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CURRENT TRENDS AND FUTURE PERSPECTIVES OF NATURAL POLYMER LOADED NANOPARTICLE BASED DRUG DELIVERY SYSTEM FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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ABSTRACT
Targeting the drug delivery system is very tough nowadays due to premature drug release at the upper GIT tract and altered pH conditions. Colon-specific drug delivery systems can overcome that problem using different polymer combinations. A nanoparticulate drug delivery system is the prominent dosage form that impacts the bioavailability and requires a low dose to excrete the therapeutic efficacy. All nanoscience and nanotechnology are applications of Nanometrology, the science of measurements at the nanoscale. NPDDSs were primarily developed to combine the colloidal stability of solid particle suspensions in biological fluids and the solubilizing properties of liquids. An ideal drug-delivery system possesses two elements: the ability to target and control the drug release. Colloidal drug carriers offer a number of potential advantages as delivery systems, such as better bioavailability for poorly soluble drugs. Researchers have created various sophisticated and multifunctional nanocarrier systems that can transport pharmaceuticals in a targeted, sustained, and regulated manner to provide therapeutic medications that are safer and more effective, particularly to ulcerative colitis. These innovative technologies are improving the pharmacokinetic profile of pharmaceuticals, increasing their systemic circulation, and decreasing the frequency of pharmacological side effects. The review focuses on the current trend and future perspectives of natural polymer-based-loaded nanoparticle-based drug delivery systems for the management of inflammatory bowel disease.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic autoimmune disorder that causes symptoms such as chronic diarrhoea, bowel obstruction, abdominal pain, weight loss, rectal bleeding and anaemia with remission and exacerbation phases, that may lead to severe complications such as colon cancer, mainly characterized by Crohn's disease (CD) and ulcerative colitis (UC) [1]. The pathogenesis and progression of Inflammatory Bowel Disease (IBD) are multi factorial, resulting from complex interactions among various elements. These factors encompass genetic predispositions, including both polygenetic and epigenetic influences, environmental factors, immunological aspects, and dysbiosis in microbial composition, both qualitatively and quantitatively. Dr. Burrill B. Crohn initially introduced this disease in 1932, terming it "regional ileitis." [2]. Ulcerative colitis predominantly impacts the colon, initiating in the rectum and advancing towards the proximal segments. In contrast, Crohn's disease can involve any part of the gastrointestinal tract (GIT), with a preference for the ileum or colon. Its inflammatory effects manifest in a non-continuous manner, characterized by segmental, asymmetrical, or transmural inflammation. [3]. While UC merely damages the mucosa and submucosal layer, CD mostly affects the entire thickness of the gastrointestinal tract [4].

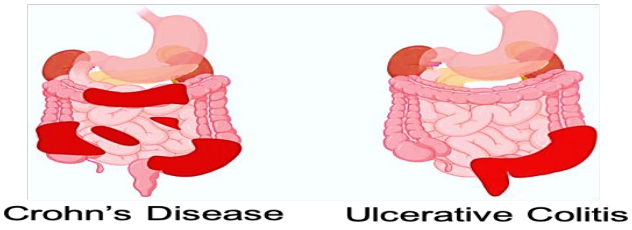

Figure 1: The regions that are impacted by Crohn's disease (CD) and Ulcerative colitis (UC)

IBD is more common in urbanised population groups from newly industrialised countries (NIC) of Asia, Africa, and South America, especially India and China, between the ages of adolescence and adulthood [5].IBD affects more than five million people worldwide, and in developed countries, there are roughly twenty-five IBD patients for every 100,000 people [6]. Around 6.8 million people worldwide were affected with inflammatory bowel disease (IBD) in 2017, and the disease's impact is steadily increasing [7].As the IBD population grows and perhaps as a result of an unexpected surge in the death rate during the COVID-19 pandemic, it is predicted that in 2021, the rising prevalence of IBD in Europe and America may level off [5]. IBD age-standardized prevalence increased from 79.5 (75.9-83.5) to 84.3 (79.2-89.9) per 100,000 people between 1990 and 2017, whereas the death rate declined from 0.61 (0.55-0.69) to 0.51 (0.42-0.54) per 100,000 people over that time [8].

