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RESEARCH ARTICLE

Histopathological investigation of the effect of coenzyme q10 on intestinal mucosa and tight junction proteins in experimental colitis model

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Deneysel kolit modelinde koenzim q10' nun intestinal mukoza ve sıkı bağlantı proteinleri üzerine olan etkisinin histopatolojik olarak incelenmesi

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Öz

Amaç: Bu çalışmanın amacı Koenzim Q10' nun sıçanlarda asetik asitle indüklenmiş deneysel kolit modelinde mukoza, goblet hücre yoğunluğu ve sıkı bağlantı proteinleri üzerine olan etkisinin araştırılmasıdır.

Gereç ve Yöntem: Çalışmada 24 adet, 10 haftalık dişi Wistar albino sıçan kullanıldı ve Kontrol grubu (n=4), Kolit grubu (n=10) ve Kolit+Koenzim Q10 grubu (n=10) olarak üç gruba ayrıldı. Deneysel kolit modeli %4' lük asetik asit ile oluşturuldu. Kolit indüksiyonundan bir gün sonra Kolit+Koenzim Q10 grubuna 10 gün boyunca gavaj yolu ile Koenzim Q10 (30 mg/kg/gün) uygulandı. Tedavi prosedürünün sonunda deney hayvanlarının sakrifikasyonu gerçekleştirildi. Kolon dokularına ait makroskobik değerlendirme yapıldı. Kolon kesitleri Masson'un üçlü boyası ve Alsian mavisi ile boyanarak mikroskobik skorlama ve goblet hücre yoğunluğu; Okludin, Zonula Okludens-1 ve Klaudin-1 immonohistokimyasal analizleri ile de sıkı bağlantı proteinleri değerlendirildi.

Bulgular: Kolit grubuna ait kolon dokularının makroskobik ve mikroskobik skorlamaları kontrol grubuna kıyasla istatistiksel olarak anlamlı şekilde artış gösterdi ($p<0.05$). Kolit+Koenzim Q10 grubunda ise makroskobik ve histopatolojik hasarın anlamlı şekilde azaldığı ($p<0.05$), benzer şekilde Koenzim Q10 uygulaması ile Alsian mavisi pozitif alan yüzdesinin kolit grubuna göre istatistiksel olarak artış gösterdiği ($p<0.05$) ve buna bağlı goblet hücre yoğunluğunun arttığı, mukozal bariyerin bütünlüğünde önemli olan sıkı bağlantı proteinlerinin de immunoreaktivitelerinde artışın olduğu dikkati çekti.

Öneri: Sonuç olarak, Koenzim Q10, asetik asit ile indüklenen kolit modelinde, kolon dokusu üzerinde histopatolojik değişimler ve sıkı bağlantı proteinleri üzerinde pozitif etki göstermiştir. Ancak Koenzim Q10'un ülseratif kolitli hastalara karşı koruyucu etkileri hakkında daha detaylı ve ileri moleküler tekniklerle desteklenmiş çeşitli deneysel ve klinik araştırmaların gerekli olduğu düşünülmektedir.

Anahtar kelimeler: Deneysel kolit, sıkı bağlantı, antioksidan, koenzim Q10

Abstract

Aim: The purpose of this study is to investigate the effect of Coenzyme Q10 (CoQ10) on the mucosa, goblet cell density and tight junction (TJ) proteins in the acetic acid-induced colitis model in rats.

Materials and Methods: Twenty-four,10-week-old female Wistar albino rats were used in the study and divided into 3 groups; Control(n=4), Colitis (n=10) and Colitis+ CoQ10 (n=10). The colitis model was induced with 4% acetic acid. One day after colitis induction, CoQ10 was administered to the Colitis+CoQ10 group by gavage (30 mg/kg/day) for 10 days. After the treatment, the sacrification of the experimental animals was carried out. The macroscopic evaluation was performed. Microscopic scoring and goblet cell density by staining sections with Masson's Trichrome and Alcian blue; TJ proteins were also evaluated by immunohistochemical analyzes of Occludin (Occ), Zonula Ocludens-1 (ZO-1), and Claudin-1 (Cl-1).

