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From Serendipity to Strategy: Repurposed Drugs and Their Mechanistic Role in Inflammatory Bowel Disease

S. Sarankarthikeyan[1]; Dr. Ariharasivakumar Ganesan[2]; C. Rejina[3]; Harish Kumar E.[4]

[1,2,3,4]Department of Pharmacology, K.M.C.H College of Pharmacy, Coimbatore, Tamil Nadu 641048.

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Abstract: Inflammatory Bowel Disease (IBD), which includes Crohn's disease and ulcerative colitis, represents an increasing global health challenge. The traditional process of drug development is both slow and expensive, leading to a growing interest in drug repurposing as a viable alternative strategy. This review emphasizes the therapeutic promise of five repurposed medications quinacrine, febuxostat, dapsone, amitriptyline, and bazedoxifene each of which targets critical inflammatory and oxidative pathways implicated in the pathogenesis of IBD. These drugs, initially approved for different medical conditions, exhibit encouraging anti-inflammatory, antioxidant, and barrier-protective properties in preclinical models of IBD. By modulating signalling pathways such as NF-κB, TLR4, and STAT3, as well as affecting gut microbiota, these agents present novel opportunities for the management of IBD, characterized by enhanced safety profiles and translational significance.

Keywords: *Drug Repurposing, Quinacrine, Febuxostat, Dapsone, Amitriptyline, Bazedoxifene, NF-κB signalling, TLR4 Pathway, STAT3 Pathway, Oxidative Stress, Gut Microbiota Modulation.*

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I. INTRODUCTION

Traditionally, Inflammatory Bowel Disease (IBD) is viewed as a peripheral ailment defined by intestinal inflammation of unknown origin, primarily impacting the ileum, colon, and rectum. They treated primarily with therapies that focus on the immune system. Many pathways include NF-kB, NOS, COX-2. Conversely, Irritable Bowel Syndrome (IBS) has been considered a disorder linked to central mechanisms, diagnosed by excluding organic causes, and is often managed with lifestyle adjustments and symptom relief strategies. There exists an overlap in epidemiological, genetic, immunological, and microbiological factors. Quality of Life (QoL) is frequently compromised in both conditions. [1,2,3] IBD diseases include Crohn's disease (CD) and ulcerative colitis (UC).

Crohn's disease (CD) is an idiopathic chronic inflammatory illness that affect all parts of the gastro intestinal tract, from mouth to anus, but most commonly involves the distal part of the small intestine or ileum, and colon. A combination of genetic tendencies, environmental impacts, and changes in gut microbiota results in imbalanced innate and adaptive immune responses. Patients with CD are more prone to weight loss, nutrient deficiencies, and in children, growth retardation, especially after glucocorticoid therapy. Crohn's disease is characterized by relapses. Other serious complications include perforation or micro perforation of the small or large bowel which may result in abscess formation. Surgical resection of the colon is not curative because CD can affect all parts of the gastrointestinal tract from mouth to anus. Numerous Crohn's disease patients exhibit low vitamin D levels, iron insufficiency, anaemia, and elevated inflammatory markers such as fecal calprotectin, erythrocyte sedimentation rate, and C-reactive protein. [4,5,6]

Ulcerative colitis is a chronic, non-specific, recurring inflammatory gastrointestinal disorder characterized by intestinal inflammation and damage of the intestinal mucosa. UC results in colonic inflammation that can affect the rectum only (proctitis) or can cause continuous disease from the rectum proximally to involve part of or the entire colon. UC is mostly a condition that affects developed Western countries. However, newly industrialized nations like China, India, and Latin America have seen rapid increases in both incidence and hospitalization rates. The frequency of UC was about 5 million worldwide in 2023. The pathophysiology and symptoms of UC are intricate and complicated. Clinical symptoms include diarrhoea, abdominal pain, gastrointestinal bleeding (rectal bleeding), and weight loss [7,8]. 47% of cases

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had the disease in the terminal ileum, 28% in the colon, 21% in the ileocolon, and 3% in the upper gastrointestinal tract. 70% of patients have disease behaviour that is characterized as non-stricturing and nonpenetrating, 17% have stricturing, and 13% of all patients have penetrating (fistulas, abscesses, or both) at diagnosis [9]. Typical manifestations include the intermittent involvement of different gastrointestinal system segments and the emergence of complications such as fistulas, strictures, or abscesses. Depending on where the disease is located, the clinical presentation might vary greatly. It may include fever, diarrhoea, stomach pain, clinical symptoms of bowel blockage, and the passage of mucus or blood or both [9,8,6]. Chronic intestinal inflammation due to inflammatory bowel disease (IBD) significantly heightens the risk of developing colitis-associated colorectal cancer (CAC). Persistent immune activation causes an imbalance in macrophage polarization pro-inflammatory M1 macrophages lead to tissue damage, while anti-inflammatory M2 macrophages, which are more common in the later stages of the disease, aid in angiogenesis, remodelling of the extracellular matrix, and immune suppression [10]. This pro-tumour microenvironment encourages the progression from dysplasia to carcinoma through the actions of cytokines (such as TNF-α, IL-6, and TGF-β), the activation of NF-κB/STAT3 pathways, and COX-2/PGE_2 signalling, ultimately speeding up malignant transformation and cancer dissemination. It is associated with an increased risk of colorectal cancer in 8-10 years after disease onset of colitis at a rate of 0.5 - 1% for every year of disease duration. The severity of the disease also has a significant impact on the transformation of the disease into colorectal cancer [10,11,12]

II. EPIDEMIOLOGY

Inflammatory/ Irritable Bowel Disease (IBD) is a long-lasting, untreatable condition that is expensive to manage, and is characterized by recurring symptoms and impairment. IBD is becoming more and more common worldwide, particularly in emerging and recently industrialized nations. IBD exhibits notable regional variations, with industrialized nations having the greatest rates. In particular, the highest disease burden for both UC and CD is reported in North America, Northern and Western Europe, and Oceania. Of all the countries, the Faroe Islands have the highest recorded incidence of UC, with approximately 44 cases per 100,000 people annually. Finland and the US follow with 35 and 32.5 instances per 100,000 according. Conversely, New Zealand has the greatest incidence of CD with 26 instances per 100,000, followed by San Marino (17.9/100,000) and Denmark (15.6/100,000), all of which have notable high rates [1,2,13]. These tendencies could be attributed to a combination of environmental factors typical in these regions, western food patterns, and genetic predisposition. In contrast, Asian countries, particularly those in Southeast Asia, consistently report the lowest incidence rates for both ulcerative colitis (UC) and Crohn's disease (CD). For UC, the Philippines (0.15/100,000), Brunei Darussalam (0.21/100,000), and Thailand (0.24/100,000) have the lowest reported cases. Likewise, the Philippines (0.16/100,000), Indonesia (0.25/100,000), and Thailand (0.28/100,000) show the lowest incidence rates for CD. These relatively low statistics may indicate not only genuine epidemiological variations but also possible underdiagnosis or restricted access to advanced diagnostic resources in certain low-income areas. To summarize, the epidemiological patterns of inflammatory bowel disease (IBD) are closely associated with levels of industrialization and urbanization, reinforcing the idea that environmental factors such as diet, sanitation, and antibiotic use play a significant role in the development of these conditions. The global age-standardized incidence rate (ASIR) of IBD increased from 4.22 per 100,000 to 4.45 per 100,000 between 1990 and 2021. The age-standardized mortality rate (ASMR) decreased to 0.52 per 100,000 in 2021 from 0.60 per 100,000 in 1990. From 1990 to 2021, age-standardized disease-adjusted life years (DALYs) decreased from 21.55 per 100,000 to 18.07 per 100,000. IBD is becoming more and more common worldwide, particularly in emerging and recently industrialized nations. Additionally, those with IBD are more likely to get cancer, which adds to the burden. 10% to 15% of IBD patients die from IBD-related colorectal cancer (CRC), which is also a major cause of IBD patients' surgical procedures [14,15,16]. The incidence of PIBD (Paediatric-Onset Inflammatory Bowel Disease) rose but the DALY and death rates decreased from 1990 to 2019. In the high Socio-demographic Index (SDI) quintile, the incidence rate was significantly higher, at 6.3 per 100,000 person-years, or 13,914 new cases in 2019. The SDI had a positive correlation with the incidence and prevalence of PIBD, whereas lower-SDI countries had higher burdens of death and DALY. Canada (19.9 per 100,000 population), Denmark (12.4 per 100,000 population), Hungary (8.5 per 100,000 population), Austria (8.1 per 100,000 population), and the United States (7.4 per 100,000 population) had the highest incidence rates of PIBD in 2019. The peak incidence rates for Crohn's Disease (CD) and Ulcerative Colitis (UC) are observed in the age brackets of 20 to 30 years and 30 to 40 years, respectively. Both CD and UC show similar incidence and prevalence rates among males and females. Nevertheless, various studies have indicated a higher occurrence of CD in females and a greater prevalence of UC in males [14,15]. In 2017, it was estimated that 6.8 million cases, 0.83 million years of lost life, and 1.02 million years of disability were caused by IBD worldwide. Despite the low death rate, the medical systems around the world are under a lot of stress because to IBD's lengthy course, hospital stays, operations, ambulatory care, and pharmaceutical consumption [15,16].

