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Natural polysaccharides for ulcerative colitis: A general overview

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ABSTRACT

Ulcerative colitis is a colonic disease characterized by the disruption of the mucosal epithelial layer and inflammation. For the treatment of this disease, various chemotherapeutic agents are available. However, the toxicities associated with chemotherapeutics greatly hamper treatment. Polysaccharide from natural resources is emerging as a potentially therapeutic substance with comparative minimum adverse effects. In this article, we are discussing polysaccharide from diverse sources (plants, edible mushrooms, and algae) which are being used in the treatment of ulcerative colitis. These polysaccharides exert their therapeutic action on ulcerative colitis through several mechanisms, including suppression of inflammatory cascades NF-κB, MAPK, IL-6/JAK2/STAT3, preventing the release of certain inflammatory mediators, modulating the intestinal microbiome, maintaining the integrity of intestinal barriers, and regulating the certain inflammatory markers. The present review compiles the role of different polysaccharides being used successfully in the management/treatment of ulcerative colitis. Special emphasis was given to explaining the biomolecular pathway.

KEYWORDS: Ulcerative colitis; Polysaccharide; Colon; Inflammatory bowel disease; Phytochemicals

1. Introduction

Ulcerative colitis (UC) is a grievous mucosal disease of the colon that comes under the category of inflammatory bowel disease. It is a burning issue that has an impact on citizens throughout the entire globe. According to updated information, inflammatory bowel disease affects 6.8 million people globally. Among these, women are more prevalently affected (57%) than men (43%) and its prevalence has still been escalating at a massive level[1]. UC is a disease-causing inflammation of the epithelial surfaces of the colon and rectum. These epithelial surfaces are generally protected by mucosal linings, which typically serve as a defense against certain pathogens but in UC, this barrier function becomes impaired, damaging the layers and eventually leading to inflammation and ulceration. Pancolitis, sigmoiditis, and proctitis are the most prevalent UC types[2]. The signs of UC include toxic megacolon, bloody stool, fissure hemorrhoids, tenesmus, and abdominal discomfort[3,4]. The ailment has been affecting several individuals, but the actual reason for the disease worsening is yet unknown. The following risk factors are believed to be the primary contributors to the development of inflammation including dietary products, genetic constitution, ecological aspects, age, gender, and certain drugs (non-steroidal anti-inflammatory drugs).

Polysaccharides are a type of carbohydrate macromolecule formed by the continuous condensation of monosaccharides that are bonded to one another through glycosidic linkages. Their structures generally consist of glucan, fructan, xylan, mannan, galactan, *etc*, or a polymer of two or multiple monosaccharides. Plants, algae, and fungi are the natural source of polysaccharides. These isolated polysaccharides are utilized to treat multiple diseases. Besides polysaccharides, drugs like aminosalicylic acid (sulfasalazine), corticosteroids (prednisolone), immunosuppressive agents (azathioprine, tacrolimus), biological agents (infliximab) are frequently used to

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treat UC. However, the safety and effectiveness of these agents remain challenging. Therefore, employing natural polysaccharides to alleviate UC is a promising alternative.

In this review article, we summarize the applications of plant-based polysaccharides in UC. These polysaccharides have been extensively used in the prevention and treatment of the disease with no/or minimum level of toxicity. The article also emphasizes the possible mechanism of action of polysaccharides in the treatment of UC.

2. UC

UC is an egregious disease that occurs in the intestinal region, specifically the rectum and colon, and generally affects the mucosal layer of the colon. In UC patients, the mucosal lining protecting the epithelial surface of the colon becomes unimpressively crippled, due to which permeability of the intestinal layer is enhanced leading to inflammation and abscesses in a particular area. UC is manifested by toxic megacolon, bloody stool, fissure hemorrhoids, tenesmus, abdominal discomfort, and a few additional indications like pyoderma gangrenosum (skin disease), cheilitis, pellagra (nutrition deficiency), uveitis, episcleritis (an eye disorder). The occurrence of UC is thought to be influenced by multifaceted etiological factors including diet, medications, genetics, lifestyle factor, and gut flora[3]. If it is left untreated, it may extend to the sigmoidal intestinal colon, which is known as "sigmoiditis," further continuing to expand up to the entire colon, referred to as "pancolitis".

