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Review Article

A REVIEW ON PHARMACOLOGICAL AND THERAPEUTIC INSIGHT OF OZANIMOD FOR COLON DISEASE IN NANO-STRUCTURE

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ABSTRACT

Current drug treatments are focused on pharmacological and chemotherapeutical treatment such as controlling the acute and chronic aggravation of diseases, maintaining remission, treating specific complications, and reducing the toxic effects. Several drugs are inappropriate for long-term therapy due to high toxicity levels and the inability to maintain remission of the therapy. An inflammatory bowel disease is a group of idiopathic, chronic, and pathological conditions which pursue protracted relapsing and remitting course cause prolonged inflammation in the gastrointestinal tract, including diarrhea, abdominal pain, bleeding, anemia, and weight loss due to dysregulated immune response. Several drugs have been come to the market to treat inflammatory bowel disease, but they are not potential to the patient due to their higher toxicity rate and low therapeutic activity. Ozanimod is an anti-inflammatory and neuroprotective oral selective modulator of sphingosine-1-phosphate selectively targeting inflammatory bowel disease like ulcerative colitis and Crohn's disease and is also involved in the treatment of multiple sclerosis. There is no serious adverse effect, as well as adverse events such as cardiac events, serious infections, or macular edema, was found in the treatment of inflammatory bowel disease. The conventional drug delivery of ozanimod has severe adverse effects, which can be reduced by nanocarrier and stability and bioavailability can be enhanced. This review discusses the Pharmacological and therapeutical insight of Ozanimod for targeting inflammatory bowel diseases like Ulcerative colitis and Crohn's disease as well as Multiple Sclerosis and the importance of nanocarriers for Ozanimod to target the colon region and recent advancement technology introduced to Ozanimod.

Keywords: Ozanimod, Inflammatory bowel disease, Sphingosine-1-phosphate receptors, Colon targeted drug delivery systems, Multiple sclerosis, Recent advancement

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INTRODUCTION

Colon diseases refer to the variety of pathological and physiological abnormalities occurred in the smooth muscles that result in clinical syndromes of disorder of small intestinal and colonic motility. An inflammatory bowel disease is a group of idiopathic, chronic, and pathological conditions which pursue protracted relapsing and remitting course cause prolonged inflammation in the gastrointestinal tract, including diarrhea, abdominal pain, bleeding, anemia, and weight loss due to dysregulated immune response. Untreatable inflammatory bowel disease getting a global healthcare problem because of continuously increasing incidence. Research study shows that approximately 6.8 million people suffered from inflammatory bowel disease and 1.6 million Americans are under inflammatory bowel disease, including kids and teenagers and growth of about 200,000 since last year [1]. The highest rate of inflammatory bowel disease can find out in developed countries rather than the developing countries and colder climates and urban areas have greater rates of inflammatory bowel disease than warmer climates and rural areas. Inflammatory bowel diseases have two classes such as ulcerative colitis and Crohn's disease [2].

Ulcerative colitis mainly represents inflammation occurred in the rectal and sigmoid colon, which refers to 40 to 50% of proctitis (inflammation of the lining of the rectum and lower end of the large intestine leading to the anus) and in the case of Crohn's disease, cecum, and ileum as ileocecal area (40% of cases) as well as the small intestine (30-40% of cases) inflammation takes place [3]. Ulcerative colitis and Crohn's disease have different conditions but they have some common symptoms. Crohn's disease mainly occurred in the last part of the small intestine as the ileum and the first part of the colon and can cause blockage in the intestine ulceration (sores) in the intestinal tract. The symptoms of Crohn's disease as diarrhea (sometimes bleeding), abdominal pain, cramping, fever, and fatigue. Ulcerative colitis mainly affected the mucosal lining of the large intestine, especially all three layers of the bowel wall. The symptoms of abdominal pain, fever and cramping, loose and bloody stools, fatigue, loss of appetite, and anemia can increase the formation of holes in the colon, liver disease, blood clots, and osteoporosis. The pathogenesis of inflammatory bowel disease is still unknown and several factors have been noticed, such as genetic, environmental, and immunological factors [4, 5].

Current drug treatments are focused on pharmacological and chemotherapeutical treatment such as controlling the acute and chronic aggravation of diseases, maintaining remission, treating specific complications, and reducing the toxic effects. Several drugs are inappropriate for long-term therapy due to high toxicity levels and the inability to maintain remission of the therapy. Drug delivery to the appropriate site with maintaining the proper therapeutic activity with less toxicity level and improved drug delivery to the target site is the major challenge to the current developers.

