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RESEARCH ARTICLE

Curcumin Effect on Rats Hepato-Renal Functions, Hematological Parameters, and Inflammatory Markers in Comparison with Celecoxib and Prednisolone

Saydat S. Abd-El Megid[1], Tarek Khamis [2, 3], Ahmed H. Arisha[4,5], Eman O. Abd-El Rahman[1], Doaa M. Abd-El Fattah[5]

[1]Department of Biochemistry, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt
[2] Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt
[3] Laboratories of Biotechnology, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt
[4] Department of Animal Physiology and Biochemistry, Faculty of Veterinary Medicine, Badr University in Cairo (BUC), Badr City, Cairo, Egypt
[1] Department of Physiology, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt

* Corresponding author: eothman321@gmail.com

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Abstract

The present study was performed to investigate curcumin's effect on hepato-renal functions, some hematological parameters, and inflammatory markers in carrageenan-injected rats compared with celecoxib and prednisolone. Sixty male rats were divided into five groups (G1 and G2: control, G3, G4, and G5: orally received celecoxib (10 mg /kg), prednisolone (5 mg /kg), and curcumin (100 mg /kg) respectively. All groups 2, 3, 4, and 5 received single subcutaneous carrageenan injection, 0.1 ml carrageenan sodium (1.5 % solution in saline), in rat paw after 14 days. Serum inflammatory markers interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)), liver function tests (alanine aminotransferase "ALT", albumin and bilirubin), kidney function tests (urea and creatinine), platelets and white blood cells (WBCs) count were measured. The results revealed that curcumin administration induced a significant downregulation in inflammatory markers compared with the carrageenan-treated group. Also, the current results revealed that curcumin has no side effects on the liver, kidney function, and on platelets and WBCs count; on the contrary, it improved the carrageenan effect on these parameters, unlike celecoxib and prednisolone. Based on the above-mentioned findings, it could be concluded that curcumin is displayed as an anti-inflammatory with minimum side effects on hepato-renal function and hematological variables, unlike celecoxib and prednisolone.

Keywords: Inflammation, Curcumin, Celecoxib, Prednisolon, Oxidative stress

Introduction

Inflammation is considered one of the most essential animal cells' protection mechanisms toward damage and infections [1]**.** Several chronic diseases, which have increased dramatically in the last three decades, may be caused by inflammation [2] Inflammation is characterized by a series of well-organized, complex responses that include both cellular and vascular events as well as unique humeral secretions. The inflammatory process is linked to a number of cytokines, pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-13 (IL-13), and Tumor necrosis factor-α (TNF-α) [3]. Inflammation can be caused by a variety of factors and the pathway of nuclear factor-kappa-β (NF-κβ)/cyclooxygynase-2 (COX-2)/inducible nitric oxide synthase (iNOS) is one of them [4]**.** Notably, NF-κβ regulates numerous mediators, like cytokines (TNF-α, IL-1β), chemokines and iNOS, to govern different inflammation stages and immunological modification [5]**.**

Anti-inflammatory medications are classified as either steroidal or nonsteroidal which are used to overcome inflammatory diseases if acute or chronic [6]**.** Celecoxib works by inhibiting COX-2 specifically, which is responsible for prostaglandin synthesis, which is an essential component of the pain and inflammation pathway. The anti-inflammatory effects of celecoxib such as inhibition of TNF- mediated NF- κβ signaling and IL-1β induction of IL-6 [7]. Since celecoxib inhibits COX-1 only weakly, it may have a smaller impact on platelet function than aspirin. Celecoxib, like all NSAIDs, comes with a boxed warning from the FDA about cardiovascular risk, which included an elevated risk of heart attacks and strokes [8]. Celecoxib is linked to the same risk of renal side effects as non-selective NSAIDs. COX enzymes manufacture prostaglandins, which affect renal function by regulating vascular tone and blood flow, COX-1 inhibition is linked to a reduction in glomerular filtration rate. Patients who take non-selective or selective COX-2 inhibitors have a two-fold increased risk of developing acute kidney injury (AKI) [9]**.** Hepatotoxicity has been linked to a variety of NSAIDs and COX-2 inhibitors, ranging from transient cholestatic and hepatocellular damage to fulminate hepatic failure [10]. Prednisone reduces inflammation by stopping polymorph nuclear leukocyte migration and reversing increased capillary permeability. It also suppresses the immune system by lowering the immune system's function and volume. Patients that receive glucocorticoids in high doses or for an extended period of time are more likely to experience side effects. Skin fragility, weight gain, an elevated risk of infection, and fractures are all possible side effects, in addition to significant cardiovascular and metabolic effects are hypertension, hyperglycemia, and dyslipidemia [11]**.** Creatinine increased due to the catabolic condition caused by steroid therapy, which includes protein degeneration and muscle tissue loss. Increased serum creatinine in patients on steroids is thought to be due to the steroid-induced diabetic state [12].

