An Acad Bras Cienc (2022) 94(4): e20201378 DOI 10.1590/0001-3765202220201378
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

HEALTH SCIENCES

Antioxidant and anti-inflammatory activity of curcumin transdermal gel in an IL-10 knockout mouse model of inflammatory bowel disease

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Abstract: Inflammatory bowel diseases are a group of inflammatory disorders of the gastrointestinal tract. Their prevalence is still low in Brazil, but the incidence is increasing annually. A variety of compounds present in *Curcuma longa* L., particularly curcumin, have been shown to reduce oxidative stress and aid in the prevention of associated diseases. This study aimed to assess the effect of curcumin transdermal gel on oxidative stress and intestinal inflammation in IL-10 knockout mice. Female mice were divided into four groups: a control group (C0) treated with vehicle and three experimental groups treated with transdermal gel containing 50 (C50), 75 (C75), and 100 (C100) mg curcumin kg^{-1} body weight. Colon malondialdehyde concentrations were lower in C50 and C75 groups. C100 treatment led to reduced catalase activity in the small intestine, whereas C50, C75, and C100 treatments resulted in decreased catalase activity in the colon. In contrast, superoxide dismutase activity increased in the small intestine of C50 and C75 mice and decreased in the colon of C50, C75, and C100 mice. Glutathione *S*-transferase activity increased in the small intestine and decreased in the colon of C75 animals. These findings suggest that curcumin transdermal gel exerts a protective effect against oxidative stress.

Key words: Intestinal inflammation, histology, oxidative stress, curcumin.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of unknown etiology that affect the gastrointestinal tract. Crohn's disease and ulcerative colitis are the main types of IBD. Environmental, genetic, microbiological, and immunological factors are believed to be involved in the progression and maintenance of these conditions. The major symptoms include mucous bloody diarrhea, fatigue, abdominal pain, and malnutrition (Maranhão et al. 2015, Vezza et al. 2016). Although the main symptoms of IBD are associated with the gastrointestinal tract, the disease is systemic, and patients often present with extraintestinal manifestations, such as dermatological, musculoskeletal, oral, ocular, cardiovascular, neurological, hepatobiliary, and pancreatic disorders (Greuter & Vavricka 2019). The worldwide increase in IBD incidence and prevalence is related to modern lifestyles, consumption of ultra-processed foods, and stress (Santos et al. 2015).

Redox imbalance is believed to underlie the pathophysiology of IBD. This mechanism is involved in the pathogenesis and progression of other chronic inflammatory diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer (Soares et al. 2015, Zhu & Li 2012). Redox imbalance is linked to the

occurrence of diarrhea, toxic megacolon, and abdominal pain, important signs and symptoms of IBD (Barbosa et al. 2010, Damiani 2007). Production of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase, glutathione *S*-transferase (GST), and catalase (CAT), increases during an inflammatory process, as these enzymes are responsible for combating oxidative stress in the intestinal mucosa. However, when the demand for antioxidant enzymes is not met, there is an imbalance between pro- and antioxidant factors, leading to the formation of lesions in the intestinal epithelium (Mandalari et al. 2011, Moura et al. 2015, Torres et al. 2011).

Oxidative stress causes genetic modifications in the cell nucleus and acts as a potent inducer of inflammatory responses by altering the synthesis of cytokines, prostaglandins, thromboxane, leukotrienes, adhesion molecules, and chemokines (Haddad 2002, Jassen-Heiniger et al. 2000, Rauhman & Macnee 2000). Inflammatory cells activated during IBD pathogenesis cause oxidative damage to cellular constituents, including lipids, leading to additional mucosal damage, dysfunction, inflammation, and intensification of the pathological process. Lipid peroxidation products, such as reactive aldehydes, induce the infiltration and activation of inflammatory cells (Trevisani et al. 2007).

The body requires endogenous production and dietary consumption of antioxidants to prevent oxidative stress and maintain homeostasis. Dietary antioxidants include vitamin E (tocopherols and tocotrienols), ascorbic acid (vitamin C), ubiquinone (coenzyme Q10), thiols (alpha-lipoic acid), carotenoids, and flavonoids (Strobel et al. 2011). These bioactive compounds positively influence the expression of genes involved in intracellular anti-inflammatory signaling and systemic anti-inflammatory responses (Dragano et al. 2013).

Studies have been directed toward the extraction and application of polyphenolic antioxidants for the treatment of IBD, as these compounds show fewer side effects than conventional drugs. Extracts of turmeric (*Curcuma longa* L.) contain a diversity of phenolic antioxidants. Curcumin, a yellow fat-soluble polyphenol and the major component of *C. longa* extract, exerts antioxidant, antimicrobial, anti-inflammatory, antiangiogenic, antimutagenic, and antiplatelet aggregation effects (Vecchi Brumatti et al. 2014). These characteristics make curcumin beneficial for the prevention and treatment of several diseases, including osteoarthritis, cancer, dyslipidemia, metabolic syndrome, hyperuricemia, nonalcoholic fatty liver disease, anxiety, ischemia/reperfusion injury, diabetes, lung disorders, and dermatological disorders (Devassy et al. 2015, Deogade & Ghate 2015, Kocaadam & Şanlier 2015, Monton et al. 2019, Prasad et al. 2014, Sadeghi et al. 2018).

