NATURAL POLYMERS FOR INFLAMMATORY BOWEL DISEASE THERAPY

Editors:
Meenakshi Jaiswal
S.K. Lanjhiyana

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Natural Polymers for Inflammatory Bowel Disease Therapy

Edited by

Meenakshi Jaiswal
Department of Pharmacy
Guru Ghasidas Vishwavidyalaya
Bilaspur 495009, Chhattisgarh
India

&

S.K. Lanjhiyana
Department of Pharmacy
Guru Ghasidas Vishwavidyalaya
Bilaspur 495009, Chhattisgarh
India

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Editors: Meenakshi Jaiswal and S.K. Lanjhiyana

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FOREWORD

In the edited book “Natural Polymers for Inflammatory Bowel Disease Therapy”, the authors explored a new frontier with enormous promise to improve the management of Inflammatory Bowel Diseases (IBD). The increased interest in natural, biocompatible polymers as drug delivery vehicles reflects not just a shift toward more sustainable materials, but also a vital requirement to enhance patient outcomes via precision medicine. This collection is especially useful because of its interdisciplinary approach that connects fundamental research with preclinical and clinical applications. The contributors provided an in-depth investigation of the ways in which innovative drug delivery systems can address the unmet requirements in IBD therapy. This research will surely be an invaluable resource for scientists, doctors, and pharmaceutical experts working to develop the area of targeted drug delivery in IBD. The combination of theoretical knowledge, cutting-edge research, and practical application ensured that readers have a thorough grasp of the potential of natural polymers in IBD treatment.

Rajiv Gupta
Principal and Dean
School of Pharmacy
Babu Banarasi Das University
Lucknow 226028
Uttar Pradesh, India

PREFACE

Inflammatory Bowel Disease (IBD), which includes Crohn's disease and ulcerative colitis, is a chronic and severe disease that affects millions of people worldwide. The ongoing challenge of managing IBD comes from the disease's complex pathophysiology, the recurrent nature of the condition, and the necessity of long-term therapeutic strategies that are both safe and effective. Despite substantial progress in comprehending the molecular mechanisms of IBD, a critical challenge remains in developing innovative drug delivery systems that can improve the efficacy and specificity of treatments.

This book, "Natural Polymers for Inflammatory Bowel Disease Therapy," seeks to illuminate the promising potential of natural polymers in transforming the treatment of IBD. The provided contents investigate the application of naturally derived polymers in the development of sophisticated drug delivery systems, highlighting their potential for biocompatibility, biodegradability, and personalized therapeutic release in inflamed tissues.

In recent decades, synthetic polymers have predominated in medication delivery. However, natural polymers are rapidly being recognized for their distinct features, which can overcome some of the limitations of synthetic equivalents. Natural polymers offer a safer profile for prolonged use, enhanced imitation of the body's components, and the possibility of more accurate targeting of inflammatory areas in the gastrointestinal system. These attributes are especially vital for the management of IBD, as reducing systemic side effects and enhancing localized medication efficacy are imperative for improved patient outcomes.

This book is an invaluable resource for academics, medical practitioners, students, and pharmaceutical professionals working in the domains of drug delivery and gastrointestinal disorders. Each chapter discusses the most recent advances in polymer-based drug delivery methods, emphasizing their applicability to IBD and offering insights into the future prospects of this exciting field. This effort bridges the gap between scientific innovation and practical application, ranging from theoretical polymer chemistry investigations to clinical assessments of medicinal effectiveness.

This collection aims to encourage ongoing creativity and interdisciplinary collaboration in the exploration of the many functions of natural polymers in IBD therapy, thereby enhancing the development of more effective and customized treatment methods for individuals with IBD.

Meenakshi Jaiswal
Department of Pharmacy
Guru Ghasidas Vishwavidyalaya
Bilaspur 495009, Chhattisgarh
India
&
S.K. Lanjhiyana
Department of Pharmacy
Guru Ghasidas Vishwavidyalaya
Bilaspur 495009, Chhattisgarh
India

List of Contributors

Arvinder Kaur	Akash Institute of Pharmacy, Bangalore-562110, India
Achal Mishra	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Bina Gidwani	Department of Pharmaceutical Quality Assurance, Columbia Institute of Pharmacy, Raipur 493111, India
Mohit Rajak	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Meenakshi Jaiswal	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Mayank Garhewal	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Mohammad Akbar Siddiqui	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Naresh Sahu	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Neha Dubey	Department of Pharmaceutics, Columbia Institute of Pharmacy, Raipur 493111, India
Nikita Verma	MATS School of Pharmacy, MATS University, Raipur-493441, India
Nidhi Agrawal	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Prashant Tiwari	Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Karnataka-562112, India
Rahul Goswami	Department of Pharmaceutical Chemistry, Columbia Institute of Pharmacy, Raipur 493111, India
Ravindra Kumar Pandey	Department of Pharmacognosy, Columbia Institute of Pharmacy, Raipur 493111, India
Rajkumar	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Rashmi Dewangan	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Shekhar Verma	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Shilpa Sahu	Department of Pharmaceutical Quality Assurance, Columbia Institute of Pharmacy, Raipur 493111, India
Sagar Sahu	Department of Pharmaceutical Chemistry, Columbia Institute of Pharmacy, Raipur 493111, India
Shiv Shankar Shukla	Department of Pharmaceutical Quality Assurance, Columbia Institute of Pharmacy, Raipur 493111, India

Sakshi Gupta	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
S.K. Lanjhiyana	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Shibangi Mukhopadhyay	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Sunil Kumar Kadiri	Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Karnataka-562112, India
Vaishali Bharat	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India
Yogesh Vaishnav	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India

CHAPTER 1

Inflammatory Bowel Disease: Overview, Variants, and Underlying Mechanisms

Vaishali Bharat[1], Mohit Rajak[1], Nidhi Agrawal[1], S.K. Lanjhiyana[1], Meenakshi Jaiswal[1] and **Sanjay Kumar Bharti[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: Chronic inflammatory diseases of the Gastrointestinal tract (GI tract) are collectively called Inflammatory Bowel Disease (IBD). These diseases include Crohn's Disease (CD) and Ulcerative Colitis (UC). IBD is an autoimmune disease characterized by persistent and recurrent inflammation of the intestinal tract. It has emerged as a major problem in the field of medicine on a global scale, with its frequency steadily growing. One theory proposes that IBD is caused by an inappropriate and persistent immune response to intestinal microorganisms, which is controlled by the genetic predisposition of a person, originating from the interaction between the host and the microorganisms. An imbalance in the homeostasis of microorganisms leads to colonization and invasion of the gut by opportunistic pathogens, which, in turn, increases the likelihood of a host immunological response and promotes the development of IBD. It is essential to identify the particular pathogens that contribute to the development of IBD to facilitate early detection of the illness. Although the etiology of IBD is largely unclear, it is known that it is caused by a complex interplay of genetic, environmental, and microbial factors, in addition to immunological interventions. This chapter discusses the epidemiology, variants, and underlying mechanisms of IBD, with a particular emphasis on the complex interplay of a large number of factors that are responsible for the pathogenesis of the disease. In addition to this, we talk about the many different therapy choices that are available to combat the condition.

Keywords: Crohn’s disease, Gastrointestinal tract, Inflammation, Inflammatory bowel disease, Intestinal barrier, Microorganisms, Pathogens, Ulcerative colitis.

[*] **Corresponding author Sanjay Kumar Bharti:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: skbharti.ggu@gmail.com

INTRODUCTION

IBD is a blanket term for a bunch of conditions that cause inflammation and swelling of the GI tract. IBD is characterized by stomach discomfort, diarrhea bloody stools, weight loss, and the influx of neutrophils and macrophages that create cytokines, proteolytic enzymes, and free radicals, leading to intestinal mucosa inflammation and ulceration [1]. Two major types of IBD are Crohn's disease and Ulcerative colitis [2]. The initial instance of IBD resembling what is now termed ulcerative colitis was documented in the late 1700s, and the name was coined in 1859 [3]. Subsequently, in 1932, CD was acknowledged as a separate condition from ulcerative colitis owing to its transmural and frequently patchy inflamed pattern that can impact any segment of the GI system [4]. Conversely, ulcerative colitis is confined to the colon, usually commencing at the rectum and extending proximally to the cecum in several cases [5]. Patients suffering from UC are at a higher risk of developing colorectal cancer throughout their lives [6]. A comparison of symptoms and cytokine profiles between CD and UC is presented in Table **1**.

UC is a nonspecific, diffuse inflammation of unknown origin that consistently damages the colonic mucosa from the rectal side, frequently resulting in erosions and ulcers [7]. CD is a chronic inflammatory disease of unknown etiology that is characterized by non-contiguous all-stratified granulomatous inflammation and fistulae [8].

Although IBD mostly affects young individuals, it can manifest at any age, with roughly 25% of patients presenting before the age of 20. The highest occurrence of IBD in childhood occurs during adolescence; nevertheless, over 20% of children with IBD will manifest symptoms before the age of 10, and roughly 5% will do so before the age of 5. The prevalence of IBD, particularly childhood-onset IBD, is rising globally. Recent studies indicate a swift increase in very early onset IBD in certain regions with historically high rates of both pediatric and adult-onset IBD [9].

Recent epidemiological research reveals that IBD has shown significant rises in frequency across all continents. The yearly incidence of IBD varies from 10.5 to 46.1 per 100,000 in Europe, 7.3 to 30.2 per 100,000 in North America, 23.7 to 39.8 per 100,000 in Oceania, and 1.37 to 1.5 per 100,000 in Asia and the Middle East [10].

Microbiomes are present in every human ecological niche studied, including the mouth cavity, skin surface, digestive system, oesophagus, lungs, and others [11]. The microbiome consists of bacteria, Archaea, viruses, phages, and fungi. Bacteria are the predominant microbiome in terms of species diversity [12].

