ejpmr, 2017,4(5), 256-266

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A CRITICAL REVIEW ON CURRENT THERAPY ON ULCERATIVE COLITIS

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Article Received on 04/03/2017 **Article Revised on 22/03/2017** **Article Accepted on 13/04/2017**

ABSTRACT

Ulcerative colitis is an inflammatory chronic disease primarily affecting the colonic mucosa. The extent and severity of colon involvement are variable. Ulcerative colitis is one of the most prevalent gastrointestinal disorders, which affects approximately 5-10% of people during their life. In recent years, abundant work has been carried out on herbal medicine to clarify their potential efficacy in ulcerative colitus prevention or management. A number of medicinal plants such as *Amomum subulatum, Scoparia dulcis, Jasminum grandiflorum, Davilla rugosa, Kielmeyera coriacea, Larrea divaricata, Qualer grandiflora, Mammea Americana, Anacardium occidentale, Ocimum sanctum, Azadirachta indica, Acorus calamus, Gingko bioloba, Curcuma longa, Withania somnifera, Polygala tenulfolia etc.* Despite of all the advances in modern and orthodox medicine, traditional medicine still plays a significant role in the lives of many people suffering with ulcerative colitus. These plants provide leads to find therapeutically useful compounds, thus more efforts should be made towards isolation and characterization of the active principles and their structure activity relationship and produce better drugs for the treatment of ulcerative colitis with fewer side effects.

KEYWORDS: Chronic disease, Herbal medicine, *Curcuma longa*, Orthodox medicine.

INTRODUCTION

Inflammatory bowel disease encompasses two idiopathic, chronic, inflammatory diseases: Crohn's disease and ulcerative colitis. Crohn's disease and ulcerative colitis are disorders of unknown cause involving genetic and immunological influence on the gastrointestinal tract's ability to distinguish foreign from self-antigens. They share many overlapping epidemiological, clinical and therapeutic characteristics. In some patients, it is not possible to distinguish which form of inflammatory bowel disease is present. There are, however, important pathological and clinical differences that distinguish these inflammatory disease processes. Clinically, Crohn's disease tends to present more frequently with abdominal pain and perianal disease, whereas ulcerative colitis is more often characterized by gastrointestinal bleeding.[1]

Cobble stoning mucosa and aphthous or linear ulcers characterize the endoscopic appearance of Crohn's disease. Ulcerative colitis presents with diffuse continuous involvement of the mucosa. Radiographic studies of patients with Crohn's disease characteristically show fistulas, asymmetry and ileal involvement. In contrast, radiographic studies of patients with ulcerative colitis show continuous disease without fistulizing or ileal disease.[2]

Pathologically, Crohn's disease features mucosal discontinuity, transmural involvement and granulomas. In contrast, ulcerative colitis does not. Crypt abscesses and granulomas are present only in Crohn's disease. It compares the appearance of the colon, the histology and endoscopic views of normal, Crohn's disease and ulcerative colitis patients.

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease that occurs more often in industrialized countries. This disease affects both men and women similarly. The disease may be acute and chronic with unpredictable relapses and remissions. Major advances have been made in many aspects of inflammatory bowel disease, including new information on the molecular basis of the disease, epidemiological considerations, immunology and genetics. The clinical and scientific understanding of ulcerative colitis has been greatly expanded far beyond our earlier knowledge.[3]

Ulcerative colitis is an idiopathic inflammatory bowel disease that affects the colonic mucosa and is clinically characterized by diarrhea, abdominal pain and hematochezia. The extent of disease is variable and may involve only the rectum (ulcerative proctitis), the left side of the colon to the splenic flexure, or the entire colon (pancolitis). The severity of the disease may also be quite variable histologically, ranging from minimal to florid ulceration and dysplasia. Carcinoma may develop. The typical histological (microscopic) lesion of ulcerative colitis is the crypt abscess, in which the epithelium of the crypt breaks down and the lumen fills with polymorphonuclear cells. The lamina propria is infiltrated with leukocytes. As the crypts are destroyed, normal mucosal architecture is lost and resultant scarring shortens and can narrow the colon.[4]

Manifestations

Arthritic complications may occur in as many as 26% of patients with ulcerative colitis. Spondolylitis occurs in 3% of these patients. The arthritic symptoms may appear before the inflammatory bowel disease and do not necessarily follow the course of the intestinal disease. Twelve to 23% of patients with ulcerative colitis have peripheral arthritis, which affects large, weight-bearing joints such as knees or ankles. Arthritis signs and symptoms usually accompany exacerbations of ulcerative colitis.[5]

Nineteen percent of patients with ulcerative pancolitis experience dermatological changes. Erythemia nodosum and pyoderma gangrenosum are commonly associated with this disease. Other dermatological sequelae include dermatitis, erythematous rash, psoriasis, carcinoma, urticaria, pityriasis, lupus erythematosus, vitiligo and ecchymosis.

Ocular manifestations of ulcerative colitis occur in 5% of patients with extensive disease or with Crohn's disease, and may include anterior uveitis, episcleritis and keratoconjunctivitis. Symptoms of these complications include headache, photophobia, blurred vision, burning and increased secretions from the eyes.