Curcumin has been suggested as a potential drug for digestive diseases, including IBD. However, its low oral bioavailability is a major limitation for clinical use, as assessed in human and non-human animal models (Vecchi Brumatti et al. 2014). Curcumin is hydrophobic, unstable at intestinal pH, and rapidly metabolized, resulting in low intestinal absorption and a short half-life (Ohno et al. 2017). Many drugs have bioavailability issues stemming from low water solubility, low dissolution rate, and instability in the gastrointestinal tract (Tzankova et al. 2019). In rodents, curcumin undergoes rapid metabolism by conjugation when administered via the oral route, showing low systemic bioavailability (Yadav et al. 2013).

Animal models can help to elucidate disease pathogenesis and identify therapy options. In a previous study, IBD animal models allowed understanding the changes in intestinal mucosa homeostasis caused by chronic inflammation

and their underlying immune mechanisms (Bamias et al. 2017). Interleukin-10 knockout mice have been widely used to investigate IBD, as they spontaneously develop colitis and exhibit histological changes similar to those observed in humans (Keubler et al. 2015). This study aimed to develop a topical formulation of curcumin for increased bioavailability and assess its antioxidant and anti-inflammatory effects in an IL-10 knockout mouse model of IBD.

MATERIALS AND METHODS

Preparation of curcumin transdermal gel

The curcumin transdermal gel formulation was developed at the Laboratório de Química e Bioquímica de Produtos Naturais (BIONAT) Universidade Federal de Viçosa, Minas Gerais, Brasil. Curcumin from *C. longa* rhizomes (molecular weight 368.38 g; ≥98.0% purity, as assessed by high-performance liquid chromatography) was obtained from Sigma-Aldrich. Pentravan®, a commercial vehicle for transdermal permeation, was used to prepare the formulations. The vehicle is a transdermal gel composed of bilayer phospholipid nanosomes. It has the ability to interrupt the lipid bilayer of the stratum corneum without dissolving it, providing optimal transdermal delivery without damaging the skin structure. This system avoids first-pass metabolism in the gut or liver, favors patient adherence, and improves treatment success.

Transdermal gel formulations were prepared by placing the appropriate amount of curcumin in a glass mortar, adding small portions of vehicle, and vigorously homogenizing the mixture using a pestle. Three formulations containing 12.5, 18.8, and 25 mg curcumin g^{-1} vehicle were prepared.

Animals

Seventeen weaned (28-day-old) C57BL/6 $IL10^{-/-}$ mice (*Mus musculus*) were used. This animal model has been widely used to study IBD (Byrne & Viney 2006, Mizoguchi & Mizoguchi 2010, Neurath 2014). According to Koboziev et al. 2011, IL-10 knockout mice spontaneously develop pancolitis and cecal inflammation at the age of 8-16 weeks. Animals were maintained in polyethylene boxes with ad libitum access to commercial feed (Presence/InVivo Animal Nutrition) and distilled water on a 12 h light/dark cycle under controlled temperature conditions (22 ± 3 °C). The experiment was initiated when the animals were 60 days old and in the initial stages of IBD. Mice were placed in individual stainless-steel cages and maintained under controlled conditions (22 ± 3 °C, 12 h light/dark cycle).

All experimental procedures were approved by the Animal Research Ethics Committee of the Federal University of Viçosa, Brazil (protocol no. 41/2019).

Experimental design

At the beginning of the experiment, mice were allocated into 4 groups. The negative control group consisted of 8 animals receiving only vehicle. Each experimental group consisted of 3 animals treated with transdermal gels containing different concentrations of curcumin. The animals were randomly distributed into groups using an online randomizer (Research Randomizer, https://www.randomizer.org), in agreement with AOAC recommendations (1997).

Mice were shaved over an area of 2 cm^2 in the distal dorsal region and received a daily application of 80 µg of transdermal gel for 4 weeks. Treatments contained the following concentrations of curcumin per kilogram of body weight: C0 (control), 0 mg (vehicle only); C50, 50 mg; C75, 75 mg; and C100, 100 mg. These values are equivalent to daily doses of 0, 1.0, 1.5, and 2.0 mg curcumin for C0, C50, C75, and C100, respectively.

At the end of the experiment, the animals were evaluated for body weight gain, calculated as body weight at euthanasia minus body weight at the beginning of the experiment., and body mass index (BMI) (Novelli et al. 2007). Then, animals were anesthetized with 100% isoflurane (Isoforine, Cristália) and euthanized. The intestine was removed whole and dissected into three regions: small intestine, cecum, and colon. A portion of each segment was immersed in Carnoy's fixative for histopathological analysis and another was stored at −80 °C for analysis of oxidative stress and antioxidant defense markers.

