Available online on 15.06.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Review Article

# Retropharmacology of Gliptins: A Focus on Inflammatory Bowel Disease

**Srikanta Chandra[1]*, Avik Das[2] , Jyotirmay Samanta[3] , Tathagata Ray[4], Lucky Mukherjee[5], Bijayan Mukherjee[6]**

1 Gupta College of Technological Sciences, Department of Pharmacology, Asansol, West Bengal, 713301

2 Assistant Professor of Gupta College of Technological Sciences , Department of Pharmacology , Asansol , West Bengal , 713301

3 Assistant Professor of Genex College of Pharmaceutical Science & Technology, Department of Pharmacology, Chinsurah, West Bengal, 712102

4 Department of Pharmaceutical Technology, JIS University, Kolkata West Bengal, 700109

5 Bengal College of Pharmaceutical Science & Research, Durgapur, West Burdwan, West Bengal, 713212

6 NRS Medical College, Department of General Medicine, Kolkata, Entally, West Bengal, 700014

## ABSTRACT

As we know inflammatory bowel disease is an emergent plight in developed & developing countries. IBD is an idiopathic ulceroinflammatory condition of the bowel which may or may not have transmural stretch. IBD has two clinic pathological condition Ulcerative colitis & Crohns's disease. In United State of America there are 1.4 million of people suffering from Ulcerative colitis. IBD has a plethora of comorbid disorders .Gastrointestinal disorder arising from cholelithiasis, cutaneous disease arising from psoriasis & metabolic disorders arising from diabetes mellitus. DPP4 which is instrumental in aggravating diabetes mellitus gets hiked in IBD too , which may have serious implications in the worsening of the latter in diabetes . Hence, in our research we probed for the anticolitic potential of a standard inhibitor of DPP4, Linagliptin to ensure the enzymes suitability as a probable target for IBD.

**Keywords:** IBD: Inflammatory Bowel Disease, UC: Ulcerative colitis, CD: Crohn's disease

**Article Info:** Received 01 May 2019; Review Completed 09 June 2019; Accepted 10 June 2019; Available online 15 June 2019

**Cite this article as:**

Chandra S, Das A, Samanta J, Ray T, Mukherjee L, Mukherjee B, Retropharmacology of Gliptins: A Focus on Inflammatory Bowel Disease, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):1013-1018

**http://dx.doi.org/10.22270/jddt.v9i3-s.2933**

***Address for Correspondence:**

Srikanta Chandra, Gupta College of Technological Sciences, Department of Pharmacology, Asansol, West Bengal, 713301

## Introduction

Inflammatory Bowel Disease (IBD) is looming large on the modern society which has raised the brows of the medical scientists in both the developed and developing countries . According to American Gastrological Society (AGS) Inflammatory Bowel Disease is defined as acute or chronic idiopathic ulceroinflammatory condition of the bowel which may or may not have transmural stretch .IBD has two encompasses pivotal kinds of pathological condition one is Ulcerative colitis (UC) another one is Crohn's disease (CD) .Ulcerative colitis is a chronic ulceroinflammatory condition primarily confined within colonic mucosa with variable distortion of the colonic architecture .Where as Crohn's disease (CD) is a chronic ulceroinflammatory condition analogues to ulcerative colitis but having a transmural infestation . Epidemiologically IBD has greater prevalence in the global prospective .So we decided to zero in on IBD in our work ahead . As suggested in the literature the course of the IBD is often complicated due to the multifactorial etiology under pinning the condition which demands closer overview . The pivotal contours may be featured astoxic megacolon , pseudopolyps and backwash ileitis . The featured encountered in the clinical course of the disease are multiferrous spanning from rectal bleeding , weight loss abdominal pain and malaise [1]. Coming to the option available for management they include both non pharmacological aspects and pharmacological aspects . Under non pharmacological aspects life style changes like monitored dieting , exercise plays a desire role in the therapy and psychological intervention also deployed to control the functional aspects of the disease . On the other hand Salfasalazine and Infliximab are still considered as a corner stone of the therapy as per as pharmacological aspects .[2] So a through search of available literature are also brought forward an important aspects which still now has remain largely on the flanked. IBD as can be conjured up is also associated with a plethora of comorbid disorders which

includes gastrointestinal disorders arising from cholilethiasis , cutaneous disease like psoriasis and metabolic disorders like diabetes mellitus . Since , Salfasalazine , Balsalazide , Infliximab are having a limitation such as hypersentivity reaction , adrenal suppression , nausea , vomiting , weakness etc[3] .Hence , we found a good rational behind probing for the anticolitic potential in our pipeline drugs that's gliptins .

