The article was received on March 16, 2021, and accepted for publishing on August 22, 2021.

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Immunopathogenesis and treatment of ulcerative colitis: from modern medicine to herbal medicines

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Abstract: *Ulcerative colitis is one of the idiopathic inflammatory diseases of the large intestine with an unknown cause, which occurs in recurrent attacks of inflammation in the lining of the mucosa and below the intestinal mucosa. Impaired mucosal immune responses, the involvement of inflammatory cytokines such as IL-1, TNF-α, and IL-6, and other inflammatory mediators such as arachidonic acid metabolites play an important role in the immunopathogenesis of ulcerative colitis. Based on medical findings on the pathogenesis of the disease, new therapies have focused on the responses of the intestinal immune system and the inflammatory process. However, the widespread use of treatments such as aminosalicylates and corticosteroids continues. Most of these drugs have severe side effects. Some patients do not respond well to these treatments and sometimes have to undergo surgery and colectomy. Therefore, extensive studies are being conducted to control and prevent disease to use natural treatment methods such as the use of antioxidants with the approach of removing free radicals that prevent the destruction of cells and tissues in the body. Today, various studies have pointed to the effects of herbal medicines as a complementary treatment in inflammatory diseases. Their low cost and high effectiveness have attracted the attention of researchers in this field. The aim of the present study is a comprehensive review of modern and traditional treatments based on herbal medicines in the field of ulcerative colitis.*

Keywords: *inflammatory bowel disease, ulcerative colitis, immunopathogenesis, modern medicine, herbal medicine*

INTRODUCTION

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by uncontrolled inflammation of the large intestine and rectum. The prevalence of UC has increased in the last two decades [1]. Due to the unknown causes of the disease, the high risk of recurrence, and the poor prognosis, UC has become a clinical challenge in terms of treatment. One of the prominent features of this disease is excretion in the form of bloody diarrhea. The disease is characterized by periods of recovery and relapse that may occur spontaneously or in response to treatment [2]. However, conventional therapies for UC treatment, in addition to being successful and preventing recurrence, may lead to a variety of side effects [3]. UC is characterized by innate immune responses. Neutrophils, the first line of innate immune cells, are responsible for intestinal tissue damage by releasing large amounts of toxic components and free radicals during stimulation during UC progression [4, 5]. Meanwhile, the response of type 2 T (Th) helper cells, including over-activity of normal T cells and non-classical killer cells and Th2 cells, and significant production of cytokines, e.g. IL-5 and IL-3, have been reported in the pathogenesis of UC. Higher cytokine levels have been reported in patients with UC, including IL-5, IL-13, and other

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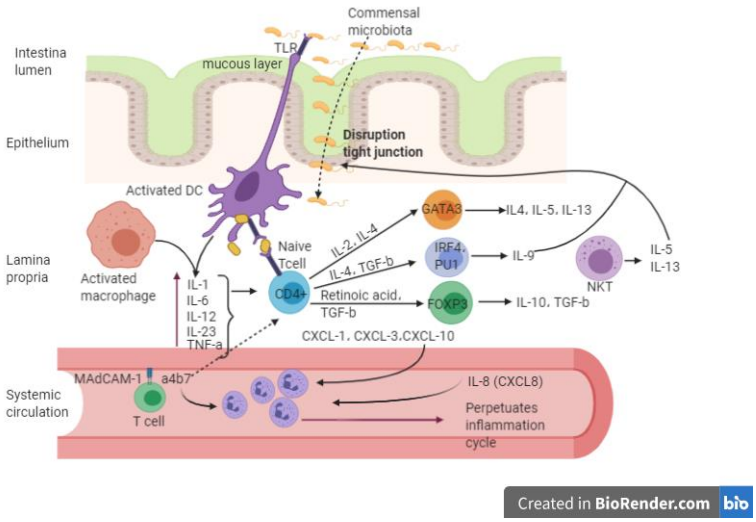
proinflammatory cytokines such as tumor necrosis factor (TNF) (Figure 1).

Figure 1: Cytokines involved in ulcerative colitis.