Preparation of intestine homogenates for analysis of oxidative stress and antioxidant defense markers

SOD, CAT, and GST activities, as well as malondialdehyde (MDA) levels, were assessed independently in the supernatant of intestinal tissues. For this, fragments (100 mg) of each region of the intestine were homogenized in ice-cold phosphate-buffered saline (PBS) for 30 s and centrifuged at 10,000 × *g* and 4 °C for 10 min. The supernatant was collected and stored at −80 °C until analysis.

MDA concentration

MDA concentration was determined by the thiobarbituric acid reactive substances assay, as described by Kohn & Liversedge (1944). A standard curve of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was used to calculate MDA values. Results are expressed as nmol MDA mg^{-1} protein.

SOD activity

Quantification of SOD activity was performed spectrophotometrically (Multiskan Go, Thermo Fisher Scientific) at 570 nm (Marklund 1985). One unit (U) of SOD activity was defined as the amount of enzyme required to inhibit the oxidation of pyrogallol by 50%. Results are expressed as U mg^{-1} protein.

CAT activity

Determination of catalase activity was based on the conversion of hydrogen peroxide (H_2O_2) to water and molecular oxygen, as described by Aebi (1984). One unit of catalase activity (U) was defined as change in absorbance in 1 min of reaction. Results are expressed as U mg^{-1} protein.

GST activity

GST activity was determined by measuring the conjugation of 1-chloro-2,4-dinitrobenzene (CDNB, molecular weight 202.6 g) with glutathione, monitored as an increase in absorbance at 340 nm (Habig et al. 1976). Absorbances readings were performed in triplicate at 0, 30, 60, and 90 min. Results are expressed as µmol min^{-1} g^{-1} protein.

Histomorphometric analysis of the small intestine, colon, and cecum

Tissue fragments were dehydrated in a graded series of ethanol and xylol and embedded in paraffin. A semi-automatic rotary microtome (Leica RM2255) was used to obtain 5 µm thick semi-serial sections. Specimens were mounted on slides (BioGlass) using Entellan mounting medium (Merck), stained with hematoxylin and eosin, and analyzed under a light microscope (Nikon Phase Contrast 0.90 Dry, Japan). Images were captured with a DIGI-PRO 5.0 M digital camera and processed using Micrometrics SE Premium (Accu-Scope). Histomorphometric measurements were performed using Image-Pro Plus version 4.0.5.29 (Media Cybernetics Inc.).

Histomorphometric analysis was conducted according to Bastos et al. (2016) and Dobrowolski et al. (2012), with modifications. The small intestine was evaluated for muscular layer

thickness, villus epithelium thickness, crypt epithelium thickness, crypt diameter, villus diameter, and villus height. The cecum and colon were assessed for muscular layer thickness, crypt epithelium thickness, crypt diameter, lamina propria diameter, and crypt depth. Measurements were taken at five different points per animal for each parameter.

Statistical analysis

Normality of data distribution was assessed by the Shapiro-Wilk test. Non-normally distributed data were transformed to $\log_{10}$ values for parametric statistical analyses. Results are presented as mean ± standard deviation. One-way analysis of variance was used to analyze continuous variables. Treatment means were then compared using the Newman-Keuls post hoc test. The level of significance was set at 0.05. All statistical analyses were performed using GraphPad Prism version 6.01.

RESULTS

Effect of curcumin transdermal gel on body weight

Weight gain was greater ($P < 0.05$) in the C100 group than in the control (C0) but did not differ ($P > 0.05$) between treated groups (C100, C75, and C50) (Fig. 1a). Treatment with curcumin transdermal gel did not alter BMI (Fig. 1b) or weights of the small intestine, colon, and cecum (Fig. 1c) compared with the control.

Effect of curcumin transdermal gel on oxidative stress

The presence of lipid peroxidation products was determined by measuring MDA levels in the small intestine and colon. MDA levels in the small intestine did not differ ($P > 0.05$) between groups (Fig. 2a). However, colon MDA concentrations were lower ($P < 0.05$) in C50 and C75 mice than in the control but did not differ ($P > 0.05$) between C100 and the other groups (Fig. 2b).

CAT activity was lower ($P < 0.05$) in the C100 group than in C0 and C50 groups, but enzyme activity in C75 animals did not differ ($P > 0.05$) from that in C50 and C100 animals (Fig. 3a). C50 and C75 treatments increased ($P < 0.05$) SOD activity in relation to C0 and C100 (Fig. 3b). GST activity was higher ($P < 0.05$) in C75, not differing ($P > 0.05$) from that of C50 an C100 (Fig. 3c). In colon samples, CAT and SOD activities were lower ($P < 0.05$) in treated groups (C50, C75, and C100) than in the control (Fig. 3d-e), whereas GST activity was lowest ($P < 0.05$) in C75 animals, not differing between the other groups (Fig. 3f).

