

ULCERATIVE COLITIS: A REVIEW OF THE DISEASE, DRUGS AND NANOCARRIERS

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Abstract: Ulcerative colitis (UC) is a gastrointestinal disorder, a subtype of Inflammatory Bowel Disease, chronic, idiopathic, remitting and recurrent, which is of worldwide concern. Several studies have sought to understand the behavior of IBD and the drugs and/or nanocarriers used to treat it. Thus, this review includes a detailed bibliographical survey on the contemporary analysis of ulcerative colitis and its etiology. It presents the most commonly used drugs for the treatment of UC, such as sulfasalazine, mesalazine and their derivatives, showing their chemical structures and metabolism. Synthetic glucocorticoids are structural analogues of the endogenous steroid hormone cortisol, which help to improve the clinical condition of patients with mild to moderate RP by interacting with glucocorticoid receptors. The review also seeks to explore the potential of bismuth subsalicylate in treatment and finally the use of nanocarriers for drug delivery. With the data presented, it is hoped that this review will provide additional knowledge on Ulcerative Retocolitis, its treatment and advances, as well as a solid basis for other researchers.

Keywords: Ulcerative colitis; drugs; bismuth subsalicylate; nanocarriers.

INTRODUCTION

Ulcerative Retocolitis (UC) is an alarming disease worldwide. The annual costs for the treatment of UC in Europe are around 12.5 to 29.1 million euros; in the USA they are between 8.1 and 14.9 billion dollars (Chauhan; Harwansh, 2024). In Mediterranean countries, patients related to Inflammatory Bowel Diseases (IBD) range from 5 per 100,000 in urban areas (Ali et al., 2024). In recent years, the incidence of IBD in the African population and in Egypt (Kamel et al., 2021) has been remarkable, with an annual incidence of IBD of 10 to 12 per 100,000 inhabitants,

which is three times more common than Crohn's disease, an IBD of the small intestine (Elghobashy; Steed, 2024).

RU is a subtype of IBD, chronic, idiopathic, remitting and recurrent (Elghobashy; Steed, 2024). It is a disease of supposedly unknown origin or etiology, in which the literature blends the starting point of the disease with the appearance of ulcers between the mucosa of the colon or in the rectum, but recognizes the possibility of spreading throughout the large intestine, with variable extension, called Extraintestinal Manifestation (EIM) (Eldakrouy et al., 2024). There is no cure for RU, but it is possible to alleviate the symptoms. Patients with long-term UC are more likely to be at risk of developing colorectal cancer, compared to people without the disease (Eldakrouy et al., 2024; Elghobashy; Steed, 2024).

However, it is important to develop new therapeutic options for RU, especially a monotherapy that combines characteristics such as: efficiency, cure of the disease, broad spectrum of action, safety, independence from association with other drugs and low side effects (ARMUZZI; LIGUORI, 2021; CAPRILLI et al., 2009; DANESE; FIORINO; PEYRIN-BIROULET, 2020; GEORGE; CROSS, 2020a; SELVAMANI et al., 2022).

Among the therapeutic alternatives that meet the requirements of RU treatment, the 5-aminosalicylate derivatives that stand out are mesalazine and sulfasalazine (ASGHAR-ZADEH et al., 2021; BARBERIO et al., 2021; BERTANI et al., 2021; SHIN et al., 2020; YAMAMOTO-FURUSHO; PARRA-HOLGUÍN, 2022). Another drug worth mentioning is bismuth subsalicylate (SSB), which has antidiarrheal, antimicrobial, antisecretory and anti-inflammatory properties, making it a valuable drug for the treatment of RU (SHETU et al., 2022; SOPENA; CANADELL; QANNETA, 2022), although there have been

few studies on its use as a therapeutic agent in cases of colitis. (FINE; LEE, 1998; MÜNCH; LANGNER, 2015; TOME; KAMBOJ; PARDI, 2021).

To improve the therapeutic profile of bismuth subsalicylate and other drugs, nanostructures with the ability to host, transport and deliver them to their site of action can be used. Nanoparticles for drug delivery include polyester dendrimer (PD), which has interesting intrinsic properties such as biodegradability, biocompatibility, entrapment efficiency, targeting capacity, controlled release and improved drug action mechanism. (DEEPA; JAISANKAR, 2019; GORAIN et al., 2019; SACHI DAS et al., 2022).

In this context, Macedo et al. 2023 theoretically evaluated the interaction of bismuth subsalicylate (SSB) with a polyester dendrimer for use as a nanocarrier. The results showed that the interactions between the nanocarrier and the drug were positive, that the interactions of Bi with Oxygen were partially covalent and that the hydrogen bonds (O⁻ H) were classified as weak or moderate. Finally, the interactions between the nanocarrier and the polyester dendrimer showed that DP is a good nanocarrier for releasing SSB.

In view of the advances in the pathology and the current work being carried out in the literature, this review seeks to provide a basis for issues relating to ulcerative colitis, so several subsections on the general aspects of the disease have been evaluated, such as the pharmacological treatments used, the drug used for treatment and a review of some of the nanocarriers used for drug delivery. The study will serve as a guideline for subsequent experimental studies interested in working with RU, drugs for its treatment and the safety of using polyester nanopolymers for drug delivery.

CONTEMPORARY ANALYSIS OF ULCERATIVE COLITIS: A COMPLEX GASTROINTESTINAL DISEASE OF UNKNOWN ETIOLOGY

Ulcerative colitis (UC) is a gastrointestinal disorder that plagues many countries on the American, European and Asian continents, characterized by inflammation of the rectal and colonic mucous membranes, with an unknown origin and triggering symptoms such as bloody stools, diarrhea, fatigue, abdominal cramps, weight loss, lack of appetite and increased likelihood of developing colon cancer. (GAJENDRAN et al., 2019; LEE; CLARK-SNUSTAD, 2020).

This disease manifests itself in mild cases, which can be treated with accessible and low-cost drugs, to moderate and severe cases, requiring hospitalization, surgery and high-cost drugs, in addition to having multiple factors, be they environmental, genetic, biological and economic that act as determinants for its incidence and prevalence in these continents (ACHRA; KARPE; FRANKLIN, 2019; BOPANNA et al., 2017; HOLANDA et al., 2021; KOTZE et al., 2020).

