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Review Article

The Role of Resveratrol in the Inflammatory Bowel Diseases

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ABSTRACT
Resveratrol is a polyphenol that possesses several biological functions that are usually related to its modulating actions against inflammatory and oxidative processes. Hence, the objective of this review was to evaluate the effects of these substances in UC and CD. This review used studies published in the MEDLINE-PubMed (National Library of Medicine) following the PRISMA guidelines (Preferred Reporting Items for a Systematic Review and Meta-Analysis). The use of resveratrol in animal and human models has led to an improvement in disease activity indices, reduction of weight loss and improvement of diarrhea and rectal bleeding. It also led to serum reduction of inflammatory markers such as Interleukin (IL)-1α, IL-6, IL-8, Tumor Necrosis Factor (TNF)-α, Interferon (IFN)-γ and COX-2 and a significant decrease in OS. It promotes the reversal of dysbiosis and stimulates the expression of Tight Junction-associated proteins, including Claudin-1, Occludin and ZO-1. Resveratrol is effective in the treatment of IBD by reducing the production of free radicals and increasing antioxidant enzymes. Besides, this polyphenol is capable of reducing the expression of inflammatory markers characteristic of UC and CD.
Key words: Resveratrol, Antioxidant, Inflammatory Bowel Disease, Ulcerative Colitis, Crohn´s Disease.

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INTRODUCTION

Inflammatory Bowel Diseases (IBD) are a group of chronic diseases that afflict the Gastrointestinal Tract (GIT) and mainly include Ulcerative Colitis (UC) and Crohn's Disease (CD). These disorders have a multifactorial etiopathogenesis, such as eating habits, genetics and hyperactivity of the immune system. Lately, studies have demonstrated the action of oxidative stress as a strong factor for the development of these diseases.[1-3]

Oxidative Stress (OS) is a phenomenon caused by an imbalance between the production and increase of Reactive Oxygen Species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products through antioxidants. Radicals superoxide, hydrogen peroxide, hydroxyl radicals and singlet oxygen are commonly defined as reactive oxygen species. Antioxidants may be intracellular enzymes such as Catalase (CAT), Superoxide Dismutase (SOD), Glutathione Peroxidase (GPX) and extracellular elements such as vitamins and minerals that can inactivate ROS.[4]

Some factors can trigger the OS, such as smoking, radiation, drugs, alcohol, among others, favoring the development of IBD. The relationship between these diseases and OS is mainly related to two mechanisms. The first is that excess ROS causes endothelial dysfunction as it reduces nitric oxide synthesis and increases the synthesis of vaso-constricting factors, such as angiotensin. Thus, there is a reduction of blood flow, causing hypoperfusion of the intestinal mucosa. The second mechanism is associated with the lesion of the intestinal mucosa due to the excess of ROS with the subsequent invasion of bacteria that will stimulate the immune response. Figure 1 shows the relation between OS, antioxidants and IBD.[5-7]

Due to the above reasons, it is important to understand the mechanisms that lead to lesions in the intestinal epithelium to study and create ways to avoid this type of aggression that has been an important factor in triggering IBD. Currently, the standard treatment for these diseases consists mainly of the use of corticosteroids, immunosuppressants, antibiotics and biological agents. In addition to having high costs, these drugs do not always manage to remission of disease and may be associated with several side effects.[8]

Phytochemicals may play an important role in the reduction of OS and may be helpful in the therapeutic approach of IBD. They are capable of reducing inflammatory processes by inhibiting oxidative damage or modulating the immune system. Resveratrol is a polyphenol that can be found abundantly in berries, red grapes and peanuts. This polyphenol possesses several biological functions that are normally related to its modulating actions against inflammatory and oxidative processes. Consequently, the objective of this review was to evaluate the effects of these substances in UC and CD.[9]

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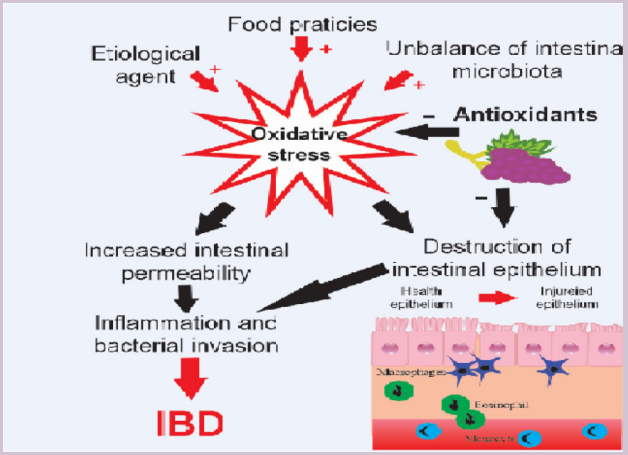

Figure 1: The relationship between oxidative stress, antioxidants and IBD. It is possible to notice the influence of several factors, such as etiological agents, eating habits and alterations in the balance of the intestinal mucosa, which together lead to oxidative stress. In contrast, the beneficial effect of the antioxidants help reducing this oxidative pathway and thereby prevent the destruction of the intestinal epithelial barrier.

