İSTANBUL UNIVERSITY PRESS

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ
Journal of Advanced Research in Health Sciences /
Sağlık Bilimlerinde İleri Araştırmalar Dergisi 2025
DOI: 10.26650/JARHS2025-1497988

INFUSION FROM *C. COGGYGRIA SCOP.* LEAVES ON THE HEPATIC OXIDATIVE STRESS IN MICE WITH DEXTRAN SODIUM SULPHATE (DSS)-INDUCED ULCERATIVE COLITIS

C. COGGYGRİA SCOP. YAPRAKLARINDAN ELDE EDİLEN SULU İNFÜZYONUN DEKSTRAN SODYUM SÜLFAT (DSS) İLE İNDÜKLENMİŞ ÜLSERATİF KOLİTLİ FARELERDE HEPATİK OKSİDATİF STRES ÜZERİNE ETKİSİ

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Citation/Atıf: Pınar D, Öztürk Seyhan N, Özsoy N, Özgür S, Can A. Infusion from *C. coggygria scop.* leaves on the hepatic oxidative stress in mice with dextran sodium sulphate (DSS)-induced ulcerative colitis. Journal of Advanced Research in Health Sciences 2025;8(1):53-58. https://doi.org/10.26650/JARHS2025-1497988

ABSTRACT

Objective: Since free radicals play a crucial role in ulcerative colitis (UC)-assotiated liver manifestations, antioxidants of plant origin have been proposed as potential therapeutic agents to counteract liver damage. This study aimed to elucidate the ameliorative effect of the aqueous infusion of the *C. coggygria* leaves (CCLAI) in comparison with a mesalamine in alleviating the oxidative stress in the liver of mice with DSS-induced UC.

Material and Methods: Two different doses of CCLAI (4% and 6%) or mesalamine (250 mg/kg body weight) were administered by oral gavage to C57BL/6 male mice once a day for 7 consecutive days. UC was induced with 3% DSS in drinking water for 5 days, except the normal and plant control groups that had access to water only.

Results: No statistical difference between all the groups was observed in the activities of AST and ALT, hepatic damage markers, suggesting that the oxidative alterations were not sufficient to cause liver damage, although oxidative stress occurred. The elevated activities of antioxidant markers (SOD, CAT, GR, GPx, GST) and increased GSH and NO levels in the colitis groups compared with the normal group may represent an initial defence mechanism against oxidative stress. These results indicate that CCLAI may attenuate oxidative stress, as demonstrated by decreased MDA levels and MPO activity and reversed levels of oxidative stress parameters towards the value of normal controls.

Conclusion: Our study provided evidence that CCLAI can reduce oxidative stress probably by scavenging ROS and modulating the oxidant/antioxidant balance in hepatic tissues.

Keywords: *Cotinus coggygria*, antioxidant activity, dextran sulphate sodium, liver, oxidative stress, ulcerative colitis

ÖZ

Amaç: Serbest radikaller ülseratif kolit (ÜK) ile ilişkili karaciğer bulgularında önemli bir rol oynadığından, bitki kökenli antioksidanlar karaciğer hasarına karşı potansiyel terapötik ajanlar olarak önerilmiştir. Bu çalışmanın amacı, C. coggygria yapraklarının sulu infüzyonunun (CCLAI), DSS ile indüklenmiş ÜK'li farelerin karaciğerindeki oksidatif stresi hafifletmede mesalamine kıyasla iyileştirici etkisini aydınlatmaktır.

Gereç ve Yöntemler: İki farklı dozda CCLAI (%4 ve %6) veya mesalamin (250 mg/kg vücut ağırlığı) C57BL/6 erkek farelere oral gavaj yoluyla ardışık 7 gün boyunca günde bir kez verildi. ÜK, sadece su verilen normal ve bitki kontrol grupları haricinde, 5 gün boyunca içme suyunda %3 DSS ile indüklenmiştir.