Preventing frequent recurrence of inflammation and maintaining remission from inflammatory episodes are the main goals of IBD treatment. Anti-inflammatory medicines (5-aminosalicyclic acid and corticosteroids), immunosuppressive drugs (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine-A, and tacrolimus), and antibiotics (metronidazole and ciprofloxacin) are all part of traditional treatment plans for IBD. The clinical effectiveness of IBD treatment has increased with the introduction of monoclonal antibody-based biological treatments [9]. It has been discovered that prolonged use of conventional drugs can result in major side effects such pancreatitis, allergic responses, nausea, and raised liver enzymes, making it difficult to control IBD, especially in older and vulnerable populations [10]. Colon delivery, which is the specific administration of a medicine to the colon, has also received a lot of interest as an alternate therapeutic option [11]. However, there are several things to keep in mind for this. For instance, the pH levels in each section of the gastrointestinal tract vary, and at unfavourable pH levels, medications may be oxidised, deaminated, hydrolysed, or altogether rendered inactive. Additionally, medications may be sensitive to the GI tract's enzymes, including salivary amylase, pepsin, trypsin in the intestine, gastric lipase in the stomach, and other enzymes produced by the gut's bacteria. The intestinal epithelium's mucus acts as a physical barrier to restrict the administration of medications taken orally. Similarly, the P-glycoprotein are efflux transporters that pump medications out of the GI tract, which prevents the optimal delivery of pharmaceuticals [12].

The common barriers erected by the colon, such as a thick mucus layer, disturbed epithelium, and altered transit time, are removed by drug nanoformulation. The use of new nano-particulate carriers for targeted medication delivery has recently been under investigation and has shown enormous promise for the treatment of IBD. Micro/nano carriers have demonstrated promise for the delivery of drugs to the colon due to their site specificity, increased drug stability through encapsulation, enhanced efficacy, decreased dose frequency, and low side effects [13]. Utilising nanocarriers to carry drugs to the colon increases their bioavailability and reduces the systemic side effects associated with oral and intravenous administration.

Nano-sized carriers (<200 nm) are thought to have higher penetration through the mucus layer as well as enhanced permeability across the inflamed intestinal epithelium in comparison to sub-micron particles [14]. However, the high production costs for synthetic nanomaterials and the resulting adverse effects have limited their use. The so-called biomacromolecules or biopolymers, which are naturally derived nanomaterials, on the other hand, are less hazardous to the environment, safe, and some are currently recognised for use as medicinal excipients [15]. This review paper includes comprehensive discussion on conventional therapy available in contrast to different drug delivery systems available and natural polymers available for the Nanoparticles formulations and comparison with the synthetic polymers available for the management of IBD and future direction of the relevant study.

Pathogenesis and progression of IBD

Inflammatory Bowel Disease (IBD) manifests primarily as prolonged inflammation and damage to the intestinal epithelial layer, displaying varied symptoms across different stages of the disease. Both Crohn's disease and ulcerative colitis share common signs, ranging from mild to severe, including diarrhea, fever, abdominal cramping, blood in the stool, decreased appetite, and unintentional weight loss. Additional symptoms may involve constipation, eye sores or swelling, fistulas, joint pain, mouth ulcers, rectal bleeding, swollen gums, and skin nodules [16]. Distinguishing characteristics between Crohn's disease and ulcerative colitis lie in the location and appearance of inflammatory lesions. Crohn's disease is marked by lesions extending through the gut wall, forming granulomas, ulcerations, and abscesses. Fistulas may develop, connecting affected areas with the bladder, vagina, or rectum. The gut wall develops a cobblestone appearance with scarring and restriction. Ulcerative colitis is characterized by crypt abscesses in the intestinal mucous membrane, bleeding, ulceration, and subsequent scarring during flares [17].

