International Journal of Scientific Research & Engineering Trends
Volume 11, Issue 1, Jan-Feb-2025, ISSN (Online): 2395-566X

Cyclooxygenases in Inflammatory Bowel Disease

K. Anil Kumar
MURTI Research Centre,
GITAM University, Bengaluru Campus, Doddaballapura, 561203, Karnataka, India

Abstract- Inflammatory Bowel Disease (IBD) is a long-term condition that presents as Ulcerative Colitis (UC), or Crohn's Disease (CD) based on its manifestations. It is characterized by inflammation in the small intestine and colon, impacting millions of individuals globally. The development of IBD is influenced by genetic, environmental, and immunological factors. Various pro-inflammatory agents such as TNF-α, IL-1β, IL-6, IL-12, TGF-β, INF-γ, COX-2, and increased reactive oxygen species contribute to significant intestinal damage. Typical symptoms of IBD include fever, abdominal pain, vomiting, diarrhea, weight loss, blood in the stool, and an elevated risk of colon cancer. Changes in colonic motility linked to IBD can worsen discomfort and diarrhea. Prostaglandins, particularly elevated in IBD patients, may modulate these alterations. The enzyme Cyclooxygenase-2, responsible for producing prostaglandins, is targeted in IBD treatment. The role of PGE2 in the pathogenesis of IBD is intricate; while it can have anti-inflammatory effects by inhibiting pro-inflammatory cytokines, it can also act pro-inflammatory in IBD. Dysregulation of PGE2 production in IBD can lead to excess levels in inflamed gut tissue, perpetuating chronic inflammation by attracting immune cells, increasing blood vessel permeability, and causing tissue damage. The context-dependent role of PGE2 in IBD warrants further research for a comprehensive understanding. Modulating PGE2 levels or its signaling pathways may provide potential therapeutic options for managing IBD. This review specifically examines the involvement of Cyclooxygenases and coxibs in treating IBD.

Index Terms-Cyclooxygenases, Inflammation, Ulcerative Colitis, Prostaglandins.

I. INTRODUCTION

Inflammation

The term "inflammation" originates from the Latin "to set on fire," and it represents the body's natural response to harmful pathogens and stimuli. When stimulated by infections, dead cells, or irritants, the innate immune system generates inflammation as a defensive immunological reaction. The initial line of defense against infections is the innate immune system, which is crucial for promptly identifying invasive infections and inducing a pro-inflammatory response. On the other hand, the adaptive immune system is responsible for establishing immunological memory and eliminating specific pathogens during the later stages of infection [1].

Inflammation manifests in two stages: acute inflammation and chronic inflammation [2]. The immune system's response to infection and injury, inflammation, is associated with the pathogenesis of various diseases such as cardiovascular, neurological, and autoimmune diseases, as well as stroke, cancer, and arthritis. The primary benefits of inflammation include eliminating harmful substances and restoring tissue integrity and physiological function.

Acute inflammation is a transient form of innate immunity that is initiated by immune cells. It is characterized by a rapid influx of blood granulocytes, typically neutrophils, followed by monocytes that differentiate into inflammatory macrophages. These macrophages multiply and impact the functions of resident tissue macrophages. The four key indicators of acute inflammation are tumor (swelling), dolor (pain), calor (heat), and rubor (redness). Following the removal of the initial harmful stimulus through phagocytosis, the inflammatory response can subside and resolve.

Inflammation involves a complex network of molecular and cellular mechanisms that coordinate various pre-existing or newly synthesized mediators to induce specific reactions. Prolonged and uncontrolled immune responses can lead to irreversible tissue damage, chronic illnesses, and chronic inflammation. Chronic inflammatory diseases, also known as non-communicable chronic diseases, are a major cause of global mortality. The lack of control over the intensity and resolution time of inflammation significantly contributes to the development of chronic inflammatory diseases.

© 2025 IJSRET

International Journal of Scientific Research & Engineering Trends
Volume 11, Issue 1, Jan-Feb-2025, ISSN (Online): 2395-566X

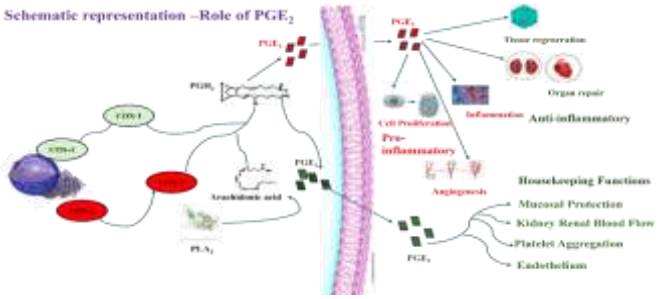

Figure 1: Schematic representation-Role of PGE_2

II. INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) encompasses conditions such as Ulcerative colitis and Crohn's disease, characterized by inflammation of the intestinal tract. IBD is a prevalent global health issue affecting populations in both developed and developing countries. Common initial symptoms of ulcerative colitis (UC) include abdominal discomfort, blood in the stool, weight loss, and vomiting, with lesions primarily found in the rectal and colonic regions. Crohn's disease (CD) symptoms can occur in any part of the gastrointestinal system and may include fever, nutritional deficiencies, diarrhea, and intestinal blockage, among others. CD typically presents as a chronic, recurrent condition with complex clinical manifestations.