## Epidemiology

There is wide variation between the incidence rates of inflammatory bowel disease (IBD) . In Europe country incidence rates range from 4.1/100,000 (Romania) to 81.5/100.000 .In Asia and the middle east incidence was lower 0.1-6.3/100.000. On the other hand USA the incidence is having intermediates rates ranging from 0 to 19.2/100.000 population. However, currently in Sweden 61,000 patients are suffering from Inflammatory Bowel Disease(IBD) . In Brazil an epidemiological study conducted by the Botucatu Medical School evaluated the incidence and prevalence of Inflammatory bowel disease in micro region of Sao Paulo State. Since , in India the first such study was conducted by Khosla et al., in the year of 1984 at Haryana in North India[4]. The study included 21,971 participants and noted a prevalence of 42.8 Ulcerative colitis (UC) patients. The next study which is conducted in 15 years later by Sood et al., from Punjab . However, incidence was calculated after 1 year later and was reported to be 6.02/100.000 . The crude overall incidence of Inflammatory bowel disease (IBD) , Ulcerative colitis (UC) and Crohn's disease(CD) from Asia was 1.37,0.76 and 0.54 per 100.000 where as in Australia it was 23.67,7.33 and 14.00 respectively bin . Data from western Asia including studies from Kuwait , Turkey and Israel revealed an incidence rate of 2.8/100.000 and 5.04/100.000 in Kuwait and Israel respectively bin.[5] However , the prevalence of 4.9/ 100.000 and 167/100.000 in Turkey and Israel respectively bin. The prevalence of Crohn's disease (CD) in japan appears to have risen very rapidly from 2.9/100.000 individually in the year of 1986 to 13.5/ 100.000 . quadrupled from 7.57 /100.000 individually in 1997 to 30.87/100.000 individuals in 2005.Over a period of 9 years the prevalence of Ulcerative colitis in Hong kong nearly tripled from 2.36/100,000 individuals in 1997 to 6.30/100,000 individuals in 2006. Crohn's disease prevalence in Singapore also increased markedly from 1.3/100,000 individuals in 1990 to 7.2 /100,000 individuals in2004.The geographical variation is more common for inflammatory bowel disease (IBD) . However , in Sweden and Netherlands pediatric patients who are suffering from Ulcerative colitis that is more common rather than Crohn's disease (CD) .Since , the most instrumental point is that Crohn's disease become more active rather than Ulcerative colitis in Sweden. In Scotland Crohn's disease is not unknown rather than England . In Asian countries specially in India subcontinent the shadow of inflammation bowel disease (IBD) is looming large on the society through the recent past. Crohn's disease may shown below the age of 20-25 years varies between 25-40 % it also affect both sex boys and girls .[6] In South Indian boys are more effected on Crohn's disease rather than South Indian girls. Most studies reporting the incidence of CD (3/5) were from the United Kingdom ,with a predominant SA migrant group . The remaining two studies from Canada described the SA paediatric population and one study compared non – immigrants to SA . The incidence of CD in SAs was consistently lower than Caucasian ,except for one Canadian paediatric study .The Benchimol study showed a lower incidence in SA compared to other groups within the same environment .The two United Kingdom studies where the incidence was examined over two time periods showed an increase in the incidence of CD in the SA population ,from 1.2 to 2.3/100000 in East London and 1.2 to 3.1/100000 in Leicester .The last migrant United Kingdom incidence studies were published in 1989.[7]

