Natural Products Analysis
https://www.sciltp.com/journals/npa

Review

Check for updates

Therapeutic Potential of Bioactive Natural Product in Crohn's Disease: Focus on Redox Homeostasis and Inflammatory Signalling

Nageswar Panda [1,2], Rajkumari Sukanya Datta [1,3], Soumyashree Tripathy [1] and Amiya Kumar Prusty [4,*]

[1] School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Odisha 752050, India
[2] School of Pharmacy, ARKA JAIN University, Jamshedpur 832108, India
[3] School of Pharmacy, DRIEMS University, Odisha 754022, India
[4] Faculty of Pharmacy, C.V. Raman Global University, Odisha 752054, India
* Correspondence: amiyaprusty@gmail.com; Tel.: +91-94372-76618

How To Cite: Panda, N.; Datta, R.S.; Tripathy, S.; et al. Therapeutic Potential of Bioactive Natural Product in Crohn's Disease: Focus on Redox Homeostasis and Inflammatory Signalling. *Natural Products Analysis* **2026**, *2*(2), 100016. https://doi.org/10.53941/npa.2026.100016

Received: 2 June 2026
Revised: 2 July 2026
Accepted: 20 July 2026
Published: 31 July 2026

Abstract: Crohn's disease can be described as an example of inflammatory bowel disease with distinctive features of oxidative stress, immune regulation disorder, and damaged integrity of the intestine. Nevertheless, although there have been many achievements in the traditional treatment of this disease using approaches such as biological and immunosuppressive drugs, the treatment has its drawbacks, including side effects, lack of effectiveness in some patients, and high costs. That is why there has been a recent trend in developing bioactive substances derived from plants, sea organisms, or even microorganisms. The bioactive substances include flavonoids, polyphenols, and saponins, as well as polysaccharides and peptides derived from sea organisms. Some examples are resveratrol, curcumin, and fucoidan, which have been proven to be efficient in regulating the biochemical processes related to disease progression and especially transcriptional activation via the NF-κB pathway and cytokine-induced inflammation. In addition, manipulation of the gut flora by probiotics is a potential complementary approach. However, the use of these compounds has been limited by the problems related to low bioavailability, quick metabolic turnover, and systemic absorption. Modern technologies in drug delivery and formulation would be necessary for the improvement of the effectiveness of these methods. Therefore, bioactive compounds could be regarded as an innovative and emerging therapeutic approach to treat Crohn's disease.

Keywords: bioactive compounds; Crohn's disease; gut health; inflammatory bowel disease

1. Introduction

Autoimmune diseases, and especially those characterized by chronic inflammation in the gut, are one of the biggest concerns for public health in today's world. They include diseases such as inflammatory bowel disease, which comprises conditions like celiac disease, Crohn's disease, and ulcerative colitis. Their mechanism of development is not fully comprehended due to the complexity of their development involving a combination of various components that include immune regulation problems, genetics, epigenetics, diet, and the environment [1] (Figure 1). Increasing scientific evidence demonstrates that the presence of a healthy gut microbiota is critical for sustaining the physiological balance of the host body. This system acts as an important component in modulating immunity, digestion, xenobiotic metabolism, synthesis of vitamins and drugs, and metabolizing nutrients. In

addition, it maintains the integrity of the intestinal mucosal barrier as well as prevents infections by invading pathogens. Due to its profound influence on regulating the physiological functions of the host body and communication with the brain through the gut-brain axis, the gut microbiota is known as the "second brain" [2]. The phenomenon of inflammation is considered to be a key element in the host's body defence mechanism. Inflammation develops when the body is exposed to any harmful stimuli, including tissue damage, chemical or physical injuries, infections, and disturbances in genetics or the immune system. Inflammation helps in eradicating dangerous elements, healing tissues, and restoring balance in the physiological functions. Yet, when prolonged or out of control, it may cause disorders [3]. The pattern of inflammation in patients suffering from Crohn's disease and ulcerative colitis has distinct features when compared with regard to location and depth. The inflammation in patients with Crohn's disease occurs transmurally, meaning that the inflammation affects the entire bowel wall and often leads to granuloma formation, which is an aggregate of immune cells. Inflammation in ulcerative colitis, on the other hand, occurs mainly at the level of the colon's mucosa. Both these conditions follow a course of remissions and relapses that have a severe impact on patients' quality of life [4]. Excess production of reactive oxygen species together with reduced antioxidants results in oxidative stress, an important factor leading to inflammation and tissue damage in Crohn's disease. In addition, oxidative stress is potentiated by pro-inflammatory agents, including cytokines and activation of the NF-κB signaling pathway, which cause the progression of the condition. Thus, treatment targeting oxidative stress and inflammation provides a rational therapy approach. Several studies have shown that natural bioactive substances like alkaloids, flavonoids from plants, microorganisms, and marine organisms, polyphenols, and terpenes can be beneficial in addressing these pathophysiological conditions. As they act as both antioxidants and anti-inflammatories, they could serve as an effective alternative or adjuvant to other treatments used for the condition. It is thus evident that modern investigations are aimed at assessing the effectiveness and safety of these substances [5]. The understanding of how bioactive compounds play a role in regulating inflammation and oxidative stress would help in creating innovative treatments that could help to reduce the burden of Crohn's disease both clinically and in terms of improving the quality of life for patients affected by this condition. Inflammatory bowel diseases such as ulcerative colitis have an increasing global incidence, with the greatest burden of cases noted in North America, especially among children. At present, anti-inflammatory medications, such as 5-aminosalicylic acid (5-ASA), are used to treat IBD through the regulation of intestinal inflammation. However, since this is a chronic disease and because IBD can be recurrent in nature, there is a need to find other avenues for treatment [6]. This review is intended to cover the use of natural bioactive products obtained from plant sources, microbes, and marine organisms in inflammatory bowel diseases, especially Crohn's disease, with special focus on their anti-inflammatory and antioxidative properties as well as effects on the gut microbiota and intestinal barrier function.

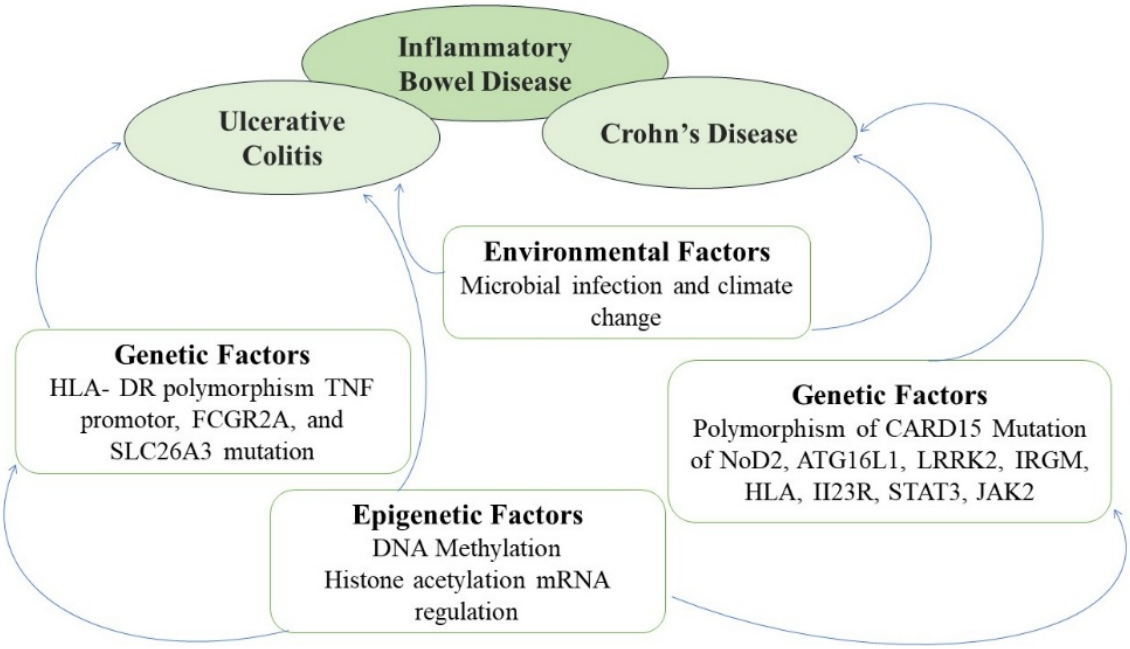

Figure 1. Different factors influenced Crohn's Disease.

2. Reactive Oxygen Species Signaling in the GI Tract

Reactive oxygen species (ROS), reactive sulfur species (RSS), and reactive nitrogen species (RNS) are among the mostly reactive chemicals that are produced in organs and tissues, under conditions known as oxidative stress, which compromise the body's natural antioxidant defense mechanism. This can lead to cellular damage and dysfunction, which can result in various diseases.

Normal metabolic activities within cells continually create modest amounts of reactive substances. They may also result from acute or long-term cellular stress, or they may arise from exposure to external stimuli such as air pollution, cigarette smoke, germs, medications, ozone, UV radiation, viruses, X-rays, etc. Both free radicals and non-radical oxidants can be considered reactive entities, free radicals are unstable due to the unpaired electrons in their outer electron orbit. Due to their extreme instability and reactivity, free radicals often combine with other molecules to oxidize them to neutralize themselves [7].