Effect of curcumin transdermal gel on the small intestine, colon, and cecum

Histomorphometric analysis revealed no differences ($P > 0.05$) between groups regarding muscular layer thickness, villus epithelium thickness, crypt epithelium thickness, crypt diameter, villus diameter, or villus height in the small intestine (Fig. 4a-f). In the cecum and colon, no differences ($P > 0.05$) were observed in muscular layer thickness, crypt epithelium thickness, crypt diameter, lamina propria diameter, or crypt depth (Fig. 5a-e). Representative photomicrographs of the small intestine, colon, and cecum of animals treated with different doses of curcumin are shown in Fig. 6. Curcumin treatment did not lead to histological modification of the small intestine, colon, or cecum.

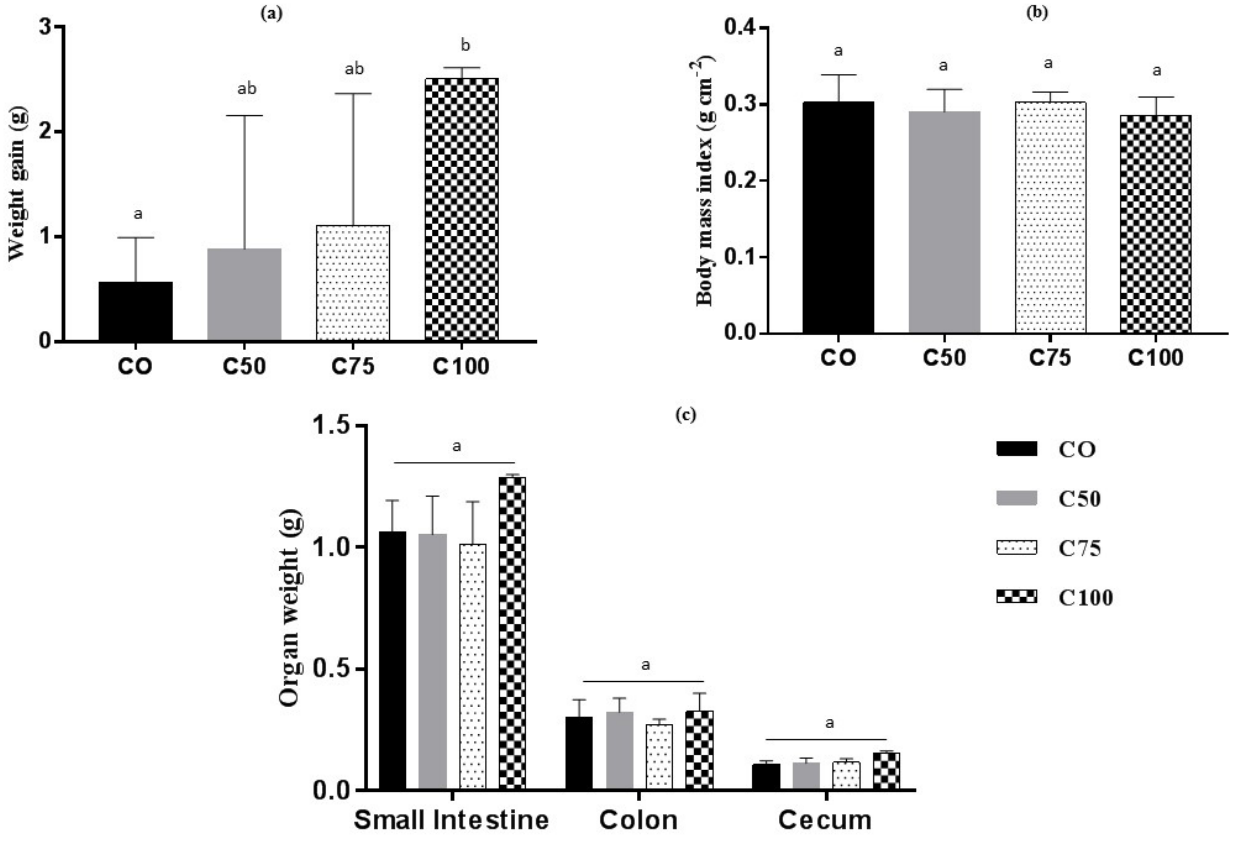

Figure 1. (a) Weight gain, (b) body mass index, and (c) organ weights of IL-10 knockout mice treated with curcumin transdermal gel for 4 weeks. Different letters above error bars indicate significant differences ($P < 0.05$) by the Newman-Keuls post-hoc test. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW.