Among the areas, the gut microbiota is the most examined because it has the most diverse microbial population. The human digestive system has roughly 1000 types of bacteria, amounting to 100 trillion microorganisms, which are likely important in controlling host homeostasis [13]. Any underlying factor that induces dysbiosis of the gut microbiota may result in immunological compromise and trigger or exacerbate IBD. For instance, the overuse of antibiotics, changes in diet, and non heritable factors, such as environmental factors, smoking, and so forth, may modify the makeup of the gut microbiota, potentially leading to the development of IBD, and thus must be considered in the etiopathogenesis of these diseases [14]. The gut microbial makeup differs between individuals with IBD and healthy individuals [15].

Although IBD is primarily linked to an imbalance of gut microbiota and its impact on the immune system, the underlying cause of dysbiosis and pathogenesis remains unclear. In recent years, advancements have been made in elucidating the pathophysiology of this illness [16]. Research indicates that the development of IBD is linked to a combination of the host's genetic vulnerability, intestinal microbiota, various environmental factors, and immunological anomalies [17]. Fig. (**1**) shows the role of gut dysbiosis in the pathogenesis of IBD. The combination of a compromised intestinal barrier and gut dysbiosis is likely to perpetuate mucosal inflammation and potentially result in IBD [18].

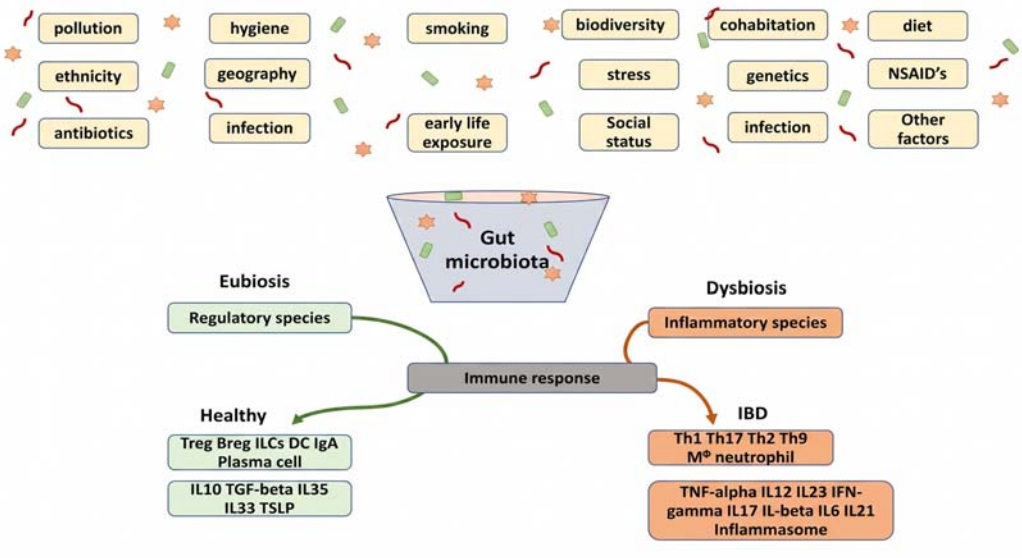

Fig. (1). Role of gut dysbiosis in the pathogenesis of IBD.

CHAPTER 2

Microenvironment in IBD: Implications for Drug Release and Nano-Based Targeting Strategies

Mayank Garhewal[1], Achal Mishra[1], Shekhar Verma[1], Naresh Sahu[1], Arvinder Kaur[2] and **Yogesh Vaishnav[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

[2] *Akash Institute of Pharmacy, Prasannahalli, Bangalore 562110, Karnataka, India*

Abstract: The microenvironment of Inflammatory Bowel Disease (IBD) presents unique opportunities and obstacles for targeted treatment and drug administration. These include altered gut microbiota, dysregulated immune responses, and chronic inflammation. This chapter explores the detailed connections between the development of advanced drug delivery systems and the IBD microenvironment, with a focus on nano-based targeting strategies. The effects of the pathogenic features of IBD, such as elevated levels of pro-inflammatory cytokines, reactive oxygen species, and intestinal epithelial permeability, on drug release kinetics and biodistribution are investigated. The chapter shows how these pathological changes can be targeted using nanotechnology to improve therapeutic outcomes, reduce systemic toxicity, and deliver medications to specific locations. Developing stimuli-responsive nanocarriers that release drugs in response to pH, redox potential, or enzymatic activity, as well as using ligand-functionalized nanoparticles for active targeting of immune cells or inflammatory tissues, are significant topics. The potential for nanoformulations driven by the microbiome and the role of the gut microbiota in controlling the effectiveness of medications are also examined. In order to bridge the gap between preclinical research and clinical application, interdisciplinary approaches are essential. The chapter concludes with a summary of the translational challenges and possible avenues for nano-based therapy in IBD.

Keywords: Dysbiosis, Fibrosis, Immune cell, Markers, Microbiota, Multifunctional targeting.

INTRODUCTION

Inflammatory Bowel Disease (IBD), which includes persistent diseases such as Crohn's disease and ulcerative colitis, is caused by long-lasting inflammation of

* **Corresponding author Yogesh Vaishnav:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: yogesh446688@gmail.com

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the gastrointestinal tract resulting from multiple mechanisms, including immune dysregulation, epithelial barrier dysfunction, dysbiosis, and ongoing remodeling of tissues. The pathological environment in which IBD lesions occur is particularly unique because of the acidic microenvironment, overproduction of relatively pro-inflammatory Reactive Oxygen Species (ROS), increased enzymatic activity, and heightened influx of immune cells, all of which affect drug release, absorption, and dosing efficacy [1, 2].

The utilization of nanotechnology is a promising breakthrough that allows for smart drug delivery strategies to be designed for the specific challenges generated by the IBD microenvironment. Nano-based systems such as pH-sensitive polymers, ROS-responsive nanoparticles, enzyme-degradable coatings, and ligand-targeted nanoparticles can be designed to only release drug payload in response to specific local stimuli (*e.g.*, pH drop, ROS surge, or total enzyme overexpression) within hyperinflammatory microenvironments. For example, pH-sensitive formulations like Eudragit-coated mesalamine tablets preferentially release active drug under acidic conditions in the colon, while others like ROS-responsive nanoparticles containing siRNA or anti-inflammatory agents can take advantage of local oxidative stress to deliver drug payloads in a more site-selective manner. Nano-carriers also improve drug mucoadhesion and increase cellular uptake to improve drug retention and efficacy and limit side effects [3, 4].

Distinct pathological features of the IBD environment, such as localized pH changes, concentrations of Reactive Oxygen Species (ROS), and increased levels of digestive or inflammatory enzymes, will determine the manner and timing of drug release from advanced delivery devices. For example, inflammation-induced acidification of gut segments can trigger pH-sensitive polymers to release their payload in the inflamed regions, while healthy regions remain largely unaffected. Elevated levels of ROS at inflamed sites can trigger specific nanoparticles designed to respond to oxidative stress, which also deliver drugs exactly where they are needed, all while minimizing often undesirable off-target effects. Similarly, enzymes overexpressed in IBD lesions that are distinct from those in healthy tissues, such as lysozyme and colonic bacterial azoreductase, can trigger localized activation of therapeutics (*e.g.*, prodrugs or nanocarrier coatings) without unwanted degradation in healthy tissues. By utilizing these features of the local microenvironment, nano-based drug delivery systems can achieve device-mediated, targeted, responsive, and precise therapeutic effects in the management of IBD [1, 3, 5].

There is an increasing number of *in vivo* studies showing the clinical utility of nano-formulations in models of Inflammatory Bowel Disease (IBD), suggesting translational progress. For example, ROS-sensitive thioketal nanoparticles

encapsulating siRNA for delivery to colitic mice can significantly reduce inflammatory burden and disease severity. Some enzyme-, pH-, and ligand-responsive nanosystems demonstrate promising biodistribution and therapeutic efficacy, including budesonide-loaded PEGylated nanoparticles, folate-decorated liposomes targeting activated macrophages, and dual-responsive hydrogels promoting the regrowth of colonic tissues. Multifunctional nanocarriers that incorporate passive targeting of disease tissues, ligand-mediated delivery to specific cells, and microenvironment-responsive release systems are moving past laboratory research into clinical testing, and several of these therapeutic approaches are demonstrating a greater degree of symptom control and mucosal healing in IBD animal models and early patient cohorts [6, 7].

Continuing challenges include variability among patients, stability of carriers during gastrointestinal transit, and regulatory issues with synthetic polymers; however, interdisciplinary partnerships are forging ahead with continued creativity in the field of individual, efficient, and biomarker-guided nanotherapeutics. This paradigm shift represents a new chapter for precision medicine in IBD and hopefully renewed hope for optimally treating this condition and enhancing the quality of life of patients.

THE IBD MICROENVIRONMENT: PATHOLOGICAL FEATURES

Inflammatory Bowel Disease (IBD), which includes Crohn's disease and ulcerative colitis, is typified by persistent, recurrent inflammation of the gastrointestinal tract. A complicated interplay between immune system failure, environmental variables, gut microbiota abnormalities, and genetic predisposition characterizes the multifactorial pathophysiology of IBD. Within the gastrointestinal tract's impacted areas, these interactions provide a very dynamic and unique milieu. Developing targeted and efficient therapies, especially those that make use of drug delivery systems and nanotechnology, requires an understanding of the pathogenic characteristics of this microenvironment [8, 9].

Inflammatory and Immune Dysregulation

Chronic, dysregulated inflammation is the central component of the IBD microenvironment. To guard against pathogens and prevent unwarranted immune reactions against commensal bacteria, the immune system in healthy people strikes a careful balance between tolerance and immune activation. But this equilibrium is upset in IBD. T cells, macrophages, dendritic cells, neutrophils, and other immune cells are drawn to the site of inflammation as a result of the gut's mucosal immune system being overly reactive [10].