In most situations, extraintestinal manifestations respond to standard medical therapy. On rare occasions, a total proctocolectomy may be necessary to control severe extraintestinal manifestations of this disease.[6]

CLASSIFICATION

The extent of colonic mucosal involvement and severity of disease correlate with the clinical manifestations of ulcerative colitis. Approximately one-third of all patients with ulcerative colitis have involvement limited to the rectum (the distal 15 cm of the large intestine) or ulcerative proctitis. Ulcerative proctitis is endoscopically characterized by edema, erythema and loss of vascular markings. Granularity, friability and frank ulceration are also seen in more severe disease.[7]

Distal or left-sided colitis is found in patients in whom the inflammatory process extends from the rectum 40 cm. Disease activity does not extend beyond the splenic flexure and there is evidence of chronic inflammation and chronic architectural distortion.

Pancolitis involves the portion of the colon beyond splenic flexure. It is characterized by hematochezia and diarrhea and may be accompanied by abdominal pain and cramps, fever and/or weight loss with persistent inflammation. Normal haustral markings disappear with generalized shortening and tubularization of the colon. In severe disease, the mucosa may be described as nodular with pseudopolyps, a reticular pattern and discrete ulcer craters.[8]

Incidence

The incidence of ulcerative colitis has remained fairly constant in those areas for which data are available for a number of years. Ulcerative colitis has been reported between 1.0 and 15.0 cases per 100,000. The literature reports a slightly higher incidence of ulcerative colitis in females than males. It is most likely to occur in early adulthood, but disease presentation can occur in the fifth or sixth decade and occasionally in the seventh or eighth decade. Diet, breast-feeding, oral contraceptives and the cessation of cigarette smoking have been implicated as risk factors for ulcerative colitis. Studies indicate a decreased risk of ulcerative colitis for current smokers; however, former smokers are at increased risk of developing the disease.[9]

SYMPTOMS

The predominant symptom in ulcerative colitis is diarrhea, which can be associated with frank blood in the stool. The patient has frequent bowel movements, which may be small in volume, as a result of irritability of the inflamed rectum (proctitis). Other symptoms include abdominal or rectal pain, fever and weight loss. Although diarrhea is the dominant complaint in patients with ulcerative colitis, some patients may complain of constipation and rectal spasm.[10]

Anatomy

The lower gastrointestinal tract may be divided into the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon and the rectum. The large intestine (colorectum) begins at the cecum, which is a pouch approximately 2–3 inches long. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the

cecum along the right posterior wall of the abdomen, under the ribs to the undersurface of the liver. At this point it turns toward the midline (hepatic flexure), becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen, goes high up into the chest under the ribs, and turns downward at the splenic flexure. Continuing along the left side of the abdominal wall to the rim of the pelvis, the descending colon turns medially and inferiorly to form the S-shaped sigmoid (sigma-like) colon. The rectum extends from the sigmoid colon to the pelvic floor muscles, where it continues as the anal canal terminating at the anus. The anal canal is approximately 4 cm long.[11]

The large intestine is approximately 5–6 feet long and 2½ inches in diameter. It is the site of salt and water absorption. Glands secrete large quantities of alkaline mucus that lubricate the intestinal contents and neutralize acids formed by bacteria in the intestine. These bacteria aid in decomposition of undigested food residue, unabsorbed carbohydrates, amino acids, cell debris, and dead bacteria through the process of segmentation and putrefaction. Short-chain fatty acids provide an energy source for the cells of the left colon. Maintenance of potassium balance is also assigned to the colon, where the epithelium absorbs and secretes potassium (K) and bicarbonate.[12]

CAUSES

Genetics

Inheritance on a polygenetic basis seems to play a role in the etiology of ulcerative colitis in about 12–15% of cases. The most firmly established and quantitatively greatest risk factor for developing ulcerative colitis is a family history. The factors responsible for variable expression of this heritable susceptibility are not known. Evidence of higher rates of ulcerative colitis in urban areas raises the issue of a transmissible agent that may be responsible for disease expression or increased susceptibility.

Environmental

Environmental factors that may potentiate the onset of ulcerative colitis are currently under investigation. Such risk factors include diet, breast-feeding and other perinatal events, occupation and social class, oral contraceptive use and most impressively, the cessation of cigarette smoking. Although the "protective" factor in tobacco smoke is unknown, several preliminary trials have shown promising results.[13]

PATHOGENESIS

The pathogenesis of ulcerative colitis remains unknown. Several theories have been proposed that implicate vascular impairment, autoimmune mechanisms, bacterial-immunological interactions and allergic or hypersensitivity reactions. Recent literature on inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis reports an intensive search for the antigens that trigger the immune response in inflammatory bowel disease. There are three major hypotheses as to these antigenic triggers. One hypothesis is that these triggers are microbial pathogens, as yet unidentified. According to this theory, the immune response in IBD is an appropriate but ineffective response to these pathogens. The second hypothesis as to the antigenic trigger in IBD is that there is some common dietary antigen or nonpathogenic microbial agent to which the patient mounts an abnormal immune response. It has been hypothesized that patients with IBD are genetically programmed to mount an intense immune response to some common luminal antigen (dietary or microbial) to which most people do not respond.