In CD, inflammation affects multiple layers of the intestine and appears as patches, while in UC, inflammation begins in the rectum and progresses proximally within the mucosal layer. Structural alterations in the enteric nervous system (ENS) have been observed in patients with CD or UC, including abnormalities in ganglia and nerve bundles. The prevalence of IBD is increasing globally, influenced by factors such as changes in diet, antibiotic use, hygiene practices, and environmental conditions.

Genetic, environmental, and lifestyle factors play a significant role in the development of IBD, with genetic predisposition increasing the risk of disease. The chronic inflammation associated with IBD can lead to complications such as colorectal cancer and cardiovascular disease. Management of IBD involves ongoing medication, surgery, and lifestyle modifications to control symptoms and prevent disease progression. Various therapeutic options, including biological agents, immunomodulators, and surgery, are available, but not all patients respond well to traditional treatments, necessitating the development of safer and more effective anti-inflammatory drugs.

Oxidative stress and inflammation are critical mechanisms in the pathogenesis of IBD, leading to intestinal damage and complications. Individuals with IBD are at increased risk for colorectal cancer, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may help reduce this risk. Furthermore, IBD has been identified as a risk factor for cardiovascular disease, highlighting the importance of managing inflammation and other risk factors in individuals with IBD to prevent cardiovascular complications. Dietary factors, including fiber intake, play a crucial role in modulating gut microbiota and may impact the development and progression of IBD. Antibiotic use can alter gut microbiota composition, emphasizing the importance of judicious antibiotic use, particularly in children, to maintain a healthy gut microbiome.

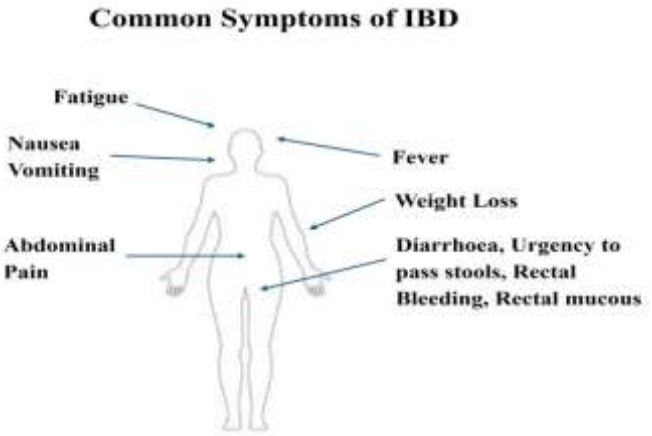

Figure 2: Common Symptoms of IBD

Cyclooxygenases

There are three isoforms of the COX enzyme known to exist: COX-1, COX-2, and COX-3. These enzymes play a crucial role in the formation of various inflammatory prostaglandins. Prostaglandins interact with G-protein coupled membrane receptors, influencing numerous physiological and pathological processes. While both COX-1 and COX-2 enzymes convert arachidonic acid into prostaglandins, they have distinct distributions and functions in the body. COX-1 is constitutively expressed throughout the body, serving various homeostatic functions such as aiding in blood clotting, maintaining gastric mucosa, and regulating renal blood flow. On the other hand, COX-2 is an inducible form involved in producing prostaglandins that mediate pain and inflammation. COX-3, a splice variant of COX-1 sensitive to acetaminophen, has an unknown function. Both COX genes encode two isoenzymes found in coral, tunicates, and vertebrates. The specific origin of these genes from early duplication events or individual duplications during evolution remains uncertain. In vertebrates, the intron-exon configuration of COX genes is conserved across species. The COX enzymes possess unique cyclooxygenase and peroxidase active sites in their catalytic domain and belong to the myeloperoxidase family. They are predominantly located on the nuclear envelope and the lumenal side of the endoplasmic reticulum membrane.

© 2025 IJSRET

COX enzymes facilitate the conversion of arachidonic acid into prostaglandin G2, subsequently reduced to prostaglandin H2. Downstream synthases convert PGH2 into various prostaglandin isomers through isomerization, oxidation, and reduction reactions. The enzyme autoinactivates over time, with a short lifespan. Both COX-1 and COX-2 proteins consist of around 600 amino acids with a calculated molecular weight of 75-80 kDa post-translational modifications. COX-2 can be induced by pro-inflammatory cytokines, growth factors, and bacterial lipopolysaccharide.