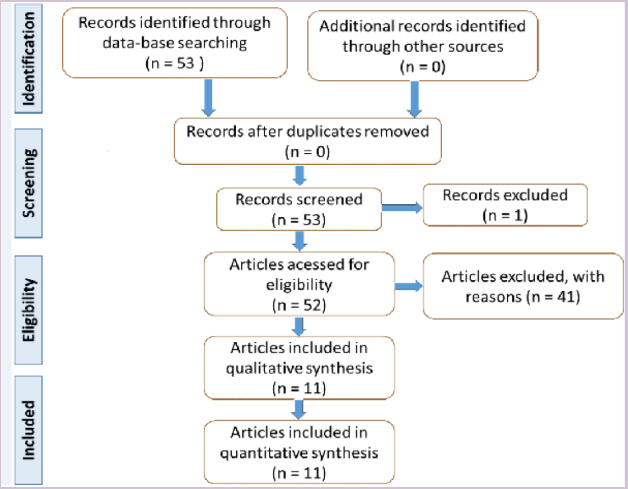

Figure 2: Flow diagram (according to PRISMA – Moher *et al.* 2009).

METHODS

Data Sources

The authors of this review searched the MEDLINE-PubMed databases following the PRISMA guidelines (Preferred Reporting Items for a Systematic Review and Meta-Analysis.[10] This review was conducted to answer the following question: Is Resveratrol effective in treating inflammatory bowel diseases?

Research

The research included randomized clinical trials, cohort studies, cross-sectional studies, case-control and experimental studies. The combinations of terms and keywords used for this search were "inflammatory bowel disease and resveratrol", "ulcerative colitis and resveratrol", "Crohn's disease and resveratrol", "colitis and resveratrol".

Based on the list of references obtained with the combination of these keywords, we selected 11 articles to construct the Table (Table 1). The flow diagram (Figure 2) shows the selection of articles and inclusion and exclusion of studies. Other studies on antioxidants and intestinal inflammatory disorders were used to build the discussion.[10-21]

Eligible criteria and study selection

Our research included qualitative and quantitative studies that discuss the use of Resveratrol and its effects on the treatment of IBD. We have included English articles from the last five years and corresponding to the keywords used for searching.

Extraction of data

Data extraction was performed by the authors who used the pre-defined data described above. Data were extracted from eligible articles that included: the date, author, study design, sample size, gender, information related to the use of Resveratrol and its relationship with IBD. Only original articles were selected for the construction of Table 1. Inclusion criteria were articles that used randomized clinical trials, cohort studies, cross-sectional studies, case-control and experimental studies. The exclusion criteria used for this search were non-English articles, case reports, poster presentations and letters to the editor.

RESULTS

The literature shows many studies with several plants and plant products that have shown beneficial effects in the treatment of experimentally induced colitis in animals.[3,22,23]

Our review included studies published between 2014 and May 2019 and in that period eleven original studies that used resveratrol for the treatment of IBD were published. Of these, two studies were performed on Wistar rats, 7 were performed on mice, two studies on humans in randomized, double-blind and placebo-controlled trials (Figure 2). These eleven studies were used to construct Table 1. Other studies with cellular models were commented in the discussion section.

The studies used in this review have demonstrated that resveratrol has a beneficial effect in the inflammatory processes. Therefore, it may be indicated in the treatment of intestinal diseases associated to inflammation.

DISCUSSION

Inflammatory Bowel Diseases

The UC is characterized by having onset in the rectum, extending up to the colon and can occur at any age, but especially between 30 and 40 years. The affected patient presents abdominal pain, bloody diarrhea, emaciation, anemia and fever. It is believed that its onset is due to an excessive immune response to bacteria in genetically predisposed patients. In Europe, the incidence of this disease approaches 24.3 for every 100,000 inhabitants.[24-28]

CD mainly affects the terminal ileum and colon but can extend from the oral cavity to the anus and usually appears in the 20-40 age range, but can occur at any age. Its clinical presentation usually includes diarrhea, abdominal pain, bleeding, fever and weight loss and there is a risk of complications such as strictures, fistulas and abscesses. Hypotheses for its etiology include genetic predisposition, microbial exposure, immune response and environmental factors. Patients with the active disease present imbalance of T helper 1 (Th1) and Th17 cells, in addition to regulatory T cell. It is known that there is an association between the disease and the more urbanized lifestyle, as well as the decrease in fiber, fruit and vegetable intake. In the city of São Paulo, in 2016, the prevalence found was 14.8 cases per 100,000 inhabitants, that is similar to other cities in the world.[3,29-32]

Table 1: Effects of resveratrol in humans with IBD and in animal models of colitis.