Results: Macroscopic and microscopic scoring of colon tissues belonging to the colitis group showed a statistically significant increase compared to the control group ($p<0.05$). In the colitis+CoQ10 group, macroscopic and histopathological damage decreased significantly ($p<0.05$), and the percentage of Alcian blue staining area and the goblet cell density increased statistically with CoQ10 compared to the colitis group ($p<0.05$). It was also noted that there was an increase in the immunoreactivity of TJ proteins, which are important in the integrity of the mucosal barrier.

Conclusion: CoQ10 showed a positive effect on histopathological changes and tight junction proteins in acetic acid-induced colitis model. However, it is thought that more detailed and various experimental and clinical studies supported by advanced molecular techniques are needed on the protective effects of CoQ10 against ulcerative colitis patients.

Keywords: Experimental colitis, tight junction, antioxidant, coQ10

Introduction

Ulcerative colitis (UC) is a chronic idiopatic disease characterized by severe mucosal inflammation affecting the mucosal and submucosal layers of the colon and rectum (Özkoç et al 2022). Although the exact cause is unknown, genetic, immunological, and environmental factors are possible etiological reasons (Ng et al 2017).

Studies on humans and experimental animals have also shown that oxidative stress is a factor in the development of ulcerative colitis (Rana et al 2014, Wang et al 2016). Increased formation of nitrogen species, reactive oxygen, and modulation of oxidative stress and redox by antioxidants have been demonstrated to play a critical function in the pathophysiology of ulcerative colitis (Pravda 2005, Rana et al 2014). 5-ASA compounds, purine analogs, methotrexate, and corticosteroids are used to treat ulcerative colitis in order to reduce symptoms and mucosal inflammation (Tripathi and Feuerstein 2019). Serious side effects of these drugs lead to the search for new treatment agents. It has been shown that various antioxidants used have healing properties in ulcerative colitis models (Aleisa et al 2014, Siracusa et al 2020, Hambardikar and Mandlik 2022).

CoQ10, ubiquinone or ubidecarenone, is a fat-soluble and vitamin-like substance located in the inner phospholipid layer of the cell membrane (Kunitomo et al 2008). It is an important cofactor in the mitochondrial electron transport system and has a function in ATP production via oxidative phosphorylation, and its level has been reported to decrease with age (Alahmar et al 2021).

The epithelial barrier dysfunction observed in inflammatory bowel diseases is associated with TJ proteins that protect intestinal epithelial integrity. The structural integrity of TJs in colon epithelial cells is one of the important factors in mucosal inflammation (Porter et al 2020). TJ proteins functions are maintaining the intestinal mucosal barrier and preventing bacterial and toxin invasion (Bhat et al 2019). TJs are made up mostly of transmembrane proteins, claudins, occludins, and ZO family proteins. Occludins and claudins are cell membrane proteins that provide the TJ complex's structural and functional foundation. Intercellular adhesion, transmembrane resistance, and intestinal mucosal barrier permeability all increase when levels of occludins protein decrease (Fries et al 2013, Zheng et al 2021).

Goblet cells are one of component of colon tissue like other principal cells and responsible fort he production of mucin. Some studies showed that the importance role of mucin produced by goblet cell in maintaining the integrity of protective mucus barries which effected may in colitis disaese (Soliman et al 2010, Fawzy et al 2013, Olıveıra et al 2014).

The effects of CoQ10 on TJ components and goblet cells in ulcerative colitis have not yet been studied. Our research aims to investigate the effects of CoQ10, which has anti-inflammatory and antioxidant properties, on the mucosa, mucin, goblet cell density, and TJ proteins in acetic acid-induced experimental colitis model in Wistar albino.