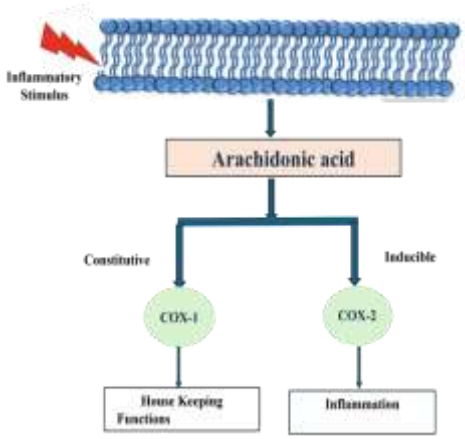

Figure 3: Role of Cyclooxygenases

Cyclooxygenases in IBD

IBD, a complex ailment, is part of a group of inflammatory gut disorders with unknown causes and long-term effects. It is impacted by genetic, immunological, and environmental factors [3]. IBD includes Ulcerative colitis, which affects the colon, and Crohn's disease, which can affect the gastrointestinal tract in both children and adults. The prevalence of IBD is increasing due to various factors such as diet, medication, hygiene, and lifestyle.

Studies have shown that inflammation may promote tumor growth by stimulating blood vessel formation and cell proliferation while suppressing the immune system and cell death [4]. Research also demonstrates a 40–50% reduced risk of developing colorectal cancer with prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) [5]. NSAIDs target cyclooxygenase (COX) enzymes to exert their anti-inflammatory and pain-relieving effects. Colorectal cancer (CRC) can be hereditary, sporadic, or associated with colitis, and various factors like genetics, chronic inflammation, and lifestyle choices contribute to an increased risk [6].

Ulcerative colitis, a common form of IBD, is associated with an increased risk of colon cancer development (CRC). Research has linked COX-2 to the development of CRC [7]. Individuals with IBD have a 60% higher incidence of CRC compared to the general population [8]. Furthermore, studies have shown that regular use of NSAIDs over a long period can reduce the risk of developing colorectal cancer and adenomas by 40–50% [4].

Epidemiological and clinical studies suggest that aspirin and other NSAIDs can slow the spread of colorectal cancer cells and improve overall survival in patients with high levels of COX-2 [9]. NSAIDs have been shown to reduce tumor growth in mouse models of colorectal cancer by targeting the COX-2 gene [10].

COX-2 plays a key role in inflammation and cancer by producing prostaglandins, particularly PGE2, which promotes tumor growth [11]. Studies have linked urinary PGE2 metabolite levels to an increased risk of various cancers, and NSAIDs have been shown to reduce PGE2 levels and potentially inhibit tumor growth [12].

Overall, the findings suggest that NSAIDs, by targeting COX-2 and reducing PGE2 levels, may have anti-tumor effects and play a role in preventing cancer development. Further research is needed to fully understand the mechanisms involved in the relationship between inflammation, NSAIDs, and cancer progression.

Tumorogenic role of PGE2

Prostaglandin E2 (PGE2), a bioactive lipid, is known to have a significant impact on various biological processes related to inflammation and cancer. Studies have shown that PGE2 can activate crucial signaling pathways controlling cell proliferation, apoptosis, angiogenesis, inflammation, and immune response, showcasing its diverse physiological functions [13]. Together with similar prostanoids like PGI2, PGE2 acts as a vasodilator, aiding in the recruitment of immune cells to sites of inflammation or injury, leading to swelling and edema [14]. Increased levels of COX-2 and PGE2 are often observed in human colon adenomas and adenocarcinomas, suggesting a role in promoting cancer development [15,16].

Elevated PGE2 levels have been associated with the exacerbation of inflammatory pathways, immune responses, and stress reactions, especially in conditions like inflammatory bowel disease (IBD), where PGE2 and COX-2 contribute to inflammation and potential carcinogenesis in the colon [17]. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly selective COX-2 inhibitors, have been used as preventive measures against colorectal cancer, with regular NSAID use showing a reduced risk of colorectal cancer development [4]. However, long-term use of these medications carries risks such as gastrointestinal toxicity and cardiovascular events due to the reduction of protective prostaglandins [18, 19].

Research has suggested that targeting specific enzymes like microsomal PGES-1 (mPGES-1) could help regulate PGE2

© 2025 IJSRET

levels without affecting the synthesis of other important prostaglandins, offering a potential strategy to address the impact of PGE2 on various diseases [20, 21]. PGE2 has been linked to the development of inflammatory diseases and angiogenesis through its effects on factors like IL-17 and vascular endothelial growth factor (VEGF) [22, 23]. Additionally, studies have shown the potential role of PGE2 in tumor growth, suggesting that targeting PGE2 synthesis pathways like mPGES-1 could be a promising approach for cancer therapy [24, 25].

