

BRIEF REVIEW ON THE NATURAL PRODUCT FOR TREATING INFLAMMATION IN THE GUT BRAIN AXIS AND CNS DISORDER

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ABSTRACT

Natural products have been used as drugs for millennia, and the therapeutic potential of natural products has been studied for more than a century. Since the mid-1880s, approximately 60% of drugs have originated from natural products. Recently, the importance of using natural products has increased, as has interest in discovering efficient new drugs. Natural drugs are desirable for the treatment of inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. Ulcerative colitis (UC) is a refractory, chronic, and nonspecific disease occurred usually in the rectum and the entire colon. The etiopathology is probably related to dysregulation of the mucosal immune response toward the resident bacterial flora together with genetic and environmental factors. Several types of medications are used to control the inflammation or reduce symptoms. Herbal medicine includes a wide range of practices and therapies outside the realms of conventional Western medicine. However, there are limited controlled evidences indicating the efficacy of traditional Chinese medicines, such as aloe vera gel, wheat grass juice, *Boswellia serrata*, and bovine colostrum enemas in the treatment of UC. Although herbal medicines are not devoid of risk, they could still be safer than synthetic drugs. The potential benefits of herbal medicine could lie in their high acceptance by patients, efficacy, relative safety, and relatively low cost. Patients worldwide seem to have adopted herbal medicine in a major way, and the efficacy of herbal medicine has been tested in hundreds of clinical trials in the management of UC. The evidences on herbal medicine are incomplete, complex, and confusing, and certainly associated with both risks and benefits. There is a need for further controlled clinical trials of the potential efficacy of herbal medicine approaches in the treatment of UC, together with enhanced legislation to maximize their quality and safety. This review discusses the discovery and development of drugs derived from natural products for the treatment of inflammatory bowel diseases.

KEYWORDS: Natural product, Drug discovery, Inflammatory bowel disease.**INTRODUCTION**

Inflammation is the first biological response of the immune system to infection or irritation. The word 'inflammation' comes from the Latin "inflammo," meaning "I set alight, I ignite." A verity of stimuli such as physical damage, ultra violet irradiation, microbial invasion, and immune reactions are responsible for inflammation. Inflammation is characterized by redness, heat, swelling, and pain. Based on timing and pathological features, there are two major categories available for inflammation: acute and chronic. Chronic inflammatory disease is characterized by persistent inflammation. On the other hand, acute inflammation occurs over seconds, minutes, hours, and days. IBD is inflammation within the gastrointestinal (GI) tract characterized by chronic or relapsing immune system activation. There are two types of IBD: ulcerative colitis and Crohn's disease.^[1] Ulcerative colitis occurs in the inner lining of the colon (large intestine) or rectum and

the common symptoms are diarrhea, abdominal cramps and rectal bleeding while those with Crohn's disease, experience pain in the abdomen, especially in the lower right side with symptoms-diarrhea, fatigue, weight loss and occasionally bleeding - and occurs in the deep layers of the intestinal wall. Generally, anti-inflammatory drugs or immunosuppressive drugs such as 5-aminosalicylic acid (5-ASA) and 6-mercaptopurine are used to treat IBD; steroids and non-steroidal anti-inflammatory drugs are effective for temporary relief of symptoms. However, drug-induced severe side effects occur, and most of these treatments are inadequate.^[2,3,4] Therefore, it is crucial to identify a new and safe drug for preventing or treating IBD.^[5] Consequently, many people with IBD turn to alternative medicine including traditional plant based remedies.^[2] A number of studies reported that plant-derived extracts or plant derivatives such as phenolic compounds and flavonoids show anti-inflammatory activity by controlling the levels of various inflammatory cytokines or inflammatory mediators including IL-1, IL-