Several drugs have been come to the market to treat inflammatory bowel disease but they are not potential to the patient due to their higher toxicity rate and low therapeutic activity [6]. Recently approved medications have focused on immune systems suppressed with non-specific inflammatory or immunosuppressant or various biologics drugs targeting pro-inflammatory cytokines or integrins (receptors used by the animal cell to bind the extracellular matrix) [7]. To the treatment of inflammatory bowel diseases, oral immunomodulators have less effectiveness and delay onset action with low bioavailability and in the case of biologics as given through parental route, have severe adverse reactions such as opportunistic infection and lymphoma. We need a kind of drug in an oral formulation that would be highly effective, safe, high bioavailability, and well-tolerated in patients with chronic immune-mediated diseases [8].

Sphingosine-1-phosphate receptors have the effectiveness on the immune-mediated inflammatory disorder, specifically ulcerative

colitis and multiple sclerosis, because of inflammatory bowel disease characterized by recirculation and accumulation of auto-reactive lymphocytes. Sphingosine–1–phosphate has several functions like controlling chronic inflammation by regulation of lymphocyte movement, heart rate, tonicity of smooth muscle, and various endothelial function by proliferation, migration, rearrangement of cytoskeleton, adhesion, inflammation, and rational target to immune-pathologic process associated with diseases. Selective sphingosine–1–phosphate receptor mainly blocks the lymphocyte egression from the lymph node and thymus, which helps to the reduction of circulating lymphocyte resulting inflammation cell infiltration in central nervous systems [9-11].

Most of the drugs are targeted to sphingosine–1-phosphate receptor to reduce inflammation such as ozanimod (ulcerative colitis, multiple sclerosis), ponesimod (chronic plaque psoriasis), amiselimod and etrasimod (ulcerative colitis), cenerimod (Systemic lupus erythematosus), and they are involved in the treatment of autoimmune diseases like Crohn's disease, atopic dermatitis, and alopecia areata. Fingolimod was the first oral non-selective modulator of sphingosine–1-phosphate analog drug approved for the treatment of relapsing-remitting of multiple sclerosis and inflammatory bowel diseases with good efficacy, tolerability, and convenient route of administration which have been key to the success of this drug. But due to the non-selectivity interaction with sphingosine-1-phosphate leads to severe adverse effects and adverse events such as hypertension, macular edema (build-up of fluid in the macula, an area of the center of the retina), pulmonary toxicity, hepatotoxicity, and hypertension [12-14].

Ozanimod is an anti-inflammatory and neuroprotective oral selective modulator of sphingosine-1-phosphate selectively targeting inflammatory bowel disease like ulcerative colitis and Crohn's disease and is also involved in the treatment of multiple sclerosis. There is no serious adverse effect, as well as adverse events such as cardiac events, serious infections, or macular edema, was found in the treatment of inflammatory bowel disease. Ozanimod targeting to multiple sclerosis and inflammatory bowel disease by regulating multiple events such as endothelial barrier integrity, lymphocyte trafficking, reduction of inflammation, and neurodegenerative brain lesion with less effect on heart rate and liver enzymes [15, 16].

Ozanimod is a BCS class I (high solubility, high permeability) drug developed by Celgene (now acquired by Bristol-Myers Squibb) and was approved by the USFDA (US Food and drug administration) on March 26, 2020. In November 2021, Ozanimod was also approved by European Commission for the treatment of adults with relapsing-remitting multiple sclerosis. According to FDA, Ozanimod can be administered an oral dose of 0.92 mg once a day for treating inflammatory and multiple sclerosis, which is under phase III trial. Before ozanimod, several drugs come to the market with high adverse events. Trial shows that ozanimod is the most preferred drug than others (fingolimod, ponesimod, etrasimod, amiselimod) to treat inflammatory bowel disease and multiple sclerosis with interferon beta-1a because of its high effectiveness and less frequency of an adverse event [17, 18].

Search criteria

This review was made after reviewing approximately 80 articles from 1995-2022, which were found on electronic database systems like google scholar, PubMed, Science Direct using keywords like ozanimod, ozanimod therapy, and treatment, ozanimod, and applications, treating diseases through ozanimod, etc. After analyzing all articles, few articles were found to be effective for the study about ozanimod in pharmacological and therapeutical efficacy in treating colonic diseases. Then a comparative study is presented in this review to make it more informative and relevant.