Reference	Model /type of the study	Treatment	Major findings	Conclusions
Kim *et al.* 2019[11]	Pathogen Free mice (female C57BL/6 (H-2Kb and I-Ab) and BALB/c (H-2Kd and I-Ad) were used in the *in vitro* and *in vivo* experiments.	Resveratrol solution (1 mg/mL) dissolved in methanol was irradiated at a dose of 50 kGy (10 kGy/h) by a cobalt-60 irradiator.	Irradiation with resveratrol has a critical role in anti-inflammatory activity via blocking MAPK and NF-κB signals in activated DCs and inducing tolerogenic DCs that are capable of both inhibiting T cell activation/proliferation and inducing regulatory T cells. Treatment conferred protective immunity and imparted protection to DSS-induced colitis in mice.	Irradiation with resveratrol has the potential to be an effective treatment against IBD. On the other hand, despite showing anti-inflammatory activities, high doses (≥ 10 μg/mL) induced cell death in normal cells.
Zhang *et al.* 2019[12]	Male BALB/c mice (DSS model of colitis).	Mice received the standard diet supplemented with 80 mg/kg resveratrol for 14 days in addition to 3.5% DSS during the first 7 days	The use of 80 mg/kg of resveratrol prolonged animal survival compared with the DSS treatment alone. The treatment resulted in the preservation of histological integrity in the colon tissue. The DSS-induced mice developed immunological deregulation, including the prominent shortening of the large intestine, thickened muscular layer, crypt damage and cellular infiltration in the inflamed colon; however, these effects were reduced by resveratrol treatment. Resveratrol also significantly decreased the accumulation of pro-inflammatory cytokines as compared with those in the colon tissue of DSS-treated mice.	The development and progression of colitis symptoms caused by DSS administration are attenuated by resveratrol. Resveratrol has the potential to work as effective anti-IBD therapeutic method.
Alrafas *et al.* 2019[13]	Female BALB/c mice (TNBS model of colitis).	Treated animals received resveratrol orally (100 mg/kg).	In the TNBS + Resveratrol group, the weight loss was significantly reversed. TNBS + Resveratrol group showed 100% of survival rate. Colitis induction caused an overall decrease in the colon length in TNBS + vehicle group compared to those treated with resveratrol. Resveratrol treatment in mice with colitis led to an increase in CD4+FOXP3+ and CD4+IL-10+T cells and a decrease in CD4+IFN-γ+ and CD4+IL-17+ T cells.	Administration of resveratrol attenuated colonic inflammation and clinical symptoms in the murine model of TNBS-induced colitis.
Zheng Z *et al.* 2019[14]	BALB/c background wild-type (WT) mice	Animals received BHA (200 mg/kg) and resveratrol (200 mg/kg) or vehicle (corn oil) daily, starting 2 days before the administration of DSS (2.5%) in the drinking water for one week.	Mkp-1 is implicated in the regulation of the Nrf2/ARE cytoprotective system *via* crosstalk with Nrf2. Through a direct interaction with the Neh2 domain of Nrf2, Mkp-1 stabilizes Nrf2, leading to increased activity of the transcription factor and upregulation of its downstream genes. Conversely, Nrf2 activates Mkp-1 transcription by binding to the ARE in the promoter of Mkp-1. Mkp-1 is involved in the regulation of both the basal and inducible expression of ARE-driven genes and has been implicated in the protective action of the Nrf2 activators. A role of the Mkp-1/Nrf2 axis in limiting inflammation in DSS-induced murine colitis has also been demonstrated.	Results showed that the action of the Nrf2 activators BHA and Resveratrol in anti-colitis and the suppression of tumorigenesis is Mkp-1 dependent. These are evidences that loss of Mkp-1 abolishes the chemopreventive effects of these agents. This study reveals a novel function of Mkp-1 in chemoprevention.

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Table 1: Cont'd.