However**,** both selective COx2 NSAID and SAID displayed several adverse effects regarding the integrity of hepatocellular damage, renal impairment and raises white blood cell counts, with varying effects on different leukocyte subtypes [13] As a result, finding newer pharmacological alternatives for the treatment of inflammation with minimum side effects is mandatory [14, 15]**.**

Curcumin has a wide range of physiological effects, including anti-inflammatory, antioxidant, and cancer-fighting properties [16]**.** Curcumin was designated as a "generally regarded as safe" chemical by the US Food and Drug Administration, and a clinical study indicated that it is extremely safe at doses of 4,000–8,000 mg/kg per day [17]. Curcumin has been shown to have therapeutic benefits in human trials, and it may play a role in the treatment of inflammatory illnesses caused by a person's lifestyle. The focus of this research was to investigate if curcumin has an anti-inflammatory benefit on rats with carrageenan-induced paw edema and explore its effects on liver function tests (ALT, albumin and bilirubin), kidney function tests (urea and creatinine), WBCs and platelets count in comparison with celecoxib and prednisolone.

Materials and methods

Experimental animal and ethical statement

Sixty male adult Wistar rats weighing 200-220 g, were used in the experimental study. The ZU-IACUC reviewed and approved this study ZU-IACUC/2 /F/61/2020. All animals were acclimatized for weeks before the current study.

Chemicals

Celebrex100 mg (celecoxib) was purchased from (Pfizer pharmaceutical company, Egypt), Solupred 20 mg (prednisolone) was purchased from (Sanofi –Aventis intercontinental company, Egypt), and curcumin was acquired in Mumbai, India, from Sisco Research Laboratories Pvt.Ltd.

Animals groups and dosing

Sixty male rats were allocated into five groups of equal size (12 rats each) G1: control group without drugs, G2:control without drugs and received subcutaneous carrageenan injection, 0.1 ml carrageenan sodium (1.5 % solution in saline) [18] after 14 days**,** G3: received celecoxib (10 mg /kg) [19] orally for 14 days then injected with carrageenan, G4: received prednisolone (5 mg /kg) [20] orally for 14 days then injected with carrageenan and G5: received curcumin (100 mg /kg) [21] **(**orally for 14 days then injected with carrageenan (0.1 ml carrageenan sodium (1.5 % solution in saline)) [18] .

Sampling

After 2 hours of carrageenan injection, rats were sacrificed and blood samples were collected from the orbital venous plexus, the capillary tube was inserted into the medial canthus of the eye (30-degree angle to the nose), and with slight thumb pressure, the blood came through the capillary tube, kept for a time, centrifuged at 3000 r. p. m for 15 minutes, the resulting supernatant (serum) was collected and used for the measurement of biochemical parameters of IL-1β, TNF-α, IL-6, liver and kidney function tests. Other whole blood samples were collected in a 3 ml lavender-top (K2EDTA) tube for WBCs and platelets count tests, these samples should be kept cool (at refrigerated temperature, but not frozen) during storage and shipping to minimize changes in cells that can occur with storage.

Biochemical determinations

Inflammatory markers

Serum IL-1β concentrations were assayed using Kit (Cat. No- RLB00) (R&D Systems, Inc, USA) with the quantitative sandwich enzyme immunoassay technique [22], Serum TNF-α concentration was assayed using Kit (Cat. No- RTA00) (R&D Systems, Inc, USA) with the colorimetric method by quantitative sandwich enzyme immunoassay technique and Serum IL-6 concentrations were assayed using Kit (Cat. No - R6000B) (R&D Systems, Inc, USA) with the colorimetric method by quantitative sandwich enzyme immunoassay technique.