6, IL-10, TNF- α , NF- κ B, NO, iNOS and COX-2. Moreover, many crude extracts and chemical constituents of plants have pharmacologic effects and clinical benefits. However, the claims of benefits of many plants or plant based medicines marketed to the general population are only supported by empirical or preliminary scientific data.^[5] Korean legislation governing the research and development of natural product-derived drugs defines a natural product as that originating from a living organism, including cells or tissue cultures produced from animals and plants. Natural products have been used as drugs for millennia in diverse Asian medical traditions: Korean Hanyak, Traditional Chinese Medicine, Japanese Kampo medicine, Indian Ayurvedic medicine, and Indonesian Jamu medicine. Early in their use, these agents were administered as teas, hot packs, powders, or liquids.^[6] Studies focused on the functions, chemical structures, activities, effective production methods, and usage of substances developed from natural products began around the end of the 18th century. The first scientific study of natural products described extraction of tartaric acid from grapes, citric acid from lemons, malic acid from apples, lactic acid from milk, and uric acid from urine. In 1805, a 21-year-old German pharmacist, Friedrich Serturmer, separated morphine from opium, which represented the first pharmacologically active plant-derived compound.² Since then, alkaloids, terpenoids, and glycosides have been isolated, and their chemical structures determined. Early in the 20th century, a microelement analysis method was developed that enabled the production of natural organic compounds from a small amount of raw material. The Russian botanist Mikhail Tswet introduced column chromatography for the separation of substances, which spurred the discovery of numerous biologically active substances, ushering in an era of natural product chemistry.^[7] Some of the most important medications developed in the 20th century were synthesized steroids, whose raw materials came from plants. Oral contraceptive pills and adrenocortical hormones are synthesized from the raw materials of *Dioscorea macrostachya* and the alkaloid diosgenin. Once the functionality of a natural product is confirmed, it may be used in a wide variety of products, including pesticides, functional foods, cosmetics, and drugs. Natural product-derived substances can be profitable; Dong-A Pharmaceutical has earned approximately 400 billion won since the 2002 approval of Stillen, the best-selling natural-product-derived drug in Korea, whose raw material is Moxa extract. In the early 1940s, approximately 90% of drugs were derived from natural products. From 1940 to the mid-1980s, most new drugs were organically synthesized. Since that time, approximately 60% of new drugs have originated from natural products. In particular, anticancer agents, as well as medications for pain, and disorders of the nervous system, metabolism, and the circulatory system are typically derived from natural products.^[8] Therefore, the aim of this review is to provide an overview of the

effects of more than 50 natural products used worldwide for the treatment of IBD. For this purpose, electronic databases including Pubmed, Scopus, Embase, and Google Scholar were searched for each of the natural products, and all retrieved plants cited here were examined by *in vitro*, *in vivo*, or clinical trials to determine their efficacy on IBD or related factors.

Herbal Medicine

The term “herb” is derived from the Latin word herba meaning “grass.” The term has been applied to plants of which the leaves, stems, or fruit are used for food, for medicines, or for their scent or flavor. Herbal medicine refers to folk and traditional medicinal practice based on the use of plants and plant extracts for the treatment of medical conditions. The use of herbs to treat diseases is almost universal among native people. A number of traditions have come to dominate the practice of herbal medicine in the West at the end of the twentieth century. Herbal medicine is one of the most common TCM modalities.^[9] It has been estimated that 28.9% of US adults regularly use one or more TCM therapies, 9.6%–12.1% of which are in the form of herbal products. Recent studies have indicated that the percentage of adults using TCM therapies for their GI symptoms ranges from 20% to 26%, but patients with functional GI disorders are more likely to make use of them, as are those with chronic GI conditions.^[10] The use of complementary medicine among patients with IBD, particularly in the form of herbal therapies, is widespread in the Western world as well as in many Asian countries including China and India.^[11] It seems that the use is continuously increasing despite the fact that only a small number of controlled trials dealing with either efficacy or safety of these natural products exist. So far, there are limited controlled evidences indicating the efficacy of TCM, such as *aloe vera gel*, *wheat grass juice*, *Boswellia serrata*, and *bovine colostrum enemas* in the management of patients with UC.^[12] Herbal medicine has always been considered to be preeminent among the various methods of healing within TCM, which is practiced extensively throughout clinics and hospitals in China alongside Western medicine. There are numerous reports in the Chinese literature about the treatment of UC with herbal remedies, while only abstracts are available in English. It was noticeable that most of the respondents using herbal therapies believe that “natural” equates with “safe” and almost 30% of patients reported that such preparations cannot cause any harm. Herbs are dilute natural drugs containing many different chemicals, and their effects may be unpredictable. A few have been tested for their side effects, quality, or the potential for cross contamination by biological and chemical pollutants in the environments in which they are grown, transported, or sold.^[13]