The events that describe the pathogenesis of RU are the depletion of the mucin layer of the intestinal mucosa, increased permeability of the mucosa to antigens in the lumen and stimulation of the immune system (DU; HA, 2020) porphyrin was shown to prevent lipopolysaccharide-induced sepsis in mice. However, studies on the inhibitory effects of porphyrin during colitis are currently lacking. In this study, we evaluated the effects of *Pyropia yezoensis*-derived porphyrin on dextran sodium sulfate (DSS). The accepted hypotheses suggest that the mucosa of the large intestine, after losing its thick mucin layer, has its epithelial cells (colonocytes) exposed to microorganisms from the lumen, in addition to having important nuclear receptors such as PPAR- γ (*peroxisome proliferator activated*

receptors - γ) with expression problems, leading to losses in the negative regulation of inflammation. (DE BRITO et al., 2020; SINGH et al., 2022).

The reduction of symbiotic bacteria and the exponential growth of harmful bacteria, a phenomenon known as dysbiosis, is responsible for the increase in antigens and the evolution of RU (XU et al., 2021) and the V3+V4 hypervariable region in the bacterial 16S rRNA gene sequence was amplified by polymerase chain reaction (PCR). Intestinal symbiont bacteria, belonging to the Bacteroidetes and Firmicutes phyla, in their metabolic processes produce substances that induce anti-inflammatory cytokines, mucin stimulators and bactericides. In contrast, harmful bacteria assimilate nutrients from the lumen, producing metabolites that increase mucosal permeability and stimulate the production of pro-inflammatory cytokines (AHMED et al., 2022; NASCIMENTO et al., 2020).

At the genetic level, the expression or inhibition of various *gene loci* is responsible for the production of cytokines, chemokines, reactive oxygen species or the inhibition of anti-inflammatory proteins (BERGEMALM et al., 2021; HUANG et al., 2022).

The immunological aspects of RU include the processing of antigens by antigen-presenting cells, recognition of pathogens through TLRs (*toll-like receptors*), signaling and activation of multiple transcription factors (nuclear factor kappa beta - NF- κ B - is described as the most common) and production of pro-inflammatory cytokines (Tumor Necrosis Factor α - TNF- α and Interleukin - IL) necessary for the transduction of signals mediated by Janus Kinase proteins, potentiating the activation and proliferation of lymphocytes. (ATREYA et al., 2018; FIORINO et al., 2018; KOCH HANSEN et al., 2014; PERGOLIZZI et al., 2021).

A diet based on the consumption of

fatty foods, rich in oleic acid, saturated fatty acids, polyunsaturated fatty acids, trans fats, monounsaturated fatty acids and linoleic acid, together with diets rich in animal protein can increase the risk of RU. On the other hand, diets rich in fruit and vegetables decrease the levels of inflammatory markers in the intestinal mucosa and positively regulate the population of commensal microorganisms in the intestinal flora, improving dysbiosis. (FRITSCH et al., 2021; SONG et al., 2022).

Histopathological data from RU show irregular intestinal crypts with interruption or loss at some points, increased distances between crypts, distorted vascular architecture, infiltrates of mononuclear cells, a decrease in goblet cells and the presence of crypt abscesses (KURUMI et al., 2022; VITALI et al., 2023). Macroscopic evaluation describes continuous colonic inflammation, starting in the rectum, erythema, loss of the vascular pattern, with erosions, bleeding and ulcerations in the most severe cases (Figure 1) (KAENKUMCHORN; WAHBEH, 2020).

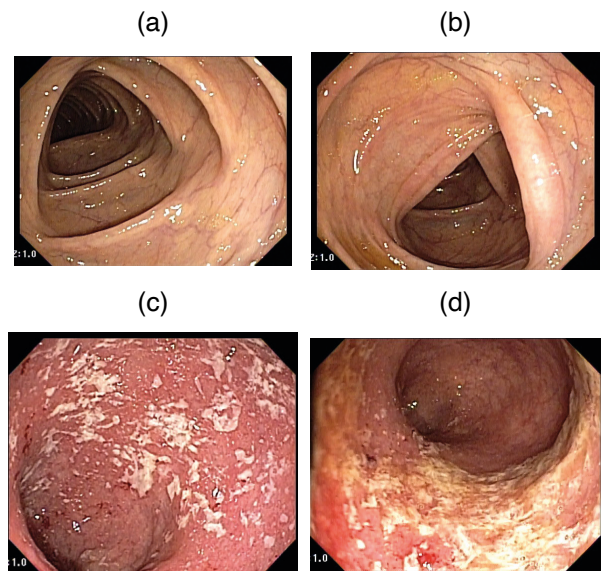


Figure 1 - Colonoscopy images of healthy portions of the large intestine, showing (a) the transverse colon and (b) the sigmoid colon. Images of the large intestine showing (c) and (d) portions of the colon affected by RU.

Source: The author, 2023.

The combination of histopathological and laboratory examinations and imaging tests, such as colonoscopy, sigmoidoscopy and endoscopic ultrasound, helps to detect lesions on the colonic mucosa, and are described as important resources for diagnosing and describing the various types of RU that exist, such as ulcerative proctitis, proctosigmoiditis, left-sided colitis, pancolitis and acute severe ulcerative colitis, as well as ruling out other diseases as common symptoms (ATREYA et al., 2020; BEZZIO et al., 2021; CARON et al., 2022; PABLA; SCHWARTZ, 2020; SEBASTIAN et al., 2021; TAFAZOLI et al., 2022; TURAN; DURMUS, 2022).

Ulcerative proctitis is defined as an inflammatory process located exclusively in the rectal mucosa. Proctosigmoiditis is described as inflammation affecting the sigmoid colon and rectum. Left-sided colitis, on the other hand, is manifested by inflammation located in the colon distal to the splenic flexure. In pancolitis, all segments of the colon are clearly inflamed (ABDULRAZEG; LI; EPSTEIN, 2019; STEED, 2019)

DRUGS COMMONLY USED TO TREAT MILD SYMPTOMS OF ULCERATIVE COLITIS

DERIVATIVES OF 5-AMINOSALICYLATES

5-aminosalicylate derivatives are described as effective drugs in patients with mild to moderate RU. 5-aminosalicylate derivatives are prescribed in initial crises and express a high probability of remission and relapse prevention. Some of the representatives of this class include mesalazine and sulfasalazine, Figure 2, with mesalazine being much better tolerated than sulfasalazine in terms of side effects (ASGHARZADEH et al., 2021; BARBERIO et al., 2021; BERTANI et al., 2021; SHIN et al., 2020; YAMAMOTO-FURUSHO; PARRA-HOLGUÍN, 2022).

