



## A critical review on Interaction between Pepto-Bismol and Metronidazole with Citrus Fruit Juices for Inflammatory Bowel Disease: A critical review on causes and possible therapies

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### ABSTRACT

The two main kinds of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis. IBD is a set of inflammatory disorders of the colon and small intestine. Whereas ulcerative colitis predominantly affects the colon and rectum, Crohn's disease affects both the small and large intestines as well as the mouth, esophagus, stomach, and anus. IBD may also affect dogs, and it is believed that the immune system, intestinal milieu, host genetics, and environmental factors interact to cause the condition. Current research has covered a wide range of delivery methods for the treatment of IBD, from new treatment preparations to complex chemical compounds utilizing Pepto-Bismol and metridanazole. A simple distribution method is preferable to a more complicated and expensive one from the standpoint of medication development. The goal of the current review was to determine how Citrulline in Citrus Fruit Juices would be affected by a combination of Pepto-Bismol and Metronidazole

**Keywords:** - . IBD, Microbiota, Ulcerative Colitis, Pepto-Bismol, Metronidazole.

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### INTRODUCTION

The two main kinds of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis. IBD is a set of inflammatory disorders of the colon and small intestine [13]. Whereas ulcerative colitis predominantly affects the colon and rectum, Crohn's disease affects both the small and large intestines as well as the mouth, esophagus, stomach, and anus [2]. IBD may also affect dogs, and it is believed that the immune system, intestinal milieu, host genetics, and environmental factors interact to cause the condition.

There is, however, continuing debate as to whether "chronic enteropathy" rather than "inflammatory bowel disease" should be used to describe the condition in dogs because of how differently it manifests and responds to therapy in canines than in people. For instance, unlike humans with IBD who frequently require immunosuppressive therapy, many dogs react to dietary modifications alone. When dietary adjustments are insufficient, some dogs may additionally require therapy with immunosuppressant or antibiotics. Intestinal biopsies are frequently carried out to determine what type of inflammation is present after other illnesses that might cause vomiting, diarrhea, and stomach discomfort in dogs have been ruled out (lymphoplasmacytic, eosinophilic, or granulomatous). Low blood cobalamin levels in dogs have been demonstrated to be a risk factor for unfavorable results [4]. Despite the fact that Crohn's and UC are quite distinct diseases, both can manifest with any of the following signs and symptoms: stomach discomfort, diarrhea, rectal bleeding, extreme internal cramps or muscle spasms in the pelvic region, and weight loss. Inflammatory bowel disease's most common extra intestinal consequence is anemia [4, 19]. Arthritis, pyoderma gangrenosum, primary sclerosing cholangitis, and non-thyroidal sickness syndrome are some of the associated symptoms or disorders (NTIS). [5] Deep vein thrombosis connections (DVT) [6].

The gastrointestinal insusceptible framework is vital to the pathogenesis of fiery gut sickness (IBD). The gastrointestinal epithelium forestalls microorganisms or antigen section into the dissemination via fixed intercellular intersections. In IBD, these intersections are blemished from either an essential hindrance capability disappointment or because of serious irritation. Extra defensive instruments incorporate bodily fluid creation by challis cells and Paneth cells emission of a-defenses with inherent antimicrobial movement. Exorbitant incendiary responses lead to proceeded with disintegration of the epithelium and further openness to digestive organisms subsequently facilitating deteriorating the aggravation.

In ulcerative colitis, there is generally mucosal irritation that prompts edema, ulcers, dying, and electrolyte misfortunes. The irritation in ulcerative colitis typically begins in the rectum and advances in a continuous design to the proximal colon. In Crohn's sickness, there are skip sores. In near 20% of patients with UC, the sickness stays bound to the rectum. Pancolitis is seen in around 15% of patients.

As the problem becomes persistent, the colon turns out to be more inflexible and short with a deficiency of the haustral markings prompting a 'lead-pipe appearance on a barium douche.

Crohn's illness can influence any fragment of the GI parcel; the sickness might incite injuries, aggravation or lead to the advancement of fistulas. The critical component of Crohn's sickness is that it includes all layers of the inside (transmural). During the later period of the sickness, the mucosa will uncover a cobblestone appearance because of the straight ulcers between the typical mucosa. Crohn's illness most influences the colon and ileum and just 5% of cases influence the gastroduodenal sections. Saving of the rectum is ordinary of Crohn's infection however anorectal intricacies like fistulas and abscesses are extremely normal.