Diet is a major source of antigens in the intestinal lumen. Dietary antigens are capable of triggering immune responses. One of the foods implicated in the pathogenesis of IBD is cow's milk. Patients with IBD and Crohn's disease demonstrate an increased incidence of antibodies to cow's milk protein. In patients with IBD, cow's milk proteins and other dietary antigens have abnormal access to the lamina propria because of the defect in the epithelial cell monolayer caused by inflammation. Normally, the intestinal epithelium is a barrier between the immune cells of the lamina propria and luminal antigens; however, in IBD, the immune cells of the lamina propria are exposed to numerous luminal antigens. These luminal antigens are capable of triggering immune responses. As a result, specific immune responses to the etiological agent may be overwhelmed by immune responses to thousands of luminal antigens that pass through the damaged epithelium.[14]

The third hypothesis relating to antigenic triggers postulates that an antigen is expressed on the patient's own cells, particularly on intestinal epithelial cells. Theoretically, the patient mounts an appropriate immune response against some luminal antigen; but because of similarities between proteins on the epithelial cells and the lumen antigen, the patient's immune system also attacks the epithelial cells. Under this autoimmune theory, the immune response is directed toward the epithelial cells and the cells are destroyed by one of two immune effector mechanisms—either antibody-dependent cellular cytotoxicity or direct cell-mediated cytotoxicity.[15]

DIAGNOSIS

Evaluations at initial presentation, at the beginning of each subsequent attack and at multiple points during each attack are required to assess the clinical picture. The extent of the evaluation should be guided by the presentation. The frequency and severity of diarrhea is a good indicator of the severity of disease. Six or more bowel movements per day are associated with

severe disease.

The increase in frequency of bowel movements during an attack, as compared to the normal number of bowel movements, is more informative than the absolute number. Fever, hypotension and tachycardia are markers for the presence of severe disease and necessitate more extensive evaluation in a hospital setting. Nocturnal bowel movements are also crucial in the history to determine severity. The differential diagnosis in ulcerative colitis includes other forms of inflammatory bowel disease, including Crohn's disease, diverticular inflammation and hemorrhage, collagenous colitis, ischemic bowel disease, radiation colitis and infectious etiologies including the following organisms: Campylobacter, Shigella, Clostridium difficile, amebiasis and Escherichia coli.[16]

Non-Invasive Diagnostic Tests

Levels of hemoglobin, leukocyte count and erythrocyte sedimentation rate reflect disease. Hypoalbuminemia and electrolyte disorders, such as hyperkalemia, are often seen with severe diarrhea. These studies play a role in clinical evaluation and are useful in confirming the initial impression and in following the subsequent clinical course of remission and exacerbations.

Non-Invasive Diagnostic Imaging

Plain abdominal x-rays demonstrate the gaseous outline of the transverse colon in the acutely ill patient. Shortening of the colon and loss of haustral markings can also be demonstrated by plain films, as well as a double-contrast barium enema. Indications of ulcerative disease include loss of mucosal detail, cobblestone filling defects and segmental areas of involvement.[17] Contrast studies are a sensitive radiological diagnostic tool to determine the extent of ulcerative colitis. Currently, the most common radiological procedures include the small-bowel series, enteroclysis, barium enema and upper gastrointestinal films.

Small-Bowel Series

This is a fast, safe procedure for visualization of the small bowel. The patient drinks a barium suspension and overhead abdominal radiographs are taken at 20–30 minute intervals. When the barium reaches the right colon, fluoroscopy is performed while moving the patient in various positions to unwind superimposed bowel loops. Compression spot radiographs are obtained with attention to the terminal ileum.[18]

Enteroclysis

Enteroclysis is more sensitive for focal lesions (such as adhesions), but has a higher rate of complications and technical difficulty. With the patient mildly sedated, a tube is passed through the nose and advanced into the jejunum. Under constant fluoroscopic imaging, barium is infused through the tube with a methylcellulose solution, resulting in distension and coating of small-bowel loops. The appearance is similar to a double-contrast enema.

Barium Enema

This is a safe, effective tool for evaluation of patients with ulcerative colitis. It demonstrates ulcer depth and fistulas. A high-density barium preparation is administered through a rectal tube. Under fluoroscopy, air is introduced until the entire colon is distended and coated with barium. Spot films are taken during the filling of the colon and a series of overhead films are taken after the patient has been positioned to demonstrate the whole colon. Post-evacuation films are also obtained.

Upper Gastrointestinal Films

These films allow evaluation of the esophagus, stomach and duodenum. Examination can be performed using single- or double-contrast techniques. In the single- contrast study, the patient drinks a barium suspension. Fluoroscopic spot radiographs are taken. During the double-contrast examination, the patient ingests effervescent gas crystals followed by a barium solution. Air distends the upper gastrointestinal tract, which is coated with barium, and a series of spot radiographs are obtained.