In response to several exogenous factors, including alcohol consumption, cigarette smoking, nonsteroidal anti-inflammatory drug (NSAID) use, and ultraviolet (UV) radiation exposure, excessive reactive oxygen species (ROS) are generated. ROS levels are also increased by infections, ischemia-reperfusion (I/R) damage, and other inflammatory events. All diseases, including cancer, are caused by redox signaling disrupting normal cellular homeostasis [8]. One important source of ROS is the gastrointestinal (GI) tract. Despite the epithelium's defensive wall, digested materials, infections, and other conditions can induce inflammation by releasing inflammatory cytokines and other mediators that deteriorate oxidative stress caused by the macrophages, PMNs, and epithelium. Some GI pathological conditions, including gastric malignancies, gastric ulcers, and inflammatory bowel disease (IBD), are influenced by oxidative stress. To enhance our comprehension of ROS-induced GI disorders and perhaps result in the creation of novel therapeutic strategies, it is imperative to grasp the signaling events that increase free radicals and the body's reaction to these processes [9] (Figure 2).

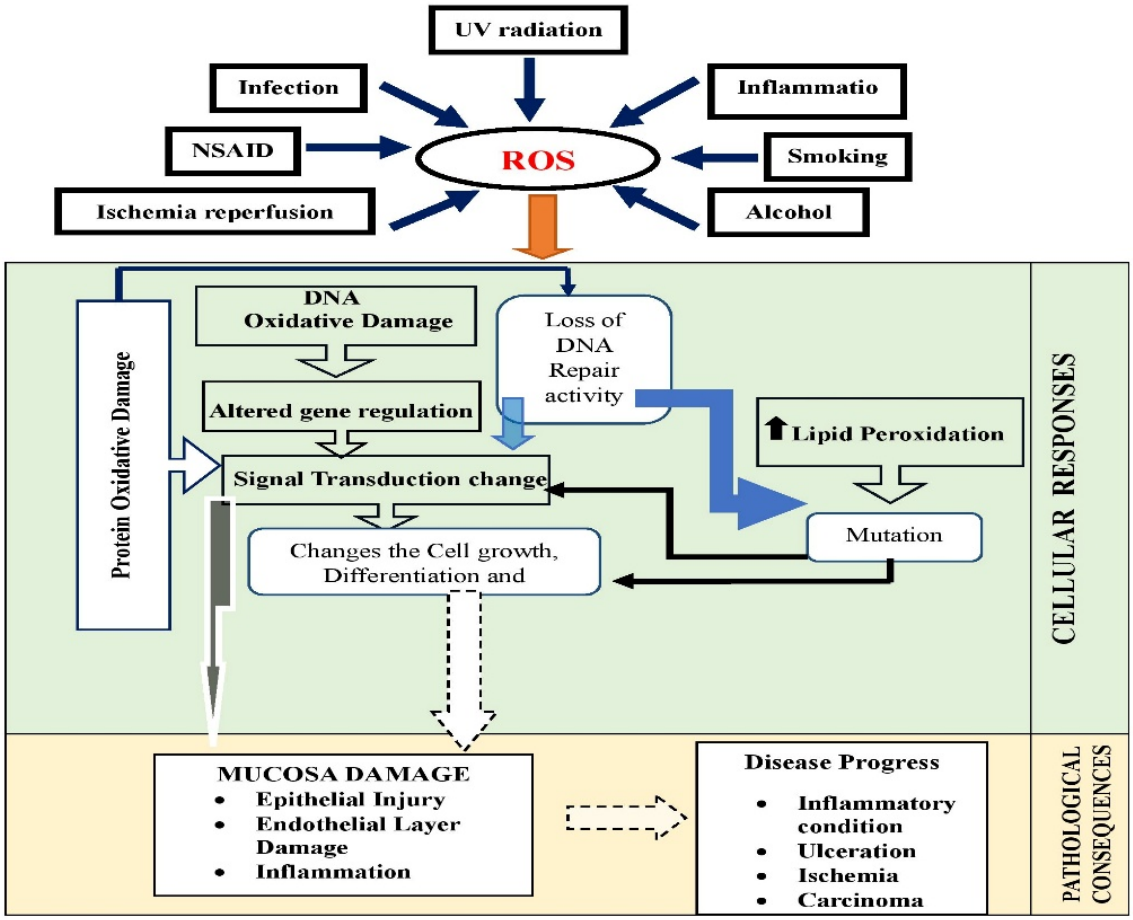

Figure 2. Pathological conditions of an inflammatory condition.

3. Mechanisms Underlying Oxidative Stress in Crohn's Disease

Oxidative stress plays an important role in the pathogenesis of Crohn's disease, which is a type of inflammatory bowel disease (IBD). Understanding the process underlying oxidative stress in Crohn's disease

involves several key factors. Crohn's disease is described by chronic inflammation in the GI tract. ROS are produced during the innate immune response in activated inflammatory cells, specifically neutrophils and macrophages. Even though physiologic ROS production serves as part of the host defense mechanism by assisting with pathogen elimination, an excess of ROS will cause oxidative stress and damage to the cells and tissues. Mitochondria can be considered as a ROS producer within the cell due to oxidative phosphorylation. During this process, electron leakage from the electron transport chain results in superoxide generation. As far as Crohn's disease is concerned, the importance of mitochondrial dysfunction as a factor influencing the pathophysiology of the disease is being appreciated. Dysfunction of the mitochondria will alter redox balance and impair endogenous antioxidant mechanisms, resulting in increased ROS formation. Moreover, damage to the mtDNA due to oxidative stress and inflammation causes further damage to the mitochondria, thus leading to a vicious cycle [10]. The formation of reactive oxygen species (ROS) and antioxidant defenses is out of balance in Crohn's disease. Increased oxidative stress results from the impairment of important enzymes like catalase, glutathione peroxidase, and superoxide dismutase (SOD). Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are examples of pro-inflammatory cytokines that increase ROS production and exacerbate oxidative damage and inflammation [11]. Oxidative stress leads to cellular injury through mechanisms such as lipid peroxidation, protein oxidation, and DNA damage, contributing to inflammation and hindering tissue repair. Moreover, oxidative stress affects the structure of the intestine, leading to increased permeability and allowing microbial antigen passage, perpetuating inflammatory processes in Crohn's disease. In addition, high levels of reactive oxygen species cause DNA damage in mitochondria, decrease ATP formation, and disturb electron transport chain functioning, causing mitochondrial dysfunction [12].

3.1. Genetic Predisposition in IBD and Reactive Oxygen Stress

One of the most significant risk factors for having IBD is family history. Relatives of patients are more likely than the general population to experience both CD and UC. Twin studies provide the most compelling evidence for a genetic component to IBD. In three extensive studies involving clone pairs from Europe, concordant IBD was observed in roughly 6% to 16% of monozygotic clone pairs and 0% to 5% of dizygotic twin pairs, respectively. Searching for genes linked to inflammatory bowel disease (IBD) has revealed that innate immune response deficits may development of IBD in certain people. The International Nomenclature Committee reclassified the first sensitivity gene found in CD (IBD1) on chromosome 16q12 as CARD15 (caspase activation and recruitment domain 15), after it was first identified as NOD2 (nucleotide-binding oligomerization domain 2). About 15–20% of Crohn's disease patients and a lesser portion of the general population have mutations in CARD15. Inflammation mediated by Th1-type T cells is linked to Crohn's disease. This results in the overproduction of IL-1B, IL-2, IL6, IL-8, and TNF-α in addition to an excess of IL-12, IL-17, IL-23, IFN-γ, and macrophage-derived cytokines. On the other hand, Th2-type T cell-mediated inflammation linked to induce the production of IL-4, IL-5, IL-10, and IL-13 is linked to ulcerative colitis [13,14].

3.2. Epithelial Cells of the Gut in Oxidative Stress and IBD

Epithelial cells of the gut play an important function in maintaining intestinal homeostasis and its role. Oxidative stress impairs the normal functioning of the epithelial lining cells in inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis. The intestinal epithelium acts as a physical barrier, controls the absorption of nutrients, and takes part in antimicrobial activities. High concentrations of ROS, mostly produced by activated neutrophils and macrophages, lead to oxidative damage. Oxidative stress can also be caused by microbial causes, environmental pollutants, nutrition, and mitochondrial malfunction, all of which can cause epithelial cells to create ROS. Cell integrity and function can be compromised by ROS's ability to harm proteins (oxidative modification), DNA (mutations), and cellular lipids (lipid peroxidation). Epithelial cell loss and intestinal wall disruption might result from excessive ROS's ability to trigger cell death pathways, such as necrosis and apoptosis (programmed cell death). Tight junctions, which are essential for preserving the intestinal wall, can be broken by oxidative stress. Because of the increased intestinal permeability (leaky gut) caused by this disturbance, harmful bacteria and antigens can enter the tissue and worsen inflammation. The hallmarks of IBD, ulceration and mucosal layer erosion, can result from oxidative damage to epithelial cells. Oxidative stress interferes with the normal functioning of the epithelium, causing the condition to deteriorate in IBD. The release of cytokines and chemokines in response to the stressed state causes the recruitment and activation of immune cells, resulting in an escalating feedback loop of inflammation and oxidative stress. Impairment of the barrier integrity leads to exposure of the tissue beneath to antigens present in the lumen, intensifying both the inflammatory reaction and the extent of tissue damage. Immune cells can also become activated due to the

engagement of CD40-CD40L interactions. All these factors result in lesions defined by crypt hyperplasia, decreased mucus production, depletion of goblet cells, and ulceration [15].

