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Therapeutic Proposals That Improve Morphological Changes Of 5-Fluorouracil-Induced Intestinal Mucositis: a Review of the Literature

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ABSTRACT

Introduction: In this study, we aimed to perform a literature review to investigate the existence of therapeutic proposals in 5-Fluoruracil-induced intestinal mucositis, which is a common side effect of chemotherapy treatment. The literature review was performed using PubMed, Science Direct, and Bireme between 2015 and 2019. The descriptors used "intestinal mucositis" AND "intestinal mucositis and 5-Fluorouracil". We excluded from the review studies, double data studies, titles and/or summaries that did not address therapeutic proposals, and articles not available in full. Were selected thirty-two articles, which had the objective of evaluating the effect of substances on the model of intestinal mucositis induced by 5-Fluorouracil; it is emphasized that no articles with clinical evaluation were found. On the other hand, several animal studies are being carried out with the main objective being the evaluation of probiotics, products of natural origin, and drug repurposing for the treatment of intestinal mucositis. The main morphological parameters evaluated were histological changes, inflammatory parameters, oxidative stress, intestinal permeability, microbiota homeostasis, cell apoptosis, and the number of goblet cells that are altered during the pathophysiology of intestinal mucositis. It was verified that there is still no evidence in the literature for the existence of effective clinical treatment for intestinal mucositis induced by 5-Fluorouracil. However, promising preclinical results were found with extracts of traditional plants, substances isolated from plants, and probiotics with emphasis on those of the genus Lactobacillus.

Keywords: Intestinal mucositis; Treatment; Probiotics; Plants; Drugs.

Introduction

Cancer is currently one of the most prevalent diseases worldwide. It is of great epidemiological importance, since its risk factors are highly varied and related to morbidity and mortality. The number of new cases of cancer has increased, and in 2017 there were 24.5 million cancer cases worldwide. Conversely, therapy for this disease includes several complications that depend on tumor location, malignancy, staging, and treatment modality[1, 2].

Surgery, radiation, chemotherapy, targeted treatments, and immunotherapy, separately or in combination, are commonly used to treat cancer. However, chemotherapy can be cited as one of the most used. It is used to eradicate malignant cells and to inhibit or prevent the growth and spread of these cells[3]. 5-Fluorouracil (5-FU) is a chemotherapeutic agent, and of its main side effects mucositis is the most common[4.5].

Mucositis is a resultant complex condition of inflammation of the oral or intestinal mucosa by the action of chemotherapeutic drugs or ionizing radiation, and it is one of the most significant side effects in the treatment of cancers. It is known as oral mucositis or intestinal mucositis, depending on the inflammation area[6,7].

Intestinal mucositis results in villous atrophy, ulceration, and loss of intestinal barrier function. Mucositis can also lead intestinal basal substances to apoptosis due to their toxicity to intestinal tissue cell renewal. This biological mechanism makes patients suffer from nausea, vomiting, diarrhea, pain, weight loss, and need for enteral or parenteral nutrition. It may also lead to malnutrition and electrolyte imbalance, resulting in an increased risk of sepsis and death[8, 9, 10, 11].

Effective therapy for this clinical condition does not yet exist, so prevention and control of mucositis symptoms are of paramount importance to avoid reducing the patient's motivation to proceed with the treatment plan and possibly compromise local control of the mucositis tumor and decrease survival rates[8,12].

Thus, the present work intends to investigate the state of the art regarding the therapeutic proposals for 5-FU-induced intestinal mucositis, through a literature review.

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Materials and Methods

In this review, we searched for articles indexed in PubMed, ScienceDirect, and Bireme electronic databases, published in English, from 2015 to 2021. The review was restricted to articles that address therapeutic proposals for 5-FU-induced intestinal mucositis.

Articles were searched from January to March 2021. Access to federated communities was made available through the CAPES journal portal to obtain the full articles. The descriptors used were: "intestinal mucositis", "intestinal mucositis AND 5-Fluorouracil" and "intestinal mucositis AND 5-fluorouracil AND treatment", and 5390 articles were found. Review studies, the duplication of data or titles, abstracts that did not meet the inclusion criteria and lack of pertinent information were all excluded, totaling 32 articles for analysis in this review.

For the discussion of the data and interpretation of the research, the approach to the theme was considered; the year of publication; the article available in full. The presentation of the articles found, both included and excluded, as well as their applied distribution, is shown in the PRISMA flow (Figure 1).