Understanding the complex interplay of PGE2 and its receptors like EP4 in diseases such as colorectal cancer provides valuable insights into potential therapeutic targets for intervention [26, 27]. Furthermore, research on the regulation of PGE2 synthesis and its downstream effects, such as the activation of peroxisome proliferator-activated receptor δ (PPARδ), sheds light on the intricate mechanisms underlying PGE2-mediated pathologies [24, 28].

In conclusion, PGE2 plays a crucial role in inflammation, cancer development, and various disease processes, highlighting the importance of further research into targeting PGE2 pathways for therapeutic purposes.

Protective role of PGE2

PGH2, derived from the digestion of AA by COX, undergoes further processing by specific PG synthases to produce a variety of PG metabolites [29]. PGs play a crucial role in promoting wound healing, reducing inflammation, and maintaining mucosal integrity in the gastrointestinal (GI) tract, thus safeguarding its health [30- 35]. In conditions like inflammatory bowel disease (IBD), the GI mucosa tends to increase its production of PG, which could serve as an adaptive response to facilitate healing [34, 36- 42]. Notably, therapies involving COX inhibitors have been shown to worsen IBD symptoms, underscoring the protective role of PGs in these conditions [43- 50].

Studies in mice have revealed that genetic deletion of enzymes involved in PG synthesis, such as COX-1, COX-2, or mPGES-1, can lead to increased susceptibility to conditions like chemically induced colitis [21, 51-52]. Furthermore, specific PG metabolites like PGE2 have been linked to tumor progression, while others like PGD2 exhibit tumor-inhibiting properties [53-56]. PGE2, in particular, has been associated with both initiating acute inflammation and exerting immunosuppressive effects that aid in tissue regeneration and restoration of homeostasis post-inflammation. Targeting COX-2 pharmacologically during later stages of inflammation has been shown to impede full tissue repair in organs like the liver, lung, and colon [57-60].

In cancer-related contexts, PGE2 plays a role in promoting angiogenesis, cell migration, and invasion via interactions with myofibroblast cells within the tumor microenvironment [61]. The immune regulatory functions of PGE2 involving regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) further highlight its significance in modulating anti-tumor immunity [62-65]. Additionally, PGE2 has been shown to enhance tissue regeneration in various organs, indicating its potential therapeutic applications in conditions requiring tissue repair [66-68].

Moreover, various natural and synthetic compounds have been studied for their effects on COX-2 and PGE2 in the context of inflammatory bowel diseases (IBD) [69-78]. These studies highlight the potential therapeutic approaches targeting COX-2 and PGE2 pathways in managing conditions like IBD.

Therefore, understanding the multifaceted roles of PGs, particularly PGE2, in health and disease underscores their significance as potential targets for therapeutic interventions and further research in various clinical settings.

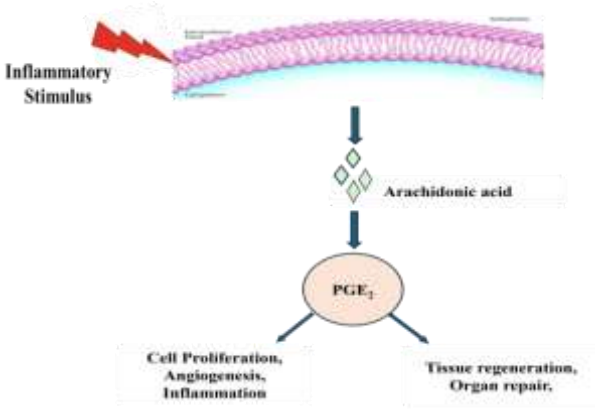

Figure 4: Role of PGE_2

Acknowledgements

Author Acknowledge Dr. K. Subbaramaiah for his valuable corrections, suggestions in preparation of the review.

V. CONCLUSION

PGE2 levels are elevated in disease. However, it is important to understand that modulating its levels via intervention is context dependent. While blocking its levels of PGE by targeting the enzymes in its synthesis and degradation is an important approach in cancer treatment and prevention. However, inhibiting its levels can have the opposite effects since PGE2 has a cytoprotective role and can be harmful. Thus, it's important to appreciate its paradoxical effects on biology. This review is an effort to highlight this fact. It's important to further investigate the signal transduction pathways by which PGE2 regulates different biological effects. The role of the receptors that mediate PGE2 effects need to be further investigated.