Chemical class

IUPAC name of ozanimod is 5-[3-[(1S)-1-(2-hydroxymethyl amino)-2,3-dihydro-1H-inden-4-yl]-1,2,4-oxadiazol-5-yl]-2-propane-2-yloxybenzonitrile and have some Physico-chemical characteristics such as half-life in the range of 17-21 h., the melting point of 134-137 ^{0}C, boiling point 648.3±65.0 ^{0}C and 100% bioavailability with oral administration [19, 20].

Pharmacological properties

After orally administered, ozanimod exhibits linear pharmacokinetics with dose-proportional increases and shows low to moderate inter-subject variability. It is showing a delayed absorption rate after the first dose due to changing the heart rate and high volume of distribution peak plasma concentration is low. It has a high volume of distribution with high protein binding capacity (>95%), attains a steady-state within 7 d, thus leading to low systemic exposure, and is eliminated through urine (26%) and feces (37%). The study says that there is no such food-drug interaction, but food containing tyramine leads to increasing the risk of severe hypertension because of sensitivity towards tyramine. It is contraindicated to a patient who is suffering from myocardial infarction, angina pectoris, stroke, transient ischemic attack and type III/IV congested heart failure and presence of Mobitz type II second degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or Sinoatrial block, patients with pacemaker. It can't use during taking of monoamine oxidase (MAO) inhibitor and patients with sleep apnea [21, 22].

Ozanimod is a sphingosine-1-phosphate receptor(S1PR) modulator agonist of sub-type of 1 and 5 (S1PR1 and S1PR5) that reduces the circulating lymphocyte count by inhibition of lymphocyte egress from lymph node when interaction with S1PR. Thus, help in the reduction of debilitating symptoms and possibly disease progression. A trial report shows that ozanimod also acts as a neuroprotective agent that can cross easily the blood-brain barrier and it's a beneficial effect on the brain by direct establishing interaction with brain cells through S1PR5 signaling [23, 24].

Mode of action

Mechanism of action of ozanimod for the treatment of ulcerative colitis still unknown; ozanimod is an orally bioavailable, small molecule that can act on sphingosine-1-phosphate receptor modulator specifically target S1PR1 and S1PR5. It helps to reduce the number of circulating lymphocytes by promoting the receptor internalization and degradation when active against the S1P1R receptor. It works on certain types of immune cells called lymphocytes which are centrally concerned in the auto-immune attack on myelin sheath and bind with local receptors present on the cell surface, helping to move toward the brain, which leads to diminishing the immune attack by reducing of B and T cell lymphocytes from lymph nodes. It binds with the S1PR1 receptor to block the source of inflammation in relapsing multiple sclerosis and inflammatory bowel disease. It can cross blood-brain barriers and modulation of the S1P receptor on microglia, oligodendrocytes, astrocytes, and neurons are proposed to have beneficial to the reduction of inflammation due to multiple sclerosis and inflammatory bowel disease [25, 26].

Pharmacological action of ozanimod in colon diseases

Ulcerative colitis and Crohn's disease have major differences as they have common symptoms with different conditions. Crohn's disease refers to the blockage in the intestine and ulceration in the intestine and it is mainly affected to the lower part of the intestine and the first part of the colon. Several symptoms can be seen in Crohn's disease, such as abdominal pain, fatigue, cramping, fever, and diarrhea. The symptoms of ulcerative colitis such as abdominal pain, fever, cramping, loose and bloody stools, fatigue, loss of appetite, and anemia and can increase the formation of holes in the colon, liver disease, blood clots, and osteoporosis [28].

Advancement of ozanimod in colon targeting drug delivery system

Colon-targeted drug delivery can be defined as the drug release at particular PH in the colon region without premature drug release maintaining the high local concentration with low dose frequency with proper therapeutic effectiveness and low adverse effects. Several drugs come to market with severe adverse effects as well adverse events, which increase patient compliance day by day. The Sphingosine-1-modulator as ozanimod has several advancements and makes itself different from other medicine by various characteristics as Ozanimod directly targets the local site and shows proper therapeutic effectivity. It can easily cross BBB (Blood-brain barrier) to reduce inflammation due to several chronic diseases. A

low dose is enough to exert therapeutic activity particularly multiple sclerosis and Inflammatory Bowel Disease. Improvement of drug utilization at the target region. Through colon targeted drug delivery of ozanimod gastric irritation not occurred at gastrointestinal tract. Patient compliance can be reduced and treatment efficacy is more than other drugs present in the market [29, 30].