Results and Discussion

By searching the databases cited, the search found 5390 studies in the period, but 5358 were rejected, as they did not meet the inclusion criteria. Thus, a total of 32 publications were selected on the subject, covering the treatment of 5-FU-induced intestinal mucositis in the period highlighted in this study (Table 01), which were accessed and read for subsequent selection of the characteristics that incorporated the research.

Regarding intestinal mucositis, this review showed there is no effective clinical treatment for this condition, since no articles were found pointing to clinical evidence. On the other hand, several types of animal research are being developed, which generally evaluate the effectiveness of a certain substance, based on the discovery of the pharmacological effect of these substances on the fundamental mechanisms involved in the pathogenesis of mucositis, such as the generation of reactive oxygen species (ROS), pro-inflammatory cytokines, mediators of apoptosis, microbiota alteration and damage and rupture of the epithelial barrier.

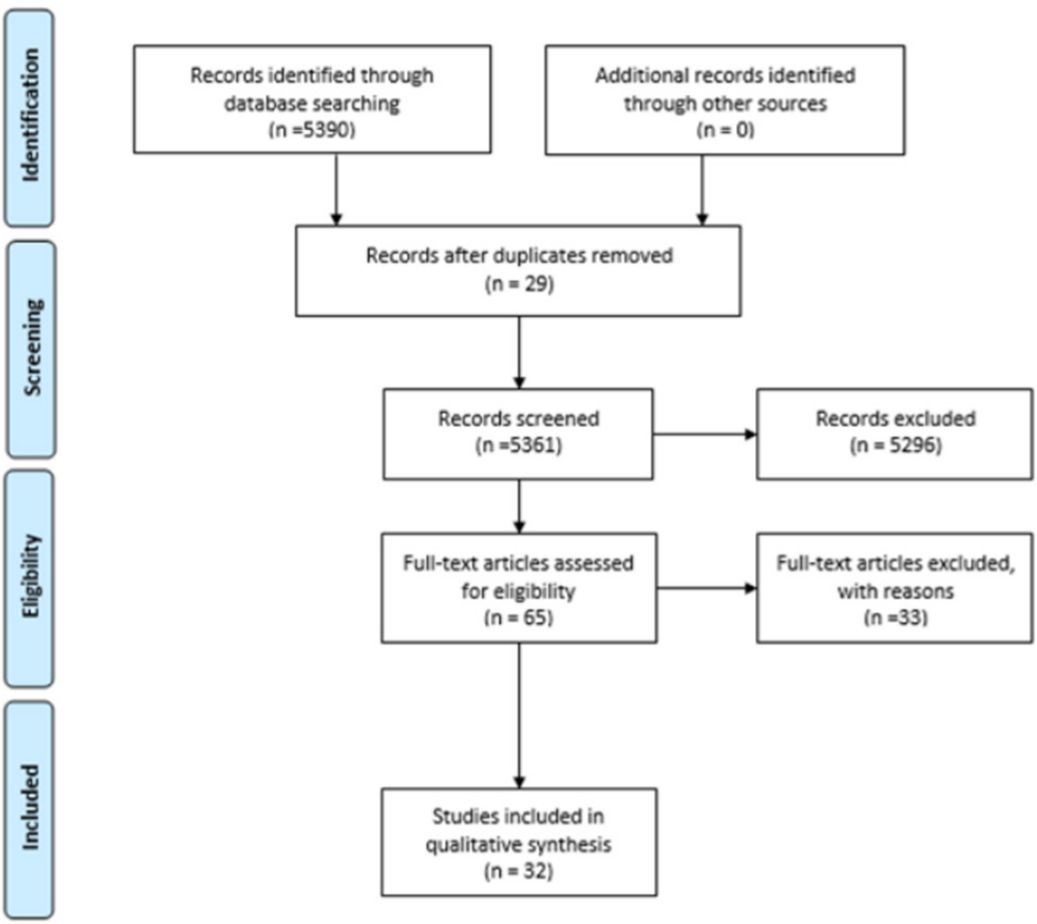

Figure 1. Prisma Flow diagram for include / exclude and data process

Table 1. Main aspects of studies on intestinal mucositis, in chronological order, in articles published from 2015 to 2019.