Material and Methods

Animals

Twenty-four healthy, mature, 10-week-old female (180-200 g) rats (Wistar albino) were provided by the Laboratory of Experimental Animals, Gazi University (Ankara, Turkey). The rats were capped in polysulfone cages with aspen shavings as bedding and at constant temperature (21–24 °C), relative(40–45%) humidity, and in 12 h light-12 h dark controlled conditions, at the Laboratory Animals Breeding and Experimental Research Center of the Faculty of Pharmacy, Gazi University (Ankara, Turkey).

Induction of colitis model

All the subjects were randomly divided into 3 groups as follows: Control group, Colitis group, and Colitis + CoQ10 treatment group. The rats were intraperitoneally anesthetized ketamine (50 mg/kg) and xylazine (10 mg/kg). Colitis model was induced by a rectal enema with 1 mL of 4% acetic acid diluted in saline (Momtaz et al 2021). A soft 6-Fr pediatric catheter was placed 6 cm into the anus. Then, 1 ml acetic acid solution was applied followed by 1 ml air. The rats were kept in the head down Trendelenburg position for 5 min. The colitis model was not applied to the control group and rats were rectally administered saline (1 mL).

The treatment procedure

The drug application was established one day after colitis induction and continued for 10 days. The control and colitis groups were orally given 1 mL of soybean oil. The CoQ10 treatment group was orally treated daily with 1 mL of soybean oil containing 30 mg/kg of CoQ10 (Ewees et al 2016).

Termination of the experimental procedure

The distal colon specimens were removed on the 10th day of the treatment protocol. The animals were sacrificed by exsanguination under general anesthesia (10 mg/kg xylazine hydrochloride and 50 mg/kg ketamine hydrochloride).

Macroscopic evaluation of colonic damage

The Wallace scoring system was used for macroscopic

evaluation. The following are the grading criteria that consider the region the presence and absence of ulcers and inflammation: (0) no inflammation and ulcer; (1) no ulcer with local hyperemia; (2) ulceration and no hyperemia; (3) only one location of inflammation and ulceration; (4) two or more regions of inflammation and ulceration; (5) and more than 2 cm long ulceration (El-Akabawy and El-Sherif 2019).

Histopathological and immunohistochemical analyses

The distal colon of rats was fixed with neutral buffered formalin (10%) solution and after the routine histologıcal procedure, samples were then embedded into paraffin wax blocks. Tissues were cut (4 µm thickness) and stained with Masson's Trichrome and Alcian blue stain. The slides were mounted and observed microscopically for histopathological changes by a histologist in a blinded fashion. All staining were analyzed using a computer imaging system (Leica DMI 4000B, LAS V4.9, Wetzlar, Germany).

In order to evaluate the colonic mucosa histological damage, the following parameters were taken into account: structural deformation of crypts, ulceration, cryptitis, glandular atrophy, and edema. Following was the analysis of each parameter: absent (0), present in 10% or less of the tissue examined (1), present in 10%–50% of the tissue examined (2), and present in more than 50% of the tissue examined (3). The final grades for each slide were calculated based on the sum of the scores (Bezerra et al 2017).

Alcian blue staining kit (Atom Scientific, United Kingdom) was used for analyzing the sulphated and acidic mucopolysaccharides with goblet cells. The AB staining intensity was evaluated using Image Pro-Plus 7 software (Media Cybernetics, Inc., Rockville, MD, USA) by randomly selecting four fields per section at 200X magnification (Shastri et al 2020, Liu et al 2018).

For immunohistochemistry, all the slides were deparaffinized with xylene, rehydration, and incubated with citrate buffer solution (pH 6.0) for heat-Induced antigen retrieval. In the next step, the samples treated with 3% H2O2 followed by a blocking solution. Then, the samples were incubated with primary antibody Cl-1 (1: 100, sc-166338; Santa Cruz), ZO-1 (bs-1329R; Bioss), and Occ (1:100, bs1495R; Bioss) overnight at 4 C. Subsequently, a secondary antibody (anti-mouse IgG anti-rabbit IgG (TP-125-BN, Thermo Scientific) was applied. After rinsing with PBS, the reaction product was revealed by streptavidin peroxidase complex. The samples were incubated with diaminobenzidine tetrahydrochloride (DAB) chromogen. For contrasting background, the slides were reacted with Mayer's hematoxylin. After dehydrating, the slides were coverslipped using mounted medium. For negative control samples were processed the same protocol, but the primary antibody was replaced by PBS. Cl-1, ZO-1, and Occ staining were analyzed using a computer imaging system (Leica DM 4000B, LAS V4.9, Wetzlar, Germany) and Image Pro-Plus 7 software (Media Cybernetics, Inc., Rockville, MD, USA) to analyze the immunostaining intensity by randomly choosing different four fields per section (Shastri et al 2020).