Nature products for treating inflammation in the GIT

Aloe Vera

Aloe vera (aloe) is a tropical plant used globally in traditional medicine. Its efficacy has been confirmed for

the treatment of UC. Aloe gel is the mucous extracted from the leaves of *Aloe vera*. Because aloe juice has anti-inflammatory effects, some doctors have used it to treat UC patients. A small-scale, double-blind, randomized controlled trial was conducted to investigate the efficacy of aloe gel for the treatment of mild-to-moderate UC, which involved oral intake of 100 mg of aloe gel for 4 weeks (30 participants) or oral intake of a placebo substance (14 participants). Nine (30%) of the 30 participants who ingested aloe gel experienced a clinical remission, while 11 (37%) showed improvement. In the control group, 1 participant (7%) experienced clinical remission, while 2 (14%) showed improvement.⁸ Nevertheless, this study had a small sample size, and, compared with other studies, the control group's response to the placebo substance was low. Although the exact mechanism of aloe is not fully understood, an *in vitro* study found that aloe gel reduced secretion of prostaglandin E2 and interleukin-18 (IL-18) in the colon mucosa, which suggested that the gel had anti-inflammatory and anti-microbial effects.⁸ In an *in vivo* study, aloe extract reduced tumor necrosis factor- α (TNF- α) levels and the expression of IL-1 β mRNA, which were indicative of anti-inflammatory effects.¹⁴

Boswellia Serrata

Boswellia serrata is an Indian mastic tree, and the resin collected from its stem has been used in traditional medicine. Boswellic acid, which is thought to contain most of the pharmacologically active ingredients present in the resin, is the substance extracted from *B. serrata*. *In vitro* and *in vivo*, boswellic acid selectively blocked 5-lipoxygenase, indicating an anti-inflammatory effect.⁹ Because IBD is associated with increased leukotriene function, the effect of boswellic acid on UC was confirmed, and its efficacy in reducing edema and inflammation in the small intestine was also confirmed. In a study using *B. serrata* in 30 chronic UC patients, its efficacy on UC with minimal side effects was confirmed.¹⁰ In animal experiments, *B. serrata* was confirmed to be effective for the treatment of CD, UC, and ileitis.

Licorice

Licorice root has been used in Chinese and Korean traditional medicine. Glycyrrhizin (chemical formula, C₄₂H₆₂O₁₆) is extracted from licorice and used as an artificial sweetener. In a study conducted on refined glycyrrhizin, diammonium glycyrrhizinate was confirmed to be useful for the treatment of UC. Diammonium glycyrrhizinate was confirmed to reduce inflammation by reducing levels of nuclear factor-kappa B (NF- κ B), TNF- α , and intercellular adhesion molecule-1 in the intestinal mucosa of mouse.¹⁵

Slippery Elm (*Ulmus Rubra*)

Slippery Elm has been used traditionally to treat coughing, diarrhea, and gastrointestinal tract diseases by Native Americans. Recently, the bark of Slippery Elm

was suggested to be effective for treating IBD patients owing to its antioxidant effects. However, further studies are needed to confirm its efficacy.

Tormentil (Potentilla Erecta)

Tormentil (Potentilla erecta) is a perennial plant belonging to the order Rosales, family Rosaceae. Its roots are rich in tannins, which have anti-inflammatory effects. In a small-scale study, tormentil was confirmed to be effective against infectious diarrhea and for the prevention of travelers' diarrhea. Another study confirmed its antioxidant effects in IBD patients.⁷ In yet another study, the administration of various doses of tormentil extract to 16 patients resulted in clinical improvement during the administration period, but the clinical activity index increased upon completion of administration.¹⁶

Wheat Grass (*Triticum Aestivum*)

Wheat juice has been used for more than 30 years as a treatment for inflammatory diseases and various gastrointestinal tract diseases, including cancer, but no clinical data are available. However, the intake of fresh wheat juice on an empty stomach has been shown to be an effective treatment. In a randomized controlled trial with a small sample size conducted in 2002, wheat juice produced a 70% improvement in distal UC patients without serious side effects.