In IBD, active dendritic cells play a role in antigen presentation, stimulating effector T cells' development from immature T cells (Th0). Pro-inflammatory mediators like TNF-α, IL-1, IL-6, cathepsins, and matrix metalloproteinases are secreted in high amounts by activated mucosal macrophages, contributing to inflammation. Proinflammatory monocytes evolve into activated macrophages, producing cytokines that further promote pathogenesis based on environmental cues [18]. The key adaptive immune cells in IBD pathophysiology are T cells, particularly Th1, Th17, and Th2 cells, releasing inflammatory cytokines. Crohn's disease is associated with Th1 and Th17 cells, marked by various cytokines. Conversely, ulcerative colitis exhibits a Th2-mediated response with specific cytokines and reduced levels of IFN-γ. [19]

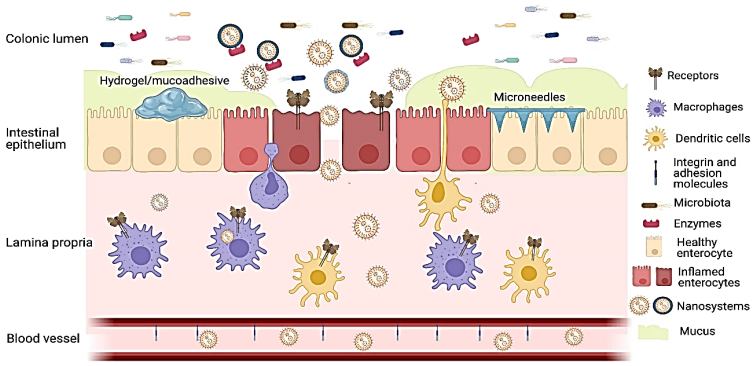

Figure 2: Schematic Diagram of pathogenesis and progression of IBD

Conventional treatment available for IBD:

The primary goal of treating IBD is to achieve and maintain remission while preventing recurrent inflammation [20]. In IBD, there is often compromised intestinal permeability, increased immune cell presence, and altered mucus formation.

Key Treatment Objectives:

1. **Symptom Reduction and Inducing Remission:** Alleviating symptoms to achieve a symptom-free period.
2. **Maintaining Remission:** Sustaining a state without active symptoms.

Anti-Inflammatory Drugs: These are the primary agents for IBD treatment, including **Aminosalicylates (ASAs):** Examples such as Sulfasalazine, Mesalamine, Balsalazine, and Olsalazine effectively reduce inflammation, particularly in ulcerative colitis. Available in various forms like suppositories, enemas, or tablets, they target symptoms such as diarrhea and abdominal pain by mitigating intestinal lining inflammation. Daily use of 5-ASAs is often recommended for long-term therapy, aiding IBD patients in achieving and preserving remission. While generally safe, common side effects may include diarrhea, nausea, vomiting, headache, stomach discomfort, fatigue, weakness, arthralgia, and myalgia [21].

MODULATION OF INTESTINAL MICROBIOTA: ANTIBIOTICS AND PROBIOTICS IN IBD TREATMENT

It's established that individuals with IBD exhibit higher intestinal bacterial counts than their healthy counterparts, with

this microbial burden correlating with disease severity. In Crohn's disease (CD), an imbalance may arise from the dominance of pathogenic bacteria like Escherichia or Shigella over protective species such as Faecalibacterium.

Antibiotics: Broad-spectrum antibiotics like metronidazole, ciprofloxacin, rifaximin, and ornidazole are commonly employed to address this microbial imbalance. Notably, combination therapy involving metronidazole and azathioprine has shown significant efficacy in reducing CD recurrence.

Probiotics: To enhance the therapeutic impact, probiotics are often used in conjunction with antibiotics. This combination aims to restore a balanced environment in the gastrointestinal tract by promoting equilibrium between detrimental and beneficial microbes. This strategy holds promise for optimizing the management of IBD and mitigating disease exacerbations [22].