Nº	Type of study	Periodical	Place of study	Main aspects	References
1	Experimental	PlosOne	Taipei	*Lactobacillus casei*variety *rhamnosus* (Lcr35) and *Bifidobacterium bifidum* (LaBi) probiotics may improve chemotherapy-induced intestinal mucositis.	Yeung *et al.*, 2015[13]
2	Experimental	Plos One	Kyoto	Saireto, a traditional Japanese herbal medicine, attenuates intestinal mucositis induced by 5-FU.	Kato *et al.*, 2015[14]
3	Experimental	Biol. Pharm. Bull.	Gyeonggi-Do	Rebamipid promotes various mechanisms of mucosal protection and attenuates mucosal lesion induced by 5-FU.	Kim *et al.*, 2015[10]
4	Experimental	Tox. reports	Goiania	The results showed Mucoadhesive formulation of *Bidens pilosa* L. to be safe and efficient against 5-FU induced intestinal mucositis in mice.	DE ÁVILA *et al.*, 2015[9]
5	Experimental	Lipids Health Dis	Belo Horizonte	Dietary supplementation with omega-3 fatty acid decreases the mucosal damage caused by 5-FU-induced mucositis.	GENEROSO *et al.*, 2015[16]
6	Experimental	Hum ExpToxicol;	Shenyang	Bu-Zhong-Yi-Qi decoction (BZYQD) inhibits 5-FU-induced intestinal mucositis, and this effect may be due to the reductionin apoptosis and necrosis in intestinalmucosal epithelia via the suppression of inflammatory cytokine upregulation.	GOU *et al.*, 2016 [17]
7	Experimental	Eur Revfor Med and Pharma Scien	Cluj-Napoca	Pretreatment with rifaximin for three consecutive days proved efficient in preventing degenerative mucosal lesions induced by 5-FU in the duodenum, jejunum and colon.	Ciobanu *etal.*, 2016[5]
8	Experimental	World Jour Gastroent	Adelaide	Low dose rhubarb extract improves selected parameters of mucosal integrity and reduces ileal inflammation, manifesting from 5-FU-induced intestinal mucositis.	Bajic *et al.*, 2016[2]
9	Experimental	ToxicologyReports	Goiânia	Curcuminoid mucoadhesive formulation (MFC) from *Curcuma longa* L. presented therapeutic potential for the treatment of intestinal mucositis in mice.	Dos Santos Filho *et al.*, 2016[18]
10	Experimental	Journal of Ethnopharmacology	Beijing	Wei-Chang-An, a traditional Chinese pharmaceutical preparation promoted the restoration of intestinal function in 5-FU-induced intestinal mucositis.	Chen *et al* 2016[6]
11	Experimental	ToxicologyReports	Goiânia	A mucoadhesive formulation containing *Bidens pilosa* L. and *Curcuma longa* L. was able to protect mice from 5-FU-induced intestinal injury.	Bastos *et al.*, 2015[19]
12	Experimental	Jour Funct Foods	Hamamatsu	Arabinoxylan supplementation effectively improved intestinal mucositis and myelosuppression.	Song *et al.*, 2016[20]
13	Experimental	Clin and Exp Pharmac and Phy	Kyoto	Probiotic *Bifidobacterium bifidum* G9- 1 attenuates 5- fluorouracil- inducedintestinal mucositis in mice via suppression of dysbiosis- related secondary inflammatory responses	Kato *et al.*, 2017[21]