Curcumin

Curcumin is a polyphenol extracted from the root of the East Indian rhizomatous perennial *Curcuma longa* (Zingiberaceae). The rhizomes of *C. longa* are used to produce turmeric, which is an ingredient in curries and other Indian dishes, and is also used as a yellow pigment. Curcumin, a primary component of turmeric, has been shown to have antioxidant, anti-inflammatory, and anti-cancer effects, and to be effective against enteritis *in vitro* and *in vivo*. Curcumin reduces local production of cytokines and chemokines, and inhibits infiltration of neutrophils into the mucous membrane. It also controls inflammation by regulating genes associated with oxidative stress and fiberization. The anti-inflammatory effect of curcumin is mediated by interference with arachidonic acid synthesis and blocking the NF- κ B activity that is associated with the synthesis of cyclooxygenase 2, 5-lipoxygenase, and inducible nitric oxide. There have been 2 human studies on IBD, including a pilot study conducted on 5 UC and 5 CD patients. In this study, 5 UC patients and 4 CD patients showed improvement. In a multi-institutional, randomized, double-blind study targeting 89 non-active UC patients, 45 patients took 1 g of curcumin every day in addition to sulfasalazine or mesalazine, while 44 patients took a placebo substance in addition to sulfasalazine or mesalazine.²³ After 6 months, 2 (4.65%) of 43 patients who received curcumin (excluding 2 patients who did not follow the protocol) experienced recurrence, compared to 8 (20.51%) of 39 patients who received a placebo substance. In addition, the curcumin-

treated group showed better average clinical activity indices and endoscopic indices than the placebo group.^[17]

Coriolus Versicolor

Coriolus versicolor is also known as the cloud mushroom, and its extracted polysaccharide constituent has anti-cancer and anti-IBD properties. In a dextran sulfate sodium (DSS)-induced colitis model, *C. versicolor* extract reduced the expression of pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6. Furthermore, it reduced expression of signal transducers and activators of transcription 1 (STAT1) and STAT6 molecules, which reduced expression of interferon-gamma (IFN- γ) and IL-4.

Inonotus Obliquus (Chaga)

Chaga is a parasitic mushroom that grows on birch trees in cold regions. Since the 16th century, Chaga has been used in Russia and Eastern Europe as a folk remedy for various diseases with few, if any, side effects. In Northern and Eastern Russia, Chaga solution has been used for the prevention and treatment of gastrointestinal tract diseases.²⁵ Chaga contains steroids, including polyphenolics, triterpenoids, lanosterol, inotodiol, trametenolic acids, and ergosterol peroxides. A recent study reported that *I. obliquus* extracts inhibited colitis in DSS-induced BALB/c mice, and reduced expression of TNF- α , IL-4, STAT1, and STAT6.^[18]

Prunus Mume

Prunus mume is a deciduous tree of the family Rosaceae, and its fruit has been used as a Korean folk remedy for fever, coughing, and intestinal diseases. The smoked and dried immature fruit of *P. mume*, which are called "Omae," have been used in traditional medicine. Omae extract was approved as a drug in 2001 by the China Food and Drug Administration (Approval No. Z11021100), and has been reported to improve colitis symptoms by reversing large intestine damage and abnormally increased cytokine secretion. A study conducted in Korea reported that *P. mume* mixture reduced the expression of TNF- α , cyclooxygenase-2 (COX-2), IL-4, STAT6, INF- γ , and STAT1 in a DSS mouse model.

Gardenia Jasminoides

Gardenia jasminoides has been used in Asia as a folk remedy, and its extract has anti-oxidant effects, such as the removal of various radicals. An *in vitro* study confirmed this anti-oxidant capability, as well as nitrite elimination, linoleic acid oxidation-blocking ability, and activities similar to superoxide dismutase and catalase. In a DSS-induced mouse model of enteritis, glycoprotein separated from the fruits of *G. jasminoides* inhibited myeloperoxidase activity and reduced the reactive substance concentration of thiobarbituric acid and the production of nitric oxide. Over-generation of inducible nitric oxide synthase (iNOS), COX-2, and NF- κ B were

also blocked by administration of the glycoprotein isolated from *G. jasminoides*.