UC is marked by the perturbation of the mucus layer. In UC, this intestinal barrier "mucus" gets distorted due to multiple factors thereby allowing the entrance of certain pernicious microorganisms. Following their entrance through breached intestinal layer, these pathogens activate the antigen-presenting cells (dendritic cells and macrophages), specialized cells of the immune system positioned near the epithelial surface. Antigen-presenting cells particularly dendritic cells bear the toll-like receptors that are responsible for the activation of dendritic cells. These cells carry antigens and travel to lymphocytes through mesenteric lymph nodes to present to specific T cells, which can be split into helper T cells (Th) including Th2, Th17, and Th9, which secrete specific cytokines interleukin (IL)-13, IL-17, tumor necrosis factor (TNF-α), and IL-9, respectively. Similarly, macrophages through phagocytosis release pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 by the activation of pathways involving such as nuclear factor-kappaB (NF-κB), mitogen-activated protein kinase (MAPK), and adenosine 5′ monophosphate-activated protein kinase. Thus, it embarks on the inflammatory cascade (Figure 1).

3. Polysaccharides used in the treatment of UC

Herbal medicines are generally derived from plants, therefore, commonly known as 'phytochemicals'. The Greek word 'Phyto' simply implies 'the plants'. Owing to their ability to alleviate a variety of medical conditions, herbal medicines are employed extensively across the world. In addition, they contain a wide variety of plant metabolites, such as alkaloids, flavonoids, and anthocyanins, which may be used to treat various diseases by suppressing certain pathways. Recently, UC is being treated with synthetic medications such as corticosteroids, aminosalicylates, immunosuppressants, and biological treatments. However, long-term usage may result in many severe complications. Herbal drugs are a tremendous choice for circumventing these obstructions, therapy with these products offers effective anti-inflammatory effects with minimal negative effects and lower toxicity.

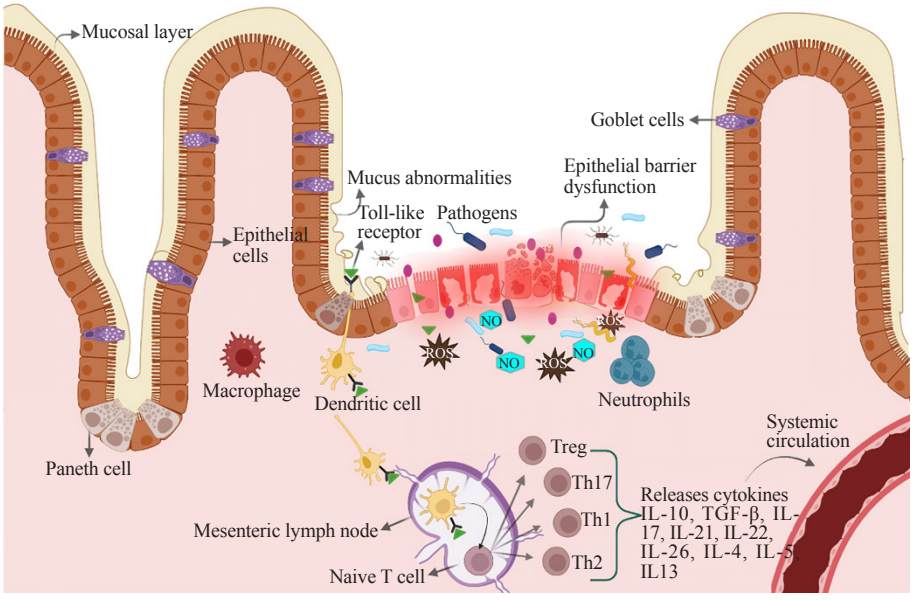

Figure 1. Pathophysiology of ulcerative colitis indicating various biomolecular pathways. IL:interleukin; TNF: tumor necrosis factor; Th: helper T cell.

Polysaccharides are a type of carbohydrate formed by the continuous condensation of monosaccharides that are bonded to one another through glycosidic linkages. The primary reservoirs of polysaccharides are plants, animals, microbes, edible fungi, and edible mushrooms. These polysaccharides include cellulose, pectins, chitosan, pullulan, and alginate. Enzyme-assisted methods, microwave-assisted methods, ultrasound methods, and hydrothermal methods are the techniques employed to extract polysaccharides from numerous resources. Polysaccharides are being employed for a few decades as they possess multiple beneficial properties such as low toxicity, bioavailability, biocompatibility, and low cost. Currently, their utilization is prodigiously enhanced in demand due to their health-promoting properties like antineoplastic, antioxidant, anticoagulant, and hypoglycemic. Besides these, natural polysaccharides are employed for colon disorders[5]. Here we are discussing the polysaccharide from the various sources being used in the treatment of UC.