14	Experimental	Journal of physiology and pharmac	Kyoto	Lafutidine, a histamine H2 receptor antagonist, can attenuate 5-FU-induced intestinal mucositis, most likely by increasing mucus production via activation of sensory afferent neurons.	Sano *et al.*, 2017[22]
15	Experimental	Front Pharmacol	Kunming	*Amomum villosum* (VOA) and its main active constituent, bornyl acetate (BA), attenuates 5- fluorouracil-induced intestinal mucositis in mice.	Zhang *et al.*, 2017[23]
16	Experimental	Nutrition	Dalian	Treatment with a probiotic mixture, (*Bifidobacterium breve, Lactobacillus acidophilus, L. casei* and *Streptococcus thermophilus*) ameliorated 5-FU-induced intestinal mucositis.	Tang *et al.*, 2017[24]
17	Experimental	Letters in Applied Microbiology	Seoul	Mulberry leaf extract fermented with *Lactobacillus* acidophilus A4 ameliorates 5- fluorouracil- induced intestinal mucositis in rats.	OH *et al.*, 2017[24]
18	Experimental	Nutrition	Tucumán	The riboflavin-overproducing strain *Lactobacillus plantarum* CRL2130 could be useful to prevent mucositis during cancer treatments and would not affect the primary treatment.	Levit *et al.*, 2018[26]
19	Experimental	Rev Col Bras Cir	Natal	Simvastatin attenuated gastric and intestinal mucositis related to 5-FU therapeutics in animal model	Medeiros *et al.*, 2018[27]
20	Experimental	JournaL ofFunctional Foods	Belo Horizonte	The results showed fruit oligosaccharide (FOS) supplementation presented protective effects on intestinal barrier function.	Galdino *et al.*, 2018[28]
21	Experimental	Front Microbiol	Belo Horizonte	Whey Protein Isolate-Supplemented maximizes the anti-inflammatory effects of *Lactobacillus casei* BL23, in preventing mucositis induced by 5-Fluorouracil in BALB/c mice.	Cordeiro *et al.*, 2018[7]
22	Experimental	Journal of MedFood	Guangzhou	Enteral Nutrition Supplemented with *Crassostrea hongkongensis* Polysaccharides can ameliorate 5-FU-induced intestinal mucositis.	CAI *et al.*, 2018[4]
23	Experimental	Phytomedicine	Tianjin	*Aquilariae Lignum Resinatum* protected against 5-FU-induced intestinal mucositis in mices.	Zheng *et al.*, 2019[29]
24	Experimental	Journal of Functional Foods	Belo Horizonte	The work demonstrates the protective effect of *Lactobacillus delbrueckii* subsp. lactis CIDCA 133 on the damage of the intestinal mucosa in a murine model of inflammation induced by a chemotherapeutic drug.	De Jesus *et al.*, 2019[10]
25	Experimental	EurJourof Pharmac	Islamabad	Diadzein could inhibit 5-FU-induced intestinal mucositis.	Atiq *et al.*, 2019[1]
26	Experimental	Phamaceuticals	Fortaleza	Cashew Gum (*Anacardium occidentale* L.) prevented 5-FU-induced intestinal mucositis.	De Miranda *et al.*, 2019[11]
27	Experimental	Food & Function	Beijing	Carboxymethyl pachyman could regulate the ecological balance of the intestinal flora and reduce colon injuries induced by 5-FU in CT26 tumour-bearing mice	Wang *et al.*, 2018[30]

28	Experimental	Pediatrics and Neonato	Taipei	Probiotics *Lactobacillus casei* variety *rhamnosus* or *Lactobacillus acidophilus* and *Bifidobacterium bifidum* do not lead to bacteremia, and had beneficial effects on mucositis.	Huang *et al*., 2019[31]
29	Experimental	Molecules	Fortaleza	Rutin attenuated the inflammatory response in intestinal mucositis.	Fidelis *et al*, 2020[32]
30	Experimental	Life Sciences	Wuhan	Andrographolide ameliorated 5-FU induced intestinal mucositis. The apoptosis of intestinal cells was also attenuated by treatment.	Xiang *et al*., 2020[33]
31	Experimental	Biomed & Phamac	Zhejiang	Berberine repaired disrupted gut microbiota, reducing the inflammatory response and protecting the intestinal mucosa.	Chen *et al*., 2020[34]
32	Experimental	Biomed & Pharma	Belo Horizonte	Pretreatment and total treatment with FOS in mucositis induced by 5-FU had beneficial effects on mouses.	Carvalho *et al*., 2021[35]

The articles presented in this review bring into their methodological scope the evaluation of products of natural origin, nutritional supplementation/ probiotics or drugs that are redirected to the treatment of intestinal mucositis.

Probiotics and Nutritional Supplements

We found 12 articles evaluating the effect of probiotics and other nutritional supplements on intestinal mucositis (IM) induced by 5-FU. The articles found in this review separately evaluated four types of probiotics, namely: *Lactobacillus delbrueckii*[10], *Lactobacillus casei* variety *rhamnosus*, *Bifidobacterium bifidum*[13,14,21], and *Lactobacillus plantarum*[26]. In addition to the combination of *L. casei* BL2, and/ or Propionibacterium freudenreichii 138 + Whey Protein isolate[7], as well as a mixture of probiotics from four strains (*Bifidobacterium breve*, *Lactobacillus acidophilus*, *L. casei* e *Streptococcus thermophilus*) [24], and the combination of mulberry leaf extract with *Lactobacillus acidophilus*[25].

The study of De Jesus *et al.*[10] demonstrated that milk fermented with *L. delbrueckii* was able to prevent weight loss, and leukopenia, in addition to preserving villus/crypt ratio, decreasing small intestine permeability, reducing goblet cell loss, and intestinal secretion of IgA. The authors also showed this strain reduced the inflammatory secretion of neutrophils and eosinophils (MPO and EPO) in ileum sections of 5-FU treated animals.