Ginger

Ginger is used as a spice and has anti-oxidant effects. In a mouse model of 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced enteritis, ginger and its constituent zingerone improved enteritis symptoms. Ginger and zingerone inhibited NF- κ B activity and reduced IL-1 β protein concentration in the large intestine.^[19]

Modern evidence for the efficacy of plants on IBD

Inonotus obliquus

Inonotus obliquus (IO) is a mushroom belonging to the inonotus genus and Hymenochaetaceae family of Basidiomycetes living as a parasite on birches in Europe and Asia. In Russia, the black, shapeless overgrowth of the birch is usually called chaga. The water extracts of IO suppressed the ulcerative colitis in DSS induced male BALB/c mice.^[18] The water extracts decreased the expression of TNF- α , IL-4 and STAT1, STAT6 compared to those of the disease group. It also showed the inhibitory activity on LPS induced TNF- α , STAT1, pSTAT1, STAT6, and pSTAT6 production in RAW264.7 cells. IO grown on germinated brown rice (IOGBR) ethanol extracts showed potent activity on ulcerative colitis in mice.^[1] IOGBR reduced proinflammatory mediators such as tumor necrosis factor (TNF)- α , cyclooxygenase (Cox)-2, interleukin (IL)-4, interferon (IFN)- γ and decreased STAT1 and STAT6 expression. Immunoglobulins (Ig) act as an important role in inflammation. Therefore, IOGBR extracts suppressed the expression of IgE and IgA in the spleen and mesenteric lymph node (MLN) compared to those of the DSS-induced colitis group. The extracts suppressed the pathogenic shortening of colon length and reduced DSS-induced colonic tissue destruction.^[20,21]

Cordyceps sinensis

Cordyceps sinensis is a fungus belonging to the family Clavicipitaceae. The water extracts of *Cordyceps sinensis* was applied to the C57Bl/6N mice to evaluate the effects of immune function of mesenteric lymph node (MLN) lymphocytes. The results indicated that the IgE concentrations in serum and MLN lymphocytes were significantly lower in *C. sinensis*-treated mice than in the control mice. The extracts increased the proportion of CD4 (+) and CD8 (+) T cells in MLN lymphocytes. Different research found that *Cordyceps militaris* extract suppresses dextran sodium sulfate-induced acute colitis in BALB/c mice by suppressing disease symptoms such as body weight loss, diarrhea and gross bleeding. The extracts prevented shortening of the colon and crypt length and the epithelial damage.

Prunus mume

Prunus mume Sieb. et Zuce belongs to the genus *Prunus* and family Rosaceae. This fruit known as Ou-mae and has been used in Korea as a folk medicine to treat fever, cough and intestinal disorders.^[22] In addition, the

unripe *P. mume* showed inhibitory activity against *Helicobacter pylori* motility. Yingsakmongkon *et al.* studied concentrated fruit juice to prevent or reduce the virus infection in human influenza. Prunates isolated from *P. mume* has inhibitory activity on the proliferation of cancer cells. Antioxidant activities of flowers and fresh fruits of *P. mume* have been examined. *Prunus mume* mixture treatment decreased the expression of TNF- α , COX-2, IL-4, STAT6, INF- γ , STAT1 in mice with DSS-induced colitis.^[20] In addition, Mume Fructus is the fruit of *Prunus mume*. The mature green fruit is heated at a low temperature until the yellowish colored pulp changes to brown. Then, the peel wrinkles and is braised until it turns black. The carbonized dried form is preserved and used. The water extracts of Mume Fructus showed 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), hydroxyl (OH \cdot), superoxide (O $_2^{\cdot-}$) radicals and nitrite scavenging activities, inhibition of linoleic acid oxidation and reducing power activity.^[22] Mume Fructus pill (FMP) has been used as a folk medicine in China. For the treatment of gastrointestinal disorders, Mume Fructus pill was approved by the State Food and Drug Administration (SFDA) of China in 2001 (Approval No. Z11021100). From the study of Liu *et al.* FMP prevented diarrhea, colon weight increase, colonic accretion, ulceration and myeloperoxidase (MPO) activity elevation. The FMP recovered colonic damage and promoted abnormal cytokine secretion in rats with colitis.