III. DRUG REPURPOSING

There are multiple steps involved in traditional drug research and discovery in order to find a novel medication and secure marketing approval. Finding novel methods to shorten the time needed for medication discovery is essential. Repurposing is usually accomplished either systematically or serendipitously.

Drug repurposing has become more significant in the modern era for finding novel therapeutic applications for pharmaceuticals that are already on the market. Because it offers a fresh method of repurposing old medications for new uses. Drug repurposing emerged as a successful strategy for drug development, despite a number of obstacles [16,17].

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Drug-repurposing technologies are becoming more numerous and more advanced. The reality that developing new drugs usually takes years and costs billions of dollars. The ultimate goal of repurposing research is to improve health and quality of life by properly anticipating clinical utility and using the predictions to save the time and expense of drug discovery and development. In vitro and in vivo screening, anecdotal evidence, the finding of coincidental beneficial effects in clinical trials, or post-market patient health record analysis have all formed the foundation for successful drug repurposing cases [18,19]. Fig 1&2.

IV. LIMITATIONS

Repurposed medications may have less than ideal binding affinity, selectivity, or potency because they were not initially designed for the novel target or pathway. For example, because of its antiviral properties in vitro, chloroquine/hydro chloroquine was repurposed for COVID-19. However, because of QT prolongation, the in vivo outcomes were unsatisfactory and even dangerous.

The dosage needed for the new indication can be too low, which would make it ineffective, or too high, which would make it poisonous [18]. For example, Thalidomide, for instance, works at higher dosages in the treatment of cancer than it did as a sedative, but its teratogenic effects are still a worry for susceptible groups.

A lot of repurposed medications are not covered by patents, which frequently makes pharmaceutical corporations uninterested because of the low profit margins. Commercializing or licensing your research findings may present difficulties for you as a researcher. Repurposing can happen without a clear grasp of how the medicine works in the new setting, which is dangerous. For example, the anti-epileptic medication valproic acid is being investigated for the treatment of cancer; however, it affects several epigenetic targets, raising the possibility of side effects. [19].

In vitro docking and genetic correlations may signal potential, but in vivo or clinical efficacy is typically not translated. Due to the complexity of human biology or insufficient bioavailability, several repurposing concepts based on computer docking, such as ACE2-binding medications in COVID, have failed in trials [20].

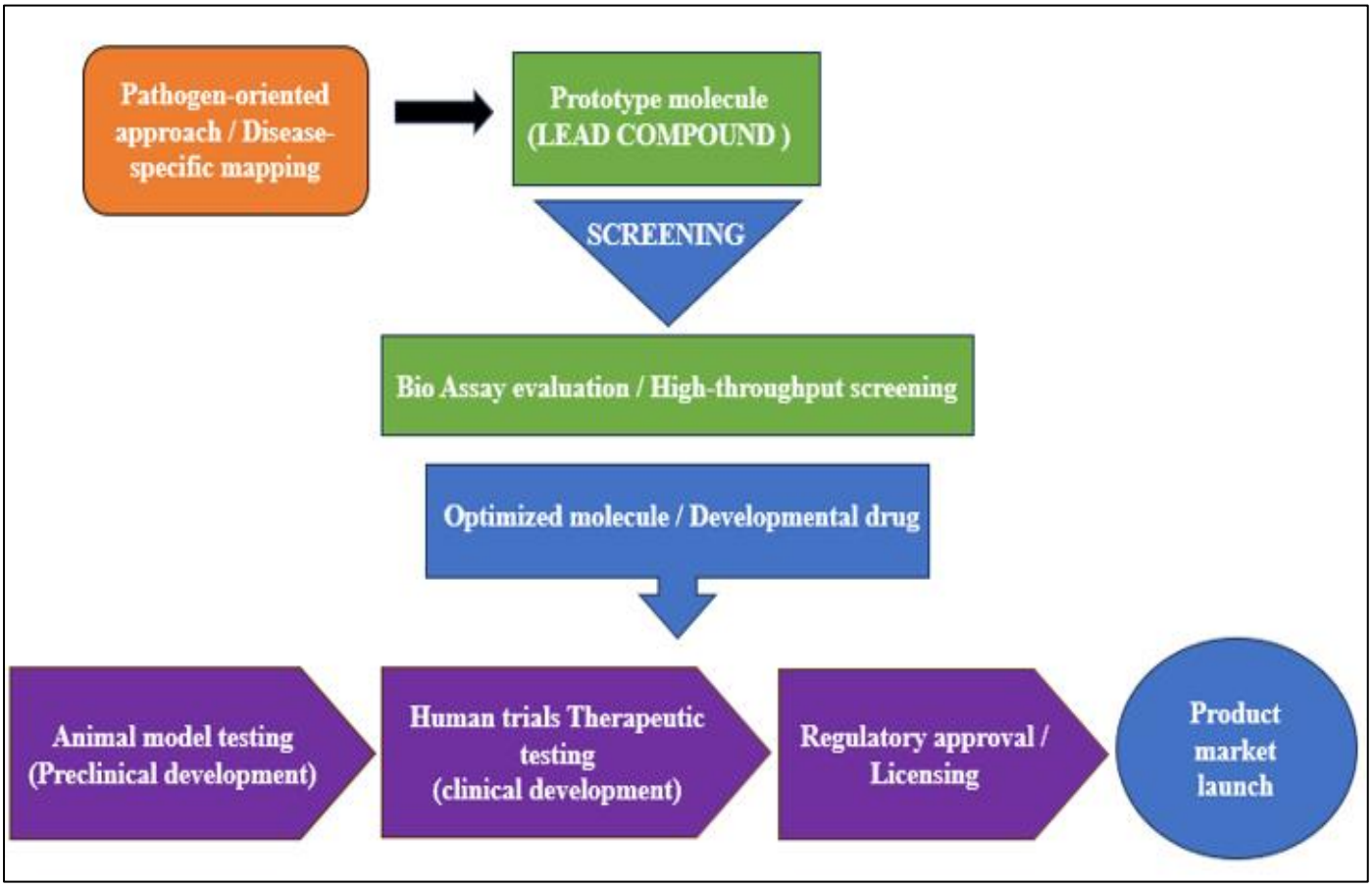

Fig 1 Traditional Drug Section

Fig 1: From disease-specific lead identification and screening to optimization, preclinical and clinical evaluation, and final regulatory approval, this schematic illustrates the sequential steps of drug discovery and development. It highlights the difficulties and checkpoints associated with introducing innovative treatments to the market by focusing on the translational process of prototype molecules into therapeutic agents.