3.1. Polysaccharides from natural plants

3.1.1. Aloe barbadensis

Aloe vera (*A. vera*) belongs to the class of Magnoliposida, and comes under the family Xanthorrhoeacae. '*A. vera*', and 'Ghritkumari' are common names of this plant. A perennial pulpy shrub known as '*A. vera*' with green leaves, arranged at the stem in a rosette form is highly rich in nutrients and various constituents. Some of these constituents are glycoproteins, flavonoids, minerals, amino acids, sterols, saponins, and vitamins. It has been widely demonstrated that polysaccharides such as acemannan, pectics, and cellulose are major active ingredients in aloe. It possesses many pharmacological activities such as immune modulating, antibacterial, antioxidation, hypolipidemic, and anticancer[6]. One study confirmed that by modifying the Janus kinase (JAK)2/signal transducer and activator of transcription (STAT)-3 signaling cascade, *A. vera* markedly improved the colon health of mice. Similarly, aloe polysaccharide demonstrated favorable outcomes by suppressing the elevated levels of related genes and interleukins, restoring colonic length, and consequently curing intestinal colonic injury[7]. *A. vera* polysaccharides also work by invigorating the Nrf2/HO-1 signaling cascade. Nrf2, a nuclear factor erythroid 2-related factor, plays a decisive role in protecting the intestinal layer by activating colonic proteins like zona occlude and occludin. These factors are sparked off by oxidative stress, resulting in the production of inflammatory and antioxidant genes, quinine oxidoreductase-1 and heme oxygenase-1. *A. vera* polysaccharides could attenuate the level of these proteins and, on top of that, normalize the aberrant level of short-chain fatty acids[8].

3.1.2. Astragalus membranaceus

This plant commonly known as 'Milkvetch', and 'Huang Qi', is a popular herbaceous plant widely used in traditional Chinese medicines for the treatment of various diseases and to promote human health. It consists of various bioactive agents that could strengthen immunity and manifest antioxidation, antineoplastic, anti-diabetic, antiviral anti-inflammatory, and immunomodulatory effects. *Astragalus membranaceous*, a perennial herb, is a member of the Leguminosae family[9]. The dry roots of this plant are rich in the polysaccharide which include α-type glycosidic linkage. Multiple methods, namely enzyme extraction, microwave-assisted procedures, *etc*. are employed to extract the polysaccharide from this plant[10]. The polysaccharide obtained from *Astragalus membranaceous* could reduce colonic aggravation by suppressing NF-κB activation. A transcriptional factor called NF-κB is responsible for generating pro-inflammatory cytokines, which negatively impact the colon. Since the NF-κB cascade is also responsible for the synthesis of several cytokines, treatment with the polysaccharide hindered the production of these inflammatory mediators, notably TNF-α, IL-6, IL-1, and some other interleukins[11]. Similarly, the nuclear factor of activated T cell (NFATc) 4 protein production is also regulated by this polysaccharide. When given at a dose of 200 mg/kg, it significantly declined cytokine levels while escalating NFATc1-c4 protein levels. As a result, it could improve trinitro-benzene-sulfonic acid-induced colitis in a rat model[12]. Correspondingly, it repairs colonic tissues by altering the helper T cell and Treg cell expression. The levels of Tfh1, Tfh17, and Tfh21 cells are negatively regulated. Conversely, it could boost the levels of Tfh10 cells and Treg cells. Consequently, the dysbiosis is repaired by retaining stability in these T cells' expression[13].