The treatment with *Bifidobacterium* G9-1(BBG9-1), was ably attenuated the inflammatory marked myeloperoxidase (MPO) activity, TNF- α, and IL- 1β, the shortening of villi, and the decrease in the number of cells in the crypts. In contrast, BBG9- 1 failed to prevent apoptosis induction. The authors suggest the ameliorative effect against 5-FU-induced intestinal mucositis through the attenuation of inflammatory responses via improving dysbiosis[20].

Levit *et al.*[26] demonstrated that *L. Plantarum* CRL2130 attenuated the pathologic changes induced by 5-FU in mice such as body weight loss, diarrhea, shortening of villus height, and elevated production of interleukin 10, an anti-inflammatory cytokine. In vitro assays using Caco-2 cells showed the effectiveness of 5-FU was not affected by *L. Plantarum* CRL2130 and that this strain exerted an inhibitory mechanism against oxidative stress.

Other researchers showed the mulberry leaf extract fermented with *Lactobacillus acidophilus* A4 has ably ameliorated the weight loss and the histopathologic parameters. The treatments also stimulated MUC2 and MUC5AC gene expression and mucin production and reduced IL- 1β expression and MPO level. These results suggest fermented mulberry leaf extract may provide synergistic therapeutic benefits of both probiotics and natural plant extracts in the prevention of 5- fluorouracil-induced mucositis[25].

Yeung and collaborators[13] found after oral *Lactobacillus acidophilus* and *Bifidobacterium bifidum* administrations, the diarrhea scores decreased, repairing of damage in jejunal villi was observed and the probiotics treatment suppressed this upregulation the TNF-α, IL-1β, and IL-6. Huang *et al.*[31] also demonstrated that *Lactobacillus casei* variety *rhamnosus* or the mixture that *Lactobacillus acidophilus* and *Bifidobacterium bifidum* could significantly inhibit serum cytokines TNF-a, IL-1β, IFNg, IL-6, IL-4, IL-10, and IL-17, and that it could improve diarrhea with jejunal mucosa repair.

In the study by Cordeiro *et al.*[7], it was observed probiotic beverages fermented by *L. casei* BL23 and *P. freudenreich* 138 were able to decrease 5-FU-induced intestinal inflammation, preserving mucosal integrity, and reducing weight loss and preserving the number. of goblet cells. The addition of Whey Protein-Isolate was found to improve the beneficial effects of *L. casei*

BL23, but not *P. freudenreichii*.

The treatment with a probiotic mixture (*Bifidobacterium breve*, *Lactobacillus acidophilus*, *L. casei* e *Streptococcus thermophilus*) ameliorated 5-FU–induced intestinal mucosal injury, preserved histopathological changes, and mucus reduced the proinflammatory cytokines (IL-4, IL-6, TNF-α) and neutrophil infiltration, but not reduced the bodyweight loss. Moreover, the treatment reduced the intestinal permeability and reestablishment of intestinal microbial homeostasis and alteration of the toll-like receptors 2 and 4 (TLR2/TLR4) signaling pathway a defense system against microorganisms[24].

The exact mechanisms by which probiotics exert their beneficial effects remain unknown. However, from the findings in this review, it was observed probiotics appear to attenuate the severity of mouse-induced intestinal mucositis by 5-FU treatment by inhibiting inflammatory parameters (cytokines and neutrophils), improving intestinal permeability and microbiota balance.

According to Van *et al.*[36], the microbiota can influence mucositis development and severity through at least five different mechanisms. These include influencing the inflammatory response, intestinal permeability, mucin layer composition, epithelial repair, resistance to harmful stimuli, and the intestinal immune system, all of which can have important implications for both mucositis severity and host health.

Prebiotics is nondigestible food ingredients that selectively stimulate the growth or activity of bacteria in the colon, that beneficially affect the host. In this sense, Galdino *et al.*[28] demonstrated that fructo-oligosaccharides (prebiotic) were also capable of reduced inflammatory infiltrate (MPO) and improved intestinal permeability, and preserved intestinal mucosa. Carvalho *et al.*[35] also found that fructo-oligosaccharides effects included maintenance of tight junctions expression with a reduction in the inflammatory infiltrate and histological score and improvement in short-chain fatty acids production. These effects contributed to the restoration and preservation of mucosal architecture.