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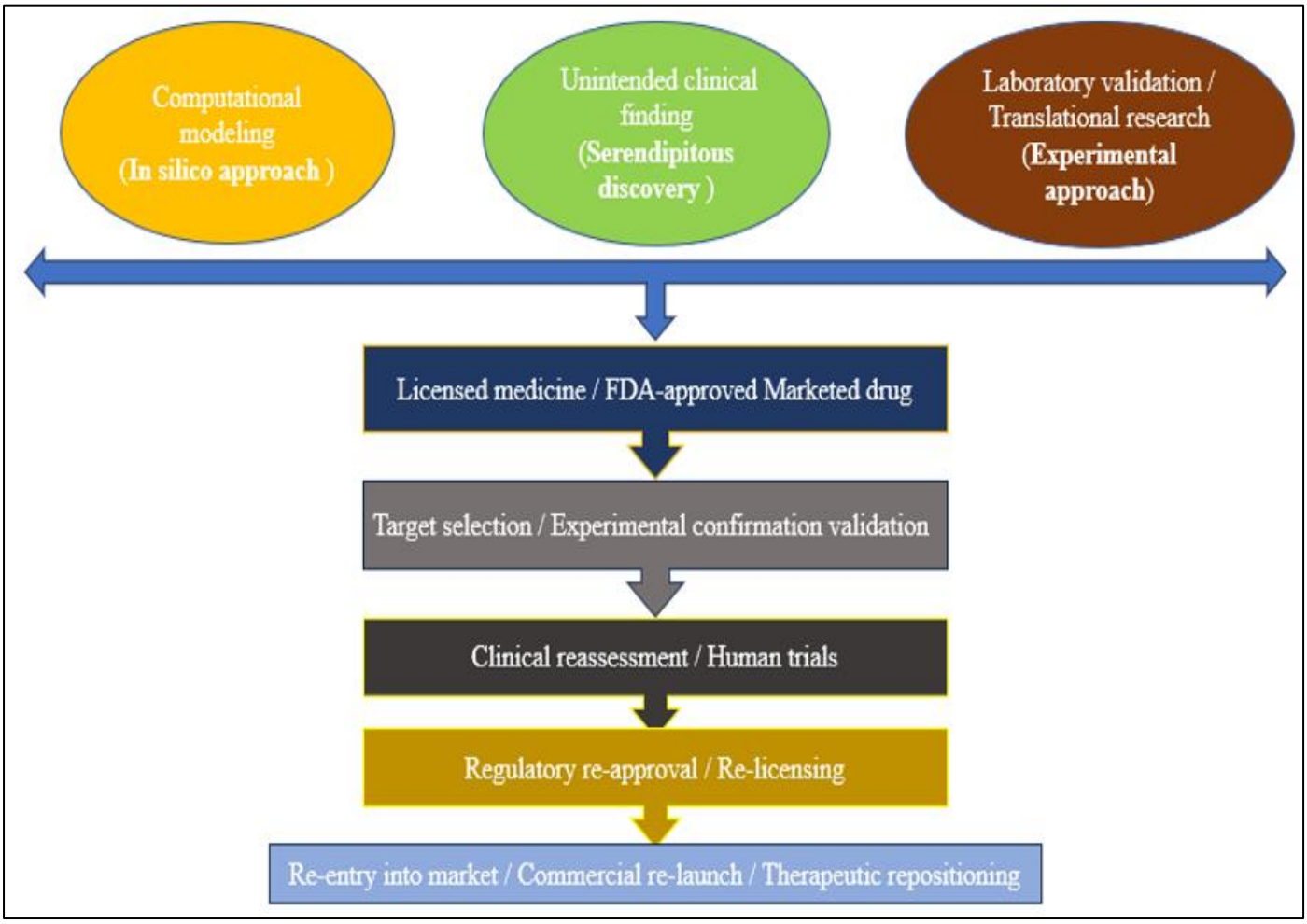

Fig 2 Drug Repurposing Section

Fig 2: The framework of drug repurposing is depicted in this diagram, whereby licensed medications are repositioned for new indications through experimental validation, computational modelling, or coincidental clinical findings. In order to enable therapeutic re-entry into the market, the process entails target confirmation, clinical reassessment, and regulatory re-approval. It emphasizes how effective repurposing techniques are at speeding up drug availability in contrast to conventional drug development.

➢ *Repurposing Drug – Quinacrine*

The Quinacrine medication, which was originally used to treat malaria, is currently being used to treat ulcerative colitis (UC) [21]. Quinacrine has been utilized to treat a number of inflammatory conditions, including giardiasis, tapeworm infestations, and connective tissue disorders including rheumatoid arthritis and lupus erythematosus. It is a potential therapy option for UC due to its possible anti-cancer effects. Using animal models of ulcerative colitis, the study examines quinacrine's anti-inflammatory, antioxidant, and anti-tumorigenic qualities [22]. Quinacrine are administered at two different doses as a colitis treatment agent in two mouse models of UC. The dextran sulfate sodium (2%) and oxazolone were induced. Inflammatory indicators (Cox-2, iNOS, p53), colon histological alterations, the clinical disease index (CDI), and general health vitals were assessed. An enzyme that produces pro-inflammatory eicosanoids, phospholipase A2, is inhibited by quinacrine. Quinacrine lowers the synthesis of inflammatory mediators by blocking this enzyme [23,24]. A decrease in inflammatory markers linked to oxidative stress and inflammation, such as Cox-2 and iNOS, has been noted. Quinacrine also affects the p53 pathway, which is involved in apoptosis and cell cycle control. This modification aids in colon healing and inflammation reduction. Quinacrine inhibits iNOS in vitro and iNOS, Cox-2, and p53 in vivo in two different colitis modelling mice. Quinacrine also interferes with the production of prostaglandins, phospholipase A2, and the arachidonic acid cascade, which are further mediators of inflammation [25,26]. Quinacrine also inhibits IL-1β, TNFα, and NF-κB. By increasing granulocyte recruitment and innate lymphoid cell accumulation and activation, IL-1β mechanistically contributes to innate immune dysfunction in intestinal inflammation. So, hampering IL-1β signalling has anti-inflammatory properties. The development of colitis and colon cancer linked to colitis seems to be significantly influenced by NF-kB signalling in myeloid cells [27,28]. In conclusion, the results of this study provide light on quinacrine's effective mechanisms for lessening colon inflammation and potentially preventing colon cancer. Fig 4,5,6.

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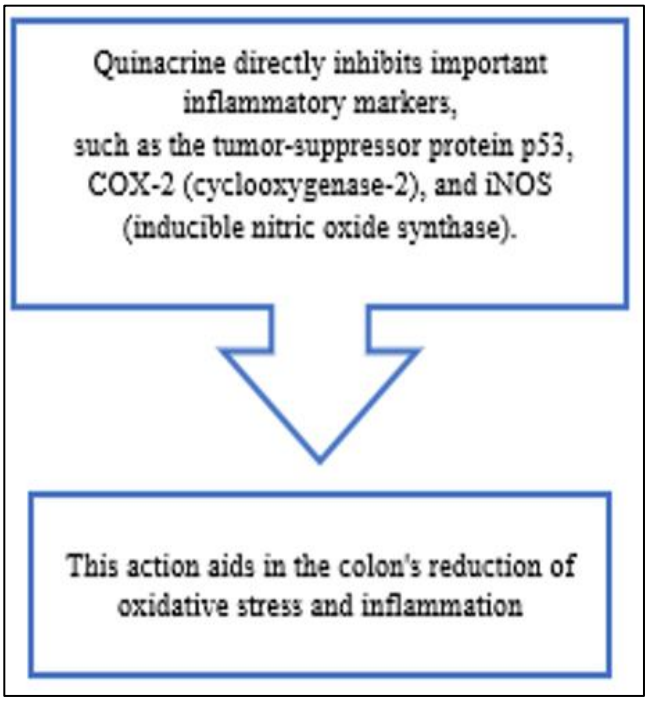

Fig 3 Downregulation of Inflammatory Markers

Fig 3 The mechanism by which quinacrine inhibits phospholipase A2 (PLA2) is depicted in this schematic. Quinacrine stops the release of arachidonic acid, a crucial precursor of pro-inflammatory mediators like prostaglandins, by inhibiting PLA2 activity. As a result, inflammatory signalling is significantly reduced, underscoring quinacrine's potential as a treatment for diseases caused by inflammation.

