OPEN ACCESS PEER REVIEW

DOI: https://doi.org/10.52756/bhietm.2023.e02.003

Chapter- 3

Unlocking the Potential of Phytochemicals in Combating Inflammatory Bowel Disease: Insights from Studies with Selected Plants Commonly Utilized in India

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Keywords: inflammatory bowel disease (IBD), ulcerative colitis (UC), T-cells, cytokines.

Abstract:

The incidence of inflammatory bowel disease (IBD) is increasing in India, with a total of 2.7 lakh cases in 2019. IBD includes two categories of chronic inflammatory conditions of the gastrointestinal tract: ulcerative colitis (UC) and Crohn's disease (CD). Both conditions cause severe morbidity to individuals and increase the risk of GI tract cancers. Long-term use of conventional synthetic drugs like corticosteroids has significant adverse effects. Patients increasingly choose to adopt plant-derived products as an alternative or complementary medicine (CAM). In India, since ancient times, plant products have been used to treat and prevent numerous digestive tract ailments. Here, we have mentioned recent research highlights of eight commonly utilized plants (*Curcuma longa*, *Zingiber officinale*, *Allium sativum*, *Boswellia serrata*, *Trigonella foenum-graecum*, *Garcinia cambogia*, *Aloe vera*, and *Punica granatum*) and their bioactive compounds used to treat IBD in both model systems and clinical trials. Many of the bioactive compounds mentioned in this article can target different drivers behind IBD pathology. Phytochemicals can modulate immune cell subsets, enhance gut epithelium regeneration, and improve gut microbiome homeostasis to inhibit aberrant immune response and promote gut barrier function leading to remission of IBD. Evidence from clinical trials indicates that these plant-derived products are safe to use, but efficacy varies depending on the nature of the preparation of the phytochemicals. New developments in targeted delivery and better absorption promise exciting advances for phytochemicals in IBD treatment.

Introduction:

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal (GI) tract. It encompasses ulcerative colitis (UC), a continuous inflammatory condition mainly restricted to the colon and rectum, and Crohn's disease (CD), which is an intermittent inflammatory condition affecting any part of the GI tract. The estimated global burden of IBD in 2019 was 4.9 million cases, with India noticing a doubling of the total number

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Mrs. Bhanumati Sarkar, Dr. (Professor) Surjyo Jyoti Biswas, Dr. Alok Chandra Samal & Dr. Akhil Pandey (eds.), The Basic Handbook of Indian Ethnobotany and Traditional Medicine [Volume: 2].
ISBN: 978-81-962683-5-0; pp. 32-45; Published online: 15th December, 2023

of patients between 1990 and 2019 (Dharni et al., 2023). The clinical presentation of IBD includes abdominal pain, diarrhoea with or without blood, rectal bleeding, weight loss, faecal inconsistency, fever, anaemia, increased risk of colon cancer, etc. The interaction between several factors, such as aberrant immune response, underlying genetic factors, gut microbiome, and environmental factors, drives IBD. When T-cells, dendritic cells, macrophages, and other mononuclear cells infiltrate the lamina propria during IBD, they release excessive inflammatory cytokines [such as Tumor necrosis factor- alpha (TNF-α), interleukin-1beta (IL-1β), interferon-gamma (IFN-γ), and IL-12], leading to pathology. Patients with IBD can display elevated Th1 and Th17 biased responses. Currently, 5-aminosalicylic acid, corticosteroids, and immunomodulators are used for the treatment of IBD. Issues with poor tolerability and ineffectiveness of conventional therapies have driven over 50% of IBD patients towards herbal medicine as a form of complementary and alternative medicine (CAM) (Sarkar et al., 2016, 2022, 2024; Jyotirmayee et al., 2023). Phytochemicals contain many bioactive compounds that can modulate the inflammation pathway, restore barrier function, and improve gut microbiota homeostasis to induce and maintain remission of IBD. Extensive *in vitro*, *in vivo* studies and some clinical trials have confirmed the efficacy of various plants found in India for treating IBD. Here, we have discussed the notable recent developments of a few selected plants and their constituents for the treatment of IBD.