3.1.3. Moringa oleifera

This is also known as a miracle tree because each of its parts embracing roots, leaves, bark, flowers, and seeds, possesses many bioactive constituents which are generally utilized to remediate agonizing diseases. Among these leaves are majorly used as they are the storehouse of various minerals, particularly, calcium, potassium, and iron as well as vitamins. Alkaloids, flavonoids, tannins, and terpenoids are some of the major phytoconstituents found in this plant. *Moringa oleifera* is well known as a 'horseradish tree' or 'drumstick tree', a member of the family Moringaceae. It is majorly cultivated in tropical and sub-tropical climatic areas, surprisingly they are also found near sandy areas as they exhibit waterstorage properties[14]. In 2007, the National Institute of Health (part of the U.S. Department of Health and Human Services) accredited *Moringa* as "Botanical of the Year". It has been employed to treat many ailments, notably cancer, microbial infection, inflammation, cardiovascular diseases, and diabetes. The polysaccharide extracted from the leaves of this plant is now frequently administered to relieve colonic disorders[15]. The monosaccharides it contains are arabinose, galactose, mannose, xylose, and glucose[16]. Interestingly, it offers an advantage of colon-specific drug delivery, as this polysaccharide is not digestible in the gastrointestinal tract[17]. *Moringa oleifera* polysaccharide manages colitis by regulating the production of

cytokines through inflammatory cascades as well as metabolizing fatty acids. Consequently, improvement is evidenced through modulation in colonic weight, length, and disease activity index[18]. The polysaccharide also exerted positive effects by regulating gut microbiota extent and immune organ markers including thymus and spleen, thereby maintaining colonic dysbiosis[19].

3.1.4. Chrysanthemum morifoleum

This perennial herb has been endorsed for epic years in China and is an ornamental plant that is regarded as an important floricultural crop in the world. It is a member of the Asteraceae family belonging to the *Chrysanthemum* genus and is a dicotyledonous species. Conveniently, it is known by the name 'Florist's daisy' and 'hangju'[20]. It is rich in constituents notably, flavonoids, amino acids, phenolic acids, and glycosides, and has become increasingly popular due to the discovery of medically beneficial polysaccharides[21]. Several pharmacological analyses have confirmed that the plant possesses various pharmacological activities, including antineoplastic, antimutagenic, antimicrobial, and anti-inflammatory. Currently, the polysaccharides extracted from this plant have shown protective effects against UC. The signal transduction pathways, NF-κB and JAK/STAT, could be impeded by *Chrysanthemum morifolium* polysaccharide. The secretion of related proteins and certain interleukins causes inflammation in the colonic tissue. By blocking these distinctive cascades, chrysanthemum polysaccharide diminishes the expression of certain cytokines and proteins [NF-κB p65, p-p65, Toll-like receptors (TLR)4, JAK2, signal transducer and activator of transcription 3 (STAT3), and p-STAT3][22]. Further, 16SrRNA sequencing analysis shows that in colitis, the gut flora may also get imbalanced. Treatment with this particular polysaccharide maintains an inequitable microbiome by reducing the prevalence of opportunistic microflora like *Escherichia* and *Enterococcus* and increasing the populations of *Butyricicoccus*, *Clostridium*, *Lactobacillus*, *Rikenellaceae*, and *Bifidobacterium*. Moreover, this polysaccharide not only maintains the dysregulated gut pathogens but also inhibits pro-inflammatory factors like IL-23, TNF-α, and interferon-γ which were responsible for colonic intestinal damage[23].

3.1.5. Scutellaria baicalensis Georgi

The golden herb, *Scutellaria baicalensis* Georgi, is officially indexed in Pharmacopoeias of Chinese, European, and British. It is currently grown in the provinces of China, Russia, North Korea, and Japan. Due to its various medicinal properties, it has been majorly used by Chinese people since long ago. It is broadly publicized by the three widespread names 'Chinese skullcap', 'Baikal skullcap', and 'Huangqin'[24]. Belonging to the family Lamiaceae, the herb *Scutellaria* is classified under the genus *Labiatae*. Throughout time, many investigations have discovered a plethora of bioactive constituents in this plant. It is the source of various constituents such as flavonoids, volatile oils, and terpenoids. Among all these constituents, flavonoids (*e.g.* baicalein, wogonin, wogonoside, oroxylin A, and glucuronide) are found abundantly. Innovatively, polysaccharides consisting of glucose, galactose, and arabinose are being isolated from *Scutellaria* to treat debilitating conditions like cancer, viral, and microbial infection[25]. Cui *et al*. investigated that polysaccharide, SP1, derived from *Scutellaria baicalensis* Georgi exhibits anti-colitis activity by hindering NF-κB and NLRP3 inflammasome. Treatment with this polysaccharide improved intestinal damage like lesions, crypts, and biochemical markers[26]. It also heals colitis by adjusting the distorted expression of gut bacteria, which causes damage to the colonic layer. The pathogens including *Bacteroides*, *Proteobacteria*, and *Staphylococcus* were massively reduced, while the firmicutes and *Bifidobacterium* were raised. Additionally, short-chain fatty acids are crucial for maintaining gut lining. This polysaccharide increased the generation of short-chain fatty acids to improve colitis[27].