Bulgular: Karaciğer hasarı belirteçleri olan AST ve ALT aktivitelerinde tüm gruplar arasında istatistiksel bir fark gözlenmemiştir, bu da oksidatif stres oluşmasına rağmen oksidatif değişikliklerin karaciğer hasarına neden olmak için yeterli olmadığını düşündürmektedir. Normal gruba kıyasla kolit gruplarında antioksidan belirteçlerin (SOD, CAT, GR, GPx, GST) aktivitelerinin ve GSH ile NO seviyelerinin artması, oksidatif strese karşı bir ilk savunma mekanizmasını temsil ediyor olabilir. Bu sonuçlar, MDA seviyeleri ve MPO aktivitesinin azalması ile birlikte oksidatif stres parametrelerinin normal kontrol değerlerine doğru gerilemesinin de gösterdiği gibi, CCLAI'nin oksidatif stresi azaltabileceğini düşündürmektedir.

Sonuç: Çalışmamız, CCLAI'nin muhtemelen ROS'u temizleyerek ve hepatik dokulardaki oksidan/antioksidan dengeyi modüle ederek oksidatif stresi azaltabildiğine dair kanıtlar sağlamıştır.

Anahtar Kelimeler: *Cotinus coggygria*, antioksidan aktivite, dekstran sülfat sodyum, karaciğer, oksidatif stres, ülseratif kolit

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Submitted/Başvuru: 03.07.2024 • **Accepted/Kabul :** 04.11.2024 • **Published Online/Online Yayın:** 23.01.2025

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis, is an immune-mediated, "chronic and recurrent intestinal inflammatory disorder" that occurs as a result of the interaction of genetic predisposition, dysregulated immune responses, and environmental factors, leading to the impairment of mucosal barrier function (1). "UC is a chronic inflammatory disease characterised by relapsing and remitting mucosal inflammation of the intestinal lamina propria, extending from the rectum to proximal segments of the colon", and developing of widespread superficial mucosal ulceration. Clinical symptoms include recurrent bloody diarrhoea, weight loss, and abdominal pain (2). UC often occurs accompanied by the intestinal barrier dysfunction resulting in colonic leakage of harmful substances, such as gut microbiota-derived high lipopolysaccharide levels and bacteria, resulting in secondary liver injuries, which in turn aggravates UC. Long-term intestinal inflammation as well as excessive generation of ROS and imbalances in redox status can cause oxidative damage and colitis-induced liver injury. The association between the development of UC and liver complications was examined in several experimental studies and related to "liver gut cross talk" (3-8).

UC constitutes a global concern, but therapeutic treatments for this disease are often associated with limited efficacy in relieving the symptoms or side effects. For these reasons, alternative and/or complementary therapies such as herbal preparations may be used to develop an effective therapeutic approach for managing UC (2, 9).

Cotinus coggygria is a well-known Balkan traditional medicine used as an anti-inflammatory, wound healing, antimicrobial, and anti-haemorrhagic agent. Accordingly, the therapeutic potential of *C. coggygria* has been focused on by many researchers and outlined in the review by Matic et al. (10). Phytochemical screening showed the presence of polyphenolic compounds (quercetin, fustin, and taxifolin), anthocyanins, gallic acid methyl ester, galanin, myrcene, alphapinene, camphene, linalool, and alpha-terpineol in the leaf infusion (11). We have previously found that *C. coggygria* leaves showed *in vitro* antioxidative activity, scavenging oxidative radicals to terminate the radical chain reaction (12). Matic et al. (13, 14) reported that the pretreatment with the *C. coggygria* extract was effective in protecting against the pyrogallol-mediated hepatotoxicity by reducing oxidative stress. Taking into consideration the results of these previous studies, we hypothesise that CCLAI may exert an antioxidant effect by improving the antioxidant status in mice with DSS-induced UC.

MATERIALS AND METHODS

Plant material: Young shoots, which include leaves and branches of *C. coggygria*, were collected from the Bartın Province of Turkey in August 2017. After separation of the leaves from the other parts, they were dried at room temperature and powdered. The botanical authentication of voucher specimens was done by Prof. Dr. Şükran Kültür and deposited in the Herbarium of the Faculty of Pharmacy, Istanbul University (ISTE 93133).

Preparation of the infusion: Two concentrations (4/100 and 6/100) of CCLAI were prepared 1 h before each treatment by adding 4 g or 6 g of dried material to 100 mL of boiling distilled water and leaving for 30 min. The infusions were filtered through cotton lint.