After the release of immune cells, cytokines act to stimulate immune responses further, induce epithelial cell apoptosis, and regulate expression (claudin-2), here as damage to the epithelial barrier leading to disruption of the epithelial barrier. They become tightly connected to the intestinal epithelial cells [6-8]. Nuclear factor-kappa B (NF-κB) is a transcription factor responsible for the expression of a variety of genres, for example, TNF-α, in response to extracellular inflammatory stimuli [9]. Because high levels of TNF have been reported in the blood [10], fecal samples [11], and mucosa [12] of patients with active UC, it is widely accepted that NF-κB plays a pivotal role in UC progression. The association of NF-κB inhibition in IBD has been further demonstrated by the experimental treatment of colitis with an anti-NF-κB oligonucleotide that improves inflammation in the colon [13]. Infiltration of neutrophils and macrophages into the mucosal tissue of the colon is an important feature of ulcerative colitis. Activated neutrophils in the intestinal mucosa produce and secrete reactive oxygen species, including superoxide ions, hydroxide radicals, and hydrogen peroxide [14]. These factors cause lipid peroxidation, increase the permeability of mucosa and blood vessels, increase the entry of neutrophils into the mucosal tissue, and the development of inflammation [15]. Reactive oxygen species damage the intestinal wall, cause ulceration, bleeding, and diarrhea by affecting cytokine genes and enzymes involved in the inflammatory response. Oxidative stress also reduces antioxidant factors as a result of increasing disease severity [16, 17]. On the other hand, patients with ulcerative colitis are at risk for colon cancer for two reasons: lack of inflammation control and drugs such as anti-tumor necrosis alpha. The risk of cancer in these patients begins to increase after 8-10 years and increases by half to one percent per year [18-21]. For this reason, research is ongoing to find effective treatment with few side effects. The use of antioxidants can be effective in controlling the disease and preventing its recurrence. Antioxidant compounds can prevent cell damage by neutralizing free radicals [22]. Herbal medicine has been used for centuries as one of the most traditional medicine methods and clinical treatment of many diseases such as infections and functional disorders. Recently, the potential effect of herbs has been suggested as a UC treatment. But drugs such as aminosalicylates, corticosteroids, and immunosuppressants continue to be widely used. Amino salicylates are administered orally or topically (suppository and enema) and are safe and effective drugs and are always one of the first treatment options in the treatment of patients with mild to moderate forms of the disease and also for persistence. They are used to relieve symptoms. Corticosteroids are one of the most common therapy inactive diseases. These drugs can be given topically, orally, or intravenously. They have a great effect on active disease control but are not suitable for reducing symptoms in the long run (or maintenance treatment). Immune-suppressing drugs or immunosuppressants are also used to treat colitis. These drugs reduce inflammation but do so by suppressing the immune system response (which initiates inflammation) [23]. However, there is a constant effort to find better drugs. The aim of this study is a comprehensive review of modern

and traditional therapies based on medicinal plants in the field of ulcerative colitis.

DISCUSSIONS

Modern medicine in the treatment of ulcerative colitis

As mentioned, the etiology of inflammatory bowel disease is unknown. Still, the influence of genetic predisposition, environmental factors, and immune system on each other has been evaluated, and the use of corticosteroid anti-inflammatory drugs, aminosalicylates, antibiotics, immunomodulators, and biological materials. They are effective methods in the treatment of ulcerative colitis [24]. Most of these drugs have severe side effects, including diarrhea, vomiting, fever, rash, growth retardation, anemia, and osteopenia, increased risk of infection, liver disorders, kidney disorders, pancreatitis, and gastrointestinal ulcers. Also, besides not all patients respond ideally to these therapies, and sometimes there is no choice but surgery and colectomy [25]. Prevention of colectomy, prevention of disease complications and death; and controlling inflammation with the least side effects of drugs are some of the important goals in treating ulcerative colitis [26]. In this part of the article, we describe modern medicine in the control and treatment of ulcerative colitis.

Amino salicylates

Amino salicylates have always been one of the first drug choices in treating patients with mild to moderate disease activity.

Sulfasalazine

Sulfasalazine is a combination of an antibacterial agent (sulfapyridine) and a salicylate (5-aminosalicylic acid). It was originally designed to treat rheumatoid arthritis and was first introduced in 1942 as a drug to treat inflammatory bowel disease (IBD). The effective therapeutic agent in treating IBD is 5-aminosalicylic acid and sulfapyridine is the only inactive carrier that allows this effective substance to be released in the colon. Despite the relative absorption of this drug in the small intestine, approximately 90% of the drug reaches the large intestine. After absorption in the large intestine, 20% of 5-aminosalicylic acid undergoes hepatic acetylation and is excreted in the urine. Approximately 15% of patients treated with sulfasalazine experience significant side effects that necessitate discontinuation of the drug [27-29].

Pentasa

One of the most common products is mesalazine, which contains micro granules coated with ethyl cellulose. The release of mesalazine in this product starts from the duodenum it continues throughout the small intestine and colon so that 50% of the 5-aminosalicylic acid of this product is released in the small intestine [28, 30]. Pentasa is a type of mesalazine released at the end of the ileum and colon, in a pH-dependent manner. The release of 5-aminosalicylic acid in this product, which occurs in the small intestine (release at pH above 7), is about 15-30% [28-32].

Closal

Used to treat active disease, it contains the 5-aminosalicylic acid molecule, which is attached to a benzoic acid derivative by azo. In the colon environment, 5-aminosalicylic acid is released by the bacterial enzyme reaction. Like sulfasalazine, almost the entire drug is transported intact to the colon, and its metabolites are rapidly excreted in the urine [33, 34].

Corticosteroids

Corticosteroids are one of the most common therapy inactive diseases. Prednisolone at a daily dose of 40 to 60 mg effectively treats severe to moderate disease the use of such systemic steroids should be limited to severe and refractory cases. Studies have shown that long-term use of corticosteroids does not affect the treatment of this disease. Although no study has directly compared the therapeutic effect of oral corticosteroids with injectable therapy, the injectable form is commonly used in more severe cases. Importantly, corticosteroids are not effective in maintaining improvement in ulcerative colitis, in addition to the side effects associated with corticosteroid use [35, 36].