## Pathophysiology of Inflammatory Bowel Disease (IBD): A General Overview

Epidemiologically ulcerative colitis (UC) has a greater prevalence in the global prospective . so , we decided to zero in on ulcerative colitis in our work ahead. As suggested in the literature the course of ulcerative colitis is often complicated due to the multifactorial etiology under pinning the conditions which demands closer overview The pivotal contours may be featured as toxic megacolon , pseudopolyps , and backwash iletis. .Toxic megacolon evolve from the stalling of the fecal movement of the colonic lumen due to the spasticity arising from the wide spread neural damage in the region associated with microbial over growth . However, in ulcerative colitis there is wide spread destruction of the luminal wall which leads to formation epithelium bulges obstructing the lumen these are commonly termed as pseudopolyps . On the other hands a common featured essentially associated with pancolitis in which the lesions spread beyond the confinds of ileocecum junction this is known as backwash ileitis.[8] Inflammatory bowel disease (IBD) is a multifactorial disorder characterized by chronic inflammation of the intestine . Since the pivotal point is that disturbance of the immune system or imbalanced interactions with microbes leads to amelioration of chronic intestinal inflammation.Th1 cells play a role in the pathogenesis of Inflammatory bowel disease (IBD) is related to chrocity of intestinal inflammation where as Th2 cells play a role in the pathogenesis of Crohn's disease (CD) However, after activation of Th17 / regulatory T (Treg cells) are pivotal component which is helped to build up intestinal inflammation. Since , Tumor necrosis factor( TNF) are plays a instrumental role to identify the pathogenesis of Inflammatory bowel disease (IBD) .[9] The intestinal epithelium cells contains different types of cells namely enterocyte , goblet cell , neuroendocrine cell , M cell or mother cell and epithelium resident intestinal stem cells. These cell structurally constitute crypts and villi . A single columnar cell lining with a tight junction and secrete mucus containing antimicrobial peptides, to protect mucosa , a mucus layer is present which is covered by epithelial surface . However, this epithelium mucus layer is composed of glycosaylated mucin, mucin from goblet cells . Since , mucin is encoded by Muc 2. However, genetic factors plays a role so here mutation of NOD2 gene is a instrumental point in the pathogenesis of inflammatory bowel disease (IBD) .[10] The intestinal epithelium which is a pivotal part of the innate immune system and play a role in the maintenance of mucosal homeostasis. Epithelium cells are very tight and highly selective between periphery and intraluminal microenvironment . Briefly , the chief determinant of the course of pathology include intestinal microbiota , intestinal epithelium dysfunction and aberrant mucosal immune response . However, chromosome 5 containing SLC222A4 and SLC22A5 also shows some aberrations in patients suffering from Crohn's disease (CD) .[11]In the modern era microbial profiles at various stages of colitis have been described and characterized that depend on the time and area within the gastrointestinal tract. It is not yet entirely clear whether changes in the composition of the microbiota are the cause or consequence of inflammatory process in the intestinal tissue. Since , the most consistent change observed among the vast majority of inflammatory bowel disease (IBD) patients is a decrease in intestinal microbiota

diversity , with slightly different findings between ulcerative colitis (UC) and Crohn's disease ( CD) patients .Since , in Crohn's disease ( CD) a decrease in Formicates is often observed , including butyrate –producing bacteria namely Faecalibacterium prausnitzii . This leads to over production of proinflammatory cytokines and downstream events. In Ulcerative colitis (UC) , several other groups of bacteria besides butyrate producing Firmicutes are often reduced , including Bacteriodes and Clostridium genera [12]. On the other hand , Enterococcus and Gamma proteo bacteria are found in higher amounts in fecal samples from Ulcerative colitis (UC) patients .Although the interaction between the host and intestinal microbiota seen to plays a crucial role in the pathogenesis of inflammatory bowel disease (IBD) .Since , a significant amount of IBD patients do not achieve clinical remission after conventional therapy , there is legitimate need for new therapeutic approaches