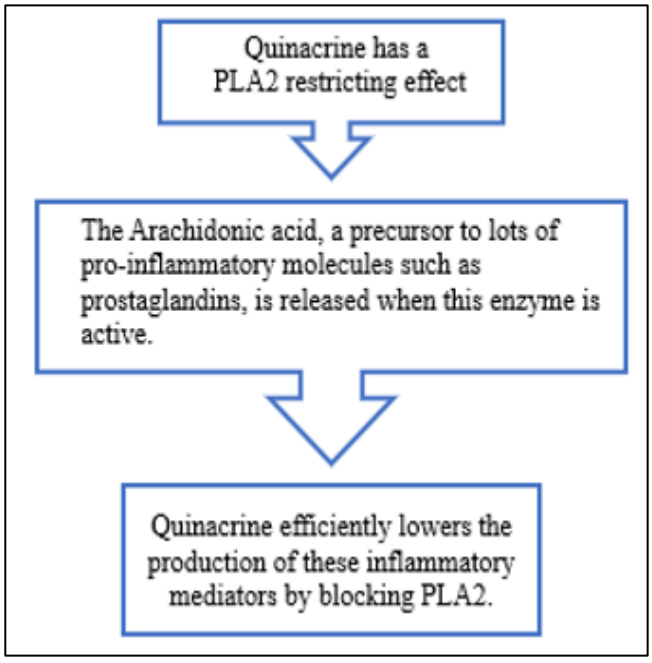

Fig 4 Phospholipase a2 (PLA2) Inhibition

This figure 4: Explains how quinacrine exerts its anti-inflammatory effect by inhibiting Phospholipase A2 (PLA2). This figure explains how quinacrine exerts its anti-inflammatory effect by inhibiting Phospholipase A2 (PLA2). By restricting PLA2 activity, it prevents arachidonic acid release, thereby reducing the synthesis of pro-inflammatory mediators like prostaglandins. This mechanism highlights quinacrine's role in dampening inflammatory pathways relevant to immune-mediated diseases. By restricting PLA2 activity, it prevents arachidonic acid release, thereby reducing the synthesis of pro-inflammatory mediators like prostaglandins. This mechanism highlights quinacrine's role in dampening inflammatory pathways relevant to immune-mediated diseases.

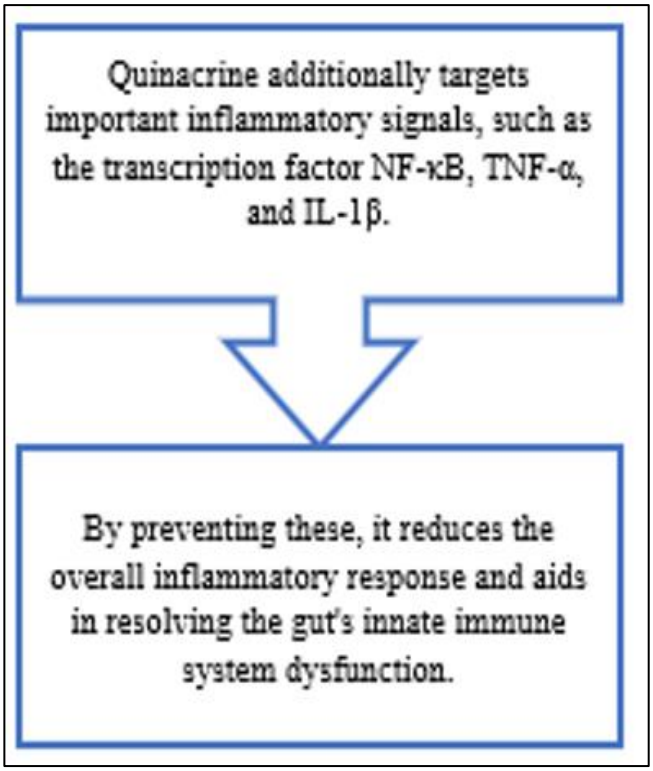

Fig 5 Inhibition of Cytokines and Transcription Factors

Figure 5: This figure depicts quinacrine's action in modulating key inflammatory mediators, including NF-κB, TNF-α, and IL-1β. By inhibiting these pivotal cytokines and transcription factors, quinacrine suppresses the inflammatory cascade and helps restore intestinal immune homeostasis, underscoring its therapeutic relevance in IBD and related disorders.

➢ *Repurposing Drug – Febuxostat*

Febuxostat is a non-purine xanthine oxidase inhibitor that has been clinically authorized to treat gout by lowering the body's uric acid levels. It has been discovered that Febuxostat possesses strong anti-inflammatory and antioxidant properties.

Febuxostat has been proposed to have anti-inflammatory and antioxidant effects because it can prevent inflammation and oxidative stress caused by xanthine oxidase. 5% acetic acid-induced UC in a mouse model. The weight, colon length, macroscopic damage, and histological changes of mice given oral non-benzothiazine (10 and 20 mg/kg/day) for three days were evaluated. Weight loss, colon shortening, and macroscopic damage were all considerably

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decreased by non-benzothiazine treatment [29,30,31]. Acetic acid can be diagnosed by a loss of goblet cells, overkill vascular density, submucosal edema, and high levels of reduced these alterations in histology and pathologic score. A therapy of acetic acid markedly raised the levels of carbonyl proteins and MDA, which are hallmarks of oxidative damage in colon tissue.

Notwithstanding, febuxostat intervention completely lowered the levels of MDA and carbonyl proteins. Febuxostat's inhibition of protein carbonylation and lipid peroxidation might end up saving colonic tissue to oxidative injury. In the colon, the depletion of GSH and SOD result in ROS to establish up, which ultimately impacts cell damage and death. GSH and SOD levels were decisively restored alongside febuxostat. [32,30,29].

An abundance physiological processes of the gastrointestinal system rely on nitric oxide, a crucial biological mediator. Excessive NO generation has been affiliated to the pathophysiology of ulcerative colitis and can be disruptive to cells. Peroxynitrite and then peroxynitrous acid (ONOOH) can be produced when NO and superoxide anion react. The xanthine oxidase enzyme is eloquent in the progression of oxidative and inflammatory diseases like IBD. It is naturally found in the intestinal tissue, and its activity amplify in trouble conditions.

Harmful oxygen radicals bring about by live xanthine oxidase can cause detriment to the intestinal tissue. The Study has also shown that the activity of xanthine oxidase can be speeded (up) by functioning neutrophils and inflammatory substances, such as TNF-α, during ulcerative colitis. Studies possess shown that clumping xanthine oxidase might be a workable treatment for diseases akin to reactive oxygen species (ROS), including IBD. [33,34].

The extremely deadly oxidants peroxynitrite and its conjugate acid could kill cells by DNA damage, peroxidation of lipids, oxidative damage to proteins, enzyme suppression, and the impact with cellular signalling pathways. Through the stimulation of the NF-κB signalling pathway, excessive NO development by induce nitric oxide synthase (iNOS) that harm the mucosa of the colon.

