NEXRES 5 (2026) 101356

Contents lists available at ScienceDirect

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Exploration of medicinal plants, their bioactive molecules and formulations from the Vidarbha region of Maharashtra, India in the treatment of inflammatory bowel disease

Nikhil Y. Yenorkar [a], Ayusha O. Dondulkar [a], Natasha S. Akojwar [a], Raksha A. Purohit [a], Prakash R. Itankar [a], Shashikant Singh [b], Satyendra K. Prasad [a,*]

[a] Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India
[b] Faculty of Pharmaceutical Sciences, Mahayogi Gorakhnath University, Gorakhpur, Uttar Pradesh, India

ARTICLE INFO

Keywords:
Dextran sulfate sodium
Disease active index
Inflammatory bowel disease
Vidarbha

ABSTRACT

The Vidarbha region of Maharashtra, India consists of several medicinal plant species which have been used by tribal peoples for the management of gastrointestinal disorders including IBD. The review focuses on exploring medicinal plants from the Vidarbha region of Maharashtra that have been investigated for the management of Inflammatory bowel disease including their pharmacology, phytochemistry, and safety evidence with special emphasis on the mechanism of action and various pathways involved in it. Data collection in the review was carried out by using published books and various search engines including PubMed, Agroforestry, Science Direct, Google Scholar, and The Plant database, and to draw the structure of a bioactive compound, Chem Draw software was used. Our study reported around 20 medicinal plants from the Vidarbha region that have been successfully investigated for their potential against IBD, some major species include *Mangifera indica* L., *Psidium* guavajava L., *Aegle marmelos* L., *Momordica charantia* L., *Acacia ferruginea* DC., *Allium sativum* L., belonging to the families viz. Anacardaceae, Myrtaceae, Rutaceae, Cucurbitaceae, Mimosaceae and Amaryllidaceae respectively out of which, 13 bioactive compounds were isolated and have been found effective against IBD. Among them, curcumin, kaempferol, rutin, quercetin, lupeol, mangiferin, and stigmasterol were prominent phytoconstituents. Further, the study also includes clinical trial data of some plants that belong to this region. According to collected data NF-kB, COX, and iNOS, STAT, MAPK levels were decreased by the plant extracts and bioactive compounds, which in turn were the main culprits for the occurrence of IBD. The review explored the medicinal role of human-friendly species of the Vidarbha region like *Mangifera indica, Psidium guajava, Aegle marmelos*, and *Momordica charantia* with their mechanism and pharmacological benefits. This study will be useful for improving knowledge about the use of medicinal plants in the treatment of inflammatory bowel disease. Thus, such a detailed information on medicinal plants from Vidarbha region used in treating IBD is reported for the first time, which will help people from these area to conserve such medicinal plants for future generations.

1. Introduction

Traditional system of medicine tends to be unique in comparison to other system of medicines, since it was developed earliest and is a culture-based healthcare practice. This implies that, the knowledge about drugs was communicated vocally by different societies of various cultures. In India, the use of the traditional medicinal plant for curing disease followed from 6000 to 4000 BCE, in Iraq it is active from 60,000 years back whereas, China has a history from 8000 years ago [1]. According to the World Health Organization (WHO), Traditional herbal medicine is a combination of knowledge, skills, and practice based on beliefs, experiences, and theories native to various cultures used in the

Abbreviations: AA, Acetic acid; CAT, Catalase; CD4, Clusters of differentiation 4; COX, Cyclo-oxygenase; DAI, Disease active index; DNBS, Dinitrobenzene sulphonic acid; DSS, Dextran sulfate sodium; TNBS, 2,4,6-Trinitro benzene sulphonic acid; GSH, Glutathione; IBD, Inflammatory bowel disease; IFN-γ, Interferon gamma; IL, Interleukins; iNOS, Inducible nitric oxide synthase; IκBα, Inhibitor of nuclear factor kappa B; JNK, c-Jun N-terminal kinase; LDH, Lactate dehydrogenase; LPO, Lipid peroxide; MAMP, Microorganism-associated molecular patterns; MAPK, Mitogen-activated protein kinase; MDA, Malondialdehyde.

* Corresponding author.
E-mail address: skprasad.rs.phe@itbhu.ac.in (S.K. Prasad).

https://doi.org/10.1016/j.nexres.2026.101356
Received 26 December 2025; Accepted 15 January 2026
Available online 16 January 2026

diagnosis, prevention, improvement, and treatment of mental and physical illness [2]. This is because it involves many health practices, routes, and beliefs including Medicinals and creatures as well as medicine from minerals, devotional therapies, manual methods, and physical activities. According to Rigveda ancient people learned to differentiate between edible plants and poisonous plants by observing the animals. Worldwide there are 2,50,000 flowering plant species, from which 50, 000–70,000 genera have been used in conventional and contemporary medicine. Of globally available plant species, only 15 % of plant species are phytochemically classified and 6 % have been screened for biological activity [3]. Indian system of medicine (ISM) is based on the theory of five elements (Panch Mahabhuta) and three humoralism (Tridosha) including Prithvi, Jala, Vayu, Agni, and Akasha, and tridosha including Vata, Pitta, and Kapha [4]. In the Ayurvedic system, around 8000 herbal remedies have been included and recommended for therapeutic uses. In ISM 2000–2500, plants used for medicine preparation, include 1200–1800 in Ayurveda, 500–900 in Siddha, and 400–700 in Unani [5]. Charak Samhita elucidates every facet of Ayurvedic medicine although the Sushruta Samhita explains the science of surgery [6]. Till now, they are used in the classical formulation of medicine in the Ayurvedic system of medicine. Many people in rural areas use herbal plants for the treatment of various diseases even though they do not know the scientific cause of the activity. Therefore, there is a huge scope of research in that area to provide scientific justification for the traditional uses of medicinal plants. There are certain government and private institutions introduced for conducting research on medicinal and aromatic plants. Currently, the Ministry of Ayurveda Unani Siddha Homeopathy (AYUSH), India maintains the ISM, as promoted by the government of India. Significant research data on several plants has been found in Indian laboratories, including *Acorus calamus* (Tranquilizer), *Allium sativum* (antihyperlipidemic), *Boswellia serrata* (anti-inflammatory), and *Curcuma longa* (anti-inflammatory), etc. [2].

According to a WHO, report, worldwide 80 % of people use traditional medication as first aid due to the adverse effects of allopathic medicines which are sometimes life-threatening. Herbal medicine has a wide spectrum of activity due to the presence of multiple phytoconstituents. There is extensive scope in developing novel drug delivery of bioactive molecules from natural origin in the treatment of various diseases [7]. However, there are some limitations associated with herbal drugs such as low solubility and low permeability. As a result, absorption of the drug is limited at the targeted site. To overcome the above issue, researchers are giving more attention to preparing effective targeted formulations by using advanced technology in treating different disorders.

2. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a severe idiopathic inflammatory disease of the gastrointestinal tract, having two types i.e. Ulcerative colitis (UC) and Crohn's disease (CD) characterized by the alteration of exacerbation and remission [8]. It is associated with symptoms like abdominal pain, diarrhoea, weight loss, bleeding in stool, and nutritional deficiencies. Over the globe, 6.8 million people are affected by it. IBD is mostly common in young and middle-aged people, and in chronic conditions, IBD may also progress to colon cancer [9]. UC was first described in 1793 by Matthew Baillie, later in London Samuel Wilks conceived the term ulcerative colitis. There are gut bacteria that play an important function in the development of UC which are *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* [10]. Another type of IBD is Crohn's disease, which was initially depicted by three scientists Dr. Burrill Crohn, Dr. Leon Ginzberg, and Dr. Gordon D in 1932. In CD, it covers the whole GIT, however, the probable location is the end part of the small intestine i.e., the ileum, and this inflammation extends over the abdomen. Here, the mortality rate is higher than in ulcerative colitis, where 70 % of people require surgery. The symptoms include irritation in the lowest right-hand side gut and loss of blood from the end part of GIT, which is usually lesser than that of UC. It is transmural inflammation spread in a noncontinuous manner and may involve any part of GIT. The gut microbiota that are linked to CD are *Blautia, Faecalibacterium,* and *Ruminococcus* [11]. The specific pathophysiology behind inflammatory bowel disease is yet to be known entirely, but some factors are considered major contributors, such as environmental factors, bacterial contamination, changes in the immune system, and genetic variations. The genetics involvement risk associated with UC is about 1.5–28 % in UC and 1.5–24 % in the case of CD [12]. Also, an imbalance in pro-inflammatory and anti-inflammatory cytokines leads to a progression of IBD. Several studies demonstrated that, in UC, high levels of lactic acid and fructose from the ingestion of protein from milk and animals, and polyunsaturated fatty acid leads to an increased progression of ulcerative colitis [13].

Current treatment for IBD includes either employment of drugs or surgical intervention. In pharmaceutical treatment, the drugs are divided into five categories such as agents that reduce inflammation, immunosuppressants, biologics, antibiotics, and corticosteroids. The anti-inflammatory agent is the first choice of drug in the cure of various disorders, as it minimizes inflammation at the wall of the intestine. Drugs involved in this category are sulfasalazine, mesalamine, Olsalazine, and balsalazide. This oral aminosalicylate is linked to several side effects such as cardio and hepatorenal toxicity and sexual dysfunction [14]. Another category which is immunosuppressant agents prohibits the activation and proliferation of lymphocytes e.g. methotrexate, cyclosporin azathioprine, 6- 6-mercaptopurine, and tacrolimus. Hepatotoxicity, pancreatitis, and stomach pain are common side effects of immunosuppressive medication. Methotrexate is also allied with leukopenia, ulcerative stomatitis, predisposition to infection, and acute pneumatics. Biologic agents including infliximab, certolizumab, natalizumab, adalimumab, and pegol act by maintaining microbial balance in the gastrointestinal tract and decreasing intestinal pH. Associated side effects of biological agents are white patches in the mouth, runny nose, joint pain, cough, painful frequent urination, and high cholesterol. Corticosteroids are the agents that reduce the inflammation by down-regulating the nuclear factor kappa B (NF-kB) and proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukins 1 (IL-1), and interleukin-6 (IL-6). Corticosteroids including prednisolone, methylprednisolone, and budesonide, have certain side effects like it causes cataracts, psychosis, bone softening, increased risk of infection, and high blood sugar [15]. Antibiotic agents e.g., clarithromycin, sulfoximine, ornidazole, and ciprofloxacin, are used as adjuvant therapy in Crohn's disease. Surgical treatments are given to those who are not responding to the pharmaceutical treatment. In surgical treatments, there are two types of surgery one is colectomy, and another is ileal pouch-anal anastomosis (IPPA). There are certain drawbacks of this surgical treatment for the reason that it causes pelvic sepsis, portal vein thrombosis, and Pouchitis, with a risk of serious effects after surgery such as pelvic nerve injury. In addition, it is a complicated treatment that has a risk of increasing disease conditions and an elevated risk of dysplasia in the pouch [16].

Currently, available pharmaceutical therapy for the management of IBD has an adverse effect that may turn life-threatening in case of toxicity. Therefore people are moving towards natural-based medicine as it has fewer side effects and low toxicity, as it originates from nature and contains a wide spectrum of components. Traditional medicine-derived compounds reported to protect intestinal barrier integrity by elevating tight junction protein zona occludens (ZO-1), claudin-1, and occludin also reduces oxidative stress, maintain gut microbiota homeostasis, and decrease proinflammatory cytokines [17].

3. Pathophysiology of IBD

The definite etiology of IBD is unknown, though some causes seem to be responsible for the progression of inflammatory bowel disorder such as environmental factors, a mutation in the gene, epithelial barrier

integrity microbial contamination and, innate immunity.

Environmental factors including excessive smoking, smoking leads to toxicity to the immune and mucous-secreting cells and causes alteration in the microbiome and autophagy. Processed meat and saturated fatty acids-rich food increases the risk of IBD. The use of antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and statins cause changes in the intestinal microbiome that may increase the risk of IBD. Microbial dysbiosis is one of the reasons for the induction of IBD, due to microbial dysbiosis the anti-inflammatory bacteria decrease and increase inflammatory bacteria. Reduction in the *Firmicutes* and elevation in *Proteobacteria* and *Bacteroidetes*. *Proteobacteria* like *Escherichia coli* disturb the permeability of the intestine, further, they modify the diversity and composition of the microbiota and produces inflammatory responses [18].