CHAPTER 3

Sources and Biomedical Utilization of Natural Polymers

Neha Dubey[1], Shilpa Sahu[2], Sagar Sahu[3], Rahul Goswami[3], Shiv Shankar Shukla[2], Ravindra Kumar Pandey[4] and **Bina Gidwani[2,*]**

[1] Department of Pharmaceutics, Columbia Institute of Pharmacy, Raipur 493111, Chhattisgarh, India

[2] Department of Pharmaceutical Quality Assurance, Columbia Institute of Pharmacy, Raipur 493111, Chhattisgarh, India

[3] Department of Pharmaceutical Chemistry, Columbia Institute of Pharmacy, Raipur 493111, Chhattisgarh, India

[4] Department of Pharmacognosy, Columbia Institute of Pharmacy, Raipur 493111, Chhattisgarh, India

Abstract: Natural polymers are derived from diverse biological sources such as plants, animals, microbes, and marine organisms. They have gained immense attention in biomedical research due to their biocompatibility, biodegradability, and inherent bioactivity. This chapter explores the various sources of natural polymers like cellulose, starch, chitosan, collagen, and alginate. This chapter also highlights their unique physicochemical properties and ecological sustainability. Furthermore, it delves into their multifaceted applications in the biomedical field, such as drug delivery systems, tissue engineering scaffolds, wound healing materials, and orthopedic and cardiovascular devices. The versatility of natural polymers lies in their structural tunability, which allows for the development of tailored solutions for complex medical challenges. By exploring current trends and challenges in the utilization of natural polymers, this chapter underscores their pivotal role in advancing sustainable and effective biomedical technologies. The limitations of traditional dosage systems, alongside enhanced and targeted drug delivery techniques, are mitigated by the use of polymers that exhibit superior bioavailability, biocompatibility, and reduced toxicity. Consequently, nanomedicines are regarded as a novel category of pharmaceuticals. This book chapter rigorously evaluates the application of natural polymers and their drug delivery methods for localised or targeted, regulated, and prolonged medication release in the treatment of life-threatening disorders.

Keywords: Biodegradability, Biomedical, Natural polymer, Physiochemical property.

[*] **Corresponding author Bina Gidwani**, Department of Pharmaceutical Quality Assurance, Columbia Institute of Pharmacy, Raipur 493111, Chhattisgarh, India; E-mail: beenagidwani@gmail.com

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INTRODUCTION

The initial phase of the era, spanning much of historical and ancient times, commenced thousands of years ago with the utilization of wood and natural fibers. Between the sixteenth and seventeenth centuries, rubber was discovered, serving as a quintessential example of a natural polymer. Proteins, nucleic acids, and polysaccharides exemplify natural polymers integral to biological systems, performing many essential functions. Certain natural polymers, such as chitin and cellulose, are crucial for preserving the structural integrity of cells in both plants and animals, whilst others, like lysozyme, offer biological protection against environmental factors. These natural polymers possess distinct physicochemical and biological properties that can be advantageous across several fields due to their compositional and origin diversity [1]. Organic polymers and their derivatives are utilized throughout various industries, including textile and paper manufacturing, food additives, functional foods and nutraceuticals, and the biomedical sector (*e.g.*, medication delivery and cosmetic applications). The utilization of polymers derived from renewable resources is beneficial due to their natural abundance, renewability, and low carbon footprint, making them essential for the development of innovative materials such as hydrogels, films, membranes, coatings, and micro and nanoparticle systems [2].

Polymers are large molecules characterized by high molecular weights, commonly referred to as macromolecules. They are composed of several smaller molecules, known as monomers. Natural polymers are those that occur naturally or are produced through biological polymerization processes, rather than synthetic methods such as insertion or distillation polymerization. Herbal polymers are derived from plants and animals. Our body is composed of proteins, nucleic acids, and other natural polymers. Furthermore, natural polymers may be employed to revitalize and replenish the skin [3]. Natural polymers are derived from sources such as flora, microorganisms, and fauna. They consist of proteins and carbohydrates that provide structural support to both plants and animals. The six principal categories of natural polymers are proteins, polysaccharides, polynucleotides, polyisoprenes, polyesters, and lignin [4]. Due to their origin, natural polymers are more cost-effective, readily available, potentially biodegradable, and biocompatible compared to the other two groups. Besides being a prevalent element of our everyday nutrition, numerous polymers possess significant uses in the food, pharmaceutical, cosmetic, prosthetic, and medical industries. Numerous frequently utilized natural polymers are derived from proteins and carbohydrates [5].

Origin of Natural Polymer

The term "polymer" is derived from the Greek words "*poly*," meaning "many," and "*meros*," meaning "parts" or "units." This illustrates the composition of polymers, which consist of several repeating units. One reason for the growing interest in natural polymers is their availability from abundant and renewable natural sources, which are also easily accessible. Polysaccharides are prevalent in nature and can be readily sourced from several organisms, including bacteria (*e.g.*, dextran, xanthan gum), plants (*e.g.*, pectin, guar gum, mannan), animals (*e.g.*, chitosan, chondroitin), and algae (*e.g.*, alginates). They may also be generated by recombinant DNA methods. The various beneficial properties of monosaccharide polymers include their high stability, non-toxicity, hydrophilicity, biodegradability, gel-forming abilities, and ease of chemical modification [6]. The structural composition of plant polysaccharides exhibits significant variability, depending on the plant and the specific plant parts from which they originate, such as leaves, seeds, roots, and tubers. Two unique structural features contribute to the richness and diversity of polysaccharides: firstly, monosaccharides can be linked in multiple configurations, either α or β; secondly, the presence of branched side chains is notable. Fig. (**1**) illustrates the categories of natural polymers.

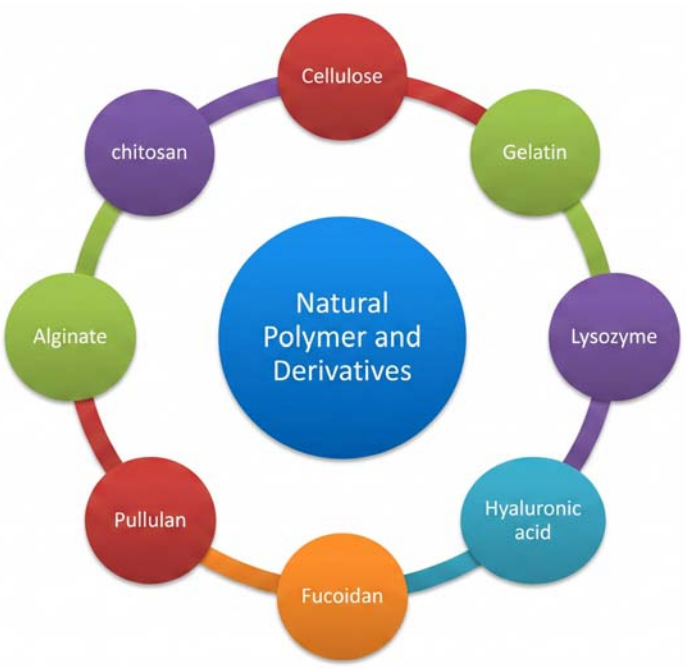

Fig. (1). Natural polymers and derivatives.

CHAPTER 4

Plant-Derived Polymers and Their Contribution to the Management of Inflammatory Bowel Disease.

Sakshi Gupta[1], Nidhi Agrawal[1], Mohammad Akbar Siddiqui[1], Meenakshi Jaiswal[1] and **S.K. Lanjhiyana[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: Inflammatory Bowel Disease (IBD) is a chronic inflammation of the small and large intestines that results from host-microbial interactions in genetically susceptible individuals. It includes Crohn's disease and ulcerative colitis, causing symptoms like diarrhoea, pain, bloody stools, and vomiting. IBD is characterised by a complex interaction of genetic, environmental, and microbial factors. It needs novel therapeutic strategies that overcome conventional anti-inflammatory and immunosuppressive treatments. Plant-derived polymers, including pectin, inulin, cyclodextrin, guar gum, cellulose, carrageenan, and alginate, have the capacity to regulate IBD. These polysaccharides are distinguished by their biodegradability, biocompatibility, and distinctive physicochemical properties, allowing them to function as efficient drug transporters while possessing intrinsic anti-inflammatory and immunomodulatory effects. Pectin and inulin have prebiotic properties, fortifying the Gastrointestinal (GI) barrier and diminishing intestinal permeability. Cyclodextrins enhance the solubility and stability of medicinal medicines, whilst guar gum and cellulose facilitate targeted drug delivery. Carrageenan and alginate are utilised in advanced encapsulation methods for targeted medication delivery. Advanced extraction methods and biotechnological improvements have further refined these polymers for medicinal use. Incorporating these natural chemicals into IBD treatment protocols shows potential for enhancing patient results, reducing unwanted effects, and promoting a more sustainable, comprehensive strategy for managing this severe disease.

Keywords: Alginate, Carrageenan, Cellulose, Cyclodextrin, Guar gum, Inflammatory bowel disease, Inulin, Pectin, Plant-derived polymer.