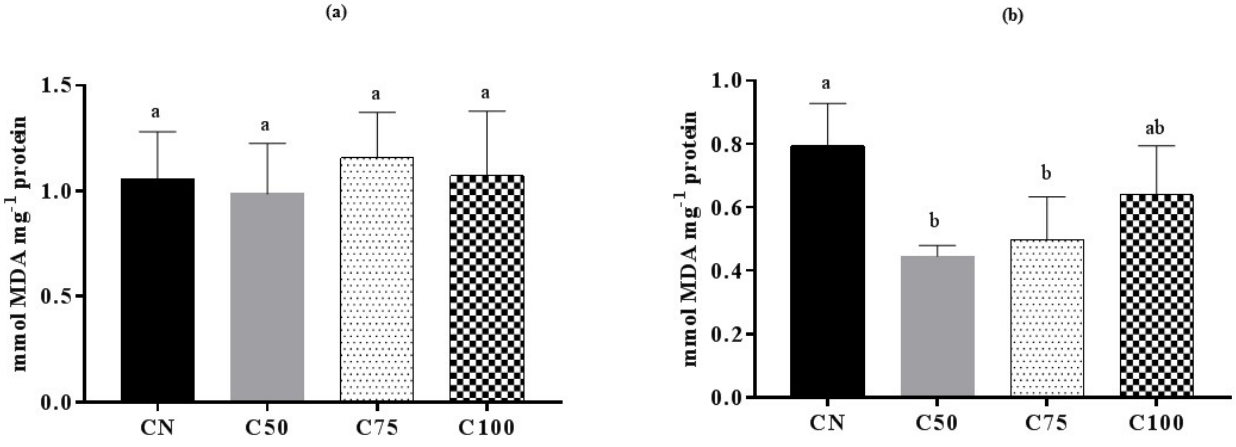

Figure 2. Malondialdehyde (MDA) concentration in the (a) small intestine and (b) colon of IL-10 knockout mice treated with curcumin transdermal gel for 4 weeks.
Different letters above error bars indicate significant differences ($P < 0.05$) by the Newman-Keuls post-hoc test. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW.

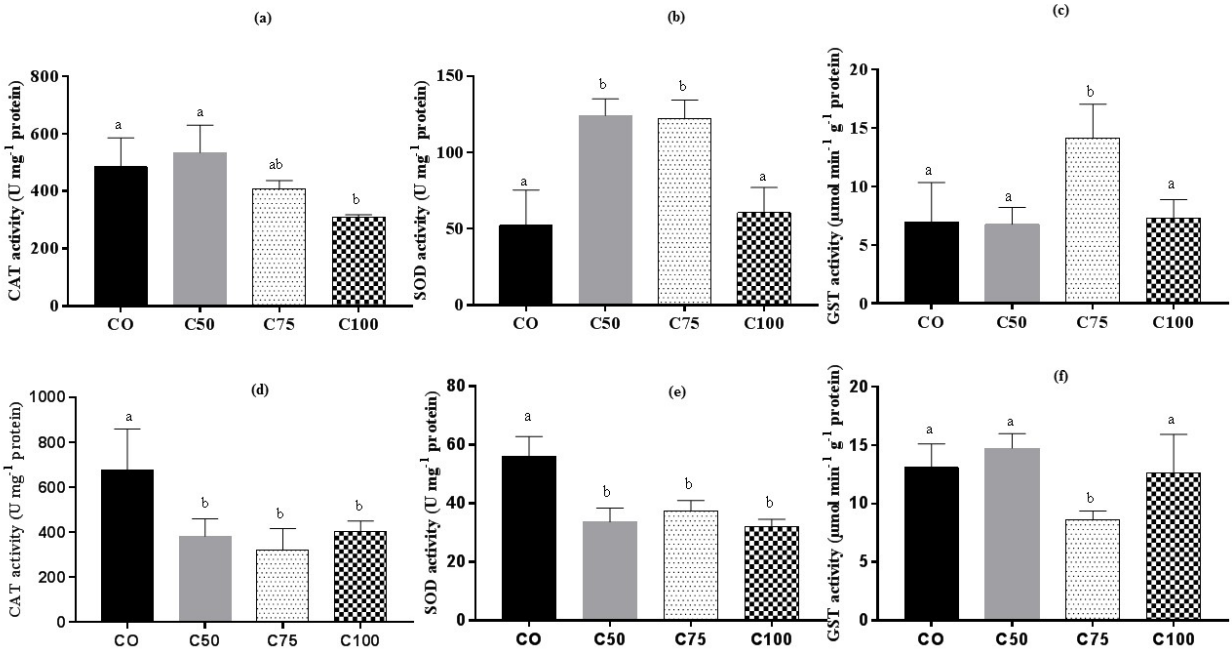

Figure 3. Antioxidant enzyme activity in the small intestine (a, b, and c) and colon (d, e, and f) of IL-10 knockout mice treated with curcumin transdermal gel for 4 weeks.
Different letters above error bars indicate significant differences ($P < 0.05$) by the Newman-Keuls post-hoc test. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW; CAT, catalase; SOD, superoxide dismutase; GST, glutathione *S*-transferase.