CORTICOSTEROIDS IN IBD TREATMENT: RAPID RELIEF AND LONG-TERM MANAGEMENT

Corticosteroids, potent anti-inflammatory agents, play a pivotal role in swiftly alleviating IBD symptoms, making them valuable for short-term use. Additionally, they serve as a transitional "bridge" for more effective long-term treatments. By suppressing the expression of cytokine synthesis-related genes, particularly NF-kB, corticosteroids effectively curb the recurrence of inflammatory cells [23]. Commonly employed drugs include prednisone, hydrocortisone, and budesonide (for UC). However, caution is warranted, as prolonged corticosteroid use may lead to severe adverse effects, including osteoporosis, cardiovascular complications, and osteonecrosis. Combining 5-ASA with topical corticosteroids sometimes demonstrates enhanced efficacy compared to monotherapy, offering a multifaceted approach to IBD management.

Thiopurines: Balancing the Immune Response in IBD

Thiopurines, crucial immunomodulators in IBD treatment, step into action once corticosteroids have successfully controlled symptoms. Azathioprine (AZA) and 6-mercaptopurine (6MP) take center stage, exhibiting their potential to alleviate symptoms and, in some cases, induce remission by dampening intestinal inflammation [24]. While the precise mechanism remains elusive, these agents likely impede protein synthesis and lymphocyte multiplication, fostering apoptosis. This orchestrated intervention helps restore immune equilibrium in the gastrointestinal tract. Despite their effectiveness, thiopurines may present mild adverse effects, such as muscle and joint pain, emphasizing the importance of vigilant monitoring during their administration.

Folate Pathways Navigation

Methotrexate (MTX), a potent folic acid antagonist, plays a pivotal role in treating Crohn's Disease (CD) within the realm of IBD therapeutics. Its primary mechanism of action centers around impeding enzymes integral to the folate pathway, disrupting key processes in inflammatory cascades [25]. However, this formidable intervention is not without its challenges. Hepatotoxicity stands out as the primary adverse effect, underlining the need for vigilant monitoring and comprehensive patient care in the pursuit of effective IBD management with Methotrexate.

Biological Therapy (Targeting TNF in IBD)

In the intricate landscape of inflammatory bowel disease (IBD), the role of pro-inflammatory cytokines, particularly TNF, takes center stage. Crafting a therapeutic strategy that hinges on suppressing the immune system to downregulate these cytokines has led to the development of groundbreaking biological therapies. Monoclonal antibodies designed to target TNF, including infliximab, adalimumab, certolizumab pegol, and golimumab, stand at the forefront of IBD management, particularly in Crohn's Disease (CD). Yet, the judicious use of these potent agents faces constraints, marked by adverse effects such as abdominal pain, headaches, diverse infectious events, and the economic considerations associated with these advanced treatments. As we tread the path of precision medicine, balancing efficacy and safety remains paramount in harnessing the full potential of biological therapies for IBD [25].

Cellular Therapy

Venturing beyond conventional avenues, cellular therapy emerges as a promising frontier in the intricate realm of inflammatory bowel disease (IBD) treatment. Diverse techniques, including the application of chlorogenic or regulatory dendritic cells (Reg-DCs), are orchestrated to enhance immune responses, offering a nuanced approach to IBD management. Autologous Hematopoietic Stem Cell Transplantation (HSCT) stands as a beacon in this therapeutic landscape, synergizing with immunosuppressive strategies to curtail receptor loss. Concurrently, mesenchymal stem cells (MSCs), extracted from various tissues, unfold as versatile

players capable of not only differentiating into chondrocytes, adipocytes, and osteocytes but also assuming a regulatory T (Treg) cell phenotype. This dual capability positions MSCs as formidable contenders, exerting control over intestinal inflammation by impeding Th17 cell development and function. As cellular therapy continues to unveil its potential, it beckons a new era of personalized and dynamic interventions in the pursuit of IBD control and remission [27].