In the Genetic factors, nucleotide oligomerization domain-2 (NOD-2) is located on the 16 q 12.1 chromosome which is mainly associated with IBD. 2404 variants gene of NOD-2 has been documented till now with specific phenotype [18]. It is found in epithelial cells, macrophages, T cells, endothelial cells, and paneth cells. NOD-2 is explicit in myeloid and paneth cells and causes autophagy by recruiting the ATG16L1 autophagy gene to the plasma membrane at a bacterial site. Mutation in the NOD-2 alters the localization of ATG16L1 to the plasma membrane, which causes the retaining of ATG16L1 protein in the cytosol. It results in a disturbance in the removal of intracellular bacteria that aggravates the release of proinflammatory cytokines that increase the risk of IBD. NOD-2 polymorphism activates signaling pathways like NF-kB and mitogen-activated protein kinase (MAPK) that lead to the release of proinflammatory cytokines such as TNF-α, IL-1β, IL-8, and IL-16, and also activates the Th1 immune response [8].

NOD-2 is coupled with receptor-interacting protein-2 (RIP-2), through CARD homotypic interaction followed by tumor growth factor-beta (TGF-β- activated kinase) TAK1, TAB2 (TAK1-Binding protein 2)-TAB3 that causes IkB kinase (IKK) complex stimulation and phosphorylation of NF-kB inhibitor α (IkBα). This activation of IkBα degrades cytoplasmic release and NF-kB translocation and elevates the release of proinflammatory cytokines. NOD-2 deficiency affects both the innate and adaptive immune system as the monocytes, macrophages, T lymphocytes, and regulatory T cells (Treg cells) are more aggravated in this case. Increased macrophages and other proinflammatory cytokines lead to the development of colitis. The mutation in NOD-2 also affects the gut microbiota homeostasis due to the altered antimicrobial activity and small intestinal crypt. In disturbed gut microbiota there is an increase in the level of Firmicutes, Bacteroides, and Bacillus which downregulates beneficial bacteria such as *Clostridium XIVa* and unclassified *Lacthnospiraceae* that increases the risk of colitis (Fig. 1) [19].

Epithelial cells and microbiota maintain homeostasis through effective mucosal motility, nutrient digestion, absorption, and immunity. However, in microbial contamination, this homeostasis gets disturbed due to inappropriate dietary habits like intake of junk, unhygienic, and contaminated foods, due to which harmful microbes enter into the gut. Disturbed homeostasis leads to alteration in gut microbiota causing disorganization of the short-chain fatty acid layer simultaneously downregulating mucin secretion and alteration in the tight protein chain layer. Due to this, the epithelial integrity breaks. Disorganized integrity of the epithelial layer allows microbes (especially *Clostridium* and *Helicobacter* species) and immune cells (like macrophages, and antigen-presenting cells) to cross the epithelial layer. These agents recruit the neutrophils and monocytes after which monocytes mature into macrophages, these mature macrophages stimulate proinflammatory mediators such as TNF-α, IL-6, and IL-23 which leads to the initiation of inflammation, and further leads to necrosis. In the case of altering the epithelial barrier, the gastrointestinal tract possessed 1000 species of microbes, due to microbial contamination, harmful bacterial species increases, and beneficial bacterial species decreased. The mucin 2 is the protein responsible for forming a protective barrier in the intestine and thereby controlling the integrity of the intestinal cell. However, the infusion of microbes inside the gut reduces the level of mucin. Toll-like receptor (TLR) plays an important part in mucin secretion; as they identify a commensal-derived product by an adapter protein such as the myeloid differentiation primary response 88 genes (MYD88) and produce mucin on the invasion of microbes. This activation of TLR M activates macrophage, epithelial cells, and dendritic cells on pathogen invasion and stimulates an inflammatory response attributed to the release of inflammatory markers. This release of pro-inflammatory cytokines activates the immune response.

Further, in case of the altered immune response, the CD4 cell differentiates the Th cell into Th1 and Th2, Treg cell, and Th17 cell after proliferation. In IBD the antigene-presenting cells (APC) release IL-12 and IL-23, IL-12 is responsible for the differentiation of CD4 T cells into Th1 cells and releases interferon-gamma (IFN-γ) as well as activates natural killer (NK) and cytotoxic cells although IL-23 emphasizes the Th17 cells and downregulates anti-inflammatory Treg cell response. Th1

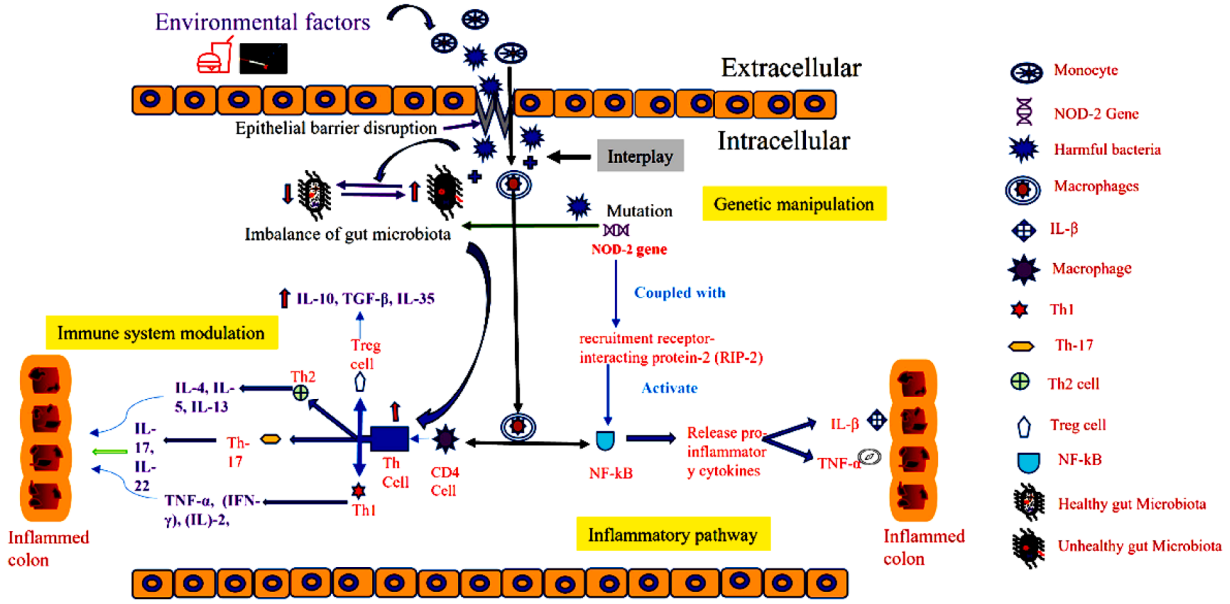


Fig. 1. Pathophysiology of IBD.

cells are mostly responsible for the stimulation of TNF-α, IFN-γ, and IL-2, which are the components of the mediated immune system and Th2 is responsible for the release of cytokines like IL-4, IL-5, and IL-13 [8]. Th1 cells stimulate transcription factor Signal Transducer and Activator of Transcription 1,(STAT1) which promotes the excessive expression of T-β and attracts CD8 T cells, NK cells, and macrophages. TNF-α induces the release of IL-6 and IL-1 which leads to NF-kb and Janus kinase (JNK) pathway activation. In UC and CD, there is an elevated level of IL-6 was observed which shows the severity of inflammation as it is involved in neutrophil infiltration and increases the STAT3 translocation that causes apoptosis resistance of T cells in the intestine by the beta cell lymphoma extra-large (Bcl-xl) and beta cell lymphoma-2 (Bcl-2) antiapoptotic gene activation.

Th17 cells release IL17A, IL-21, and IL-22 which provoke inflammatory response by STAT3 activation. Th-17A allows neutrophil infiltration in inflamed tissue and promotes the production of pro-inflammatory cytokines by macrophages. Treg cells are beneficial for downregulating inflammation as they release anti-inflammatory cytokines like IL10, TGF-β, and IL-35 which maintain the homeostasis of gut mucosa [20]. IL-10 maintains the function of intestinal epithelia by regulating microflora and stem cell intestinal renewal. Another anti-inflammatory cytokine TGF-β regulates immunological homeostasis. IL-10, reduces the effect of IL-17 and impedes antigen-presenting cells. Although, it restricts the CD4 T cell's proliferation and proinflammatory cytokines and chemokines release. TGF-β mainly reduces T-cell proliferation via Treg differentiation [8].

4. Methodology

Data collection: The data related to traditional medicine, Inflammatory bowel disease, and the Vidarbha region were collected using electronic databases such as PubMed, Web of Science, Scopus, Google Scholar, and Agroforestry. The duration of the studies collected for the present study was from 2000 till date. Data regarding traditional medicinal plants were obtained from published books and various journals. Information about forests, climatic conditions, fertile land, etc. were obtained from Agroforestry. For the database search, we used keywords like "Traditional medicinal plant" # IBD and Vidarbha region # Traditional medicinal plant # IBD. The structure of bioactive molecules drawn by using Chem Draw software.

Inclusion criteria: In the review we mainly focused on the medicinal plants found in a Vidarbha region of Maharashtra, India that are used for the management of IBD. Here we included 20 medicinal plants namely *Boswellia serrata, Psidium guavajava, Mangifera indica* etc. In this review, we reported the medicinal plants from the Vidarbha region which are traditionally used for gastric problems and inflammatory disorders. Included data comprises the research articles on medicinal plants which explain ethnobotanical survey, i*n vitro* and i*n vivo* studies, and observational study. The medicinal plants included in the study showed phytochemical and pharmacological evidence, mechanism of action and efficacy which supports the effectiveness of plant.

Exclusion criteria: We excluded the plants which was not native to the Vidarbha region, and were not reported to have gastroprotective activity.

5. Vidarbha region

Vidarbha region is situated in the Northern region of Maharashtra state of India, it constitutes 11 districts, and it comprises 21 % population of Maharashtra. There are four regions that share the boundary with Vidarbha region i.e., Madhya Pradesh state to the Northside, Chhattisgarh state to the East, Telangana state to the South, along with Marathwada and North Maharashtra to the West [21]. Marathwada region of Maharashtra comprises 16.53 % area covered by forest and possesses two types of soil red soil and black cotton soil, and a semiarid climate condition is seen due to low rainfall [22]. Some of the major species found in this region belong to the family Moraceae, Fabaceae, Rutaceae, Boraginaceae, and Salvadoraceae [23]. In the western Maharashtra region, 30.7 % of the area is covered with moist deciduous forests, semi-evergreen, and dry deciduous and evergreen forests. Most of the plant species are found belonging to the family Rubiaceae, Anacardaceae, Moraceae and Apocynaceae [24]. 70 % of land in Vidarbha is under cultivation and is mostly classified as black cotton soil, loamy soil, and brown soil (the western region of Vidarbha, where the dry deciduous forest is situated). Rainfall condition in this region is 540 mm to 860 mm whereas some appreciable changes occur in topology, geology, rainfall, and climate. In the Eastern Vidarbha region of Maharashtra, the climate is subhumid with a yearly rainfall of 1250 mm, and the nature of the soil is neutral to slightly acidic, noncalcareous, and free from salt accumulation. In the last few years, most of the plants have been processed through cultivation, gardening, and social forestry. Nowadays plants grow naturally on roadsides, in forests, and as a weed, consistently in cultivated fields [25]. Gondia district of Vidarbha region has 47.08 % forest area and 37.92 % forest-covered is southern mixed dry deciduous in nature and is surrounded by lofty hills. In this region, one-third part of the district is covered by jungle, which constitutes larger plants that are found to be applicable in medicine. In this region, 13 species of pteridophytes have been identified. People belonging to tribal communities use this pteridophyte for treatment purposes, as they are found to be effective against bacteria, fungi, viruses, cancer, rheumatism, fertility, diabetes, and diuretics, and act as a hepatoprotective [26]. There are 52 plants belonging to 34 families, found in the Wardha region, being known for their antidysentery property and stomach ailments. People use distinct parts of these flora-like seeds, roasted seeds, tubers, fruits, leaves, powder, latex, decoction, plant cold extract, leaf ash, and leaf decoction to gain their medicinal benefits [27]. The percentage of forest area covered in different districts of the Vidarbha region is depicted in Fig. 2.