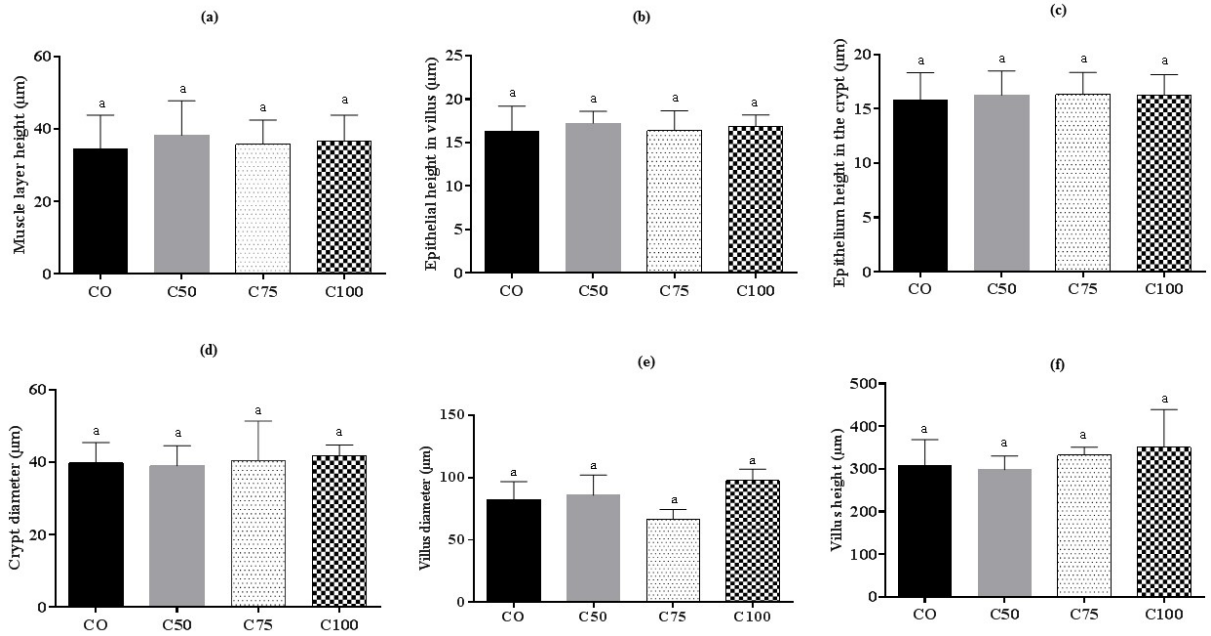

Figure 4. Effect of the curcumin transdermal gel on the small intestine of IL-10 knockout mice with intestinal inflammation. (a) muscle layer height, (b) epithelial height in villus, (c)epithelium height in the crypt, (d) crypt diameter, (e) villus diameter and (f) villus height.
Different letters above error bars indicate significant differences ($P < 0.05$) by the Newman-Keuls post-hoc test. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW.

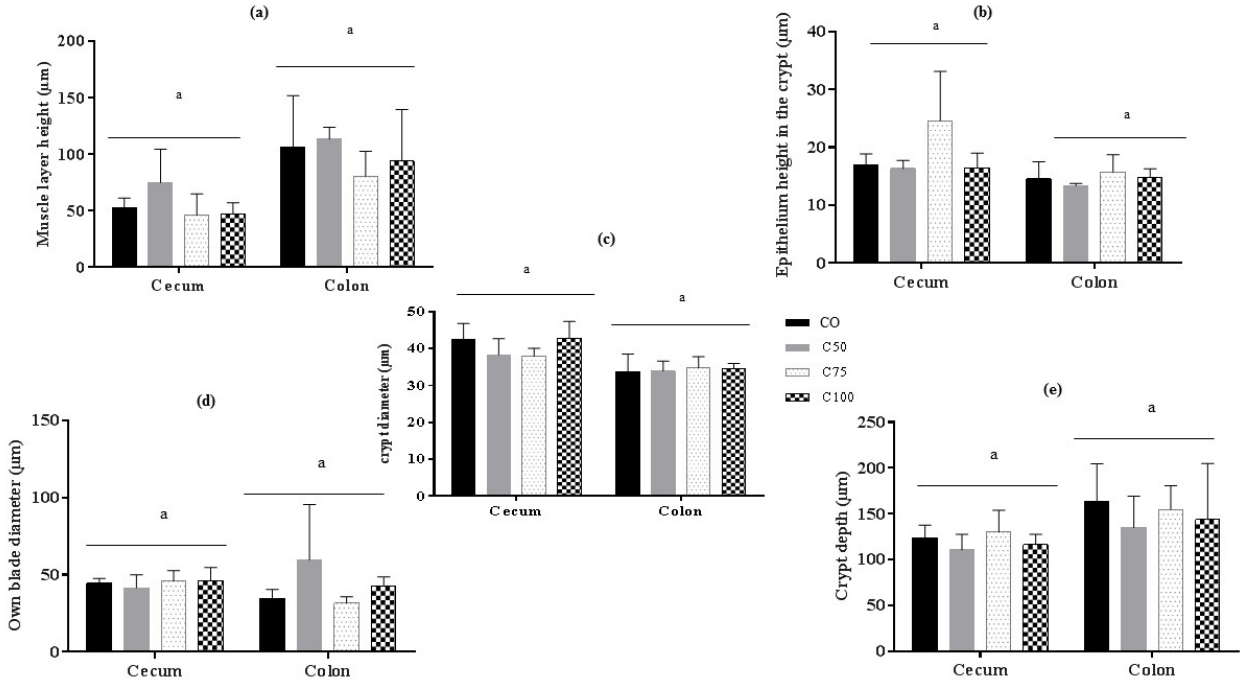

Figure 5. Effect of the curcumin transdermal gel on the colon and cecum of IL-10 knockout mice with intestinal inflammation. (a) muscle layer height, (b) epithelial height in the crypt, (c) crypt diameter, (d) own blade diameter, (e) crypt depth.