Mayangsari *et al.* 201[8][15]	Male BALB/c mice (DSS model of colitis) and Human intestinal Caco-2 cell line.	The DSS + Resveratrol group was fed with the AIN-93G based diet containing 0.1% (w/w) resveratrol in the standard diet for 14 days before and during DSS treatment. Caco-2 cell monolayers were treated with resveratrol (100 μM) before TNF-α stimulation.	Resveratrol can prevent barrier defects and inflammation possibly through the suppression of neutrophil infiltration in colitic mice. In line with the *in vivo* study, resveratrol was shown to suppress TNFα-induced inflammatory signaling and IL-8 production in human intestinal Caco-2 cells.	Dietary resveratrol suppresses colitis and colon barrier defects, restores colonic tight junction structure, suppress colonic pro-inflammatory expression and neutrophil infiltration into colonic tissues in DSS-administered mice.
Wagnerova *et al.* 2017[16]	Investigative study with thirty-seven (male and female) C57BL/6 mice with DSS-induced colitis.	Resveratrol was dissolved in 50% ethanol and administered to the DSS + Resveratrol group using oral gavage at concentration 100 mg/kg/d for 11 days.	Intake of 1.5% DSS caused weight loss in all DSS groups compared to control mice. Weight loss, stool consistency and discomfort did not show any protective effect of resveratrol in males and showed even adverse effects in females. In females, the activity of myeloperoxidase was lower compared to males. Resveratrol did not have any effect on TNF-αlevels.	Taken together, these results for the first time propose possible diverse effects of resveratrol in DSS-induced colitis model depending on the sex of the animal. However, this conclusion must be confirmed by further analyses.
Samsamikor *et al.* 2016[17]	Double-blind, placebo controlled, clinical trial with fifty-six patients. Men and women ≥18 years. With mild to moderate active UC	Capsules containing 500mg of trans-resveratrol or placebo once daily for 6 weeks.	Results showed that resveratrol increases the antioxidant capacity and reduces the oxidative stress in patients with mild to moderate UC. The serum level of MDA in the resveratrol group reduced significantly at the end of the 6th week compared to the beginning of the study and the placebo group. The serum levels of SOD and TAC decreased in resveratrol group after 6 weeks and was significantly lower than placebo group. The serum levels of SOD decreased, whereas MDA increased significantly during the study in placebo group.	Data indicate that the use of resveratrol supplementation can improve the disease activity and quality of life in patients with UC at least partially through reduction of oxidative stress.
Yildiz *et al.* 2015[18]	Investigative study with thirty-five Wistar-Albino female rats with induced colitis for TNBS.	Resveratrol was administered intraperitoneally at (10mg/kg/day) for 5 days before the induction of colitis.	The levels of the MDA in the colitis and control groups significantly increased compared to level of the resveratrol group suggesting that this polyphenol successfully inhibited lipid peroxidation induced by TNBS ($p < 0.05$).	Resveratrol proved to have a beneficial effect on TNBS colitis in rats and can be considered as adjuvant agent in IBD treatments.
Da Silva de Souza *et al.* 2015[19]	Investigative study with male Wistar rats with Ischemia/ reperfusion Injury.	Resveratrol was orally administered daily at a dose of 10 mg/kg for 5 days.	Resveratrol increased the activity of the antioxidant enzymes G6PDH and glutathione peroxidase and increased GSH content. The increase in glutathione peroxidase activity may result in the scavenging of both lipoperoxides and ROS, thus reducing oxidative stress in the ileum. However, resveratrol reduced oxidative stress, reflected by decreases in TBARS and carbonyl protein group levels. On the other hand Resveratrol decreased catalase activity.	Oral treatment with resveratrol reduced the oxidative stress in the ileum and attenuated the morphologic changes that occurred in the myenteric plexus of the ileum in rats subjected to ischemia/reperfusion.

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Table 1: Cont'd.

Samsami-Kor *et al.* 2015[20]	Randomized, double blind study (control and 50 patients with active moderate to moderate UC).	500mg of resveratrol or placebo capsule for 6 weeks.	The use of resveratrol decreases the clinical activity index score, serum level of inflammatory factors such as IL-1b, hs-CRP, TNF-alfa and IL-6 and the activity of NF-kB in PBMCs, whereas it increased the IBDQ-9 scores.	The supplementation with resveratrol can improve quality of life and disease clinical colitis activity at least partially through inflammation reduction in patients with UC.
Sharma *et al.* 2014[21]	Investigative study with female C57BL/6 mice with DSS-induced colitis.	100 mg/kg of Resveratrol	a) Acute colitis is associated with increased TACE and decreased TIMP-3 and SIRT-1 levels; b) activation of SIRT-1 increases TIMP-3 and decreases TACE expression, c) treatment with SIRT-1 activator and selective TACE inhibitor effectively ameliorates acute colitis. Treatment with resveratrol significantly elevated SIRT-1 and TIMP-3 and suppressed TACE mRNA expression.	The use of Resveratrol is associated with amelioration of the disease.

BHA: butylated hydroxyanisole; ARE: antioxidant response elemento; Mkp-1: mitogen-activated protein kinase phosphatase; Nrf2: nuclear factor-erythroid 2 related factor 2; RSV: resveratrol; TNBS: 2,4,6-trinitrobenzenesulfonic acid; RES: Resveratrol; γ-Res: Gamma-Irradiated Resveratrol; MAPK: Mitogen Activated Protein Kinases DCs: dendritic cell; DSS: dextran sulfate sodium; UC: Ulcerative Colits; MAD: Malondialdehyde; SOD: superoxide dismutase ;TAC: total anti-oxidant capacity; TNBS: trinitrobenzene sulphonic acid; CD4: lymphocyte T CD4; FOXP3: forkhead box P3 ; IL-10: Interleukin 10; IL-17: Interleukin 17; IFN-γ: Interferon γ; DMSO: Dimethyl Sulfoxide IBD: Inflammatory Bowel Disease; G6PDH: Glucose-6-phosphate Dehydrogenase; GSH: Reduced Glutathione; ROS: Reactive Oxygen Species; TBARS: Thiobarbituric acid-reactive substances; IL-1b: Interleukin 1b; hsCRP: high-sensitivity C-reactive protein; TNF-alfa: Tumor Necrosis Factor-alfa; IL-6: Interleukin 6; NF-kB: factor nuclear kappa B; PBMC's: Peripheral Blood Mononuclear Cells; IBDQ-9: Inflammatory Bowel Disease Questionnaire-9; TACE: TNF-a converting enzyme; TIMP-3: Tissue inhibitor of metalloproteinase; SIRT-1: silent information regulator; DSS: dextran sulfate sodium.