6. Medicinal plants reported against IBD

There are distinct varieties of medicinal plants found in the Vidarbha region of Maharashtra, that are traditionally used by scientific as well as tribal communities for the treatment of various diseases including inflammatory bowel disease. Traditional herbal medicine has a low adverse effect compared to pharmaceuticals, as it originates from natural sources. The protective mechanism of medicinal plants and their bioactive in the treatment of IBD is depicted in Fig. 3. Here we have explained the traditionally used medicinal plants from different districts of the Vidarbha region with their scientific justification in the treatment of IBD.

6.1. *Acacia saligna (Labill.)*

Acacia saligna L. belongs to the Fabaceae family and is locally found in the Wardha district of the Vidarbha region. Shoots of this plant are beneficial in curing bowel syndrome. Heba et al. (2020) have reported the effect of *A. saligna* butanolic extract (ASBE) and its nanoformulation in the colitis model. In a study, the author has prepared butanolic extract, and *A. saligna* butanolic nano-extract and checked its protective activity in 2 ml of 4 % acetic acid-induced UC. Silver nanoparticles of ASBE were prepared by the spontaneous emulsification method, and it was administered in the form of nano-emulsion via the intraperitoneal route. From the study, it was observed that ASBE consisted of flavonoids, saponins, quercetin, and a polyphenolic compound which would be responsible for reducing oxidative stress and inflammation. From a macroscopy, it has been observed that when ASBE was combined with silver nanoparticles it showed better improvement with no evidence of ulceration than ASBE extract alone. 100 mg/kg of ASBE nano-extract has a more prominent effect on inflammatory biomarkers as it greatly downregulated the level of elevated pro-inflammatory agents such as cyclooxygenase-2 (COX-2), prostaglandin-E2 (PGE2), and (IL-1β). From

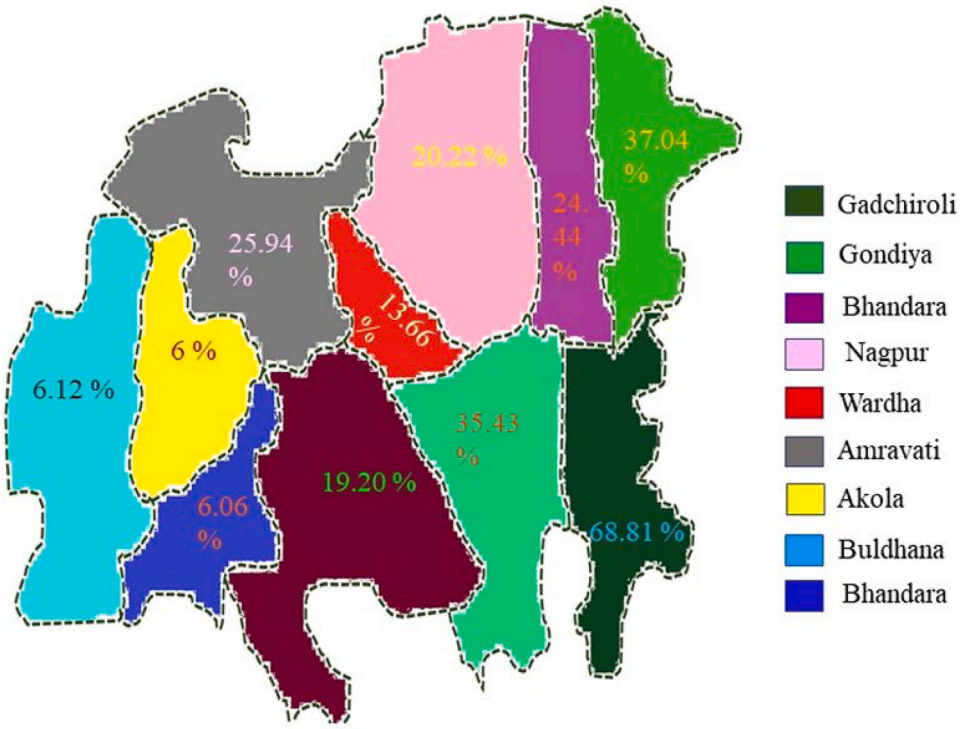


Fig. 2. Percentage of forest area covered in different districts of Vidarbha region.

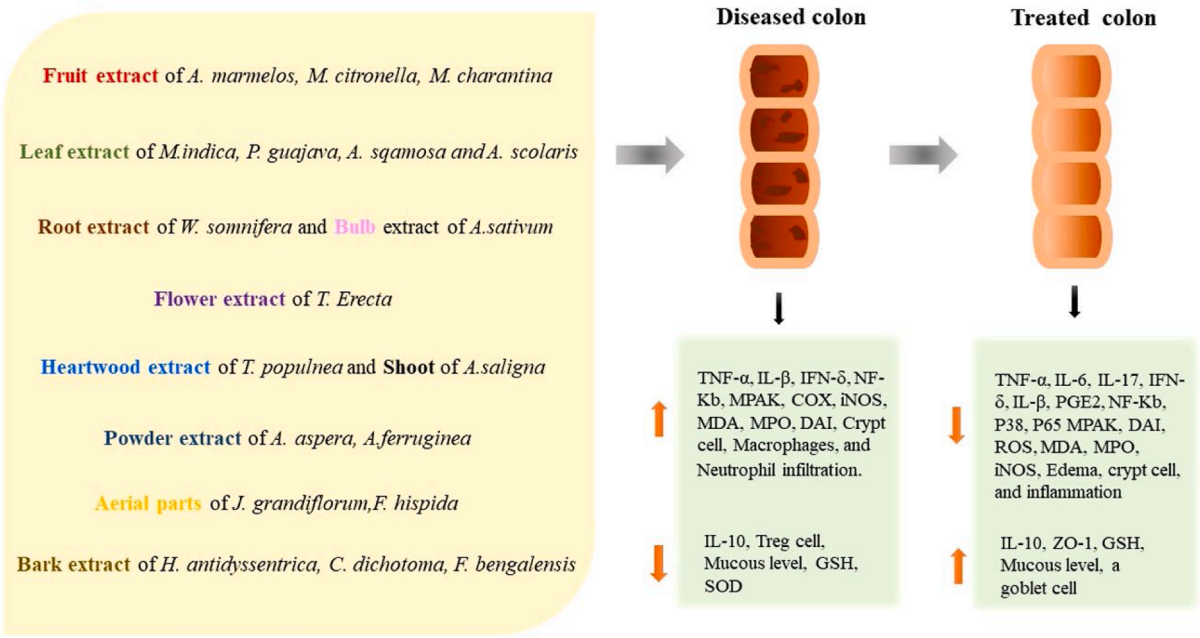


Fig. 3. Protective effect of medicinal plants and their bioactive against IBD.

the histopathology of the inflamed colon, it proved that the ASBE nano-extract revealed better improvement in damaged colonic tissue than single extract treatment and showed better results than standard dexamethasone. After treatment, it showed intact mucosa with glandular structure and goblet cells. So, from this observation, it was concluded that the ASBE+ silver nanoparticle revealed better results as compared to a single extract and standard dexamethasone [28]

6.2. *Acacia ferruginea DC. (Mimosaceae)*

Acacia ferruginea DC. is locally found in the Wardha district of the Vidarbha region in Maharashtra and is conventionally used as a remedy for bowel disease. Sakthivel et al. (2014) evaluated the potential of *A. ferruginea* in curing colitis. Here, the author prepared a methanolic extract of powder plant material and determined its protective activity against 3 % AA-induced UC rat model. Phytochemical evaluation of the extracts revealed the ubiquity of polyphenolic compounds, terpenoids,

flavonoids, alkaloids, tannins, steroids, etc., which may act as active phytoconstituents responsible for the prevention of disease. In this study, methanolic extract at a dose of 10mg/kg mixed with gum acacia was administered intraperitoneally and assessed for various parameters such as the level of superoxide dismutase (SOD), nitric oxide (NO), inducible nitric oxide synthetase (iNOS), malondialdehyde (MDA), glutathione (GSH), myeloperoxidase (MPO) and COX-2, along with the effect on Nf-kB transduction pathway. Observation suggested that a decrease in NO, and MPO levels, prevented the GSH, which acts as a natural antioxidant and increases the level of SOD. Inflammatory markers such as TNF-α, IL-1β, IL-6, and proteins like COX-2 and iNOS were downregulated. Further, the extract also inhibited the translocation of Nf-kB. Histopathological evaluation revealed that the methanolic extract prevented colonic damage and mucosal injury as compared to UC rats. Hence, the study revealed that the methanolic extract of *A. ferruginea* effectively prevented disease when compared with standard sulfasalazine [29].

6.3. *Alstonia scholaris L. (Apocynaceae)*

Kandhare et al. (2016) investigated the protective role of the alkaloidal fraction of leaves of *A. scholaris* (AFEAS) on AA induced ulcerative colitis rat model. *A. scholaris* is locally grown in the Nagpur region of Vidarbha, Maharashtra. In this study, intrarectal instillation of AA increases the level of MDA, MPO, NO, xanthine oxide (XO), and proinflammatory cytokines and decreased SOD and GSH levels. Imbalance in the above factors leads to a progression of inflammation and further cause necrosis, and mucosal damage. In the performed study, UC was induced by rectal administration of 4 % AA and the above-mentioned factors were evaluated. After oral administration of 40 and 80 mg/kg of AFEAS, the macroscopic score, stool consistency, ulcer index, and body weight of the animal were improved. In the case of serum estimation, the level of lactate dehydrogenase (LDH), colonic nitrate, colonic xanthine oxide, and colonic carbonyl content was increased, and the increased level of these parameters caused the progression of the disease, which was found to improve after the administration of AFEAS in AA-induced colitis rats. It was detected that, after AFEAS administration the level of GSH and SOD were increased. When AFEAS was administered, they found that the level of MDA and MPO were improved and reduced pro-inflammatory cytokines such as TNF-α and IL-1 which were elevated in the AA-treated group. Histopathological study of the AA-induced colitis rat produced necrosis, colon tissue erosion, crypt formation, edema, inflammation, and loss of goblet cells. However, after treatment with AFEAS, histopathological results showed that oral instillation of AFEAS ameliorated the extent and severity of cell damage induced by AA. From the study, it was concluded that treatment with an AFEAS attenuated acetic acid-induced ulcerative colitis, by its anti-inflammatory and antioxidant capacity via downregulation of reactive oxygen species (ROS) and pro-inflammatory Cytokines [30].

6.4. *Annona squamosa L. (Annonaceae)*

Annona squamosa is grown in a Nagpur, Bhandara, Gadchiroli district of the Vidarbha region of Maharashtra. Ibrahim et al. (2015) performed a study on *A. squamosa* leaf aqueous extract against AA-induced ulcerative colitis. UC was induced by intrarectal administration of 4 % AA, in the treatment group 300 mg/kg aqueous extract was administered. Results revealed that the aqueous extract of *A. squamosa* showed high free radical scavenging activity in DPPH assay with an IC_{50} value of 157.2 μg/ml as well as higher antioxidant capacity. The *in vivo* results suggest that the aqueous extract elevated the level of catalase, SOD, and GSH, and a decrease in MDA level was observed. From the histopathological staining, it was found that AA-induced colonic tissue showed distorted crypt cells and ulcers, and reduced goblet cells were observed, after treatment with an aqueous extract of *A. squamosa* improved histopathological score was found. The increased proinflammatory cytokines such as TNF-α, IL-6, TGF1β C-reactive protein, and 8-hydroxy 2′-deoxyguanosine (8-OHDG) were reduced after aqueous extract administration also the vascular endothelial growth factor (VEGF) and T3 and T4 level were found to be increased after treatment. Hence from the results it was proven that the aqueous extract of *A. squamosa* effectively ameliorated AA-induced ulcerative colitis [31].