## Treatment of Inflammatory Bowel Disease (IBD) & Emerging Challenges:

Inflammatory bowel disease ( IBD) is looming large on the modern society which has raised the brows of the medical scientists in both the developed and developing countries. IBD has two clinicopathological condition Ulcerative colitis & Crohn's disease .Coming to the option available for management they include both non pharmacology aspects and pharmacology aspects . Under the non-pharmacological aspects lifestyle changes like monitored dieting and exercise may play a desire role in the therapy and psychological intervention also a deployed to control the functional aspects of the disease. On the other hand sulfasalazine and mesalamine are still considered as corner stone of the therapy as per as pharmacological aspects are concern they may be deployed as step up and top down schedule. However, mesalamine is still the preferred one because of better side effect profile. Salfasalazine have play a role in the treatment of inflammatory bowel disease . This prototype drugs are contain mesalamine and sulfapyridine moieties. However , Mesalamine having an active site in colon show the effectiveness in the distal ileum. On the other hand in the modern era 45% patients are taken salfasalazine but pivotal point is that it shows emergent nuance namely hypersensitivity reaction. Dose related adverse effects are nausea , vomiting , headache . However, bone marrow suppression and hepatitis are very common nuance of Salfasalazine . In the modern days steroidal drugs play a role in the treatment of inflammatory bowel disease . Corticosteroids are used as a step up therapy in the treatment of inflammatory bowel disease . However , Corticosteroids are associated with different types of adverse effect namely adrenal suppression , fluid retention and another one is hypertension . According to National Institute of Health they have been developed methyl Prednisolone acetate at a dose of 5 mg per day . However, using of methyl prednisolone acetate having common nuance it suppress the bone . Calcium supplementation is needed at a dose of 1000-1500 mg/day body weight where as vitamine D is used at a dose of 800 units per day. Few year laters different types of immunomodulators are used namely Azathioprine and its derivative Marcaptopurine.[13] However, these drugs shows different types of adverse effects namely nausea , vomiting , leucopenia , and pancreatitis. However, Toclizumab is a monoclonal antibody which is blocked IL-6 receptors and has been approved for rheumatoid arthritis . IL-6 along with TGF- β increases the production of IL-17 producing T helper cells which is inhibit differentiation of regulatory T cells. This imbalance of T helper 17 cells to regulatory T cells can leads to immunogenic intolerance and its ameliorates different types of immune mediated conditions. ( Toclizumab is associated with inflammatory bowel disease but now a days it arising different types of adverse effects namely headache , nausea , hypersensitivity reaction .[14] Since , thiopurines plays a putative role in the treatment of inflammatory bowel disease (IBD) . A plethora of anti TNF antibodies are available namely Adalizumab , Cetolizumab , Golimumab .Infliximab is a chimeric mouse – human monoclonal antibody directed specifically to TNF. It was ameliorates as a therapeutic agent for immune mediated diseases and in IBD it is recently used chiefly in the treatment of Crohn's disease and Ulcerative colitis . Infliximab also has beneficial effects in the healing of fistulas in Crohn's disease . Since , the mechanism of action of Infliximab involves its binding to both soluble and membrane bound TNF ,with subsequently inhibition of the biological activity of this cytokine .It should be administered intravenously at a dose of 5 mg/kg and variable dosing schedule .However , Infliximab is having some limitation . It is associated with acute infusion and delay infusion . Briefly acute infusion reactions can have symptoms including flushing , headache , dizziness , chest discomfort [15].On the other hand delayed infusion reaction which are type III immune complex –mediated reaction are associated with joint pain , rash and fatigue . Azathioprine and 6 –marcaptopurines are two most commonly used thiopurine compounds in inflammatory bowel disease (IBD) in management . Because of their slow onset , requiring at least 12-17 weeks of continuous therapy to produce noticeable effect. Briefly , thiopurines have a specific role in inflammatory bowel disease (IBD) i.e one of maintaining long term remission . The recommended dose is 1.5-2.5 mg /kg for azathioprine and 0.75 -1.5 mg /kg for 6 Mercaptopurine . Since , common side effects associated with Thiopurines are leucopenia , hepatotoxicity , pancreatitis and gastric intolerance . A full blood count and liver function test should be conducted before starting a thiopurine and continued every 2 weeks for the first 2 months .[16]

## Comorbidities Associated with Inflammatory Bowel Disease: A Brief Overview

Ulcerative colitis is a plethora of comorbid disorder namely gastrointestinal disorder arising from cholelithiasis , cutaneous disease like psoriasis , metabolic disorder like diabetes mellitus. Psoriasis is a chronic hyperproliferative immune mediated inflammatory skin disease. However, 1-3% population suffered from this disease . Pathophysiology of psoriasis having different factors are include namely genetic predisposition another pivotal point is that environmental factors which are associated with skin disease . However, different types of immune mediated facts are responsible for pathology of psoriasis . On the other hand T cell or helper T cell play a role in the pathology of psoriasis. Cytokine , denditric presenting cell they are play a role in the pathology of psoriasis. Since , the top most factors are that TH1, TH17 , TNF alpha , IFN gama , IL 17 , IL 22 they are play a major role in the pathology of psoriasis .[17]

Inflammatory bowel disease (IBD) is a group of clinic pathological condition of the gastro intestinal tract . Ulcerative colitis is associated with cardiovascular disorder namely hypertension. Cardiovascular is one of the main reason of death in developing countries and its prevalence is increase with age. The impact of Cardiovascular disorder on Inflammatory and bowel disease is the same as for the general population, increase complication and remaining a common cause of mortality. Venous thrombolism ( VTE) which is a common manifestation now a days and it is directly associated with inflammatory bowel disease( IBD) . Atherosclerosis is a common phenomenon in several immune based inflammatory disease particularly

rheumatoid arthritis and systemic vascular system are well known . However, different types of adverse effects are shows like hypertension, hyperglycemia , hyperinsulinemia and hyperlipidemia . However rheumatoid arthiritis, inflammatory activity control can reduce cardiovascular complications. Aminosalicylates reduce platelet activation whereas azathioprine inhibitis formation of platelet – leukocyte aggregate.[18]