Statistical analysis

SPSS 22.0 was used to statistical analysis of experimental data. The results are expressed as a mean ± Standart error of the mean (SEM). An one-way analysis of variance -ANOVA- was used to analyze statistical differences between the experimental groups followed by Tukey's post-hoc. Analyses were considered as significant at ($p<0.05$).

Results

Figure 1A illustrates the ulceration, hyperemia, and mucosal edema caused by acetic acid in the colon. When compared to the control group, the colitis group's macroscopic score considerably increased ($p<0.001$). The difference between the Colitis group and the Colitis+CoQ10 group was substantially lower ($p< 0.05$) (Figure 1B).

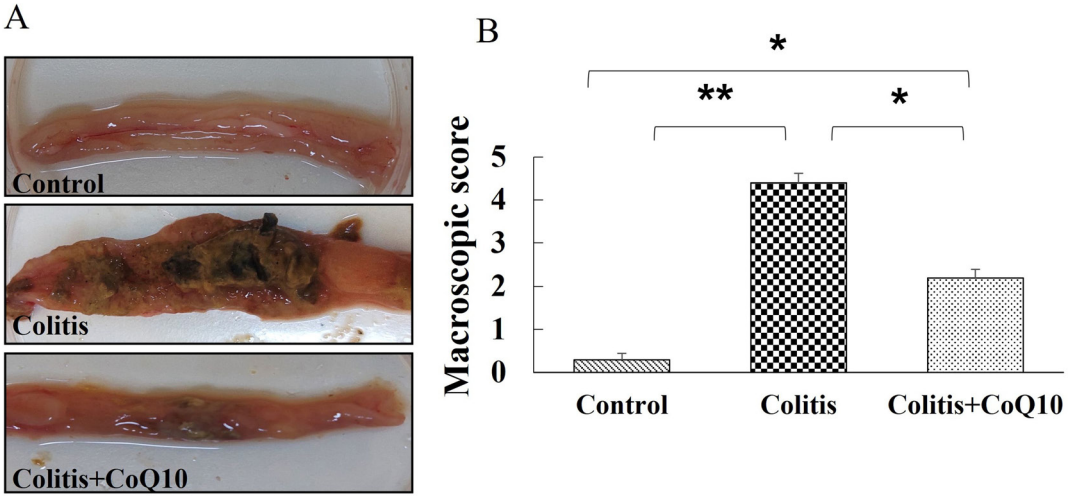

Figure 1. (A) Macroscopic presentation of the colon of experimental groups. (B) Macroscopic score, Statistical significance between the experimental groups was analyzed by one-way ANOVA and Tukey's post-test, * $p<0.05$ and ** $p<0,001$. (Data are expressed as a Mean ± SEM).