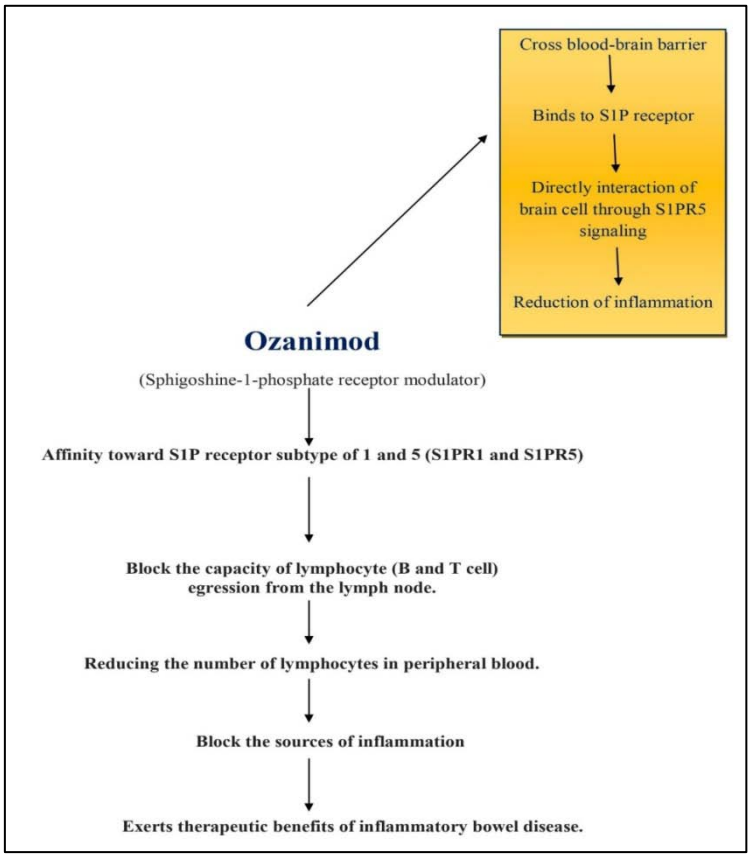

Fig. 1: Flow chart representation of the mechanism of action of ozanimod [27]

Studies conducted on ozanimod for colon diseases

Brian G Feagan, William J Sandborn, *et al.*, did a study on ozanimod induction therapy for patients with moderate to severe Crohn's disease on single-arm, phase 2, prospective observer-blinded endpoint study. All patients started treatment with a 7-day dose escalation (4 d on ozanimod 0·25 mg daily followed by 3 d at 0·5 mg). Patients received ozanimod 1·0 mg oral capsule daily for a further 11 w, for a 12-week induction period, followed by a 100-week extension. The primary endpoint was a change in Simple Endoscopic Score for Crohn's Disease (SES-CD) from baseline to week 12, as determined by a blinded central reader. Data are reported for the intention-to-treat population. This trial is registered with ClinicalTrials. gov, number NCT02531113 and EudraCT, number 2015–002025–19, and is completed [31].

Giancarlo Comi, Ludwig Kappos, *et al.*, did an investigation on the Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM) with a multicenter, randomized, minimum 12-month, phase 3 trial. These 3 trials were done at 152 academic medical centers and clinical practices in 20 countries all over the world. Done study on the age group in the range of 18-55 with relapsing multiple sclerosis, baseline expanded disability status scale (EDSS) score of 0·0–5·0, and either at least one relapse within the 12 mo before screening or at least one relapse within 24 mo plus at least one gadolinium-enhancing lesion within 12 mo before screening. Participants were randomly assigned 1:1:1 by a blocked algorithm stratified by country and baseline EDSS score to at least 12 mo of treatment of either once-daily oral ozanimod 1·0 mg or 0·5 mg or weekly intramuscular interferon beta-1a 30 µg. Participants, investigators, and study staff were masked to treatment assignment. The primary endpoint was annualized relapse rate (ARR) during the treatment period and was assessed in the intention-to-treat population. Safety was assessed in all participants according to the highest dose of ozanimod received. This trial is registered at ClinicalTrials. gov, number NCT02294058 and EudraCT, number 2014–002320–27 [32].