Budesonide

Initially used to treat asthma and allergic rhinitis, it is structurally different from prednisolone. This structural difference has resulted in more local anti-inflammatory activity and a higher affinity for receptors than prednisolone. Budesonide has a metabolism of about 90% in the first hepatic passage. This low systemic bioavailability reduces the toxicity of the drug. The effect of oral budesonide in treating endoscopic findings similar to prednisolone has been reported [37, 38].

Antibiotics

Bacterial flora plays an important role in the pathogenesis of inflammatory bowel disease. In the case of infectious complications of inflammatory bowel disease, antibiotics have a therapeutic role in cases where the disease is active. But unlike Crohn's disease, these drugs are not very effective in treating an active disease or maintaining recovery in patients with ulcerative colitis [39, 40].

Immune-regulating drugs

The use of these drugs in the clinic for patients with inflammatory bowel disease is mainly due to the following reasons: 1 - Chronic active disease; 2 - Steroid-dependent disease; 3 - Long-term maintenance of disease recovery after treatment with biological agents; 4 - Prevention of the immune response to biological agents. Patients treated episodically with infliximab show a greater immune response to these agents, and concomitant use of immunomodulatory drugs reduces the immune response to Infliximab [41, 42].

Methotrexate

It is a folic acid antagonist that has anti-metabolic and anti-inflammatory activity. It is used in patients with Crohn's disease. Intramuscular injection of MTX at a weekly dose of 25 mg for 16 weeks is effective in patients with active Crohn's disease. A controlled study reported that a low oral dose of MTX of 12.5 mg per week was not effective in treating active ulcerative colitis. However, no controlled studies have been performed on the role of subcutaneous or intramuscular MTX in the active disease of ulcerative colitis [43, 44].

Cyclosporine A

This drug has been considered due to its immunomodulatory properties and therapeutic effect in patients with inflammatory bowel disease. Cyclosporine A may be appropriate in severe, fulminant, as well as steroid-resistant cases. For example, continuous infusion of cyclosporine can be effective in patients with severe colitis who have not responded to steroid therapy after 7 to 10 days. In one study, 82% of patients with active disease who did not respond to steroid therapy responded to intravenous cyclosporine-4 therapy. After six months of follow-up, 44% of respondents eventually underwent colectomy despite continuing maintenance treatment with oral CYA (45, 40). It seems that immunomodulators' use is effective in avoiding colectomy after induction of recovery by cyclosporine [45].

Immunosuppressive

Immunosuppressive drugs are commonly used when treatment with aminosalicylates and steroids is not effective or when steroids cannot be stopped to reduce inflammation without reactivating the symptoms and relapse. If the patient is dependent on treatment with steroid drugs, this method can be considered to receive immunosuppressive drugs, and then, slowly reduce or even stop using steroids without recurrence of inflammation. Slowly, for this reason, immunosuppressive drugs are sometimes called "steroid-sparing" drugs. In this group, azathioprine (Imuran, 2 to 2.5 mg/kg per day) and its active metabolite (6-mercaptopurine 6-MP); (1 to 1.5 mg/kg per day) as well as methotrexate and cyclosporine. Azathioprine and 6-mercaptopurine are effective treatments for persistent remission in both Crohn's disease and ulcerative colitis. Although their onset is slow (months), they are generally uncomplicated and well-tolerated. Other treatment regimens include intramuscular methotrexate to induce remission (15-25 mg weekly) and persistence remission (15-25 mg per week) in active Crohn's disease, as well as intravenous cyclosporine (2-4 mg/kg daily). Title Facilitators for severe ulcerative colitis are steroid-resistant. Due to the possibility of short-term or long-term side effects, and the need for careful follow-up, patients who need these drugs should be treated by a gastroenterologist [46].

Biological therapies

Recent advances in medical knowledge regarding the pathogenesis of inflammatory bowel disease have led to the introduction of new therapies that target specific aspects of the immune system and inflammatory processes in inflammatory bowel disease. One of these included in clinical therapy is treatment with anti-TNF-α. This cytokine drug is a key factor in the pathogenesis of inflammatory bowel disease. To date, only Infliximab (Remicade®), Certolizumab (Cimzia®), and Adalimumab have been shown to have a significant effect on inflammatory bowel disease. Recent data have shown that Infliximab is effective in inducing and maintaining recovery and the gradual reduction of steroids in patients with ulcerative colitis It should be noted that due to the increased risk of infection in patients using these drugs, examination of infectious foci such as chest mammography test before starting treatment is necessary [47-49].

Traditional medicine with a focus on herbs in the treatment of ulcerative colitis

Different types of herbs are used to control inflammation or reduce the symptoms of colitis. The herbal medicine includes a wide range of therapies within and outside the realm of modern medicine. However, the effectiveness of medicinal plants has limited evidence. Potential benefits of medicinal plants include high acceptance of these drugs by patients, good efficacy, relative safety, ease of use, and relatively low cost.

The effect of herbs on hundreds of people has been tested in ulcerative colitis. However, it seems that all over the world, herbal medicine has been widely used to treat and control the disease. In this part of the article, we will discuss some studies on medicinal plants concerning the control and treatment of ulcerative colitis.