3.3. Mucosal Immune Cells in Oxidative Stress and IBD

In the gastrointestinal tract, B cells and T lymphocytes, which release cytokines and antibodies when activated, constitute the adaptive immune system, while epithelial cells, macrophages, neutrophils, dendritic cells, and natural killer (NK) cells form the innate immune system. Through an effective mechanism, the mucosal defense system can discriminate between pathogenic and non-pathogenic gut microbes with precision. Under normal circumstances, the GI mucosa closely regulates the ratio of pro-inflammatory (TNF-α, IL-1, IL-6, IL-8, IL-17, and IL-23) to anti-inflammatory (IL-5, IL-10, IL-11, and TGF-β) cytokines. IBD affects innate and adaptive immunity, whereas CD just affects adaptive immunity, which can maintain inflammation but not cause it [16,17]. A disturbance of the equilibrium between T helper (Th) cells and regulatory T cells, namely the intolerance of regulatory T cells, is the immunological mechanism that underlies the pathophysiology of IBD. According to reports, Th1 cell-mediated inflammation in CD is typified by a rise in the production of IL-12, IL-17, and IL-23, while Th2-type T cell-produced cytokines in UC include IL-4, IL-5, IL-10, and IL-13 [18]. The Th1 response in CD is triggered by the microbiota, which results in the production of interferon-γ and TNF-α and damages the mucosal wall. Not only are leukocytes activated via the NF-κB signaling pathway, but CD patients' mucosal IECs are as well. Th2 cytokines produced by NK cells in UC stimulate the defence system, and IL-13 mostly causes IEC death, which feeds back favorably on NK cells [19–21]. Further tissue damage might arise from the increased formation of reactive oxygen species (ROS) during respiration, leukotriene and prostaglandin metabolism by other immune cells, including monocytes and leukocytes, during inflammation.

3.4. Oxidative Stress and Environmental Factors in Inflammatory Bowel Disease

It seems that environmental elements have a crucial function in the pathophysiology of both CD and UC. Some of the previously established connections, like smoking cigarettes, have been supported by recent high-quality research. Additionally, other risk variables, like hormone use, nutrition, stress, and vitamin D status, are known. All of these factors have been identified as risk factors for incident disease, but not many studies have looked at how these environmental factors influence the course of the disease naturally, and even fewer have looked at whether changing these factors can improve patient outcomes. Thorough and meticulous research on environmental disclosure in the management of the disease is required, especially if altering environmental factors can be demonstrated to lower the chance of recurrence, considering the inadequate response rates to current immunosuppressive therapy and ongoing worries about long-term safety cost and safety [22]. Anxiety and depression are prevalent in IBD patients. Evidence does, however, point to the possibility that pre-illness stress, anxiety, or depression could affect the likelihood of developing IBD. In fact, there is a great deal of biological validity for this theory. Mice that are depressed due to reserpine injections intracerebroventricularly are more vulnerable to reactivation of chronic colitis; this effect is mitigated by amitriptyline treatment. Additionally, the autonomic nervous system (particularly the sympathetic nervous system) can operate as a mediator for the effects of depression and stress [23,24]. Apart from underlying host genetics and microbial makeup, there probably exists significant variation in sensitivity to each environmental effect among individuals, both in isolation and in co-dependence with other disclosure. Determining the process of IBD development would be greatly aided by additional research on the environment's function in conjunction with genetics, immunologic processes, and microbiota.

3.5. Redox Signalling Pathways Involved in IBD

It is well known that non-radical ROS, including H_2O_2, produced by Nox enzymes in non-phagocytic tissues operate in a range of signalling pathways in a variety of cell types. The various biological effects that ROS elicit rely on the particular species that are produced, their longevity, and their subcellular sites [25]. The gastrointestinal mucosa maintains a complex equilibrium in redox signalling. Reactive oxygen species formed by immune cells invading the mucosae, including neutrophils, can operate as potent microbicidal mechanisms to protect weakened mucosae from microbial invasion. For many years, researchers have examined redox reactions and redox signalling, primarily concentrating on their roles in the development of disease. Subtoxic levels of oxidative stress have been linked in the last ten years to a number of fascinating activities, including the regulation of tissue wound healing, protective inflammatory modulation, and mucosal homeostasis maintenance. It has been demonstrated that resident gut microbial communities initiate redox signalling in the mucosa, which expresses phagocyte-like but different enzymes. The colonic mucosal epithelium is at the middle of this delicate balance, and new research

indicates that these barrier-forming cells may be able to precisely regulate redox signaling to determine how an inflammatory event plays out [26].

4. Bioactive Compounds Management in Crohn's Disease

4.1. Andrographolide

Andrographolide, which is obtained from the plant Andrographis paniculata, has remarkable anti-inflammatory and immunomodulatory effects. Andrographolide suppresses important inflammatory mediators such as NF-κB and STAT3, hence modulating the expression of pro-inflammatory cytokines and enzymes. Research shows that Andrographolide can lower the production of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8. By lowering the levels of these cytokines, Andrographolide may help mitigate the chronic inflammation that is a feature of Crohn's disease [27]. Effects on GALT may be significant for Crohn's disease since the gut-associated lymphoid tissue is implicated in the local immune response in the gut. Some research indicate that andrographolide has antioxidant effects that can help minimize oxidative stress. Because oxidative stress contributes to the pathogenesis of Crohn's disease, lowering it may help protect gut cells from harm and improve disease prognosis. Research on andrographolide's impact on Crohn's disease is currently in its early phases. The majority of investigations have focused on its overall anti-inflammatory and immunomodulatory properties rather than direct clinical trials in Crohn's disease patients. Given the encouraging preclinical evidence, andrographolide may be explored as part of a comprehensive therapy strategy, but further clinical trials are required to validate its effectiveness and safety in Crohn's disease management. In recent research of an oxazolone (OXZ)-induced UC rat model, andrographolide dramatically increased colon length and spleen coefficient while considerably lowering colonic disease activity index and mortality in a dose-dependent manner. These findings indicate that andrographolide might be a possible therapy for UC [28]. Andrographolide holds promise due to its anti-inflammatory, immunomodulatory, and antioxidant properties, which could potentially benefit Crohn's disease management. However, its effectiveness in this context requires further clinical validation. As with any supplement or alternative therapy, it should be used under the guidance of healthcare professionals to ensure safety and efficacy in managing Crohn's disease.

4.2. Caffeic Acid Phenethyl Ester

Caffeic acid phenethyl ester (CAPE), a phenolic molecule in honey bee propolis, is said to have anti-inflammatory properties primarily by blocking NF-κB. CAPE effectively suppresses pro-inflammatory cytokines and MPO activity in a DSS-induced experimental mouse model of colitis, thereby improving the function of the epithelial barrier [29].

4.3. Cannabis sativa L.

Plants belonging to the Cannabaceae family, specifically *Cannabis sativa* L., are native to Central Asia. All parts of the gastrointestinal tract, involving the pancreas, stomach, liver, and small and large intestines, have cannabinoid receptors. Throughout the enteric nervous system, enteric neurons, nerve fibers, and terminals all have CB1 and CB2 receptors. Both healthy and inflammatory human colonic epithelium had CB1 receptors. In the human colon, macrophages and plasma cells contain both CB1 and CB2 receptors. In addition to its anti-inflammatory properties, cannabis use has a general pharmacological effect on the gastrointestinal tract by reducing motility, secretion, and gastric/colonic emptying [30]. Research has consistently demonstrated that although cannabinoid antagonists or cannabinoid receptor deletion increased inflammation, therapy with cannabinoids or cannabinoid agonists decreased inflammation [31].

4.4. Curcumin

Curcuma is a genus in the Zingiberaceae family. Curcumin works through a variety of methods to produce anti-inflammatory and antioxidant benefits. Research has shown that pretreating DCs with this substance inhibits the phosphorylation of mitogen-activated protein kinase and NF-κB p65 translocation that are caused by lipopolysaccharide, which reduces inflammation [32]. Moreover, it lowers the uttering of TNF-α, IL-6, IL-12, and IL-1, which prevents DCs from inducing TH1-type responses. Curcumin can prevent TH17 activation, which lowers the generation of proinflammatory cytokines, including IL-6, IL-21, and IL-17, as well as impede the stimulation of the TH1 subgroup by decreasing macrophage activation. An important mediator in prostaglandin synthesis, cyclooxygenase-2 (COX-2) is an inflammatory enzyme that is triggered by NF-κB and activator protein 1 (AP-1) signaling. It increases inflammatory bowel disease (IBD) [33,34].

4.5. Epicatechin

Epicatechin, which is a flavonoid derived from the diet, including fruits like apples, dark chocolate, and green tea, has proven antioxidant and anti-inflammatory effects. It acts on the inflammatory signaling pathway, mainly NF-κB, and reduces the synthesis of pro-inflammatory cytokines, such as TNF-α and IL-6 [33]. Epicatechin can be helpful in treating Crohn's disease by regulating immune function, such as T cell and macrophage activities, and hence decrease inflammatory processes. The ability of epicatechin to be an excellent antioxidant allows for the removal of free radicals and helps protect the epithelium from oxidative stress and maintain the structural integrity of the intestine. Moreover, epicatechin can affect the gut microbiota composition and have prebiotic functions that help regulate immune processes. Nevertheless, the use of epicatechin is hindered by its low bioavailability [35]. However, the preliminary results have shown that epicatechin provides some positive effects in inflammation and oxidative stress; yet, more research is necessary to validate the effectiveness of epicatechin for Crohn's disease treatment. Epicatechin is suggested to be used [36]. Epicatechin may be considered as a method of managing Crohn's disease thanks to the anti-inflammatory and antioxidant properties of this substance. However, more research should be done to prove the safety and effectiveness of epicatechin as a medication.

