs and symptoms of colon irritation in trinitro-benz ene sulfonic acid (TNBS) prompted model of intestinal irritation. in addition GS effectively attenuated the severity of disorder, the fecal score and colon inflammation. In vitro, studies in CD4+ cells remoted from the intestinal lamina propria confirmed that GS efficaciously regulates the characteristic of effector T cells and additionally attenuate the generation of IL-2, IL-four and IFN-γ in addition to T mobile proliferation (Renga et.al. 2009). Guggulsterone inhibits LPS- or IL-1b-precipitated ICAM-1 gene expression, NF-κB transcriptional hobby, IκB phosphorylation/degradation, NF-κB DNA-binding and also decreased the severity of DSS-triggered murine colitis as assessed via scientific disease activity rating, colon duration, and histology (Kim et.al. 2006). several compounds inside the gum resin from C. mukul have proven lipid peroxidation and

Cox inhibitory sports (Francis et.al. 2004). The methanolic extract of the gum resin from C. mukul was located to inhibit NO production in lipopolysaccharide-activated mouse perito-neal macrophages (Ando et.al. 2004). a few critical oil, chloroform extract, and sesquiterpenoid compounds remoted from the oleogum resin of C. mukul showed a extensive variety of anti-bacterial interest in opposition to both gram positive and gram negative micro organism (Sabir et.al. 2004).

Terminelia chebula

The aqueous extract of T. chebula has been proven to enhance antioxidant fame inside the liver and kidney and efficaciously modulate oxidative stress of aged rats. The ethanolic fraction of T. chebula enhance the recovery charge of gastric lesions triggered via indomethacin and also inhibt lipid peroxidation in the gastric mucosal tissue of rats (Bang et.al. 2012). similarly, the ethanolic extract of T. chebula has proven large-spectrum interest in opposition to certain multidrug-resistant bacteria, which includes methicillin-resistant Staphylococcus aureus(S. aureus) and extended spectrum β -lactamase-producing enteric micro organism and T. chebula. additionally, this extract interact synergistic with tetracycline, chloramphenicol and ciprofloxacin against S. aureus and/or Escherichia coli (E. coli) (upward push et.al. 2012). The butanol fraction of T. chebula fruit had also vast spectrum activity towards six intestinal micro organism, specially Clostridium perfringens and E. coli (Shin et.al.). A have a look at has also shown that the aqueous extract from T. chebula inhibit inducible nitric oxide synthesis through de- creasing iNOS protein and iNOS mRNA stages.

Studies on herbal plant effective in IBD

Plant	Part	Species	Result	Study
Boswellia carterii	Oleogum resin ethanolic extract	***Rats***	Immunomodulatory properties	**Chevrier *et al***
	Terpenoids from oleogum resin	***Rats***	↓NO production in lipopolysaccharide-activated mouse peritoneal macrophages	**Yoshikawa *et al***
	Essential oleo gum oil	***Mice***	Antimicrobial activities against various microorganisms including fungi, Gram-positive and Gram-negative bacterial strains	**Camarda *et al***
Cassia fistula	Crude extract of fruit	***Rats***	Significant antimicrobial activity	**Kumar *et al***
Commiphora mukul	Terpenoids and guggulusteroids	***Mice***	↓Lipid peroxidation and Cox inhibitory activities	**Francis *et al***
	Methanolic extract of gum resin	***Rats***	↓inflammatory mediators such as IFN-δ, IL-12, TNF-α, IL-1β and NO ↓NO production	**Matsuda *et al***
Commiphora mukul	The essential oil, chloroform extract	***Rats***	Wide range of inhibitory activity against both Gram positive and Gram negative bacteria	**Saeed *et al***
Cydonia oblonga	Pulp and peel polyphenolic extract	***Rats***	Radical scavenging and antimicrobial activities	**Fattouch *et al***
Cydonia oblonga	Pulp and peel phenolic extract	***Rats***	Antioxidant activity	***Silva et.al***
	Aqueous and organic seed extracts	***Rats***	Antibacterial activity	Kaur *et al*

Foeniculum vulgare	n-butanol and aqueous extract of fruit Aqueous extract	***Rats*** ***Mice***	Moderate antioxidant activity ↓NO production	De Marino *et al* Baliga *et al*
Avicennia marina	Plant Leaves	***Rats***	↓Colonic lipid peroxides, serum nitric oxide, ↑SOD and glutathione levels	Rise *et al.*
Bombax malabaricum	Phytochemicals	***Rats & Mice***	↓Ulcer score and MPO	Jagpat *et al*
Withania somnifera	Root extract	***Rats***	Improve Histology and decrease lipid peroxidation	Pawar *et al*
Malus spp.	Polyphenolic extract	***rats***	↓IFN-δ, IL-12, TNF-α, IL-1β and NO	Jung *et al*
Inonotus obliquus	Total mushroom	***Mice***	↓ IFN-δ, IL-12, TNF-α, and prevent epithelial crypt damage	Debnath *et al*
Coriolus versicolor	Total mushroom	***Mice***	↓ IFN-δ, IL-12, TNF-α, STAT-6, Increase IgE	Lim *et al*
Bacopa monieri	Herbal extract	***Rats***	↓ IgG & IgM in serum, Antioxidant	Yamada *et al*
Cordyceps militaris	Mushroom	***Rats***	Prevent shortning of colon length, prevents epithelial crypt damage	Han *et al*
Mume fructus	Fruit extract	***Rats***	↓ colonic inflammation, ↓ TNF- α IL-4	Liu *et al*

Synthetic Drugs used in Inflammatory Bowel Disease

Cllasification	**Examples**
5- Amino salisylic acid derivatives	Sulfasalazine Mesalamine Balsalazide Olsalazine Butyrate Metronidazole Rifaximin
Floroquinolones	Ciprofloxacin Norfloxacin
Cortecosteroids	Hydrocortisone Methylprednisolone Prednisolone Budesonide Dexamethasone
Immunosuppressant's	Azathioprine 6- Mercaptopurine Methotrexate Cyclosporine
TNF- Inhibitors	Infliximab Adalimumab Certolizumab Golimumab Natalizumab Vedolizumab

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 immuneresponses, changing the intraluminal milieu or influence visceral sensory and motor functions.

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