Animals: The experimental protocol was approved by Istanbul University Aziz Sancar Experimental Medicine Research Institute Animal Experiments Local Ethics Committee on 26 October 2017. A total of 56 C57BL/6J male mice were housed at an adequate temperature of 22°C, under a 12-h day/night cycle, and fed a commercial diet with free access to drinking water. Animals underwent a one-week acclimatisation period.

Animal groups and UC induction: The animals were divided into seven groups with 8 animals each: Group I (C_{normal}), used as the normal control, was given sterile tap water. Group II, served as the UC control group (C_{DSS}). Groups III (C_{CCLAI4}) and IV (C_{CCLAI6}), V (DSS + CCLAI4) and VI (DSS + CCLAI6) or VII (DSS + M) were orally administered two different doses of CCLAI (4% and 6%) (2 ml/kg body weight) or mesalamine (250 mg/kg body weight) for 7 consecutive days. Groups V, VI, and VII were subjected to UC induced by drinking water containing 3% (w/v) DSS (MW 36.000-50.00; MP Biomedicals, USA) for 5 days (starting at day 3 until day 7). Blood samples were taken from each mouse into EDTA-containing tubes through direct intracardiac intervention 24 h following the last treatment. The livers were collected and processed for biochemical analysis.

Biochemical analyzes

The activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the blood samples were evaluated using Reflotron® analyser and commercially available strips (Roche Diagnostics, Switzerland). The protein concentrations were determined using the bicinchoninic acid (BCA) protein assay. The antioxidant status was evaluated by measuring the extent of lipid peroxidation (LPO) (15) and activities of antioxidant enzymes such as superoxide dismutase (SOD) (16), catalase (CAT) (17), glutathione reductase (GR) (18), and glutathione peroxidase (GPx) (19), glutathione-S-transferase (GST) detoxifying enzyme activity (20), myeloperoxidase (MPO) activity (21), as an indicator of inflammation, as well as reduced (GSH) glutathione (22) and nitric oxide (NO) (23) levels.

Statistical analysis

The results were analysed using Graphpad Prism 9.0 (GraphPad Software, San Diego, CA, USA). A one-way analysis of variance (ANOVA) followed by the Tukey–Kramer Test was performed for the evaluation of statistical differences. All data values were expressed as the mean±SD.

RESULTS

In this study, the antioxidative effect of CCLAI on hepatic oxidative stress was demonstrated in a mouse model of DSS-induced UC.

There was no change in either the AST or ALT levels of the DSS-treated animals (Table 1).

Table 1: AST and ALT levels in hepatic tissue samples of mice with DSS-induced UC.

Group	ALT (U/L)	AST (U/L)
C_{normal}	23.10±1.92	25.93±1.25
C_{DSS}	26.40±2.02	29.23±2.05
C_{CCLAI4}	24.88±6.17	27.19±1.90
C_{CCLAI6}	21.46±3.69	26.65±1.85
DSS+CCLAI4	24.07±4.19	28.89±2.36
DSS+CCLAI6	25.47±4.30	29.74±2.91
DSS+M	23.82±3.84	26.55±1.86

Values are means±SD, from 8 animals. ALT: Alanine Aminotransferase; AST: Aspartate transferase; C_{normal}: Normal control; C_{DSS}: Ulcerative Colitis Control Group; C_{CCLAI4}: 4% aqueous infusion of *C. coggygria* leaves; C_{CCLAI6}: 6% aqueous infusion of C. coggygria leaves; DSS: Dextran sodium sulphate induced ulcerative colitis group; M: Mesalamine-treated ulcerative colitis group

Table 2: Effects of CCLAI and mesalamine on oxidative stress markers in hepatic tissue samples of mice with DSS-induced UC