Saleem et al. (2013) have studied the curative effect of the alcoholic extract of *Annona squamosa* on AA-induced ulcerative colitis. In this study, sulfasalazine was used as a standard against the ethanolic extract of *A. squamosa.* Intrarectal administration of 4 % AA produced inflammation, distorted crypt cells, necrosis, diarrhea, damaged colon epithelium, and reduced goblet cells which resulted in UC. When a high dose of 300 mg/kg of ethanolic leaf extract of *A. squamosa* was given, it showed a reduction in necrosis, diarrhea, ulcer index, distorted crypt cell, and mucosal inflammation, and the goblet cell was found to be normal. The level of MDA and MPO was found to be decreased in the treatment group, so the oxidative stress was ultimately reduced. After administration of ethanolic leaf extract of *A. squamosa* there was improvement in the level of SOD, GSH, and catalase (CAT). From the above study, it was concluded that the ethanolic extract of *A. squamosa* attenuated the AA-induced ulcerative colitis. It showed reactive oxygen scavenging and anti-inflammatory activity, which may be attributed to the presented chemical constituents such as flavonoids and polyphenols [32].

6.5. *Agele marmelos L. (Rutaceae)*

Another plant found in the Chandrapur, Gadchiroli, Akola, and Wardha districts of the Vidarbha region, *Agele marmelos,* is traditionally used in the treatment of IBD and is locally called Beal. *A. marmelos* has medicinal properties as it acts as an anti-inflammatory, anti-diabetic, etc. Behera et al. (2012) have studied the protective effects of *A. marmelos* in UC and indomethacin-induced enterocolitis. They prepared the pulp extract using the unripe fruit of *A. marmelos* and assessed the phytoconstituents present in it by phytochemical screening. IBD was induced by 4 % AA administration and enterocolitis was induced by indomethacin, and it was evaluated for the following parameters such as disease activity index DAI, SOD, and MDA level. After oral administration of 250 mg/kg extract, the macroscopic evaluation like DAI, colon length, and animal weight were improved, MDA level increased in the case of IBD and showed more ROS hence the oxidative stress increased, which was decreased after oral administration of the extract. After treatment with extract, a significant downregulation in the level of MDA was observed. In the histopathology, the colitis-induced group represented distorted crypt cell formation, lymphoid hyperplasia, neutrophil infiltration, and submucosal inflammation, these all-histopathological parameters were improved in both cases after *A. marmelos* extract was administered. The above-observed result concluded that the unripe fruit peel extract of *A. marmelos* showed a potential effect against AA-induced IBD and indomethacin-induced enterocolitis [33].

6.6. *Allium sativum L. (Amaryllidaceae)*

Allium sativum commonly known as garlic is found in a Bhandara, Gadchiroli, Nagpur, Amravati and also other districts of Vidarbha region of Maharashtra. Traditionally it is used as a gastroprotective, stomachic, and other inflammatory disorders. In a study performed by Recinella L et al. (2022), the assessment of the anti-inflammatory and antioxidant effect of *Allium sativum* extract on LPS-induced UC was designed. In that, they prepared hydroalcoholic garlic extract (GHE)and garlic water extract (GWE) and checked their protective activity against LPS-induced ulcerative colitis. Results of HPLC-DAD-MS analysis revealed that the GWE was rich in catechin and benzoic acid and GHE was rich in catechin, other compounds such as gallic acid, chlorogenic acid, p-coumaric acid, benzoic acid,t-ferulic acid, resveratrol, naringenin and, hesperetin were present. The toxicological and pharmacological studies revealed

that GHE 1–100 μg/ml downregulated the inflammatory markers including TNF-α, IL-6, NF-kB, and COX-2, in LPS induced colitis model. GWE at a dose of 1–100 μg/ml inhibited TNF-α, NF-kB, and IL-6 and at a higher concentration, it suppresses COX-2 gene expression in LPS induced colitis model. Both GHE and GWE extract reduced LPS-induced PGE2 levels in extracted colon specimens hence it showed an anti-inflammatory effect. In an LPS-induced RAW 264.7 cell line, the catechin from the garlic extract significantly suppressed iNOS, COX-2 protein further reduces IL-6, TNF-α mRNA level. The GHE was more effective in reducing the gene expression of COX-2, IL-6, and PGE2 levels than GWE in LPS-induced RAW264.7. Further, they assessed the effect of garlic extract on the 5HIIA/5-HT ratio induced by LPS, results revealed that the LPS-induced ratio of 5HIIA/5-HT was found to be decreased more in the GHE (100 μg/ml) than GWE. LPS causes the overproduction of ROS, which increases oxidative stress and leads to disturbed gastrointestinal barrier integrity, both the GHE and GWE extracts showed antioxidant activity by increasing the production of catalase, superoxide dismutase, and glutathione peroxidase. Therefore from the above results it was concluded that GHE and GWE, particularly GHE were more effective in the prevention of LPS-induced inflammatory bowel disease [34].

Tannikulu et al. (2020) have performed a study on garlic oil in treating AA-induced IBD. The study included the preparation of garlic oil and determined its potential against AA-induced colitis. The 5 % AA-treated animals presented macroscopic damage and increased hydroxyproline level, which is a crucial component of a structural protein and plays a crucial role in the synthesis and stability of collagen and it has major importance in wound healing. Animals were administered 5 ml/kg garlic oil intrarectally and 5 ml/kg intraperitonially hence it reduced the level of hydroxyproline, TNF-α and IL-β. Also, the macroscopic score was improved in both cases. In the case of histopathology, the distorted crypt cells, edema, neutrophil infiltration, and necrosis were reduced in both intrarectal and intraperitoneal administration, whereas topical treatment showed better response. Therefore, from the study, it was concluded that the intrarectal administered garlic oil significantly attenuated the AA-induced IBD [35].

Another study was performed on Allicin, which is the main component of garlic and has certain activities like anti-inflammatory and antioxidative, etc. Li et al. (2015) evaluated the protective effect of allicin, allicin with sulphasalazine, and allicin with mesalazine in the treatment of 50mg/kg in 50 % ethanol trinitrobenzene sulphonic acid (TNBS)-induced UC and assessed its activity on P38 and JNK pathways. IBD was induced by administrating the TNBS using a catheter and its clinical changes were determined viz. macroscopic scores and histopathological scores. When the allicin 30 mg/kg and allicin combined with mesalazine were administered, it showed better results than sulphasalazine. Allicin with a mesalazine improved macroscopic characteristics which were disturbed by TNBS. The histopathological results showed a decrease in distorted crypt cells, edema, and neutrophil infiltration. It also downregulated the level of proinflammatory cytokines, which were more released in the induced animal. Intragastrically administered allicin with mesalazine reduced the progression of NF-kB transduction pathways and reduced expression of P38 and JNK pathways in Caco-2 cells. Therefore, from the study, it was concluded that the allicin significantly alleviated the TNBS-induced inflammatory bowel disease particularly when administered with mesalazine [36].

6.7. *Achyranthes aspera L. (Amaranthaceae)*

A.aspera is locally found in the Amravati district of the Vidarbha region, Maharashtra, and traditionally its various parts are used in the treatment of IBD. In a study conducted by Bhatt et al. (2013), they prepared a methanolic extract of *A. aspera* (MeAa) and assessed its protective activity against 120 mg/kg in 50 % ethanol Dinitro benzene sulphonic acid (DNBS) induced IBD. A methanolic extract 200 mg/kg was administered via the oral route, and it was observed that the treated group showed a reversal in body weight loss, increased water intake and food intake, and reduced DAI as compared to the DNBS-treated group. Certain biological parameters were altered by DNBS such as MDA, MPO, NO, and SOD. The group treated with a higher dose of MeAa showed a decrease in the MDA, MPO, and NO levels, and it significantly improved level of SOD which ultimately reduced the level of oxidative stress. The histopathological assessment revealed that, after the treatment with a high dose of MeAa, it downregulated the necrosis, inflammation, edema, inflammatory cell infiltration, and reduced level of fibrosis. Therefore, the above study revealed that the MeAa potentially improved the physical, biological, and histopathological parameters that were altered by DNBS. Hence it was concluded that the MeAa effectively ameliorated the IBD [37].

6.8. *Boswellia serrata R. (Burseraceae)*

Boswellia serrata is grown in Nagpur, Gadchiroli, and Bhandara districts of the Vidarbha region of Maharashtra. It is traditionally used to treat inflammatory disorders. A study performed by Thanewala et al. (2021) aimed to determine the anti-inflammatory potential of novel standardized Boswellia extract in DSS-induced IBD. IBD was induced by 2.5 % DSS and the treatment group was administered with novel standardized Boswellia serrata extract consisting of 41 mg/kg of acetyl-11-keto-β-boswellic acid (AKBA) and beta boswellic acid (BBA) 4.1 mg/ml solution for 10 days. The DAI was found to be lower compared to the DSS group, and the length of the colon, and body weight was increased in the treatment group. Histopathological study revealed that the disease group showed distorted crypt cells and lesions, after the treatment with AKBA and BBA the crypt cells and lesions were improved in a dose-dependent manner. Therefore from the study, it was concluded that the novel standardized extract prominently ameliorates IBD [38]

6.9. *Cordia dichtoma G. (Forst) (Boraginaceae)*

Cordia dichtoma G. is commonly called Bhokar in Marathi and is found in the Amravati, Gadchiroli, Washim, Wardha, and Gondiya districts of the Vidarbha region of Maharashtra. A study included the preparation of different extracts using barks of *C. dichtoma* its fractionation and assessment of their protective activity against 5 % AA-induced UC in mice. For treatment, ethyl acetate extract, methanol extract, and n-hexane extract were administered, however, the 50 mg/kg of methanolic fraction of methanolic crude extract was found to be more effective than the other extracts as well as standards such as sulphasalazine and mesalamine. After treating the animals with a methanolic fraction of methanolic crude extract all altered parameters were improved such as MDA and MPO, while oxidative stress and neutrophil infiltration were downregulated and levels of TNF-α, PGE_2, and COX were reduced, the activated ROS system was downregulated. The histopathology and macroscopic results suggested that there was a decrease in diarrhea and abdominal pain. In the histopathology, the group treated with a methanol fraction of methanolic crude extract showed less edema, and no distorted crypt cells were observed. By considering the above results, the study concluded that the methanolic fraction of methanolic crude extract of *C. dichtoma* bark could be fruitful as a complementary agent in ulcerative colitis [39].

6.10. *Ficus hispida L.f. (Moraceae)*

Study undertaken by Gunaseelan et al. (2015) developed and evaluated the curative effect of ethanolic extract of *F. hispida* in the treatment of AA induced IBD. It is locally found in the Bhandara district of the Vidarbha region of Maharashtra. *F. hispida* alcoholic extract was obtained from the aerial part by using the Soxhlet extraction process. In this study, IBD was induced by intracolonic administration of 1 mL 4 % AA, and its clinical changes were determined in animals such as colonic mucosal damage index (CMDI), DAI, morphological and

histopathological changes with LDH, MDA, and NO level were measured. Results showed that after treatment with acetic acid CMDI and DAI were increased. Histopathological study revealed distorted crypt formation, neutrophil infiltrations, erosion, and necrosis. When animals were orally treated with an 400 mg/kg of alcoholic extract of *F. hispida* it was found that the level of MDA, NO, and LDH were normalized, CMDI and DAI were decreased and macroscopic score, as well as histopathological score, were improved. From the study, it was concluded that the ethanolic extract of *F. hispida* effectively attenuated AA IBD [40].