Different letters above error bars indicate significant differences ($P < 0.05$) by the Newman-Keuls post-hoc test. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW.

DISCUSSION

In the present study, C100 treatment attenuated weight loss, indicating an improvement in the morphological parameters of animals affected with IBD. Nutrient malabsorption is a common sign of IBD resulting from the reduction of the intestinal absorptive area, bile salt deficiency, bacterial overgrowth, gastrointestinal narrowing, and inflammation. These factors lead to compromised nutritional status, characterized by weight loss and lack of vitamins and minerals (e.g., iron, folic acid, vitamin B12, vitamin D, and calcium) (Jimenez & Gasche 2019). Fat digestion and absorption can also be impaired in IBD. The intestinal surface is altered by inflammation, depletion of the circulating bile pool (as a result of bile acid malabsorption), or intestinal dysbiosis, resulting in deficiency of fat-soluble vitamins (Quigley 2013).

IBD is also associated with oxidative stress, defined as the imbalance between production and neutralization of free radicals, such as reactive oxygen (ROS) and nitrogen species (RNS). This leads to oxidation of biomolecules and consequent loss of biological function. Oxidizing molecules cause DNA damage, protein oxidation, lipid peroxidation, necrosis, and cell apoptosis (Stamler et al. 1997). MDA is a biomarker of elevated intracellular ROS concentrations, indicating lipid peroxidation. An experimental study showed that IBD is associated with an increase in biomarkers of oxidative stress in colonic tissue and blood, such as lipid peroxidation products (Damiani et al. 2007). Oxidative stress plays a central role in cell damage. Defense and elimination mechanisms may be insufficient to deal with ROS overproduction (Schanaider et al. 2005). Curcumin, however, scavenges free radicals and

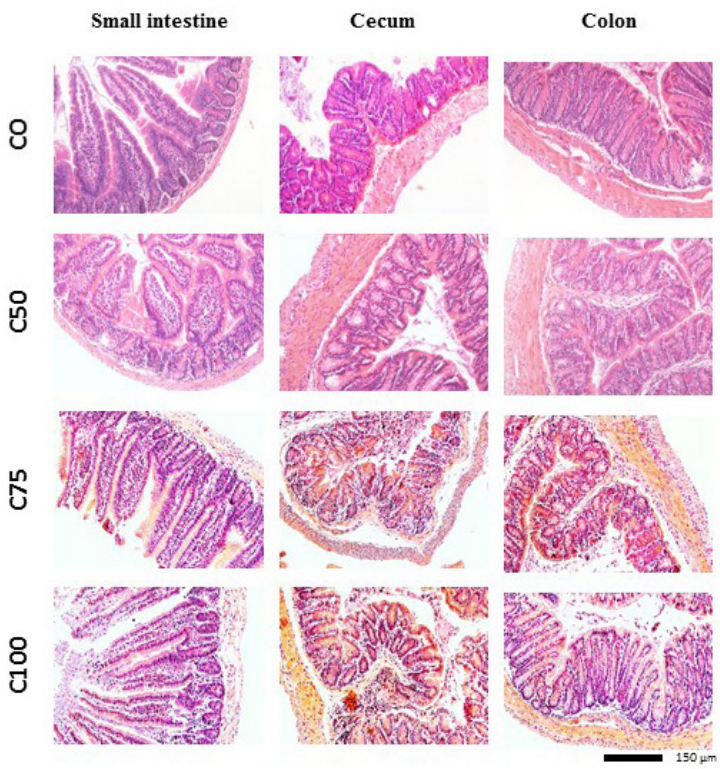

Figure 6. Representative photomicrographs of the small intestine, cecum, and colon of IL-10 knockout mice treated with different doses of curcumin. C0, control (vehicle); C50, transdermal gel containing 50 mg curcumin kg^{-1} body weight (BW); C75, transdermal gel containing 75 mg curcumin kg^{-1} BW; C100, transdermal gel containing 100 mg curcumin kg^{-1} BW.

inhibits lipid peroxidation, thereby protecting cellular macromolecules, such as DNA, from oxidative damage (Bianchi & Antunes 1999).

Direct action of the non-enzymatic antioxidant (curcumin) was evidenced by the reduction in CAT activity in the small intestine and colon and SOD and GST activities in the colon. The synergistic effects of curcumin and endogenous antioxidants seemed to rebalance cellular redox homeostasis in mice with IBD, decreasing the need for the enzymes that compose the body's first line of antioxidant defense.