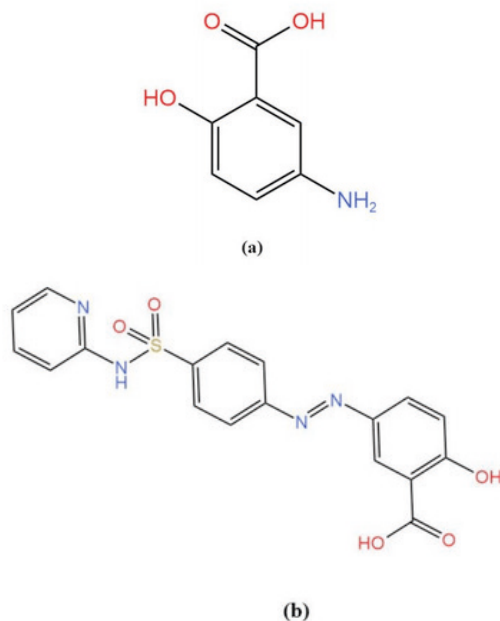


Figure 2 - Chemical structure of (a) mesalazine and (b) sulfasalazine.

Source: The author himself

Mesalazine is described as an aminosalicylate drug with anti-inflammatory properties, acting to inhibit inflammatory mediators such as prostaglandins, leukotrienes and cytokines. Mesalazine is absorbed in the stomach and small intestine, undergoing N-acetylation type metabolization in the intestinal mucosa, with *N-acetyl-5-aminosalicylic acid* as the main metabolite. The metabolites generated are excreted by the kidneys, although there is a concentration of metabolites that is eliminated through the feces (VARUM et al., 2022; VELOSO; MACHADO; NOBRE, 2021; ZHANG et al., 2022).

The chemical structure of sulfasalazine is reported to be a combination of sulfapyridine (antibiotic) and mesalazine (anti-inflammatory). The drug is absorbed in the intestine. After being absorbed, sulfasalazine undergoes the action of bacterial azoreductases in the colon, releasing sulfapyridine and mesalazine. The free drug and its metabolites are widely distributed

throughout the body. Metabolism is carried out by the liver, with the metabolic events of sulfopyridine being acetylation, hydroxylation and glucuronidation. After the drug has been metabolized, its metabolites are eliminated via the faeces or urine, (Figure 3) (MUSHTAQ; SARKAR, 2020).

The mechanism of action of 5-aminosalicylate derivatives includes the inhibition of some key elements of the inflammatory cascade, such as the enzymes cyclooxygenases, lipoxygenases and phospholipase A₂, as well as inflammatory mediators such as platelet aggregation factor, nuclear factor- κ B, tumor necrosis factor- α , tumor necrosis factor- β , interleukin-1 and leukotrienes (GÓMEZ-MUÑOZ et al., 2001; QURESHI; COHEN, 2005).

The cohort study by Yamamoto-Furusho and Parra-Holguín (2022) showed that colitis patients treated with mesalazine multimatrix orally, topically or both achieved 35.1% induction in 8 weeks and 93.2% remission in 12 months, with no adverse effects related to the use of mesalazine multimatrix.

The studies carried out by Mansuri et al. (2023) found that the use of oral sulfasalazine suspension in children under the age of 18 with RU and early onset ulcerative colitis triggered a 50% remission rate without the need to resort to other classes of drugs such as steroids, immunomodulators and biologics for a period of 1 year of monotherapy.

According to Yasutomi et al. (2019), switching from mesalazine to sulfasalazine was effective in 59% of patients with active ulcerative colitis whose mesalazine-based medications included multimatrix mesalazine, time-dependent mesalazine and pH-dependent mesalazine. However, in this study, the adverse effects of sulfasalazine were more significant than the previous drugs.

Side effects for the use of 5-aminosalicylate derivatives are uncommon, with reports of

diarrhea, fever, pancreatitis, skin symptoms, leukopenia, pneumonia, kidney dysfunction, liver dysfunction and cardiotoxicity. (JENA et al., 2022; SUZUKI et al., 2022).

It has been proven that the use of mesalazine is not recommended for pregnant women, due to side effects on the fetus, such as gastrointestinal bleeding and kidney failure, caused by the transplacental transfer of the drug. After crossing the placenta, the drug reaches the amniotic fluid and can be ingested until it reaches the intestine. In the intestine, the poorly absorbed drug causes inflammation in the vulnerable membranes, with prolonged inflammation being the correlation with the side effects observed, such as bleeding, ulcers and colonic dilation. (NII et al., 2021).

SYNTHETIC GLUCOCORTICOIDS

Synthetic glucocorticoids (SG) are structural analogues of the endogenous steroid hormone cortisol, a stress hormone derived from cholesterol and synthesized in the adrenal glands, with metabolic, anti-inflammatory and immunosuppressive properties due to their actions on cytosolic glucocorticoid receptors (PONTES et al., 2019; SCHERHOLZ; SCHLESINGER; ANDROULAKIS, 2019; ZHANG et al., 2019).

Glucocorticoid receptors are members of the nuclear hormone receptor superfamily, so the association between GS and the inactivated cytosolic glucocorticoid receptor results in the formation of an activated glucocorticoid-receptor complex that translocates to the nucleus, directly activating or inactivating promoter regions of target genes. (BARTLETT; LAPP; HUNTER, 2019; MAURICE-DROR; PERETS; BAR-SELA, 2018).