© 2025 IJSRET

REFERENCES

1. T. H. Mogensen, "Pathogen recognition and inflammatory signaling in innate immune defenses," Clinical Microbiology Reviews 22 (2009): 240–273.
2. B. B. Aggarwal, M. E. Van Kuiken, L. H. Iyer, K. B. Harikumar, and B. Sung, "Molecular targets of nutraceuticals derived from dietary spices: potential role in suppression of inflammation and tumorigenesis," Experimental Biology and Medicine (Maywood) 234, no. 8 (2009): 825–849.
3. C. Abraham and J. H. Cho, "Inflammatory bowel disease," The New England Journal of Medicine 361 no. 21 (2009): 2066-2078.
4. W. E. Smalley and R. N. DuBois, "Colorectal cancer and nonsteroidal anti-inflammatory drugs." Advances in Pharmacology 39 (1997): 1–20.
5. J. R. Vane, "Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs," Nature 231 (1971): 232–235.
6. A.Ekbom, C. Helmick, M. Zack, and H. O. Adami, "Ulcerative colitis and colorectal cancer. A population-based study," The New England Journal of Medicine 323 (1990):1228–1233.
7. C. E. Eberhart, R. J. Coffey, A. Radhika, F. M. Giardiello, S. Ferrenbach, and R. N. DuBois, "Up-regulation of cyclooxygenase-2 gene expression in human colorectal adenomas and adenocarcinomas," Gastroenterology 107 (1994): 1183–1188.
8. L. J. Herrinton, L. Liu, T. R. Levin, J. E. Allison, J. D. Lewis, et al., "Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010," Gastroenterology 143, no 2 (2012): 382–389.
9. A.T. Chan, S. Ogino and C. S. Fuchs, "Aspirin use and survival after diagnosis of colorectal cancer," JAMA 302 (2009): 649–658.
10. P. C. Chulada, M. B. Thompson, J. F. Mahler, C. M. Doyle, B. W. Gaul et al., "Genetic disruption of Ptgs-1, as well as Ptgs-2, reduces intestinal tumorigenesis in Min mice," Cancer Research 60 (2000): 4705–4708.
11. D. Wang and R. N. DuBois, "The role of COX-2 in intestinal inflammation and colorectal cancer," Oncogene 29 (2010):781–788.
12. L. J. Murphey, M. K. Williams, S. C. Sanchez, L. M. Byrne, I. Csiki, J. A. Oates, et al., "Quantification of the major urinary metabolite of PGE2 by a liquid chromatographic/mass spectrometric assay: determination of cyclooxygenase-specific PGE2 synthesis in healthy humans and those with lung cancer," Analytical Biochemistry 334 (2004): 266–275.
13. D. Wang, J. R. Mann, and R. N. DuBois' "The role of prostaglandins and other eicosanoids in the gastrointestinal tract," Gastroenterology 128 (2005):1445–1461.
14. J.L. Wallace, "Prostaglandin biology in inflammatory bowel disease" Gastroenterology clinics of North America 30, no. 4 (2001):971–980.
15. S. Pugh, "Thomas GA. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E2," Gut 35 (1994): 675–678.
16. C. S. Williams, W. Smalley, and R. N. DuBois, "Aspirin use and potential mechanisms for colorectal cancer prevention," Journal of Clinical Investigation 100 (1997):1325–1329.
17. A.V. Sampey, S. Monrad, and L. J. Crofford, "Microsomal prostaglandin E synthase-1: the inducible synthase for prostaglandin E2," Arthritis Research Therapy 7 (2005):114–117.
18. R. S. Bresalier, R. S. Sandler, H. Quan, et al., "Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial," The New England Journal Medicine 352 (2005): 1092–1102.
19. S. D. Solomon, J. J. McMurray, M. A. Pfeffer, et al., "Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention," The New England Journal of Medicine 352 (2005): 1071–1080.
20. M. Murakami, H. Naraba, T. Tanioka, et al., "Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2," Journal of Biological Chemistry 275 (2000): 32783–32792.
21. S. Hara, D. Kamei, Y. Sasaki, A. Tanemoto, Y. Nakatani, M. Murakami, "Prostaglandin E synthases: Understanding their pathophysiological roles through mouse genetic models," Biochimie 92 (2010): 651–659.
22. A.F. Sheibanie, J. H. Yen, T. Khayrullina, F. Emig, M. Zhang, et al., "The proinflammatory effect of prostaglandin E2 in experimental inflammatory bowel disease is mediated through the IL-23-->IL-17 axis," Journal of immunology 178, no 12 (2007): 8138–8147.
23. M. Nakanishi, T. Sato, Y. Li, A. J. Nelson, M. Farid, et al., "Prostaglandin E2 stimulates the Production of vascular endothelial growth factor through the E-prostanoid-2 receptor in cultured human lung fibroblasts," American journal of respiratory cell and molecular biology 46 no 2 (2012): 217–223.
24. D. Wang, H. Wang, Q. Shi, S. Katkuri, W. Walhi, B. Desvergne, et al., "Prostaglandin E(2) promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferator-activated receptor delta.," Cancer cell 6 (2004): 285–295.
25. M. Nakanishi, D. C. Montrose, P. Clark, P. R Nambiar, G. S. Belinsky, et al., "Genetic deletion of mPGES-1 suppresses intestinal tumorigenesis," Cancer Research 68, no 9 (2008): 3251–3259.