UC inclines patients toward the extraintestinal contribution of the skin, eyes, and bones. Most normally these incorporate fiery arthropathies and essential sclerosing cholangitis. Cd specially goes after the ileum and colon yet can include the throat, duodenum, or stomach. Pediatric-beginning cases have more noteworthy upper GI parcel association. As on account of UC, Album inclines patients toward extraintestinal signs including joint inflammation, aphthous stomatitis, uveitis, erythema nodosum, and ankylosing spondyloarthropathy [3, 15].

In Crohn sickness, the occurrence of kidney illness and gallstones is high a direct result of malabsorption of bile salts and unsaturated fats. Patients with Crohn sickness who go through resection of the ileum however unblemished colon are likewise bound to foster calcium oxalate renal stones.

### **Causes**

IBD is a complicated illness that develops when environmental and genetic variables combine, causing immune reactions and intestinal inflammation [3].

### **Diet**

Diet is a topic that IBD patients are particularly interested in, yet little is known about how food affects these people. The significance of dietary counseling for IBD patients has recently been highlighted in reviews. The finest evidence-based diets for patients should be promoted, and they should include monitoring for the objective resolution of inflammation [2].

According to a 2022 study, diets with higher intakes of fruits and vegetables, fewer processed meats and refined carbohydrates, and a preference for water over other liquids for hydration were linked to a lower risk of IBD active symptoms, though an increase in fruit and vegetable consumption did not alone lower the risk of Crohn's disease symptoms [1].

Dietary habits are linked to an increased risk of ulcerative colitis. Moreover, those with the healthiest eating pattern in their highest tertile had a 79% decreased incidence of ulcerative colitis. [10].

IBD patients who are sensitive to gluten are more likely to experience flare-ups. Patients with ulcerative colitis and Crohn's disease, respectively, exhibited gluten sensitivity in 23.6% and 27.3% of cases, respectively [11]. An increased risk of inflammatory bowel disease and relapses may be linked to a diet heavy in protein, especially animal protein, and/or sugar.

It has been observed that high protein intake in diet in particular, animal protein it can increase the risk of IBD's and their relapses. N-3 polyunsaturated fatty acids can prevent and protect whilst n-6 polyunsaturated fatty acids may lead to ulcerative colitis.

Involving low residue diet can relieve symptoms like diarrhea and abdominal pain. Also intake of cold food helps in decreasing diarrhea.

Foods to avoided:

It has been found in the studies that the food that cause increase in stool output can be avoided for e.g. fresh vegetable and fruits, nuts, beans, kernels, caffeinated beverages, seeds.

Note: Inflammatory Bowel Disease initially cannot be caused or cured by what we eat or depends on our diet but it has been found that changes in diet and some food can be associated in the underlying inflammatory factors that can expedite symptoms or the disease.

While some certain food can also show opposite reactions such as it can promote healing process.

Diet can also have a influence on treatment of the Inflammatory Bowel Disease. Until it has been not found if control in diet can lead to patient on treatment to go on non medical treatment. Instead it has been seen that diet can only improve that quality of life and helps to relieve in symptoms which can increase patient compatibility and provides more easy life during the treatment [12, 13].

All the medical science discovery or researches that are in process is to provide patient mor e and more easy treatment which can aggravate the result in less time and it has been focused to increase the patient compatibility because it can help patient body to be more active and helps increase immunity to fight the

disease and this can provide strength to the body and also helps to prevent further deterioration of the body.

### Microbiota

A change in the gut micro biome may be a factor in the development of inflammatory gut disorders because of microbial symbiosis and immunity [1]. The variety of commensal bacteria is observed to be 30–50% lower in IBD patients, with particular declines in Bacillota (particularly Lachnospiraceae) and Bacteroidota. The fact that people with IBD are more likely to have had an antibiotic prescription in the two to five years preceding their diagnosis than people without the condition provides more proof of the significance of gut flora in the development of the condition [2]. Environmental influences, such as concentrated milk fats (a frequent component of processed foods and sweets), or oral drugs like antibiotics and oral iron preparations, might affect the enteral flora [16].