Aloe vera

Aloe vera is a tropical plant used in traditional medicine around the world. Aloe vera has anti-inflammatory activity and has been used by some doctors for patients with UC. Aloe vera gel is widely used orally by patients with inflammatory bowel disease and is undergoing therapeutic evaluations for this disease [50]. This study aimed to investigate the effects of aloe vera in vitro on the production of active oxygen metabolites, eicosanoids, and interleukin-8, all of which can be pathogenic in inflammatory bowel disease. The antioxidant activity of aloe vera in free cell systems, radical generator, and luminescence was evaluated in a colorectal mucosal biopsy sample. The production of eicosanoids was measured by sampling and measuring interleukin eight by Caco-2 epithelial cells in the presence of Aloe vera by enzyme-linked ELISA. The study's findings showed that aloe vera gel had a dose-dependent inhibitory effect on the production of reactive oxygen metabolites. Aloe vera inhibited the production of prostaglandin E2 but so far had no effect on the production of B2 thrombosis and also reduced the release of interleukin-8 by Caco-2 cells. The results of this study show the anti-inflammatory effects of aloe vera gel in vitro and confirm that aloe vera gel can have favorable therapeutic effects in the treatment of inflammatory bowel disease [51]. In another study aimed at investigating the effect of aqueous extract of aloe vera gel on gastric acid secretion and colonic histopathology in the model of induction of acute ulcerative colitis by acetic acid enema on 32 Wistar rats (200-250 g); The animals were randomly divided into four groups: healthy group, acetic acid-induced colitis group, aloe vera treatment group (for eight days) and sulfasalazine treatment group. After ether anesthesia, the animals were induced with acute colitis using acetic acid. After treatment, colon biopsies were removed from the distal 10 cm section for histopathological studies. The scoring system (Bita 2012) was used to compare histopathological features quantitatively. Stomach acid concentration was measured by the titration method. The results were considered as the mean and standard deviation of expression, and $P < 0.05$ was significant. The results showed that treatment with an aqueous extract of aloe vera did not reduce gastric acid. Histological results showed an inflammatory response in the ulcerative colitis group. Aloe vera extract reduced the severity of histopathological symptoms of ulcerative colitis, although it was less effective than sulfasalazine. Thus, it can be concluded that according to the improving effects of this extract, it seems that this plant can be used to eliminate colon disorders. However, further studies are needed to determine the effective dose of this plant in reducing gastric acid secretion [52].

Jujube

Jujube (Ziziphus Vulgaris Lam) has been known as a medicinal plant in East Asian countries since ancient times. It is used in traditional medicine in these areas to treat diseases such as liver disorders, anemia, shortness of breath, vomiting, and cardiovascular diseases. Hypertension and gastrointestinal disorders are used [53, 54]. Phytochemical studies on different jujube species have shown the presence of compounds such as cyclopeptide alkaloids, flavonoids, sterols, tannins, and Triterpenoid saponins, and the key role of these compounds in scavenging radicals and proven, free. Numerous effects, such as antioxidant and anti-inflammatory effects have been attributed to this plant [55]. In a study by Yue et al. (2015) on the protective effects of jujube on inflammatory bowel disease, they induced colitis by injecting TNBS (Trinitrobenzene sulfonic acid) into the rat colon and found that jujube polysaccharides They significantly reduced the severity of colitis, which was characterized by less weight loss, decreased score of disease activity index, and improved mucosal damage in rat colitis. Jujube polysaccharides also inhibit inflammatory responses and reduce tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 IL-6), and myeloperoxidase (MPO) activity in rat colitis. They also found that by examining tight junction proteins, jujube improves intestinal wall activity, thus protecting against inflammatory bowel disease by enhancing intestinal wall function [56]. In a study conducted by Karawya et al. (2016), regarding the effects of jujube on acetic acid-induced colitis, they concluded that increased levels of myeloperoxidase and caspase-3 are associated with changes in the crypts and destruction of goblet cells. By administering jujube extract, a significant decrease in myeloperoxidase and caspase three was observed compared to the control group. Jujube extract was also found to act as a treatment for acetic-acid-induced colitis in rats [57].

Turmeric

Turmeric is known by its scientific name (Curcuma longa). Curcumin is the active ingredient in the rhizome of the turmeric plant with the chemical name (diferuloylmethane). In addition to Curcumin, it contains several chemical compounds, including volatile oils, zinc, aqueous acids, and aqueous acids, oats, oats, and oranges in the yolk sac [58-60]. In traditional medicine, turmeric is known as anti-flatulence, and its consumption with food improves digestion and reduces bloating. Also, its effect on stimulating and producing bile and thus digesting fats improves digestion. Therefore, this substance in people with chronic gastrointestinal disorders and people who feel tired and bloated after eating is recommended. In laboratory studies,

oral administration of aqueous and methanolic turmeric extract to rabbits significantly reduces gastric acid secretion and Ingredients of gastric juice, Oral administration of turmeric methanolic extract reduces gastric juice secretion. It prevents damage caused by histamine, indomethacin, rasping, mercaptamine, methanol, hydrochloric acid, sodium hydroxide, and sodium chloride on the stomach and duodenum [61-63]. In one study, administration of 300 mg of turmeric twice daily to patients with duodenal ulcers showed that after four weeks, about 50% of patients recovered. After 8 and 12 weeks, all patients achieved complete recovery without any side effects [64]. Also, in a study performed on 98 patients with ulcerative colitis, the effect of this herbal product at a dose of 2 grams per day in the treatment and prevention of recurrence of the disease was significantly better than placebo. In another clinical study performed on ten patients with gastric ulcers, administration of 1 gram of turmeric per day accelerated wound healing and reduced gastric pain [65].