Group	C_{normal}	C_{DSS}	C_{CCLAI4}	C_{CCLAI6}	DSS+CCLAI4	DSS+CCLAI6	DSS+M
NO (nmol/g tissue)	97.13± 10.72	167.82± 37.10*	99.18± 15.87^{f}	115.47± 21.26^{f}	129.54± 24.83^{f}	139.03± 35.00	125.18± 26.56^{f}
GSH (nmol/g tissue)	484.05± 22.34	726.86± 46.27*	509.61± 20.21^{f}	508.67± 38.93^{f}	582.52± 65.68^{f}	625.71± 64.91$^{*;f}$	575.6± 62.71^{f}
MPO (nmol/g tissue)	0.94±0.14	2.54± 0.65*	1.18± 0.21^{f}	1.24± 0.25^{f}	1.79± 0.53$^{*;f}$	1.99± 0.53*	1.56± 0.28$^{*;f}$
GST (U/mg protein)	257.82± 14.19	402.14± 49.17*	250.42± 25.14^{f}	264.17± 15.34^{f}	291.36± 39.75^{f}	309.01± 33.79^{f}	272.70± 26.81^{f}
GPx (U/mg protein)	128.31± 9.11	290.32± 33.48*	138.16± 9.76^{f}	130.99± 13.41^{f}	169.13± 19.45$^{*;f}$	176.50± 26.20$^{*;f}$	157.51± 16.07^{f}
GR (U/mg protein)	100.12± 12.79	212.75± 22.23*	110.57± 11.03^{f}	113.44± 7.30^{f}	158.42± 14.83$^{*;f}$	161.15± 17.85$^{*;f}$	145.19± 14.18$^{*;f}$
CAT (U/mg protein)	139.37± 14.85	244.57± 9.15*	130.7± 19.81^{f}	139.76± 7.13^{f}	179.84± 13.06$^{*;f}$	184.05± 26.12$^{*;f}$	162.22± 21.48^{f}
SOD (U/mg protein)	2.52±0.28	4.66± 0.24*	2.71± 0.27^{f}	2.86± 0.14^{f}	3.16± 0.38$^{*;f}$	3.29± 0.21$^{*;f}$	3.53± 0.37$^{*;f}$
MDA (nmol/g tissue)	16.2±2.3	31.73± 6.21*	15.6± 2.5^{f}	18.0±3.4^{f}	23.6± 3.6$^{*;f}$	26.7± 2.8$^{*;f}$	22.0± 3.8$^{*;f}$
Protein (mg/ml)	6.26±0.62	5.05± 0.67*	5.13± 0.34*	5.09± 0.64*	5.03 ± 0.47*	4.91± 0.67*	5.38± 0.69

Values are means of 8 animals±SD, from. Activities were expressed as units SOD (one unit of SOD inhibits the rate of increase in absorbance at 560 nm by 50 %), mmol of H_2O_2 /min per mg of protein (for CAT), nmol of NADPH oxidised/min per mg of protein (for both GPx and GR), nmol conjugate formed/min per mg of protein (for GST), units of MPO per g wet tissue (1 U of activity was defined as the amount that consumes 1 mmol H_2O_2/min).
* Values significantly different from C_{normal}; fValues significantly different from C_{DSS} (one-way ANOVA followed by Tukey–Kramer Test), p<0.05; NO: Nitric oxide; GSH: Reduced glutathione; MPO: Myeloperoxidase; GST: Glutathione-S-transferase; GPx: Glutathione peroxidase; GR: Glutathione reductase; CAT: Catalase; SOD: Superoxide dismutase; MDA: Malondialdehit; C_{normal}: Normal control; C_{DSS}: Ulcerative Colitis Control Group; C_{CCLAI4}: 4% aqueous infusion of *C. coggygria* leaves; C_{CCLAI6}: 6% aqueous infusion of C. coggygria leaves; DSS: Dextran sodium sulphate induced ulcerative colitis group; M: Mesalamine-treated ulcerative colitis group

Regarding the oxidative stress markers, we observed a significant ($p<0.05$) increase in the activities of CAT, SOD, GR, GPx, and GST as well as hepatic non-enzymatic GSH and NO levels in the DSS mice group when compared with the untreated mice. As expected, DSS caused an increase in MDA levels, as a marker of lipid peroxidation, and MPO activity, as a marker of neutrophil infiltration in the hepatic tissue of mice with UC compared to normal controls ($p<0.05$). However, these levels were reversed in CCLAI- and mesalamine-treated animals towards the value of normal controls, although the difference was significant (Table 2).