The proliferation of colonic inflammation and damage has a significant impact by neutrophil infiltration into the lining of the colon. MPO has been used deeply for evaluating colonic inflammation as a biomarker of neutrophil infiltration. The application of acetic acid drastically improved the colonic tissues' MPO activity [1]. IL-10 diminishes NF-κB activity and stops the synthesis of cytokines that cause inflammation like TNF-α, IL-1β, and IFN-γ [34,35]. In one word, febuxostat drastically reduced acetic acid-induced NF-kB in the colon tissues, however acetic acid induction hindered the NF-kB pathway. Fig 6,7,8.

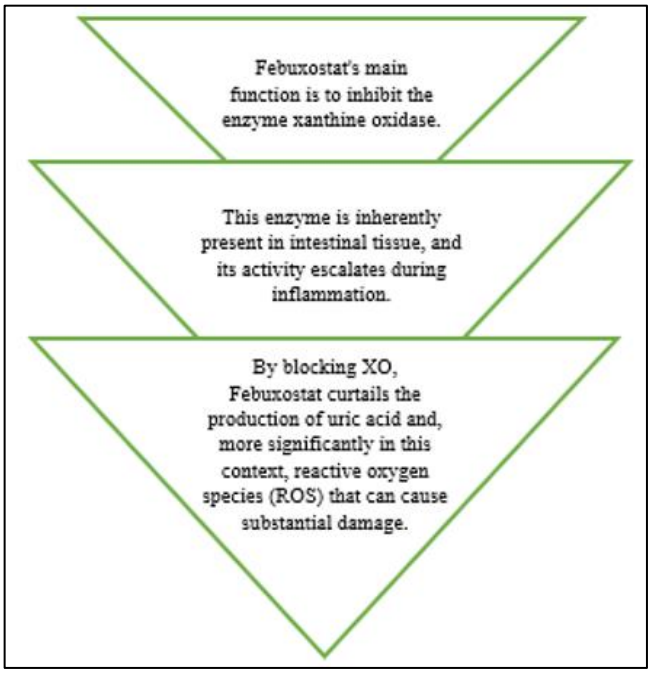

Fig 6 Xanthine (XO) Inhibition

Figure 6 shows how febuxostat inhibits xanthine oxidase, an enzyme that is upregulated during intestinal inflammation. Febuxostat inhibits XO, which lowers the production of uric acid and reactive oxygen species (ROS). This lessens tissue damage caused by oxidative stress and shows promise as a treatment for oxidative damage associated with IBD.

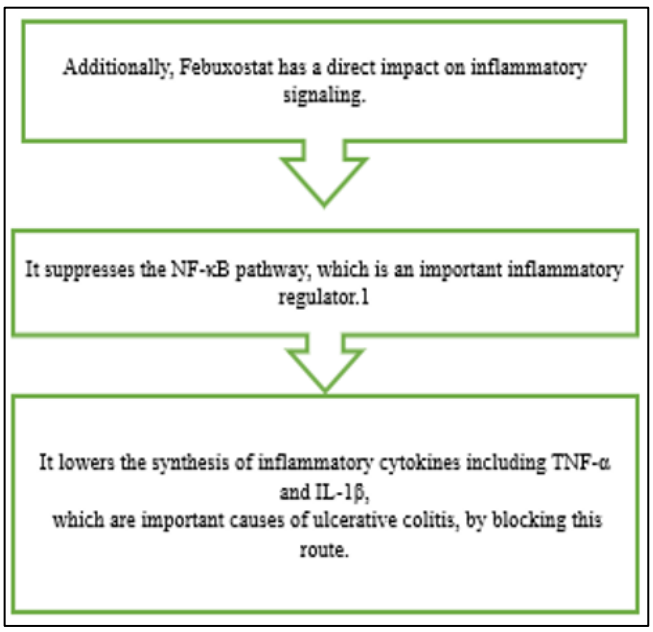

Fig 7 Blocking Inflammatory Pathways

This figure 7 Ddemonstrates how febuxostat modulates inflammatory signaling pathways, specifically by suppressing the NF-κB axis. Febuxostat reduces intestinal inflammation and aids in the treatment of ulcerative colitis by downregulating NF-κB-mediated transcription, which in turn reduces the release of important pro-inflammatory cytokines like TNF-α and IL-1β.

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Fig 8 Reducing Neutrophil Infiltration

This figure 8 illustrates how febuxostat directly targets NF-κB signaling to modulate inflammatory pathways in addition to inhibiting xanthine oxidase. By suppressing NF-κB, febuxostat reduces tissue damage and mucosal inflammation by lowering the production of cytokines like TNF-α and IL-1β, which are key players in the pathophysiology of ulcerative colitis.

➢ *Repurposing Drug- Dapsone*

Dapsone has demonstrated potential in lowering inflammation and has long been used to treat respiratory and dermatological issues. This examines how it might be used to treat colitis. Dihydropteroate synthase can be inhibited by the antimicrobial medication dapsone.

Dapsone has also gained recognition as an anti-inflammatory medication in recent decades [36]. Its anti-inflammatory qualities have been associated with reducing oxidative stress, inhibiting neutrophil myeloperoxidase, and improving a number of inflammatory skin conditions. Additionally, it can stop neutrophils from migrating to areas of inflammation. In addition, it is a frequent antibiotic used to treat leprosy in conjunction with rifampicin and clofazimine. It is used as a second-line treatment for pneumocystis pneumonia and to prevent toxoplasmosis in people with compromised immune systems [37,38]. For this investigation, thirty male Wistar rats weighing between 250 and 300 g were chosen at random. After being randomly assigned to five groups, which included healthy rats, colitis was brought on by administering 100 mg/kg of 2,4,6-trinitrobenzenesulfonic acid (TNBS) Intra-rectally. Rats were given dapsone (10, 12.5, and 20 mg/kg) via gavage every day [39]. Body weight, colon length, macroscopic damage, and histological alterations are among the clinical parameters that are assessed. Cytokines that promote inflammation are Significant drops in TNF-α and IFN-γ levels show that dapsone has an anti-inflammatory impact. Malondialdehyde (MDA) and glutathione (GSH) levels are indicators of oxidative stress. Dapsone strengthens the body's antioxidant defence by raising GSH and lowering MDA levels, which helps shield colonic tissues from oxidative stress [39,37,36]. Following treatment with 20 mg/kg/d dapsone, rats' necrotic area length dramatically shrank. In comparison to the TNBS group, dapsone (20 mg/kg/d) significantly reduced the macroscopic appearance of colitis. The microarchitecture of the colon was retained by dapsone, especially at a dose of 20 mg/kg/d. By preventing cytokine overproduction and blocking TLR4/NF-kB signalling, dapsone decreased inflammation. [39,40].

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A rat model of acetic acid-induced colitis, which is typical of ulcerative colitis, showed that dapsone could successfully reduce inflammation. Fascinatingly, dapsone reduced edema and immune cell infiltration while maintaining mucosal structure in this investigation. It effectively reduced the inflammatory response and mitigated tissue damage in this animal model of CD [40,41]. Finally, Dapsone achieve its anti-inflammatory actions and reduce the overproduction of inflammatory cytokines, dapsone inhibited the TLR4/p65-NFκB pathway. Fig 9,10.