In both diseases, immunosuppressants and anti-TNF-α agents are commonly used, which in addition to high cost may be associated with side effects or unsatisfactory patient response.

Antioxidant Therapies Targeting Oxidative Stress in IBD

The OS induced by ROS generation is one of the main causes of several chronic human disorders, such as cancer, diabetes, Alzheimer's disease and other neurodegenerative, cardiovascular, pulmonary, hepatic and renal diseases in addition to IBDs. It disrupts the intestinal epithelial barrier and increases its permeability, further exacerbating inflammation. Despite the overproduction of ROS having a major influence on the OS, a deficiency in dietary and enzymatic antioxidants also contributes to the development of OS. Thus, even if this uncontrolled stress is destructive to the gastrointestinal tract, the endogenous antioxidant defenses can counteract the effects caused by excess ROS. These defense mechanisms ensure that concentrations of these species are under control and do not exert harmful effects. The endogenous antioxidant system consists mainly of intracellular enzymatic antioxidants, such as Superoxide Dismutase (SODs), Glutathione Peroxidase (GPX) and Catalase (CAT); intracellular non-enzymatic antioxidant glutathione; and extracellular antioxidants, including vitamins, minerals, ceruloplasmin and uric acid. The actions of these antioxidants include neutralizing activity against free radical species, inhibiting the production of reactive species, regulating antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, depleting glutathione and preventing damage to lipids, proteins and acids nucleic acids. In summary, antioxidants lead to a significant anti-inflammatory effect and contribute greatly to the improvement of inflammation in the intestinal mucosa. There are studies that propose that the antioxidant activity may be partially responsible for the intestinal anti-inflammatory effects presented by the 5-amino-salicylates and prednisolone, which are two drugs still very used in the treatment of IBD.[5,33-39]

Besides, IBDs are caused by the convergence of microbial, environmental and genetic factors. Diet significantly alters these interactions, affecting both the host and the microbiota and it can rapidly and dramatically alter the structure and function of the microbiota and therefore, dietary factors can participate in both the pathogenesis and the treatment of these diseases. In fact, it has been reported that in the induced models of colitis, Vitamin E supplementation reduced oxidative stress and promoted anti-inflammatory activities in the tissues, since it decreased levels of pro-inflammatory substances such as Tumor Necrosis Factor-α (TNF-α) and increased levels of anti-inflammatory substances such as glutathione and superoxide dismutase.[40-42]

Other studies have shown that ascorbic acid significantly reduced clinical signs, inflammatory cytokine levels, MPO (myeloperoxidase) and MDA (Malondialdehyde) and was able to inhibit NF-κB (Nuclear Factor κB), COX-2 (cyclo-oxygenase-2) and iNOS (Nitric Oxide Synthase) in the colon. Also, these findings suggest that ascorbic acid contributes to the reduction of OS and inflammatory response in induced colitis and has the potential to prevent and treat IBD clinically.[43]

The use of antioxidants may also help to maintain the phase of remission of IBD, in the actions of drugs such as corticosteroids and amino-salicylates. And in the establishment of adequate concentrations of EROS, Vitamins, minerals and ceruloplasmin, which are extracellular antioxidants.[1,33,44]

Thus, the endogenous and exogenous antioxidants neutralize the effects caused by the reactive oxygen species, besides exerting other innumerable functions, inhibiting the pro-inflammatory actions, exacerbating the anti-inflammatory actions, reducing the effects of the OS, therefore it can have effects interesting in the IBD.[40]

Resveratrol

Resveratrol (3,4,5'-trihydroxystilbene) is a polyphenol contained mainly in grapes, red wine and peanuts. Among its main functions is the amplification of the function of antioxidant enzymes and the aid in the prevention against metabolic diseases. This compound was isolated in 1940 for the first time from roots of white hellebore and has significant participation in traditional Chinese and Japanese medicine as an antiplatelet and anti-inflammatory agent, being detected in 1963 in roots of *Polygonum cuspidatum* (common plant of the oriental culture). Currently, the greatest interest lies in its cellular defensive function against OS.[45-47]

Mayangsari and Suzuki[15] conducted a survey where male BALB/c mice were divided into the control group, DSS (Dextran sulfate sodium) induced group and DSS group treated with resveratrol. The severity of disease was monitored daily by the disease activity index, as measured by weight loss, presence of blood in the feces and presence of diarrhea. In addition to blood samples, colon tissues were collected for histological and immunofluorescence analysis. The results of the study showed that dietary resveratrol can suppress colitis according to the disease activity index and reduced damage to the colon by suppressing the production of inflammatory cells. Despite these findings, it was not possible to determine the risks of using resveratrol concerning its efficacy and a new study is needed to determine the optimal therapeutic dose.