[*] **Corresponding author S.K. Lanjhiyana:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: sklanjh1975@gmail.com

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INTRODUCTION

IBD has markedly risen across Europe and North America over the past 25 years, with a twofold increase in incident cases in the UK during the previous 20 years. The condition, conventionally categorized as Crohn's disease and ulcerative colitis, is a complicated 'continuum' disease with a comparable etiology encompassing genetic, environmental, and microbial influences [1]. Treatment is predominantl empirical, requiring current input to ensure optimal long-term outcomes for patients. The etiology of elevated illness incidence remains unclear; however, hypotheses about diminished microbial exposure during early life, the westernization of nutrition, and the hygiene theory may contribute to this phenomenon [2]. IBD is a persistent inflammatory condition of the GI system, marked by abnormal immune response and changes in the gut flora. The diagnosis of IBD and its subtypes requires the evaluation of clinical symptoms and clinical methods. Molecular markers, including serological, histological, and faecal signs, can aid in differential diagnosis. Treatment techniques often encompass pharmaceutical measures to manage inflammation and, in extreme instances, surgical procedures. Probiotics, live microorganisms, drug-loaded natural polysaccharide systems, and genetically modified probiotics are potential approaches to the treatment of IBD [3]. The inflammation sites of Crohn's disease and ulcerative colitis are illustrated in Fig. (**1**).

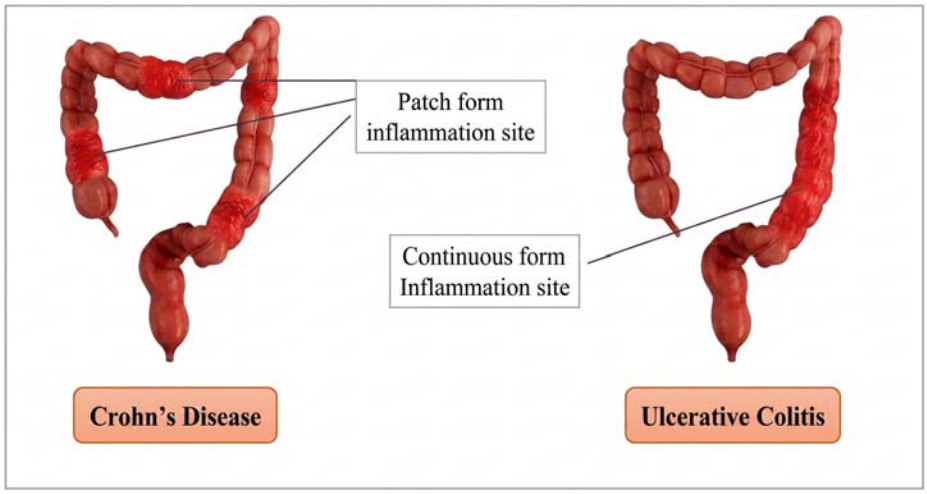

Fig. (1). Schematic illustration of Crohn's disease and ulcerative colitis.

Polysaccharides are a class of pharmacologically active compounds with anti-inflammatory, immunomodulatory, glycolipid, and anticancer properties. They are well known for their safety and can serve as substrates for certain gut

microbiomes to enhance the spread of beneficial bacteria. The International Scientific Association of Probiotics and Prebiotics (ISAPP) defines prebiotics as substances preferentially employed by host bacteria and confer health benefits [4]. The health-enhancing properties of polysaccharides derived from the same source but exhibiting varying structural types are frequently associated with the composition, diversity, enterotypes, or metabolites of the gut microbiome. Understanding the probable processes of dietary polysaccharide-gut microbiome-host interactions and the correlation between polysaccharide structure and prebiotic activity will contribute to the advancement and improvement of plant-derived polysaccharides in the food sector. They are essential in the management of IBD due to their anti-inflammatory and immunoregulatory properties. They modulate inflammatory cytokines, the intestinal microbiota, and the immune system, and can attach to the ulcerated surface of the colon [5]. Polysaccharides can function as drug carriers, exhibiting effective controlled-release properties, high affinity, and biodegradability. They can efficiently mitigate and manage IBD through several mechanisms, rendering them appropriate for immediate intervention and the continuous release of therapeutic agents. This chapter offers a summary of the classifications and therapeutic mechanisms of polysaccharides [6].

Basic Introduction to Plant-derived Polymers

Pectin

Pectin is a heteropolysaccharide consisting of a linear polymer of Galacturonic Acid (GalA), referred to as Homogalacturonan (HG). It is categorized as High-Methoxyl Pectin (HMP) and Low-methoxyl Pectin (LMP). HMP originates from the extraction of juice by-products, whereas LMP is generated by acid, alkaline, or enzymatic de-esterification processes. Sunflower Heads (SH) serve as an alternative source of natural LMP, potentially containing up to 20% of this polysaccharide. LMP possesses a net negative charge due to the free carboxyl groups of the GalA residues, which engage with positively charged amino acids, facilitating its penetration through the mucus layer of the intestinal wall. The extraction of pectin requires the use of strong acids and is both time- and energy-intensive. Ultrasound-Assisted Extraction (UAE) has been examined for its benefits, such as reduced energy expenses and enhanced yield and quality [7, 8]. The chemical structure of pectin is illustrated in Fig. (**2**).

Inulin

Inulin, discovered by German scientist Rose in 1804, is a fructose-containing polymer found in the roots of Inula helenium, a perennial plant native to temperate parts of Europe, Asia, and Africa. It is classified as a fructan and

CHAPTER 5

Exploring the Role of Polymers Derived from Animals in the Treatment of Inflammatory Bowel Disease

Rashmi Dewangan[1], Nidhi Agrawal[1], S.K. Lanjhiyana[1], Sanjay Kumar Bharti[1] and **Meenakshi Jaiswal[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: Inflammatory Bowel Disease (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract. The primary challenge in IBD treatment is the limited bioavailability of therapeutic agents at the inflamed site, necessitating higher systemic doses that can lead to adverse effects. Animal-derived polymers are becoming recognized as efficient carriers for targeted drug administration due to their biocompatibility, biodegradability, and ability to enhance drug retention in the colon. Natural polymers such as gelatin, chitosan, collagen, hyaluronic acid, albumin, and chondroitin sulfate demonstrate potential in improving drug absorption, modulating inflammation, and extending drug release. These biomaterials exhibit mucoadhesive properties, prolong intestine retention, and promote mucosal healing, hence enhancing therapeutic efficiency. Moreover, they can be engineered to encapsulate anti-inflammatory agents and biologics, ensuring localized pharmacological effectiveness while minimizing systemic toxicity. Innovative methods, including enzymatic and biological modifications, have been explored to improve the structural and functional properties of these polymers, hence increasing their effectiveness in drug delivery applications. Notwithstanding these advancements, challenges remain in refining polymer formulations for improved stability, precise release, and controlled degradation. This chapter highlights recent developments in animal-derived polymeric nanocarriers for the treatment of IBD, emphasizing their role in enhancing drug targeting and therapeutic effectiveness. The progression of innovative animal-derived polymers or their derivatives with superior properties remains a crucial area for future research, offering potential improvements in IBD therapy.

Keywords: Animal-derived polymers, Inflammatory bowel disease (IBD), Nano-carriers, Natural polymers, Targeted drug delivery.

[*] **Corresponding author Meenakshi Jaiswal**: Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: jaiswalmeenakshiggu@gmail.com

INTRODUCTION

Inflammatory Bowel Disease (IBD) encompasses Crohn's Disease (CD) and Ulcerative Colitis (UC), both of which are persistent inflammatory disorders of the gastrointestinal tract [1]. The highest prevalence is observed in North America an Northern Europe, with 9–20 cases per 100,000 individuals per year [2]. UC is more prevalent in adults, while CD is more common in children [3]. The prevalence of IBD is rising in traditionally low-risk areas, including Asia, the Middle East, and South America, presumably attributable to urbanization and westernized lifestyles [4]. Environmental factors, including diet, pollution, and hygiene, affect the emergence of disease in people with a genetic disposition [5]. Before the age of 20, an appendectomy reduces the chance of UC by 69%, but it increases the risk of CD [6]. IBD often presents throughout the first three decades of life, causing chronic recurring inflammation [7]. It causes significant morbidity and mortality and is associated with an increased risk of Colorectal Cancer (CRC) [8]. While CD can affect any part of the gastrointestinal system and is characterized by transmural inflammation that results in strictures and fistulas, UC primarily affects the colon, causing surface mucosal inflammation [9]. Immunological dysregulation, gut microbiota, environmental variables, and genetic vulnerability all contribute to its emergence, although the exact cause is still unknown [10]. Systemic disorders may arise from IBD, which typically manifests as a relapsing-remitting pattern in early adulthood [11]. Intestinal epithelial barrier deficiencies and increased immunological activity are linked to IBD, which causes tissue deterioration over time [12]. CRC is the leading cause of cancer-related mortality, and it is a major risk factor for the disease. An important public health issue that demands improved treatment strategies is the growing incidence of IBD worldwide [13]. Due to the complex physiology and environment of the gastrointestinal system, colorectal medication distribution in IBD faces significant challenges [14]. Drug formulations that are both targeted and resistant to stomach transit are required because the colon's located farther from the stomach [15]. Formulation design is crucial because changes in intestinal fluid volume, transit time, and pH affect the breakdown and absorption of medications. [16] Drug mobility is limited by the increased viscosity of colonic contents, while medications may become inactive or lose their efficacy due to colonic bacterial enzymatic destruction [17]. Additionally, pharmacologically active, inert, or possibly dangerous metabolites may be produced *via* intestinal metabolism. Drug bioavailability may be hampered by inadequate solubility and high dosage requirements, necessitating the use specially designed delivery systems [18]. In order to ensure targeted and effective therapy, colorectal medication administration strategies in IBD include a variety of cutting-edge techniques [19]. For targeted drug release, colon-specific biodegradable methods of delivery include enzyme-sensitive polymers or bacterial fermentation of