Radiological Diagnosis Computed Tomography (CT)

CT scanning is a valuable tool in the diagnostic evaluation of patients with ulcerative colitis and is complementary to contrast exams. CT can accurately image the bowel wall and the extra luminal disease extension. Oral contrast and/or IV contrast is administered to the patient before the examination, allowing for opacification of the stomach, small bowel and colon Magnetic Resonance Imaging (MRI). MRI is an ideal imaging tool, but its application is limited. Technical advances have reduced the imaging time and decreased motion artifacts. The technique has demonstrated usefulness in evaluating the severity of disease and colonic wall thickness.

Endoscopic Diagnosis

Endoscopy is essential at initial presentation to establish diagnosis and determine the extent of disease. It may also be useful at the time of subsequent attacks to determine recurrence of ulcerative colitis or extension of disease activity, and for surveillance for dysplasia.

Flexible Sigmoidoscopy

Lower abdominal symptoms should be evaluated by flexible sigmoidoscopy. This allows examination from the rectum through the sigmoid colon and takes approximately 10–20 minutes.

This procedure is simple to perform and easily tolerated. Patients may experience slight cramping or pressure in the lower abdomen; however, as soon as air leaves the colon the discomfort resolves. This examination allows for a limited endoscopic view when the patient is known to have only limited ulcerative proctitis.[19]

Colonoscopy

Colonoscopy is a procedure that takes 30–60 minutes and allows examination of the entire large intestine from the rectum through the colon to the terminal ileum. Sedation is administered so the patient does not experience significant discomfort. The colon must be completely empty for colonoscopic examination to be thorough and safe. Patients are routinely placed on a liquid diet for 1–2 days before the examination and administered oral laxative and/or enemas to clear the colon. The physician inserts a long, flexible, lighted colonoscope into the rectum and guides it into the colon and potentially to the terminal ileum. The colonoscope transmits images of the inside of the colon to a monitor, viewable by the physician. Air may be insufflated into the colon to improve visibility. During the procedure, a variety of instruments can be utilized through the biopsy channel of the scope (snares or forceps for obtaining tissue specimens). Colonoscopy is a sensitive and specific diagnostic tool in ulcerative colitis.

TREATMENT

The primary goal of therapy in ulcerative colitis is to reduce acute and chronic inflammation ultimately resulting in complete clinical and endoscopic remission. Medical therapies, as well as surgical intervention, are the current modalities for treatment of ulcerative colitis. Approximately 70% of patients respond favorably to medical regimens and go into remission. Surgery cures ulcerative colitis. Surgery is indicated for those patients who are unresponsive to medical therapy and have a severely compromised quality of life. Growth failure in children, life-threatening complications such as severe bleeding, toxic megacolon, impending perforation, intolerance to immunosuppression, colonic strictures and dysplasia or carcinoma is also indications for surgery.[20]

MEDICAL THERAPY

Anti-inflammatory drugs (adrenocorticosteroids and compounds containing 5-aminosalicylic acid) are the mainstays of medical therapy. These medications in a variety of forms are used orally and topically to reduce inflammation of the colon and rectum.

Treatment Approaches

Treatment in ulcerative colitis is individualized to the specific needs of the patient and alterations in treatment strategies are made according to the response attained. Nevertheless, we present a guide to the most common approaches used with our patients.

Mild Acute Relapsing Ulcerative Colitis

Mild disease is associated with four or fewer loose bowel movements daily with occasional blood, abdominal cramps, and, infrequently, tenesmus. Systemic symptoms are not present. For proctitis or proctosigmoiditis, symptomatic treatment with antidiarrheals, rectal steroids (or rectal 5-aminosalicylic acid [5-ASA]) and occasionally oral 5-ASA is recommended. Left-sided colitis or pancolitis is treated with rectal steroids and oral 5-ASA.

Moderate Acute Relapsing Ulcerative Colitis

In patients with moderate disease, bowel movements range from 4–8 daily with urgency, a nocturnal pattern, blood in the stool, abdominal discomfort, and some systemic symptoms such as weight loss, mild anemia and low-grade fever (less than 100º F). Proctitis or protosigmoiditis is treated symptomatically (antidiarrheals, bulk agents). Rectal steroids (rectal 5-ASA) and oral 5-ASA are used in increasing doses. In left-sided or pancolitis, oral steroids are added and 5-ASA is used for maintenance therapy.