Gardenia jasminoides

Gardenia jasminoides Ellis (GJE) is a flowering plant which belongs to the genus *Gardenia* and family Rubiaceae. It has traditionally been used as folk medicine in many Asian countries. The ethanol and water extracts from *Gardenia jasminoides* Ellis have been researched to evaluate their antioxidant activity. Both extracts showed high antioxidant activity by scavenging various radicals. The extracts showed strong reducing power, nitrite scavenging activity, linoleic acid oxidation inhibition, superoxide dismutase-like (SOD-like) activity, and catalase activity *in vitro*. Glycoprotein isolated from *Gardenia jasminoides* Ellis (GJE) fruits suppressed MPO activity, TBARS level, and NO production and inhibited the over production of iNOS, COX-2, and NF-kappa- β (p50) in DSS-induced mice.^[23]

Chrysanthemum indicum

Chrysanthemum indicum Linné is an herb that belongs to the genus of *chrysanthemum* and family of Asteraceae. It has traditionally been used as folk medicine in China and Korea and treats various immune-related disorders, hypertension and various infectious diseases including pneumonia, colitis, stomatitis, carbuncle and fever. Butanol-soluble fraction of *Chrysanthemum indicum* inhibited on the auricle edema in mice.

***Benincasa hispida* Cogn.**

Waxgourd (*Benincasa hispida* Cogn.) belongs to a family of Cucurbitaceae and has been used in traditional Chinese medicine to treat inflammation and high blood pressure. It is good for mineral detoxification, lowering fever and strengthening the function of the bladder and small and large intestines. The seed extracts of *Benincasa hispida* inhibits the histamine secretion and show antitumor effects by enhancing immunoreactions. Different parts of the wax gourd such as the peel, core and pulp as well as fresh seeds have antioxidant capacity. Water extract from dry seeds of *Benincasa hispida* showed strong antioxidant activity by scavenged DPPH, ABTS and hydroxyl radical in a dose-dependent manner. The extracts also showed inhibitory activity on linoleic acid oxidation and nitrite radical. The dried seed extracts produced significant reduction in ulcer index in Wistar albino rats. Further, the extracts reduced MDA content along with increasing CAT levels when compared to the control group.^[24]

Avicennia marina

Avicennia marina (*A. marina*) is a plant of the Acanthaceae, commonly known as grey mangrove or white mangrove. *A. marina* decreased the colonic lipid peroxides, glutathione peroxidase, and serum nitric oxide, lesion score and wet colon weight, and increased the colonic and erythrocyte superoxide dismutase and glutathione levels compared with colitis control.

Patrinia scabiosaefolia

Patrinia scabiosaefolia Fisch belongs to the family Valerianaceae. In Asia, the plants are usually used to treat anti-inflammatory diseases, especially for colonic inflammations, virus infections, hepatitis, and uteritis. The root extracts of *Patrinia scabiosaefolia* Fisch suppressed weight loss, diarrhea, gross bleeding, infiltrations of immune cells, prevented shortening of colon length and enlargement of spleen size, down regulated the abnormal secretions and mRNA expressions in mice with DSS induced colitis.^[25] Histological study indicated that the extracts reduced edema, mucosal damage, the loss of crypts.

***Ficus bengalensis* Linn**

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

Withania somnifera

Withania somnifera (Dunal), belongs to the family Solanaceae, is used as a medicine since 2500 years in

Indian medicinal classic “Ayurveda”. Aqueous extract of its the root showed anti-oxidant activity by reducing H₂O₂ and NO. It has lipid peroxidation inhibition activity. The extracts scored positively on histopathological parameters like necrosis, edema, neutrophil infiltration in TNBS-induced IBD rat model.