3.2. Polysaccharides from edible mushrooms

3.2.1. Tremella fuciformis

The crown of fungi is universally known by various names, particularly, 'snow fungus', 'silver ear fungus', 'white jelly fungus', and 'snow mushroom'. It is a member of the Tremellaceae family, generally sprouts on the putrified trunk of hardwood trees like oak and willow, and is found in subtropical, tropical, temperate, and freezing zones. The fungus is extensively utilized by Chinese and East Asian citizens due to the plethora of health-promoting effects like anti-inflammatory, antioxidant, cytokine stimulating, anti-tumor, anti-diabetic, hypoglycemic, hypolipidemic, neuroprotective effects[28]. Additionally, it is also used for skin purposes as a moisturizing agent, anti-wrinkle agent, and anti-aging agent[29]. The *Tremella fuciformis* polysaccharide is an acidic polysaccharide with a molecular weight ranging from 5.82×10^5 Da to 3.74×10^6 Da. Generally, it is procured from the fruit-bearing segment and mycelia. Mannose, xylose, fucose, glucuronic acid, glucose, and galactose are the foremost monosaccharides it encompasses[30]. This ingestible fungal polysaccharide is employed to alleviate a wide range of health problems, such as gastroenteritis, and respiratory and cardiovascular ailments. Its application in the treatment of UC is currently being investigated. Xiao *et al*. found that treating dextran sulfate sodium (DSS)-induced colitis with *Tremella fuciformis* polysaccharide (at 100 and 200 mg/kg) gave satisfactory results. It retained the intestinal permeability and upregulated the level of intestinal protein marker *i.e.* glycoprotein A33. Besides, it increased the expression of tight junction proteins, mainly zona occludent and occludin, which are responsible for maintaining the integrity of the colonic epithelial layer. Simultaneously, it inhibited interleukins IL-6, IL-1β, and TNF-α, responsible for inflammation. Over and above that, in lipopolysaccharide-stimulated Caco-2 cells, this polysaccharide restrained the release of pro-inflammatory mediators and also conserved the tight junction proteins and mucosal layer

function[31]. Moreover, this polysaccharide acts by invigorating the transcription factor Foxp3+T cells and ultimately suppresses the release of inflammation-triggering mediators. In addition, it is also responsible for balancing the intestinal flora and mucosal membrane immunoglobulins, particularly, IgA as they are extremely prominent in regulating the microbiome. In this manner, polysaccharide exerts its anti-colitis effect on UC[32].

3.2.2. *Flammulina velutipes*

This is a comestible fungus that grows in northern cold climatic regions; it is, therefore, popularly recognized as a 'winter mushroom'. The Japanese term for this fungus is 'enoki', and it is often cultivated therein. It belongs to the family Physalacriaceae and has high medicinal therapeutic value including hepatic protection, anti-tumor, antimicrobial, anti-hypertensive, and immunomodulatory activities along with nutritional benefits[33]. Currently, the polysaccharide is extracted by ultrasound-assisted method, hot water, ultrasonic, microwave, and enzyme-based methods and exhibits various health-related benefits. It usually consists of glucose, mannose, and galactose[34]. The water-soluble *Flammulina velutipes* polysaccharide was isolated by Zhang *et al*. from the fruiting bodies and evaluated for the potential to mitigate colitis clinical symptoms and mucosal impairment. This polysaccharide dramatically reduced the expression of certain biomarkers such as myeloperoxidase and nitric oxide. Additionally, it demonstrated antioxidant properties leading to a decrease in plasmatic diamine oxidase levels and a rise in intestinal superoxide dismutase activity and short-chain fatty acids production. Furthermore, it downregulated the expression of TLR4 and NF-κB thereby exhibiting an anti-inflammatory effect[35]. Furthermore, according to Zhao *et al*., this polysaccharide could ameliorate the signs of UC by altering the expression of certain cytokines, genes, and proteins of intestinal tight junctions, short-chain fatty acids, and the control of intestinal flora. The initial pathogenesis of DSS-induced colitis included physiological responses, mucosal destruction, intestinal ulcers, serum cytokines, and modification of the gut microbiota. Treatment with these fungal polysaccharides thereby maintained the levels of goblet cells, pro-inflammatory cytokines, and nitric oxide while reducing the pathological effects. Tight junction protein synthesis and short-chain fatty acids extents are both augmented in colitis tissue. Additionally, the prediction of gut microbiota modification by PICRUSt (software to predict microbial community) demonstrated the ability of *Flammulina velutipes* polysaccharide to modify biogenesis, ultimately, alleviating UC[36]. Another study showed that the polysaccharide also diminished the inflammatory response in macrophages after being chelated with zinc[37].