Ulcerative colitis is an emergent plight in developed and developing countries. Ulcerative colitis is a chronic ulceroinflammatory condition of the bowel primarily confined with colonic mucosa with variable distortion of the colonic architecture. Ulcerative colitis is associated with cholelithiasis or gall bladder stone or intrahepatic stone or common bile duct stone. However, the reason of association between ulcerative colitis and cholelithiasis are leads to cholecystitis , cholangitis , pancreatitis.[19]

Inflammatory bowel disease ( IBD) is a group of inflammatory intestinal disorders comprising two types of disease : Ulcerative colitis another one is Crohn's disease . Ulcerative colitis is a chronic ulceroinflammatory condition primarily confined within colonic mucosa with variable distortion of the colonic architecture. Since , inflammatory bowel disease is associated with peripheral artery disease (PAD) . Traditionally, the incidence of this disease is relatively stable in Western countries; however the IBD incidence has been increasing in Asian countries in the past few years. Peripheral arterial disease ( PAD) is the narrowing of arteries other than those that supply blood to brain or heart , causing a considerable burden on health care systems worldwide . The prevalence of peripheral vascular disease in the general population is 12 % to 14% , affecting upto 20 % of people > 70 years . According to the Taiwan National Health Insurance ( NHI) data analysis, the incidence of invasive PAD treatment is increasing. Traditional risk factors for PAD are an older age, male sex , hypertension , diabetes , hyperlipidemia , obesity , smoking and family history of vascular disease. [20]

## Association Inflammatory Bowel Disease and Diabetes Mellitus: A Brief Overview

Inflammatory bowel disease (IBD) is a emergent plight as in the modern era. According to American Gastrological Society Inflammatory bowel disease is an acute or chronic idiopathic ulceroinflammatory condition of the bowel which may or may not have a transmural stretch. Inflammatory bowel disease encompasses two pivotal kinds of pathological condition one is ulcerative colitis( UC) another one is crohn's disease . Ulcerative colitis is a chronic ulceroinflammatory condition of the bowel primarily confined within colonic mucosa with variable distortion of the colonic architecture. However, the featured encountered in the clinical course of the disease are multiferous spanning from rectal bleeding , abdominal pain , weight loss and malaise .Inflammatory bowel disease are associated with diabetes mellitus .They are multifactorial association , interventional aggrevession and shared complication. Various factors link diabetes comorbidity to ulcerative colitis .They may range from loss of metabolic homeostasis leading to a disarray in intestinal microflora and risk of altered responses in the gut brain axis due to several associated complication. Interventional aggrevession is also common as evident from precipitation of hyperglycemia due to chronic use of corticosteroids in inflammatory bowel disease patients and adding to this are the varieties of shared complications prevalent in this patients which may manifest as neurological hepatobiliary , osterioarticular and vascular symptoms.[21]