4.6. Indoles

Indoles are members of the group of molecules found naturally in cruciferous plants such as broccoli, cabbage, cauliflower, and Brussels sprouts. Significant molecules among these are I3C (indole-3-carbinol) and DIM (3,3′-diindolylmethane). Such molecules have been extensively studied for their anti-inflammatory, antioxidative, and anticarcinogenic properties [37]. Indoles like indole-3-carbinol (I3C) and 3,3′-diindolylmethane (DIM) show promising properties of having a good effect against inflammatory conditions associated with Crohn's disease due to their ability to regulate certain inflammation pathways through cytokines (like TNF-α, IL-6) and transcription factors [38]. Indoles also affect the composition of gut microbiota, allowing for the growth of beneficial microorganisms and aiding in the treatment of dysbiosis that is one of the main hallmarks of inflammatory bowel disease. Moreover, their antioxidative effect protects the cells of the intestines from oxidative stress, while studies on animals with colitis show a reduction in inflammatory markers. Overall, these results reveal the possible usefulness of indoles in the case of IBD, despite the lack of clinical evidence [39]. Indoles like I3C and DIM can help with intestinal health of people having Crohn's disease as they have the capability to maintain the integrity of the epithelial cells and reduce the permeability of the intestines to avoid the movement of pathogens and endotoxins that cause inflammation. Indoles protect the cells from oxidative stress that is the major cause of inflammation [40]. Furthermore, indoles have prebiotic characteristics, influencing the balance of gut microbiota, encouraging the growth of good bacteria and inhibiting the reproduction of pathogenic strains, which is essential in the treatment of inflammatory bowel disease. They may affect the metabolism of estrogen, indirectly having an anti-inflammatory effect [41]. Indole-3-carbinol (I3C) and its metabolite DIM may help maintain a healthy composition of gut microbiota, thus aiding in managing disease pathology in Crohn's disease. While mostly explored for their anticancer properties, their potential in regulating inflammation and immune reactions may help in cases of inflammation-related diseases. The human research on cruciferous vegetables shows a positive effect on gut microbiota by stimulating good bacteria and killing bad bacteria, making this information applicable to inflammatory bowel disease [42]. However, while the mechanisms and indirect results of human use seem promising, there still are no large-scale human trials conducted on the influence of either I3C or DIM on Crohn's disease [43]. In smaller studies, diets such as an increase in cruciferous vegetables have been observed to decrease inflammation in IBD. Indole compounds, based on their anti-inflammatory, antioxidant, and microbiome-regulatory effects, may present a possibility for use in patients with Crohn's disease, where immune modulation can be expected [44]. However, the data available is still insufficient, mainly based on animal studies or general studies involving anti-inflammatory treatments, and no specific studies related to the application of indole compounds in Crohn's disease treatment have been carried out.

4.7. Lignan

Lignans, which are phenolic compounds present in plants and belong to the group of polyphenols, can be found in seeds, grains, and vegetables. Lignans do not serve as direct treatment measures for patients with Crohn's disease; however, they might be used as complementary treatments. These compounds possess antioxidant and anti-inflammatory effects; hence, they are able to influence immune reactions and decrease inflammation in the intestines [45]. In addition to the above, evidence suggests that lignans can influence the gut flora composition, an essential component in the creation of inflammatory bowel disease. However, there is little information available on this subject [46]. A balanced gut microflora is of great significance for the treatment of Crohn's disease because

dysbiosis is frequently seen in patients suffering from this disease. Lignans can have a prebiotic effect by stimulating the proliferation of helpful bacteria and thus maintaining the stability of the intestines. They also have antioxidant activity that helps counteract the oxidative stress associated with inflammatory bowel disease [47]. Furthermore, lignans may help with the modulation of immune response, contributing to the regulation of inflammatory processes. However, even though the possible mechanisms look promising, the direct clinical data on the effects of lignans on Crohn's disease are not sufficiently provided. The available evidence comes mainly from more general research related to polyphenols found in plants and IBD. Therefore, additional research is needed to prove the effectiveness of the proposed treatment method [48]. Lignans should only be viewed as supportive dietary factors, not as the main treatment option for Crohn's disease. Patients should always seek medical advice before making any modifications to their diet or taking supplements, especially when the disease is active.

4.8. Lycopene

Lycopene, which is a powerful antioxidant present in tomatoes and other red fruits, has been researched for its health benefits, including its effects in the case of an inflammatory disease called Crohn's disease. While research is still ongoing, here's what we know so far about its potential role in managing Crohn's disease. Crohn's disease is characterized by chronic inflammation of the gastrointestinal tract. Lycopene, due to its antioxidant and anti-inflammatory properties, may help reduce oxidative stress and inflammation in the body, which are thought to play a role in Crohn's disease [49,50]. Lycopene has been suggested to influence the immune system by inhibiting pro-inflammatory cytokines (chemical Lycopene has been suggested to influence the immune system by inhibiting pro-inflammatory cytokines (chemical messengers that promote inflammation), which might help in managing flare-ups of Crohn's diseasethat promote inflammation), which might help in managing flare-ups of Crohn's disease. Lycopene may also have beneficial effects on the gut microbiome, potentially promoting a healthier balance of gut bacteria. A balanced microbiome is thought to be important in controlling inflammation in Crohn's disease. In Crohn's disease, oxidative stress can damage tissues and exacerbate inflammation [51]. The antioxidant properties of lycopene would be able to counteract the damaging free radicals within the body, thereby reducing symptoms [52]. Several researchers have studied lycopene as an overall anti-inflammatory and antioxidant action in IBDs (inflammatory bowel diseases). Some studies point out that lycopene acts against oxidation and inflammation in IBD, but there is little evidence about its action in Crohn's disease [53]. Clinical investigations involving tomato-based products rich in lycopene have shown potential reductions in disease activity and symptoms in some IBD patients, though Crohn's disease was not evaluated separately [54]. Additionally, animal studies demonstrate that lycopene can attenuate inflammatory cytokine production and oxidative stress in intestinal tissues. However, translation of these findings to human Crohn's disease requires further investigation [55]. Despite various studies having been done to investigate the role of lycopene and diets consisting of tomatoes in cases of IBD, clinical trials involving Crohn's disease have not been performed extensively. The dosage that would give the maximum effect in the treatment of the disorder is not known at present.

4.9. Naringenin

Grapefruits are rich in Naringenin (4′,5,7-trihydroxyflavanone flavonoid), which is a glycone [56]. Naringenin, a flavonoid found largely in grapefruit and oranges, has received attention due to its possible health advantages, which include anti-inflammatory, antioxidant, and immune-modulating capabilities. Several investigations have indicated that Naringenin has anti-inflammatory properties. It may reduce pro-inflammatory cytokines and enzymes such TNF-α, IL-6, and COX-2. This might be especially effective in Crohn's disease, which is characterized by persistent inflammation. It may affect many inflammatory pathways, including the NF-κB pathway, which plays a role in the inflammatory response. Naringenin can reduce intestinal inflammation by regulating these pathways. Naringenin is a compound with anti-oxidant properties that could be able to neutralize free radicals and eliminate oxidative stress. Since oxidative stress contributes to the development of Crohn's disease, the presence of antioxidant properties within Naringenin could assist in minimizing some of the damage done by oxidative stress. By doing so, it may be possible to protect the gut epithelial cells from oxidative stress [57]. Naringenin Modulates immune responses through its effect on immune cell balance and cytokine production, leading to reduced inflammation in Crohn's disease. It also influences the microbiota composition of the gut, contributing to intestinal homeostasis. It has poor bioavailability, thereby limiting its therapeutic applications. In addition, it interacts with enzymes involved in drug metabolism such as CYP3A4 [58]. Naringenin has some interactions with the medicines that are metabolized by enzymes like CYP3A4, hence interfering with the treatment of Crohn's disease using medications. Even though there have been some positive results achieved in the preclinical studies and the preliminary clinical studies, more research is required to confirm its safety and

efficacy [59]. Naringenin possesses anti-inflammatory, antioxidant, and immunomodulating characteristics, indicating its possible usefulness in treating Crohn's disease. Nonetheless, its clinical effectiveness and safety should still undergo further studies. Its administration must be done as part of an integrated management approach.

4.10. Plantaginaceae

The plant known as *Plantago ovata* is tiny and has distinctive blooms. The plant's leaf juice has been used to treat gastric ulcers and discomfort associated with inflammatory diseases. The herb possesses antioxidant and anti-inflammatory qualities. It suppresses the expression of intercellular adhesion molecule-1, inhibits protein kinase C, and reduces inflammation brought on by leukotriene B4 and 5-hydroxy-6,8,11,14-eicosatetraenoic acid. Short-chain fatty acids are produced when *Plantago ovata* seeds are dissolved by enzymes, and these fatty acids are beneficial to those with ulcerative colitis. In an open clinical study, 105 patients with UC in remission were randomly randomized to receive 10 g of b.i.d. *Plantago ovata* seeds, 500 mg of t.i.d. mesalazine, or 10 g of b.i.d. *Plantago ovata* seeds with mesalazine at the same doses. The three groups' six-month recurrence rates (40, 35, and 30%) did not differ from one another [60,61].

4.11. Quercetin

A naturally occurring flavonoid found in a variety of fruits, vegetables, and grains is quercetin. Its possible anti-inflammatory and antioxidant qualities have been investigated; they might be important in the treatment of Crohn's disease. Quercetin (3,3′,4′,5,7-penta-hydroxy flavone), a polyphenol with anti-inflammatory and antioxidant qualities, is abundant in onions [62]. Glutathione (GSH), malondialdehyde, and serum nitrous oxide (NO) concentrations are all decreased by glycoside-rutin, which is highly helpful in treating inflammatory bowel disease (IBD) in experimental animals produced by DSS. It also regulates body weight and oxidative stress in terms of MPO. According to Lin et al., dietary quercetin reduces the symptoms of colitis in mice caused by Citrobacter retention by boosting the anti-inflammatory cytokine IL-10 in colon tissues and reducing pro-inflammatory cytokines (IL-6, IL-17, and TNF-α) [63].