polysaccharides [20]. Pharmaceuticals are encapsulated in matrix-based methods using biodegradable or pH-sensitive polymers to prevent early release [21]. Although gastrointestinal transit time is the basis for timed-release techniques, drug administration may be impacted by motility variations [22]. By improving drug retention in the intestinal mucosa, bioadhesive techniques improve absorption and efficacy [23]. The uniformity of drug distribution and absorption by colonic macrophages is enhanced by multiparticulate systems like microspheres [24]. Enzyme-mediated drug release, stability, and biocompatibility are all offered by polysaccharide-based delivery systems [25]. For controlled release, pH-sensitive coatings dissolve at colonic pH and shield medications from stomach acid [26]. Although variations in viscosity may affect effectiveness, pressure-controlled formulations use increased intestinal lumen pressure to start drug release [27]. To enhance targeted drug delivery, osmotic and pulsincap systems combine timed-release mechanisms with pH-sensitive coatings [16]. Animal-derived natural polymers, which use colonic bacterial enzymatic breakdown for precise release, are crucial for colon-specific drug delivery in IBD [15]. Compared to synthetic polymers, they are safer because they are non-toxic, biodegradable, and biocompatible [28]. Collagen, gelatin, chitosan, and hyaluronic acid are examples of animal-derived polymers that are valued for their structural similarity to human biomolecules, biocompatibility, and biodegradability [29]. Strict ISO 10993 testing is necessary for safety, as impurities or inadequate purification can cause cytotoxic or inflammatory reactions [30]. Additionally, these polymers may possess antigenic properties, such as α-Gal epitopes, that trigger an immune response [31]. In order to ensure increased purity, improved biocompatibility, and reduced immunogenicity, advanced purification and chemical modification techniques are employed to remove or mask antigenic residues [32]. In addition, they are affordable, easily obtainable, and free of adverse effects [29]. The properties of animal-derived polymers and their application in targeted medication delivery for the management of IBD are covered in this chapter.

THE IMPORTANCE OF ANIMAL-DERIVED POLYMERS IN IBD

Animal-derived polymers enhance stability, bioavailability, and controlled release, and are considered significant for targeted colorectal drug delivery in IBD [30]. Chitosan, hyaluronic acid, collagen, gelatin, and chondroitin are examples of polymers that are used as excipients in formulations such as tablets, hydrogels, microparticles, microspheres, nanoparticles, nanovesicles, and composites (Table **1**) [31]. These biopolymers enhance mucoadhesion, prevent drug degradation, and facilitate targeted delivery to inflamed areas, thereby minimizing systemic side effects (Fig. **1**) [32].

CHAPTER 6

Microbial-Derived Polymers: Revolutionizing Inflammatory Bowel Disease Treatment

Rashmi Dewangan[1] and **Nikita Verma**[2,*]

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

[2] *MATS School of Pharmacy, MATS University, Raipur 493441, Chhattisgarh, India*

Abstract: Inflammatory Bowel Disease (IBD), comprising Crohn's disease and ulcerative colitis, is a persistent gastrointestinal disorder marked by immune dysregulation and imbalances in gut flora. Conventional therapy modalities, including corticosteroids, immunosuppressants, and monoclonal antibodies, frequently result in side effects and inconsistent patient responses. Recent advancements in biomaterials have underscored the potential of microbial-derived polymers as novel therapeutic carriers for the management of IBD. Polymers isolated from microbes are sourced from bacterial, fungal, and algal origins. Bacterial polysaccharides, such as xanthan gum, dextran, pullulan, curdlan, and bacterial cellulose, provide superior biocompatibility, muco-adhesive characteristics, and controlled drug release potential. Polymers derived from fungi, such as xanthan-like polymers, chitosan, and β-glucan, have bioadhesive and antibacterial properties that facilitate mucosal healing. Algal polysaccharides such as alginate and carrageenan facilitate pH-sensitive drug release, ensuring precise delivery to the inflamed intestinal mucosa. Microbial-derived polymers function as multifaceted carriers in IBD drug delivery, developing advanced formulations including hydrogels, nanoparticles, dendrimers, nanofibers, nanosuspensions, microspheres, and vesicles. Hydrogels enable prolonged drug release, preserving moisture and enhancing mucosal regeneration. Nanoparticles and microspheres improve drug stability and bioavailability, facilitating accurate targeting of inflamed regions. Dendrimers and nanofibers have substantial drug-loading capacities, facilitating sustained and controlled therapeutic effects, whereas nanosuspensions enhance solubility and absorption. This chapter discusses microbial-derived polymers, their optimal characteristics for colorectal drug delivery, classifications based on charge, various biological sources, and the multifunctional roles of these polymers as therapeutic carriers. By utilizing these advanced drug delivery technologies, microbial polymers are enabling more effective and targeted treatments for IBD, resulting in diminished side effects and enhanced patient compliance.

* **Corresponding author Nikita Verma** MATS School of Pharmacy, MATS University, Raipur 493441, Chhattisgarh, India; E-mail: nikitaverma510@gmail.com

Meenakshi Jaiswal & S.K. Lanjhiyana (Eds.)

Keywords: Alginates, Beta-glucan, Exopolysaccharides, IBD, Microbial-derived polymers.

INTRODUCTION

The mucosal immune system maintains a balanced response between pro- and anti-inflammatory micellar responses in a healthy gut [1]. This allows for appropriate defence against pathogens while also preventing an overwhelming immune response against a large number of harmless food antigens and commensal microbes [2]. Due to the hyperactivation of immune effector cells that produce high quantities of pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, the immunological response in IBD is turned towards pro-inflammation [3]. Nuclear Factor kappa B (NF-κB), a transcription factor, is essential for the regulation and modulation of the mucosal immune system [4]. NF-κB is widely expressed in all cell types and triggers several pro-inflammatory genes, including pro-inflammatory cytokines [5]. Increased NF-κB p65 expression in biopsied tissue from IBD patients, especially those with Crohn's disease, indicates that NF-κB is significantly overactivated in IBD [6]. IBD is a serious public health issue on a global scale [7]. Current therapeutic techniques, such as immunosuppressants, biological therapies, and anti-inflammatory drugs, are often ineffective and have detrimental effects on health [8]. The use of natural compounds to target key pathogenic pathways in IBD is therefore of great interest [9]. Seaweed contains a wide range of structurally varied biologically active compounds. Intestinal epithelium cells, reactive oxygen, nitrogen, cytokines, chemokines, adhesion molecules, and nuclear factor NF-kB [10, 11]. This is why it is necessary to consider a personalised medicine delivery method for IBD. The novel tailored drug-delivery approach can deliver medication directly to the site of inflammation based on the pathological characteristics associated with IBD, improving medication accumulation and reducing adverse effects [11]. A better knowledge of the mechanisms underlying the effects of polysaccharides from different algal species, each with a distinct structure and molecular weight, on intestinal microbes, as well as immunological and epithelial cells, will aid in the development of pharmaceuticals and nutritional supplements [12]. Faecal transplantation, medication therapy, and surgery are all part of the treatment for IBD [13]. However, because many patients have post-operative recurrence, which lowers their quality of life and causes more intestinal damage, surgery does not cure the problem [14]. Mesenchymal Stem Cells (MSCs) have recently attracted a lot of attention due to their immunomodulatory and tissue-healing capabilities, which makes cell-based therapies a promising treatment option for IBD. MSCs release a variety of bioactive compounds that can influence immune responses and hasten tissue regeneration, including growth factors and anti-inflammatory cytokines [15]. Understanding the effects of these interactions on human health is

still necessary, though. For instance, individuals with inflammatory bowel illness have been shown to express TLR4 more than normal [16]. Sulfated polysaccharides, found in seaweed, have demonstrated an anti-inflammatory effect on the illness. Using an enzymatic process, LMW-ulvan, a new low molecular weight sulfate Ulva polysaccharide, was produced. [17] The availability of treatments with a variety of modes of action, such as anti-integrins that block leukocyte trafficking or anti-tumor necrosis factor and anti-interleukin [18]. These studies generally showed that active targeting is a promising strategy for improving drug accumulation and uptake in IBD inflammatory tissues, even though more research is needed to evaluate the efficacy and stability of various targeted ligands and formulations in IBD models [19].

Microbial-derived polymers have numerous advantages over synthetic polymers for the treatment of IBD, owing to their biocompatibility, biodegradability, and biological functioning [20, 21]. In contrast to synthetic polymers, which frequently necessitate surface modification to enhance biocompatibility or cellular contact, microbial polymers inherently possess bioadhesive and immunomodulatory characteristics, hence facilitating mucosal healing and medication retention at inflamed intestinal sites [22]. They are biologically derived, non-toxic, and able to replicate the natural extracellular milieu, facilitating epithelium regeneration [23]. Additionally, microbial polymers like dextran, xanthan gum, gellan gum, pullulan, and bacterial cellulose exhibit mucoadhesive and pH-sensitive properties, facilitating targeted and prolonged release of drugs in the colon, thus reducing systemic adverse effects [24]. Synthetic polymers, by contrast, can provide hazardous breakdown products and lack biological recognition, hence constraining their therapeutic efficacy in chronic inflammatory disorders such as IBD [20]. Microbial-derived polymers integrate natural bioactivity, environmentally sustainable manufacturing, and patient safety, rendering them exceptional prospects for colon-targeted delivery of drugs and mucosal tissue healing in IBD treatment [25]. This chapter will examine microbial-derived polymers, their categorization, and their function in the management of IBD.

MICROBIAL-DERIVED POLYMERS

Microbial-derived polymers can be produced by various microorganisms, including bacteria, actinomycetes, yeast, archaea, and fungi [19]. Every biopolymer has distinct characteristics and can be modified for the colon-targeted drug delivery in the treatment of IBD [20].