## Role of Incretins in Modulating Inflammatory Bowel Disease

Inflammatory bowel disease is an incurable chronic inflammatory intestinal disorder of the gastrointestinal tract that dramatically impacts quality of life .According to American Gastrological Society ( AGS) inflammatory bowel disease (IBD) is defined as an acute or chronic idiopathic ulceroinflammatory condition of the bowel which may or may not have transmural stretch. Inflammatory bowel disease(IBD) encompasses two pivotal kinds of pathological condition namely ulcerative colitis (UC) and another one is crohn's disease ( CD) . Ulcerative colitis(UC) is a chronic ulceroinflammatory condition primarily confined with an colonic mucosa with variable distortion of the colonic architecture. Since Ulcerative colitis (UC) is epidemiologically associated with diabetes mellitus ( DM) . Briefly, incretin is a metabolic hormone secreted from the pancreatic beta cell islet of langerhence . However , incretin mimetic and DPP4 inhibitors first introduced in the year of 2005 as an antidiabetic agents . After few year 2007 sitagliptin was discovered . Glucagon like peptide 1 ( GLP-1) have a function through binding to GLP 1 receptor and is involved in the amelioration and progression of different types of disease. Since , GLP-1 receptor is widely expressed in many organs and tissue including gastrointestinal tract , heart , central nervous system endocrine pancreas. However , in the modern days GLP-1 has a predominant role in the pathogenesis of type 2 diabetes mellitus.[22] Type 2 diabetes is a complex metabolic disorder characterized by hyperglycemia arising from a combination of insufficient insulin secretion together with resistance to insulin action. However two most recently approved classes of therapeutic agents for the treatment of type 2 diabetes , glucagon like peptide-1 receptor agonists and DPP4 inhibitors exert their action through potentiation of incretin receptor signaling . Incretins are gut derived hormones , principally GLP-1 and glucose depedent insulinotropic peptide that are secreted at low basal levels in the fasting state. Ulcerative colitis patients with colectomy showed a slower release of GLP-1 in response to intake of glucose. Consistently , postprandial GLP-1 response was also impaired in patients with ileostomy . It was unknown wheather the colectomy or inflammatory state affects the GLP -1 release in IBD. However , GLP- lr m RNA levels was reduced in which promotes mucosal epithelium restoration in a self repair mechanism .[23] The close associations of diabetes with ulcerative colitis and a dearth of effective medications against these two conditions prompted us to look for a common solution which can address these two shared pathologies conveniently . In the process we narrowed in on an emergent group of antidiabetic drugs conceptualized in 1902 . Two major incretin based hormone GLP and GIP originate from the gut and can promote pancreatic beta cell growth along their enterohepatic effect beside therapeutic convergence leading to better efficacy . This mode of therapy can serve as an efficacious mean to circumvent the spectra of hypoglycemia a common menace in diabetic therapy.[24] However , IBD is relevantly associated with metabolic disorders like diabetes mellitus epidemiologically . Behind the epidemiological relevance there are some technical reasons . Dipeptidyl peptidase is an enzyme which binds to its substrates namely GLP and GIP . Both of these are potent incretins .Among these GLP can be further subclassified into GLP1 and GLP 2 .While GLP 1 is reported to be involved in hyperglycemic control , GLP 2 has been documented as a potent enterotrophic agent . Being incretins ,both GLPs and GIP are vulnerable to cleavage by dipeptidyl peptidases( DPP4 group of enzymes) which make these important physiological peptides short lived. Dearth of trophic peptides

at times of acute and chronic injury, halts the local repair mechanisms which promotes the progression of inflammatory damage in IBD patients expressed . Hence ,therapies aimed at boosting GLP2 can be a newer strategy in the treatment of IBD.[25]

## Gliptins: Focus on Anticolitic Potential

Inflammatory bowel disease denotes a group of disorders characterized by chronic intestinal inflammation , the aetiology is unknown . Inflammatory bowel disease encompasses two pivotal kinds of pathological condition one is ulcerative colitis (UC) and another one is Crohn's disease( CD) . Ulcerative colitis is a chronic idiopathic ulceroinflammatory condition of the bowel primarily confined within colonic mucosa with variable distortion of the colonic architecture. Since, Ulcerative colitis(UC) is associated with diabetes mellitus (DM) . Since , different types of gliptins are reported namely sitagliptin , vildagliptin , Tenligliptin , saxagliptin etc . for treatment of diabtes mellitus (DM) .[26] Gliptins inhibit the dipeptidyl peptidase 4 (DPP4) as a results insulin secretion is increased where as glucagon released is decreased that's why blood glucose levels are decreased . Since gliptins are having different advantages briefly , Glucagon like peptidase (GLP) and Gastro intestinal polypeptide (GIP) or insulin trophic peptide or glucose dependent insulin trophic peptide both are enzymes secreted from small intestine. They looks like a agonist but they acts as an antagonist . When ligand bind to the glucagon like receptors then ligand blocks GLP and GLP that's why glucagon release is decreased and insulin secretion is increased as a result blood glucose levels are maintained . Randomized control trial reported that Setagliptin and Vildagliptin having a anti inflammatory potential . However , Sitagliptin are not free from clinical contraindication. Sitagliptin is the first generation DPP4 inhibitor for the treatment of type2 diabetes mellitus. Sitagliptin acts by inhibiting DPP4 enzyme increase the levels of incretins , mainly Glucagon like peptide -1 ( GLP1) . However , GLP 1 has a very short half life 1-2 min and is metabolized quickly by DPP4 enzyme . GLP is produced by intestinal L cells , which augments glucose dependent-insulin secretion , during the phase of nutrient absorption from gastrointestinal tract( GIT) . Sitagliptin is the forerunner in this arena. However the drug is associated with the occurance of a plethora of side effects like upper respiratory tract infection , nasopharyngitis and headache to name a few. Vildagliptin is the second DPP4 inhibitor and is indicated for the control of hyperglycemia in patients with type 2 diabetes mellitus . Vildagliptin produces sustained inhibition of DPP4 and produce moderate increase in GLP1 and GIP. Teneligliptin is the third generation Gliptin which offers a pharmacodynamic advantage with unique J shaped anchor locked domain which signifies for its potent and long duration of action . Inflammatory bowel disease having a plethora of comorbid disorders such as gastrointestinal disorders arising from cholelithiasis , cutaneous disease like psoriasis [27]