4.12. Resveratrol

Resveratrol is an active ingredient present naturally in several plants like grapes, berries, and peanuts. It possesses remarkable anti-inflammatory and antioxidant actions and has therefore generated much interest because of the possibility of using it for treating inflammatory conditions such as Crohn's disease. Crohn's disease involves chronic inflammation of the digestive system, causing damage to the digestive tract [64]. Recent research shows that Resveratrol can be used to influence important inflammatory signaling pathways in the body and consequently reduce the production of inflammatory mediators such as pro-inflammatory cytokines. In addition, its antioxidant effect can also be used to counteract oxidative stress, which plays an important part in the development of Crohn's disease [65,66]. Resveratrol can be good for the gut microbiota, which is thought to influence the development and degree of Crohn's disease, according to some studies. The preclinical studies that have been done mainly using animal models and in vitro have yielded some promising results about resveratrol as a treatment for Crohn's disease [67,68]. These studies help to understand how Resveratrol would influence the pathophysiology of Crohn's disease, more specifically, its oxidative stress and inflammation. Resveratrol was shown to decrease the concentrations of inflammatory mediators like TNF-alpha, IL-6, and IL-1beta, which are essential for inflammation in Crohn's disease in rats with colitis, a disease that is similar to the disease under investigation [69–71]. Resveratrol can help reduce inflammation and tissue injury in the gut due to the regulation of NF-kB, which is a transcription factor that plays a role in inflammation. Another study has found that the NLRP3 inflammasome, which is a protein complex associated with the inflammatory response and IBD, such as Crohn's disease, can be inhibited by resveratrol [72]. Resveratrol administration has been demonstrated to lower reactive oxygen species (ROS) and restore the balance of antioxidants in the gut in preclinical models of colitis, a popular model used to research Crohn's disease [73]. Resveratrol can be an important mechanism through which the intestines' epithelial barrier can be protected from oxidative damage, ensuring the integrity of the mucosal barrier in inflammatory bowel disease [67]. Preclinical data obtained from studies aimed at IBD management revealed Resveratrol to have an effect on gut flora composition, an important factor in the development of IBD, although no specific results are yet available for Crohn's disease. In experiments with animals, administration of Resveratrol has been shown to influence the composition of gut flora, possibly decreasing intestinal inflammation [74]. In terms of mechanisms of action, both in vitro and animal studies show that Resveratrol is capable of suppressing pro-inflammatory cytokine levels, including TNF-α, and reducing oxidative stress, two important factors in chronic intestinal inflammation. In addition, due to the capability of Resveratrol in modulating the immune system via regulation of

T-cell functions, Resveratrol could serve as an efficient agent for controlling the inflammatory response in intestines [75]. The mechanism of action of Resveratrol includes boosting the activity of antioxidants through stimulation of enzymes such as superoxide dismutase (SOD) and catalase to reduce oxidative stress in patients suffering from Crohn's disease. According to experimental research, Resveratrol is able to inhibit T-helper cells activation, particularly the activation of Th17 cells, and induces macrophages to shift from pro-inflammatory type M1 to anti-inflammatory type M2, contributing to the reduction of inflammatory response in intestines [76]. However, despite the promising results in laboratories and animal experiments, there is not enough information regarding the impact of resveratrol in clinical practice.

4.13. Tannins

The tannins, which belong to the polyphenolic compound category, present in food items such as tea, coffee, fruits, and herbal preparations, possess a considerable amount of astringent, anti-inflammatory, and antioxidative potential and therefore can play a significant role in the treatment of Crohn's disease. Studies done on experimental animal models of colitis (TNBS/DSS-induced colitis model) revealed that tannic acid showed an ability to decrease the intestinal inflammation and improve the integrity of the mucosa, thereby reducing histological damage [77]. Such an effect was linked with the suppression of pro-inflammatory cytokines such as TNF-α and IL-1β, in addition to the improvement in the antioxidative defenses by increasing the enzymatic activity of GPx and SOD [78]. Grape seed extract treatment of DSS-induced colitis animals shows positive effects, such as better histological changes, fewer instances of mucosal damage, and low levels of pro-inflammatory cytokines, showing its potential for decreasing inflammation and injury of tissues [79]. There is some observational data regarding green tea polyphenols that might benefit patients with ulcerative colitis, which is very similar to Crohn's disease, and reduce inflammatory biomarkers. More clinical data needs to be obtained [80]. Green tea, which is abundant in catechins, which belong to the class of tannins, can possibly help decrease inflammation in the intestine and prevent oxidative damage, making green tea useful for CD, but there is insufficient clinical research to substantiate this assumption [81]. Another study conducted among patients with ulcerative colitis found that grape seed extract positively affected the symptoms of the disease, decreased its activity, and significantly increased patients' quality of life [82]. However, even though some promising results have been obtained through both preclinical and clinical studies, there is still no clinical evidence regarding tannins' effectiveness and safety when used in treating Crohn's disease.

4.14. Zingiberene

Zingiberene, a sesquiterpene found in *Zingiber officinale* (ginger), is known to possess anti-inflammatory, antimicrobial, and antioxidant activities. It acts on the NF-κB and MAPK signaling pathways involved in inflammation and regulates the production of pro-inflammatory cytokines and enzymes. Zingiberene can also play an important role in combating inflammation in patients with Crohn's disease due to its free radical scavenging activity. Commonly referred to as ginger, the rhizome of *Zingiber officinale* is a medicinal plant [83]. The ginger-derived nanoparticles (GDNPs) consist of a significant amount of biologically active chemicals (6-gingerol and 6-shogaol), high quantities of lipids, a small number of proteins, and approximately 125 microRNAs. In DSS and AOM-DSS mice models, GDNPs have been demonstrated to improve intestinal healing and decrease acute colitis and CAC, respectively. In response to oral GDNPs, there was an increase in the survival and proliferation of intestinal epithelial cells (IECs), a decrease in inflammatory cytokines (TNF-α, IL-6, and IL-1β), and an increase in anti-inflammatory cytokines (IL-10 and IL-22). These data suggest that GDNPs may have a protective and healing effect [84]. While some initial studies have demonstrated the anti-inflammatory, antioxidant, and antimicrobial capabilities of Zingiberene, evidence for its benefits in Crohn's disease patients is scarce at the moment. At present, most investigations revolve around the compound's anti-inflammatory and antioxidant properties without paying particular attention to their relevance to a specific disease such as Crohn's disease (Table 1).

Effective management of bioactive compounds in Crohn's disease requires a comprehensive approach that combines dietary strategies, nutritional supplements, pharmacological treatments, and lifestyle modifications. Modifying these techniques to suit the needs of the individual and observing their effect is an important factor in managing diseases and enhancing quality of life. Do not make any modifications without consulting the appropriate health professionals.

Table 1. Shows the bioactive phytochemicals for inflammatory bowel disease: Preclinical evidence.

Sl. No	Phytochemicals	Model	Treatment	Results	Ref.
1	Cannabinoids	mouse colitis (Di-nitrobenzen sulfonic acid)	Cannabidiol Injection (5–10 mg/kg)	Decrease colonic weight loss and inflammation	[85]
2	Cannabinoids	mouse colitis (Trinitrobenzene sulfonic acid)	2-AG-degrading enzyme MAGL Inhibition	Decrease in both microscopic and histological inflammation	[86]
3	Curcumin	Dextran sulfate sodium Mouse	Curcumin 2.0% (wt/wt)	↓Disease in histological colitis scores, ↓loss of body weight, ↓NF-κB, ↓decrease in activity index	[87]
4	Epicatechin	Ulcerative colitis rat model Colitis Induced with Dextran Sodium Sulfate (DSS)	50 mg/kg	Similar to sulfasalazine, green tea polyphenols (GTP) and EGCG increased antioxidant levels and lessened the severity of colitis	[36]
5	Naringenin	Colitis mouse induced with Dextran sodium sulfate (DSS)	2.0% (wt/wt)	iNOS (inducible NO synthase) ICAM-1 (intercellular adhesion molecule 1)	[88]
6	Catechins	Colitis mouse induced with Dextran sodium sulfate (DSS)	18–20 g	By increasing the F/B value, you can stimulate the Keap1-Nrf2-ARE signaling pathway, regulate the proliferation of Lactobacillaceae and Lachnospiraceae, and affect the downstream antioxidant protease and gut microbiome	[89]
7	Hesperetin	Oral hesperetin treatment in diabetic patients provoked with streptozotocin	5–6 g	Reduced the morphological and functional defects in the kidney brought on by diabetes in tight correlation with the modulatory effects	[90]
8	Genistein	Induced by hydroxyl radicals in 90.5% of the used C6 rat glioma cell line	Higher antioxidant properties at the doses 25–200 µg/mL	It's used to treat neurodegenerative and cardiovascular	[91]
9	Beal	Wistar albino rats	Induction of indomethacin-induced enterocolitis using a 10 mg/kg single dose of Indomethacin and induction of colonic acidosis using 1 milliliter of 4% Acetic acid solution (transrectal)	antioxidant and mast cell stabilizing effects, demonstrating protective effects in inflammatory bowel disease	[91]
10	Laminarin	Induced by alloxan injection	200 mg/kg Intraperitoneal	*Laminaria japonica* (LJP) reduces blood sugar and cholesterol levels in mice. Halt the body weight loss, lower fasting blood glucose, and raise serum insulin levels in diabetic mice	[92]
11	Quercetin	Streptozotocin-induced diabetic rat	2–3 g	showed antimicrobial and antioxidant activities	[92]
12	Oxymatrine	Male-specific pathogen-free mice	2.5 g/kg	In protracted toxicity studies, changes in body weight (loss) and growth rate are significant markers of negative effects	[36]
13	Palmatine	Fluoxetine mice	10 mg/kg	Increase in the neurotransmitter level	[70]
14	Pentoxifylline	One of the most widely utilized substances to induce hepatitis in rats is D-galactosamine (D-GAL)	500 mg/kg, body weight, on day 0	Its ability to control blood flow. PTX decreases plasma fibrinogen concentrations, which lowers blood viscosity, ↑ flexibility of red and white blood cells, and inhibits platelet aggregation and thrombus formation	[70]

5. Limitations

The bioactive compounds from natural sources proved to be effective for the treatment of Crohn's disease; however, some restrictions hinder the implementation of such products. Firstly, the lack of standardization leads to inconsistency in terms of the compounds used, their bioavailability, and effects. Additionally, clinical trials conducted to prove the effectiveness of the treatment are typically not enough because of the small number of patients used. Another factor that should be taken into account is the low bioavailability, interaction with the drugs, and the complexity of dosage determination. Moreover, the ethical side of using natural products remains a problem. Overall, more research, new ways of delivering the compounds, and standardization are needed before their use in the treatment of Crohn's disease.