Kim *et al.*[11] performed a study with C57BL/6 and Balb/c mice that were irradiated with resveratrol-gamma and showed that this use is non-toxic to dendritic cells and has immunosuppressive properties, being a therapeutic proposal to be considered in the treatment of IBD.

Zhang *et al.*[12] investigated the action of turmeric and resveratrol in UC induced by DSS. To do this, Balb/c male rats were divided into four groups; one group maintained a standard diet; another three received a DSS 3.5% p/v for UC induction. One of these groups was supplemented with the turmeric diet (50 mg/kg) and the other, resveratrol (80 mg/kg). The index of disease activity, TNF-α and IL-6 concentrations were also measured. The study showed that the survival rate was improved with the use of turmeric and resveratrol, with resveratrol exhibiting greater efficiency for these criteria. The use of resveratrol also reduced weight loss and improved diarrhea and rectal bleeding. The authors postulated that resveratrol is effective in treating colitis, but it is necessary to investigate the concentrations that should be used.

In the study by Zheng, *et al.*[14] resveratrol was used as an activator of erythroid nuclear factor 2 (Nrf2). Nrf2 plays a promising role in the reduction of the inflammatory response and the prevention of colon cancer due to UC and CD. The tests were performed on male Wistar rats that had DSS-induced colitis. Resveratrol was given daily at a dose of 200 mg/kg. The treatment showed efficacy in reducing colitis severity, with serum levels of markers such as IL-6, TNF-α and COX-2 and a significant decrease in OS. This study provided further arguments about the effective role of resveratrol in combating inflammatory and oxidative imbalance and innovates by exposing the efficacy of resveratrol as an indirect protective factor by the activation of Nrf2 and not by its direct action on tissues.

In a case-control study Alrafas *et al.*[13] resveratrol was not only used with the classical anti-inflammatory approach, but also with the innovative intention of returning intestinal homeostasis and the physiological biota of animals with colitis. Resveratrol was given orally in the amount of 100 mg/kg. Results showed reversal of dysbiosis and reduction of inflammatory markers. This research indicated a new treatment for colitis by reducing the intestinal lesion while returning the original biota. This process facilitates the regression of inflammatory conditions and returns to the body physiological functions, effectively mitigating the damage caused by inflammatory and intestinal oxidative disorders, characteristic of IBD.

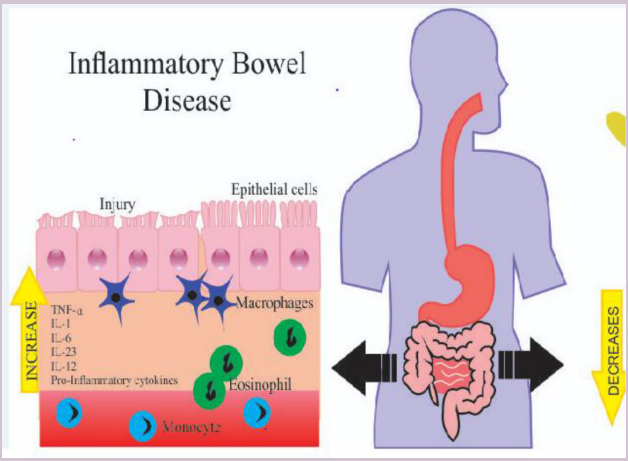

Figure 3: Inhibition of epithelial cells in IBD due to the increase of inflammatory cells and cytokines, such as TNF-α (Tumor Necrosis Factor-α), IL-1 (Interleukin-1), IL-6, IL-12 and IL-23 and the anti-inflammatory effect of resveratrol.

Recently, resveratrol is specifically efficient in the treatment of IBD in experimental models by reducing the production of ROS and increasing the activity of antioxidant enzymes such as superoxide dismutase. This polyphenol was able to reduce the expression TNF-α, IL-8 and Interferon (IFN)-γ, which are inflammatory markers in the UC and CD frames. Figure 3 shows the injury of epithelial cells and the effect of resveratrol reducing the pro-inflammatory state.[48]

In one study using a human colonic epithelial cell line, the cells were treated with varying concentrations of Oxyresveratrol (OXY) that showed stimulated the expression of Tight Junction-associated proteins, including Claudin-1, Occludin and ZO-1, which form a rigid connection between two adjacent cells. This rigid structure is important in intestinal barrier function, which regulates the transport of harmful substances through the epithelial layer. Therefore, OXY strengthens the integrity of the intestinal tight junctions barrier via activation of MAPK (Mitogen Activated Protein Kinases) pathways.[49]