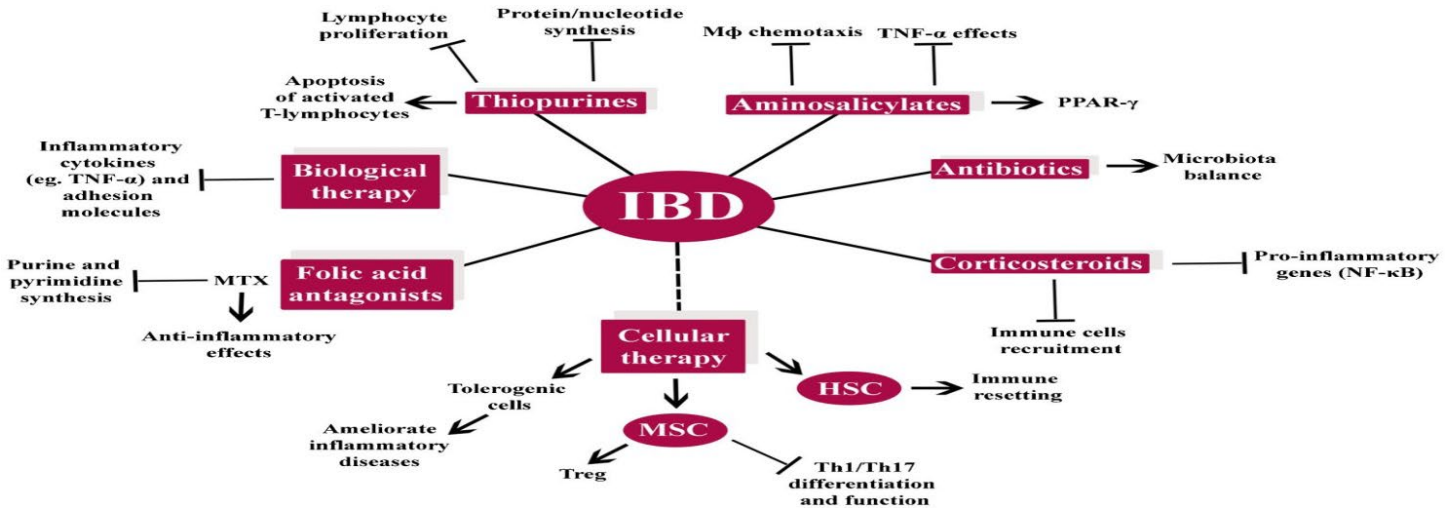

Fig 3: Pathophysiology of Inflammatory bowel disease

Rationality of Designing Nanoparticles for IBD

The landscape of inflammatory bowel disease (IBD) therapy is poised for a transformative shift, acknowledging the limitations of conventional therapeutics. The quest for optimal therapeutic benefits has been hampered by systemic adverse effects and a lack of targeted site-specific delivery. In the realm of IBD, where precision is paramount, the colon emerges as the focal point [28]. Enter Nanoparticle-Based Drug Delivery, a cutting-edge solution designed to surmount these challenges. Encapsulating therapeutic agents within nanoparticles revolutionizes drug delivery dynamics. This approach ensures precise medication delivery to the targeted site, optimizing therapeutic concentration and mitigating adverse effects. The tailored surface properties of these nanoparticles enhance mucosal affinity, strategically positioning the drug for optimal disposition at the inflamed site while minimizing the risk of toxicity. The result is an innovative paradigm that elevates bioavailability, reduces required dosage, and heralds a new era of efficacy in IBD therapeutics [29]. The integration of nanoparticles in drug delivery for inflammatory bowel disease (IBD) hinges on meticulous considerations. Factors such as the choice of chemicals in formulation, particle size, surface charge, ligand attachment, coating with surfactants, route of administration, dose, and dosing frequency play pivotal roles.

In essence, nanoparticles are particulate materials with at least one dimension falling within the 1–1000 nm range. The method employed in their creation significantly influences their size. While conventional dosage forms aim for increased bioavailability throughout the body, the essence of targeted NP drug delivery is to curtail systemic partitioning. Instead, it amplifies bio-distribution to the specific area of concern—in the case of IBD, the intestine.