6. Conclusions

The discovery of bioactive compounds from various biological sources seems to be a promising strategy to cope with oxidative stress and inflammation in the case of Crohn's disease. Compounds such as flavonoids, peptides, polyphenols, polysaccharides, and saponins are crucial players in the biological processes leading to

diseases. According to preliminary trials, promising results were obtained from the use of plant-based bioactive compounds such as curcumin, quercetin, and resveratrol to fight oxidative stress and inflammation. Besides, bioactive compounds of marine origin, such as fucoidan and astaxanthin, and those of microbial origin, such as probiotics and prebiotics, can help regulate the gut microbiota and immunity. The translation of preliminary findings into clinical practice is accompanied by some difficulties due to such problems as low bioavailability of bioactive compounds, insufficient studies at the clinical stage, and improper dosage methods. Further research requires more knowledge about the precise action mechanisms of the bioactive compounds, which is needed along with the development of efficient methods of delivery.

Author Contributions

N.P.: Conceptualization, methodology, investigation, data curation, writing—original draft preparation, visualization. R.S.D.: Methodology, validation, formal analysis, writing, review, and editing. S.T.: Investigation, data curation, visualization, literature review, writing, review, and editing. A.K.P.: Conceptualization, supervision, project administration, resources, funding acquisition, writing, review, and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

The authors acknowledge the School of Pharmacy and Life Sciences at Centurion University of Technology and Management in Odisha, India, for providing appropriate resources for the review effort.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. El Menyiy, N.; El Allam, A.; Aboulaghras, S.; et al. Inflammatory Auto-Immune Diseases of the Intestine and Their Management by Natural Bioactive Compounds. *Biomed. Pharmacother.* **2022**, *151*, 113158. https://doi.org/10.1016/j.biopha.2022.113158.
2. Jandhyala, S.M.; Talukdar, R.; Subramanyam, C.; et al. Role of the Normal Gut Microbiota. *World J. Gastroenterol.* **2015**, *21*, 8787–8803. https://doi.org/10.3748/wjg.v21.i29.8787.
3. Saygın, O. *Temel ve Klinik Yönleriyle İnfertilite*; Akademisyen Kitabevi: Ankara, Turkey, 2022. (In Turkish)
4. Talley, N.J.; Abreu, M.T.; Achkar, J.P.; et al. An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease. *Am. J. Gastroenterol.* **2011**, *106*, S2–S5. https://doi.org/10.1038/ajg.2011.58.
5. Sandborn, W.J.; Feagan, B.G.; Lichtenstein, G.R. Medical Management of Mild to Moderate Crohn's Disease: Evidence-Based Treatment Algorithms for Induction and Maintenance of Remission. *Aliment. Pharmacol. Ther.* **2007**, *26*, 987–1003. https://doi.org/10.1111/j.1365-2036.2007.03455.x.
6. Fakhoury, M.; Negrulj, R.; Mooranian, A.; et al. Inflammatory Bowel Disease: Clinical Aspects and Treatments. *J. Inflamm. Res.* **2014**, *7*, 113–120. https://doi.org/10.2147/JIR.S65979.

7. Vona, R.; Pallotta, L.; Cappelletti, M.; et al. The Impact of Oxidative Stress in Human Pathology: Focus on Gastrointestinal Disorders. *Antioxidants* **2021**, *10*, 201. https://doi.org/10.3390/antiox10020201.
8. Bhattacharyya, A.; Chattopadhyay, R.; Mitra, S.; et al. Oxidative Stress: An Essential Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. *Physiol. Rev.* **2014**, *94*, 329–354. https://doi.org/10.1152/physrev.00040.2012.
9. Cai, H.; Harrison, D.G. Endothelial Dysfunction in Cardiovascular Diseases: The Role of Oxidant Stress. *Circ. Res.* **2000**, *87*, 840–844. https://doi.org/10.1161/01.RES.87.10.840.
10. Tian, T.; Wang, Z.; Zhang, J. Pathomechanisms of Oxidative Stress in Inflammatory Bowel Disease and Potential Antioxidant Therapies. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 4535194. https://doi.org/10.1155/2017/4535194.
11. Novak, E.A.; Mollen, K.P. Mitochondrial Dysfunction in Inflammatory Bowel Disease. *Front. Cell Dev. Biol.* **2015**, *3*, 62. https://doi.org/10.3389/fcell.2015.00062.
12. Chen, Y.; Gibson, S.B. Is Mitochondrial Generation of Reactive Oxygen Species a Trigger for Autophagy? *Autophagy* **2008**, *4*, 246–248. https://doi.org/10.4161/auto.5432.
13. Heuschen, U.A.; Hinz, U.; Allemeyer, E.H.; et al. Backwash Ileitis Is Strongly Associated with Colorectal Carcinoma in Ulcerative Colitis. *Gastroenterology* **2001**, *120*, 841–847. https://doi.org/10.1053/gast.2001.22434.
14. Almenier, H.A.; Al Menshawy, H.H.; Maher, M.M.; et al. Oxidative Stress and Inflammatory Bowel Disease. *Front. Biosci.-Elite* **2012**, *4*, 1335–1344.
15. Rao, R. Oxidative Stress-Induced Disruption of Epithelial and Endothelial Tight Junctions. *Front. Biosci.* **2008**, *13*, 7210–7226. https://doi.org/10.2741/3223.
16. Xavier, R.; Podolsky, D. Unravelling the Pathogenesis of Inflammatory Bowel Disease. *Nature* **2007**, *448*, 427–434. https://doi.org/10.1038/nature06005.
17. Baumgart, D.C.; Sandborn, W.J. Crohn's Disease. *Lancet* **2012**, *380*, 1590–1605.
18. Uniken Venema, W.T.; Voskuil, M.D.; Dijkstra, G.; et al. The Genetic Background of Inflammatory Bowel Disease: From Correlation to Causality. *J. Pathol.* **2017**, *241*, 146–158. https://doi.org/10.1002/path.4817.
19. Pacher, P.; Beckman, J.S.; Liaudet, L. Nitric Oxide and Peroxynitrite in Health and Disease. *Physiol. Rev.* **2007**, *87*, 315–424. https://doi.org/10.1152/physrev.00029.2006.
20. Knutson, C.G.; Mangerich, A.; Zeng, Y.; et al. Chemical and Cytokine Features of Innate Immunity Characterize Serum and Tissue Profiles in Inflammatory Bowel Disease. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E2332–E2341. https://doi.org/10.1073/pnas.1222669110.
21. Hiller, F.; Besselt, K.; Deubel, S.; et al. GPx2 Induction Is Mediated through STAT Transcription Factors during Acute Colitis. *Inflamm. Bowel Dis.* **2015**, *21*, 2078–2089. https://doi.org/10.1097/MIB.0000000000000464.
22. Ananthakrishnan, A.N. Environmental Risk Factors for Inflammatory Bowel Disease. *Gastroenterol. Hepatol.* **2013**, *9*, 367–374.
23. Mawdsley, J.E.; Rampton, D.S. Psychological Stress in IBD: New Insights into Pathogenic and Therapeutic Implications. *Gut* **2005**, *54*, 1481–1491. https://doi.org/10.1136/gut.2005.064261.
24. Rampton, D. Does Stress Influence Inflammatory Bowel Disease? The Clinical Data. *Dig. Dis.* **2009**, *27*, 76–79. https://doi.org/10.1159/000268124.
25. Neish, A.S. Redox Signaling Mediated by the Gut Microbiota. *Free Radical Res.* **2013**, *47*, 950–957. https://doi.org/10.3109/10715762.2013.833331.
26. Campbell, E.L.; Colgan, S.P. Control and Dysregulation of Redox Signalling in the Gastrointestinal Tract. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 106–120. https://doi.org/10.1038/s41575-018-0079-5.
27. Izzo, A.A.; Sharkey, K.A. Cannabinoids and the Gut: New Developments and Emerging Concepts. *Pharmacol. Ther.* **2010**, *126*, 21–38. https://doi.org/10.1016/j.pharmthera.2009.12.005.
28. Lal, S.; Prasad, N.; Ryan, M.; et al. Cannabis Use Amongst Patients with Inflammatory Bowel Disease. *Eur. J. Gastroenterol. Hepatol.* **2011**, *23*, 891–896. https://doi.org/10.1097/MEG.0b013e328349bb4c.
29. Borrelli, F.; Aviello, G.; Romano, B.; et al. Cannabidiol, a Safe and Non-Psychotropic Ingredient of the Marijuana Plant *Cannabis sativa*, Is Protective in a Murine Model of Colitis. *J. Mol. Med.* **2009**, *87*, 1111–1121. https://doi.org/10.1007/s00109-009-0512-x.
30. Alhouayek, M.; Lambert, D.M.; Delzenne, N.M.; et al. Increasing Endogenous 2-Arachidonoylglycerol Levels Counteracts Colitis and Related Systemic Inflammation. *FASEB J.* **2011**, *25*, 2711–2721. https://doi.org/10.1096/fj.10-176602.
31. Deguchi, Y.; Andoh, A.; Inatomi, O.; et al. Curcumin Prevents the Development of Dextran Sulfate Sodium (DSS)-Induced Experimental Colitis. *Dig. Dis. Sci.* **2007**, *52*, 2993–2998. https://doi.org/10.1007/s10620-006-9138-9.
32. Malinowski, B.; Wiciński, M.; Sokołowska, M.M.; et al. The Rundown of Dietary Supplements and Their Effects on Inflammatory Bowel Disease—A Review. *Nutrients* **2020**, *12*, 1423. https://doi.org/10.3390/nu12051423.