Turmeric - *Curcuma longa* :

Curcuma longa, or turmeric, is a perennial, rhizomatous plant in the ginger family, Zingiberaceae. The roots of turmeric are used as a spice. In Ayurvedic and Unani medicine, turmeric has been used for centuries to treat liver disorders, allergies, skin lesions, bronchitis, and as a general antiseptic. The chief active ingredient of turmeric is the polyphenolic compound curcumin, which has received extensive attention from researchers and clinicians over the past decades. Research has been conducted on the beneficial properties of curcumin, including its anti-inflammatory, antioxidant, anti-cancer, neuroprotective and hepatoprotective effects, as well as the molecular pathways it modulates (Kotha & Luthria, 2019).

Several *in vitro* and *in vivo* studies on colitis models have identified various molecular targets that curcumin can influence to exert its prophylactic and therapeutic potential against IBD. Inflammation in IBD results from aberrant activation of various cell signalling pathways. Curcumin modulated nuclear factor kappa β (NF-κβ), JAKs/STATs, mitogen-activated protein kinases (MAPKs) that were activated in chemically-induced experimental colitis models. This, in turn, reduced the production of numerous pro-inflammatory factors such as IFN-γ, TNF-α, IL-1, IL-6, IL-8, IL-12, and IL-23. Amelioration of colonic damage following curcumin treatment was associated with reduced inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), Myeloperoxidase (MPO), and caspase-1 activities and lowered levels of nitrite, Matrix metalloproteinases (MMP-1, MMP-3, and TIMP-1), monocyte chemoattractant protein-1 (MCP-1). Curcumin can also obstruct the activation of the NLRP3 inflammasome in the

dextran sodium sulfate (DSS)-induced colitis model (Karthikeyan et al., 2021). The development of IBD involves changes in the balance of various immune cells. Curcumin has been demonstrated to modulate both T and B-cells to improve the disease outcome. Curcumin reduced excessive Th1, and Th17 activation and proliferation and promoted infiltration and enrichment of regulatory T-cells in colon tissue (Xiao et al., 2022). In DSS-induced colitis mice, curcumin can upregulate regulatory B cells by inhibiting TLR/MyD88 pathway to improve disease pathology (Huang et al., 2023). Recently, it has been shown that curcumin can protect the intestinal epithelium and promote its repair after injury by down-regulating miR-195-3p (Wang et al., 2024).

Very importantly, many clinical trials in different age groups have investigated curcumin's safety and efficacy for managing IBD. The first multi-center randomized placebo-controlled double-blind clinical trial in UC patients found curcumin (1 g) two times per day together with sulfasalazine or mesalamine showed a markedly improved relapse rate (4.7%) compared to the placebo group with only the standard drug treatment (20.5%). This was accompanied by a noticeable drop in the clinical activity index (CAI) and endoscopic index (EI) scores of the disease following curcumin intake. Bioenhanced curcumin (BEC) as add-on therapy in UC patients led to better clinical and endoscopic remission with improved clinical response compared to placebo (Banerjee et al., 2021). Currently, a lot of attention is being given to colon-targeted delivery of curcumin in micro- and nano-formulations to improve its solubility and bioavailability for better clinical effects (Laurindo et al., 2023).

Ginger - *Zingiber officinale* :

Ginger, the rhizome of *Zingiber officinale* from the Zingiberaceae family, is globally one of the most commonly used spices and has a long history of medicinal use for various ailments (e.g., asthma, diabetes, nausea, gingivitis, etc.) and is a component of numerous tonics. Ginger contains more than 400 bioactive compounds, but most of its medicinal effects are attributed to four phenolic compounds: gingerols, shogaols, paradols, and zingerone (Erfani, 2021).