## Antioxidant potential of gliptins:

Dipeptidyl peptidase inhibitors, a promising group of antihyperglycemic drugs , inhibits the enzyme , DPP-4 , that destroy GLP-1 and GIP thereby increase the levels as a result by which blood glucose level fall. Antioxidant property is an essential mechanisms by which it reduces oxidative stress in diabetic patients there by preventing beta cell damage and occurance of microvascular and macrovascular complications. The in vitro antioxidant potential of gliptins has been proved by the work of Aparna et al. in 2015 . The antioxidant potential of gliptins have also been hinted in the work of other workers (Puja Das et al .2017) who have unequivocally opined that the gliptins may give protections against oxidative damage by triggering the expression of certain genes which boosts antioxidant reserve in the body .The gamut of therapeutic effects shown by gliptins have largely been attributed to its antioxidant potential by multiple authors . For example kramar et al have found a correlation between antidiabetic activity of Sitagliptin with its antioxidant potential . The anti-inflammatory potential of Vildagliptin has been largely attributed to the antioxidant mechanism elicited by it . Hence , the inflammatory bowel disease which like any other inflammatory pathology has got an oxidative component is expected to show improvements due to the antioxidant component of gliptins .[28]

## Conclusion:

Inflammatory bowel disease is an emergent nuance in developed and developing countries . IBD is associated with a plethora comorbid disorders. Gliptins plays a putative role in the amelioration of inflammatory bowel disease.

## References:


1 . Atricia Kiesler , Ivan J . Fuss , Warren Strober ; Experimental Models of Inflammatory Bowel Diseases ; Cellular and Molecular Gastroenterology and Hepatology 2015;1:154-170

2. Bernard Khor , Agnes Gardet , Ramnik J. Xavier ; Genetics and pathogenesis of inflammatory bowel disease ; International Journal of Science , Vol: 17 , No 2 , 16 June 2011 , PP : 307 -317

3. Babickova J , Hyosin A ; Pathological and therapeutic interactions between bacteriophages , microbes and the host in inflammatory disease ; World Journal of Gastroenterology ; Vol :16 , No : 2 , 2015

4. Bram Verstockt , Marc Ferrante , Severine Vermeire, Gert Van Assche ; New treatment option for inflammatory bowel disease ; The Japanese Society of Gastroenterology ,6th February 2018 ,53 :585 -590

5. Cullen G , Kroshinsky D, Cheifetz AS , Korzenik JR ; Psoriasis associated with anti –tumor necrosis factor therapy in inflammatory bowel disease : a new series and a review of 120 cases from the literature ; Aliment Pharmacol Ther , 2011 Dec ,; 34 (11-12): 1318-27

6. Daniel M. Autenrieth , Daniel C.Baumgart ; Toxic Megacolon , Inflammatory Bowel Disease , Volume 18 , No : 3, March 2012

7. Duk Hwan Kim , Jae Hee Cheon ; Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies ; IMMUNE NETWORK , Vol. 17, No 1: 25-40 February ,2017

8 .Dianz Zaidi , E. Wine ; Regulation of Nuclear Kappa –Light 0-Enhancer of Activated B Cells in Inflammatory Bowel Diseases ; World Journal of Gastroenterology , 2018 ;V olume :17 , No:2 , Page no : 172-185

9. Efstathios Antoniou , Gerogios Antonios Margonis ,Anastasios Angelou , Anastasia Pikouli , Paraskevi Argiri , Ioannis Karavokyros , Apostolos Papalois , Emmanouil Pikoulis ; The TNBS –induced colitis animal model : An overview; Annals of Medicine and Surgery 11 (2016) 9-15

10. Giovanni Maconi , Federica Furfaro , RobertabSciurti , Cristina Bezzio , Sandro Ardizzone , Roberto de Frenchis ;Glucose intolerance and diabetes mellitus in ulcerative colitis : pathogenetic and therapeutic implications ; World Journal of Gastroenterology 2014 April 7;20(13):3507 -3515

11. Gary R . Lichtenstein , Edward V. Loftus Jr , Kim L. Isaacs , Miguel D. Regueiro, Lauren B. Gerson , Bruce E. Sands ; ACG Clinical Guideline : Management of Crohn's Disease in Adults ;American Journal of Gastroenterology 2018; 113 :481 – 517