An analysis showed that intestinal cells exposed to lipopolysaccharides derived from bacteria had lower levels of prostaglandin E2 and COX2 expression after exposure to resveratrol. Also, NF-κB levels were appreciably reduced. Another significant activity was observed in the reduction of mitochondrial damage and programmed cell death, which is also a preponderant factor in the pathogenic mechanisms of UC and CD.[50]

A study that analyzed the difference in the effect of resveratrol on DSS-induced colitis in rats has resulted in resveratrol not being able to decrease inflammation in females or males. However, neither the weight of the mice nor the amount of resveratrol used was considered in the study, nor did they use a control group to compare the results.[16]

A prospective, randomized, double-blind, placebo-controlled study enrolled 56 patients undergoing the Simple Clinical Colitis Activity Index Questionnaire (SCCAIQ) and IBD Questionnaire-9 (IBDQ-9) evaluated the use of supplements and 500 mg of resveratrol. The results obtained were an increase in IBDQ-9 that evaluates the quality of life of the patient and a decrease in SCCAIQ that evaluates the severity of symptoms in UC. It was possible to conclude that resveratrol increases antioxidant capacity and reduces OS in patients with mild to moderate

UC, improving disease activity and quality of life. However, this study was not able to assess the disease activity in patients who underwent a colonoscopy and was not able to assess the level of OS in the colon.[17]

In a double-blind randomized study, a 500mg daily supplementation of resveratrol for six weeks confirmed the improvement in the quality of life of IBD patients, with a proven reduction in inflammatory markers and symptom attenuation, thus configuring this compound as a new treatment approach of these diseases. It also evaluated important inflammatory markers in IBD, such as TNF-α, NF-kB and C-reactive protein. This study had 50 patients, which is interesting since there are few clinical trials with this focus.[20]

In a study by Yildiz, *et al.*[18] resveratrol was used as a preventive factor for IBD, contrasting with traditional research aimed at treating these diseases. Resveratrol was used in dimethylsulfoxide solution and administered intraperitoneally in Wistar rats (10 mg/kg/day), before the induction of colitis by TTBS (trinitrobenzenesulfonic) administration. Histological analysis revealed that the group pretreated with resveratrol demonstrated potential preventive power in IBD and regulation of the production of anti-inflammatory cytokines that reduced both tissue damage and loss of function due to fibrotic scarring. This study is relevant for the understanding of the effects of resveratrol on IBD and means an advance in research on methodological innovations in the treatment of this condition.

In another study, cell culture of RAW 264.7 cells (mouse macrophages) was used *in vitro* and showed immunomodulatory properties exerted by nanoparticles loaded with resveratrol, since they promoted macrophagic activity under basal conditions and inhibited this activity when stimulated with lipopolysaccharide. *In vivo* experiments, the use of resveratrol showed that, after the evaluation of macroscopic symptoms, inflammatory markers and function of the intestinal barrier, fibroin nanoparticles loaded with resveratrol had a better effect than the isolated treatments, being similar to those produced by glucocorticoid dexamethasone. For that reason, the silk fibroin nanoparticles constitute an attractive strategy for the controlled release of resveratrol, showing immunomodulatory properties and intestinal anti-inflammatory effects.[51]

In addition to a human colon cancer cell line used extensively in biological and cancer research (HT-29) study, colon epithelial cells were pretreated with resveratrol and/or 5-aminosalicylic acid and then exposed to a combination of cytokines (IL-1α, TNF- α, IFN-γ). The data showed that resveratrol in concentrations twenty times lower than 5-aminosalicylic acid was able to significantly reduce Nitric Oxide and Prostaglandin E-2 (PGE-2) production, induced iNOS expression and COX-2 and the formation of ROS induced by cytokine challenge. However, 5-aminosalicylic acid did not exhibit any effect on the degradation of NFκβ. Resveratrol down-regulated the JAK-STAT pathway, decreasing the levels of activated STAT1 in the nucleus. Furthermore, resveratrol decreased cytokine-stimulated activation of the Stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK/JNK) pathway but did not counterbalance the cytokine-triggered negative feedback mechanism of STAT1 through p38 MAPK. These results showed that resveratrol may be considered as a future nutraceutical approach, promoting remission periods, limiting the inflammatory process and preventing colorectal cancer, which is common in these patients.[52]

A study by Serra *et al.*[53] using human colon cancer cell line (HT-29) showed that cyanidin-3-glycoside (C3G) and resveratrol have a more efficient anti-inflammatory activity than 5-aminosalicylic acid. Therefore, both polyphenols may be interesting nutraceuticals, giving complementary benefits to conventional therapy.