Recent clinical trials have shed light on the safety and efficacy of ginger in treating UC. Daily consumption of 2000mg dried ginger powder in capsules for 12 weeks has been shown to reduce serum TNF-α and Malondialdehyde (MDA) [an indicator of oxidative stress] among mild to moderate UC patients compared to control. At 12 weeks, the disease severity scores and quality of life were also improved following ginger intake compared to placebo (Nikkhah-Bodaghi et al., 2019).

Mechanistic insights into ginger's beneficial effects on IBD have been revealed in many *in vivo* studies. Ginger has been found to act on NF-κβ, STAT, MAPK, and mTOR pathways, and also on NLRPs and TLR. Both gingerol and 6-shogaol can reduce inflammatory TNF-α, IL-6, and IL-1β in animal models of UC. Gingerol treatment can also reduce COX-2 and MCP-1 activity (Ballester et al., 2022). Ginger extract ameliorated the IBD symptoms and significantly improved body weight, fecal bleeding, and stool consistency in DSS-induced colitis in mice.

Apart from reducing proinflammatory cytokines, it increased the expression of tight junction proteins in colon tissue, leading to better disease outcomes. Specifically, it increased the expression of ZO-1, E-cadherin, occludin, mucin-1, and mucin-2 (Kim & Kim, 2018). Ginger can restore gut microbiota diversity and function, promoting UC healing by reversing dysbiosis (Guo et al., 2021).

Recently, considerable interest has developed in edible ginger-derived nanoparticles (GDNPs), which have an average size of ~230 nm and negative zeta potential. GDNPs contain a considerable amount of 6-gingerol and 6-shogaol, along with some proteins, lipids, and microRNAs. Oral administration of GDNPs has been shown to accelerate tissue repair and reduce symptoms in UC and UC-associated cancer models in animals. They can reduce inflammatory cytokines such as TNF-α, IL-6, and IL-1β, increase anti-inflammatory cytokines like IL-10 and IL-22, and promote the survival and proliferation of intestinal epithelial cells (Zhang et al., 2016).

Garlic - *Allium sativum* :

Allium sativum L., or garlic, is one of the most used plants in cooking and also in ethnomedicine. It contains more than 200 bioactive substances such as diallyl disulfide, S-allyl cysteine, diallyl thiosulfonate (allicin), diallyl trisulfide, E/Z-ajoene, N-acetylcysteine, steroids, peptide, saponins, flavonoids, terpenoids, etc. This wide array of garlic components is responsible for its anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and other therapeutic activities.

Studies have shown that garlic extract could stimulate the secretion of anti-inflammatory IL-10 while simultaneously suppressing the production of various proinflammatory cytokines such as TNF-α, IL-6, IL-1α, IL-8, and IL-12 in whole blood or peripheral blood mononuclear cells (PBMCs) taken from IBD patients. Furthermore, when combined with methylprednisolone, a drug commonly used in IBD treatment, garlic extract displayed an additive effect (Hodge et al., 2002). Allicin, a derivative of alliin, is a major component of raw garlic extract and has been attributed to Th1-inhibitory effects. Also, alliin can reduce inflammation in the gut by MAPK-NF-κβ/AP-1/STAT-1 inhibition and PPARγ modulation (L. Shi et al., 2017).

Allicin rapidly decomposes into other sulfur compounds like diallyl sulfide (DAS), diallyl disulfide (DADS), etc. These compounds have also shown their curative effect in Dinitrobenzene sulfonic acid (DNBS)-induced colitis models by decreasing colon weight/colon length ratio in inflamed gut tissue. This study found that diallyl disulfide reduced IL-6 and IP-10 levels, while diallyl sulfide inhibited NO and STAT1 activity in IFN- γ-induced inflammation in intestinal cells (Fasolino et al., 2015).

Due to some reported adverse effects associated with fresh garlic extract intake, aged garlic extracts are sometimes preferred and are rich in several bioactive and more bioavailable compounds such as S-allylcysteine (SAC) and S-allylmercaptocysteine (SAMC). S-

Allylcysteine has been shown to reduce the production of various cytokines, including IL-1β, TNF-α, and IL-8, that contribute to IBD pathology (Zugaro et al., 2023).