The GS help to improve the clinical condition of patients with mild to moderate RU by interacting with glucocorticoid receptors present in intestinal epithelial cells and the immune system, culminating in the

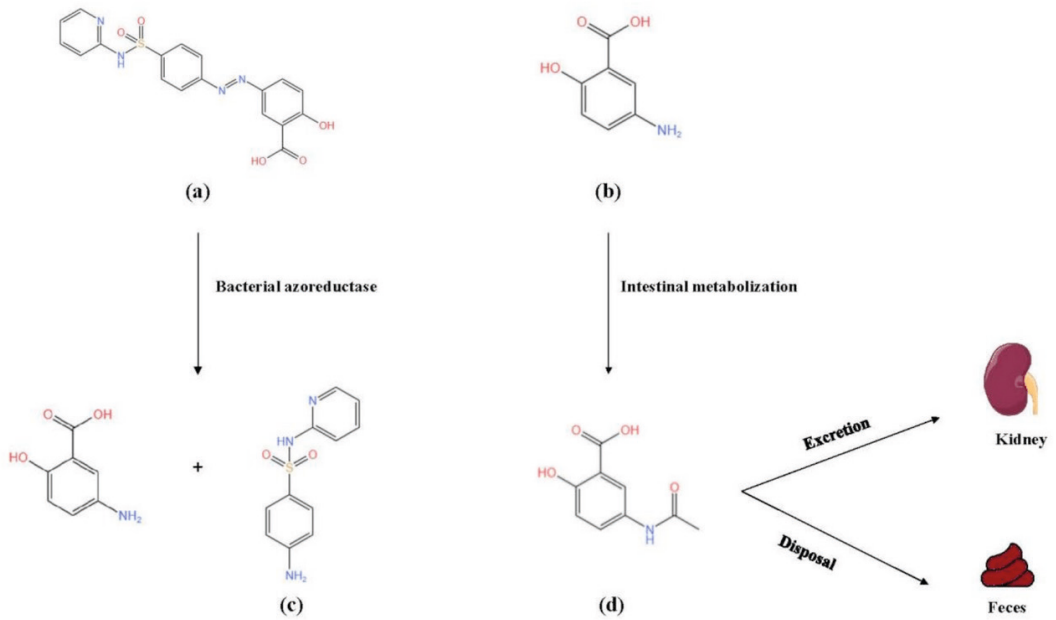


Figure 3 - Metabolic process undergone by (a) sulfasalazine and (b) mesalazine. The action of bacterial azoreductases releases the drugs (b) mesalazine and (c) sulfapyridine; however, mesalazine undergoes intestinal metabolism into (d) *N-Acetyl-5-aminosalicylic acid*.

Source: The author, 2023.

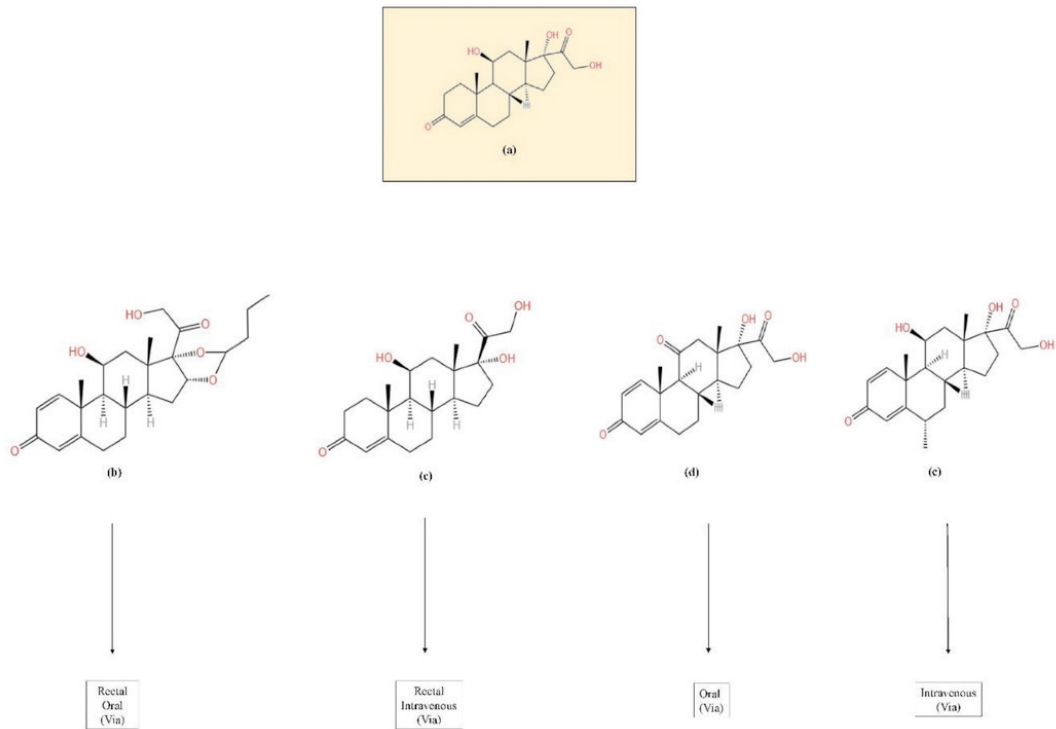


Figure 4 - Chemical structure of (a) cortisol, endogenous steroid hormone, and synthetic glucocorticoids: (b) budesonide, (c) hydrocortisone, (d) prednisone, (e) methylprednisolone, with their main routes of administration used to deliver formulations to patients with RU .

Source: The author, 2023.

interruption of the inflammatory process installed in the colonic mucosa. The main GS used to treat RU include budesonide and hydrocortisone (rectal use), budesonide multimatrix system (local oral use), prednisone (systemic oral use), methylprednisolone and hydrocortisone (intravenous use), Figure 4 (CLARISSE; BECK, 2021; GEORGE; CROSS, 2020b).

The use of budesonide and hydrocortisone in the form of foam or enema promotes the optimization and retention of these drugs, providing uniform distribution in portions such as the rectum and distal colon. These statements are based on the fact that drugs administered topically have higher levels, reduced concentration and less systemic effect (DATE et al., 2018; RUBIN et al., 2014; SANDBORN et al., 2015).