6.11. *Ficus bengalensis L. (Moraceae)*

The present study was conducted to determine the effect of an aqueous extract of *ficus bengalensis* bark against TNBS-induced IBD, and the standard used was prednisolone. The *F. bengalensis* is locally grown in the Amravati, Buldhana, and Gondiya districts of the Vidarbha region, Maharashtra, and is traditionally used in the treatment of inflammatory bowel disease. In this study, the authors used the bark of the plant and macerated it with distilled water for 48 h then evaporated it to get an aqueous extract. IBD was induced by administering 120 mg/kg in 50 % ethanol TNBS by Teflon cannula via the anal route. Aqueous extract of bark *F. bengalensis* (AEFB) was administered via an oral route at a dose of 250 and 500 mg/kg and assessed its protective activity against IBD. It was observed that AEFB at a higher dose inhibited the reduction of food intake, water intake, body weight, and mucosa. It reduced disease activity index DAI, MDA, MPO, and NO levels and reduced oxidative stress significantly. The mesenteric mast cell degranulation was increased by TNBS, whereas on treatment with AEFB, mesenteric mast cell degranulation was downregulated. The histopathological results showed that administered AEFB effectively reduced hyperplasia, edema, and infiltration of inflammatory cells and decreased mild necrosis and ulceration. Therefore, from this study, it was concluded that the presence of flavonoids and phenolic compounds in the bark of *F. bengalensis* may be responsible for anti-inflammatory activity, as flavonoids have mast cell stabilizing effects [41].

6.12. *Jasmine grandiflorum L. (Oleaceae)*

J. grandiflorum is locally grown in the Amravati district of the Vidarbha region of Maharashtra and is traditionally used for the treatment of IBD. Shaikh et al. (2021) performed a study on *J. grandiflorum,* here they prepared methanolic extract by using the aerial part of the shrub and determined its protective potential in 4 % AA induced IBD. The phytochemical screening of the extract confirmed the presence of flavonoids, tannins, phenolic compounds, and steroids. The extract was administered by oral route; it was found that400 mg/kg orally administered extract significantly reduced the ulcer index, lesion, and abdominal pain. There was a decrease in the concentration of membrane protein i.e., 5-claudin and occludin that causes increased permeability of the membrane, so this membrane protein concentration was elevated by the administered extract. In the AA group, the concentration of proinflammatory cytokines was increased such as TNF-α, IL-6, Il-1β, and INF-γ these increased levels of inflammatory cytokines promoted the disease progression. The extract significantly downregulated the levels of these proinflammatory cytokines. The inflammatory pathways such as NF-kB, P65, and caspase-3 were downregulated by extract, which also decreased the level of MPO and MDA and increased the GSH level. Histopathological study revealed decreased distorted crypt cell, edema, necrosis, and reduced neutrophil infiltration. Therefore, from the study, it was observed that *J. grandiflorum* showed anti-inflammatory, antioxidant, and immunomodulatory activity so *J. grandiflorum* acted as a potential therapeutic agent in the treatment of IBD [42].

6.13. *Momordica charantia L. (Cucurbitaceae)*

Nie et al. (2024) studied the ameliorative effects of *Momordica charantia* polysaccharide (MCP) in DSS-induced ulcerative colitis by altering the gut microbiota. In the study, disease-control mice received 2.5 % DSS, and the treatment groups were administered 200 mg/kg and 500 mg/kg of MCP by oral gavage for one week. The result revealed that the treatment group showed lower DAI, and reduced inflammation in addition the histopathological findings showed the improvement in the recovery of extensive mucosal inflammation and edematous submucosal tissues induced by DSS, hence the histological injury score was found to be lower in MCP treated group. The pro-inflammatory cytokines such as IL-6, TNF-α, IFN-γ, IL-1β and COX-2 were found to increase in the disease control group by oral administration of MCP, and the elevated proinflammatory cytokines were found to decrease, Furthermore, chemokines like Cxcl1 and Cxcl2 expression were downregulated in the treatment group. Quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) and western blot analysis revealed that the MCP-treated group showed a higher expression of mRNA and protein of MUC2. Further, it normalized the level of epithelial tight junction protein including Occludin, Claudin, and Zo1. Antimicrobial agents secreted by the epithelial cell are Reg3b and Reg3g which were found to be elevated in MCP treated group compared to the DSS group, which play a crucial role in the colonization and penetration of microbes. They conducted a fecal microbiota transplantation (FMT) experiment to check the therapeutic effect of MCP-altered microbiota on colitis, in that they administered a combination of ampicillin, vancomycin, neomycin, and metronidazole for seven days which led to a reduction of bacterial phylotypes. Donor mice were treated with 500 mg/kg of MCP, fecal microbiota of these mice were transplanted to the DSS recipients group. From the results it was observed that the FMT-MCP group showed less DAI, intestinal injury, and an increase in colon length compared to the FMT-Control group. The level of pro-inflammatory cytokines decreased in the FMT-MCP group. The RNA and protein expression of Muc2 were increased in the FMT-MCP group, and expression of tight junction protein, antimicrobial agents namely Reg3b and Reg3g, and Ki67 levels were found to be elevated in the FMT-MCP group suggesting the increased proliferation rate of intestinal epithelial cells. In the FMT-MCP group, there are more amount of *Allobaculum, Dorea,* and *Sutterella* and a lower amount of the *Oscillospira* and *Ruminococcus* microbiota were found, hence it revealed that FMT-MCP could ameliorate colitis by altering the gut microbiota. Another study was performed to check the effect of MCP in LPS-induced Raw264.7 cells, results showed that there is a dose-dependent decrease in the level of TLR4, NF-kB, and MAPK pathways. Collectively it suggested that inhibiting signaling pathways MCP, maintain the stable immune state [43]

Nal et al. (2019) assessed the anti-inflammatory efficacy of ethanolic *Momordica charantia* fruit extract against the 5 % W/V 100 mg/kg TNBS-induced UC model and simultaneously they measured the carotenoid concentration in the extract by using HPLC analysis. *M. charantia* (Cucurbitaceae) is locally found in the Wardha, Gadchiroli, Akola, and Gondia districts of the Vidarbha region and is naturally used in the treatment of inflammatory illness. Orally administered *M. charantia* ethanolic extract 300 mg/kg enhanced anti-inflammatory cytokine IL-10 levels in the colon and in serum and downregulated the levels of the pro-inflammatory cytokines such as IL-1β, IL-17, TNF-α as well as reduced Th 1 cells. Histopathological analysis showed that ethanolic fruit extract effectively attenuated lesions and damaged crypt in the colon. From the HPLC analysis, it was found that the concentration of carotenoid was 11.73–0.35 mg/g. Hence above study revealed that the ethanolic *M. charantia* effectively attenuated the colitis condition and from HPLC analysis it was found that is a *M. charantia* richer source of carotenoid than other carotenoid-rich food [44].

Veloza et al. (2019) studied the protective effect of BG-4 peptide isolated from the seed of *B. guard* in the lipopolysaccharide (LPS) macrophage and 3 % DSS-induced UC model. In LPS-induced

RAW.264.7 macrophages they found that BG-4 extract 375 ug/ml effectively downregulated proinflammatory biomarkers such as TNF-α, IL-1-β, and IL-6 and lowered the number of inflammatory proteins COX-2 and iNOS, which was observed to be elevated in the case of colitis. 15 mg/kg intraperitoneal administered BG-4 also reduced DAI, the elevated level of MPO in the DSS-induced colitis model, elevated MPO level causes the host tissue damage by facilitating inflammation. It was observed that BG-4 significantly downregulated the concentration of TNF-α, IL-1-β, and IL-6 in serum. Histopathologically IP administration of BG-4 ameliorated the distorted crypt cells and increases the goblet cells. Oxygen radical absorbance capacity assay (ORAC) was performed for antioxidant activity, and it was indicated that the BG-4 has better free radical scavenging properties. Therefore, from the study, it was revealed that BG-4 from bitter guard alleviated inflammatory bowel disease [45].

6.14. *Mangifera indica L. (Anacardiaceae)*

Mangifera indica (Mango) is a medicinal plant found in Chandrapur, Buldhana, Nagpur, Wardha districts of Vidarbha region in Maharashtra. A study conducted by Gutierrez-Sarmiento et al. (2023), evaluated the curative potential of *Mangifera indica* bars in DSS-induced colon inflammation. In a study, colonic inflammation was induced by administrating 3 % DSS, and in the treatment, they prepared a mango diet (DMango) by mixing 200 g of the mango-based bar and 710 g of Purina rodent chow 5001 (D5001) standard diet. DMango diet was supplemented with 7.9 % soya protein,1.25 % soyabean oil, and 1 % Sucrose and sulfasalazine 100 mg/kg used as a standard. The results revealed that the DAI was decreased in the DMango + DSS group than in the standard diet group D5011+DSS, it also prevented reduction in the colon length. The morphological and histological characteristics were assessed by immunofluorescence staining, and the result showed that the DMango diet prevented distorted crypt cells, and inflammation, reduces ulcers, and increased goblet cell production compared to a standard diet. The mucin 2 glycoprotein MUC2 concentration was improved in the DMango diet and downregulated histological injury score. In the PCR study, in a cecum sample DMango group showed lesser DNA. The richness and evenness analysis of intestinal microbiota showed that the DMango + DSS diet administration suggested an increase in the richness of undiscovered species compared to a standard diet. The DMango diet Showed major microbial diversity as the Shannon index was found to be higher in this group. The ratio of firmicutes and Bacteroides was normal in the control group. DMango diet improves *Clostridia* class and downregulates the plenty of Bacilli class. This DMango diet promoted the growth of *Clostridium XIVa, Butirycicoccus, and Kineothrix*, it also encouraged the growth of *Clostridiales, Clostridium IV, Flintibactor, Intestinimonas, Mediterraneibacter, Schaedlerella* genera as well as Lachnospiraceae and Ruminococcaaeae families. DMango diet enriches KEGG pathways, diet facilitates the metabolism of carbohydrates and amino acids as well as promotes cofactors and vitamin metabolism, as well as the metabolism of terpenoids and polyketides, it also attenuates gut dysbiosis. It was observed that the DMango diet plays a crucial role in starch metabolism, sucrose metabolism, amino sugar, and nucleotide sugar metabolism. From the above study, it was concluded that the DMango diet effectively attenuated DSS-induced colonic inflammation as compared to the standard diet D5001 [46].

Marquez et al. (2010) have developed and assessed the potential of *Mangifera indica* aqueous leaf extract (MIE) on the 3 % DSS-induced colitis rat model. In a study, 150 mg/kg MIE leaf extract was prepared and administered orally as well as rectally. Orally administered extract was mixed with carboxymethylcellulose (CMC), and rectally it was administered by using suppositories, and its activity was assessed against increased pro-inflammatory cytokines, elevated MPO, LPO level, and GSH level. Observed results suggested that treatment with MIE both orally and rectally decreased the mucosal damage and downregulated the ulceration and macroscopic score. DSS administration elevated MPO and LPO levels after MIE treatment the level of MPO and LPO were reduced, where LPO served as an indicator of cell membrane damage. GSH is a natural antioxidant present in the body, whereas in the case of the DSS colitis model GSH level was decreased. Treatment with MIE extract via both routes elevated the GSH level. After treatment with MIE, the level of TNF-α, and IL-6 declined, and simultaneously levels of COX-2 and iNOS also decreased. Histopathological evaluation showed that the treatment with an aqueous extract of *M. indica* by both routes minimized inflammation. Hence, according to the results, it was concluded that the MIE adequately protected DSS-induced UC [47].

6.15. *Morinda citronella L. (Rubiaceae)*

Ming et al. (2018) conducted a study on the plant *M. citronella*, which is locally found in the Nagpur, Bhandara, and Amravati districts of the Vidarbha region and is locally called noni. The study included the extraction of polysaccharide from *M. citronella* by hot water extraction and characterized it for molecular weight, NMR analysis, monosaccharide analysis, and methylation analysis and further examined for the ameliorative effect of its extract contrary to 2.5 % DSS-induced IBD. From their results, it was observed that the monosaccharide component consisted of galactose, galacturonic acid, rhamnose, and arabinose also it contains glucose, therefore, it has a neutral nature. From the macroscopic analysis, it was observed that the length of the colon gets shorter in the DSS group which reduced the weight of animals. Treatment with 10 mg/kg Noni fruit polysaccharide (NFP) normalized the colon length and weight of animals and attenuated the DAI score. The histopathology study suggested that the treatment with NFP ameliorated inflammatory cell infiltration and damaged crypt by DSS. Administration of NFP improved the reduced level of ZO-1 and occludin, which was observed in immunofluorescence microscopy. The confocal microscopy resulted in the administered NFP repressed mucus disruption. The mucus disruption gets reduced, and it promotes tissue protection. From the result, it was concluded that extracted NFP is a proteoglycan type of polysaccharide that showed significant protection against DSS-induced inflammatory bowel disease [48].