Recent publications suggest that other substances from garlic, such as Propyl-propane thiosulfonate (PTSO) and a water-soluble garlic polysaccharide, can have anti-inflammatory activities leading to an amelioration of colitis in mice models. They can enhance the intestinal barrier function and promote a healthier balance of microbiota in the gut (Vezza et al., 2019).

Indian olibanum - *Boswellia serrata* :

Boswellia serrata, found in dry, hilly areas of India, has been used in traditional Indian medicine systems for treating inflammatory conditions and arthritis-associated pain. The gum resin obtained from this tree contains different active ingredients in its extract, namely, β-boswellic acid (β-BA), 11-keto-β-boswellic acid (KBA), and acetyl-11-keto-β-boswellic acid (AKBA). All these ingredients have been shown to exert several antioxidant and anti-inflammatory effects.

Boswellia serrata extracts (BSE) are known to reduce several proinflammatory cytokines in different cellular models of inflammation and also can improve tissue lesions, reduce nitric oxide and lipid peroxidation levels in animal models of UC (Hartmannet al., 2014). A semisynthetic form of acetyl-11-keto-beta-boswellic acid (sAKBA) has been shown to reduce the infiltration of leucocytes and platelets to inflamed venules by inhibiting P-selectin in experimental murine colitis induced by DSS (Anthoni et al., 2006).

Over the years, several clinical trials have reported the beneficial effect of BSEs compared to standard care. One of the earliest clinical trials reported that a dose of 350 mg thrice daily for 6 weeks was as good as sulfasalazine (1 g thrice daily) treatment in alleviating different parameters in UC grade II and III patients. Importantly, BSE treatment achieved a better remission rate of 82% of treated UC patients compared to 75% among sulfasalazine-treated patients (Gupta et al., 1997). BSE administration in a lecithin-based delivery system (Casperome®) attenuated symptoms in the UC remission phase, reducing the need for other medications (Pellegrini et al., 2016). Several other clinical trials with BSE have found it to be either better or equivalent to the standard treatment options in terms of efficacy and usually safe (Gupta et al., 2001).

Fenugreek - *Trigonella foenum-graecum* :

In Ayurveda, the seeds and leaves of the plant *Trigonella foenum-graecum* (family Fabaceae), commonly known as fenugreek, have been used as medicine since ancient times. These are native to India and are also distributed throughout the world. In India, fenugreek is consumed as a condiment, and it is reported to help in digestion, act as a tonic to improve overall well-being, induce labour, and stimulate lactation. Usually, the leaves and seeds are used to prepare extract or powder.

Several model systems have demonstrated the anti-inflammatory effects of diosgenin, a steroidal saponin found in *T. foenum-graecum*. Diosgenin can suppress the production of IL-1, IL-6, ROS, and NO in macrophages by preventing NF-κβ and AP-1 activation (Jung et al., 2010). In the trinitrobenzene sulfonic acid (TNBS)-induced colitis model in rats, diosgenin reduced several proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IFN-γ, as well as inflammatory markers COX-2 and iNOS in the colon. It also promoted the secretion of anti-inflammatory IL-10 and relieved oxidative stress by increasing SOD and GSH levels. Histopathological observations also indicated attenuated colonic damage in diosgenin-treated animals. Administration of diosgenin inhibited NF-κβ/Ikβ-α and Bax/Caspase-1 signaling pathways (Tang et al., 2020). The potential of diosgenin in managing IBD warrants further research, specifically in its ability to promote regulatory T-cell enrichment and activity in the intestine (Huang et al., 2010).