Severe Acute Relapsing Ulcerative Colitis

Severe attacks are characterized by the passage of six or more bloody stools daily accompanied by systemic symptoms such as fevers of 100º F or greater, weight loss, tachycardia, anemia with hemoglobin count of 10 g/dl or less and hypoalbuminemia. For proctitis or protosigmoiditis, double-dose rectal steroids (plus rectal 5-ASA) along with increased oral 5-ASA or oral or intravenous steroids, are recommended. In left-sided or pancolitis, no antidiarrheal medications are recommended. A combination of oral 5-ASA, rectal steroids, intravenous steroids and intravenous antibiotics (i.e., ciprofloxacin and/or metronidazole) is recommended. In protracted cases, the addition of intravenous cyclosporine is considered. The usual dose is 4 mg/kg given in a four-hour intravenous infusion (2–6 pm) for a period of 5–7 days. Trough levels are followed (normal range 100–250 mg/dl) as well as renal (kidney) function while on intravenous cyclosporine. If there is no major improvement of symptoms within one week after the initiation of intravenous cyclosporine, the patient is usually referred for surgery.[21]

SURGICAL THERAPY

Surgery in ulcerative colitis should be reserved for those patients with refractory disease, complications associated with the medical therapy, or complications of colitis. Colectomy may be used in pediatric patients for amelioration of growth retardation in prepubescent children affected by ulcerative colitis. Current surgical alternatives include total proctocolectomy with Brooke ileostomy, the intra-abdominal Koch pouch and restorative

proctocolectomy with ileal pouch-anal anastomosis.

Elective colectomy cures ulcerative colitis and has a very low mortality rate (less than 1%). The procedure should almost always be a total colectomy with ileostomy or one of two internal ileal pouch alternatives. The Brooke ileostomy (standard) is a half-dollar–sized segment of terminal ileum that protrudes and is spouted from the right lower quadrant of the abdomen. The patient attaches a double-faced adhesive ring to the skin and then to an opaque sack (which can be emptied) that collects the 750-1000 ml of material that the ileum produces daily. Ostomy societies can be very helpful in adjusting to the inconvenience and psychological issues of an ileostomy. The Koch pouch (continent) ileostomy is an alternative to the Brooke ileostomy. An internal reservoir is created from reshaped ileum with a nickel-sized nipple valve opening onto the lower abdominal wall. The patient catheterizes the pouch through a nipple valve to remove ileal contents. The main disadvantage of this approach is that the valve may become incontinent within 2–5 years in 25–30% of patients, necessitating surgical repair.

The most popular ileostomy alternative is the ileal pouch-anal anastomosis. The surgery involves creation of a new rectum from the small bowel and attaching the pouch of ileum to the anal canal. The pouch-anal anastomosis may be performed using a hand-sewn or stapled technique.

In patients with persistent disease activity or the development of dysplasia or cancer, a mucosectomy (stripping) may be performed before the anastomosis. Those who do not advocate anal stripping believe that preservation of a few centimeters of rectal mucosa produces better functional results. In the patient with fulminant colitis, the colon may be removed first, leaving the creation of the pouch, restoration and the removal of the rectum for a time when the patient has recovered from the colitis and is in better nutritional condition. This is a three-stage procedure, as a temporary ileostomy is made above the pelvic pouch to allow healing.

In patients with more chronic and stable disease, the procedure may be performed in two stages (with a temporary ileostomy). Select patients are candidates for a restorative proctocolectomy performed in a single step. After a temporary protective ileostomy is closed, patients can defecate through their anus. After one year, most patients have five bowel movements per day. Incontinence is uncommon, although some patients experience nocturnal soiling. Although pouchitis is a complication in 25% of patients, the ileoanal pouch is an acceptable and successful alternative to standard ileostomy.

Complications

The complications of ulcerative colitis can be divided into those that affect the colon and those that are extracolonic.

Toxic Megacolon

The most feared complication of ulcerative colitis is the development of toxic megacolon. It occurs as a result of extension of the inflammation beyond the submucosa into the muscularis, causing loss of contractility and ultimately resulting in a dilated colon. Dilation of the colon is associated with a worsening of the clinical condition and development of fever and prostration. This diagnosis is based on radiographic evidence of colonic distention in addition to at least three of the four following conditions: fever higher than 38.6ºC, neutrophil leukocytosis greater than 10,500 cells/mm^3, heart rate greater than 120 beats/minute and/or anemia. At least one sign of toxicity must also be present (dehydration, electrolyte disturbance, hypotension, or mental changes). Physical exam reveals a tender abdomen over the distribution of the colon. There may be rebound tenderness, abdominal distention and hypoactive or absent bowel sounds.

Perforation

Colonic perforations are usually a complication of toxic megacolon. However, perforation can also present in severe ulcerative colitis even in the absence of toxic megacolon. Most perforations occur in the left colon, commonly in the sigmoid colon. Perforations tend to occur more often during the first episodes of colitis. Steroid therapy has been suggested to be a risk factor for colonic perforation, but this is controversial. Surgical management is indicated for perforation. X-rays of the abdomen reveal colonic dilation, usually maximal in the transverse colon, which tends to exceed 6 cm in diameter. Segments of the right and left colon may also be dilated. Serial plain abdominal x-rays of the abdomen taken at 12–24-hour intervals are useful in following the clinical course. The goal of medical therapy is to reduce the likelihood of perforation and to return the colon to normal motor activity.