### Breach of intestinal barrier

One important pathogenic factor in IBD is loss of intestinal epithelial integrity [8]. Acute and chronic inflammatory processes in IBD colitis and associated cancer are caused by dysfunction of the innate immune system as a result of abnormal signaling through immune receptors called toll-like receptors (TLRs), which activate an immune response to molecules that are widely shared by multiple pathogens [9]. One major environmental element in the development of IBD is changes in the makeup of the gut flora. Damage to the intestinal epithelium is brought on by unfavorable alterations in the intestinal microbiota that trigger an improper (uncontrolled) immune response. Intestinal epithelium breaches allow the microbiota to spread deeper, which in turn triggers more immunological reactions.

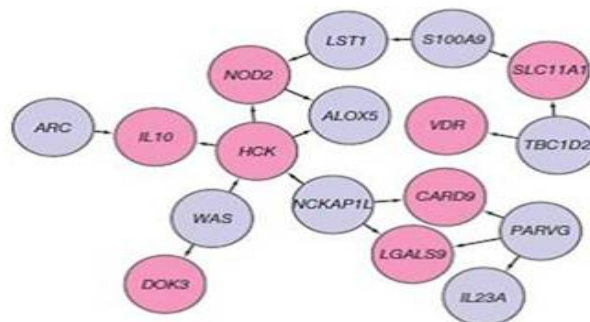
### Oxidative stress and DNA damage

Pereira et al analysis of evidence from various studies concluded that DNA damage and oxidative stress are likely involved in the pathogenesis of inflammatory bowel disease (IBD). Patients with IBD compared to control patients had substantially higher 8-OHdG levels measuring oxidative DNA damage, as well as inflamed mucosa compared to non-inflamed mucosa.

### Genetics

IBD has a genetic component, which has been known for more than a century [1]. Studies of ethnic groups (such as Ashkenazi Jews and Irish people), family clustering, epidemiological studies, and twin studies are only a few examples of the research that has aided in our knowledge of genetics. Understanding of the genetic underpinnings has greatly increased with the development of molecular genetics, especially in the last ten years [17]. In 2001, NOD2 was the first gene to be linked to IBD. Since then, genome-wide association studies have advanced knowledge of the disease's genetics and etiology. There are already more than 200 single nucleotide polymorphisms (SNPs, or "snips") that have been linked to IBD risk. In 2012, one of the largest genomic studies on IBD was released. The findings indicated that commensally microbiota is changed in inflammatory bowel illnesses in a way that makes them pathogens. According to other research, gene changes linked to IBD may disrupt cellular processes and interactions with the micro biota that support healthy immune responses [6].

Several studies have shown that deregulation of micro RNAs contributes to IBD and favors colorectal cancer. A small team started single-cell RNA sequencing analysis in 2020 utilizing biopsy samples from IBD patients to look for potential treatment targets as shown in Fig 1.



**Fig 1** Related location pane while blue genes are not in IBD-related loci, pink genes are.

### Epidemiology

IBD caused 51,000 deaths worldwide in 2013 and 55,000 fatalities in 1990 [7]. The correlation between the rise in meat consumption across the world and the rise in IBD cases since World War II supports the idea that eating animal protein causes IBD. Nevertheless, a number of environmental risk factors,

including smoking, air pollution, green space, urbanization, and Westernization, have been associated to both increased and decreased risk of IBD. In Europe, inflammatory bowel illnesses are on the rise. IBD prevalence and incidence have progressively increased over the past few decades throughout Asia, which may be connected to dietary changes and other environmental variables. IBD affects 0.8% of the population in the UK. Similarly, around 270,000 (0.7%) of Canadians have

## METHODOLOGY

### We used the Synthesis process, IBD, Ulcerative Colitis and recent treatments in IBD Involved Medications in IBD are-

The reason for clinical treatment is to stop the deviant irritation so digestive tissue gets an opportunity of mending. The indications of loose bowels and stomach agony ought to be reduced as it does. Clinical treatment can focus on lessening the recurrence of eruptions and supporting reduction once the side effects are decided to be taken care of [3].

Amino salicylates, which are headache medicine comparative prescriptions including balsalazide (Colozal), mesalamine (Asacol, Apriso, Lialda, Pentasa), olsalazine (Dipentum), and sulfasalazine, are commonly utilized as the principal line of treatment (Azulfidine).