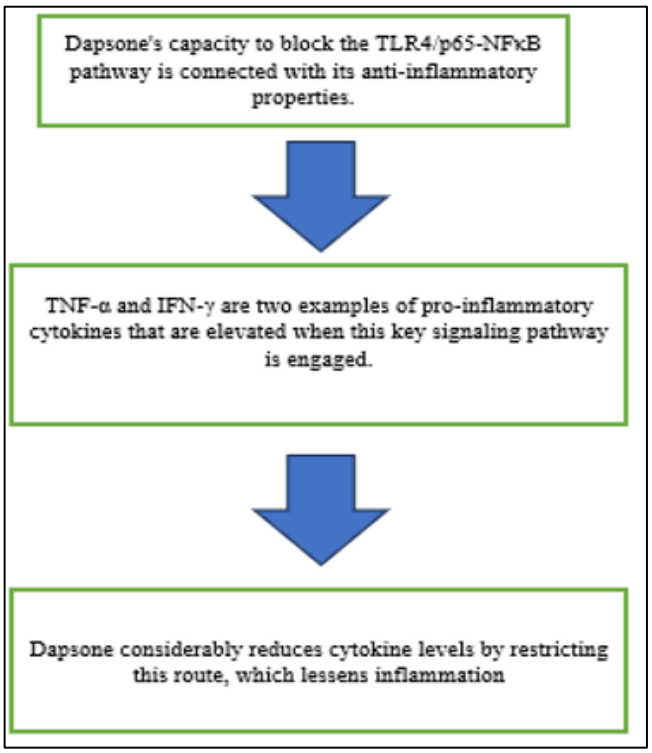

Fig 9 Modulation of Inflammatory Pathways

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This figure 9 highlights that dapsone mediates its anti-inflammatory effects by modulating the TLR4/p65-NFκB signaling pathway. By suppressing this cascade, dapsone reduces the expression of pro-inflammatory cytokines such as TNF-α and IFN-γ, thereby attenuating mucosal inflammation and contributing to immune regulation in IBD pathology.

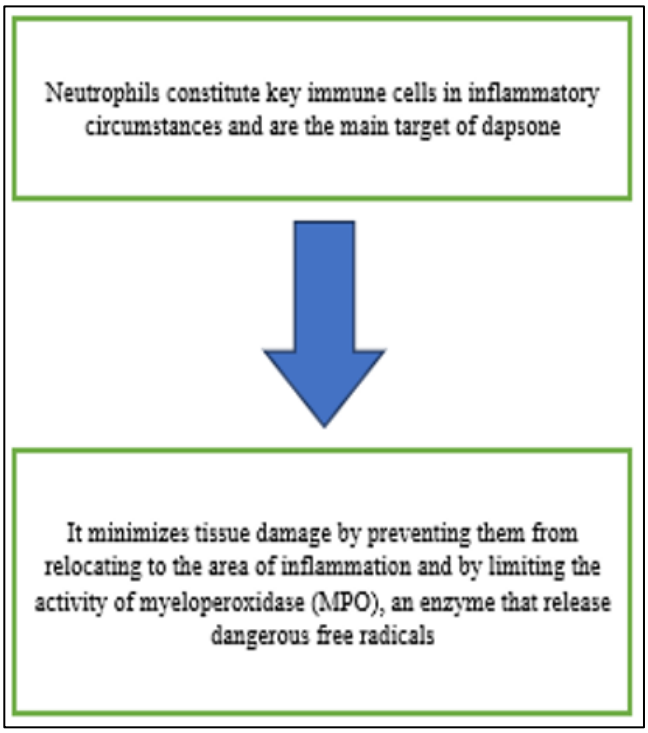

Fig 10 Neutrophil Inhibition

This figure 10 illustrates that dapsone exerts its therapeutic effect by targeting neutrophils, the primary immune cells driving inflammation in IBD. By blocking neutrophil migration to inflamed sites and suppressing myeloperoxidase (MPO) activity, dapsone reduces oxidative stress and tissue injury, thereby mitigating the inflammatory cascade in intestinal pathology.

➢ *Repurposing Drug - Amitriptyline*

Amitriptyline, a pleiotropic tricyclic antidepressant, possesses antioxidant and anti-inflammatory properties. Amitriptyline was effectiveness in preventing infiltration of leukocytes and myeloperoxidase activity in a rat model of ulcerative colitis. Though amitriptyline's anti-inflammatory properties have been extensively investigated, the precise mechanisms toward its effect are yet a mystery [42,43].

Our study demonstrated how amitriptyline accelerated the repair of intestinal mucosal injury and diminished proinflammatory cytokine levels in mice with DSS-induced colitis. The suppression of the TLR-4/MD-2 signalling pathway may be responsible for this protective effect [44,45]. The primary line of defence against a hostile environment in the intestinal tract is the intestinal barrier, which is comprised of the mucus and epithelial layer.

While TJ proteins which includes ZO-1, claudin-1, and occluding aid to hold onto the integrity of the epithelial layer between intestinal epithelial cells, mucins in the colon, such as mucin-2, are vital for the maintenance of the mucosal barrier. TJ and mucin 2 protein expression has dropped in mice with DSS-induced colitis. Interestingly, amitriptyline treatment seems to effectively increase these low levels again [46,47]. The results shown suggest amitriptyline can possibly lessens DSS-induced colitis via regulating the intestinal mucosal barrier's function. The fluctuations of cytokine levels brought on by DSS were significantly undone by amitriptyline, foremost those of TNF-a, IL-1b, and IL-6. The invasion of inflammatory cells is often associated with variations in cytokine levels. Amitriptyline safely avoided the DSS-induced incorporation of CD11bþ neutrophils and F4/80þ macrophages, based on the study, which also evaluated the infiltration of immune cells, mainly neutrophils and macrophages [48,49]. Moreover, transcriptome analysis disclosed that the cytokine- cytokine receptor interaction pathway, which is essential for inflammation, also been profoundly affected by DSS treatment. RNA sequencing analysis following amitriptyline treatment revealed significant alterations in gene expression in the colons of mice with DSS-induced colitis [48,49].

The findings demonstrated that amitriptyline substantially downregulated a number of genes that regulate very significant signalling pathways that contribute to inflammation, especially TNF, JAK-STAT, NF-kB, and TLR signaling pathways. Amitriptyline can mitigate the secondary immunological response by blocking the NF-kB signaling pathway in osteoblasts, synoviocytes, and chondrocytes [49,50]. Amitriptyline's impact on the TLR-4/NF-kB signaling pathways instantly assist in hindering the inflammatory responses correlated with DSS-induced colitis. By boosting the production of proinflammatory cytokines that are necessary for the enhancement of both the innate and adaptive immune responses, TLR-4 plays an essential role in the awakening of macrophages [50,49,51].

Microbial components that excite the TLR-4/MD-2 complex initiate a signalling cascade that engages NF-kB and produces proinflammatory cytokines. Therapeutic approaches that target TLR-4 have demonstrated promise in reducing intestinal inflammation, suggesting that the TLR-4/NF-kB signaling pathway could be a useful target for the management of IBD [51,52].

Our investigation also revealed a notable increase in MD-2 protein expression in RAW264.7 cells after LPS stimulation, which was reversed with amitriptyline treatment. These results suggest that inhibiting the overactivation of the TLR-4/MD-2 signalling pathway contributes to the anti-inflammatory effects of amitriptyline in DSS-induced colitis. The idea of repurposing amitriptyline to manage inflammation in auto immune diseases like IBD. This expansion of amitriptyline’s therapeutic potential beyond psychological disorders and pain management highlights the value of drug repurposing [49,50,52].

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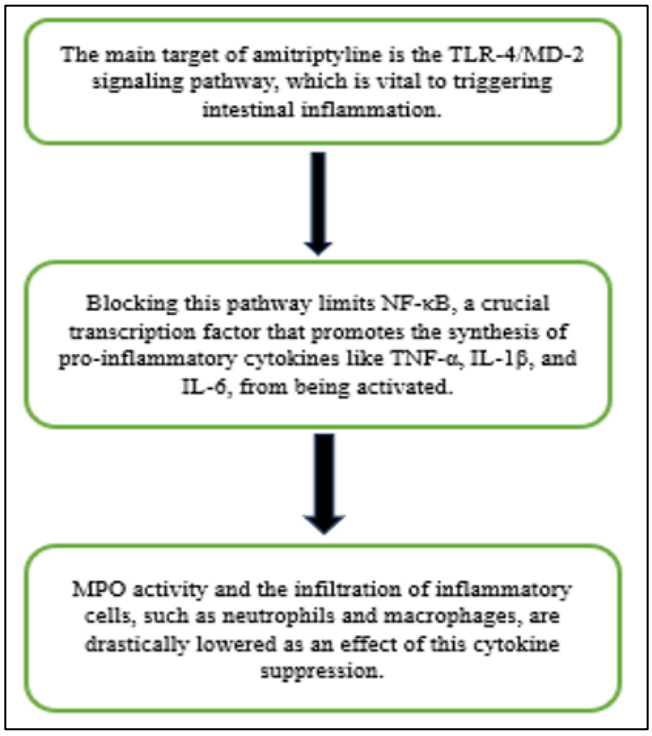

Fig 11 Modulation of Inflammatory Pathways

Fig 11 : In IBD, amitriptyline reduces the transcription of important cytokines like TNF-α, IL-1β, and IL-6 by targeting the TLR-4/MD-2–NF-κB signaling axis. In the end, this suppression reduces intestinal inflammation and mucosal damage by lowering MPO activity and limiting neutrophil and macrophage infiltration.