In turn, Generoso *et al.*[16] showed omega-3 supplementation less weight loss decreased intestinal permeability and bacterial translocation besides preserving the mucosal integrity and reduced number of apoptotic cells the ileum mucosa. Cai *et al*[4] also observed the enteral nutrition supplemented with Crassostrea hongkongensis Polysaccharides showed to positively influence in intestinal mucositis, since, ameliorate atrophy of the villi with fewer goblet cells, reducing pro-inflammatory cytokine secretion (IL-2), releasing anti-inflammatory cytokines (IL-10), inhibiting inflammatory pathways, improving the barrier function, preventing epithelial cell apoptosis and eliminating pathogenic bacteria.

In summary, Table 2 shows the synthesis of effective probiotics and supplements in the studies.

Plant extracts and substances isolated

We found 16 articles in which the authors investigated the protective effect of products of natural origin, plant extracts, or even plant-isolated substances. A common feature of this group is that the investigated substances had a traditional use and/or already had evidence of antioxidant and anti-inflammatory activity[9,11,12,14,18]. The main parameters included histological evaluation, body weight, inflammatory and oxidative parameter evaluation, apoptosis evaluation, and investigation of the probable way in which the substances acted.

Atiq *et al.*[1] demonstrated that diadzein, an isoflavone in nature and isolated from plants such as soybean, was able to inhibit 5-FU-induced intestinal mucositis. It did this by preventing leukopenia, decreasing morphometric and histopathological changes, inhibiting oxidative stress with the equilibrium of GSH, GTS, MDA, catalase and nitrite concentrations, as well as the preservation of goblet cells' equilibrium in the inflammatory parameters (COX-2, TNF-α, p-JNK, IL-6 , IL-1β).

Table 2. Concentration of probiotics and supplements used in preclinical studies for intestinal mucositis induced for 5-Fluorouracil

Probiotic/Nutritional supplement	Concentration
L. delbrueckii subsp. *lactis* CIDCA 133 fermented milk	7.5 x 10^7 CFU/ml
Mulberry leaf extract fermented with *L. acidophilus* A4	100 µg/ml and 10^9 CFU/ml(A4)
L. plantarum	10^8 CFU/ml
L.casei and P. freudenreichii 138 with Whey Protein	10^9 CFU/ml
Probiotic mixture (*B. breve*, *L. acidophilus*, *L. casei*, and *S. thermophilus*).	10^9 CFU
L. casei variety rhamnosus and *L.acidophilus* with *B. bifidum*	10^7 CFU
B. bifidum	10^9 CFU
Fructo-oligosaccharides	240 mg (6% of total kg)
Crassostrea hongkongensis Polysaccharides	0,0195 mg / mL
Dietary supplementation with omega-3 fatty acid	3.5 % fish oil

Miranda *et al.*[11] showed that Cashew Gum (a polysaccharide) was able to reverse weight loss, prevent histopathological changes, decrease the number of mast cells, and reduce leukopenia. Moreover, Cashew Gum also reduced oxidative stress, the expression of COX-2 and IL-1β, and the concentration of MPO.

Bu-Zhong-Yi-Qi's decoction (BZYQD), a water extract of Chinese traditional herbal medicine, was able to inhibit morphological signs of intestinal damage, including shortened villi height. Crypt destruction, apoptosis, and necrosis in intestinal mucosal epithelia were also reversed, accompanied by reduced neutrophil infiltration, nitrite levels, and inflammatory factors (TNFα and IL1ß) and increased levels of reduced glutathione[17].

Aquilariae Lignum Resinatum, also a traditional Chinese medicine treatment, improved food-intake and reduced injury of the intestinal mucosa, relieved body weight loss and severe diarrhea through up-regulating the expression of proliferating cell nuclear antigen (PCNA) and inhibiting the levels of cyclooxygenase-2 (COX-2) and tumor necrosis factor-α (TNF-α) in ileum segments[29].

Kato *et al.*[14], found Saireito, a Japanese traditional herbal medicine, reduced the increase in apoptotic cells on the intestinal crypts, such as the expression of TNF-α and IL-1β mRNA, body weight loss, diarrhea, and potentially reduced tumor growth. In contrast, the administration of Saireto did not alter the anti-proliferative action of 5-FU in the intestinal crypts.

A mucoadhesive containing curcuminoids from *Curcuma longa* L. showed significant results towards body weight loss, as all the animals treated had body weight loss reduced. Besides that, curcuminoids demonstrated a protective effect on 5-FU-induced intestinal mucositis, not only by reducing the shortening in the duodenal villi height and crypt depth but also by decreasing histological severity scores. Besides, there was less apoptosis on intestinal cells, greater expression of Ki-67, and significantly diminished tissue oxidative stress and free radical production[9].