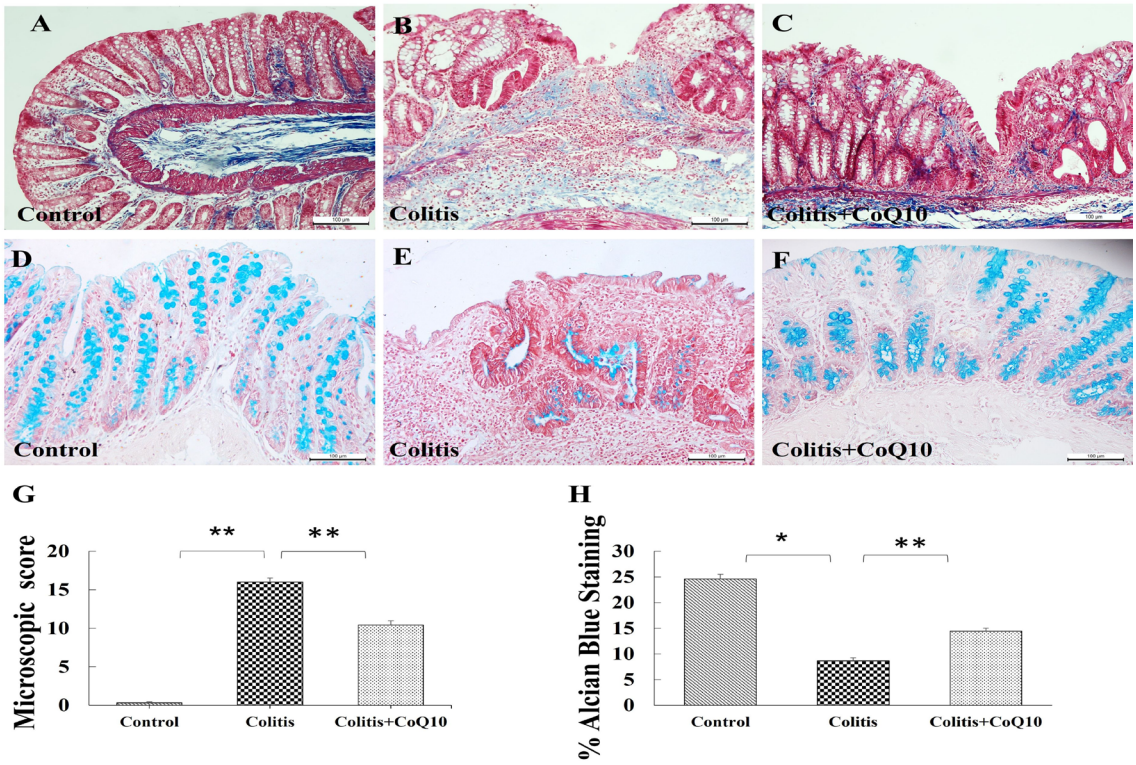

Figure 2. Masson Trichrome (A-C) and Alcian Blue staining (D-F) (Magnification, x20). Microscopic score and % Alcian Blue Staining. Statistical significance between the experimental groups was analyzed by one-way ANOVA and Tukey's post-test, * p <0.05 and ** p<0,001. (Data are expressed as a Mean ± SEM)