This shift from conventional medications to targeted NP-delivered drugs offers manifold advantages: heightened disease-fighting efficacy, superior tissue biodistribution, and a reduced impact on healthy organs. The era of precision-driven IBD therapeutics is unfolding, where nanoparticles emerge as crucial agents in reshaping the landscape of drug delivery [30]. 0In recent days, artificially synthesized synthetic targeted nanoparticles have been subjected to safety issues and high manufacturing costs and they are not biodegradable. In contrast, nanoparticles prepared from naturally occurring polymers such as pectin chitosan alginate, etc. are considered as GRAS (Generally regarded as safe) and can be easily metabolized by gut microorganisms which causes reduced toxicity. Polymeric nanoparticles have gained significant interest and significance in the field of drug delivery over the past few decades. They were identified as colloidal systems with 1-1000 nm-sized particles. The diagnosis of IBD has also improved with the introduction of NPs. Dextran-coated NPs have been demonstrated to be effective as CT contrast agents for GI tract imaging in IBD

patients. Since traditional iodinated and barium-based CT agents are not selective for GI tract inflammation, this could be highly helpful [31].

Additionally, polyethylene glycol-based nanocarriers loaded with quantum dots and connected with cell adhesion molecules were developed as useful nanodevices for accurate IBD diagnosis. In the current work, we reviewed various nanomaterials used in the diagnosis and treatment of IBD based on our prior research. Recent developments in nanotechnology have made NPs effective weapons to use in the fierce battle against IBD. In this study, we concentrate on various NPs used in the diagnosis and treatment of IBD.

Natural Polymers used for the preparation of NPs:

Main component of nanoparticles is polymers, surface active agent and aqueous phase. Polymers are the main structural unit of nanoparticles. Properties of polymers like natural polymers mainly chitin, alginate, agarose, gelatin, albumin, lecithin etc. are used to fabricate nanoparticles for their advantages like enzymatic degradation in the colonic environment, ability to accumulate in the targeted organ, biocompatibility, biodegradability and mucoadhesive properties. Natural polymers are readily available, biocompatible, have bio-decomposition qualities, and are simple to modify. The main reasons that biocompatible polymers have gained popularity are because they are affordable, simple to fabricate, and exceptionally durable in biological fluid. In the design of novel molecules for targeted drug delivery applications, biodegradable polymers place a pronounced focus on synthetic chemistry. Natural polymer targets the drug more effectively in a specific tissue or organ due to improved proliferation, adhesion, and target utilization. Biodegradable biomaterials containing natural polymers don't have continuous inflammatory effects, have good permeability, and have good therapeutic effects. The activity of natural polymers depends upon some features such as the delivery of the molecularly specific medication on need, A targeted agent's ability to be used in conjunction with immunotherapy and radiation, and the usage of biodegradable polymers with FDA approval [32].

FUTURE PROSPECTIVE OF NPS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

It is clear from the above that natural polymers like starch, gelatin, and chitosan are no longer only typical excipients for use as binders, disintegrant, or diluents, but are instead being employed in new ways. often used as medicinal medication carriers. Efficiency of release and delivery. variables affect the production of bioactive compounds in these systems. such as molecular weight, drug loading, polymer breakdown, kind of polymer weight, particle size, drug and polymer interactions, and a number of other technological and pharmaceutical considerations. Natural Polymers may not yet benefit from the robustness and accessibility similar to the creation of formulations for synthetic polymers. They are crucial because of their great biocompatibility and safety. A variety of medication delivery methods are being prepared, with the potential for the purpose of achieving the formulator's desired shielded or targeted distribution of bioactive substances.