CHAPTER 7

Advancements in Nano Drug Delivery Systems Using Natural Polymers

Nidhi Agrawal[1], Rashmi Dewangan[1], Mohammad Akbar Siddiqui[1], Sakshi Gupta[1], S.K. Lanjhiyana[1] and **Meenakshi Jaiswal[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: With improvements in therapeutic efficacy, accuracy, and safety, nano Drug Delivery (DD) technologies have brought about a revolution in the pharmaceutical and healthcare sectors. Natural polymers have garnered a substantial amount of attention among the different materials that have been investigated for the purpose of nano DD. The utilization of these systems has become significant in nanomedicine for targeted drug administration, enhancing biocompatibility, safety, permeability, retention time, and reducing toxicity. An appropriate biodegradable polymer can be used as the drug carrier for targeted and sustained DD. This chapter summarizes current research and new developments in the field, highlighting the promise of natural polymer-based nano-DD methods and emerging polymers with unique characteristics suitable for DD applications.

Keywords: Biodegradable polymer, Controlled release, Nano drug delivery, Natural polymers, Targeted therapy.

INTRODUCTION

Biodegradable Polymers (BDP) found in nature are extensively utilized in drug delivery due to their natural abundance, biodegradability, biocompatibility, and reduced toxicity [1 - 4]. These encompass protein-based polymers such as albumin, gelatine, soy, and collagen, as well as polysaccharides like chitosan, agarose, dextran, hyaluronic acid, alginate, carrageenan, and cyclodextrin. Nevertheless, the use of natural polymers as drug carriers poses challenges due to their extensive molecular weight ranges and heterogeneity across batches (Fig. **1**) [5 - 9]. These polymers have a wide range of proven medicinal actions, including antioxidant, wound healing, antimicrobial, and anti-inflammatory, fields has

* **Corresponding author Meenakshi Jaiswal**: Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: jaiswalmeenakshiggu@gmail.com

fostered growing confidence over its potential to significantly enhance clinical detection and treatment of diseases. Such a system encompasses *in vitro* and *in vivo* features, fabrication of advanced biocompatible materials, nutraceuticals, and medication delivery systems [10 - 16]. The primary motivation for interest in Nanoparticles (NPs) for medical applications is their distinctive characteristics, including a high surface-to-mass ratio, quantum properties, and their capacity to adsorb or serve as carriers for other materials [17, 18].

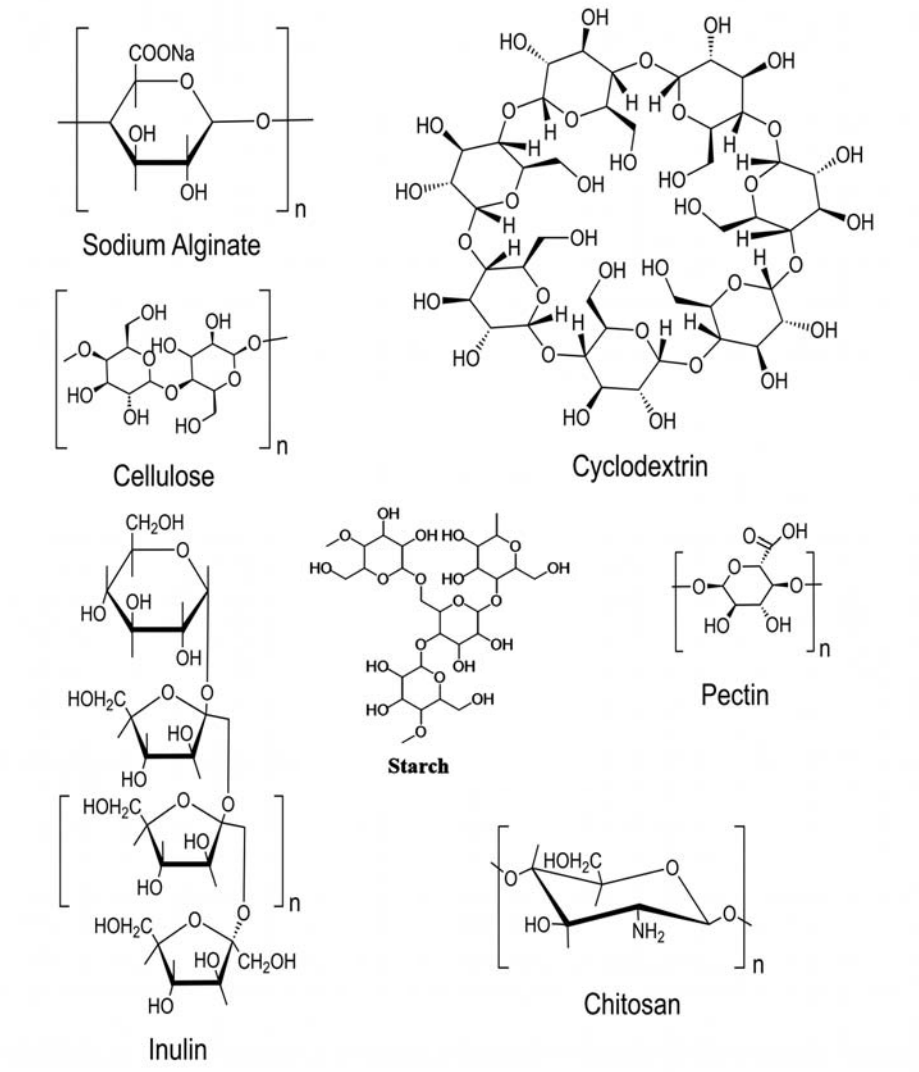

Fig. (1). Chemical structures of some natural polymers used in DD.

NATURAL POLYMERS USED IN NANO DD SYSTEMS

Cyclodextrins

β-Cyclodextrins (βCD), a type of cyclic oligosaccharide, are widely used, particularly for the delivery of hydrophobic drugs. These oligosaccharides are composed of 7 glucose units and have a hydrophilic outer layer and a hydrophobic interior. In one of the cyclodextrin-based nanoformulations, ginsenoside Rg3 and quercetin are successfully co-delivered, increasing the efficiency of chemo-immunotherapy for colorectal cancer. This method improves DD and malignant targeting and extends survival in animal models when used in combination with anti-PD-L1 therapy [19].

A novel βCD–Mel–AgNPs nanosystem was developed by the researchers, which improves the therapeutic potential of Melphalan. The formation of a robust complex with βCD markedly enhanced the drug's stability and solubility, minimizing its hydrolysis and degradation. The integration of Silver Nanoparticles (AgNPs) into the βCD–Mel complex not only enhanced the stability of the NPs but also offered a viable platform for targeted DD [20]. Also, the βCD@DB complex, combined with plasmonic gold NPs and polyethylene glycol, represents a notable progression in improving the delivery and effectiveness of Dacarbazine in cancer treatment. This advanced nanosystem overcomes the shortcomings of Dacarbazine, including poor solubility and instability, while enhancing its biocompatibility and controlled release properties [21].

Cellulose

Cellulose, the primary skeletal element in plants, is a nearly limitless polymeric raw material characterized by its intriguing structure and properties. They are hydrophilic, chiral, biodegradable, chemically modifying, and capable of creating diverse semicrystalline fibre morphologies [22]. An investigation demonstrates the feasibility of using Vetiver zizanioides root agro-waste for the enzymatic synthesis of Cellulose Nanoparticles (CNPs). The results demonstrate that pectinase and viscozyme are proficient in generating crystalline cellulose nanocrystals, whereas cellulase produces cellulose nanofibers. The synthesized CNPs demonstrate favourable characteristics, including non-toxicity, biodegradability, and biocompatibility, rendering them appropriate for use in textile and drug-delivery systems. This research highlights the beneficial utilization of agro-waste while adhering to green chemistry principles, thereby fostering sustainable practices in material production [23]. One of the research reports effectively synthesized and characterized a novel micellar DD system utilizing ethyl cellulose grafted with polyethylene glycol. The resultant

CHAPTER 8

Natural Polymers in Combination Therapies for Inflammatory Bowel Disease Management

Mohammad Akbar Siddiqui[1], Nidhi Agrawal[1], Sakshi Gupta[1], Meenakshi Jaiswal[1] and **S. K. Lanjhiyana[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: Inflammatory Bowel Disease (IBD) is a chronic Gastrointestinal (GI) condition characterized by relapsing inflammation, which significantly impacts patients' quality of life. Despite advancements in treatment, current therapeutic strategies face limitations in achieving targeted drug delivery to the inflamed intestinal regions. Combination therapies integrating natural polymers have emerged as a promising approach to enhance drug efficacy, stability, and bioavailability while minimizing systemic side effects. This chapter explores the pathophysiology of IBD, the challenges associated with conventional treatments, and the role of combination therapies utilizing natural polymers. Specifically, the discussion highlights the potential of polymer-based drug delivery systems incorporating small molecules, probiotics, and biologics. Natural polymers such as alginate, chitosan, and pectin offer biocompatibility and colon-specific degradation, making them ideal carriers for drug targeting. The synergistic effects of polymer-based combination therapies offer a novel therapeutic avenue for improving IBD management. Future studies should prioritize refining formulation methods and undertaking comprehensive clinical trials to ensure these approaches are both effective and safe.

Keywords: Biologics, Combination therapy, Inflammatory bowel disease, Natural polymers, Probiotics, Small molecule.

INTRODUCTION

Overview of Inflammatory Bowel Disease (IBD)

IBD is a long-term, recurring disorder that impacts the GI tract. This condition is marked by non-infectious, chronic inflammation that primarily impacts the lining of the GI tract, leading to ongoing structural and functional damage of the

* **Corresponding author S. K. Lanjhiyana:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: sklanjh1975@gmail.com

epithelium with few common symptoms such as abdominal pain with cramping, bloody diarrhoea, and weight loss, which necessitates long-term therapy [1]. IBD is categorized into two primary subtypes based on pathological characteristics and disease manifestation. Ulcerative Colitis (UC) predominantly targets the mucosal layer of the colon, causing inflammation in a continuous pattern along the inner lining. In contrast, Crohn's Disease (CD) may affect various locations within the GI tract in a discontinuous manner, with the terminal ileum being the most commonly impacted region. These subtypes represent distinct clinical entities, necessitating tailored treatment strategies [2]. Though the specific causes of IBD are unclear, it is believed that genetic, immune system, and environmental factors are involved. The IBD is more prevalent in developed countries, with incidence rates ranging from around 5.3 to 63.6 per 100,000 individuals [3].