Liver function

Serum ALT concentrations were assayed using Kit (Cat. No-MET 5123) (Cell Biolabs, Inc, USA) with the colorimetric method by Henley and Pollard [23] and Bergmeyer *et al.* [24] serum bilirubin concentrations were assayed using Bilirubin Assay Kit (Cat. No - ab235627) (Abcam, USA) with a colorimetric method according to Jendrassik *et al.* [25] and serum albumin concentrations were assayed using kit (Cat. No- ab235628) (Abcam, USA) according to colorimetric endpoint method according to modified bromcresol green binding assay (BCG) [26].

Kidney function

Urea concentrations were assayed by using Kit (Cat. No - ab83362) (Abcam, USA) according to the enzymatic, colorimetric method (urease) modified Berthelot reaction [27] and serum creatinine concentrations were assayed using Kit (Cat. No- ab65340) (Abcam, USA) according to Jaffé [28].

Blood platelets and WBCs counts

Blood was collected in EDTA vials, and a full haemogram was carried out for blood platelets and WBCs counts using an automated hematological analyzer (Mindray BC 6800, Shanchon Mindray Bio-Medical Electronica Co. Ltd. China) [29].

Statistical analysis:

The obtained results are expressed as (mean ± SEM). The one-way analysis of variance (ANOVA) test has been done to test the significant changes among different groups. Duncan considered the kit range test as a post-test. The measurable examination was done utilizing IBM SPSS version 24.0. The graphs were generated using GraphPad Prism 8.0.2

Results

Oral administration effect of celecoxib, prednisolone and curcumin on inflammatory markers.

The current study's findings revealed a significant *($p< 0.05$)* increase in the mean value of IL-1β, TNF-α and IL-6 in the carrageenan injected group when compared with control one. However, celecoxib, prednisolone and curcumin administration induced a significant improvement in these parameters (Table, 1).

Oral administration effect of celecoxib, prednisolone and curcumin on liver function tests.

The current study's findings revealed a significant *($p< 0.05$)* increase in the mean value of ALT and bilirubin in carrageenan, celecoxib and prednisolone groups when compared with a control group. While curcumin demonstrated a significant *($p< 0.05$)* reduction in these parameters when contrasted to celecoxib and prednisolone groups (Table 2). In the current study carrageenan, celecoxib, prednisolone and curcumin groups showed a non-significant difference in the mean value of albumin level when compared with the control group (Table 2).

Table (1) Consequence of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on IL1β (pg/L), TNF-α (pg/L) and IL-6 (ng/L) in carrageenan induced paw edema in rats

Groups / Parameters	Control	Carrageenan	Celecoxib-carrageenan	Prednisolon-carrageenan	Curcumin -carageenan
IL-1β (pg/L)	4.382±0.39^{b}	8.54±0.31^{a}	5.7±0.64^{b}	5.10±0.21^{b}	6.14±0.17^{b}
TNF-α (pg/L)	10.65±1.21^{c}	24.87±1.66^{a}	18.74±1.25^{b}	16.37±1.06^{bc}	16.96±0.87^{b}
IL-6 (ng/L)	39.05±4.3^{b}	82.61±5^{a}	54.32±3.08^{b}	49.61±2.47^{b}	48.39±2.03^{b}

Values are mean of 8 rats per group ±S.E.M. ^{abcd}values bearing different superscripts are sig. different at P < 0.05 based on Tukey's Honestly Significant Difference (Tukey's HSD) test. IL-1β: Interleukin-1β ; TNF-α: Tumor necrosis factor-α ; IL-6: Interleukin-6

Table (2): Influence of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on Liver function enzymes (Alanine transaminase (ALT) (IU/L), Albumin (g/L), Bilirubin (mg/dl) in carrageenan induced paw edema in rats

Groups / parameters	Control	Carrageenan	Celecoxib-carrageenan	Prednisolone-carrageenan	Curcumin - carrageenan
ALT (IU/L)	35.67±1.20 ^{b}	51.00±1.15 ^{a}	57.00±2.89 ^{a}	58.67±2.02 ^{a}	38.67±1.20 ^{b}
Alb (g/L)	3.90±0.15^{ab}	4.37±0.12^{ab}	3.70±0.06^{b}	4.53±0.12^{a}	4.33±0.24^{ab}
Bilirubin (mg/dl)	1.30±0.06^{c}	1.70±0.06^{b}	3.17±0.15 ^{a}	3.30±0.06 ^{a}	1.40±0.06^{bc}

Values are mean of 8 rats per group ±S.E.M. ^{abcd}values bearing different superscripts are sig. different at P < 0.05 based on Tukey's Honestly Significant Difference (Tukey's HSD) test. ALT: Alanine aminotransferase; ALB: Albumin.