© 2025 IJSRET

26. M. Mutoh, K. Watanabe, T. Kitamura, Y. Shoji, M. Takahashi, et al., "Involvement of prostaglandin E receptor subtype EP(4) in colon carcinogenesis," Cancer research 62, no. 1 (2002): 28–32.
27. A.Chandramouli, B. C. Onyeagucha, M. E. Mercado-Pimentel, L. Stankova, N. A. Shahin, et al., "MicroRNA-101 (miR-101) post-transcriptionally regulates the expression of EP4 receptor in colon cancers," Cancer biology & therapy 13, no 3 (2012): 175–183.
28. V. G. Peddareddigari, D. Wang, and R. N. DuBois, "The tumor microenvironment in colorectal carcinogenesis," Cancer microenvironment 3 (2010): 149–166.
29. E. Stack, and R. N. DuBois, "Regulation of cyclo-oxygenase-2," Best Practice & Research Clinical Gastroenterology 15 (2001): 787–800.
30. I.Dey, M. Lejeune, and K. Chadee, "Prostaglandin E2 receptor distribution and function in the gastrointestinal tract," British Journal of Pharmacology 149 (2006): 611–623.
31. R. Ferrer, and J. J. Moreno, "Role of eicosanoids on intestinal epithelial homeostasis," Biochemical Pharmacology 80 (2010): 431–438.
32. F. Halter, A. S. Tarnawski, A. Schmassmann, and B. M. Peskar, "Cyclooxygenase 2- implications on maintenance of gastric mucosal integrity and ulcer healing:controversial issues and perspectives," Gut 49 (2001): 443–453.
33. W. F. Stenson, "Prostaglandins and epithelial response to injury," Current Opinion in Gastroenterology 23 (2007): 107–110.
34. J. L. Wallace, and P. R. Devchand, "Emerging roles for cyclooxygenase-2 in gastrointestinal mucosal defense," British Journal of Pharmacology 145 (2005): 275–282.
35. D. Wang, J. R. Mann, and R. N. DuBois, "The role of prostaglandins and other eicosanoids in the gastrointestinal tract," Gastroenterology 128 (2005): 1445–1461.
36. S. Melgar, M. Drmotova, E. Rehnstrom, L. Jansson, and E. Michaelsson, "Local production of Chemokines and prostaglandin E2 in the acute, chronic and recovery phase of murine experimental colitis," Cytokine 35 (2006): 275–283.
37. Y. Raab, C. Sundberg, R. Hallgren, L. Knutson, and B. Gerdin, "Mucosal synthesis and release of prostaglandin E2 from activated eosinophils and macrophages in ulcerative colitis," American Journal of Gastroenterology 90 (1995): 614–620.
38. D. S. Rampton, and C. J. Hawkey, "Prostaglandins and ulcerative colitis," Gut 25 (1984): 1399–1413.
39. P. Sharon, M. Ligumsky, D. Rachmilewitz, and U. Zor, "Role of prostaglandins in ulcerative colitis. Enhanced production during active disease and inhibition by sulfasalazine," Gastroenterology 75 (1978): 638–640.
40. A.Wiercinska-Drapalo, R. Flisiak, and D. Prokopowicz, "Effects of ulcerative colitis activity on plasma and mucosal prostaglandin E2 concentration," Prostaglandins Other Lipid Mediators" 58 (1999): 159–165.
41. S. Yamashita, "Studies on changes of colonic mucosal PGE2 levels and tissue localization in experimental colitis," Gastroenterologia Japonica 28 (1993): 224–235.
42. A.Zifroni, A. J. Treves, D. B. Sachar, and D. Rachmilewitz, "Prostanoid synthesis by cultured Intestinal epithelial and mononuclear cells in inflammatory bowel disease. Gut. 24 (1983) 659–664.
43. D. J. Berg, J. Zhang, J. V. Weinstock, H. F. Ismail, K. A. Earle, and H. Alila, et al., "Rapid development of colitis in NSAID-treated IL-10-deficient mice," Gastroenterology 123 (2002): 1527–1542.
44. G. F. Bonner, "Exacerbation of inflammatory bowel disease associated with use of Celecoxib," American Journal of Gastroenterology 96 (2001): 1306–1308.
45. G. Cipolla, F. Crema, S. Sacco, E. Moro, F. de Ponti, and G. Frigo, "Nonsteroidal anti-inflammatory Drugs and inflammatory bowel disease: current perspectives," Pharmacological Research 46 (2002): 1–6.
46. J. M. Gornet, Z. Hassani, R. Modiglian, and M. Lemann, "Exacerbation of Crohn's colitis with severe colonic hemorrhage in a patient on rofecoxib," American Journal of Gastroenterology 97 (2002): 3209–3210.
47. H. Kefalakes, T. J. Stylianides, G. Amanakis, and G. Kolios, "Exacerbation of inflammatory Bowel Diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality," European Journal of Clinical Pharmacology 65 (2009): 963–970.
48. K. Kurahara, T. Matsumoto, M. Iida, K. Honda, T. Yao, and M. Fujishima, "Clinical and endoscopic features of nonsteroidal anti-inflammatory drug-induced colonic ulcerations," American Journal of Gastroenterology 96 (2001): 473–480.
49. B. K. Reuter, S. Asfaha, A.Buret, K. A. Sharkey, and J. L. Wallace, "Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2," Journal of Clinical Investigation. 98 (1996): 2076–2085.
50. V. P. Singh, C. S. Patil, N. K. Jain, and S. K. Kulkarni, "Aggravation of inflammatory bowel disease by cyclooxygenase-2 inhibitors in rats," Pharmacology 72 (2004): 77–84. [PubMed:15331912]
51. T.O. Ishikawa, M. Oshima, and H. R. Herschman, "Cox-2 deletion in myeloid and endothelial cells, but not in epithelial cells, exacerbates murine colitis," Carcinogenesis 32 (2011) 417–426.
52. O. Morteau, S. G. Morham, R. Sellon, L. A. Dieleman, R. Langenbach, and O. Smithies, O, et al., "Impaired mucosal defense to acute colonic injury in mice lacking cyclooxygenase-1 or cyclooxygenase-2," Journal of Clinical Investigation 105 (2000): 469–478.