William J. Sandborn Bryan G. Feagan, *et al.*, did a study on the long-term efficacy and safety of Ozanimod in Moderately to severely active ulcerative colitis and results from the open-label extension of a randomized phase 2 touchstone study. Patients receiving placebo or ozanimod HCl 0.5 mg or 1 mg during the double-blind period could enter the OLE [ozanimod HCl 1 mg daily]. Partial Mayo score [pMS] clinical response and remission were assessed through OLE week 200 and summarized descriptively using observed cases [OC] and non-responder imputation [NRI]. Endoscopy was required at OLE week 56 and the end of treatment. Parameters associated with endoscopy were summarized at weeks 56 and 104 [OC], and week 56 [NRI]. C-reactive protein and fecal calprotectin were assessed. Adverse events were monitored throughout the study. 197 patients receiving double-blind treatment, 170 entered the OLE. Discontinuation rates were 28% at year 1 and 15–18% annually through year 4. Partial Mayo measures indicated clinical response and remission rates at OLE week 200 of 93.3% and 82.7%, respectively, using OC and 41% and 37% with the more conservative NRI analysis. At weeks 56 and 104, respectively, histological remission rates were 46.3% and 38.5%, and endoscopic improvement rates were 46.4% and 46.5% [OC]. No new safety signals were identified during ≥ 4 y of follow-up [33].

Various approaches for colon targeted drug delivery systems

Ozanimod is targeting to colon region it follows several approaches for successful targeting, particularly Inflammatory bowel diseases

such as Ulcerative Colitis and Crohn's disease and multiple sclerosis. Ozanimod drug should not be premature released in the upper GI tract and not be broken down in the strong acid present in the stomach and have to disintegrate in the colonic environment at particular pH and reaching to the target site[31]. Various approaches have been developed to achieve colonic targeting area as follows–

pH-dependent drug delivery approach

Due to different pH environments (stomach–1.5-3.5, small intestine–5.5-6.8, and colon 6.4-7.5), drugs must have to stable in the stomach and small intestine and need to release in the colonic environment. That's why polymer materials are used to coat the drug, which helps to stabilize the drug and release it at particular pH.

Table 1: pH-dependent polymers

Polymer	pH
Eudragit L 100	6.0 [34]
Eudragit S 100	7.0 [35]
Eudragit L-30D	5.6 [36]
Polyvinyl Acetate phthalate	5.0 [37]
Hydroxy-propyl methylcellulose phthalate	4.5-4.8 [38]
Polyvinyl acetate phthalate	5.0 [39]
Cellulose acetate trimellate	4.8 [40]

Time-dependent drug delivery approach

The time-dependent drug delivery approach is also known as delayed or sustained, the pulsatile release which occurred after the pre-determined lag time (time for transit from mouth to colon). The time-dependent formulation is consisting of pH-dependent polymers because it is influenced by the gastric transit time and it depends upon the size of the particle and gastric motility [41].

Bacteria dependent drug delivery approach

GI microflora played an important role in metabolism. Microflora release enzymes that help to metabolize both endogenous and exogenous materials such as carbohydrates, proteins substance by breaking their internal bonds. Microflora secrets such enzymes like glucuronidase, azoreductase, deaminase, and urea dehydroxylase. Bacteria-dependent drug delivery approach consists of a prodrug, coating with biodegradable azo compound, hydrogels, Polysaccharides as carriers [42].

Ozanimod in nanostructure

In the treatment of Inflammatory bowel disease as Ulcerative Colitis and Crohn's disease and also Multiple Sclerosis pharmaceutical dosage forms are showing instability, solubility issue, low absorption at targeting site, low site-specificity, shorter half-life, the large volume of distribution in the systemic circulation, and low therapeutic windows leads to drugs showing low therapeutic efficacy with the high adverse effect that problem can be overcome through targeted drug delivery system as nanocarrier [43, 44].