33. Desai, N.; Momin, M. Colon Targeted Bioadhesive Pellets of Curcumin and Cyclosporine for Improved Management of Inflammatory Bowel Disease. *Drug Delivery Transl. Res.* **2020**, *10*, 1288–1301. https://doi.org/10.1007/s13346-020-00756-x.
34. Mazieiro, R.; Frizon, R.R.; Barbalho, S.M.; et al. Is Curcumin a Possibility to Treat Inflammatory Bowel Diseases? *J. Med. Food* **2018**, *21*, 1077–1085. https://doi.org/10.1089/jmf.2017.0146.
35. Asakura, H.; Kitahora, T. Antioxidants and Polyphenols in Inflammatory Bowel Disease: Ulcerative Colitis and Crohn Disease. In *Polyphenols: Prevention and Treatment of Human Disease*, 2nd Ed.; Academic Press: London, UK, 2018; pp. 279–292. https://doi.org/10.1016/B978-0-12-813008-7.00023-0.
36. Barbalho, S.M.; Bosso, H.; Salzedas-Pescinini, L.M.; et al. Green Tea: A Possibility in the Therapeutic Approach of Inflammatory Bowel Diseases? *Complement. Ther. Med.* **2019**, *43*, 148–153. https://doi.org/10.1016/j.ctim.2019.01.015.
37. Oz, H.S.; Chen, T.; de Villiers, W.J. Green Tea Polyphenols and Sulfasalazine Have Parallel Anti-Inflammatory Properties in Colitis Models. *Front. Immunol.* **2013**, *4*, 132. https://doi.org/10.3389/fimmu.2013.00132.
38. Wang, D.W.; Xiang, Y.J.; Wei, Z.L.; et al. Andrographolide and Its Derivatives Are Effective Compounds for Gastrointestinal Protection: A Review. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 2367–2382.
39. Dicarlo, M.; Teti, G.; Verna, G.; et al. Quercetin Exposure Suppresses the Inflammatory Pathway in Intestinal Organoids from Winnie Mice. *Int. J. Mol. Sci.* **2019**, *20*, 5771. https://doi.org/10.3390/ijms20225771.
40. Dryden, G.W.; Lam, A.; Beatty, K.; et al. A Pilot Study to Evaluate the Safety and Efficacy of an Oral Dose of (−)-Epigallocatechin-3-Gallate–Rich Polyphenon E in Patients with Mild to Moderate Ulcerative Colitis. *Inflammatory Bowel Dis.* **2013**, *19*, 1904–1912. https://doi.org/10.1097/MIB.0b013e31828f5198.
41. Zhang, M.; Viennois, E.; Prasad, M.; et al. Edible Ginger-Derived Nanoparticles: A Novel Therapeutic Approach for the Prevention and Treatment of Inflammatory Bowel Disease and Colitis-Associated Cancer. *Biomaterials* **2016**, *101*, 321–340. https://doi.org/10.1016/j.biomaterials.2016.06.018.
42. Zhang, M.; Wang, X.; Han, M.K.; et al. Oral Administration of Ginger-Derived Nanolipids Loaded with siRNA as a Novel Approach for Efficient siRNA Drug Delivery to Treat Ulcerative Colitis. *Nanomedicine* **2017**, *12*, 1927–1943. https://doi.org/10.2217/nnm-2017-0196.
43. Ju, S.; Mu, J.; Dokland, T.; et al. Grape Exosome-like Nanoparticles Induce Intestinal Stem Cells and Protect Mice from DSS-Induced Colitis. *Mol. Ther.* **2013**, *21*, 1345–1357. https://doi.org/10.1038/mt.2013.64.
44. Chessa, M.; Caddeo, C.; Valenti, D.; et al. Effect of Penetration Enhancer Containing Vesicles on the Percutaneous Delivery of Quercetin through New Born Pig Skin. *Pharmaceutics* **2011**, *3*, 497–509. https://doi.org/10.3390/pharmaceutics3030497.
45. Lin, R.; Piao, M.; Song, Y. Dietary Quercetin Increases Colonic Microbial Diversity and Attenuates Colitis Severity in *Citrobacter rodentium*-Infected Mice. *Front. Microbiol.* **2019**, *10*, 1092. https://doi.org/10.3389/fmicb.2019.01092.
46. Khan, M.N.; Lane, M.E.; McCarron, P.A.; et al. Caffeic Acid Phenethyl Ester Is Protective in Experimental Ulcerative Colitis via Reduction in Levels of Pro-Inflammatory Mediators and Enhancement of Epithelial Barrier Function. *Inflammopharmacology* **2018**, *26*, 561–569. https://doi.org/10.1007/s10787-017-0364-x.
47. Fernandez-Banares, F.; Hinojosa, J.; Sanchez-Lombrana, J.L.; et al. Randomized Clinical Trial of *Plantago ovata* Seeds (Dietary Fiber) as Compared with Mesalamine in Maintaining Remission in Ulcerative Colitis. *Am. J. Gastroenterol.* **1999**, *94*, 427–433. https://doi.org/10.1111/j.1572-0241.1999.872_a.x.
48. Guo, F.; Tsao, R.; Li, C.; et al. Green Pea (*Pisum sativum* L.) Hull Polyphenol Extracts Ameliorate DSS-Induced Colitis through Keap1/Nrf2 Pathway and Gut Microbiota Modulation. *Foods* **2021**, *10*, 2765. https://doi.org/10.3390/foods10112765.
49. Chen, Y.J.; Kong, L.; Tang, Z.Z.; et al. Hesperetin Ameliorates Diabetic Nephropathy in Rats by Activating Nrf2/ARE/Glyoxalase 1 Pathway. *Biomed. Pharmacother.* **2019**, *111*, 1166–1175. https://doi.org/10.1016/j.biopha.2019.01.030.
50. Chang, T.; Neelakandan, C.; Define, L.; et al. Effects of Glucose on Cell Viability and Antioxidant and Anti-Inflammatory Properties of Phytochemicals and Phytochemically Modified Membranes. *J. Phys. Chem. B* **2014**, *118*, 11993–12001. https://doi.org/10.1021/jp5080187.
51. Sahoo, D.K.; Heilmann, R.M.; Paital, B.; et al. Oxidative Stress, Hormones, and Effects of Natural Antioxidants on Intestinal Inflammation in Inflammatory Bowel Disease. *Front. Endocrinol.* **2023**, *14*, 1217165. https://doi.org/10.3389/fendo.2023.1217165.
52. Punitha, R.; Manoharan, S. Antihyperglycemic and Antilipidperoxidative Effects of *Pongamia pinnata* (Linn.) Pierre Flowers in Alloxan Induced Diabetic Rats. *J. Ethnopharmacol.* **2006**, *105*, 39–46. https://doi.org/10.1016/j.jep.2005.09.037.
53. Bhanot, A.; Shri, R. A Comparative Profile of Methanol Extracts of *Allium cepa* and *Allium sativum* in Diabetic Neuropathy in Mice. *Pharmacogn. Res.* **2010**, *2*, 374. https://doi.org/10.4103/0974-8490.75460.
54. Zhou, S.; Wu, X.; Huang, Y.; et al. Microwave-Assisted Aqueous Two-Phase Extraction of Alkaloids from *Radix Sophorae Tonkinensis* with an Ethanol/Na_2HPO_4 System: Process Optimization, Composition Identification and Quantification Analysis. *Ind. Crops Prod.* **2018**, *122*, 316–328. https://doi.org/10.1016/j.indcrop.2018.06.004.