DISCUSSION

Many drugs are converted to metabolites in the extramitochondrial, microsomal system in the hepatocytes that uses some oxidative enzymes and regulates redox homeostasis. Oxidative stress may impair redox homeostasis and cause intestinal barrier dysfunction, decreased immunity, and dysbiosis, which in turn can trigger intestinal dysfunction and secondary liver injury. Liver injury is a common complication or manifestation of UC and should not be neglected in the management of UC (24).

Liver complications after the induction of UC by the administration of DSS, an animal model that mimics UC symptoms, have been demonstrated in several studies (4-8, 25). In our earlier study (unpublished data), it was shown that a 7-day administration of CCLAI was able to significantly reduce the oxidative stress markers in the colon tissues of mice with DSS-induced UC. Considering these results, in this study, we evaluated the possible oxidative stress attenuating effect of CCLAI in the liver tissue caused by DSS-induced UC.

Two doses of CCLAI (4% and 6%) were evaluated in colitis mice, in comparison with a mesalamine, a metabolite of sulfasalazine used as a drug control, which was administered at a commonly used dose in animal studies (250 mg/kg body weight). Mesalamine is used for the treatment of IBD and was reported to be an efficient ROS scavenger (26). Dose selection for preparing the infusion from leaves was based on a preliminary experiment reported by Eftimov et al. (11), who showed that the administration of aqueous infusion from *C. coggygria* leaves at a concentration of 1; 2 and 4% for 30 days did not cause liver toxicity. The AST and ALT levels, used as a marker of liver damage, were in the normal range, suggesting that the oxidative changes found in our acute colitis model (3% DSS, v/v, for 5 days) may not be sufficient to cause liver injury, although oxidative stress may be induced by this exposure.

Cellular membranes, due to their high content of oxidisable polyunsaturated fatty acids (PUFAs), are extremely susceptible to free radical assaults. High levels of oxidants like lipid hydroperoxides (LOOH), the major primary products produced during the propagation stage of lipid peroxidation and their secondary products such as malonaldehyde and 4-hydroxynonenal, which may serve as "oxidative stress second messengers" can induce tissue oxidative stress and redox imbalance leading to impaired mucosal integrity (26). As lipid peroxidation can initiate the development and progression of degenerative processes in the digestive system, such as inflammation and cancer, scientists tried to find strategies to prevent and treat it. *In vivo* studies in animal models showed increased levels of MDA (lipid peroxidation products) and oxidative reactive sensitivity of the intestinal epithelium and liver (6-8).

ROS are produced during normal physiological cellular metabolism; however, an increased ROS production or decreased ROS-scavenging capacity disrupts redox homeostasis, causing oxidative stress damage. In fact, the activity of ROS-scavenging enzymes such as CAT, SOD, GR, and GPx has been shown to be significantly altered in the liver of UC (6-8).

Superoxide is the first generated ROS that is produced by transferring an electron to O_2 through the mitochondrial electron transport chain (mETC), NADPH oxidases (NOXs), and xanthine oxidase (XO) in biological systems. SOD, which converts superoxide into hydrogen peroxide and oxygen, plays a protective role against oxidative damage, because it neutralised radical electrons at an initial stage and terminates chain reactions (27). Superoxide is not harmful to cell function directly because its oxidising power is mild compared to the hydroxyl radical, but if not properly removed, it potentially may lead to cell death. Previous studies have demonstrated that under the condition of inflammation and oxidative stress in UC pathogenesis, SOD activity increases as a defence reaction against oxidative damage (28). Contrary to the previous studies that reported the decreased SOD activity in only the DSS-treated group (6, 8, 25), our study indicated that the liver tissue SOD activity was elevated in the colitis group, compared to the normal group. These results were found to be consistent with those reported by Rtibi et al. (7).

CAT and GPx catalyse the reduction of hydrogen peroxide (H_2O_2) or organic hydroperoxides to water and an oxygen molecule or the corresponding stable alcohols, respectively, using GSH as the reductant, which in turn is oxidised to form glutathione disulphide (GSSG). The reduced form of cellular GSH is a more prevalent antioxidant, functioning in the detoxification of reactive oxygen metabolites. GPx, together with GR, acts as an enzyme couple in the reduction of peroxides with concomitant oxidation of GSH to GSSG, which is converted back to GSH by GR in a NADPH-dependent manner, forming a GSH redox cycle, which is an important intracellular detoxication mechanism for peroxide elimination and maintenance of GSH levels. It was reported that these two enzymes together with GSH form an antioxidant barrier and protect the cells against peroxide damage and mucosal inflammation in mouse models of UC (28, 29).