Table 2: Convenient delivery system for ozanimod

Conventional drug delivery system	Targeted polymeric drug delivery system
Affect healthy tissues or organs	Don't [45]
Non-specific	Specific [46]
Low bioavailability	High bioavailability and biocompatibility [47]
Lower efficacy	Efficacy is high [48]
Lower therapeutic effect	The therapeutic effect is high [49]
High toxicity	Low toxicity [50]
A high dose is required	Required low dose [51]
Chances of side effects are high	Chances of side effects are low [52]

Nanocarriers show some ideal characteristics which influence the ozanimod drug to target inflammatory bowel diseases and multiple sclerosis as toxicity can be reduced after targeting to specifically target region leading to reduction of adverse effects as well as adverse events. Drug absorption rate at the target site can be enhanced leads to enhancement of bioavailability. The dosing frequency of ozanimod would be less compared with the conventional drug delivery system of ozanimod. Drug leakage can be reduced through nanocarriers. The release rate can be controlled and predictable. Through nanocarriers, formulation bypass first-pass metabolism. Target selectivity toward disease site [53, 54].

Convenient route of administration for ozanimod

The oral route is the most preferred route for conventional drug delivery systems to the colonic environment. Oral administration is most convenient in the treating of colonic diseases such as ulcerative colitis, Crohn's disease, amoebiasis because targeting region concentration can be achieved, reducing side effects because of unnecessary systemic absorption can be overcome. Compare to the parenteral route, the oral route is the best convenient for patients because avoidance of pain and possible contamination through injection and self-administration could not possible in parenteral preparation.

In another route of administration to targeting the colon as the Rectal route of administration is not suitable for targeting local diseases. The rectal route may provide the shortest route for targeting the colon but it has difficulty in administration and is very tough to reach the proximal part of the colon. The Rectal route of administration is very uncomfortable for patients and that's the biggest disadvantage of the rectal route [55]. The topical application may provide therapeutic efficacy but the time to reach the concentration in the colonic environment is more; that's the drawback of topical formulation to targeting local treatment of colonic diseases.

Table 3: Convenient route of administration for ozanimod

Topic	Oral	Parenteral	Rectal	Topical
First-pass metabolism	Attained	Not attained	Not attained	Not attained [56]
Painful administration	No	Yes	No	No [57]
Onset of time	Slow	Fast	Fast	Fast [58]
Dose requirement	High	Small	Small	Small [59]
Patient compliance	Less	More	More	More [60]
Bioavailability	Compare to parenteral less	100% (Parenteral>oral>rectal>topical)	Compared to oral less	Compared to rectal less [61]

Future prospect of ozanimod

Nanocarrier provides target specificity at the target site and shows proper therapeutic efficacy with fewer adverse effects and enhancement of bioavailability leads to a high absorption rate compared to conventional drug delivery systems. Though the conventional drug delivery system of ozanimod can be severe side effects and enhancement of toxicity level, that problem can be decreased by introducing nanocarrier to the ozanimod drug. After encapsulated drug in nanocarrier contraindication of tyramine can be reduced and absorption can be enhanced and local as well as therapeutic concentration can be achieved and also bioavailability and dosage administration frequency reduced through Nanocarrier of ozanimod [62, 63].

CONCLUSION

Ulcerative colitis mainly represents inflammation occurred in the rectal and sigmoid colon, which refers to 40 to 50% of proctitis (inflammation of the lining of the rectum and lower end of the large intestine leading to the anus) and in the case of Crohn's disease, cecum, and ileum as ileocecal area (40% of cases) as well as the small intestine (30-40% of cases) inflammation takes place. Ozanimod is an anti-inflammatory and neuroprotective oral selective modulator of sphingosine-1-phosphate selectively targeting inflammatory bowel disease like ulcerative colitis and Crohn's disease and is also involved in the treatment of multiple sclerosis with high target specificity with high therapeutic activity and low adverse effect. The conventional drug delivery of ozanimod has severe adverse effects, which can be reduced by nanocarrier and stability and bioavailability can be enhanced. The main motto of this article is a pharmacological and therapeutical insight of ozanimod in the treatment of colonic diseases and various advanced strategies applied in the treatment of inflammatory bowel diseases to get proper therapeutic efficacy with less adverse effects.

CONSENT FOR PUBLICATION

Not applicable

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AUTHORS CONTRIBUTIONS

Soumyadip Ghosh, Debgopal Ganguly, Subhabrota Majumder designed the work and revisions in the manuscript. Soumyadip Ghosh provided maximum effort in the correction, collect documents, makes proper format. Debgopal Ganguly did a proper literature survey and designed the manuscript. Subhabrota Majumder helped in the correction and provided important data. All the authors design the final manuscript.

CONFLICT OF INTERESTS

Declared none

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