55. Yang, Q.C.; et al. Identification of *In-Vivo* and *In-Vitro* Metabolites of Palmatine by Liquid Chromatography-Tandem Mass Spectrometry. *J. Pharm. Pharmacol.* **2009**, *61*, 647–652. https://doi.org/10.1211/jpp/61.05.0014.
56. Thompson, M.K.; Tuma, R.F.; Young, W.F. The Effects of Pentoxifylline on Spinal Cord Blood Flow after Experimental Spinal Cord Injury. *J. Assoc. Acad. Minor. Physicians Off. Publ. Assoc. Acad. Minor. Physicians* **1999**, *10*, 23–26.
57. Van Boekel, M.; Fogliano, V.; Pellegrini, N.; et al. A Review on the Beneficial Aspects of Food Processing. *Mol. Nutr. Food Res.* **2010**, *54*, 1215–1247. https://doi.org/10.1002/mnfr.200900608.
58. Bengmark, S.; Martindale, R. Prebiotics and Synbiotics in Clinical Medicine. *Nutr. Clin. Pract.* **2005**, *20*, 244–261. https://doi.org/10.1177/0115426505020002244.
59. Lewis, J.D.; Abreu, M.T. Diet as a Trigger or Therapy for Inflammatory Bowel Diseases. *Gastroenterology* **2017**, *152*, 398–414. https://doi.org/10.1053/j.gastro.2016.10.019.
60. Reifen, R.; Nur, T.; Matas, Z.; et al. Lycopene Supplementation Attenuates the Inflammatory Status of Colitis in a Rat Model. *Int. J. Vitam. Nutr. Res.* **2001**, *71*, 347–351. https://doi.org/10.1024/0300-9831.71.6.347.
61. van Steenwijk, H.P.; Bast, A.; de Boer, A. The Role of Circulating Lycopene in Low-Grade Chronic Inflammation: A Systematic Review of the Literature. *Molecules* **2020**, *25*, 4378. https://doi.org/10.3390/molecules25194378.
62. Imran, M.; Ghorat, F.; Ul-Haq, I.; et al. Lycopene as a Natural Antioxidant Used to Prevent Human Health Disorders. *Antioxidants* **2020**, *9*, 706. https://doi.org/10.3390/antiox9080706.
63. Caseiro, M.; Ascenso, A.; Costa, A.; et al. Lycopene in Human Health. *LWT* **2020**, *127*, 109323. https://doi.org/10.1016/j.lwt.2020.109323.
64. Chiu, H.-F.; Venkatakrishnan, K.; Golovinskaia, O.; et al. Gastroprotective Effects of Polyphenols against Various Gastro-Intestinal Disorders: A Mini-Review with Special Focus on Clinical Evidence. *Molecules* **2021**, *26*, 2090. https://doi.org/10.3390/molecules26072090.
65. Matsumura, Y.; Kitabatake, M.; Kayano, S.-i.; et al. Dietary Phenolic Compounds: Their Health Benefits and Association with the Gut Microbiota. *Antioxidants* **2023**, *12*, 880. https://doi.org/10.3390/antiox12040880.
66. Clarke, J.O.; Mullin, G.E. A Review of Complementary and Alternative Approaches to Immunomodulation. *Nutr. Clin. Pract.* **2008**, *23*, 49–62. https://doi.org/10.1177/011542650802300149.
67. Prakash, V.; Bose, C.; Sunilkumar, D.; et al. Resveratrol as a Promising Nutraceutical: Implications in Gut Microbiota Modulation, Inflammatory Disorders, and Colorectal Cancer. *Int. J. Mol. Sci.* **2024**, *25*, 3370. https://doi.org/10.3390/ijms25063370.
68. Gu, Y.; Lou, Y.; Zhou, Z.; et al. Resveratrol for Inflammatory Bowel Disease in Preclinical Studies: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* **2024**, *15*, 1411566. https://doi.org/10.3389/fphar.2024.1411566.
69. Rahal, K.; Schmiedlin-Ren, P.; Adler, J.; et al. Resveratrol Has Anti-Inflammatory and Antifibrotic Effects in the Peptidoglycan-Polysaccharide Rat Model of Crohn's Disease. *Inflamm. Bowel Dis.* **2012**, *18*, 613–623. https://doi.org/10.1002/ibd.21843.
70. Moura, F.A.; de Andrade, K.Q.; Dos Santos, J.C.F.; et al. Antioxidant Therapy for Treatment of Inflammatory Bowel Disease: Does It Work? *Redox Biol.* **2015**, *6*, 617–639. https://doi.org/10.1016/j.redox.2015.10.006.
71. Dziąbowska-Grabias, K.; Sztanke, M.; Zając, P.; et al. Antioxidant Therapy in Inflammatory Bowel Diseases. *Antioxidants* **2021**, *10*, 412. https://doi.org/10.3390/antiox10030412.
72. Meng, T.; Xiao, D.; Muhammed, A.; et al. Anti-Inflammatory Action and Mechanisms of Resveratrol. *Molecules* **2021**, *26*, 229. https://doi.org/10.3390/molecules26010229.
73. Blagov, A.V.; Orekhova, V.A.; Sukhorukov, V.N.; et al. Potential Use of Antioxidant Compounds for the Treatment of Inflammatory Bowel Disease. *Pharmaceuticals* **2023**, *16*, 1150. https://doi.org/10.3390/ph16081150.
74. Ismail, E.N.; Zakuan, N.; Othman, Z.; et al. Polyphenols Mitigating Inflammatory Mechanisms in Inflammatory Bowel Disease (IBD): Focus on the NF-κB and JAK/STAT Pathways. *Inflammopharmacology* **2025**, *33*, 759–765. https://doi.org/10.1007/s10787-024-01607-8.
75. Muro, P.; Zhang, L.; Li, S.; et al. The Emerging Role of Oxidative Stress in Inflammatory Bowel Disease. *Front. Endocrinol.* **2024**, *15*, 1390351. https://doi.org/10.3389/fendo.2024.1390351.
76. Chandimali, N.; Bak, S.G.; Park, E.H.; et al. Free Radicals and Their Impact on Health and Antioxidant Defenses: A Review. *Cell Death Discovery* **2025**, *11*, 19. https://doi.org/10.1038/s41420-024-02278-8.
77. Boaru, D.L.; Fraile-Martinez, O.; De Leon-Oliva, D.; et al. Harnessing the Anti-Inflammatory Properties of Polyphenols in the Treatment of Inflammatory Bowel Disease. *Int. J. Biol. Sci.* **2024**, 14, 5608–5672. https://doi.org/10.7150/ijbs.98107.
78. Zhang, Y.; Zhang, J.; Yan, J.; et al. Application of Fermented Chinese Herbal Medicines in Food and Medicine Field: From an Antioxidant Perspective. *Trends Food Sci. Technol.* **2024**, *148*, 104410. https://doi.org/10.1016/j.tifs.2024.104410.
79. Nunes, S.; Danesi, F.; Del Rio, D.; et al. Resveratrol and Inflammatory Bowel Disease: The Evidence So Far. *Nutr. Res. Rev.* **2018**, *31*, 85–97. https://doi.org/10.1017/S095442241700021X.
80. Malaguarnera, L. Influence of Resveratrol on the Immune Response. *Nutrients* **2019**, *11*, 946. https://doi.org/10.3390/nu11050946.

81. Xiang, Y.; Zhang, M.; Jiang, D.; et al. The Role of Inflammation in Autoimmune Disease: A Therapeutic Target. *Front. Immunol.* **2023**, *14*, 1267091. https://doi.org/10.3389/fimmu.2023.1267091.
82. Jawhara, S. How Do Polyphenol-Rich Foods Prevent Oxidative Stress and Maintain Gut Health? *Microorganisms* **2024**, *12*, 1570. https://doi.org/10.3390/microorganisms12081570.
83. Macáková, K.; Kolečkář, V.; Cahlíková, L.; et al. Chapter 6-Tannins and Their Influence on Health. In *Recent Advances in Medicinal Chemistry*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 159–208.
84. He, Q.; Guo, K.; Wang, L.; et al. Tannins Amount Determines Whether Tannase-Containing Bacteria Are Probiotic or Pathogenic in IBD. *Life Sci. Alliance* **2023**, *6*, e202201702. https://doi.org/10.26508/lsa.202201702.
85. Wang, X.; Quan, S.; Li, J.; et al. Protective Effects of Grape Seed Proanthocyanidin Extract in Preventing DSS-Induced Ulcerative Colitis Based on Pharmacodynamic, Pharmacokinetic and Tissue Distribution. *Curr. Drug Metab.* **2022**, *23*, 496–505. https://doi.org/10.2174/1389200223666220609151836.
86. Anwar, S.; Alrumaihi, F.; Sarwar, T.; et al. Exploring Therapeutic Potential of Catalase: Strategies in Disease Prevention and Management. *Biomolecules* **2024**, *14*, 697. https://doi.org/10.3390/biom14060697.
87. Oz, H.S. Chronic Inflammatory Diseases and Green Tea Polyphenols. *Nutrients* **2017**, *9*, 561. https://doi.org/10.3390/nu9060561.
88. Fan, F.-Y.; Sang, L.-X.; Jiang, M. Catechins and Their Therapeutic Benefits to Inflammatory Bowel Disease. *Molecules* **2017**, *22*, 484. https://doi.org/10.3390/molecules22030484.
89. Pantalos, G.; Vaou, N.; Papachristidou, S.; et al. Antioxidant and Anti-Inflammatory Phytochemicals for the Treatment of Inflammatory Bowel Disease: A Systematic Review. *Appl. Sci.* **2024**, *14*, 2177. https://doi.org/10.3390/app14052177.
90. Srinivasan, A.R. Treat to Target in Crohn's Disease: A Practical Guide for Clinicians. *World J. Gastroenterol.* **2024**, *30*, 50.
91. Newman, R.A.; Lansky, E.P.; Block, M.L. *Pomegranate: The Most Medicinal Fruit*; Basic Health Publications, Inc.: Laguna Beach, CA, USA, 2007.
92. Jang, W.Y.; Kim, M.-Y.; Cho, J.Y. Antioxidant, Anti-Inflammatory, Anti-Menopausal, and Anti-Cancer Effects of Lignans and Their Metabolites. *Int. J. Mol. Sci.* **2022**, *23*, 15482. https://doi.org/10.3390/ijms232415482.