© 2025 IJSRET

53. M. Nakanishi, A. Menoret, T. Tanaka, S. Miyamoto, D. C. Montrose, and A. T. Vella, et al., "Selective PGE (2) suppression inhibits colon carcinogenesis and modifies local mucosal immunity," Cancer Prevention Research (Phila) 4 (2011): 1198–1208.
54. M. Nakanishi, D. C. Montrose, P. Clark, P. R. Nambiar, G. S. Belinsky, and K. P. Claffey et al., "Genetic deletion of mPGES-1 suppresses intestinal tumorigenesis," Cancer Research 68 (2008): 3251–3259.
55. J. M. Park, Y. Kanaoka, N. Eguchi, K. Aritake, S. Grujic, and A. M. Materi, et al., "Hematopoietic prostaglandin D synthase suppresses intestinal adenomas in ApcMin/+ Mice," Cancer Research 67 (2007): 881–889.
56. P. Sinha, V. K. Clements, A. M. Fulton, and S. Ostrand-Rosenberg, "Prostaglandin E2 Promotes tumor progression by inducing myeloid-derived suppressor cells," Cancer esearch 67 (2007 :4507–4513.
57. K. Fukunaga, P. Kohli, C. Bonnans, and L. E. Fredenburgh, and B, D. Levy, "Cyclooxygenase 2 plays a Pivotal role in the resolution of acute lung injury," Journal of Immunology 174, no 8 (2005): 5033–5039.
58. D. W. Gilroy, P. R. Colville-Nash, D. Willis, J. Chivers, and M. J. Paul-Clark, et al., "Inducible Cyclooxygenase may have anti-inflammatory properties," Nature medicine 5 no 6 (1999): 698–701.
59. J. L. Wallace, "COX-2: a pivotal enzyme in mucosal protection and resolution of Inflammation," Scientific World Journal (2006): 6577–6588.
60. H. Yin, L. Cheng, R. Langenbach, and C. Ju, "Prostaglandin I(2) and E(2) mediate the protective effects of cyclooxygenase-2 in a mouse model of immune-mediated liver injury," Hepatology 45, no 1 (2007): 159–169.
61. R. Kalluri, and M. Zeisberg, "Fibroblasts in cancer," Nature reviews Cancer 6, no 5 (2006): 392–401.
62. S. Sharma, S. C. Yang, L. Zhu, K. Reckamp, and B. Gardner, et al., "Tumor cyclooxygenase-2/ prostaglandin E2-dependent promotion of FOXP3 expression and CD4+ CD25+ T regulatory cell activities in lung cancer," Cancer research 65, no 12 (2005): 5211–5220.
63. X. L. Yuan, L. Chen, M. X. Li, P. Dong, and J. Xue, et al., "Elevated expression of Foxp in tumor infiltrating Treg cells suppresses T-cell proliferation and contributes to gastric cancer progression in a COX-2-dependent manner," Clin Immunol 134 no3 (2010): 277–288.
64. S. Y. Lee, H. K. Choi, K. J. Lee, J. Y. Jung, and G. Y. Hur, et al., "The immune tolerance of cancer is mediated by IDO that is inhibited by COX-2 inhibitors through regulatory T cells,"Journal of immunotherapy 32 no 1 (2009): 22–28.
65. M. Mandapathil, M. J. Szczepanski, M. Szajnik, J. Ren, and E. K. Jackson and et al., "Adenosine and prostaglandin E2 cooperate in the suppression of immune responses mediated by adaptive regulatory T cells" The Journal of biological chemistry 285 no 36 (2010): 27571–27580.
66. W. Goessling, et al., "Genetic interaction of PGE2 and Wnt signaling regulates developmental specification of stem cells and regeneration," Cell 136 (2009): 1136–1147.