De Ávila *et al.*[9] also used a mucoadhesive to treat 5-FU induced mucositis, made of *Bidens pilosa* L. (*Asteraceae*). Most of the elements investigated, such as body weight, morphometric and histological analysis, the evaluation of the small intestine, and expression of Ki-67, Bax, MPO, and MDA, had significant results in the groups treated compared with the 5-FU group. Another study investigated the effect of a mucoadhesive containing not only *Bidens Pilosa* L. (*Asteraceae*) but also *Curcuma longa* L. (*Zingiberaceae*). It protected against 5-FU intestinal damage regarding the size of the crypts and villi and weight loss, promoted the increase of blood cells, and recovered the proliferative activity of the intestinal tissue in the animals with mucositis, due to the significant expression of Ki-67, Bax, and Bcl-2[19].

Bajic *et al.*[2] showed rhubarb, *Rheum* spp, a perennial herbaceous plant with anthraquinones as its main active ingredient, in the form of a relatively low-dose aqueous extract, offers partial protection to the distal intestinal mucosa against tissue damage and inflammation associated with 5-FU induced intestinal mucositis.

Wei-Chang-An is a traditional Chinese pharmaceutical preparation with potential anti-inflammatory action that reduced body weight loss, alleviating severe diarrhea and gastric emptying (GE), and gastrointestinal transit. Further evaluations also validated that Wei-Chang-An promoted intestinal mucosal recovery, evaluated enterocyte proliferation activity, maintained tight junction integrity, and improved inflammatory disorders[6].

Song *et al.*[20] demonstrated that Arabinoxylan has immunomodulatory effects through activation of NK cells, dendritic cells, modulating cytokines and tumor cell-induced apoptosis, and suppressed the side effects associated with 5-FU in mice, alleviating oxidative stress and myelosuppression.

Xiang *et al.*[33] found that Andrographolide, a labdane diterpenoid, significantly ameliorated 5-FU-induced weight loss, diarrhea, and apoptosis. Besides, Andro markedly downregulated the 5-FU-induced protein expression of caspase8/3, Bax, and the phosphorylation of p38.

Rutin, a flavonoid, prevents intestinal inflammation by inhibiting MDA, MPO, COX-2, oxidative stress and mastocytosis. This flavonoid also stimulates increased villi and increased the GSH concentrations[32]. The authors propose that the action mechanism is the inhibition of COX-2. This hypothesis agrees with Miranda *et al.*[12], in a study that demonstrated that troxerutin, a flavonoid derived from rutin, also reduced the effects of intestinal mucositis for reduction of COX-2.

Zhang *et al.*[23] demonstrated that volatile oil of A. *villosum* and bornyl acetate prevented diarrhea, reversed weight loss, and reduced food intake. Besides, it improved histopathological changes in intestinal mucositis, perhaps due to a reduction in inflammatory parameters, decreased p38 MAPK and caspase-3 proteins, and improved the function of the intestinal mucosal barrier. Bornyl acetate also contributed to the regulation of intestinal microbiota balance.

Interestingly, Chen *et al.*[34] demonstrated that the likely mechanism by which Berberine (isoquinoline alkaloid) would exert its protective effect on intestinal mucositis would be through the regulation of the intestinal microbiota. Wang *et al.*[30] also demonstrated that this mechanism is important for intestinal mucositis. The authors found that Carboxymethyl pachyman (a polysaccharide) could regulate the ecological balance of the intestinal flora and reduce colon injuries induced by 5-FU.

In this article, we observed that the researchers

mainly investigated a wide variety of plants of traditional use, as well as polysaccharides and flavonoids with antioxidant and anti-inflammatory action.

Drug Repurposing

In this review, we also found 4 papers that evaluated the effect of drugs that were originally recommended for other pathologies, but which have been suggested as an alternative for the treatment of 5-FU-induced intestinal mucositis. Medeiros *et al.*[27] investigated the effect of simvastatin, a drug used to treat high cholesterol.

The authors found simvastatin reduced weight loss, improved histopathological scores, and decreased expression of proinflammatory cytokines (TNF-α, IL-1ß, and IL-6). The authors did not investigate the likely mechanism of action related to improvement observed with drug use; however, the study suggests that a likely action in COX-2 could explain the decrease in cytokines.