The patient should have nothing by mouth. A nasogastric tube is placed in the stomach for suction and decompression of the upper gastrointestinal tract. The use of the rolling technique, during which the patient lies on the abdomen for 10–15 minutes every 2 hours while awake, allows for passage of gas and easier decompression of the dilated colon. Intravenous fluids are given to replete water and electrolytes. Broad-spectrum antibiotic coverage is instituted in anticipation of peritonitis resulting from perforation. Intravenous steroids are usually administered in doses equivalent to more than 40 mg of prednisone per day. Close monitoring of the patient's clinical condition is essential and signs of deterioration, such

as increasing abdominal girth, development of rebound tenderness, or hypotension, should prompt immediate action.

Colectomy occurs in about 25% of patients and is required in almost 50% of patients with pancolitis. Surgical intervention is undertaken if the patient does not begin to show signs of improvement during the first 24–48 hours of medical therapy, as the risk of perforation increases markedly. Colectomy with creation of an ileostomy is the standard procedure, although single-stage proctocolectomy is done occasionally. If surgical therapy is performed before there is colonic perforation, the mortality is approximately 2%. In cases in which there has been bowel perforation, however, the mortality risk increases to 44%.[22]

Strictures

Clinically relevant strictures are uncommon in ulcerative colitis. However, some degree of narrowing may be seen in approximately 12% of surgical specimens. Histologically, strictures present with hypertrophy and thickening of the muscularis mucosa without evidence of fibrosis. Strictures tend to occur late in the course of disease, usually 10–20 years after onset of disease. Most strictures occur in the sigmoid and rectum, with an approximate length of 2–3 cm. The most common presenting symptoms are diarrhea and fecal incontinence. Strictures have been associated with malignancy and biopsy of the strictures is warranted. In fact, in patients with long-standing history of ulcerative colitis, a stricture should be considered potentially malignant.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by fibrosing inflammation of extra- and intrahepatic bile ducts. It is frequently associated with ulcerative colitis. Patients may have symptoms of fatigue, pruritis, abdominal pain, fever, or jaundice. This usually appears in men after 10–15 years of very mild, even subclinical, pancolitis, and may necessitate liver transplantation in some patients.[23]

HERBAL THERAPY

`Herbal drugs constitute a major share of all the officially recognized systems of health in India *viz*. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. More than 70% of India's 1.1 billion populations still use these non-allopathic systems of medicine. Currently, there is no separate category of herbal drugs or dietary supplements, as per the Indian Drugs Act. However, there is a vast experiential-evidence base for many of the natural drugs. This offers immense opportunities for Observational Therapeutics and Reverse Pharmacology. Evidence-based herbals are widely used in the diverse systems and manufactured, as per the pharmacopoeial guidelines, by a well-organized industry. Despite of all the advances in modern and orthodox medicine, traditional medicine still plays a significant role in the lives of many people suffering with ulcerative colitus.

A number of medicinal plants such as *Amomum subulatum, Scoparia dulcis, Jasminum grandiflorum, Davilla rugosa, Kielmeyera coriacea, Larrea divaricata, Qualer grandiflora, Mammea Americana, Anacardium occidentale, Ocimum sanctum, Azadirachta indica Acorus calamus, Gingko bioloba, Curcuma longa, Withania somnifera, Polygala tenulfolia, Rheum spp, Melissa officinalis, Salvia lavendulaefolia, Biota orientalis, Celastrus paniculatus, Evodia rutaecarpa, Coptis chinensis, Crocus sativus, Hypericum perforatum, Rosa Alba, Tinospora Cordifolia, Zingiber Officinale, Sesamum Indicum, Emblica Officinalis, Panax Ginseng, Lipidium Meyenii, Commiphora whighitti and Ilex Paraguariensis.*

Amomum subulatum

Amomum subulatum Roxb. (Large cardamom) commonly used as a spice. Methanolic extract of fruits of large cardamom shows antiulcer activity.[24] This extract again fractionized successively by petroleum ether (60-80), ethyl acetate and finally with methanol. Essential oil obtained from the dried fruits of *Amomum subulatum* by steam distillation process. Antiulcerogenic activity of those fractions like petrol soluble fraction, ethyl acetate soluble fraction, methanol soluble fraction, methanol insoluble fraction and essential oil investigated. Ethanol reduces the secretion of bicarbonates and production of mucus results ulcer in gastric mucosa.[25]

Total methnolic fraction (860, 1720 mg/kg), petrol soluble fraction (262 mg/kg), ethyl acetate soluble fraction (196 mg/kg), methanol insoluble fraction (790 mg/kg) and essential oil (200 mg/kg) produce significant ulcer protection against ethanol induced ulcer but methanol soluble fraction (465 mg/kg) found ineffective. Petrol soluble, ethyl acetate soluble, methanol insoluble fraction also found to increase gastric wall mucus in ethanol induced ulcer. Antiulcereffect may be due to cytoprotective and strengthening effect on gastric mucosa. Ethyl acetate soluble fraction produce highest activity and shows presence of phenolic compound. Thus phenolic compounds (flavanones, aurones or anthocyanins) present in this fraction, may be responsible for gastroprotection effect. Total methanolic extract of the fruit does not show any significant ulcer protection against aspirin induced ulcer. Aspirin causes ulcer by inhibition of cyclooxygenase pathway of arachidonic acid metabolism results overproduction of leukotriene and other products of 5-lipoxygenase pathway.[26] So total methanolic extract may did not produce any effect on cyclooxygenase pathway. Histamine may be involved in the formation of pylorus ligated ulcers. No fraction found significantly effective against pylorus ligated ulcer. So ulcer protective effect of

fraction is involved in direct protective effect of on gastric mucosa.

