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ORIGINAL ARTICLE

Effects of Short-Term Oral Administration of Curcumin on Achilles Tendon Healing in Rats

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Abstract

Objective: Tendon healing, in terms of histologic and functional characteristics, is always inferior to its normal level due to the poor vascularity and low metabolic rate. Curcumin possesses anti-inflammatory, anti-oxidant and healing effects. This study aimed to investigate effects of curcumin on Achilles tendon experimental injury using histopathology, biomechanical and functional evaluations.

Design: Experimental study.

Procedures: Twenty four adult male rats were divided into control and treatment groups. After aseptic preparation, complete transverse tenotomy through the middle section of right Achilles tendon, followed by modified Kessler suture placement was performed. Normal saline and curcumin (100 mg/kg) were administered orally for seven days after surgery in control and treatment groups, respectively. Sampling was done six weeks later.

Results: Lower peri-tendinous adhesion was found in the treatment group. Histopathology revealed significant increase in density and arrangement of collagen fibers, decrease in fibroblast and inflammatory cells and lower vascularity in treatment group compared to control groups which indicates earlier maturation of granulation tissue by curcumin. Significant increase in maximum load, yield load, stress and absorbed energy in the treatment group were noted by biomechanical analysis. Improved functionality was also found in the treatment group according to hind paw print analysis.

Conclusion and clinical relevance: The present study indicated that short-term oral administration of curcumin resulted in improved structural, biomechanical properties and functionality of the Achilles tendon in rats.

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1. Introduction

Tendons are fibrous and highly organized connective tissue that transmit force between muscle and bone. Due to high mechanical stresses they withstand, they are prone to different types of injury from mild strain to complete rupture. The limited vascularity and relatively poor cellularity make tendon repair challenging and slow.[1] On the other hand, the healed tendon does not gain the characteristics of intact tendon in terms of structure and mechanical functionality.

It is believed that anti-inflammatory and antioxidant agents help tendon healing process by reducing inflammation and protecting cells against the oxidative damage produced by inflammation, respectively.[2,3]

Curcumin, the most active component of rhizome of *Curcuma longa* L. (common name: turmeric), possesses number of pharmacological activities, including antioxidant, anti-cancer, antimicrobial, anti-inflammatory, angiogenic, and wound-healing effects.[4-9]

Reportedly, increased fibroblast proliferation and collagen deposition with high cross linking of collagen fibers, accelerated wound maturation, and increased tensile strength were observed when curcumin was administered topically on experimental dermal wounds.[10-12] Recently, Güleç *et al*. reported improved Achilles tendon repair by long term orally administered curcumin, however, Achilles functional index (AFI) as the most valuable indicator for Achilles tendon recovery was not studied.[13]

The present study was carried out to evaluate the efficacy of short term oral administration of curcumin on the healing of rat Achilles tendon. The objective of this study was to investigate the effects of orally administered curcumin on the healing of experimentally transected rat Achilles tendon via the assessment of histopathological, biomechanical and functional parameters.

2. Materials and Methods

Animals

Adult male Sprague Dawley rats (n = 24) weighing 200 ± 20 g were acclimatized in polyethylene cages (two rats per cage) with wood chip bedding under natural light/dark cycle, fed with standard pellet diet and had free access to water. The rats were divided randomly into two groups. All animal experiments were performed in a humane manner, and also in accordance with the Institutional Animal Care Instructions (002/F/93).