Malabar Tamarind - *Garcinia cambogia* :

Garcinia gummi-gutta [formerly known as *Garcinia cambogia* (Malabar tamarind)] has several reported ethnomedicinal properties. This plant is native to India, Sri Lanka, and Nepal and has culinary applications to impart sharp sour flavour in food preparations. *G. gummi-gutta* fruit extract is used against gastrointestinal disorders, rheumatism, oedema, irregular menstruation, and intestinal parasites in traditional Indian medicine. Analysis of phytochemistry reveals the presence of alkaloids, flavonoids, phenolic compounds, saponins, tannins, carbohydrates, and proteins in the extracts. The major bioactive constituents are hydroxycitric acid (HCA) (an organic acid) and garcinol (a benzophenone) along with different xanthones and amino acids (Semwal et al., 2015). According to research, these bioactive compounds possess anti-obesity, hypolipidemic, anti-cancer, and anti-parasitic properties.

G. cambogia extract containing 51.2% HCA was found to be promising in the treatment of TNBS/ethanol-induced colitis in rats. Application of the extract significantly reduced inflammatory IL-1β and PGE2 levels with improved macroscopic colonic damage. The treatment was accompanied by lowered myeloperoxidase, COX-2, iNOS activity, and reduced DNA damage in colonocytes (dos Reis et al., 2009). Other active ingredients, such as Garcinol, have shown anti-inflammatory effects in LPS-stimulated RAW 264.7 macrophage cell line by downregulating activation of NF-κβ and/or JAK/STAT1 pathways. Garcinol-treated cells had lower iNOS and COX-2 expression, leading to reduced intracellular ROS levels in LPS-treated cells (Liao, Sang, Liang, Ho, & Lin, 2004). Reduction in proinflammatory cytokines by garcinol, guttiferone K, and guttiferone M has been demonstrated in other cell lines as well (Semwal et al., 2015). The blend of multiple bioactive compounds in *G. gummi-gutta* extract makes it an intriguing plant for further exploration. Several clinical studies containing *G. gummi-gutta* extract or its constituents have been carried out to assess efficacy for anti-obesity, hypolipidemic potential. Most formulations have been safe, but some trials and products lacked efficacy.

Ghrita Kumari - *Aloe vera* :

The perennial green herb, *Aloe vera* (*Aloe barbadensis* Miller, family Xanthorrhoeaceae), commonly referred to as Ghrita Kumari in Sanskrit and Bengali, is extensively used for the treatment of several skin problems, cuts, injuries, digestive issues, diabetes, etc. Although this plant is native to North Africa, the *Aloe barbadensi*s has been naturalized and commercially cultivated in semi-arid and arid parts of India. Its extract has anti-oxidant, anti-inflammatory, anti-microbial, and wound-healing properties. *Aloe vera* contains more than 75 bioactive compounds, including several vitamins, enzymes, minerals, lignin, saponins, sugar, salicylic acids, and about 20 non-essential and 7 essential amino acids (Surjushe et al., 2008; Sarkar, 2017).

Aloe vera gel, or its different constituents, has been evaluated in several animal models of colitis. Rats with DSS-induced colitis were treated with *Aloe vera* compounds such as aloin, aloesin, and aloe-gel which resulted in the decrease of disease activity index, plasma level of leukotriene-B(4), TNF-α, and PGE2.. Myeloperoxidase activity and TNF-α and IL-1β m RNA expression were significantly reduced in the colonic tissue of the treatment groups compared to the control group (Park et al., 2011). Another study in rats identified aloin A as the key bioactive component of *Aloe vera* extract that could enhance mucus secretion in the colon to alleviate UC. Oral intake of *Aloe vera* decreased pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) and increased IL-10 levels. It also attenuated pPI3K and p-AKT expression but enhanced p-PKC and p-ERK expression (Shi et al., 2021). *Aloe vera*-derived nanovesicles have improved epithelial cell junctions and reduced permeability and damage in mouse UC models (Choi et al., 2023). Aloe polysaccharides have also been identified as contributors to UC disease improvement in animals. Glucomannan, an *Aloe* polysaccharide, can improve UC in animals by preventing intestinal barrier disruption and promoting epithelium regeneration through activation of intestinal stem cells (Zhang et al., 2023).