Scoparia dulcis

Freeze-dried aqueous extract of the aerial parts of *Scoparia dulcis L.* produced reduction gastric hypersecretion and ulcer in rodents.[27] Aqueous freeze-dried extract of *Scoparia dulcis* mixed up with water and extracted with n-butanol. The antiulcerogenic activity of the resulting aqueous phase and butanolic phase which is flavonoid-rich were also investigated. Pre-treatment with the aqueous extract of *Scoparia dulcis* (0.5-1 g/kg, p.o.) produce significant reduction in ulcer in dose dependent manner against indomethacin and ethanol induced ulcer. Aqueous extract and flavonoid-rich fraction produce antiulcer effect by decreasing volume of gastric juice, total acidity and by increases in pH in pylorus ligated induced ulcer. But the water phase was found inactive.

Flavonoid-rich fraction found 4-8 times more active than the aqueous extract in the pylorus ligature model. Both histamine and bethanechol stimulated gastric acid secretion but potently inhibited by aqueous extract of *Scoparia dulcis.* So it may due to blockade or inhibition of a common target in the cascade of events that leads to gastric acid secretion such as the H + K + ATPase. Flavonoid-rich fraction inhibit H + K + ATPase, it (0.01-1 mg/ml) prevented the hydrolysis of Mg + -ATP by the isolated rabbit gastric H + K + ATPase with IC 50 = 500 µg/ml. Cirsitakaoside and quercetin active principle of flavonoid-rich fraction produces inhibition of the gastric H + K + ATPase activity *in vitro*.[28],[29] Inhibition of gastric secretion by the aqueous extract of *Scoparia dulcis* may be due to the inhibition of the H + K + ATPase enzyme.

Jasminum grandiflorum

Jasminum grandiflorum L. is a folk medicine. Antiulcer activity of *Jasminum grandiflorum L.* was investigated using 70% ethanolic extract of leaves. It also produces *in vitro* antioxidant activity.[30] Ethanolic extract of leaves produces antisecretory activity which is observed by the significant (P<0.01) reduction of the gastric juice volume, free acidity and total acidity and increase in gastric juice pH when compared to ulcer control in aspirin plus pylorus ligation- induced ulcer model. Extract also produce significant (P<0.01) reduction in ulcer index in ethanol induced ulcer may be due to its antioxidant activity. In acetic acid induced chronic ulcer model gastric lesions occur due to the release of histamine, which increases the capillary permeability and back diffusion of hydrochloric acid (HCl). Pretreatment with the extract showed complete regeneration of mucosal glandular structure. Thus antisecretory and antioxidant activities of the extract may responsible for its antiulcer activity.

Davilla rugosa

Davilla rugosa Poiret is a commonly used Brazilian folk medicine. Antiulcer action of the fractions of the hydroalcoholic extract of *D. rugosa* stems was studied in rats.[31] These extracts were shown to protect rats from developing gastric ulcers. Further, the daily oral dose of 800 mg/kg of the extract for 30 consecutive days was reported to pro-duce no toxic effects.

Kielmeyera coriacea

Kielmeyera coriacea Mart. is a Brazilian cerrado plant belonging to family Guttiferae and is popularly known as "Pau Santo". Xanthone, triterpenes and a biphenyl from *Kielmeyera coriacea* had shown antifungal activity against cladosporium cucumorinum and candida albicans.[32] Oral administration of 30mg/kg of *Kielmeyera coriacea* showed significant antiulcer activity in ethanol-acid and indomethacin models but not in acute stress model suggesting a direct protective effect of *Kielmeyera coriacea* on gastric mucosa and increased resistance to necrotizing agents.[33]

Ethanol-acid causes gastric mucosal ulcers either by a direct effect on gastric epithelium, or are modulated indirectly by release of vasoactive products from mast cells[34], resulting in release of mediators such as histamine.[35] Endogenous histamine formation and its release from mast cells in gastric mucosa have also been implicated in pathogenesis of gastric ulcers produced by acute stress.[36] Indomethacin induces gastric ulceration by inhibition of prostaglandin biosynthesis which is known to play important role in maintaining mucosal integrity. The exact mechanism underlying the protective action of extract against ethanol and indomethacin induced gastric lesions are yet to be investigated.