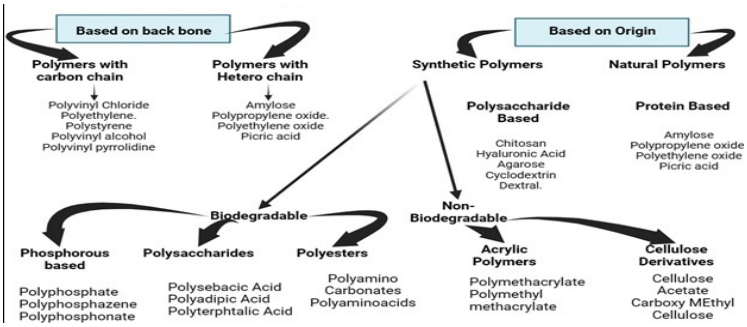

Fig 4: Various types of natural polymers used in Nanoparticulate drug delivery formulations.

Recently, researchers have focused on modifying chitosan and starch for use in nano drug delivery. Using natural polymers could be one approach to prevent the dangers that nano drug delivery might pose. This is due to the fact that natural polymers are often harmless, non-immunogenic, biocompatible, and biodegradable in nature. Therefore, this review examines the most recent developments in the use of three ubiquitous natural polymers such as starch, alginate, and chitosan in nano drug delivery. Brain malignancies may be targeted using starch-coated magnetized iron-oxide nanoparticles.

Magnetic resonance imaging and histopathology findings demonstrated that surface modifications with polyethylene oxide increased transport to cancer cells resulting in a larger concentration of particles in the glioma compared to the rest of the brain. In gene therapy, proteins are also used as nanocarriers. Because injecting naked DNA into live tissue causes enzymatic destruction and limited cellular uptake owing to repulsion between the negatively charged DNA and cell membrane, viral and non-viral vectors are utilized for the transfection of DNA into cells [33].

Even while the potential applications of nanomedicine and nano drug delivery systems are well understood, their actual influence on the healthcare system including cancer therapy and diagnosis remains relatively small. This is explained by the fact that there have only been two decades of substantial study on the topic, making many important basic characteristics still unknown. The idea of precisely releasing certain medications at the affected locations, the technology to evaluate these occurrences, the impact of the medicine at the cellular and tissue levels, and the theoretical mathematical models of prediction are still in their infancy. Many studies in the field of nanomedicine are focused on formulation and biomaterials, which seem to be the first steps towards biomedicine applications. Research involving animals and interdisciplinary teams will yield valuable data that might be used in pharmacological therapy and diagnostic tests. These kinds of studies demand a significant investment of time and resources. The trend towards more targeted medications and diagnostics is becoming more widespread, therefore there is hope for a more sophisticated and multi-faceted approach to nanomedicine and nano-drug delivery technology in the future.

CONCLUSIONS

In conclusion, this manuscript serves as a beacon in the evolution of IBD therapeutics, highlighting the limitations of conventional approaches and propelling us toward the frontier of nanoparticulate drug delivery systems. The strategic integration of natural polymers—chitin, alginate, and chitosan—presents a scientifically robust avenue, promising heightened efficacy and diminished toxicity.

The focus on natural polymers underscores not just their inherent biocompatibility but also their potential for controlled degradation, steering clear of the pitfalls associated with synthetic counterparts. The envisaged future involves meticulously designed therapeutic systems, amplifying drug bioavailability while circumventing undesired effects.

As we anticipate a paradigm shift in IBD management, the manuscript advocates a harmonized synergy among researchers, industries, and regulatory bodies. The convergence of natural polymers and nanotechnology represents a scientific leap toward precision medicine in IBD, promising not just treatments but a fundamental redefinition of therapeutic efficacy. The trajectory ahead holds the promise of a scientifically enlightened era, elevating IBD therapeutics to unprecedented levels of precision and impact.

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Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Ankita Basak, Soumyadip Ghosh, Debgopal Ganguly, Soukat Garain, Riya Ghosh, Ananta Choudhury, Himangshu Deka, and Jahnabi Sarmah, designed the work and made the required corrections and revisions in the manuscript. Soumyadip Ghosh, Debgopal Ganguly, and Ankita Basak corrected that content performed the literature survey, and also contributed to designing the manuscript. All the authors designed the final manuscript.

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