Another experimental study evaluated the effects of resveratrol on changes in the myenteric plexus and oxidative stress in the ileum, characteristic of IBD. Significant OS reduction, reduced/oxidized glutathione ratio reduction and attenuation of changes in antioxidant enzyme activity were observed. Thus, there was an improvement in the morphological profile and the neuronal population that was previously altered due to ischemia/reperfusion.[19]

An additional study carried out with C57BL/6 mice analyzed the involvement of the TNF-α Converting Enzyme (TACE) in colon inflammation and the regulation of this inflammation by the Tissue Inhibitor of Metalloproteinase (TIMP), an endogenous TACE inhibitor, which is positively associated with the silent information governor (SIRT). The study showed that resveratrol significantly elevated SIRT-1 and TIMP-3 and suppressed TACE mRNA expression and was associated with disease improvement.[21]

Moreover, ongoing and future research is expected to provide more evidence and explanations regarding the use of diets and functional foods to control IBD. It appears that the alternative therapies based on diets and functional food will be the future of IBD management.[9]

CONCLUSION

The OS disrupts the intestinal epithelial barrier and increases its permeability leading to changes such as IBD. Still, the endogenous antioxidant defenses can counteract the effects caused by excess of ROS. The actions of these antioxidants include the neutralizing activity against free radical species, the inhibition of the production of reactive species, the regulation of antioxidant enzymes. Resveratrol is effective in treating IBD by reducing the production of ROS and increasing antioxidant enzymes. Furthermore, this polyphenol can reduce the expression of TNF-α, IL8 and IFN-γ.

In this way, we can suggest that the use of resveratrol can be indicated as a coadjutant in the treatment of IBD since it has low cost, is not associated with adverse effects and is efficient in combating oxidative stress that is closely related to the symptoms reported by patients. Despite this, further human studies are still needed to identify the optimal doses and the best means of administration of this compound.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ARE: Antioxidant response element; **BHA:** Butylated hydroxyanisole; **C3G:** Cyanidin-3-glycoside (C3G); **CAT:** Catalase; **CD:** Crohn´s Disease; **COX-2:** Clyclo-oxigenase; **DCs:** dendritic cell; **DMSO:** Dimethyl Sulfoxide; **DSS:** Dextran sulfate sodium; **FOXP3:** Forkhead box P3; **G6PDH:** Glucose-6-phosphate Dehydrogenase; **GIT:** Gastrointestinal tract; **GPX:** Glutathione peroxidase; **GSH:** Reduced Glutathione; **hsCRP:** High-sensitivity C-reactive protein; **IBD:** Inflammatory Bowel Disease; **IBDQ-9:** IBD Questionnaire-9; **IFN:** Interferon; **IL:** Interleukin; **iNOS:** Nitric Oxide Synthase; **MAPK:** Mitogen Activated Protein Kinases; **MDA:** Malondialdehyde; **MKP-1:** Mitogen-activated protein kinase phosphatase; **MPO:** Myeloperoxidase; **NF-κB:** Nuclear Factor κB; **Nrf2:** Erythroid nuclear factor 2; **OS:** Oxidative stress; **OXY:** Oxyresveratrol; **PBMC's:** Peripheral Blood Mononuclear Cells; **PGE-2:** Prostaglandin E-2; **RES:** Resveratrol; **ROS:** Reactive oxygen species; **RSV:** Resveratrol; **SAPK/JNK:** Stress-activated protein kinase/c-Jun NH2-terminal kinase; **SCCAIQ:** Simple Clinical Colitis Activity Index Questionnaire; **SIRT:** Silent information governor; **SOD:** Superoxide Dismutase.

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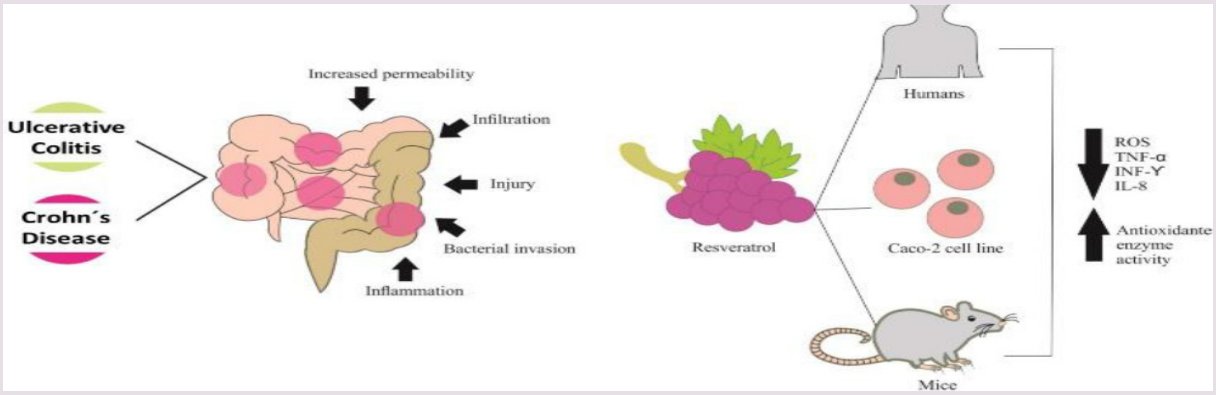
GRAPHICAL ABSTRACT



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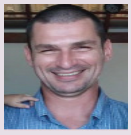

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