According to Hibi et al. (2020), the use of 2 mg of budesonide foam twice a day for 6 weeks relieved the clinical symptoms of patients with RU. To substantiate this claim, the author carried out a *post hoc* analysis with Japanese data from phase II and phase III clinical trials, in which an improvement in mucosal healing, the elimination of bleeding, a reduction in the frequency of bowel movements and, consequently, clinical remission were observed after topical administration of budesonide foam.

For Zhang et al. (2019), the use of combined hydrocortisone/dexamethasone and mesalazine enemas helped relieve colitis symptoms in mice with distal ulcerative colitis induced by dextran sulfate sodium. The mice treated with combined enemas showed better scores on the Mayo score, as well as a decrease in the inflammatory molecules associated with ulcerative colitis.

Multimatrix budesonide is formulated as modified-release gastro-resistant tablets. After swallowing the tablets, a significant percentage of the drug is absorbed in well-defined intestinal

portions such as the ileum and caecum, with the effective dose being a concentration of 9 mg of multimatrix budesonide over 8 weeks. Metabolism is hepatic, mediated by CYP3A4 (cytochrome P450 3A4). The inactive metabolites found are 6 β -hydroxybudesonide and 16 α -hydroxyprednisolone, however, due to extensive metabolization, the drug has a high elimination rate (DILGER et al., 2009; FELLERMANN et al., 2019; LÓPEZ-SANROMÁN et al., 2018).

In the review article by Maconi et al. (2021), a randomized controlled study showed that the use of multimatrix budesonide at doses of 6 or 9 mg in patients with mild to moderate ulcerative colitis led to an endoscopic improvement of the colonic mucosa compared to the placebo group, as well as equally superior clinical and endoscopic remission rates in patients with left-sided ulcerative colitis.

In the review article by Battat et al. (2019), the outcome of histological and endoscopic remission was correlated with the various drug therapies indicated for the treatment of UC, including multimatrix budesonide. The use of multimatrix budesonide as a locally acting oral corticosteroid for 8 weeks showed induction rates combined with histological remission in 15% of patients with ulcerative colitis.

Prednisone is an ester prodrug that is converted by enzymes into its active metabolite, prednisolone, with around 70% of inactive prednisone being converted into prednisolone by the liver enzyme 11- β -hydroxydehydrogenase type I (11 β -HSD-1). Biotransformation is reported to be rapid and extensive, with prednisone participating as a substrate in metabolization by CYP3A and P-GP. Elimination of the metabolites occurs in the urine (BERGAMASCHI et al., 2005; FLOWER, 2009; QIN et al., 2013).

George et al. (2020) carried out a literature review based on several randomized clinical trials whose clinical remission of patients with CR or Crohn's disease was achieved on drug regimens with or without corticosteroids. The RU patients had a condition classified as moderate to severe and the corticosteroid of choice was prednisone at doses of 20 to 40 mg/day. The attempt to eliminate corticosteroids from the treatment of patients with RU resulted in a clinical remission rate 24% lower than the overall clinical remission rate.

Methylprednisolone is a methylated derivative of prednisolone. Intravenous administration of methylprednisolone results in immediate availability, eliminating the need for methylprednisolone to be absorbed. Distribution is largely dependent on binding to plasma proteins. Methylprednisolone is metabolized by cytochrome P450A isoenzymes, CYP3A4 and CYP3A5. Methylprednisolone undergoes metabolic processes such as oxidation, reduction and hydroxylation which culminate in the formation of up to 15 metabolites. The elimination half-life is concentrated at intervals of 1.8 to 5.2 h and elimination occurs via the urine (CARRIER et al., 2013; FURMAN, 2019; NAGORI et al., 2019; SIDDIRAJU; LAL PRASANTH; SIRISHA, 2016).

For Dulai et al. (2022), the use of methylprednisolone in doses of 40-60 mg every 24 hours intravenously or hydrocortisone in doses of 100 mg every 8 hours intravenously helped resolve rectal bleeding and the frequency of bowel movements in hospitalized patients with moderate to severe ulcerative colitis. Therefore, these drugs can contribute to the treatment of patients with ulcerative colitis who are hospitalized or post-discharge.

Intravenous hydrocortisone is presented as a sodium phosphate salt and distribution is systemic, with hydrocortisone reaching organs such as the kidneys, intestines,

muscles and liver. In the liver, hydrocortisone is metabolized, with a small amount of the drug present in unchanged form. The inactive metabolites of hydrocortisone include glucuronides and sulphates, the elimination half-life of the original compound is 1-2h and elimination is via urine and bile (CEVC; BLUME, 2004; HINDMARSH; GEERTSMA, 2017; MINIGH, 2008).

In the cohort study by Schauer et al. (2021), adult patients admitted to hospitals in New Zealand with an outbreak of inflammatory bowel disease were treated with intravenous therapy with 60 mg of methylprednisolone per day and 100 mg of hydrocortisone every 6 hours, with the intention of analyzing which drug was more effective in resolving the outbreak. The results showed that patients treated with methylprednisolone needed more rescue therapy compared to hydrocortisone therapy, but the secondary mineralocorticoid effects were lower with methylprednisolone.

Although widely used to treat RU, corticosteroids have undesirable side effects that limit their use as anti-inflammatory drugs. The main side effects reported from the use of corticosteroids are Cushing's syndrome, psychiatric disorders, central serous chorioretinopathy, dysphonia, gastric problems, cardiovascular alterations, diabetes and susceptibility to fractures (BARTA et al., 2023; BERTHELOT; LE GOFF; MAUGARS, 2013).

EXPLORING THE POTENTIAL OF BISMUTH SUBSALICYLATE IN THE TREATMENT OF ULCERATIVE COLITIS

Bismuth subsalicylate (BSS) is a derivative of acetylsalicylic acid with antidiarrheal, antimicrobial, antisecretory and anti-inflammatory properties, making it a valuable drug for the treatment of RU due to its pharmacological properties that can be used to develop a clinical remission in patients affected by RU. (SHETU et al., 2022; SOPENA; CANADELL; QANNETA, 2022).