6.16. *Psidium guajava L. (Myrtaceae)*

Zhang et al. (2024) studied the curative effect of Psidium guajava seed oil against DSS-induced IBD. Psidium guajava is traditionally used for diarrhea and inflammatory disorders, as it is found in Nagpur, Bhandara, and Gadchiroli districts of the Vidarbha region of Maharashtra. In the study, *Psidium guajava* seed oil (TKSO) was found to consist of linoleic acid, oleic acid, and linolenic acid consisting of total fatty acid 87.386 %. IBD was induced by administering 3.5 % DSS orally for a week and the treatment was given at 200 mg/kg as a lower dose L-D and 400 mg/kg as a higher dose H-D and 50 mg/kg of standard 5-aminosalicylic acid. Results revealed that the DAI was reduced in the treatment group and colon length, and body weight were improved in the treatment group compared to the DSS group. In the case of the colonic organ index, the liver and spleen indices were increased in the DSS group, so the thymus index was observed to be elevated. After treatment with TKSO, the thymus index was reduced as it downregulated organ stress. The colon length, bleeding, and atrophy of colon tissue were improved as of the normal group on H-D treatment. L-D and H-D of TKSO treatment significantly reduced intestinal damage, and tissue ulcers and reinstated the structure. The structural integrity was well repaired by H-D treatment of TKSO. The SEM and TEM analysis were performed for ultrastructure analysis of colonic epithelium, from the study it was observed that the L-D and H-D recovered the disturbed microvillous structure showed smoother arrangements, and maintained tight junction protein. The various inflammatory markers including TNF-α, IL-6, and IFN-β were aggravated after DSS administration, treatment with H-D TKSO reduced this marker and showed closer to the control group. The mRNA expression of TNF-α, IL-6, and IFN-β was decreased in colonic tissue after

treatment with H-D. Tissue protein claudin-1 and occludin expression were improved as of the normal group when treated with doses of TKSO. Treatment with TKSO increases the Chao index and Shannon indices which indicates the homogeneity and relative abundance of gut microflora. Community abundance at the phylum level was analyzed, from the study it was found that the ratio of Firmicutes and Bacteroides (F/B) was decreased in the DSS group, and after being treated with TKSO the F/B ratio was found to be increased. Further, they carried out a Spearman analysis to assess the relationship between intestinal microbiota and short-chain fatty acid (SCFA), results showed that the TKSO treatment elevates SCFA levels in colitis mice. The caecal content analysis showed that TKSO treatment increases levels of propionic acid, hexanoic acid, butyric acid, isobutyric acid, valeric acid, and isovaleric acid in DSS-challenged mice. Therefore from the study, it was concluded that the *Psidium guajava* oil effectively treated DSS-induced ulcerative colitis [49]

The plant *Psidium guajava* L. is locally obtained from the Chandrapur, Wardha, Nagpur, and Gadchiroli districts of the Vidarbha region and is routinely used for IBD. Jose et al. (2020) prepared an ethanolic extract of *P. guajava* leaf and administered it via the rectal route in the 4 % AA-induced UC rat model and assessed the parameters like ulcerative index, macroscopic analysis, level of MDA, LPO, GSH, and NO From the observation, it was found that the ulcer index in the treatment group was improved as well as normalized the stool consistency. Also, it was observed that after administration of ethanolic *P. guajava* extract, the level of WBC, RBC, and hemoglobin got normalized which was disturbed in the AA group. The MDA, and LPO, level was decreased by ethanolic extract and increased the level of GSH which acts as a natural antioxidant. Finally, they detected the level of NO which plays a significant role in tissue destruction caused by inflammatory and autoimmune systems. Thus, in the case of the AA model, the level of NO increased; hence they measured stable metabolite of NO that is nitrate or nitrite in the blood by using spectrophotometry. From the result, it was confirmed that pre-treatment with ethanolic extract reduced nitrate levels. Therefore, from the results, they concluded that the ethanolic extract of *P. guajava* 500 mg/kg was effectively ameliorated AA induced UC [50].

6.17. *Thepsia populnea L. (Sol. ex Corrêa) (Malvaceae)*

Nirmal et al. (2015) conducted a study on *T. populnea* which is locally found in the Nagpur district of Vidarbha region of Maharashtra. The objective was to determine the protective effect of varying extracts from the heartwood of plant *T. populnea* in the chronic colitis model. The aqueous extract of *T. populnea* seemed to be more beneficial as compared to another extract. UC was induced by rectally administered 5 mg in 100 ml ethanol DNBS and the different extracts of *T. populnea* were given via the oral route. In the colitis model, various parameters were assessed viz. macroscopic and microscopic score, ulcer index, MDA, MPO, histopathology, and proteas level in the colon. The microscopic study revealed that the level of neutrophils, macrophages, and lymphocytes was increased in the treated group. After treatment with 200 mg/kg heartwood aqueous extract, there was a significant decrease in the level of lymphocytes, neutrophils, and macrophages. Treatment with aqueous heartwood extracts downregulated the level of MDA and MPO. From the histopathological study, it was found that aqueous heartwood extract of *T. populnea* ameliorated the severity and extent of histopathological features and cell damage. Therefore, from the study, it was concluded that aqueous heartwood extract of *T. populnea* effectively alleviated DNBS-induced UC [51].

6.18. *Tagetes erecta L. (Asteraceae)*

Meurer et al. (2019) prepared a hydroalcoholic extract of the *T. erecta* flower and evaluated its ameliorative potential against 5 % DSS-induced UC. *T. erecta* is locally found in the Amaravati district of the Vidarbha region and is traditionally used for the treatment of inflammatory gut diseases. Here the author induced ulcerative colitis by orally administering DSS, it altered certain parameters which ultimately contributed to the progression of the disease. When the 300 mg/kg extract was administered, a decrease in the macroscopic score was observed. The extract also ameliorated the distorted crypt cell, reduced neutrophil infiltration, diarrhea, and abdominal pain, also it showed a decrease in the level of MPO which leads to downregulating oxidative stress. Certain proinflammatory cytokines were activated in the DSS-treated group like TNF-α, IL-6, and proinflammatory T cells, which contributed to disease progression, which was found to be reduced by administration of the extract. This decrease in the proinflammatory cytokines may be due to the presence of lutein in the extract. The level of SOD got normalized and GSH and CAT levels were elevated in the treatment group. The histopathological report suggested that there was no distorted crypt cell formed, and reduced edema and necrosis on treatment. Therefore, from the above study, it was concluded that *T. erecta* hydroalcoholic extract could be used as a nutritional supplement in the treatment of IBD [52].

6.19. *Withenia somnifera L. (Dunal) (Solanaceae)*

Pawar et al. (2011) have developed a thermoreversible rectal gel using *W. somnifera* aqueous root extract in the treatment of IBD. In this study, the IBD was induced by 100 mg/kg in 50 % ethanol TNBS by rubber catheter. The TNBS-treated animal showed clinical changes like higher DAI, diarrhea, abdominal pain, and weight loss and the chemical changes include an increased level of MDA and decreased level of SOD. After the induction of IBD, from the 4th to the 14th day thermoreversible gel was applied intrarectally, and the results were assessed after the 14th day. The histopathological results of the colon showed normal mucosa, no distorted crypt cell formation, and reduced edema. In the case of standard mesalamine, animals showed some distorted crypt. The macroscopic result reported that there was a decrease in DAI, and diarrhea, also the levels of NO, IFN-γ, and IL-12 were decreased. The *W. somnifera* aqueous root extract 100 mg/kg gel also showed a significant increase in antioxidant enzymes like SOD and GSH. Hence, from the study, it was revealed that the antioxidant and anti-inflammatory effect of *W. somnifera* aqueous root extract potentially attenuated the TNBS-induced IBD [53].

7. Clinical trials on IBD

Vahdat et al. (2020) studied the meta-analysis of a randomized control trial on resistant starch intervention for circulating inflammatory biomarkers. Resistant starch is a diet component that is an undigestible starch that resides in the small intestine and is then fermented into SCFA in the colon. In a study amongst the 413 publications, 213 were promoted for the second screening, and from that 185 studies were omitted due to the lack of relevance. After a final screening, 13 studies with 14 effective sizes were included and these studies were published between 2011–2019. Of the 13 studies, 10 studies were parallel design and three studies were cross-over design. The total participants included were 672, 329 in the intervention group and 343 in the control group. Based on the Down and Black assessment tool seven studies were found to be good quality and the rest of low-quality. Results revealed that the resistant starch showed a nonsignificant reduction in C-reactive protein (CRP) concentration. Similarly, the effect of resistant starch on TNF-α was assessed, and the result showed that a decrease in TNF-α was observed in serum as compared to the control group. Resistant starch also reduced the level of IL-6 proinflammatory cytokine. From the observed results it was concluded that the resistant starch showed an anti-inflammatory effect [54].

Morshedzadeh et al. (2021) performed an open-labeled randomized control trial to study the effect of flaxseed supplementation on metabolic syndrome parameters, insulin resistance, and inflammation in UC patients. 70 participants were selected for study, amongst them 64 were

finalized and divided equally into control group and intervention group. The 30 g of flaxseed supplementation reduced the level of fasting blood sugar (FBS) as compared to the control group and also showed a slight decreased in insulin, triglyceride, total cholesterol, and high-density lipoprotein (HDL). Further, the flaxseed supplementation decreases the Simple Clinical Colitis Activity Index (SCCAI) score, as it decreases the level of proinflammatory cytokines TNF-α and also reduces CRP [55]

Johari, and Gandhi, (2012) performed a randomized single-blind parallel-group study in ulcerative colitis patients to check the efficacy of the plant *Holarhhea antidysentrica* L. The study consisted of 30 patients treated with mesalamine tablets alone, mono-herbal tablets, and mesalamine combined with the mono-herbal tablet. They prepared a tablet of 760 mg using *H. antidysentrica* bark extract in the WHO-certified company manufacturing unit. All the patients were included after the completion of certain processes like informed consent, inclusion, and exclusion criteria. They were included 18 males and 12 females aged between 20–60 years and the protocol of the study was designed in such a way that, group I was treated with mesalazine, group II treated with monoherbal tablet, and group III treated with a combination of both mesalazine and monoherbal tablet. Before the study, the patients complained about symptoms like bloody stool, abdominal pain, increased bowel frequency, and severe diarrhea. When the mesalazine was administered, patients experienced relief from constipation and diarrhea, also abdominal pain was reduced, but the group I showed some infection in the stool. In group II, when the 750 mg/kg monoherbal tablet was administered, it was observed that abdominal pain, diarrhoea, and stool frequency were reduced. In the last group, when the mesalazine was combined with a monoherbal tablet, it gave better results than groups I and II and showed no side effects. Hence from the results, it was revealed that the mesalazine combined with monoherbal tablet of *H. antidyssentrica* potentially attenuated the UC without any side effects and reemission of the symptoms [56].

A randomized multicenter double-blind placebo-controlled trial was performed by Hanai et al. to evaluate the effect of curcumin on the treatment of UC. In a study total of 89 participants of age between 18–65 years were selected, of them 45 were in the intervention group and 44 patients were in the placebo group. In a study, 2 patients from the intervention and 5 from the placebo control group were excluded, so the final 43 patients in the intervention group and 39 in the placebo group were included. 43 patients were administered 2 g of curcumin, 1 g after breakfast, and 1 g after the evening meal with sulfasalazine (1.5–3 g/day) and the placebo group was given sulfasalazine or mesalamine 1–3 g/day. Both the group was evaluated for clinical activity index (CAI) and endoscopic index (EI), and results revealed that the patient who received curcumin with sulfasalazine was found to be better in improving CAI and EI index as compared to the placebo group. In a 6-month follow-up assessment, it was observed that 2 patients from the intervention group and 8 of the placebo group experienced relapses during 6 months. Safety data evaluation showed, there were no serious adverse effects were observed. Hence the study concluded that curcumin revealed the potential to treat UC without any serious adverse effects [57].