Another study found that Lafutidine, an antiacid histamine H2 receptor antagonist with mucosal protective properties via sensory afferent neurons showed protective effects in intestinal mucositis-induced 5-FU. Lafutidine was able to reduce diarrhea, histopathological changes, MPO, TNF-α, IL-1β, and apoptosis, but did not decrease weight loss. However, it is worth noting that Lafutidine increased mucus production (number of goblet cells) via activation of sensory afferent neurons[22].

Kim *et al.*[15] demonstrated that rebamipide, an anti-gastric ulcer and gastritis agent, showed clinical and histological mucosal protective effects and also preventative effects against apoptosis. It decreased inflammatory cytokines (TGF-β1, TNF-α) and macrophage accumulation, preserved the concentration of GSH, and suppressed iNOS expression and diarrhea.

In an experimental study, Ciobanu *et al.*[5] proposed a different approach for microbiota modulation, by using rifaximin, an antibiotic. Rifaximin reduced histopatological scores, preserved goblet cell number, and decreased the expression of TLR. The authors explained that the gut microbiota plays a key role in this phase, through the activation of TRL, and then can also up-regulate NFκB.

Thus, we can observe that drugs with a different mechanism of action showed some effects in 5-FU-induced intestinal mucositis.

Conclusion

From this review, it was possible to recognize a considerable number of studies involving intestinal mucositis. The information gathered demonstrates that substances isolated from plants, probiotics with emphasis on those of the genus *Lactobacillus*, nutritional supplements, and even repurposed drugs were evaluated in connection with 5-FU-induced intestinal mucositis, and these showed a protective effect on several morphological parameters (Figure 2). However, no results were observed with research with humans. Thus, although there are many studies, the treatment of intestinal mucositis remains a gap in science and there is a need for future research with clinical evaluation on the subject.

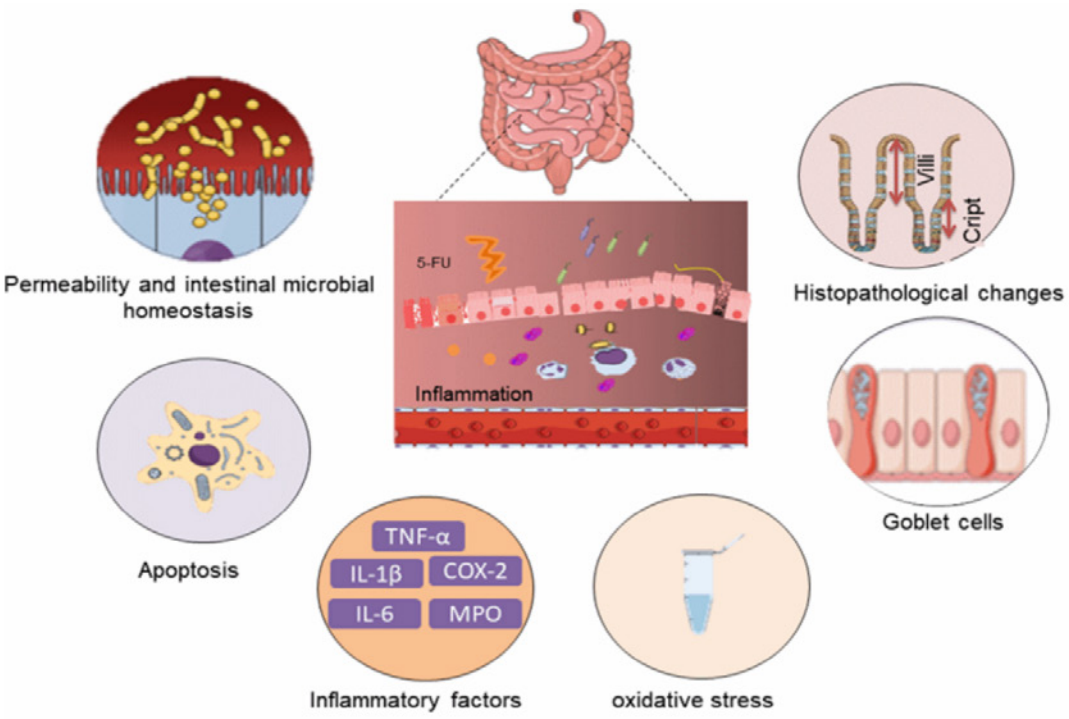

Figure 2. Main parameters evaluated in intestinal mucositis induced for 5-FU.

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