Larrea divaricata

Anti-ulcerogenic effect of the methanolic extract of *Larrea divaricata* Cav. leaves was investigated against absolute ethanol and 0.6N HCl induced ulcer in rats.[37] Dose dependent ulcer protection found in case of pretreatment with the extract. Extract inhibit ulcer by 97% and 100% against 0.6N HCl induced ulcer at a dose of 300 mg/kg and 400 mg/kg and produce 96%, 96% ulcer protection in ethanol induced ulcer at a dose of 300 mg/kg and 400 mg/kg. Effect of extract on blocking endogenous sulfhydryl (SH) groups with *N*-ethylmaleimide was also studied in ethanol induced ulcer animals. Because ethanol produce of free radicals and decrease of the levels of nonprotein SH compounds in the gastric mucosa leads gastric ulcer. But antiulcer effect of extract was not decreased when endogenous SH groups were blocked by *N*-ethylmaleimide. Thus, SH groups are not involved in the anti-ulcerogenic activity of the *Larrea divaricata. In vitro* antioxidant activity of the extract also studied using 1,1diphenyl-2-picrylhydrazyl (DPPH) test method. So, antiulcerogenic activity of methanolic extract of *Larrea divaricata may* due to its antioxidant activity.

Qualer grandiflora

Qualer grandiflora Mart (Vochysiaceae), popularly known as "Pau terra" is native to Brazilian cerrado.

Antiulcer activity of hydroalcoholic extract of bark of *Qualer grandiflora* (500mg/kg) was evaluated.[38] It exhibited decrease in ulcer index induced by HCl/ethanol solution indomethacin / bethanechol and stress in mice. It is well reported that the suppression of prostaglandin synthesis by NSAIDs (indomethacin) results in increased susceptibility to mucosal injury and gastroduodenal ulceration.[39] Cholinomimetic agents (bethanechol) administered in association with NSAIDs have a synergistic effect on gastric injury induced by increased secretion of acid and pepsin in the stomach.[40],[41] In pylorus ligated model, results suggested that Qualer grandiflora (p.o) reduced the severity of gastric lesion only without effect on pH, gastric acidity or volume. Furthermore, phytochemical investigation of Qualer grandiflora hydroalcoholic bark extract suggested probable involvement of terpene, steroid, saponin, phenolic compound and tannin for aforementioned activities.[42]

Anacardium occidentale

Antiulcerogenic effect of a 70% ethanolic extract of cashew *(Anacardium occidentale* L.) leaves was investigated against HCl/ethanol induced ulcer and found that extract inhibit gastric lesions significantly in dose dependent manner.[43] Freeze-dried hydroethanolic extract was washed with petroleum ether first and then extracted with dichloromethane and methanol. The dichloromethane (3.92 mg/kg) and methanol fractions (257.12 mg/kg) considered as 400 mg/kg of hydroethanolic extract and were tested for their anti-ulcer activity. Methanol fractions produce significant ulcer protection but dichloromethane fraction did not produce ulcer protection against HCl/ethanol induced ulcer. Anti *H. pylori* effect of fruits of cashew also investigated.[44] Phytochemical investigation shows the presence of various flavonoids, mainly quercetin glycosides and saponins in ethanol extract. Flavonoid are free radical scavengers, plays important role in gastric ulcer also an increase mucosal prostaglandin content and decrease in histamine secretion from mast cells by the inhibition of histidine descarboxylase.[45] Quercetin was also found to prevent gastric mucosal lesions.[46] Various saponins also found to possess antiulcer activity.[47],[48] Since methanol is a bad solvent for tannins so the active component of the methanolic fraction is a substance other than tannin. Therefore, flvanoids and saponin are mainly responsible for antiulcer activity of *Anacardium occidentale.*

Ocimum sanctum

Ocimum sanctum, popularly known as Tulsi in Hindi, is a sacred plant that belongs to the family *Labiatae*. *Ocimum sanctum* contains a number of chemical constituents that interact in a complex way to elicit their pharmacodynamic responses. *Ocimum sanctum* is highly effective in a wide spectrum of diseases and reported to possess anticarcinogenic, anthelmintic, antiseptic, antirheumatic, antistress and antibacterial properties.[49] Clinical trials have reported the usefulness of *Ocimum sanctum* in heart diseases[50] and diabetes.[51] *Ocimum sanctum* also possess anti-inflammatory and immunomodulatory properties, attributed to its potential to inhibit cyclooxygenase and lymphokines.[52] The fixed oil obtained from *Ocimum sanctum* L. showed significant antiulcer activity against aspirin, indomethacin, alcohol, histamine, reserpine, serotonin and stress induced ulceration in rats.

Azadirachta indica

Azadirachta indica A. Juss, commonly known as "Neem," has been extensively used in India as an ayurvedic medicine for the treatment of various diseases, such as, leprosy, intestinal helminthiasis and respiratory disorders in children.[53] Antiulcer and cytoprotective potential of *Azadirachta indica* (neem) stem bark extract was evaluated in albino rats. *A. indica* significantly inhibited gastric ulceration induced by indomethacin. This action was accompanied by a dose-dependent decrease in total gastric acidity. It was proposed that *A. indica probably* act via histamine H2 receptor.

CONCLUSION

From this study we can conclude that studies with new active principles obtained from plant sources can results in novel and effective pattern of treatment. Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Many medicinal plants have shown significant activity. These plants provide leads to find therapeutically useful compounds, thus more efforts should be made towards isolation and characterization of the active principles and their structure activity relationship. The combination of traditional and modern knowledge can produce better drugs for the treatment of ulcerative colitis with fewer side effects.

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