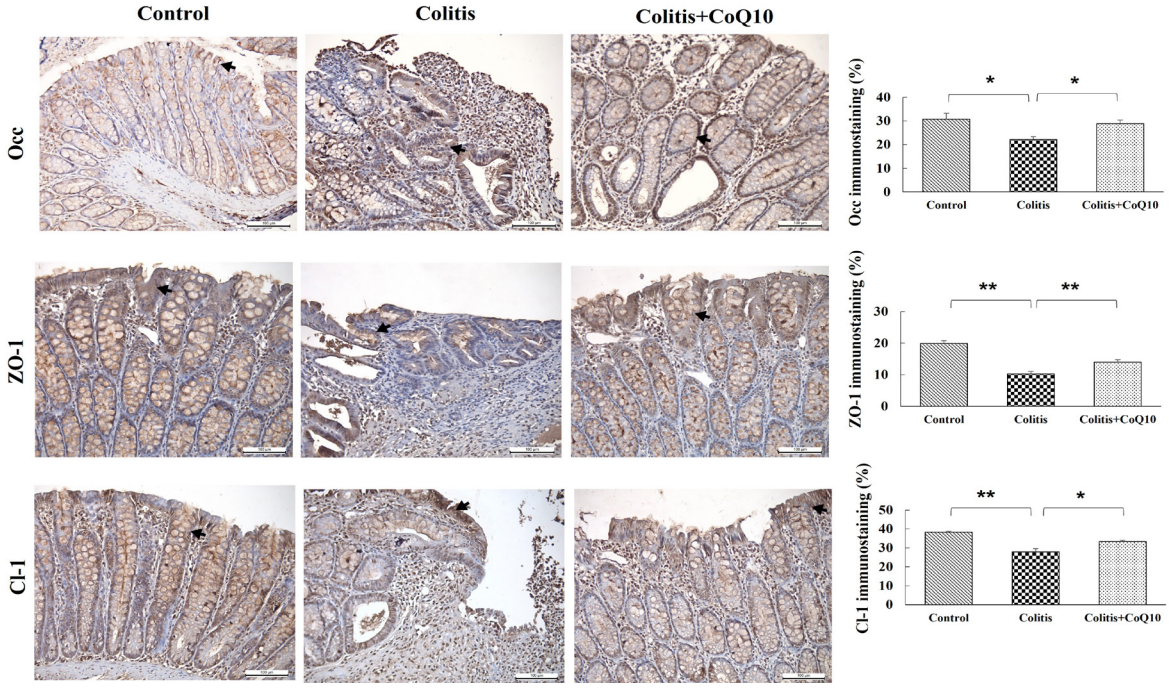

Figure 3. Immunohistochemical analysis of Occ, ZO-1, and Cl-1 colonic tissue of experimental rats. Arrows indicate positive staining. Statistical significance between the experimental groups was analyzed by one-way ANOVA and Tukey's post-test, * p <0.05 and ** p<0,001. (Data are expressed as a Mean ± SEM)

The histopathology of the colon was evaluated using Masson Trichrome staining. Histological analyses of colon specimens of control group displayed normal histological structure without inflammation. The simple columnar epithelium with goblet cells and the lamina propria showed normal structure. Colonic mucosa demonstrated mucosal damage, distortion of crypts, ulceration, and edema in the colitis group. goblet cell depletion was recognized in the mucosal layer. The lamina propria appears mononuclear lymphocytic infiltration and fibrotic changes.

Regarding microscopic scoring, the control group had significantly lower scores compared with the colitis group (Figure 2G). With CoQ10 treatments, the microscopic scoring showed significantly lower compared with the colitis group. Alcian blue staining was applied to analyze mucus density in the goblet cells (Figure 2). In the colitis group, the alcian blue positive area significantly decreased compared with the control group ($p<0.05$). In the colitis+CoQ10 group was significantly increased ($p<0.001$) alcian blue positive area also mucus levels compared with the colitis group (Figure 2F).

Occ, ZO-1 and Cl-1 immunostaining positive areas were significantly (respectively, $p< 0.05$; $p<0.001$; $p<0.001$) reduced in the Colitis group compared with the control group. After CoQ10 treatment, these proteins immunoreactivities increased in the Colitis+CoQ10 group compared with the Colitis group (respectively, $p<0.05$; $p<0.001$; $p<0.05$) (Figure 3).

Discussion

The pathogenesis of UC is yet understood, however it is an inflammatory illness characterized by chronic inflammation, ulceration, and damage to the colonic mucosa (Zhu et al 2019). This study showed that Coenzyme Q10 positively affects histomorphological change, and TJ expression and goblet cells in the colon, using an AA-induced UC rat model.

In the present study, the use of rectal 4% acetic acid to induce an ulcerative colitis model was accepted as an animal model phenotypically similar to human colon inflammation in rodent studies. The AA-induced colitis model is widely used for experimental models in animals as a model to mimic human UC (Karakoyun et al 2018, Shao et al 2019).

In this research, in colitis-induced rats, macroscopic and microscopic damage such as inflammation, hemorrhage, ulceration, and mononuclear lymphocytic infiltration were induced in colon tissue. Many studies have demonstrated macroscopic and histopathological changes like our results (Ewees et al 2016, Ahmad et al 2018, Wang et al 2021). Elbastawisy and Mohamed (2022) showed mucosal ulceration, hemorrhage, and distorted crypts in the mucosa layer of colon of acetic acid-induced rats. Another study reported similar findings in an albino rat models of acetic acid-induced colitis (El-Ghannam et al 2022).