**1) Balsalazide(Colozal)-** Mitigating drug called balsalazide is utilized to treat IBD. It works by bringing down stomach torment, digestive aggravation, the runs, and harm to substantial parts by delivering mesalamine all through the body. For people, 5 years old and more established with gentle to reasonably dynamic ulcerative colitis, balsalazide containers are managed. For male patients, 18 years old and more established with gentle to respectably dynamic ulcerative colitis, balsalazide pills are endorsed. Balsalazide works inside in the guts to reduce illness related irritation and related symptoms. The disodium salt is normally managed. Balsalazide makes the digestive organ discharge mesalazine, once in a while alluded to as 5-aminosalicylic corrosive or 5-ASA. Its benefit over that drug in treating ulcerative colitis is believed to be the section of the dynamic fixing past the small digestive system to the internal organ, which is where ulcerative colitis is generally dynamic. It has a place with the class of drugs known as infection changing antirheumatic drugs (DMARDs), which are a group of medications.

MOA-It is obscure how 5-aminosalicylic corrosive functions, be that as it may, it appears to have neighborhood as opposed to fundamental calming impacts (in the GI parcel). In patients with persistent provocative entrails illness, there is an expansion in the development of arachidonic corrosive metabolites in the mucosa through both the cyclooxygenase and lipoxygenase pathways, which catalyze the arrangement of leukotrienes and hydroxy eicosatetraenoic acids from arachidonic corrosive and its metabolites. Consequently, it is plausible that 5-aminosalicylic corrosive lessens irritation by hindering the cyclooxygenase and lipoxygenase catalysts that are associated with the colon's age of arachidonic corrosive metabolites [2].

**2) Mesalamine(Asacol, Apriso, Lialda, Pentasa)-** By repressing Cox and lipoxygenase movement, mesalamine lessens the creation of prostaglandins. The medication mesalamine is utilized to treat ulcerative colitis, a problem that outcomes in enlarging and ulcers in the rectum and colon lining, as well as to hold ulcerative colitis side effects back from returning. Mesalamine has a place with the gathering of medications known as mitigating specialists. It capabilities by keeping the body from creating a specific substance that could prompt irritation. Mesalamine is likewise used to diminish the event of ulcerative colitis side effects. Just grown-ups ought to utilize some mesalamine brands, while others are just implied for youngsters who are no less than 5 years of age.

MOA-Despite the fact that the specific components of mesalazine are obscure, it is accepted that mesalazine changes the fiery reaction coming about because of the cyclooxygenase and lipoxygenase pathways by bringing down the amalgamation of prostaglandin and leukotriene. It appears to locally harm the gastrointestinal mucosa. Mesalazine has a scope of mitigating pharmacological activity systems. It appears to localizedly affect the mucosa of the colon while decreasing irritation by means of a few mitigating systems. There have been a few proposed 5-ASA activity targets. The ongoing hypothesis holds that 5-ASA invigorates a sort of atomic receptor made of manufactured materials. A significant receptor called PPAR-gamma intervenes the impacts of 5-ASA treatment in IBD by transrepression of a few significant objective qualities including atomic variable B, signal transducers, and record activators.

**3) Sulfasalazine(Azulfidine)-** Prostaglandin hindrance, which causes local medication impacts in the colon, is one designated system. The medication is partitioned into sulfa and 5-aminosalicylic corrosive by intestinal microorganisms, which is then assimilated and wiped out by means of the kidneys and stomach related juice. A class of drug known as a sickness changing enemy of rheumatic medication is sulfasalazine (DMARD). Sulfasalazine might slow the movement of your disease by lessening joint distress, enlarging, and irritation.

MOA-90% of a sulfasalazine portion arrives at the colon, where microorganisms utilize most of it into sulfapyridine and mesalazine (otherwise called 5-aminosalicylic corrosive or 5-ASA). Most of the sulfapyridine is consumed and afterward further used, while most of the mesalazine isn't and stays in the colon. The two metabolites are dynamic. Urinary discharge incorporates acetylated mesalazine, unmetabolized sulfasalazine, and a combination of unmodified, hydroxylated, and glucuronidated sulfapyridine. Sulfasalazine and its metabolites seem to have immunosuppressive, antimicrobial, and mitigating properties, while the specific instrument of activity is hazy. Furthermore, it appears to obstruct the antiporter for cystine and glutamate.