12. Giorgos Bamias , Theresa T. Pizarro , Fabio Cominelli ; Pathway –based approaches to the treatment of inflammatory bowel

disease ;American Journal of Gastroenterology,2016 January ;167(1) : 104 -115

13 .H.Sales –Campos , P.J .Basso , V.B.F .Alves , M.T.C .Fonseca , G.Bonfa , V.Nardini , C.R.B .Cardoso ; Classical and recent advances in the treatment of inflammatory bowel diseases; Brazilian Journal of Medical and Biological Research (2015) 48(2) : 96 -107

14 . Hyo Sun Lee , Soo –Kyung Park , Dong I1 Park ; Novel treatments for inflammatory bowel disease ; The Korean Journal of International Medicine , Volume 33 , No :1 January 2018, Page no : 20 -27

15 . J.E.KRAWISZ , P.SHARON , W.F . STENSON ; Quantitative Assay for Acute Intestinal Inflammation Based on Myeloperoxidase Activity ;World Journal of Gastroenterology ; Volume 87 , No 6 , 2016 , PP :578-598

16. Jaroslaw Nowakowski , Adrian .A . Chrobak , Dominika Dudek;Psychiatric illness in inflammatory bowel disease – psychiatric comorbidity and biological underpinnings;Psychiatr .Pol .2016;50(6) :1157-1166

17 .Kathleen .A , Julie S . Jurenka ; Inflammatory Bowel Disease Part I: Ulcerative Colitis – Pathophysiology and Conventional and Alternative Treatment Options ; Altern Med Rev 2003 ; 8(3) : 247 -283

18. Konstantinos H. Katsanos , Konstantinos A . Papadakis ; Inflammatory Bowel Disease : Updates on Molecular Targets for Biologics ;Gut and Liver , Vol 11 , No 4, July 2017 , PP 455-463

19. Kern JS , Herz C , Haan E , Moore D , Nottelmann S , Von Lilien T , Greiner P , Schmitt –Graeff A , Bruckner – Tuderman L , Has C ; Chronic colitis due to an epithelial barrier defect : the role of kindlin -1 isoforms ; J Pathol .2007 Dec;213 (4) : 462-70

20. Lalit Kanodia , Mondita Borgohain , Swranamoni Das ; Effect of fruit extract of *Fragaria vesca L.* on experimentally induced inflammatory bowel disease in albino rats ; Indian Journal of Pharmacology ; February 2011 , vol 43 , No :1 , PP 18-21

21. Neeraj Narula , David T. Rubin , Bruce E. Sands ; Novel Therapies in Inflammatory Bowel Disease : An Evaluation of the Evidence ;American Journal of Gastroenterology ,2016 ;3:38 -44

22 . Neal Goldstein , Mohanpal Dulai ; Contemporary Morphologic Definition of Backwash Ileitis in Ulcerative Colitis and Features That Distinguish It From Crohn Disease ; American Journal of Clinical Pathology , 2006 ; 126 :365-376

23. Nishida .A , Serban DE ; Gut microbiota in the pathogenesis of inflammatory bowel disease ; American Journal of Gastroenterology ,2018 January ; 18(2) : 59-73

24. Patel MA , Patel PK , Patel MB ; Aqueous Extract of *Ficus bengalensis* Linn . Bark for Inflammatory Bowel Disease ; J Young Pharm , Vol : 2 , No : 2 , 2010; 130-136

25. Restellini S, Chazouilleres .O , Frossard .JL ;Hepatic manifestations of inflammatory bowel disease ;World Journal of Gasteroenterology, 2017 , April ;37 (4) : 475 -489

26. Sheng Zhang Lim, Eng Wee Chua ; Revisiting the Role of Thiopurines in Inflammatory Bowel Disease Through Pharmacogenomics and Use of Novel Methods for Therapeutic Drug Monitoring ;Frontiers in Pharmacology , 2018 , 8th October , Volume 9 : 590-610

27.Saskia van Hemert , Anne C. Breedveld , Jorgen M.P.Rovers , Jan , P.W. Vermeiden , Ben J.M.Witteman , Marcel G. Smits , Nicole M. de Roos ; Migrane associated with gastrointestinal disorders : review of the literature and clinical implications ; Frontiers in Neurology , November 2014 , Volume 5

28. Aparna Das, Arup Ray; Antioxidant property of Gliptins ; International Journal of Biomedicine; Volume:8, No:20;2015.