Curcumin

In a study to determine the therapeutic effect of Curcumin on ulcerative colitis caused by sodium dextran sulfate (DSS) and discover the relevant mechanism, 60 mice were randomly divided into 6 groups. A was the normal control group, B was the model group, and group C was the 1.5 mg/kg dexamethasone group. Groups D, E, and F received 15, 30, and 60 mg/kg of Curcumin, respectively. Mice were killed seven days after treatment. The expression of TNF-α and MPO in colon tissue was determined by ELISA and the expression of P38MAPK mRNA and P.P38MAPK was evaluated by immunohistochemistry and RT-PCR. The results obtained in groups F, D, C, E, TNF-a, and MPO levels decreased significantly. P38MAPK mRNA expression was decreased in groups F, E, C, D, and there was a significant difference between E and F. As a result, Curcumin has therapeutic effects, which play an important role in the treatment of UC by inhibiting the P38MAPK pathway and thus reduce TNF-α. Because there is a risk of recurrence and cancer in UC patients and Curcumin has beneficial effects in preventing cancer, Curcumin can prevent cancer. It should also be noted that Curcumin is inexpensive and has no specific side effects, and can lead to a new generation of anticancer drugs [66].

Silymarin

Silybum is a flavonoid compound extracted from the sage plant. This plant is an annual or biennial of the chicory family distributed in Europe and some parts of the United States and Iran [67, 68]. The substance in the seed extract of this plant includes silybin A and B, silibinin, apigenin, dihydrosilibin, dioxycylcysteine, silycrestin, dioxylcydianine, etc. Dried seed extract contains 1 and 4% of silymarin, which contains flavonoids such as silybin A and B, silybinine, silycristine, and dihydroxycylin [69]. This plant has antioxidant and anti-inflammatory properties [70]. Silymarin also acts as a cell membrane stabilizer and cell glutathione enhancer, responsible for detoxification and free radical scavenging in the body. Laboratory data indicate that silymarin stimulates neutrophils and chemo toxic and phagocytic activity. It does not affect. But when neutrophils are stimulated, silymarin prevents the release of myeloperoxidase. Inoculation of neutrophils with silybin prevents the movement of leukocytes (FLMP) [71]. In a double-blind, placebo-controlled trial in patients with alcoholic cirrhosis, treatment with silymarin increased leptin secretion, which induced lymphoblast deformity. Also, the number of T8 cells was reduced, and lymphocytosis was significantly suppressed compared to the control group [72]. In a study to evaluate the effect of silymarin on acetic acid-induced colonic ulcers in mice, 32 adult, Blab/C mice, weighing approximately 36 4 4 g were divided into four groups of 8. The face was intact and without induction of disease, and the control group had an intestinal ulcer (colitis) and was not treated. The wound treatment groups were treated with 40 and 80 mg/kg silymarin. Rats in the treatment group received silymarin daily for 14 days before the onset of the disease and then for one week after the disease´s onset. The drugs were given orally. To make a wound, 1 ml of 4% acetic acid was injected intrarectally. One week after the wound was diagnosed, part of the colon was removed for histological studies, and colonic lesions were examined by the Morty method. Alkaline phosphatase concentration was measured by ELISA. The extent of tissue edema was also assessed. Based on the results, the concentration of alkaline phosphatase enzyme in the wound group showed a significant increase ($P < 0.05$) compared to the control group. In contrast, in the silymarin groups, this increase was significant (0.05). $P < 0$) was controlled compared to the colitis group. As a result, it can be said that the use of silymarin can be considered as a proposed method in the treatment of disease [73].

Chamomile

Chamomile, with the scientific name of Matricaria chamomilla, is an annual, fragrant plant with a height of 20 to 40 cm that goes by car on farms and roadsides. The plant is now widely distributed in Europe, West Asia, North Africa, North and South America, and Australia. Chamomile is one of the oldest medicinal plants known to man, and its use dates back to ancient Greece [74]. In to investigate the effect of aqueous this plant in the animal model of colitis induction

by acetic acid, five groups of 7 adult male NMRI rats in the weight range of 280-230 g were tested. Three groups received different doses of aqueous extract of chamomile (30 mg/kg, 20, 10), and the fourth group received the solvent orally. The last group was considered the control group. To induce colitis, rats were kept on an empty stomach for 36 hours and then subjected to mild anesthesia with ether.

2 ml of 4% acetic acid was injected into the colon. Twenty-four hours later, macroscopic observations of the stool showed signs of colitis. The results showed that in this study an aqueous extract of chamomile at doses of 30 and 20 mg/kg significantly reduced the ratio of weight to colon length. Also, the highest dose of the extract (30 mg/kg) reduced the severity and extent of inflammation. Histopathological studies of the colon showed that the therapeutic effect of chamomile aqueous extract at doses of 30 mg/kg and 20, 10 is more complete with increasing dose. As a result, it can be concluded that aqueous chamomile extract is effective in the treatment of ulcerative colitis in this model and has significantly reduced inflammatory and ulcerative parameters of ulcerative colitis [75].