**4) Olsalazine**-Incendiary gut infection and ulcerative colitis are both treated with the calming medicine olsalazine. A result of salicylic corrosive is olsalazine. It is dormant without anyone else (prodrug) and the microbes in the colon change it into mesalamine. In the treatment of digestive provocative diseases, mesalamine capabilities as a calming drug. Patients who have experienced ulcerative colitis use olsalazine to prevent the condition from reoccurring. It capabilities inside the colon by aiding the decrease of irritation and other sickness related side effects[8-12].

MOA-Olsalazine, when taken orally, is changed into mesalamine, which is respected to be the remedially viable compound for treating ulcerative colitis. Mesalamine's (and sulfasalazine's) method of activity is unsure, however it is by all accounts effective as opposed to fundamental. Patients with persistent fiery inside sickness have higher mucosal creation of arachidonic corrosive (AA) metabolites, both through the cyclooxygenase pathways, for example, prostanoids, and through the lipoxygenase pathways, for example, leukotrienes (LTs), and hydroxy eicosatetraenoic acids (HETEs). Mesalamine might decrease aggravation by hindering cyclooxygenase and prostaglandin.

**5) Adalimumab(Humira)**- Joint pain, psoriatic joint inflammation, ankylosing spondylitis, Crohn's infection, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, uveitis, and adolescent idiopathic joint pain all are sicknesses that this monoclonal neutralizer is utilized to treat. It is given as an intramuscular infusion. Upper respiratory parcel diseases, bothering at the infusion site, redness, and cerebral pain are common antagonistic impacts [15].

Serious diseases, threat, hypersensitivity, reactivation of hepatitis B, various sclerosis, cardiovascular breakdown, liver disappointment, and aplastic paleness are instances of additional secondary effects. Despite the fact that it isn't encouraged, a few sources demonstrate that utilization during breastfeeding might be protected. Adalimumab is a monoclonal neutralizer and infection changing antirheumatic drug (DMARD) that represses growth rot factor-alpha (TNF).

MOA-Growth putrefaction factor-alpha (TNF-alpha) is a system that gives by adalimumab, which keeps it from connecting with the p55 and p75 cell surface TNF receptors. In vitro, adalimumab likewise kills surface cells that express growth rot factor when supplement is available. 2,3 Adalimumab neither ties nor renders lymphotoxin idle (Growth rot factor-beta).

A normally happening cytokine called TNF partakes in commonplace fiery and immunological responses. 3 Patients with rheumatoid joint pain, psoriatic joint inflammation, and ankylosing spondylitis have more significant levels of TNF in their joint synovial liquid, which is urgent for the pathologic aggravation and joint harm that are the essential results of these circumstances. TNF levels are higher in psoriasis plaques also. Treatment with adalimumab for plaque psoriasis might decrease epidermal thickness and Treatment with adalimumab for plaque psoriasis might diminish epidermal thickness and fiery cell penetration. It is obscure how these pharmacodynamicsrelates to the mechanism(s) by which adalimumab produces its restorative results. Adalimumab likewise changes natural responses brought by or constrained by TNF, like adjustments in the centralizations of grip atoms that control leukocyte development during irritation [20].

**6) Infliximab**-When different drugs have neglected to control the side effects of reasonably to seriously dynamic Crohn's sickness or ulcerative colitis in grown-ups and kids, an infliximab infusion is directed. For the treatment of reasonably to seriously dynamic rheumatoid joint pain, psoriatic joint pain, and dynamic ankylosing spondylitis, infliximab infusion is utilized alone or in mix with different drugs (like methotrexate). The skin condition constant extreme plaque psoriasis, which causes tenacious red regions and white scales, is correspondingly treated with infliximab infusion. Patients who can't be treated with different drugs use it. The resistant framework is reinforced and further developed by the monoclonal immunizer infliximab.

MOA-A monoclonal IgG1 neutralizer called infliximab ties to solvent and transmembrane variants of TNF-with incredible partiality, keeping them from flagging the supportive of incendiary fountain. At the point when an immunizer ties to TNF, TNF is kept from connecting with its receptors. TNF-(lymph toxin), a comparable cytokine that involves similar receptors as TNF-Name, isn't killed by infliximab. Expanded degrees of atomic variable B inhibitor, diminished degrees of endothelial grip particles and intense stage

proteins, and diminished lymphocyte and leukocyte relocation to locales of aggravation are ramifications of TNF-being obstructed.