In previous studies, Alcian blue was used to detect the loss of mucins and goblet cells in colitis and the colitis group had considerably fewer goblet cells than the control group (Soliman et al 2010, Olıveıra et al 2014). Mucin depletion has been linked to inflammatory bowel disease (IBD) like symptoms and might reduce the efficiency of the mucous barrier in preventing bacterial infection of the colon mucosa (Fawzy et al 2013). In our study, we showed that the loss of the goblet cell with the decreasing of the alcian blue positive area in the colitis group compared to the control group. This finding supports that goblet cells in the intestine may be important regulators of ulcerative colitis susceptibility.

As we all know, the mucosa layer and the destruction of the mucosal barrier of colon play a significant role in the pathophysiology of colitis (McCole 2014, Kaur and Goggolidou 2020). TJ proteins are an important structural factor of this mucosal barrier. The expression of TJ proteins in the intestinal epithelium changes when the barrier's integrity is lost. As a consequence, these proteins prevent the invasion of bacteria and toxins. In IBD patients, immune cells infiltrated the mucosa layer and this process induces pro-inflammatory cytokines (Bhat et al 2019).

In our study, the TJ proteins were evaluated by immunohistochemical analyses. Occ, ZO-1, and Cl-1 are the major TJ proteins that form the basic structure of TJ in the intestinal barrier (Bhat et al 2019). In the colitis group, TJ proteins expression were reduced compared with the control group. This agrees with the findings of prior studies (Zhou et al 2018, Yu et al 2018). The changes of TJ structure in UC can be connected to the degree of inflammation and the severity of the disaese. Previous studies showed that loss of TJ proteins such as occludin and ZO-1 and reduced mucin in colitis patients and in rodent intestinal inflammation model (Kucharzik et al 2001, Li et al 2014, Nighot et al 2015).

CoQ10 is also known as ubiquinone, it is a crucial component of the mitochondrial respiratory chain, however, there is minimal research on its effectiveness in preventing or treating UC (Bhagavan and Chopra 2006). Lee et al (2017) reported that CoQ10 reduced the inflammation via the inhibition of p-STAT3 and IL-17 in the colitis mice model. Furthermore, Ewees et al (2016) suggested that CoQ10 significantly decreased malondialdehyde content, myeloperoxidase activity, and nitrate/nitrite production in iodoacetamide (IA)-induced UC in rats. In another study, the researchers reported that Coenzyme Q10 treatmants protect against acetic acid-induced UC model mainly through regulation of Nrf2/HO-1 and caspase-3 pathways (Khodir et al 2017). In our study, also CoQ10 exhibits a protective effect on the

colon mucosal barrier. The results in the AA-induced colitis model showed that CoQ10 affects the immunoexpression of TJ proteins and maintained the integrity of the epithelial barrier. In this study, CoQ10 treatment effectively the abnormalization of TJs by regulating the expressions TJs proteins. This may be related to the regulation of pro-inflammatory cytokines. In addition, Alcian blue staining showed that CoQ10 treatment significantly the protection of goblet cells compared with the colitis group. This finding may be via MUC2 which is an important molecule of the protective mucus layer of the intestine. However, future studies are needed to clarify this idea.

Conclusion

In conclusion, CoQ10 was capable of reversing the histopathological changes and tight junction protein expression of acetic acid-induced colitis. Furthermore, more clinical research is considered necessary on the protective effects of CoQ10 against patients with ulcerative colitis. To determine the underlying mechanism of CoQ10 therapeutic effect, more research is needed.

Conflict of Interest

The authors did not report any conflict of interest or financial support.

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During this study, any pharmaceutical company which has a direct connection with the research subject, a company that provides and / or manufactures medical instruments, equipment and materials or any commercial company may have a negative impact on the decision to be made during the evaluation process of the study or no moral support.

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Author Contributions

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Ethical Approval

The experimental procedures were approved by the Experimental Animal Ethics Committee of Gazi University (G.U.ET- 21.076).

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