67. B. J. Frisch, et al., "In vivo prostaglandin E2 treatment alters the bone marrow microenvironment and preferentially expands short-term hematopoietic stem cells," Blood 114 (2009): 4054–4063.
68. T. E. North, et al., "Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis," Nature 447 (2007): 1007–1011.
69. H. Kohno, R. Suzuki, S. Sugie, and T. Tanaka, "Suppression of colitis-related mouse colon carcinogenesis by a COX-2 inhibitor and PPAR ligands," BMC Cancer 5 (2005): 46.
70. T. Ortiz, F. Argüelles-Arias, M. Illanes, J. M. García-Montes, E. Talero, L. Macías-García, A. Alcudia, V. Vázquez-Román, V. Motilva, and M. De-Miguel, "Polyphenolic Maqui Extract as a Potential Nutraceutical to Treat TNBS-Induced Crohn's Disease by the Regulation of Antioxidant and Anti-Inflammatory Pathways," Nutrients 12 no 6 (2020): 1752.
71. K. Kim, J. H. An, S. M. Park, G. Lim, K. W. Seo, and H. Y. Youn. "Amelioration of DSS-induced colitis in mice by TNF-α-stimulated mesenchymal stem cells derived from feline adipose tissue via COX-2/PGE2 activation," Journal of Veterinary Science 24 no 4 (2023): e52.
72. Z. Zhang, X. Wu, S. Cao, L. Wang, D. Wang, H. Yang, Y. Feng, S. Wang, and L. Li, "Caffeic Acid Ameliorates Colitis in Association with Increased Akkermansia Population in the Gut Microbiota of Mice," Oncotarget 7 (2016): 31790–31799.
73. X. D. Wen, C. Z. Wang, C. Yu, L. Zhao, Z. Zhang, A. Matin, Y. Wang, P. Li, S. Y. Xiao, W. Du, T. C. He, and C. S. Yuan, "Panax notoginseng attenuates experimental colitis in AOM/DSS mouse model," Phytotherapy Research 28 no 6 (2014): 892–898.
74. V. S. Kotakadi, Y. Jin, A. B Hofseth, L. Ying, X. Cui, S. Volate, A. Chumanevich,P. A. Wood, R. L. Price, A. McNeal, U. P. Singh, N. P. Singh, M. Nagarkatti, P. S. Nagarkatti, L. E. Matesic, K. Auclair, M. J. Wargovich, and L. J. Hofseth, "Ginkgo biloba extract EGb 761 has anti-inflammatory properties and ameliorates colitis in mice by driving effector T cell apoptosis," Carcinogenesis 29 no 9 (2008): 1799–1806.
75. L. P. Manzo, F. M. de-Faria, R. J. Dunder, E. A. Rabelo-Socca, S. R. Consonni, A. C. de Almeida, A. R. Souza-Brito, and A. Luiz-Ferreira, "Royal Jelly and Its Dual Role in TNBS Colitis in Mice," Scientific World Journal 2015 (2015): 956235.
76. M. S. Lee, J. Lee, and Y. Kim, "Green Tea Extract Containing Piper retro fractum Fruit Ameliorates DSS-Induced Colitis via Modulating MicroRNA-21

© 2025 IJSRET

Expression and NF-κB Activity," Nutrients 14 no 13 (2022): 2684.
77. T. Larussa, M. Oliverio, E. Suraci, M. Greco, R. Placida, S. Gervasi, R. Marasco, M. Imeneo, D. Paolino, L. Tucci, E. Gulletta, M. Fresta, A. Procopio, and F. Luzza, "Oleuropein Decreases Cyclooxygenase-2 and Interleukin-17 Expression and Attenuates Inflammatory Damage in Colonic Samples from Ulcerative Colitis Patients," Nutrients 9 no 4 (2017): 391.
78. A.Maitham, Z. Khajah Ahmed, E. L. Hashim, Y. Khaled, Orabi, Sanaa Hawai, G. Hanan, Sary, "Onion bulb extract can both reverse and prevent colitis in mice via inhibition of pro-inflammatory signaling molecules and neutrophil activity," PLoS One 15 no 10 (2020): e0233938.

© 2025 IJSRET