The antioxidant defense system of the human body consists of a series of antioxidant enzymes and numerous endogenous and exogenous antioxidant compounds that neutralize ROS (Khan et al. 2015, Lopez et al. 2016). Free radicals are formed by the catalytic action of enzymes during electron transfer processes in cellular metabolism and by exogenous factors. In IBD, ROS and RNS are generated via activation of inflammatory cells. Reactive species are often observed in early disease stages and are correlated with IBD severity and progression (Zhu & Li 2012). Topical application of curcumin promoted ROS elimination through direct (detoxification of oxidative radicals) and possibly indirect (enhanced endogenous antioxidant enzyme activity) actions.

Studies have shown that intestinal epithelial cells produce high levels of ROS and RNS during infiltration of inflammatory cells (e.g., neutrophils and macrophages), characterizing a hallmark of IBD pathophysiology (Maloy & Powrie 2011, Zhu & Li 2012). Sivalingam et al. (2007) found that curcumin plays an important role in protecting mitochondria against oxidative stress and increasing glutathione levels. In an animal model of insulin resistance, curcumin contributed to the increase in glutathione, glutathione reductase,

SOD, CAT, and peroxidase activities, favoring the antioxidant defense system (Panahi et al. 2018).

We did not observe a dose-dependent increase in enzyme activity, allowing us to infer that curcumin, whether at high or low doses, is effective in activating oxidative stress mediators and enzymes. Our results confirm the antioxidant and anti-inflammatory effects of curcumin reported in the literature (Abrahams et al. 2019, Baradaran et al. 2020, Belhan et al. 2020, El-Naggar et al. 2019, Peres et al. 2015).

Histomorphometric analysis did not show an improvement in intestinal inflammation with curcumin gel treatment. However, treatments seemed to prevent the disease from worsening, maintaining the inflammatory process at a constant level.

Crypt depth is indicative of the compensatory capacity or hyperplasia of epithelial cells induced by morphological damage to the intestinal mucosa by inflammation. Reduced villus height in combination with increased crypt depth suggests an increase in the rate of epithelial desquamation, possibly to ensure an adequate rate of cell turnover and guarantee the replacement of cells in the apical region of the villi (Oetting et al. 2006). Thus, the higher the ratio of villus height to crypt depth, the better the absorption of nutrients and the lower the energy losses associated with cell renewal (Liu et al. 2020). In our study, the lack of histological changes in treated mice can be attributed to the short treatment duration. We can infer that preservation of the mucosa was promoted by a reduction in oxidative stress, induc the transcription of genes involved in the synthesis of glutathione by the intestinal mucosa. (Lutgendorff et al. 2009). There is also the reduction of the transcription factor linkage NF-kB to DNA, with consequential reduction of the expression of inflammatory mediators (Bai et al. 2006, Hegazy et al. 2010, Truusalu et al. 2008). The fact of the animal has not histologically worsened is already a gain, since these animals are very inflamed and tend to worsen their stage of the disease over time.

Preceding the change in tissue morphology, we have changes in biochemical, enzymatic and genetic parameters, in the most recent scientific literature, the frequency of IBD extra-intestinal manifestations (MEI) varieswas shown to range from 21-47% (Carvalho et al. 2018). The chronic inflammatory state of IBD is perceived as a set of aggressive cellular immune responses to a certain type of colonic bacterial flora. Susceptibility to the disease is conferred by certain genes that encode the immune responses triggered by environmental stimuli. Therefore, the pathogenesis of IBD and, possibly, its extraintestinal manifestations, is based on a relationship between genetics, immune dysregulation, microbial flora, and barrier dysfunction (Carvalho et al. 2018).

Overall, the results showed that, although no differences in villus height or crypt depth were observed between groups, C100 animals treated had a higher weight gain, indicating that nutrient absorption and nutritional status were enhanced.

CONCLUSION

This study demonstrates the protective effects of curcumin transdermal gel on oxidative stress and its potential as adjunctive therapy in IBD.

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How to cite

ARAUJO FO, FELÍCIO MB, LIMA CF, PICCOLO MS, PIZZIOLO VR, DIAZ-MUÑOZ G, BASTOS DSS, OLIVEIRA LL, PELUZIO MCG & DIAZ MAN. 2022. Antioxidant and anti-inflammatory activity of curcumin transdermal gel in an IL-10 knockout mouse model of inflammatory bowel disease. An Acad Bras Cienc 94: e20201378. DOI 10.1590/0001-3765202220201378.

Manuscript received on August 25, 2020;
accepted for publication on December 08, 2020

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FOA and MBF performed the experimental study and histological analysis; CFL carried out statistical analysis; DSSB performed oxidative stress analysis; MCGP, LLO, VRP, GDM, and MAND conceptualized and designed the experimental study; FOA wrote the original manuscript; and MAND edited the final manuscript. All authors read and approved the final version of the manuscript.