Pathophysiology of UC and CD

Patients with UC exhibited reduced diversity of Firmicutes and increased levels of γ-proteobacteria, Enterobacteriaceae, and sulfite-reducing deltaproteobacteria. The role of these changes in intestinal inflammation is still uncertain. Interleukin (IL-13), produced by T helper (Th2) and natural killer T cells, works with Tumour Necrosis Factor-α (TNF-α) to regulate tight junction gene expression and affects membrane integrity, thereby increasing gut permeability. Activated antigen-presenting cells (APCs), recognizing commensal microbiota through Toll-like Receptors (TLR2 and TLR4), initiate the differentiation of CD4+ T cells into effector subsets such as Th2, Th9, and Treg [4]. Th2-associated cytokines like IL-5 and IL-13 dominate in UC, although the overall role of Th2 cells is inconclusive. Th9 cells, producing IL-9, also contribute to UC by hindering mucosal healing and disrupting the mucus layer's protective functions. The CD is driven by Th1 cells, leading to small bowel inflammation and increased proinflammatory cytokines (IFN-γ and IL-17A) [5]. The Th17 pathway, influenced by cytokines like IL-6 and IL-23, interacts with the Th1 response. Increased levels of transcription factors (*e.g.*, STAT4, T-bet) and cytokine receptors (IL-12Rβ2) promote Th1 differentiation. Consequently, both Th1 and Th17 pathways contribute to CD development, with mortality mainly due to pulmonary disease and certain cancers [6].

Diagnosis

Precise identification of IBD is essential for effective management. Nevertheless, no serum or faecal biomarkers are sufficient for assessing suspicious and confirmed IBD cases. Innovative methods for identifying biomarkers, such as genetic expression technology using the Applied Biosystems GeneChip system in peripheral blood [7], tissue biopsies from mucous membranes [8], assessment of

mRNA expression levels in bloodstream leukocyte cell RNA [9], and c-microRNAs [10], have demonstrated encouraging results. Following diagnosis, many IBD medications fail to achieve clinical remission and frequently result in side effects, including diarrhea, renal dysfunction, and opportunistic infections like TB. Additionally, evaluating inflammation through endoscopy is both costly and invasive. The initial method of combining phenotype and serology information is inadequate for differentiating CD from UC; thus, it is complicated to predict accurate clinical outcomes [11].

The study of metabolism is becoming an effective technique for analyzing metabolites in biological samples. It can significantly impact the early identification of IBD, the establishment of therapeutic targets, and the implementation of targeted therapies [12]. For instance, T1259 serum biochemical levels can distinguish IBD from normal individuals [13]. Likewise, serological and fecal biochemical screening has shown promise for distinguishing juvenile IBD from healthy individuals by measuring Fecal Calprotectin (FC) and metabolites like choline [14]. Fecal FC assessment is not limited to pediatric cases; in patients with UC. FC exceeds C-Reactive Protein (CRP) in predicting clinical outcomes and therapeutic response, including inflammation and mucosal healing. The comprehensive functions of FC in IBD patients, such as therapy forecasting, prediction of disease recurrence, and relapse after surgical intervention, are reviewed by Mumolo *et al*. [15]. Metabolic assessment serves as a valuable tool for identifying specific biomarkers that distinguish among IBD subclasses. By employing diverse statistical methods, researchers can analyze metabolites to uncover both the similarities and variations in their profiles, thereby characterizing disease phenotypes. For instance, biopsies from individuals with active UC exhibit elevated levels of glutamine and glutathione when evaluated against control tissues or those from individuals with inactive UC [16]. Nevertheless, the high cost of biochemical methods and spectroscopic instruments poses significant challenges to their accessibility, particularly in developing countries.

Challenges in Current IBD Treatments

A primary challenge in the management of IBD is the limited ability of therapeutically active agents to reach the colonic region effectively. Minimizing drug releases in the upper GI tract is critical due to the significantly different pH values of the GI tract, *i.e*., low/acidic to high/alkaline pH, as well as varying transit times [17, 18]. In IBD, particularly Ulcerative Colitis (UC), the colonic pH can decrease, which poses a significant challenge for effective treatment. Optimizing drug release in the colonic region with high enzymatic degradation and a pH environment, results in poor absorption of drugs in the inflamed colon

CHAPTER 9

Advancement in Bioengineered Natural Polymers for Combating IBD: Current Progress and Future Prospects

Shibangi Mukhopadhyay[1], Yogesh Vaishnav[1], Achal Mishra[1], Sanjay Kumar Bharti[1], Rajkumar[1] and **Meenakshi Jaiswal[1,*]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India*

Abstract: Inflammatory Bowel Disease (IBD) is a persistent, relapsing, and untreatable disorder that impacts the intestines. The ineffectiveness of prolonged therapy, substantial side effects due to systemic exposure, and increased risks of infection and malignancy from immunosuppression are obstacles to contemporary clinical treatments. To reduce the systemic toxicity of these medicinal agents and enhance intestinal adhesion and retention while targeting the mucosa, polymeric systems have been developed as delivery approaches. To address IBD, we elucidated pharmaceutical delivery techniques derived from polymers. Smart bionanomaterials, which are biocompatible nanoscale substances that respond to environmental stimuli, can facilitate treatment and diagnostics. These materials can deliver live probiotics and drugs, mostly amino salicylates and corticosteroids, to the inflamed regions of the gastrointestinal tract, particularly the colon, in the context of IBD. Smart bionanomaterials offer several advantages, such as regulated release, stimulus responsiveness, targeted dispersion, and encapsulation. These attributes make them an indispensable adjunct in the diagnosis and treatment of IBD. The improvement of therapeutic intervention techniques and sophisticated delivery technology offers insights into the design and development of polymeric systems for medication administration from bench to bedside in the treatment of IBD.

Keywords: Amino salicylates, biocompatibility, colon-targeted therapy, drug delivery techniques, encapsulation, environmental stimuli.

INTRODUCTION

Colon-targeted diseases encompass a group of autoimmune disorders, with Inflammatory Bowel Diseases (IBD) being the most significant. IBD is

* **Corresponding author Meenakshi Jaiswal**: Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; E-mail: jaiswalmeenakshiggu@gmail.com

characterised by chronic and acute inflammatory conditions, mucosal ulceration, oedema, and haemorrhage within the Gastrointestinal (GI) tract. IBD is becoming more and more common among young people and is becoming a dangerous condition that makes them much more likely to get colon cancer [1]. The causes of IBD are still being studied. Some of the most important ones are genetic predispositions, environmental factors, and the integrity of the intestinal mucosal barrier. Compared to healthy colon mucosa, a sick colon disrupts the equilibrium among the gut bacteria, the immune system, and the internal environment of the intestine. This makes the inflammation in the intestine worse. Sometimes, an imbalance of Reactive Oxygen Species (ROS) and the breakdown of tight junctions make intestinal tissues more permeable. This raises the levels of oxygen and antigens, which can make the immune system work too hard. This enhancement of the immune system facilitates colon-targeted cancer therapy. IBD is largely divided into two variants: Ulcerative Colitis (UC) and Crohn's disease (CD). UC is less detrimental as it is localised to a specific region of the mucosal layer in the colon; CD is a chronic and aggressive form of inflammation that penetrates deeper into the intestinal wall and impacts the GI tract [2]. The principal aims of IBD treatment are to maintain remission from inflammatory episodes and prevent recurrent inflammation. Conventional therapeutic regimens for IBD include 5-aminosalicylic acid-based anti-inflammatory agents, corticosteroids, immunosuppressive drugs (tacrolimus, cyclosporine-A, methotrexate, azathioprine, and 6-mercaptopurine), and antibiotics (ciprofloxacin and metronidazole). The advancement of biological therapeutics utilising monoclonal antibodies has enhanced the clinical efficiency of IBD treatment [3].

It is problematic to regulate IBD, specifically in sensitive and elderly individuals, because long-term use of standard drugs has been linked to the most common side effects, such as pancreatitis, allergic responses, nausea, and elevated liver enzymes. Although the drugs indicated above provide clinical remission, they are ineffective and have severe side effects over time. Drug Delivery Systems (DDSs) are being developed to rigorously distribute payloads to the inflammatory intestinal mucosa. These systems can usually be delivered orally, intraperitoneally, intrarectally, or intravenously. Intrarectal administration is unsuccessful elsewhere but effective for treating distal lesions. More importantly, in developing countries, inappropriate needle overuse increases the risk of AIDS. Inserting needles is painful, invasive, and not very popular [2]. After reading most publications, it is evident that the more recent technologies employed in various delivery systems to treat IBD rely entirely on the usage of various polymers that increase the effectiveness of various medication combinations. Due to their self-assembled hierarchical structure, ease of manufacturing, and ability to alter chemical properties, polymeric DDSs have shown clinical efficacy and

widespread use in a range of illnesses, with exceptional biodegradability and biocompatibility [4].