The pharmacokinetic aspects of SSB include its hydrolysis into Bi^{3+} and salicylic acid, Figure 5. This is followed by the absorption of the salicylate compound and the formation of non-absorbable salts of Bi^{3+} (bismuth oxychloride and bismuth hydroxide). Once absorbed, the salicylate compound is widely distributed throughout most of the body's tissues. On the other hand, tissue metabolization of salicylate is significant, however, hepatic microsomal and mitochondrial biotransformation take the lead over tissue metabolism. The metabolites excreted in the urine include phenolic salicylic glucuronide, gentisic acid, gentisuric acid, as well as unchanged salicylic acid itself (AKPINAR; AKAY; UNSAL, 2017; BUDISAK; ABBAS, 2022; FURMAN, 2018; VALE, 2016) therefore, investigated. Patients and methods Consecutive H. pylori-positive patients with dyspepsia were randomly allocated to one of the three sequential regimens: The first group was given lansoprazole 30mg b.i.d. plus amoxicillin 1g b.i.d. for the first 5days, followed by lansoprazole 30mg b.i.d., clarithromycin 500mg b.i.d., and metronidazole 500mg t.i.d. for the second 5days (standard sequential, SS.

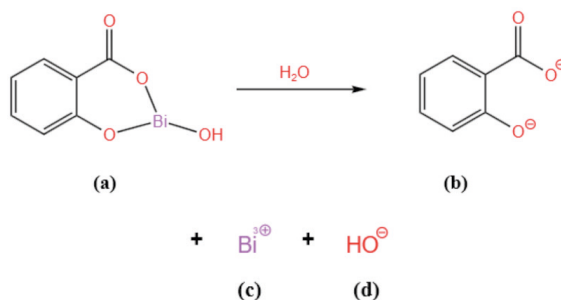


Figure 5 - Hydrolysis of (a) SSB resulting in the formation of (b) salicylate compound, (c) Bi^{3+} and (d) OH^- .

Source: The author, 2023.

The pharmacodynamic aspects of SSB include the mechanisms of action of both Bi^{3+} and the compound salicylate (PAPICH, 2016). The antibacterial mechanisms of Bi^{3+} compounds may be related to bismuth-protein interaction properties and enzyme inhibition, with records of strong interactions between the Bi^{3+} ion and thiolate and oxygen residues, leading to the formation of complexes with cysteine, glutathione tripeptide, cysteine-metallothionein-rich proteins and metalloregulatory proteins (JIN et al., 2004).

The mechanism of action of the salicylate compound is based on the inhibition of the cyclooxygenase-1 and cyclooxygenase-2 isoenzymes, resulting in the interruption of the production of bioactive prostanoids derived from arachidonic acid (prostaglandins and thromboxanes) that are important for the pathogenesis of RU (Figure 6). Some prostanoids have an effect on colonic secretion and motility, so blocking prostanoid synthesis may help to alleviate bouts of diarrhea in the colon of patients with colitis. (HEENEY et al., 2021; NAKAHATA, 2008; PATRIGNANI; PATRONO, 2015; SAHOO; PAIDSETTY, 2015).

As for anti-diarrheal properties, in the study by Bardhan et al. (2001), when treating male children with acute diarrhea caused by enterotoxigenic *Escherichia coli* or rotavirus,