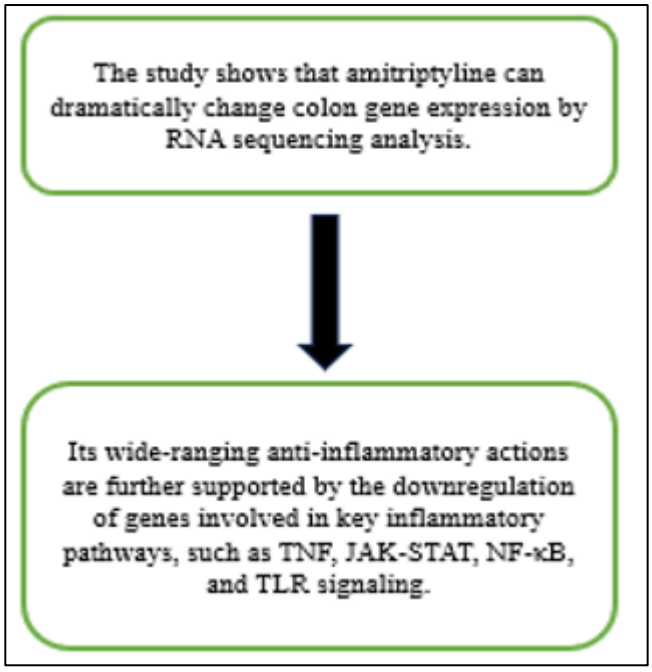

Fig 12 Modulation of Gene Expression

Fig 12: Amitriptyline downregulates several inflammatory pathways, such as TNF, JAK-STAT, NF-κB, and TLR signaling, and significantly changes the expression of colon genes, as shown by RNA sequencing. Its therapeutic potential in reducing intestinal inflammation through multi-targeted molecular regulation is highlighted by this broad-spectrum suppression.

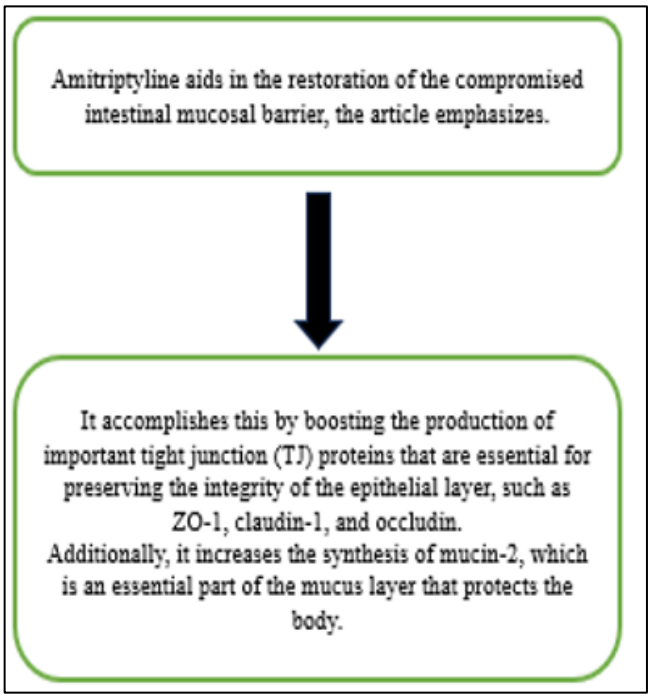

Fig 13 Restoration of the Intestinal Barrier

Fig 13 : By upregulating tight junction proteins like ZO-1, claudin-1, and occludin, amitriptyline strengthens epithelial integrity and aids in the restoration of the damaged intestinal mucosal barrier. Additionally, it increases the production of mucin-2, which strengthens the mucus layer and offers more defense against microbial invasion and luminal damage.

➢ *Repurposing Drug – Bazedoxifene*

Bazedoxifene (BZA), a third-generation selective estrogen receptor modulator approved for postmenopausal osteoporosis holds promise as an IBD treatment. Evidence also supported that BZA exerts significant anti-inflammatory effects by inhibiting STAT3, NF-κB/NLRP3 and MAPK signalling. Male C57BL/6J mice (21–24 g) by administering 3% (w/v) DSS in drinking water continuously for 7 days. bazedoxifene acetate (BZA, 5 mg/kg) suspended in Carboxyl Methyl Cellulose-Na (CMC Na) was administered orally by gavage once daily for 7 days [53,54,55].

IBD is still very difficult to treat clinically because of its low effectiveness, possible side effects, and emergence of treatment resistance. BZA has a positive reproductive safety profile in postmenopausal women with osteoporosis, according to several clinical trials, including 3-, 5-, and 7-year randomized, placebo-controlled Phase III studies. This suggests that BZA is safe for long-term therapy of chronic illnesses like IBD. The gp130-STAT3 signalling pathway has been linked to CD pathogenesis, especially in individuals who do not respond to anti-TNF antibody therapy. BZA considerably improves the DSS-induced colitis model in mice, as shown by reduced colon length shortening, lower

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histological scores, and increased expression of intestinal mucosal barrier-associated proteins like Claudin 1, Occludin, Zo-1, Muc2, and E-cadherin [56,57,58]. The role of gut microbiota in the anti-inflammatory effects of BZA is a noteworthy breakthrough. This discovery not only clarifies the molecular mechanism of BZA but also suggests that it may be used therapeutically to alter the gut flora. An especially interesting line of inquiry is how BZA indirectly affects host inflammatory responses by changing the gut microbiome. Future research, including examining BZA's mode of action in several IBD models and evaluating its potential efficacy in clinical IBD treatment, is guided by this groundbreaking discovery [56,57,58]. Numerous signalling pathways and cellular interactions characterize the complex treatment landscape of both acute and chronic colitis. BZA's therapeutic efficacy and mechanism of action in chronic colitis models, even as they provide fascinating insights into the drug's involvement in reducing colitis in an acute environment. All things considered, our research highlights the role that gut microbiota plays in the creation of medications for IBD and provides fresh perspectives for upcoming medication development and therapeutic uses [59,56].

BZA exhibits efficacy similar to that of IFX in reducing colitis symptoms in mice produced by DSS. NF-κB and STAT3 signaling pathways are regulated, and the composition and abundance of intestinal microbiota are altered as part of the underlying mechanisms. BZA highlights a potential treatment for IBD medications and are especially noteworthy since they point to a unique function of gut microbiota in the therapeutic activity of BZA [59,60].