3.2.3. *Lentinula edode*

The second-largest and most highly regarded medicinal-esculent mushroom in the globe is *Lentinula edode*, often known as 'shiitake'. It is extensively farmed in Japan and other countries in Asia. It is regarded as a saprophyte because it is typically nurtured on dead wood from sweetgum, oak, and hornbeam. It belongs to the Basidiomycetes family of Agaricaceae and is a rich source of proteins, carbohydrates, lipids, minerals, and vitamins. Certain polysaccharides including lentinans, glucans, and mannans are being extracted from this specie of fungus and used in various health aspects. These polysaccharides have antiparasitic, antiviral, immunoregulatory, hypocholesterolemic, hepatoprotective, antioxidant, and antidiabetic effects[38]. The mitogen-activated protein kinase pathway and the transcription factor Elk-1 are attenuated by *Lentinus edode*. Nitric oxide, myeloperoxidase, malondialdehyde, and the inflammatory mediators responsible for dysbiosis are consequently decreased. Additionally, it also modulates the expression of PPARγ receptor and physiological changes involving changes in colon weight and length[39]. Interestingly, polysaccharides treat the colitis contingent upon the dose and impede necroptotic cell death in Caco-2 cells. It also hinders RIPK1-RIPK3-MLKL (mixed lineage kinase domain-like pseudokinase) necroptosis signaling cascade, thereby, diminishing phosphorylated MLKL. It was found that the anti-inflammatory and anti-necroptotic effects of polysaccharides relied upon their carbohydrate-rich content[40].

3.2.4. *Pleurotus eryngii*

This is a culinary medicinal mushroom that is incredibly rich in nutrients like vitamins, proteins, and carbohydrates. It is popularly known by different names, 'The king trumpet mushroom', 'The king oyster mushroom, 'Dhingri mushroom', and 'French horn mushroom'. It is generally cultivated in East Asia on various agro wastes including, sawdust, rice husks, kenaf stalks, *etc*. *Pleurotus eryngii* belongs to the class of Agaromycetes of the Pleurotaceae family and exhibits health-promoting properties such as immunomodulatory, anti-inflammatory, anti-hyperglycemic, anti-aging, and antioxidant effects[41]. Pharmacologically active substances, including polysaccharides, peptides, sterols, and monoterpenes, can be isolated from this species[42]. The most frequently extracted polysaccharide is glucan which has an anti-inflammatory impact by suppressing TNF-α[43]. *Pleurotus eryngii* β-type glycosidic polysaccharide was found to be effective in reducing the high levels of neutrophils, macrophages, immune cells, and certain pro-inflammatory cytokines like TNF-α and IL-6, which are accountable for colonic intestinal damage. This is because polysaccharide has a non-digestibility property that enables them to potentially target the colon. Western blotting was also used to examine the proteins (p-38, COX-2, TLR-4, and iNOS) responsible for the inflammation and found that treatment with this specific polysaccharide suppresses the elevated level of these particular proteins. Additionally, it restored the altered intestinal microflora by regulating the production of certain microorganisms[44]. Another study revealed that this polysaccharide supplementation could repair intestinal colon damage by increasing the levels of short-chain fatty acids, which are essential for maintaining the intestinal layer while

Table 1. Therapeutic mechanisms of polysaccharides for ulcerative colitis.