Oral administration effect of celecoxib, prednisolone and curcumin on kidney function tests.

The result of the contemporary investigation showed a significant *(p< 0.05)* increase in mean value of urea and creatinine in carrageenan and celecoxib and prednisolone groups when compared with the control one. However, the result demonstrated a significant *(p< 0.05)* reduction in curcumin group when compared with celecoxib and prednisolone groups (Table 3).

Oral administration effect of celecoxib, prednisolone and curcumin on WBCs and platelets counts

The results of the contemporary investigation showed that the mean value of WBCs significantly decreased *(p< 0.05)* in carrageenan, celecoxib, prednisolone and curcumin groups when compared with control group. While curcumin and prednisolone showed a significant *(p< 0.05)* increase in WBCs in comparison to celecoxib group (Table 4). Also the present findings indicated a substantial increase *(p< 0.05)* in mean value of platelet count in carrageenan, celecoxib and prednisolone groups when compared with control group. While curcumin one demonstrated a significant *(p< 0.05)* reduction in comparison to celecoxib and prednisolone groups (Table 4).

Table (3): Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on Kidney function enzymes (Urea and Creatinine) (mg/dl) in carrageenan-induced paw edema in rats.

Groups / Parameters	Control	carrageenan	Celecoxib-carrageenan	Prednisolone-carrageenan	Curcumin -carrageenan
Urea (mg/dl)	22.10±0.65^{c}	28.03±0.75^{b}	35.43±0.96^{b}	42.37±0.73^{a}	26.47±2.49^{c}
Creatinine (mg/dl)	0.60±0.02^{c}	0.80±0.03^{b}	0.90±0.05^{b}	1.33±0.05 ^{a}	0.59±0.02^{c}

Values are mean of 8 rats per group ±S.E.M. ^{abcd}values bearing different superscripts are sig. different at P < 0.05 based on Tukey's Honestly Significant Difference (Tukey's HSD) test.

Table (4): Impact of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on White blood cells (WBCs) (10^3/ µl) and Platelet count (10^3/ µl) in carragenin induced paw edema in rats.

Groups / parameters	Control	Carageenan	Celecoxib-carageenan	Prednisolone-carageenan	Curcumin -carageenan
WBCs (10^3/ µl)	34.67±3.18^{a}	7.67±0.33^{c}	7.83±0.44^{c}	20.00±0.58^{b}	24.67±0.88^{b}
Platelet count (10^3/ µl)	337.00±33.45^{d}	584.00±14.53^{bc}	754.67±29.24^{a}	669.67±45.92^{ab}	477.33±28.96^{cd}

Values are mean of 8 rats per group ±S.E.M. ^{abcd}values bearing different superscripts are sig. different at P < 0.05 based on Tukey's Honestly Significant Difference (Tukey's HSD) test. WBCs: White Blood Cells.

Discussion

Inflammation is a homeostatic defensive mechanism that protects the body from foreign invaders. Chronic inflammation, on the other hand, may exacerbate the effects of several diseases [30]**.** As a result, there are a number of ongoing studies targeted at reducing the incidence of excessive inflammation.

Steroid hormones are the most effective anti-inflammatory medications since they may block all inflammatory pathways; nevertheless, tolerance to these treatments is easily built. As a result, NSAIDs are frequently utilized. By suppressing prostaglandin synthesis in the upper gastrointestinal tract, NSAIDs, on the other hand, induce substantial adverse effects [31].

In recent years, there has been an increase in the number of clinical trials aimed at developing safer and also more powerful anti-inflammatory medications. Curcumin is one of the most well-known bioactive constituents of *Curcuma longa*, with anti-inflammatory, antioxidant, and anti-cancer activities [32]. The current study was aimed to look at curcumin's anti-inflammatory properties as well as its impact on hepato-renal function and hematological WBCs and platelets counts when compared to celecoxib and prednisolone.