Suskind et al. (2013) conducted a force dose titration study of curcumin in pediatric patients with IBD. The study included a total of 11 participants of age between 11 and 18 years old, 7 boys and 4 girls. 6 patients were affected with CD and 5 were affected with UC. The study got approval from the Seattle Children's Hospital Institutional Review Board. Of the 11 patients, only 9 completed a study, and the treatment group was administered 500 mg of curcumin two times a day for 3 weeks. The dose was increased up to 1 g twice a day by using a dose force titration design at week 3 for a further 3 weeks and again it was titrated at a dose of 2 g twice a day on week 6 and continued for another 3 weeks. The results of the clinical assessment showed improvement in the Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI) and all the laboratory measures such as CRP, amylase and alanine transaminase (ALT), Complete blood count (CBC) were found in the normal range. From the study, it was concluded that curcumin was well tolerated up to 2 g per day in pediatric patients with no sign of toxicity [58].

Gupta et al. (2000) performed an open nonrandomized monocentric clinical trial on 30 patients having severe colitis and assessed the protective effect of *Boswellia serrata* gum resin against it. In this study, they took 13 females and 17 males of age group 18–48 having chronic colitis. They showed certain symptoms such as abdominal pain, and diarrhoea with blood or without blood. Out of 30 patients, 20 were administered with *B.serrata* gum resin 900 mg, thrice a day for six weeks and the remaining 10 patients were treated with 3gm sulfasalazine, sulfasalazine used as a standard. After treatment, it was observed that patients treated with *B. serrata* gum resin downregulated bloody diarrhea and lower abdominal pain. Similarly, it showed an effect on leukotrienes which is a crucial mediator of acute inflammation, which restricts the synthesis of leukotrienes. Electron microscopy revealed that after treatment there was an absence of inflammatory cells, reduced ulceration, and loss of fibrous tissue. Histopathology of rectal mucosa demonstrated improvement in histopathological factors like loss of distorted crypt structure and loss of hypercellularity of lamina propria. From the above study, it was concluded that *B. serrata* gum resin revealed a protective effect against chronic colitis with minimum side effects. It was also suggested that the protective effect of *B. serrata* gum may be due to Boswellic acid [59].

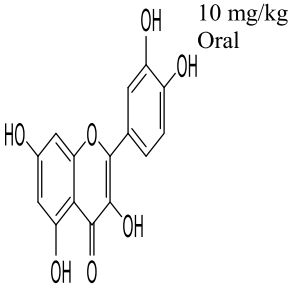
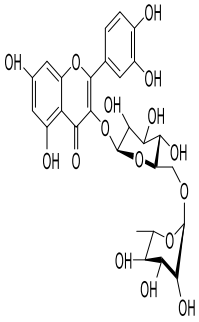
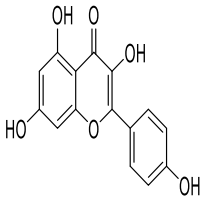
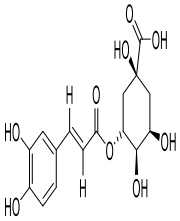
8. Bioactive compounds from reported plants against IBD

There are several bioactive molecules isolated from their respective medicinal plants known for the treatment of IBD and are proven to be responsible for their potential against IBD. Some of the bioactive molecules isolated from the plants found in the Vidarbha region with respect to their dose, formulation, animal model, and outputs are represented in Table 1.

9. Herbal nanomedicine and IBD

Herbal nanomedicine is an emerging field of nanotechnology that consist of herbal extracts and isolated bioactive components. The nanotechnology term was coined by Norio Taniguchi at Tokyo Science University in the year 1974. Nanomedicine is used since ancient times in the form of Bhasma in therapeutics; Bhasma is like ash that is formed when metal ions and herbal drugs are transformed into a higher oxidative state known as metal ion nanoparticles. For modern nanotechnology, Bhasma acts as a model for the extension of nanomedicine as Bhasma showed better relevance with modern nanotechnology [88]. For the delivery of herbal extracts nanoparticles serve as a carrier that conquered drawbacks associated with herbal drugs which are low solubility, permeability, and stability [89]. Nanoparticulate material is defined as a material having a size range from 1 to 100 nm, as it is fabricated by atomic or molecular level materials. Therefore, it can freely move inside the human body as compared to the larger particles hence it increases the permeation as well as solubility of herbal drugs. Nanoparticles have three layers viz., surface layer, shell, and core, the surface layer plays a crucial role in functionalization with metal ions, surfactants, and polymers. The core is a fundamental part of nanoparticles [90]. There are certain mechanisms through which therapeutic agents attached to nanoparticles may be dissolved, encapsulated, entrapped, or adsorbed on the surface or inside the nanocarrier. Due to the small particle size of nanoparticles, the surface area increases so the drug encounters the larger area of the body at a minimum concentration hence at a minimum concentration it gives an effective therapeutic efficacy and low side effects, also gives sustained and controlled release of action because nanocarriers remain in blood circulation for a prolonged time so that the bioavailability of the drug ultimately gets increased [91]. In nanomedicine, there are various types of nano-drug delivery systems including polymeric nanoparticles, liquid crystals, solid lipid nanoparticles, silver nanoparticles, phytosomes, and micro and

Table 1
Bioactive molecules isolated from medicinal plants from Vidarbha region against IBD.

Sr no.	Medicinal Plant	Bioactive molecule	Structure	Dose/ Route	Formulation	Animal model	Results	References
1.	***Morinda citronella* L.**	Quercetin		10 mg/kg Oral	Suspension	2.5 % DSS in mice	Quercetin revitalized the intestinal host-microbe relationship to treat colitis via rebalancing the pro-inflammatory, anti-inflammatory, and bactericidal functions of enteric macrophages.	[60]
				50 mg/kg Oral	Suspension	2 % AA	Quercetin decreases the ROS and MDA levels and improves histological parameters.	[61]
				30 mg/kg Oral	Administered with a dietary supplement	Citrobacter rodentium-induced colitis mouse model	It Suppresses the production of pro-inflammatory cytokines and increases anti-inflammatory cytokines i. e. IL-10 level.	[62]
				1 mg/kg Oral	Suspension	5 % DSS	Decreased the level of proinflammatory cytokines and nitric oxide expression as well as inhibited NF-kB signalling pathways.	[63]
2.	***Cordia dichtoma* G.**	Rutin		57 mg/kg/ day Oral	Suspension	T cell-dependent colitis model (CD4+ CD62L+ *T* cells)/Mice	The treatment group showed a decrease in DAI, MPO, TNF-α, IFN-γ, IL-6, and IL-17, and maintained the release of IL-10. It also downregulated the NF-kB expression as well as the protein expression of COX-2 in the ulcerative group. Histopathology showed that there was no crypt formation observed.	[64]
3.	***Annona quamosa* L.**	Kaempferol		50 mg/kg Oral	Suspension	3.5 % DSS	Kaempferol inhibited protein expressions of NF-κB, TLR4, and I-κB induced by LPS. Also, it declined the level of inflammatory cytokines. Kaempferol maintaind the integrity of the mucosal barrier by restoring membrane protein ZO-1, occluding and claudin-1.	[65]
4.	***Acacia saligna* L.**	Chlorogenic acid		60 mg/kg Oral	Suspension	100 mg/kg TNBS	It protected intestinal microbiota from oxidative stress.	[66]
				20 mg/kg Intracolonic	liposomal Suspensions	TNBS 4 mg/ 0.1 ml 30 % ethanol in mice	Liposomal chlorogenic acid reduced oxidative stress and inhibited NF-kB activation.	[67]
				7- 14 mg/kg Oral	Suspension	2.5 % DSS in mice	Decreased the expression of IFNγ, TNFα, and IL-6.	[68]
				10 μl/g Oral	Suspension	2.5 % DSS in mice	Reduced the level of myeloperoxidase activity and downregulated TNF-α, IL-,6 and improves IL-10 activity.	[69]
				3,60,120 mg/kg Intragastric	Suspension	5 %DSS in mice	Reduced oxidative stress, Apoptosis in colon also reduced ERK1/2, p -ERK, p38, p-p38, JNK, and p-JNK protein expression	[70]

(*continued on next page*)

Table 1 (*continued*)

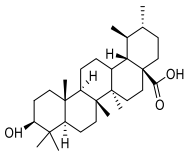
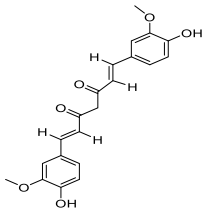
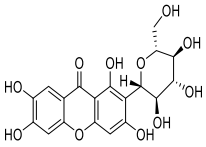
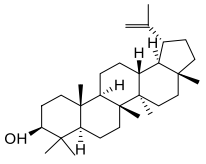
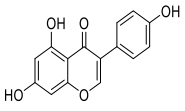
Sr no.	Medicinal Plant	Bioactive molecule	Structure	Dose/ Route	Formulation	Animal model	Results	References
5.	***Psidium guajava* L.**	Ursolic acid		200 mg/kg Oral	Suspension	3 % DSS	Reduced IL-6 level and downregulated MAPKs, IL6/STAT3, and PI3K inflammatory pathways	[71]
				10, 20 mg/ kg Oral	Suspension	4 % DSS in mice	Inhibited NF-kB signalling suppressed IκBα phosphorylation in the colon and suppressed TNF-α	[72]
				20 mg/kg Oral	Suspension	5 % DSS	Suppressed COX-2, NO, and NF-kB signalling pathways.	[73]
6.	***Curcuma longa* L.**	Curcumin		100 mg/kg Oral	With 0.2 ml of 0.5 % ethanol	5 % DSS	Curcumin downregulated the concentration of proinflammatory cytokines TNF-α, IL-6, and IL 17. Curcumin maintained the homeostasis of Treg and Th-17 cells.	[74]
				100 mg/kg Oral	suspension	3 %DSS in mice	Improved ulcer index, histological score, and reduced level of proinflammatory cytokines also it downregulated oxidative stress.	[75]
				8 μg/ml	*In vitro* cell line study	Caco-2 cell	Starch nanoparticles significantly reduced the concentration of pro-inflammatory cytokines like TNF-α, and IL-6 and increased IL-10 expression.	[76]
				50 mg/kg Oral	W/O/W Emulsion	3.5 % DSS in mice	Porous polymeric nanoparticles downregulated the expression of proinflammatory cytokines as well as reactive oxygen species and the level of MPO. It elevated the level of IL-10 and improved histological parameters.	[77]
7.	***Mangifera indica* L.**	Mangiferine		60 mg/kg Oral	Suspension	5 % DSS	It reduced the level of proinflammatory cytokines.	[78]
				50 mg/kg Oral	Suspension	4 % DSS	Mangiferin inhibited the mRNA expression of proinflammatory cytokines, NF-κB and MAPK signaling. It also downregulated the TNF-α and IL-1β.	[79]
8.	***Achyranthes aspera* L.**	Lupeol		1 mg/25 g animal in corn oil	Emulsion	2 % DSS in mice	Lupeol modulated TWIST gene expression, NF-κB, mediated inflammation, and assisted in the downregulation of TNF-α and IL 1 and 2	[80]
				50 mg/kg Oral	Suspension	4 %DSS in mice	Lupeol decreased cytokines, including IL-12, IL6, IL-1β, and TNFα, and increased anti-inflammatory cytokines like IL-10.	[81]
9.	***Ficus bengalensis* L.**	Genistein		10 mg/kg Oral	Oral solution	3 % DSS in mice	Genistein reduced IL-6, TNF-α, IFN-γ, and IL-1. Also significantly downregulated the M1 macrophages and contributed to the M2 macrophage.	[82]