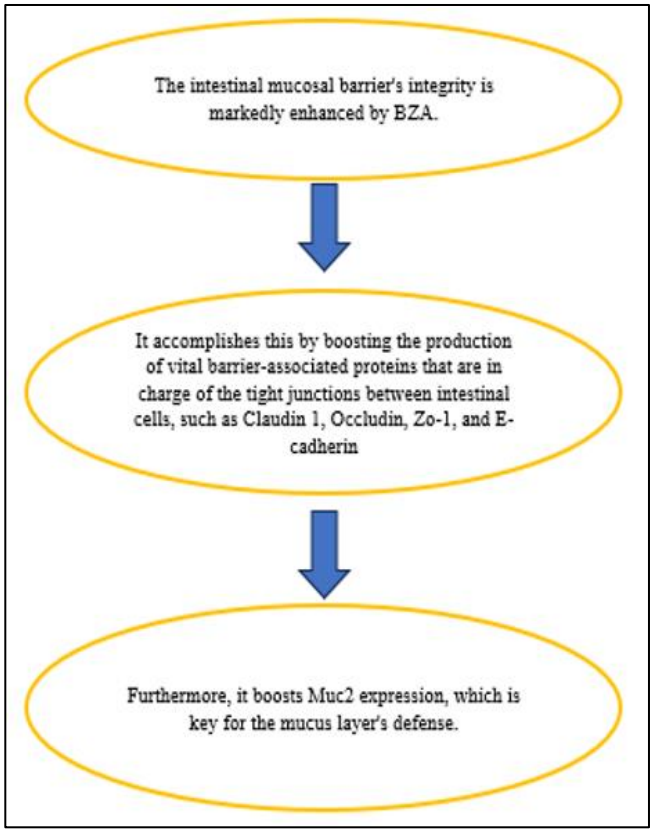

Fig 14 Restoration of the Intestinal Barrier

Fig 14: By upregulating important tight junction proteins that maintain epithelial cohesion, such as occludin, ZO-1, E-cadherin, and claudin-1, bazedoxifene (BZA) improves the integrity of the intestinal mucosal barrier. Furthermore, it increases the expression of Muc2, which strengthens the mucus layer and offers an essential barrier against inflammation and microbial invasion.

Fig 15 Inhibition of Inflammatory Signalling

Fig 15: By inhibiting important signaling pathways implicated in colitis, such as NF-κB, MAPK, and STAT3, bazedoxifene (BZA) produces strong anti-inflammatory effects. BZA decreases the synthesis of pro-inflammatory mediators and lowers intestinal inflammation in general by blocking these cascades.

➢ *Benefits, Drawbacks, Advantages and Disadvantages of Drug Repurposing.*

- *Benefits*

Due to proven safety, preclinical toxicology and Phase I trials are no longer necessary, greatly cutting down on time. optimizes research and development resources while requiring a smaller financial investment than de novo drug discovery. Attrition in subsequent trial phases is reduced when pre-existing pharmacokinetic, pharmacodynamic, and toxicological profiles are present. uses previous human safety data to reduce patient risk. Enables a speedier transfer into human studies by utilizing current safety and clinical data. Repurposed medications enable quick patient access by avoiding drawn-out production and regulatory procedures.

- *Drawbacks*

In novel indications, off-target activities may result in unexpected toxicity. Further trials are required to confirm the efficacy for new uses, even with established safety profiles. In new indications, drugs may exhibit toxicity risks due to

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their limited therapeutic windows or off-target effects. Since not all pharmaceuticals have a molecular basis for novel clinical applications, the repurposing of therapeutics is often limited by a lack of mechanistic clarity. The possibility of exploiting regulatory shortcuts can result in unequal access in situations with limited resources. It might be challenging to design suitable trials for repurposed medications due to various objectives, dosage, duration, and diverse populations. In novel indications, off-target activities may result in unexpected toxicity. Further trials are required to confirm the efficacy for new uses, even with established safety profiles. In new indications, drugs may exhibit toxicity risks due to their limited therapeutic windows or off-target effects. Since not all pharmaceuticals have a molecular basis for novel clinical applications, the repurposing of therapeutics is often limited by a lack of mechanistic clarity. The possibility of exploiting regulatory shortcuts can result in unequal access in situations with limited resources. It might be challenging to design suitable trials for repurposed medications due to various objectives, dosage, duration, and diverse populations [61,62,63].

V. DISCUSSION

This review explores the evolving landscape of drug repurposing and explains an increasing prevalence and impact of Inflammatory Bowel Disease (IBD) globally, especially in newly industrialized nations and highlights the pressing necessity for innovative and more effective treatment options.

Conventional drug development for IBD is a lengthy process, tends to have limited effectiveness, and can be costly, frequently impeded by high failure rates in clinical trials. In this context, drug repurposing has surfaced as a feasible and strategic method, enabling researchers to investigate the unexplored potential of existing medications that have established safety profiles.

This review has analyzed several repurposed drugs—including quinacrine, febuxostat, amitriptyline, dapsone, and bazedoxifene—each of which targets unique, yet frequently overlapping, inflammatory and oxidative pathways pertinent to IBD pathology. These medications represent a variety of pharmacological categories, originally designed for ailments such as malaria, gout, depression, dermatological infections, and osteoporosis, but now exhibit considerable promise in reducing symptoms of colitis and alleviating tissue damage.

Quinacrine reveals anti-inflammatory and antioxidant properties by influencing apoptosis and reducing inflammatory cytokines. Its mechanism encompasses the inhibition of phospholipase A2 and the suppression of pro inflammatory mediators like NF-κB, IL-1β, and TNF-α. Notably, its pro-apoptotic action in inflamed colon tissue and modulation of the p53 pathway suggest a dual role in controlling inflammation and preventing carcinogenesis associated with colitis.

Febuxostat, which was originally prescribed for gout, demonstrated significant anti-inflammatory and antioxidative properties in experimental models of ulcerative colitis (UC). By inhibiting xanthine oxidase, it reduced oxidative stress indicators, such as malondialdehyde (MDA) and carbonyl proteins, while restoring levels of antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH). Furthermore, Febuxostat decreased NF-κB signalling and lowered neutrophil infiltration, highlighting its potential role in protecting the integrity of the intestinal mucosa. Amitriptyline contributes to the enhancement of intestinal barrier integrity and the regulation of immune cell infiltration, indicating its potential to reduce epithelial dysfunction in colitis. This tricyclic antidepressant has shown promising anti-inflammatory effects by targeting the TLR-4/NF-κB signalling pathway. Additionally, it has restored the expression of tight junction proteins (ZO-1, claudin-1, occludin) and mucin levels, thereby reinforcing the epithelial barrier. The restoration of intestinal barrier function, along with a decrease in cytokine release and immune cell infiltration, makes amitriptyline a noteworthy candidate for the treatment of ulcerative colitis.

Dapsone, acknowledged for its antimicrobial and dermatological functions, has additionally exhibited anti-inflammatory effects in colitis through the inhibition of TLR4/NF-κB signaling and the suppression of cytokines such as TNF-α and IFN-γ. The preservation of mucosal architecture and the reduction of oxidative stress markers in treated models emphasize its role in IBD treatment. Bazedoxifene, a selective estrogen receptor modulator (SERM), has surfaced as a unique repurposed agent that operates on both immune and microbial fronts. By inhibiting the STAT3 and NF-κB pathways, it mitigates inflammation. In addition, it modifies the gut microbiota, promoting beneficial SCFA-producing bacteria while suppressing pro inflammatory species. This dual effect of Bazedoxifene on host immunity and microbial composition illustrates a novel therapeutic approach that aligns with the current insights into the gut–immune–microbiota axis in IBD pathogenesis.

VI. CONCLUSION

Since traditional drug development for inflammatory bowel disease (IBD) can often be tedious, costly, and not efficient, drug repurposing offers a promising approach to addressing the lacking therapeutic challenges in IBD. Quinacrine, febuxostat, amitriptyline, dapsone, and bazedoxifene are examples of repurposed agents that display a variety of pharmacological actions, but they all share mechanisms that include reducing oxidative stress, preventing inflammatory pathways, and protecting the epithelial barrier.

Their translational potential is demonstrated by their positive effects on gut microbiota and their capacity to modulate important signalling cascades like NF-κB, TLR4, and STAT3. Thorough clinical validation is crucial, even though preclinical data are promising. When taken as a whole, these results demonstrate drug repurposing as a clever, effective, and strategic way to advance options for treatment for the management of IBD.

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