When it comes to tackling IBD, both natural and synthetic polymers have a role to play. Polysaccharides and other naturally occurring polymers are highly valued not only because they are cost-effective and biodegradable, but also due to their adhesive properties, which allow them to remain at target sites where they are needed most. Research into synthetic polymers has been robust due to their adaptability in terms of chemical composition, molecular weight, structure, and post-modification ease. IBD is a group of conditions that includes UC and CD, and recently developed synthetic polymers are helping to improve therapy for these conditions. One of the main obstacles to IBD is the lack of appropriate materials for targeted drug delivery, controlled release, and the mitigation of systemic adverse effects. Such synthetic polymers include polyphenols, cationic polymers, Polyethylene Glycol (PEG), polyesters (PLGA, PCL, *etc*.), and polyacrylates, among others [5]. Drug delivery techniques for IBD frequently use synthetic polymers, which have limited systemic bioavailability and poor oral absorption. Consequently, a considerable amount of the drug might not reach the intended sites in the intestines, thereby reducing its therapeutic efficacy. An increase in intestinal inflammation and disruption of gut microbiota are two ways in which some of these polymers, such as polyethylene microplastics, exacerbate inflammatory bowel disease symptoms. They could interact badly with the gut flora or create toxic by-products. One example is the potential for inflammation and other gastrointestinal problems caused by some emulsifiers used in synthetic formulations, which might undermine the integrity of the gut barrier. Due to their less damaging nature, natural polymers have been used far more than synthetic polymers. For hydrogels that exhibit low toxicity potential, biodegradability, and sensitivity to particular environmental stimuli, natural polymers are usually the way to go because they are more environmentally friendly. Proteins such as gelatin, chondroitin sulphate, and hyaluronic acid, and carbohydrates such as pectin, chitosan, and alginate are examples of natural polymers. There are a number of advantages to using these natural polymers for drug delivery rather than manufactured polymers. It is difficult to modify them to meet the needs of drug deliverydue to their inadequate mechanical properties and tensile strength. And because they are already there, they might provoke immune responses that would make them useless as biomaterials for oral drug delivery [6].

The creation of innovative bionanomaterials, which are safe nanoscale materials that respond to environmental cues, has made it much easier to find and treat illnesses. In recent decades, smart materials have gained prominence and are particularly intriguing for medical applications. Conductive hydrogel cardiac patches composed of smart materials have demonstrated encouraging outcomes in

CHAPTER 10

Clinical Applications of Natural Polymers in Inflammatory Bowel Disease: Challenges in Translating Research into Practice

Prashant Tiwari[1,*] and **Sunil Kumar Kadiri**[1]

[1] *Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru 562112, Karnataka, India*

Abstract: Inflammatory Bowel Disease (IBD), including Crohn's disease and ulcerative colitis, is a progressive and disabling disease characterized by relapsing gastrointestinal tract inflammation. However, an age of precision medicine for IBD is still far away, as severe side effects, high relapse rates, and compromised long-term efficacy are still challenging obstacles in conventional therapy. In fact, natural polymers, including alginate, chitosan, pectin, hyaluronic acid, and guar gum, have received considerable attention as novel therapeutic agents and delivery systems in recent years for the treatment of various diseases, which could be attributed to their cell-friendly features (biocompatibility and biodegradability) and their inherent bioactivities, such as anti-inflammatory activity, antioxidant activity, and mucosal healing activity. Several of these polymers have also demonstrated promise in improving drug delivery systems, supporting intestinal repair, and influencing gut microbiota, thereby overcoming certain shortcomings of existing IBD treatments. This chapter discusses natural polymer-based clinical applications in IBD and their functions as advanced drug delivery systems, biomaterials for tissue repair, and prebiotics that maintain gut health. It also discusses the major obstacles that limit the translation of these results into clinical practice, including formulation stability, scalability, patient heterogeneity, and regulatory complexities. Case reports and recent clinical trials are discussed to further illustrate these concepts. In addition, the chapter identifies further research opportunities, in particular, the convergence of polymer engineering, nanotechnology, and personalised medicine in IBD. In doing so, the chapter aims to inspire new approaches to the clinical exploitation of natural polymers to ultimately enhance patient outcomes.

Keywords: Antiinflammation, Biocompatibility, Chitosan, Clinical translation, Drug delivery, Natural polymer.

[*] **Corresponding author Prashant Tiwari:** Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda SagarUniversity, Bengaluru 562112, Karnataka, India; E-mail: prashanttiwari-sps@dsu.edu.in

Meenakshi Jaiswal & S.K. Lanjhiyana (Eds.)

INTRODUCTION

Overview of Inflammatory Bowel Disease

Crohn's Disease (CD) and Ulcerative Colitis (UC) are the two primary relapsing, chronic, Gastrointestinal (GI) conditions within the IBD spectrum. These diseases are characterized by intestinal mucosal damage and complex immunological disturbances, which may manifest with symptoms such as diarrhea, weight loss, and abdominal pain. IBD is a global disease affecting millions, with rising rates in both developed and developing countries [1,2]. The pathogenesis of IBD is multifactorial and involves alterations in the gut microbiota, environmental triggers, and genetic factors that contribute to an aberrant immune response [3,4].

A disruption of the balance between certain pro-inflammatory and anti-inflammatory signals that maintain intestinal homeostasis is a key player in the pathogenesis of IBD. The pro-inflammatory cytokines Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-12 (IL-12) play an important role in the perpetuation of inflammation [5]. Further promoting inflammation, mucosal repair is suppressed, while epithelial permeability is increased, thereby aggravating the loss of integrity of the intestinal barrier [6]. Traditional therapies are aimed at decreasing inflammation and inducing remission; however, their success remains limited and adverse effects often complicate disease management.

Need for Novel Therapeutic Approaches

While advances have been made in IBD therapy, such therapies have significant limitations. Corticosteroids, immunosuppressants, and biologics targeting specific cytokines, such as anti-TNF drugs, are examples of standard therapeutic modalities. These drugs have transformed the management of IBD, but they are neither curative nor do they induce sustained remission in a large proportion of patients. In addition, long-term treatment with them is associated with even more adverse effects, such as infections, malignancies, and secondary loss of response to therapy due to antibody development [7, 8].

The emergence of precision medicine brings new therapeutic modalities tailored to individual patients based on their disease characteristics. Natural polymers derived from microbes, plants, and animals are of interest as potential alternatives for the treatment of IBD. Restoring gut flora, enhancing mucosal healing, and targeted drug delivery to the inflamed site are just some of the unique properties these biocompatible and biodegradable materials possess [9, 10].

One of the challenges in IBD drug therapy is to achieve targeted drug delivery with minimal systemic side effects. Conventional oral formulations are often ineffective at specifically reaching the inflamed tissues because they are released prematurely in the upper gastrointestinal tract. Natural polymers such as alginate, chitosan, and pectin have shown to be promising carriers for the delivery of IBD drugs *via* pH-sensitive or enzyme-mediated drug delivery systems [11, 12]. Such vehicles can enhance treatment efficacy and reduce off-target effects by allowing the controlled release of therapeutic drugs at the inflammatory site. Dysbiosis, defined as a loss of beneficial bacteria and an expansion of harmful bacteria, exacerbates colonic inflammation. Prebiotic and probiotic natural polymer-based compositions, such as guar gum and inulin, were found to be effective in maintaining anti-inflammatory effects and microbial homeostasis [13, 14]. The topic of gut microbiota modification is also being opened up by natural polymer engineering to deliver therapeutics to bacteria.

Bioactive scaffolds that stimulate epithelial regeneration and repair damaged tissue have been developed based on natural polymers such as collagen and hyaluronic acid [15, 16]. These approaches also focus on restoring intestinal barrier function, which is critical for sustained remission, in addition to targeting the inflammatory component of IBD.

While nature's polymers may have exciting potential, there are barriers to translating them into therapeutics [17, 18].

NATURAL POLYMERS: PROPERTIES AND POTENTIAL

Natural polymers hold great potential to improve therapeutic strategies for Inflammatory Bowel Disease (IBD), particularly for tissue regeneration, drug delivery system development, and gut microbiota regulation. This section briefly reviews the types of natural polymers relevant to the treatment of IBD and their functional properties and biocompatibility.

Types of Natural Polymers Relevant to IBD

Polysaccharides

The natural polymer family crucial for drug delivery and other therapeutic applications is polysaccharides. They possess excellent biocompatibility and biodegradability, and are abundant in nature. Common IBD-linked polysaccharides are:

Alginate: Alginate is a natural polymer isolated from brown seaweed and has been widely studied due to its ability to form hydrogels under physiological

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Meenakshi Jaiswal

Dr. Meenakshi Jaiswal is an associate professor in the field of Pharmaceutical Chemistry, currently serving in the Department of Pharmacy at Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.), India. She has authored 34 research papers published in reputed national and international journals, alongside 04 books and 35 book chapters with renowned international publishers. Her prolific research output is further evidenced by 30 patents either published or granted on both national and international platforms. Her academic excellence has been recognized through numerous accolades, including five national and four international awards, celebrating her outstanding contributions to the field. She holds life memberships with key professional bodies, such as the Association of Pharmaceutical Teachers of India (APTI) and the Chhattisgarh Pharmacy Council of India (CGPCI), reflecting her active engagement with the academic and professional pharmaceutical community.

S.K. Lanjhiyana

Dr. S.K. Lanjhiyana is an associate professor with over 20 years of experience in pharmaceutical education and research. He is presently associated with the Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.). His research interests is Pharmaceutics, with specialized focus on formulation development and characterization, colon-specific drug delivery systems, and novel controlled and sustained drug delivery technologies. He has made substantial contributions to pharmaceutical field with 48 research papers in prestigious national and international journals, along with 09 books, 40 book chapters, and 31 patents. He has successfully completed major and minor research projects funded by top Indian agencies including the University Grants Commission (UGC), All India Council for Technical Education (AICTE), and Chhattisgarh Council of Science & Technology (CGCOST). He holds life memberships with key professional bodies, such as the Association of Pharmaceutical Teachers of India (APTI), Indian Pharmaceutical Association (IPA), Chhattisgarh Pharmacy Council of India (CGPCI), Indian Society for Technical Education (ISTE).