Actuated monocytes and T lymphocytes, which produce TNF, are additionally instigated to go through apoptosis. 3. Its TNF-inhibitory impacts were displayed in human fibroblasts, endothelial cells, neutrophils, and epithelial cells, and B-and T-lymphocytes are named. The age of tissue-debasing chemicals made by chondrocytes or potentially synoviocytes is likewise animated by infliximab. Infliximab decreased synovitis and joint disintegrations in collagen-prompted joint pain and permitted dissolved joints to recuperate, as per a transgenic mouse study where polyarthritis was welcomed on by combined degrees of human TNF- $\alpha$  [16].

**7) Ustekinumab(Stelara)-** A biologic medication called ustekinumab (Stelara) is utilized to treat grown-ups and kids matured six and more seasoned with moderate to extreme plaque psoriasis, grown-ups with moderate to serious psoriatic joint pain, and grown-ups with moderate to extreme Crohn's infection and Ulcerative Colitis by diminishing irritation. After different prescriptions have neglected to work, this one is recommended. It is controlled as an infusion at home. IL-12 and IL-23, two provocative proteins, are hindered by ustekinumab [19, 20].

An organic medication called ustekinumab can require numerous months to begin working. Long haul utilization of biologics is likewise normal. Colitis side effects from returning. Mesalamine has a place with the gathering of medications known as mitigating specialists. It capabilities by keeping the body from producing a specific compound that could prompt irritation. Mesalamine is likewise used to decrease the event of ulcerative colitis side effects. Just grown-ups ought to utilize some mesalamine brands, while others are just implied for youngsters who are no less than 5 years of age. MOA-Despite the fact that the specific components of mesalazine are obscure, it is accepted that mesalazine changes the incendiary reaction coming about because of the cyclooxygenase and lipoxygenase pathways by bringing down the union of prostaglandin and leukotriene. It appears to locally harm the digestive mucosa. Mesalazine has a scope of mitigating pharmacological activity components. It appears to localized affect the mucosa of the colon while lessening aggravation by means of a few calming instruments. There have been a few proposed 5-ASA activity targets. The ongoing hypothesis holds that 5-ASA invigorates a sort of atomic receptor made of engineered materials. A significant receptor called PPAR-gamma intercedes the impacts of 5-ASA treatment in IBD by transrepression of a few significant objective qualities including atomic element B, signal transducers, and record activators [17].

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#### **Medical uses**

Bismuth subsalicylate, a derivative of salicylic acid, has anti-inflammatory [15] and bactericidal properties [8]. It serves as an antacid as well.

#### **Metronidazole**

Metronidazole is an antibiotic and antiprotozoal drug that is marketed under the brand names Flagyl and others. Endocarditis, bacterial vaginosis, and pelvic inflammatory disease are all treated with it either on its own or in combination with other antibiotics. Draconculiasis, giardiasis, trichomoniasis, and amebiasis can all be treated with it. For a first bout of mild-to-moderate *Clostridium difficile* colitis, it is an alternative.

### **DISCUSSION**

Current research has covered a wide range of delivery methods for the treatment of IBD, from new treatment preparations to complex chemical compounds utilizing Pepto-Bismol and metridanazole. A simple distribution method is preferable to a more complicated and expensive one from the standpoint of medication development. If the distribution method results in a notable and noticeable increase in efficacy or a sizable decrease in adverse effects when compared to current medicines, it is a compensating factor. There for new treatment in IBD there is huge requirement of investor and within a limited time period it has to be proven that the Interaction between Pepto-Bismol and Metronidazole with Citrus Fruit Juices for Inflammatory Bowel Disease is successful.

**CONCLUSION**

The goal of the current review was to determine how Citrulline in Citrus Fruit Juices would be affected by a combination of Pepto-Bismol and Metronidazole. Even so, there is not as much proof to support its use in managing inflammatory bowel disease symptoms. After carefully examining several publications published across the world, we discovered that there is a considerable probability it would improve the patient's quality of life. The cruelest aspect of IBD symptoms is that they impair quality of life, necessitating further study to demonstrate a cure. The current treatment is not sufficient enough to cope up with the disease so the new treatment in need of an hour. Our intention is to draw attention to this condition in order to encourage researchers to look into it and develop some effective treatment.

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