In a randomized, double-blind, placebo-controlled trial conducted on patients with active ulcerative colitis, oral *Aloe vera* treatment was administered for four weeks (100 ml twice daily). The results showed a significant decrease in the colitis activity index and histological disease activity in the treatment group compared to the placebo group (Langmead et al., 2004).

Pomegranate - *Punica granatum* :

Punica granatum (Pomegranate), referred to as “dadima” in Sanskrit, is a deciduous shrub distributed throughout the world. Over the centuries, in Indian culture, many different parts of the plant have been used to treat various ailments. The fruit of the plant *P. granatum* (PG) has the potential to prevent cancer, cardiovascular disease, Alzheimer’s disease, diabetes, dental conditions, arthritis, obesity, and UV radiation-induced skin damage. Pomegranate is rich in polyphenolic compounds such as ellagitannins (ET) and ellagic acid (EA), which contribute to its anti-inflammatory and antioxidant activities. Punicalagin is the major ellagitannin extracted from pomegranate. In different preclinical animal models of IBD, the researchers have

investigated the effectiveness of pomegranate extracts, several polyphenolic compounds found in pomegranate, and their different metabolites. Supplementation of pomegranate extract or its different constituents can reduce inflammation and improve anti-oxidant activities. Thus, it alleviates symptoms of IBD, prevents leakage by reducing tissue damage in the colon, and promotes wound healing (Marin et al., 2009). The protective effect of pomegranate beverage containing ellagic acid and ellagitannins in DSS-induced colitis model in rats is attributed to lowered proinflammatory cytokines TNF-α and IL-1β production as well as reduced COX-2 and iNOS expression. Pomegranate beverage intake was able to modulate the miR-145/p70S6K/HIF1α axis (Kim et al., 2017). Pomegranate juice or ellagic acid can inhibit NF-κβ, ERK1/2 MAPKs, JNK, and STAT3 signalling pathways to suppress inflammation (Marin et al., 2013). Intestinal commensal bacteria convert ellagic acid to Urolithin A (UA) which can upregulate miR-10a-5p. This halts CD4+ T cell activation and proliferation in murine gut (Zhang et al., 2019). Pomegranate extract enhances intestinal barrier regeneration by modulating epithelial and stromal cell communication and inhibiting pathogenic bacterial biofilm formation (Rizzo et al., 2023). Supplementation of *P. granatum* peel aqueous extract (6 g of dry peel/day) along with standard treatment showed effectiveness in managing UC cases in a randomized, placebo-controlled clinical trial (Kamali et al., 2015).

Conclusion:

Significant progress has been made in the past decades to decipher the complex immune network, genetic predisposition, gut microbiota dysbiosis, and other factors like diet and stress behind the development of IBD pathology. Since the management of IBD includes both induction and maintenance of remission, the adverse effects of conventional synthetic drugs become more prominent with long-term use. With the increase in IBD cases in India, it may be wise to pay close attention to the traditional knowledge of Indian plant-derived molecules to develop cost-effective and safe drugs. Figure 1 summarizes previous research indicating that various phytochemicals found in plants can target multiple IBD-promoting factors, ultimately reducing symptoms of the disease. However, attention must be paid to instances of adverse interaction of conventional drugs with phytochemicals if they are administered together. Long-term efficacy and safety must be established in clinical trials for the widespread use of these plant-derived compounds to treat IBD. Evidence-based research on immunomodulatory phytochemicals, their bioavailability, and targeting using newer delivery technologies presents hope for a breakthrough in IBD therapy.

Conflicts of Interest:

None

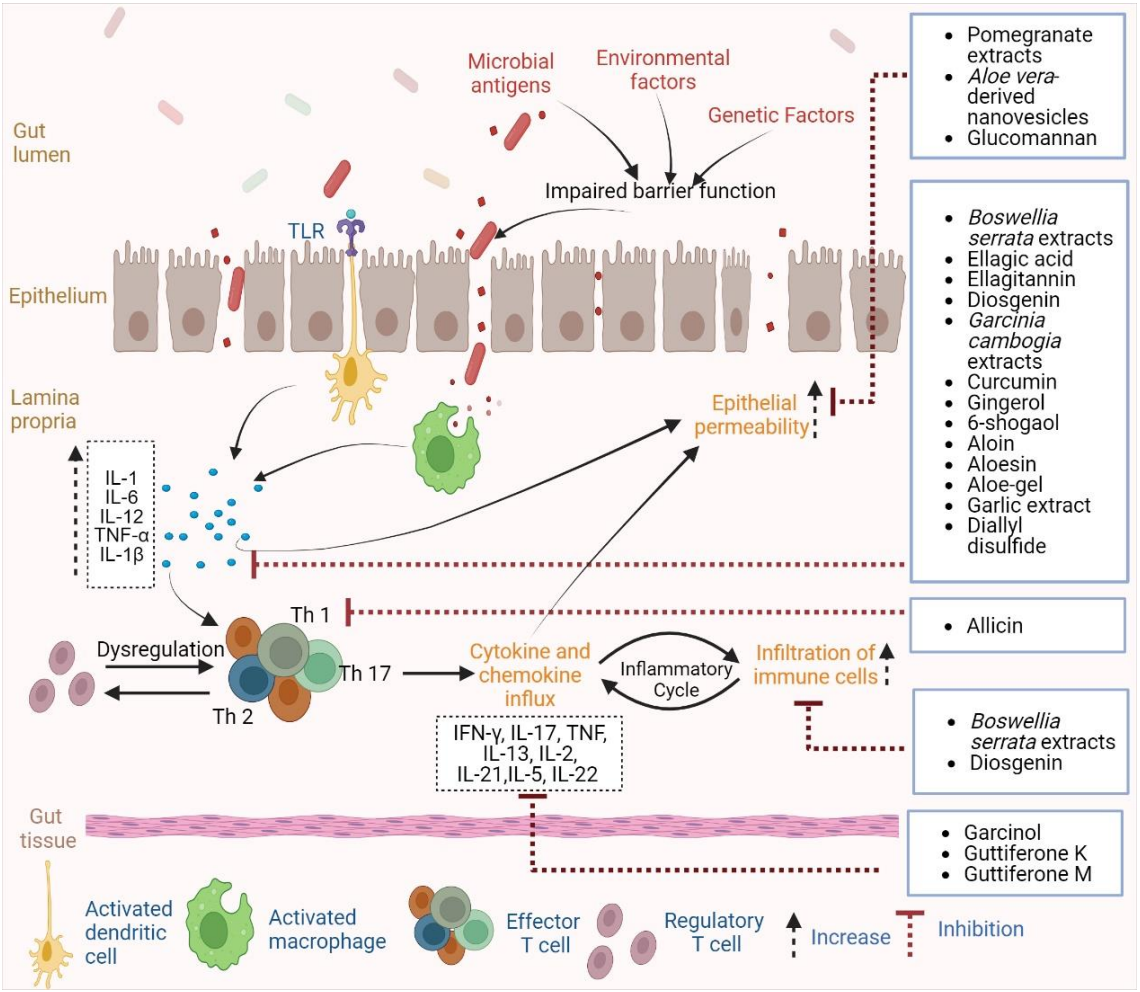

Figure 1. Phytochemicals can modulate different targets to induce and maintain inflammatory bowel disease remission. Created with BioRender.com

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HOW TO CITE

Shantanabha Das, Atri Das and Puja Mishra (2023). Unlocking the Potential of Phytochemicals in Combating Inflammatory Bowel Disease: Insights from Studies with Selected Plants Commonly Utilized in India. © International Academic Publishing House (IAPH), Mrs. Bhanumati Sarkar, Dr. (Professor) Surjyo Jyoti Biswas, Dr. Alok Chandra Samal & Dr. Akhil Pandey (eds.), *The Basic Handbook of Indian Ethnobotany and Traditional Medicin [Volume: 2]*, pp. 32-45. ISBN: 978-81-962683-5-0 DOI: https://doi.org/10.52756/bhietm.2023.e02.003