The result of the current study revealed that curcumin administration induced a considerable reduction in inflammatory markers (IL1β, TNF-α and IL-6) that is accordance to Heeba *et al.,* [33] who show that carrageenan injection resulted in four times increasing in the level of TNF- α especially in comparison to the animals in the control group. Curcumin, quercetin, and their combination pretreatments reduced TNF-a secretion by 32, 28 and 63 percent when compared to carrageenan-injected rats. Curcumin suppressed TNF-induced production of adhesion molecules on human umbilical vein endothelial cells that is in accordance with Gupta *et al.* [34], because diferuloylmethane inhibits cytokine-induced transcript levels for leukocyte adhesion

molecules, it may be interacting with TNF-induced signalling at an early stage. Curcumin has anti-inflammatory capabilities, according to the findings, for a variety of reasons. First of all**,** its ability to reduce pro-inflammatory transcription factors (NF-κβ and Activator protein-1 (AP-1)). Second of all, inhibition of lipoxygenase enzyme and COX2**.** Third of all, decreasing the production of the pro-inflammatory cytokines and prostaglandin E2 [35].

The findings of the present work regarding that curcumin-treated group showed a significant decrease in ALT and bilirubin compared to celecoxib and prednisolone. These findings are in accordance with Nachimuthu *et al.* [36] and Coulter and Director [37] who reported that the rate of serum aminotransferase increases was three-fold higher than the threshold limit of the standard parameters, 1.1 percent in patients who received celecoxib in comparison to 0.9 percent in blind study patients. However, the study showed no significant difference in albumin between all groups. In the same line with Kevin *et al.,* [20] who observed that prednisolone treatment increased ALT, AST, ALP, and total bilirubin levels, but had no effect on serum albumin levels. The selective COX-2 inhibitors such as celecoxib and rofecoxib, as well as non-selective NSAIDs, can cause liver damage. They can cause decreasing in bile flow, hepatocellular, or mixed liver damage, all of which can be life-threatening. Sriuttha *et al.*, [38] recommended that only 8 studies with three NSAIDs (celecoxib, etoricoxib, and diclofenac) reported clinically significant hepatotoxicity based on the hepatotoxicity justification criteria, according to this data. Diclofenac had the largest proportion of hepatotoxicity events among the three NSAIDs, with a range of 0.015–4.3 ($\times 10^{-2}$), followed by celecoxib with a range of 0.13–0.38 ($\times 10^{-2}$), and etoricoxib which was in the range of 0.005–0.930 ($\times 10^{-2}$). Turmeric powder in poultry diets can reduce inflammation and damage cells in organs, especially the liver and kidney, resulting in lower levels of liver enzymes ALT, AST, and ALP [39].

The outcomes of the contemporary investigation illustrated that curcumin-treated group showed a significant decrease in the level of urea and creatinine compared to the celecoxib and prednisolone group, and the same results were previously reported by Van Acker *et al.*, [12]. Both plasma creatinine concentration and urine creatinine excretion rise most likely as a result of prednisone's catabolic action. Non-selective inhibition of prostaglandin synthesis has antinatriuretic and vasoconstrictor effects and lowers glomerular filtration rate frequently (GFR). The COX-2 enzymatic pathway, which is found in the macula densa of the kidney, is primarily responsible for sodium sensing. Inhibition of this enzyme has an antinatriuretic effect, which is clinically expressed as edema and is often linked to blood pressure being destabilized among patients with hypertension who have been medicated. Furthermore, it has the potential to cause cardiovascular disease in those who are predisposed, so nonselective NSAIDs may cause acute hemodynamically induced renal function deterioration in one out of every five patients within a few days of NSAID use [40]. Curcumin has recently been proven to have a therapeutic effect in a model of chronic renal failure, reversing not only systemic but also glomerular hemodynamic abnormalities. The induction of the master regulator of antioxidant response nuclear factor erythroid derived 2 (Nrf2), suppression of mitochondrial dysfunction, the inflammatory response inhibition, maintenance of antioxidant enzymes, and avoidance of oxidative stress are all attributed to curcumin's protective effect in the kidney [41]

The result of the study showed a significant reduction in WBCs count in the carrageenan group compared to curcumin and prednisolone groups indicating the improved effect of curcumin and prednisolone on carrageenan side effects on WBCs. The result of the investigation showed also a significant improvement in platelets count in the curcumin group (after its increase by carrageenan) when compared with celecoxib and prednisolone groups [42]. Curcumin protects against the lowering in leukocyte and

platelet counts, which is likely owing to its antioxidant and anti-inflammatory properties. Shah *et al.* [43] studied the mechanism of platelet aggregation by curcumin; they showed that the inhibitory effect of curcumin on platelet aggregation was caused by the inhibition of platelet agonists epinephrine, platelet-activating factor, and Arachidonic acid (AA). Curcumin affects cellular responses by modifying membrane fluidity or directly controlling enzymes and ions-transporter function [44]**.**

Conclusions

Based on the previous mentions it could be speculated that curcumin represents new valid anti-inflammatory and hepato-nephroprotective effects and also showed its ability to overcome the side effects of inflammation on platelets and WBCs count. However, future studies are needed to understand the activity of curcumin and/or the possible toxicity increases after its administration for a long period before starting any clinical trials.

Conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

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الملخص العربي

تأثير الكركمين على وظائف الكبد والكلى وبعض المتغيرات الدموية ودلالات الالتهالب للجرذان بالمقارنة مع السيليكوكسيب والبريدنيزولون

سيدات سعد عبدالمجيد[1] ،طارق خميس كمال[2,3] ،احمد حامد عريشة[4,5] ،إيمان عثمان عبدالرحمن[6] ،دعاء محمد عبدالفتاح[7]
[1] قسم الكيمياء الحيوية كليه الطب البيطري جامعة الزقازيق، الزقازيق، مصر،44519
[2] قسم الفارماكولوجيا كليه الطب االبيطري، االزقازيق، مصر،44519
[3] معامل التكنولوجيا الحيوية، جامعة الزقازيق، الزقازيق، مصر ، 44519
[4] قسم الفسيولوجية والكيمياء الحيوية كليه الطب البيطري جامعة جامعة بدر بالقاهرة ،مدينة بدر،االقاهرة ، مصر،44519
[5] قسم علم وظائف الاعضاء، كلية الطب البيطري جامعة الزقازيق،الزقازيق، مصر 44519

يعتبر الالتهاب استجابة تلقائية تجاه أي تغييرات في الأنسجة إما أن تكون التغيرات داخلية أو خارجية .ويتمثل دور الالتهاب فى حماية وظيفة الخلية ومنع تلف الأنسجة. وبالرغم من ذلك قد يؤدى الالتهاب الي امراض قد تكون حادة أو مزمنة , وقد يؤدي الالتهاب المزمن إلى الوفاة. لذلك هناك دائما حاجة لاكتشاف مضادات اللالتهابات جديدة لخفض الآثار الجانبية ولذلك تم العمل علي الكركمين للتحقق من تاثيره كمضاد للالتهاب ومعرفة آثاره الجانبية بالمقارنة مع السيليكوكسيب والبريدنيزولون ضد الجرذان المصابة بالالتهاب الناجمة عن كاراجينان. أجريت الدراسة على 60 جرذا من ذكور الجرذان البالغة والتى تم تقسيمها إلى خمس مجموعات متساوية. المجموعة 1: المجموعة الضابطة,مجموعة 2: المجموعة الضابطة دون ادوية والتى تلقت الكاراغنان بعد 14 يوم من بدء التجربة , المجموعة 3: والتى تناولت السيليكوكسيب (10ملغ / كغ) عن طريف الفم لمدة 14 يوما ثم تم حقنها بالكاراغنان, المجموعة 4: تناولت البريدنيزولون (5 ملغ / كغ) عن طريق الفم ثم حقنت بالكاراغنان بعد 14 يوما , والمجموعة 5: تناولت الكركمين (100 ملغ / كغ) عن طريق الفم ثم تم حقن كاراغنان بعد 14 يوما. تم جمع عينات الدم لقياس كلا من انترلوكين وان بيتا , ومعامل نخر الورم الفا, وانترلوكين 6. ايضا تم اختبار وظائف الكبد والكلى وعدد خلايا الدم البيضاء والصفائح الدموية . أشارت النتائج إلى أن الكركمين يمكن أن يستخدم كمضاد للالتهابات فهو يقلل من عوامل الالتهاب انترلوكين وان بيتا , ومعامل نخر الورم الفا, وانترلوكين 6 مشابها لتاثير السيليكوكسيب والبريدنيزولون فى الجرذان المصابة بالالتهاب الناجم عن كاراجينان وليس له أي تأثير ضار على وظائف الكبد (الألبومين والبيليروبين) ووظائف الكلى (اليوريا والكرياتينين) على عكس سيليكوكسيب وبريدنيزولون . كما أظهر االكركمين قدرته على التغلب على الآثار الجانبية للالتهاب على عدد خلايا الدم البيضاء والصفائح الدموية . ومع ذلك، مازال هناك حاجة إلى دراسات مستقبلية لفهم نشاط الكركمين و / أو الزيادات المحتملة في السمية بعد تناوله لفترة طويلة قبل بدء أي تجارب .