Category	Source	Common name	Family	Outcomes	References
Plant	*Saururus chinensis*	Lizard's tail, sam-baekcho	Saururuaceae	Reduces IL-6, TNF-α, inflammatory marker-MPO, and UC symptoms, maintains SCFAs levels	[54]
	Dendrobium huoshanense	Mihu	Orchidaceae	Decreases serum levels of IL-1β, TNF-α, IL-17, and TGF-β by inhibiting NF-κB cascade	[55]
	Scutellaria barbata	Barbed skullcap	Lamiaceae	Hinders NF-κB/STAT3 cascade, reduces level of interlukins (IL-6, IL-18, IL-β), IFN-γ and TNF-α	[56]
	Atractylodes macrocephala	Bai zhu	Compositae	Modulates gut microbiome and SCFAs secretion, enhances colonic weight	[57]
	Malva sylvestris	Mallow	Malvaceae	Ameliorates macroscopic and microscopic parameters and inhibits inflammation symptoms of colitis	[58]
	Mesona chinensis	Mesona	Lamiaceae	Inhibits TNF-α, IL-1β, and IL-1, maintains tight junction proteins levels, regulates intestinal microflora	[59]
	Salsola imbricata Forssk	Salsola baryosoma	Chenopodiaceae	Mitigates the macroscopic parameters and reduces the levels of nitric oxide, malondialdehyde, interlukins, and cytokines	[60]
Fungus	*Dictyophora indusiata*	Stinkhorn mushroom, phallus indusiata	Phallaceae	Impedes NF-κB, STAT3, and NLRP3 cascades, reduces the level of oxidative stress, regulates inflammation and intestinal barriers	[61]
	Phoma herbarum YS4108	Stem canker	Didymellaceae	Restores intestinal immune response, improves ulcerative colitis symptoms and production of SCFAs (butyrate), maintains gut microbiome	[62]
	Sporisorium reilianum	Maize head smut fungus	Ustilaginaceae	Regulates intestinal gut microbiome, decreases markers (MPO)	[63]
	Lentinula edode	Shiitake	Agaricaceae	Decreases the level of inflammatory mediators, myeloperoxidase, attenuates mitogen-activated protein kinase pathway	[39]
	Hericium erinaceus	Lion's mane, white beard	Hericiaceae	Reduces cytokines, reactive oxygen species, malondialdehyde, and induces superoxide dismutase, and short-chain fatty acids	[46]
Algae	*Eucheuma cottonii*	Guso, sea-bird nest	Solieriaceae	Downregulates pro-inflammatory cytokines IL-1 and IL-6, upregulates IL-10, diminishes clinical symptoms	[53]
	Sargassum fusiforme	Hijiki	Sargassaceae	Increases the level of tight junction proteins (ZO-1, Occuludin), SCFAs, diminishes IL-1β and IL-6 secretion	[64]
	Gracilaria lemaneiformis	Asparagus	Gracilariaceae	Modulates intestinal microbiota and SCFAs, inhibits inflammatory proteins CCL25 and CCR9	[50]
	Gracilaria fischeri	Sarai Woon	Gracilariaceae	Reduces the level of certain inflammatory markers and modulates the epithelial tight junction proteins (claudin and occludins)	[65]

IL: interleukin; TNF: tumor necrosis factor; MPO: myeloperoxidase; UC: ulcerative colitis; SCFA: short-chain fatty acid; NF-κB: nuclear factor-kappaB; STAT3: signal transducer and activator of transcription 3; IFN: interferon; NLRP3: NOD-like receptor thermal protein domain associated protein 3.

inhibiting the production of certain cytokines[45].

3.2.5. Hericium erinaceus

One of the most popularly used mushrooms is *Hericium erinaceus* which belongs to the Agaricomycetes class of the Hericiaceae family. Vernacular names of it are 'Lion's Mane', 'Old Man's Beard', 'White Beard', and 'Yamabushitake'. It is found abundantly on deadwood or hardwood in European countries. This fungus has received approval from the China Food and Drug Administration due to its diverse therapeutic activities, for instance, anticancer, immunomodulatory, antioxidant, antihyperlipidemic, and anti-aging effects. Recently, polysaccharides, including α-*D*-glucans, xylans, and galactoxylans isolated from its fruiting bodies, are thought to be the primary physiologically active components and are being used to treat intestinal colon diseases. The polysaccharide from *Hericium erinaceus* dramatically reduced H_2O_2 and acetic acid-induced colitis through a variety of mechanisms. Except for reducing the release of malondialdehyde, reactive oxygen species, and certain cytokines, it induces the expression of short-chain fatty acids and superoxide dismutase. The damaged mitochondrial membranes were also healed by this polysaccharide. Additionally, this polysaccharide improved cell survival and guarded against reactive oxygen species after H_2O_2 was produced in Caco-2 cells to further establish the link between antioxidants and mitochondrial function[46]. Similarly, it could reduce colitis by diminishing intestinal markers like myeloperoxidase, nitric oxide, and malondialdehyde as well as certain cytokines. Additionally, it maintains the mucosal intestinal layer integrity by increasing certain intestinal flora, vermicular bacteria, and actinobacteria[47].