Ginger

Ginger, which is used as a spice in various parts of the world, is a complementary treatment for some diseases, especially gastrointestinal diseases such as nausea and vomiting, and its anti-inflammatory, antioxidant and anti-ulcer properties have already been proven. It is classified in the Emonographs Valley as a plant with its properties and drug interactions [76]. A study aimed at investigating the effect of ginger as an anti-inflammatory and antioxidant food on quality of life, disease activity and serum levels of some inflammatory factors and oxidative stress in patients with mild to moderately active ulcerative colitis 46 patients with colitis Mild to moderate active took four capsules daily containing 500mg of dried ginger root powder or similar placebo for six weeks with meals. Use of accurate and valid questionnaires and serum levels of total antioxidant capacity (TAC), malondialdehyde (MDA), Tumor necrosis factor α (TNF-α), high sensitivity C-reactive protein, and nuclear factor kappa B (NF-kB) were evaluated before and after the intervention. The results showed that ginger consumption reduced the level of serum MDA factor in the experimental group compared to the placebo group (P = 0.04). Also, Besides TNF-α and disease activity in the ginger group decreased after six weeks of intervention compared to the beginning of the study. There was an increase in urinary incontinence from 1% to 3% (P> 0/05). It was concluded that consumption of 2 g of dried ginger root powder for six weeks reduces oxidative stress in patients with mild to moderately active ulcerative colitis [77].

Turpentine (Pistacia atlantica)

One of the plants used in cancer treatment prescriptions is turpentine. It is known as Bane and grows in the cities of central and western Iran. The scientific name is turpentine (Pistacia atlantica) and from the family Pistachio or Anacardiaceous [78, 79]. This study aimed to evaluate the therapeutic and protective effects of turpentine oleoresin in acetic acid-induced colitis in rats. Turpentine oleoresin dissolved in twine 80 (1% v/v) at doses of 100, 200, and 400 mg Kg was administered orally to animals. In this treatment, three days after induction of colitis, mice were treated for six days. After determining the most effective dose in the treatment, in this method, the animals were treated for six days with the optimal dose of gum. Finally, for microscopic and macroscopic examinations, the animals were anesthetized with ether, and the colon was removed. Based on the results obtained in turpentine oleoresin treatment in a dose-dependent manner, it showed significant effects in inducing recovery in acetic acid-induced colitis in the rats (P <0.05). But in the protective method, no significant difference was observed between the treatment and negative control groups (P> 0.05). The results of this study showed the beneficial anti-inflammatory and wound healing properties of turpentine oleoresin in the treatment of acetic acid-induced colitis in rats [80].

Frankincense (Boswell serrate)

Frankincense extract has been used for many years to treat arthritis, heal wounds and strengthen the female hormonal system. According to previous studies, frankincense can positively affect brain development and possibly the formation of dendrites and axons and improve the relationship between them [81]. Frankincense has been used as an anti-inflammatory, anti-arthritis؛ analgesic in treating diseases related to chronic intestinal diseases, asthma, cerebral edema, and other diseases. Several clinical studies have confirmed their biological activity, and studies that have specifically investigated the mechanism of action of this plant have confirmed their anti-inflammatory and anti-tumor activity. Bosolic-acids are considered the main active ingredient in frankincense and are responsible for its therapeutic effects. In a study aimed at investigating the therapeutic effects of frankincense, based on the results of studies reviewed in this article, frankincense with anti-inflammatory, anti-arthritis, antimicrobial, and analgesic effects and with the least side effects in traditional and modern medicine in the recommended therapeutic doses can be effective in treating many diseases [74]. In vitro, animal studies and models have shown that boswellic acid can inhibit selective 5-lipoxygenase with the effects of inflammation and arthritis [83]. Studies show that Bosolic-

acid derivatives have strong anti-inflammatory properties and do not have the known side effects of steroids. Among these derivatives, AKBA and KBA are the strongest inhibitors of the 5-LOX enzyme with IC IC502.8 and M1.5 In different clinical studies, the efficacy of frankincense extract at a dose of 300 mg 3 times a day has been comparable with sulfasalazine and mesalazine to treat Crohn's disease and colitis [84].In a study of 30 patients with chronic UC, 20 patients were given 900 mg of frankincense gum daily in 3 doses for six weeks, and ten patients were given 3 grams of sulfasalazine daily in 3 doses for six weeks. This study showed that frankincense has beneficial effects on the disease because 14 patients out of 20 patients were directed to recovery and 18 patients out of 20 patients showed improvement in one or more parameters. In the sulfasalazine group, 4 out of 10 patients showed improvement, and 6 out of 10 patients showed improvement in one or more parameters [85]. In animal models, studies have shown that frankincense is effective in the treatment of inflammatory bowel diseases, including colitis and Crohn's disease [86].

Licorice

Licorice (Glycyrrhiza glabra L) is a perennial herb [87]. Licorice root contains various compounds such as flavonoids, sterols, amino acids, starches, essential oils, and saponins. Its major saponin is glycerin or glycyrrhizin [88, 89]. In addition to the above compounds, licorice root contains other compounds such as beta-glucuronosyl-glucuronide, asparagine, goose, sucrose, resin, volatile oils, flavonoid compounds as well as Coumarin compounds [90, 91].