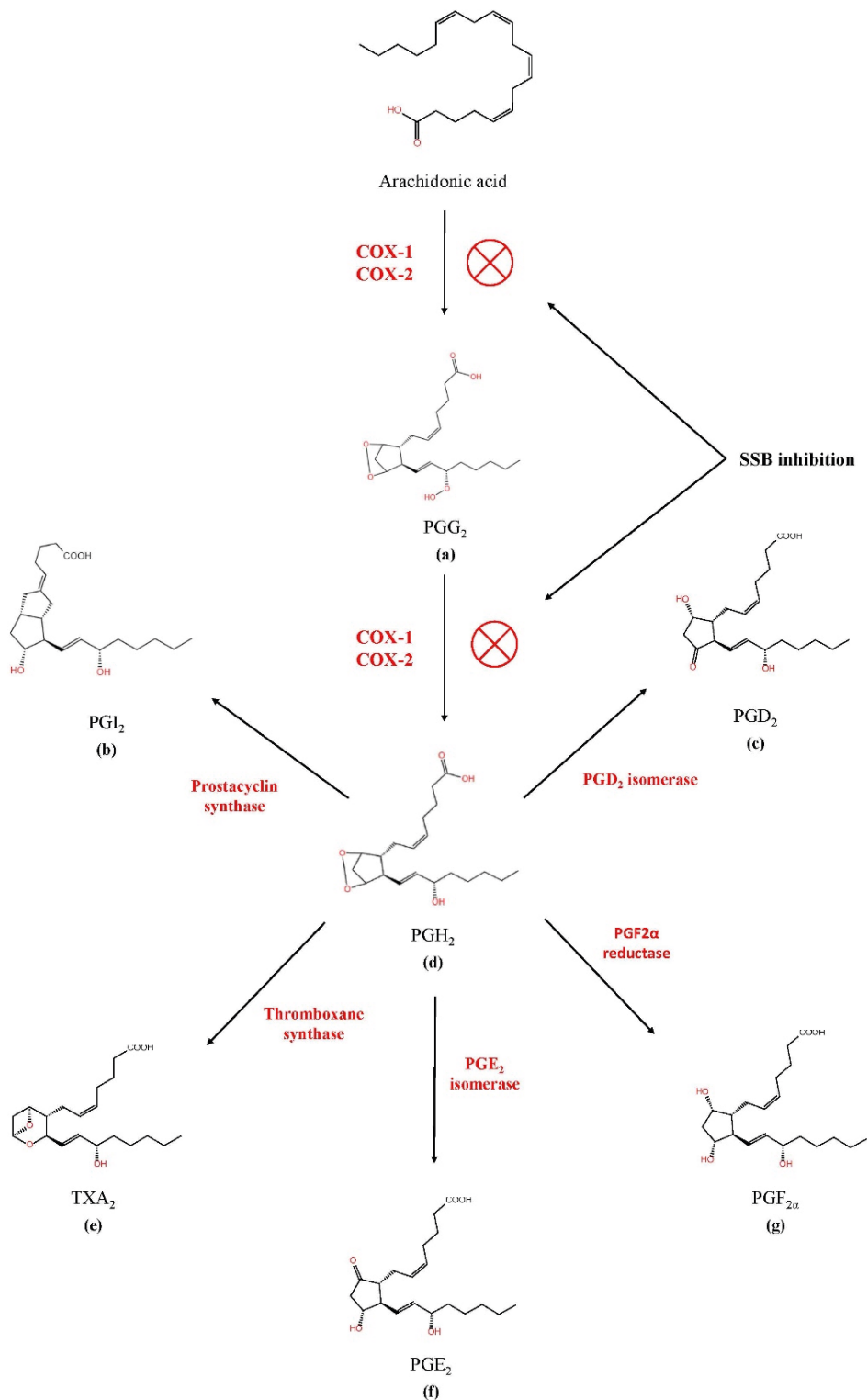


Figure 6 - Inhibition of the enzymes cyclooxygenase 1 and 2 (COX-1 and COX-2) by bismuth subsalicylate. The metabolites prevented from forming from prostaglandin G₂ (a), are prostaglandin H₂ (d) and related metabolites such as: prostacyclin (b), prostaglandin D₂ (c), thromboxane A₂ (e), prostaglandin E₂ (g) and Prostaglandin F_{2α} (g).

Source: The author himself.

with oral rehydration and monotherapy with 200 mg/kg/day of SSB, a reduction in bowel movements was obtained in children infected with enterotoxigenic *Escherichia coli*, showing the anti-diarrheal and antibacterial effects of SSB.

The bacterial strains most commonly found in the colon of RU patients include bacteria such as: *Enterobacter spp*, *Campylobacter spp*, sulfate-reducing bacteria, *Clostridium spp*, *Enterococcus faecalis*, *Fusobacterium spp*, *Bifidobacterium spp* and *Rhodococcus erythropolis*. These bacteria are microbiological agents that cause dysbiosis and are also correlated with inflammatory phenomena in the colonic mucosa. However, there are records attesting to the inhibitory capacity of SSB on pathogenic bacteria, which are responsible for maintaining the inflammatory condition of the RU (BARTON et al., 2016; GUO; LIU; HAO, 2020).

The mechanism by which bacteria influence the RU includes metabolic processes related to the bacteria themselves. One example is sulphate-reducing bacteria, which produce hydrogen sulphide from organic compounds available in the colon (KUSHKEVYCH; DORDEVIĆ; VÍTĚZOVÁ, 2021).

In the treatment of RU with SSB, flatulence and, consequently, the foul odor can be reduced by the binding of bismuth to hydrogen sulfide, forming bismuth sulfide. Hydrogen sulphide is said to be a toxic thiol produced by bacteria in the colon, and its high concentration is an essential factor in the pathogenesis of RU (FURNE et al., 2001; SUAREZ et al., 1998).

The presence of a metallic element such as Bi in the chemical structure of the drug should not be a major cause for concern. After all, there is a consensus that compounds containing Bi have low to moderate absorption after ingestion. However, when Bi is absorbed, it shows a distribution throughout the soft tissues and bones, which subsequently leads

to high renal and hepatic concentrations of Bi (FOWLER; SULLIVAN; SEXTON, 2015).

Despite being a metal, Bi is almost non-toxic. In addition, the Bi atom is not stable in the body and decomposes into Bi (III), which is a soluble and easily excreted form. The accumulation half-life of Bi in the human body is 5 days, but patients under chronic use of Bi compounds tend to accumulate Bi in the kidneys for years. Side effects unique to Bi are rare, but when present include: nephrotoxicity, hepatotoxicity and neurotoxicity (BADRIGILAN et al., 2020; PAIK; SEN, 2018; PELEPENKO et al., 2022) bismuth-based nanomaterials (Bi-based NMs).

Suarez et al. (2000), when investigating the effect of SSB administration in rats, found that the use of SSB, in alternative routes to oral (intracolonic), contributes to the reduction of Bi absorption, resulting in undetectable serum and urinary levels of Bi in rats (<1.5µ/L) and, thus, fewer side effects from Bi are observed. Thus, intracolonic administration of SSB may be a safer alternative for SSB administration.

NANOCARRIERS FOR DRUG DELIVERY

Today, nanoparticles are gaining ground and attention in various strategic sectors. Some examples of nanoparticle applications involve their use in environmental remediation (sequestration of antibiotics in wastewater), engineering (magnetic, optical and ceramic materials), biomedicine (evaluation of cytotoxicity in erythrocytes), the textile sector (improvement of natural fiber composites) and catalysis (photocatalytic activities of nickel oxide nanoparticles). (ANSARI MOGHADDAM et al., 2023; JINO et al., 2023; KUMARI; PANDEY, 2023; LI et al., 2023; LYTVYN et al., 2023).

Structures of nanometric dimensions (whose sizes are between 1 and 100 nm) are called nanoparticles, however, if these

nanometric structures have the ability to host a drug, either by encapsulation or adsorption on their surface, they will be classified as a nanocarrier (HAIDER et al., 2022; VOUITIS et al., 2023).

The main advantages of using nanocarriers for drug delivery include the intrinsic characteristics of each nanocarrier. Examples to be cited are reduced toxicity, biocompatibility with the drug, prolongation of the drug's circulation time, improvement of pharmacokinetic aspects, elimination of solubility problems for insoluble drugs, protection against degradation, response to stimuli and, consequently, delivery of drugs to specific sites (KHIZAR et al., 2023; MORADI et al., 2022; ZHANG et al., 2023).

Nanocarriers for drug delivery can exist as inorganic nanocarriers (mesoporous silica nanoparticles, gold nanoparticles, *upconversion* nanoparticles, magnetic nanoparticles, carbon nanotubes and metal-organic structures) or organic nanocarriers (liposomes, polymeric micelles, nanoemulsions, dendrimers, polymeric nanocapsules and nanogels). (AHMADI et al., 2021; CHINTAMANENI et al., 2022; KESHARWANI et al., 2019; LIU et al., 2020; TALEGHANI et al., 2021).

According to Fathi et al. (2018), chitosan copolymer-gold hybrid nanoparticles proved to be capable of encapsulating and delivering the antineoplastic erlotinib to lung adenocarcinoma cell lines in vitro. The hybrid nanoparticles with erlotinib achieved cytocompatibility, superior cytotoxicity to the free drug, as well as thermoresponsive drug release in temperature ranges from 25°C to 60°C.