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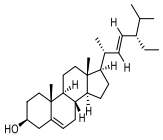
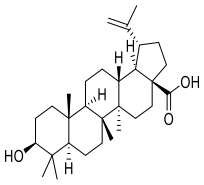
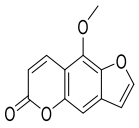
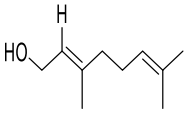
Table 1 (*continued*)

Sr no.	Medicinal Plant	Bioactive molecule	Structure	Dose/ Route	Formulation	Animal model	Results	References
10.	***Alstonia scholaris* L.**	Stigmasterol		400 mg/kg Oral	Suspension	2.5 % DSS in mice	Stigmasterol increased the level of butyrate, butyrate maintained the Treg and Th cell balance by activating the PPARg receptor, and hence it maintains intestinal homeostasis. It decreased the level of IL-17 A and increased IL-10 and TGF-b. It also elevated the level of helpful gut bacteria like Ruminococcus and helicobacter.	[83]
11.	***Aegela marmelos* L.**	Betulinic acid		20 mg/kg and 50 mg/ kg Oral	Suspension	1 % TNBS in mice	Oral administration of betulinic acid inhibited fibrotic factors like Tnc, Col1a2, Col3a1, Timp-1, and α-SMA) as well as inflammatory factors in tissue and improves intestinal integrity.	[84]
12.	***Ficus hispida* L.**	Bergapten		10 mg/kg and 30 mg/ kg Oral	Suspension	4 % Acetic acid	Orally administered bergapten reduced proinflammatory cytokine levels, and mast cell degranulation. It improved histological conditions	[85,86]
13.	***Jasmine grandiflorum* L.**	Geraniol		30 and 120 mg/kg Oral	Geraniol oral suspension	1.5 % DSS	Oral administration of geraniol substantially reduced IL-17, TNF-α, and IFN-γ. It also inhibited the expression of COX and NF-kB and improved histological scores.	[87]

nanoemulsions, this nano-drug delivery system potentiates the activity of the herbal extract. There are certain nanoformulation preparations of bioactive molecules that showed better therapeutic effects than conventional therapy.

Ohno et al. (2017) prepared curcumin nanoparticles and assessed their protective activity against the DSS-induced colitis model. From the study, it was found that the oral administration of 0.2 % (W/W) curcumin nanoparticles was mixed with powder from rodent diets. The result revealed that the curcumin nanoparticle reduced DAI, and improved histopathological score as 4 % DSS administration caused distorted crypt cell, edema, and ulcer. Further study includes assessment of TNF-α, and NF-kB in HT-29 cells, immunohistochemical analysis revealed that the curcumin nanoparticle significantly downregulates TNF-α and NF-kB expression. The proinflammatory cytokines such as TNF-α, IL-6, IL-1β, and chemokines CXXL1 and CXCL2 mRNA expression were found to be downregulated after a curcumin nanoparticle administration. Also, the level of Gr-1 positive neutrophil in colonic mucosa was decreased in the DSS+ curcumin nanoparticle group as shown in a flow cytometry analysis. PCR analysis was performed to determine the effect of curcumin nanoparticles on gut microbiota composition. The DSS administration reduced the level of *Clostridium* cluster IV, *Clostridium* subculture XIVa, and *Clostridium* XI and increased in the *Lactobacillales* species, after administration of curcumin nanoparticles the level of beneficial bacteria was increased and *Lactobacillales* was found to be decreased. From the flow cytometry analysis, it was observed that the curcumin nanoparticle significantly improved the level of CD103 CD8α which was decreased in the DSS group, this leads to increased Tregs cell level in the colonic mucosa. Hence from the study, it was concluded that the oral bioavailability of curcumin was found to be increased by curcumin nanoparticles, and curcumin nanoparticles successfully ameliorate DSS-induced UC [92].

In another study, Deng et al. prepared berberine (BBR) nanostructured lipid carrier (NLC) in the treatment of ulcerative colitis. Berbenin NLC (BBR-NLCs) was prepared by using high-pressure homogenization. BBR-NLCs were assessed for particle size, and it was observed that the prepared nanoparticle was in the range between 30–200 nm which was optimal for cellular uptake. Biocompatibility was performed on BBR, BBR-NLCs, and NLC, there was no toxicity observed in all three orally administered groups in the *in vivo* study. The cellular uptake study suggested that BBR and BBR-NLCs (5μg/ml) were both internalized in RAW.264.7 and Caco-2 cells but the BBR-NLCs showed a greater internalization effect than free BBR. The BBR-NLC substantially decreased diarrhea, and occult blood, and reduced DAI more potentially than free BBR. Histopathological results revealed that BBR-NLCs showed a protective effect to a greater extent by reducing neutrophil infiltration, damage to crypt cells, and inflammation. DSS causes disturbance in membrane integrity by reducing ZO-1 protein, administration of BBR-NLCs more significantly protected barrier integrity by normalizing ZO-1 level, as shown in immunofluorescence analysis. Proinflammatory cytokines such as IL-6, IL-1β, matrix metalloprotein 9 (MMP-9), chemokine (C-X3-C motif receptor 1 (CX_3 CR1), and COX-2 played a major role in DSS induce UC, treatment with the BBR-NLCs suppressed all these DSS induced parameters. Immunofluorescence analysis demonstrated that the BBR-NLCs successively inhibit LPS-induced NF-kB translocation. Therefore from the study, it was revealed that BBR-NLCs may have the potential as a novel therapeutic agent for the treatment of UC [93].

Similarly, in another study, Sahu et al. prepared silver nanoparticles of naringin, diosmin, and hesperidin and evaluated their antibacterial activity against common pathogens and cytotoxicity in HL-60 cells.

Results revealed that the prepared silver nanoparticles of naringin showed better cytotoxicity than the rest of the two nanoparticles of hesperidin and diosmin. In the antibacterial study, nanoparticles of naringin, diosmin, and hesperidin showed better antibacterial activity against *E. coli, S. aureus*, and *P. putida*, hence from the study it was concluded that the nanoparticles exhibited considerable cytotoxicity and antibacterial activity [94].

Zhang et al. (2018) formulated the (NPs-PEG-FA) and (NPs-PEG) by versatile single-step surface functionalizing technique and nanoparticle loaded with 6-shogaol (NPs-PEG-FA/6-shogaol) and evaluated its protective activity against the DSS-induced UC model. The particle size of NPs-PEG and NPs-PEG-FA were 264.4 nm and 249 nm and the percent encapsulation efficiency of 6-shogaol in NPs-PEG-FA were 35.8 μg/mg and 52μg/mg. Biocompatibility study in colon-26 cells and RAW264.7 macrophage cells by MTT assay, showed that at 48 hr the cell viability was decreased in a RAW264.7 macrophage in an NP-treated group at 1 mg/ml concentration but not in the NPs-PEG-FA group. Toxicity of NPs-PEG-FA was assessed in healthy mice, result showed that oral administration of NPs-PEG-FA did not show any change in body weight, and normal hematological parameters were observed as of the normal group. Further in vitro cell uptake studies of NPs-PEG-FA were performed using fluorescently (Dil) labeled NPs in colon-26 and RAW264.7 macrophages. The fluorescence microscope result confirmed that the NP-PEG-FA showed higher fluorescence inside the cell than the control. From the flow cytometry analysis, it was suggested that the NP-PEG-FA revealed that the nanoparticle showed stronger cellular uptake. Then they encapsulated NP-PEG-FA in a hydrogel system consisting of chitosan/alginate in a special weight ratio. The *in vivo* biodistribution of NP-PEG-FA in the GI tract was assessed by administering NP-PEG-FA with DiR using an *in vivo* imaging system. Immunofluorescence analysis revealed that the NP-PEG-FA/DiR treated mice showed better intensity in the colon at 6 hr and 12 hr of post-administration. After confirming oral administration of NP-PEG-FA hydrogel into the colon, they determine the effect of NP-PEG-FA/6shogaol in DSS-induced UC. From the ELISA study, it was observed that the NP-PEG-FA/6-shogaol significantly reduced the level of inflammatory markers lipocalin-2 level and the level as well as MPO level. NP-PEG-FA/6-shogaol also reduced mRNA expression of TNF-α, IL-6, IL-1β, and iNOS. It also elevates the Nrf-2 factor and heam oxygenase (HO) level. Therefore it was concluded that the NP-PEG-FA/6-shogaol efficacially ameliorated DSS-induced UC [95].

10. Conclusion

This review explored the use of traditional medicinal plants from the Vidarbha region of Maharashtra, India in the treatment of inflammatory bowel disease. The review reported a study of 20 medicinal plant extracts and 13 isolated bioactive compounds that were obtained from the Vidarbha region. From the collected data, it was observed that the medicinal plant extract chemically showed the presence of triterpenoids, Flavonoids which widely exhibit antiinflammatory properties. Basically, it acts through the inhibition of proinflammatory cytokines such as TNF-α, IL-β, and IFN-γ, protein like COX, iNOS and it also acts by reducing the expression of inflammatory pathways like NF-kB and MAPK so the inflammation in the colon may get reduced. Overall, this study will be useful for improving knowledge about the use of medicinal plants in the treatment of inflammatory bowel disease and will also enlighten people about the conservation of medicinal plants. The review provides all essential data that provoke scientists to perform additional research on medicinal plants and educate about their efficacy and conservation.

11. Limitations

In traditional medicinal plants sometimes it is difficult to understand the potential of particular components due to the presence of multiple phytocomponents in a plant extract. It is difficult to standardize the dose of herbal medicine and face long-term safety and efficacy issues. There are lack of clinical trial data on herbal medicine which also limits the use of herbal medicine. Some extract are unstable and may degrade over time.

12. Scientific gaps

The review consists of information about the use of traditional medicinal plants from the Vidarbha region of Maharashtra in the treatment of inflammatory bowel disease. Data includes various medicinal plants and isolated phytoconstituents from a plant that has been found in different areas of the Vidarbha region. From the collected data, we came to know some scientific gaps regarding medicinal plants. Though there are some plants that have been explored scientifically various medicinal plants have mere traditional importance, and scientifically sufficient evidence is not available. There are medicinal plants that need pharmacological as well as pharmacodynamic and pharmacokinetics studies to elaborate their actual efficacy. In the future, if this lacuna is fulfilled then there will be more medicinal plants explored to society from the Vidarbha region in the treatment of inflammatory bowel disease in a scientifically acceptable way.

13. Future scope

In the future, efforts should focus on exploring medicinal plants based on specific mechanisms of action and, a detailed study of various pathways that play a crucial role in various disorders, particularly IBD. Further, research should concentrate on the isolation of active phytoconstituents, their molecular mechanism, and the development of targeted pharmaceutical formulations that enhance the potential of phytoconstituents. Furthermore, clinical trials on phytoconstituents and medicinal plant extracts must be performed to strengthen the scientific basis. This could revolutionize natural medicine and explore new treatment options.

Funding source

The authors acknowledge Mahatma Jyotiba Phule Research Fellowship, Government of Maharashtra, India for providing research fellowship to Mr. Nikhil Y. Yenorkar (Letter No.: Fellowship2022_1491 dated 13/12/2022).

CRediT authorship contribution statement

Nikhil Y. Yenorkar: Data curation, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft. **Ayusha O. Dondulkar:** Data curation, Investigation, Methodology, Software, Writing – original draft. **Natasha S. Akojwar:** Data curation, Investigation, Methodology, Software, Writing – original draft. **Raksha A. Purohit:** Investigation, Methodology, Software, Writing – original draft. **Prakash R. Itankar:** Conceptualization, Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Shashikant Singh:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Satyendra K. Prasad:** Conceptualization, Data curation, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have disclosed that there are no conflicts of interest. Further, consent from all the co-authors has been taken and the authors are entirely responsible fo the composition and content of the article.

Acknowledgement

The authors acknowledge Mahatma Jyotiba Phule Research

Fellowship, Government of Maharashtra, India for providing research fellowship to Mr. Nikhil Y. Yenorkar (Letter No.: Fellowship2022_1491 dated 13/12/2022).

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