One of the most well-known therapeutic properties of licorice rhizome has been its use in gastric ulcers [92], and its flavonoids are anti-Helicobacter pylori [93]. Licorice derivatives increase the prostaglandins concentration, inhibit gastrin secretion, and increase the lifespan of gastric epithelial cells, thereby healing gastric ulcers [94]. Some studies indicate the effects of some compounds of licorice extract on the gastrointestinal tract.

Evidence has also reported that glycerin in licorice can improve intestinal mucosal inflammation in mice by reducing the expression of NF-κB, TNF-α, and ICAM-1 in inflamed mucosa [95]. Clinical studies on licorice combined with other herbs have shown that licorice can be effective in controlling UC [96]. The anti-estrogenic function of glycerin has been proven to be high in concentration. Glycerin binds to estrogen receptors, thus acting as an antagonist for estrogen. However, estrogenic activity has also been reported for licorice and attributed to its isoflavone compounds [97]. Studies show that glycyrrhizin may inhibit the effect of mineralocorticoids by acting on 11b-hydroxysteroid dehydrogenase. Evidence has shown that glycerin can also suppress plasma renin activity and aldosterone secretion. Also, besides studies have shown that licorice has chemoprotective effects through its effect on Bcl-2 /Bax and is also effective in inhibiting cancer [98, 99].

Ulmus fulva

Ulmus fulva is a plant that can naturally prevent inflammation and help heal damaged and injured gastrointestinal tissue. It also helps to facilitate excretion naturally. Ulmus fulva extract has a beneficial role in maintaining the health of the gastrointestinal tract, especially the stomach. It should also be noted that this plant plays an important role in eliminating nutritional deficiencies and electrolyte imbalances in the body. This effective herbal substance can help control possible anemia by stopping bleeding. This herbal substance is a supplement that is made from the bark of the Ulmus fulva tree and is in powder form. This plant has long been used by Native Americans to treat coughs, diarrhea, and other gastrointestinal ailments. A recent study on slippery elm as a supplement for the treatment of IBD confirmed the antioxidant effects of slippery elm for use in patients with IBD. Research so far has been promising, but the available evidence is insufficient for the widespread use of slippery elm in the treatment of IBD [100,101].

Triticum aestivum

Triticum aestivum is used to treat various gastrointestinal problems. In a study in which Triticum aestivum was used for one month in patients with UC with conventional colitis medications, clinical outcomes improved in 78% of patients. Those who received a placebo improved 30% of clinical outcomes. The dose of Triticum aestivum is initially increased to 20 ml per day and 20 ml per day to a maximum of 100 ml per day. Triticum autism appears to be effective and safe as an adjunct therapy in the treatment of UC [102].

Bromelain

One of these supplements has long been used as a wound healer in traditional medicine, one of which is pineapple [103]. Pineapple contains phytonutrients, vitamin C and Bromelain. Bromelain is derived from the root of the pineapple fruit, and according to laboratory and clinical studies, several properties have been mentioned for it [104, 105]. Human and animal studies demonstrate the beneficial effects of Bromelain in reducing pain, wound healing and burn debridement, as well as its anti-inflammatory, anti-edematous, anticoagulant and cumulative platelet inhibitory properties. The major pharmacological effects of Bromelain

are related to its proteolytic properties [104-106]. Studies have shown that oral Bromelain decreases dose-dependently levels of bradykinin, plasmacins, prostaglandin E2, and thromboxane B2 in patients with inflammation [105, 107]. Bromelain, Bromelain selectively inhibits thromboxane and changes the ratio of thromboxane to prostacyclin in favor of anti-inflammatory prostacyclin [108]. Also, besides it has been shown that Bromelain stimulates leukocytes to increase interleukin-1, 6, 8 levels and alpha tumor necrosis factor in the inflammatory region. Increased cytokines, especially interleukin 8, lead to the uptake of granulocytes and monocytes into the inflammatory region and increase phagocytic and chemotactic, chemotaxis activity [104, 105, 109, 110]. The anti-edematous properties of Bromelain are due to increased vascular permeability following fibrinolysis and increased circulating edema fluid reabsorption. Fibrinolysis activity of bromelain has been attributed to increased conversion of plasminogen to plasmin. Plasmin also breaks down fibrin, thereby increasing vascular permeability [106]. Other studies have shown that nutritional supplements, including Bromelain, trypsin, and papain, are effective in wound healing [103]. Other experimental results also show that the combination of bromelain and trypsin is effective in wound healing and reduction of edema and inflammation in those who have undergone major abdominal laparotomy [111]. Bromelain has anti-inflammatory properties and is used as a facilitator of gastrointestinal excretion and blood thinner. It is also used to treat sports injuries, sinusitis, osteoarthritis, and swelling from bromelain. Bromelain has been studied for use as an adjunct in the treatment of IBD, especially treating ulcerative colitis. Emerging research on pineapple shows that bromelain is an active ingredient in pineapple that may help treat UC by relieving inflammation. The mechanism that is primarily responsible for its anti-inflammatory effects is still unknown. However, proteolytic activity has been identified for the anti-inflammatory effects of bromelain on T cell activation and cytokine secretion in vitro and mouse models of inflammatory diseases [112, 113]. The major anti-inflammatory mechanism of action of bromelain appears to be proteolytic activity. However, there is also evidence of hormonal activity, such as acting through the intracellular signaling pathway. Bromelain has been reported to help reduce cell surface receptors, such as the hyaluronic acid receptor CD4, which is involved in leukocyte migration and the induction of inflammatory mediators [114, 115]. Also, besides bromelain has been reported to significantly reduce CD4 T cells, which in animal models are the primary inflammatory factors in the gut [116]. In a study performed on a clinical trial of bromelain in the treatment of mild ulcerative colitis, clinical and endoscopic evidence showed improvement [117].