Yamada *et al.* conducted a comparative study of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi. Among them, Ashwagandha (*Withania somnifera*) and Brahmi (*Bacopa monnieri*) are commonly found in India. They compared the immunostimulatory effects of Ashwagandha and Brahmi with the effect of Echinacea and observed the Brahmi diet enhance immune function by increasing the levels of IgA and IgG in the serum of male Sprague Dawley rats.^[26]

Garcinia cambogia

Garcinia cambogia, known as Malabar tamarind, is native to Southeast Asia. Its fruit extracts have been suggested to have a variety of pharmacological properties including antiulcer activities.^[27] The anti-inflammatory activity of a garcinia extract was assessed in TNBS-induced colitis rats. The extracts treatment improved the macroscopic damage and reduced MPO activity, COX-2 and iNOS expression. It was also able to reduce PGE2 and IL-1 β colonic levels. It did not show any mortality nor toxicity signals after oral administration. *Garcinia cambogia* (also known as Malabar tamarind) is a plant native to Southeast Asia. Its fruit extract has various pharmacological effects, including anti-ulcer activity. In a TNBS-induced mouse model of enteritis, *G. cambogia* extract produced anti-inflammatory effects; it inhibited expression of myeloperoxidase, COX-2, and iNOS, and reduced concentrations of prostaglandin E2 and IL-1 β .

Flavonoids

Flavonoids can act as antioxidants that prevent production of free radicals. Rutin (3-*O*-rhamnosyl-glucosyl-quercetin) is a common flavonoid found in buckwheat, parsley, and apricot. Rutin has been shown to be effective in the TNBS-induced colitis and acetic acid-induced colitis models in mice. Rutin was also effective in a DSS-induced mouse model, and has been confirmed to produce anti-inflammatory effects through inhibition of IL-1 β and IL-6 gene expression. Rutin has been confirmed to possess preventive and treatment effects in intestinal diseases. Low-dose Rutin improves enteritis symptoms through its regulation of pro-inflammatory mediator genes, such as IL-1 β , IL-6, granulocyte-macrophage colony-stimulating factor, and Inos.^[28,29]

In vitro Studies of Plant on IBD Related Factors

Scouring rush (*Equisetum hyemale* L.) is a perennial herb belong to the family Equisetaceae. Different extracts of this plant showed antioxidant and anti-inflammatory activities. The extracts have reducing power, metal-chelating activity, superoxide and nitrite scavenging

abilities. The extracts showed inhibitory activity on NO, iNOS and COX-2 production in RAW 264.7 macrophages. *Schizonepeta tenuifolia* is an herb belonging to the family of Lamiaceae. The methanol extracts from this plant showed inhibitory activity on iNOS in LPS-stimulated RAW 264.7 cells with highly antioxidant properties. *Antrodia salmonea* T. T. Chang et W. N. Chou (Polyporaceae), a new species of the genus *Antrodia*, identified in 2004. Ethanol extracts from this plant showed nitric oxide (NO) production, expression of inducible nitric oxide synthase (iNOS) and COX-2 proteins inhibition and enzymatic antioxidant activity.^[30]

CONCLUSIONS

A great deal of evidence suggests that chronic inflammation promotes development of numerous human diseases, including IBD. Various herbal products have been used for the treatment of IBD. In this review we found that these natural products have shown their usefulness in IBD by different mechanisms of action such as inhibiting the production of NO, Cox-2, immunomodulatory properties, antimicrobial activities, antioxidant activities, and antiulcer properties IBD for their pro-inflammatory cytokines and NO and Cox-2 inhibitory and antioxidant properties. Considering the devices of action of these plants, the mixture or combination of some of them may be beneficial due the numerous mechanisms involved in IBD. Based on the some *in vitro* studies, some plants are more effective to reduce IBD related factors. However, the exact mechanisms behind the anti-IBD effects of some of these natural products are still unclear. Therefore, additional *in vivo* research will be needed to determine their effects and to find which specific factors are involved in improving IBD in humans. Interest is growing in the development of efficient new drugs derived from natural sources for the treatment of IBDs, such as UC and CD. As frequently reported in clinical trials, many intestinal disease patients have tried natural products and show great interest in them. This patient preference should encourage the development of new drugs derived from natural products.

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