3.3. Polysaccharides from algae

3.3.1. Gracilaria lemaneiformis

The red algae, *Gracilaria lemaneiformis* is commonly known as 'asparagus'. It comes under the *Rhodophyta phylum* in the Gracilariaceae family. It has multiple nutrients like amino acids, proteins, and fibers and is popularly used for various purposes. Polysaccharides are currently being isolated from this specie due to their diverse bioactivities such as anti-neoplastic, immunomodulatory, and anti-inflammatory[48]. Lu *et al*. isolated sulphated polysaccharides from *Gracilaria lemaneiformis*, which healed the mucosal layer by decreasing the pro-inflammatory cytokines responsible for colon dysbiosis. It also decreases the biochemical marker, myeloperoxidase and ultimately resulting in the decline of neutrophils. It maintains the tight junction thereby preventing pathogens to enter[49]. Furthermore, it exerts its effects by maintaining the intestinal microbiome and reinforcing the short-chain fatty acids. This polysaccharide regulates immune organ markers and the expression of specific proteins responsible for inflammatory responses. CCL25 and CCR9 are both causative proteins for inflammation. *Gracilaria* polysaccharide showed a favorable outcome in treating colitis by inhibiting these two proteins[50].

3.3.2. Gracilaria caudata

It is alternatively called 'J Agardh', marine red algae belonging to the family Gracilariaceae. There are 190 species of *Gracilaria*, among them, this species is typically used for various purposes. This species is generally found in tropical and temperate zones. The algae are a high source of sulphated polysaccharides. The sulphated polysaccharide possesses various biological activities including antineoplastic, antioxidant, and anti-inflammatory[51]. The colitis induced by acetic acid was cured by *Gracilaria caudata* polysaccharide. The effect of the 10.0 mg/kg sulphated polysaccharide treatment was significant. Myeloperoxidase, glutathione peroxidase, and malondialdehyde are three biochemical indicators of oxidative stress whose elevated expression results in colonic perturbations. As a result, the administration of this polysaccharide mitigated the elevated nitric oxide level in colon tissue, which was detected through Western blotting. Additionally, physical factors such as body weight, colon length, and stool consistency were controlled, and *Gracilaria caudata* polysaccharide treated colitis through an anti-inflammatory effect[52].

3.3.3. Eucheuma cottonii

It is an edible red alga that belongs to the Solieriaceae family. It is majorly found in countries in Southeast Asia. The vernacular name used for this specie is 'guso'. The constituents found in this alga include polyunsaturated fatty acids, polyphenols, and other phytochemicals. The polysaccharides extracted from this alga attenuate DSS-induced colitis in animals. Additionally, polysaccharides significantly boosted the anti-inflammatory cytokine IL-10 level in colon tissue of mice treated with DSS while reducing the levels of the pro-inflammatory mediators TNF-α, IL-1, and IL-6 in serum. According to this finding, polysaccharides are potentially effective in treating colitis[53].

4. Conclusion

Table 1 also lists some other polysaccharides. All of these polysaccharides obtained from natural resources like plants, edible mushrooms, and algae offer many therapeutic potentials along with higher safety and fewer side effects. Due to these benefits, they are being widely utilized to attenuate various intestinal disorders such as UC. These polysaccharides could treat UC by maintaining the integrity of intestinal tight junctions and mucosal layer. They could also modulate the gut microflora and escalate the production of short-chain fatty acids. It may also exert its effect by suppressing cascades like NF-κB, MAPK, IL-6/ JAK2/STAT3, and thereby, the release of certain inflammatory mediators.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

NS conceptualized the work and AA involved in data acquisition. NS and AA drafted and edited the manuscript. DK edited the final version of the manuscript.

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