The experiments carried out by Albalawi et al. (2021) showed the anti-leishmanicidal effect of magnetic Fe nanoparticles O₃₄ coated with piroctone olamine in vitro and in vivo. The magnetic nanoparticles of Fe O₃₄

decreased the concentration of *Leishmania major* amastigotes with a dose-dependent IC₅₀ of 350 µg/mL and CC₅₀ of 358.3 µg/mL, the mechanism of action probably being the induction of NO, a mediator necessary for the elimination of intracellular parasites, such as amastigotes in this case.

The multi-walled carbon nanotubes developed by Solhjoo et al. (2021) proved to be efficient for delivering the antineoplastic drug 5-fluorouracil. The experiments involved the action of the nanotubes in normal tissues (pH = 7.4) and tumor tissues (pH = 5.0) simulated in molecular dynamics, however, the nanotubes showed efficient loading of the drug in neutral conditions and better release of the drug in acidic pH, proving the hosting and transport potential of the nanocarrier.

According to Liu et al. (2021), prussian blue nanoparticles, presented as PEGylated mesoporous cube-shaped carriers, acted as a photothermal agent and vehicle for the antineoplastic paclitaxel. Studies with tumor cells in vitro showed an increase in the release of the nanocarried drug after irradiation by an infrared laser in cell culture with Prussian blue nanoparticles. In vivo studies showed an inhibition of tumor growth in mice after injection of Prussian blue nanoparticles associated with infrared laser irradiation.

BOW-TIE POLYESTER DENDRIMER: AN EFFICIENT NANOPOLYMER FOR HOSTING AND DELIVERING DRUGS

Among the many existing nanocarrier options for drug delivery, dendrimers are one of the most prominent due to their applications in biomedicine (relevant applications in drug delivery, genes, antigen nanocarrier, theranostics, catalysis) and industry (subsidizing sectors such as pharmaceuticals, agrochemicals and textiles). (PATEL et al., 2022).

Dendrimers are nanometric, hyper-ramified, radially symmetrical and three-dimensionally monodispersed polymers, with their structure subdivided into central core molecules, branches and surface functional group (YOUSEFI; NARMANI; JAFARI, 2020).

The main positive points of dendrimers as nanocarriers are: (a) the ability to host charged or neutral drugs, (b) increased solubility of the active ingredient, (c) maintenance of the therapeutic concentration of the drug in the blood, (d) protection of the hosted compound and (d) increased drug release rates. (ASADULLAH KHAN et al., 2022; KARATAS et al., 2022).

Among the various types of dendrimers available for drug delivery, polyester dendrimers are an interesting alternative, as they can add some desirable characteristics, such as improving drug stability, increasing solubility, providing a hydrophobic core for encapsulation and, if necessary, serving as a controlled drug release system. (GUPTA et al., 2021; SAMROT et al., 2020).

If the dendrimer is developed for oral administration, it must protect the drug from the acidic contents of the stomach. Oral administration causes the drug to fragment in the stomach and manifest anti-inflammatory and antibacterial effects immediately, and it is desirable that these effects are strictly directed at the colonic mucosa (ROBERTS et al., 2022).

Releasing the drug only in the colon with RU would circumvent the adverse effects of the salicylate compound such as: (a) gastrointestinal irritation, (b) damage to the gastric mucosa and (c) damage to the small intestinal mucosa. Therefore, encapsulation of the drug in the core of the dendrimer would be the most appropriate, since this strategy could protect the structure of the drug from a pH oscillation, when the drug-nanocarrier system reaches the stomach of the patient

with RU (HANDA et al., 2018; LANAS et al., 2011; MAINGI; KUMAR; MAITI, 2012).

However, when the drug is adsorbed onto the surface functional groups of the dendrimer, the pre-established interactions between the two may subsequently be broken due to the high pH of the stomach. In this case, it is interesting to choose an alternative route of administration to the oral one that maintains the therapeutic properties of the drug in question (BADALKHANI-KHAMSEH; EBRAHIM-HABIBI; HADIPOUR, 2019).

Drug administration by rectal route can be an alternative to oral route for drug delivery nanosystems. Unlike the oral route, the rectal route bypasses problems such as gastric discomfort, unwanted metabolic phenomena and the patient's inability to swallow the pharmaceutical form (KOCABAS et al., 2024; PUROHIT; HANNING; WU, 2018).

In the colon, the drug can disassociate from the dendrimer and have its ester bonds broken by esterases present in the colonic mucosa. As for bioavailability, the rectal route increases the absorption rate of drugs, leading to higher concentrations of the absorbable active ingredient (POORNIMA et al., 2023; S. DHANESHWAR; VADNERKAR, 2011).

CONCLUSION

The chapter presents relevant information on the use of bismuth subsalicylate (BSS) as a potential drug against Ulcerative Retocolitis (UC), due to its antidiarrheal, antimicrobial and anti-inflammatory activities. It is worth noting that UC is a pathology that represents a significant challenge for global health, because in addition to its high prevalence and high treatment costs, it is still characterized by not having sufficient records describing its origin or etiology.

Although RU has no cure, some drugs are used to treat mild to moderate symptoms, such as 5-aminosalicylate derivatives,

mesalazine and sulfasalazine, and some classes of glucocorticoids, but both can have undesirable side effects. Therefore, in order to contribute to research into new drugs with the ability to develop clinical remission in patients affected by RU, this study highlights the main characteristics of bismuth subsalicylate.

Another important point refers to nanocarriers as an alternative for efficient drug delivery, due to the fact that they have fundamental benefits such as biocompatibility, reduced toxicity, as well as solving solubility problems and, above all, protecting drugs from degradation, thus allowing precise delivery to target sites.

As an example of a nanocarrier, the review emphasizes the properties of the bow-tie polyester dendrimer, which provides stability and controlled release of the drug, thus circumventing adverse effects and being a crucial point for specific RU treatments.

Thus, it is hoped that this chapter will add more information about RU, as well as providing new lines of study with polyester dendrimers and stimulating research and development of current therapies, combining efficacy and safety to treat this pathology, as well as serving as a basis for future research into the interaction between dendrimers and drugs.

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