Qing Dai

Qing Dai herbal medicine is traditionally used in Chinese medicine to treat patients with UC, but there is a lack of published information about the effects of Qing Dai in the treatment of UC. In a study of the mechanisms of action of Qingdai, nine patients with active UC who received common medications but were willing to take Chinghai as an alternative drug were studied. UC severity was determined based on the clinical activity index (CAI). Also, besides 5 out of 9 patients were evaluated endoscopically based on the Mats grading system. Each patient received 2 grams daily of Qing Dai orally and continued with other UC medications as prescribed. Electron rotation resonance was used to discover the working mechanisms of Qingdao. After four months of treatment with Qingdai, the CAI score decreased. Similarly, the degree of endoscopic mats decreased. Six of the seven patients treated with prednisolone at the time of enrollment were able to discontinue the corticosteroids. Electron rotation resonance showed that Qingdai has a strong hydroxyl radical scavenging activity. Qingdai showed significant clinical and endoscopic efficacy in patients who failed to respond to conventional medications. Modification of the activity of hydroxyl radicals seems to be a potential mechanism by which this drug acts. Still, the final decision on the ability to produce therapeutic effects of Qingdai in the treatment of colitis is due to the anti-inflammatory effect of this drug in the treatment of UC patients has shown that further research is needed on the therapeutic effects of this herbal medicine [118].

Tea grass

Tea grass (Hypericum perforatum), a perennial plant with yellow flowers belonging to the Clusiaceae family, is used to treat anxiety, depression, ulcers, and as an antioxidant, analgesic, and nervous system protector [119]. This plant has antibacterial and antiviral effects [120], which acts by inhibiting the transcription factor NF-Kb [121] and with serine/threonine kinase) which belongs to the protein kinase C family (PKC) [122]. Tea grass has a significant effect on wound healing and an anti-inflammatory effect [123]. The beneficial effect of tea grass on the healing of oral mucosa in the golden hamster has been investigated [119]. In a study, the effects of tea grass on histopathological changes and Malondialdehyde (MDA) levels obtained from colonic tissue of rats with colitis were evaluated. Seventy male Sprague Dawley rats were divided into seven equal groups. Colitis was caused by acetic acid in them. Groups 1 and 2 received one cc of oral solution at 600 and 300 mg, respectively. In groups 3 and 4, 1 cc of the gel was enema 20% and 10%,

respectively. In group 5, 1 cc of Asacol was injected as a positive control group, and one cc of normal saline was injected as a negative control group in group 6. Group 7 received only the base gel via enema. Rat colon samples were evaluated for histopathological changes and tissue MDA after seven days of treatment. Based on the results, tea grass extract in both oral and enema forms had reduced therapeutic effects on the rats' tissues in which colitis had developed by reducing MDA activity. In the enema form, 20% gel showed a better effect than 10% gel. In the oral form with a dose of 600 mg/kg, a better therapeutic effect was observed than 300 mg/kg. Therefore, it can be concluded that tea grass can be used as a treatment of choice, especially in the form of enema in colitis [124].

Other treatments under consideration

As medical knowledge of the pathogenesis of inflammatory bowel disease progresses, the search for more effective treatments with fewer side effects continues. Some of these new therapies for Crohn's disease include Certolizumab and Adalimumab.

The treatments under consideration for the treatment of ulcerative colitis include peroxisome proliferator-activated receptor gamma (PPAR-anti-visilizumab, gamma) integrin therapy [32].

CONCLUSIONS

At present, medical treatment for ulcerative colitis is not entirely desirable, and none of the drugs that are now available and commonly used to treat this disease completely cure the disease. Continuous advances in the basic sciences related to ulcerative colitis provide the basis for further understanding of the cause of this disorder. Studying herbal medicines and using them in combination with other medicines used in the treatment of ulcerative colitis can open bright horizons for doctors to control this disease, which of course for the use of herbal medicines along with modern medicine. Extensive studies are needed.

We hope that these studies will lead to more specific and effective treatments for the complete cure of these diseases.

Acknowledgments

The authors wish to thank all staff of Gastroenterology and Liver Disease Research Center Baqiyatallah University of Medical Sciences, Tehran, Iran, and Applied Virology Research Center, Baqiyatallah University of Medical Science, Tehran, Iran, for their cooperation in implementing experimental procedures and analysis of data.

Conflict of interest

No conflict of interest is reported by the authors.

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