In this study, the observed increase in GR and GPx activities in the DSS-induced colitis group may be due to high GSH levels. Considering that GR and GPx cooperate with GSH in the breakdown of organic hydroperoxides, the simultaneous induction of GPx activity and elevation of GSH levels may be an indicator of the antioxidant response to hepatic oxidative stress.

Increased generation of superoxide radicals induces SOD activity in the hepatic tissue of DSS-treated mice. However, an increase in SOD activity without a concomitant increase in CAT

and/or GPx activities may be damaging because increased SOD activity leads to an elevation of the levels of H_2O_2, which is a relatively stable ROS that must be eliminated by CAT or GPx. Therefore, a concomitant increase in CAT and/or GPx activity, as observed in the CCLAI- and mesalamine-treated UC groups, may have beneficial effects against oxidative stress

NO produced by iNOS contributes to tissue injury and inflammatory processes as a mediator of macrophage and neutrophil function. The production of high NO by activated macrophages in inflamed tissues can be toxic and lead to tissue damage. The generation of increased NO and O_2^- by activated macrophages can lead to the formation of highly cytotoxic peroxynitrite (-$ONOO^-$), which induces tissue injury through mechanisms leading to lipid peroxidation. It has been elucidated in both experimental animals and humans that an enhanced production of NO is associated with inflamed mucosa, which is characterised by macrophage infiltration and release of inflammatory mediators, the potent inducers of iNOS. Therefore, NO may participate in the pathogenesis of UC, augmenting the extent of tissue damage. It was reported that the NO levels and expression of the iNOS increased in experimental animal models of UC (30).

Myeloperoxidase is a membrane-bound, haem-containing peroxidase released exclusively by neutrophils, tissue macrophages and to a lesser extent by monocytes. MPO provides an estimate for activated neutrophil infiltration in tissues (31). H_2O_2, formed as a result of the dismutation of the superoxide radical, may react with the chloride ion via the myeloperoxidase enzyme which catalyses the formation of hypochlorous acid, which is a potent cytotoxic oxidant. Increased MPO activity has been observed in the inflamed colonic and hepatic mucosa in animal models with UC (6-8, 25). As the reduction of ROS production may be due to the downregulation of hepatic antioxidant defence activities due to the decrease of their substrates, our findings of a reversed levels of oxidative stress parameters in mice treated with CCLAI towards the value of normal controls were consistent with these observations.

We suggested that oral administration of CCLAI may counteract the hepatic oxidative stress through reduced production of ROS, as assessed by decreased MDA levels and MPO activity, reversed GST and antioxidant enzymes (SOD, CAT, GPx, and GR) activities as well as GSH and NO levels towards the normal values. As in previous reports (13, 14), *C. coggygria* has been proven to be a hepatoprotective agent under *in vivo* conditions, mostly through its antioxidant action in reducing oxidative damage.

Our results corroborate with previous studies indicating that antioxidants can comprehensively reduce oxidative stress derived from DSS-induced UC in the liver tissue (4-8).

CONCLUSION

The present study results revealed that CCLAI has a comparable therapeutic potential with mesalamine against DSS-induced oxidative stress, which indicates that CCLAI may be a therapeutic option to relieve UC.

Ethics Committee Approval: This study was approved by Istanbul University Animal Experiments Local Ethics Committee Presidency (Date: 26.10.2017, No: 35980450-050.01.04).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.P., N.Ö.S., N.Ö; Data Acquisition- D.P., N.Ö.S., N.Ö., S.Ö.; Data Analysis/Interpretation- D.P., N.Ö.S., N.Ö.; Drafting Manuscript- D.P., N.Ö.S., N.Ö.; Critical Revision of Manuscript- D.P., N.Ö., A.C.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This work was supported by Istanbul University Research Fund (Project No. TDK-2018-28983).

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