Surgical procedure

General anesthesia was induced with intraperitoneal injection of ketamine (80 mg/kg, Alfasan, Woerden, The Netherlands) and xylazine (5 mg/kg, Alfasan, Woerden, The Netherlands) combination. After aseptic preparations, a longitudinal skin incision on the posterior aspect of the rats' right hind limb was made to expose the Achilles tendon. Complete transverse tenotomy was performed using 10 blade at the midsubstance of the tendon which followed by modified Kessler suture repair with 4-0 nylon (Figure 1). Then, the skin incision was sutured in a simple interrupted pattern. After recovery from anesthesia, the rats were housed individually in clean cages with fresh bedding. No immobilization was applied post-surgery, and the rats were allowed to move freely in their cages. The rats in control group received 1 mL normal saline once daily for seven days post-surgery by oral gavage. In treatment group, the rats were gavaged 100 mg curcumin (C7727; Sigma-Aldrich Co, St Louis, USA, CAS: 458-37-7) suspended in normal saline using the same regimen.

Figure 1. Modified Kessler suture repair of transected rat Achilles tendon.

Achilles functional index

Functional performance of Achilles tendon was determined from the measurement of hindpaw prints of walking rats (n = 6) at the end of each week after surgery for six consecutive weeks. The AFI was calculated according to Murrell *et al*. as follows:[14]

AFI = 74(PLF) + 161(TSF) + 48(ITF) – 5

where PLF is print length factor, TSF is toe spread factor and ITF is intermediate toe factor which represent the

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difference between the experimental and contralateral print measurements. At the end of week six, the rats were sacrificed with intra-cardiac overdose of thiopental sodium (50 mg/kg; Sandoz, Kundl, Austria).

Macroscopic evaluation

Upon dissection, adhesion formation between the operated tendons and the surrounding connective tissues was assessed qualitatively and classified according to Tang *et al*. as 0 = None, 1-2= mild, 3-4 = Moderate, 5-6 = Severe adhesion.[15]

Histopathological evaluation

Samples (six sample from each group) were routinely formalin fixed, paraffin embedded, sectioned at 5 µm longitudinally, and stained with hematoxylin and eosin and Masson's trichrome. Quantitative histopathological studies included number of inflammatory cells, fibroblasts (ovoid-shaped tenoblasts), and newly formed vessels in 0.25 mm^2 of granulation tissue of each section. For collagen density, the average distance between the adjacent collagen bundles with longitudinal arrangement of fibers was measured in 10 microscopic fields, where a lower value represents a higher density. FIJI software (version 2.0.0; National Institutes of Health, USA) and Image-pro Insight software (version 8.0; Media Cybernetics Inc., Rockville, USA) were used for image analysis.

Mechanical evaluation

The Achilles tendons (six sample from each group) were harvested between the calcaneus and musculotendinous junction. Samples were wrapped in saline-soaked gauze and stored at -20º C until mechanical testing. Before testing, suture materials were removed and tendons were allowed to thaw at room temperature. Tendons were mounted on mechanical testing machine (STM-50) equipped with a 500 N load cell. The tension test took place at the constant velocity of 60 mm/min. For each tendon the force-elongation curve was plotted and the following mechanical parameters were recorded: ultimate load (N), yield point (N), ultimate stress (MPa), ultimate strain (%), energy absorption (J), and stiffness (MPa/mm).

Statistical analysis

The AFI data were analyzed by two-way repeated measures analysis of variance (ANOVA) followed by Bonferroni's post hoc test. Macroscopic scores were analyzed with Mann Whitney test. Student *t* test was used for quantitative histopathological parameters. The mechanical properties of operated tendons of two experimental groups and intact tendons was analysed by one-way ANOVA followed by Tukey's post hoc test. All Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software (version 21, IBM Corp., Armonk, USA) and *p* values less than 0.05 were considered to be statistically significant.

3 Results

Achilles functional index

The mean values and the standard deviation of AFI obtained in the experimental group along with the periods analyzed are described in Figure 2. There were no significant differences between groups during the first two weeks of study ($p>0.05$). Curcumin administration resulted in progressive functionality of Achilles tendon from week three toward the end of study compared to control group. Based on intragroup studies, no significant differences were found until week five in control group ($p>0.05$), while in treatment group, AFI improvement started earlier at week three with weekly significant changes ($p<0.05$).

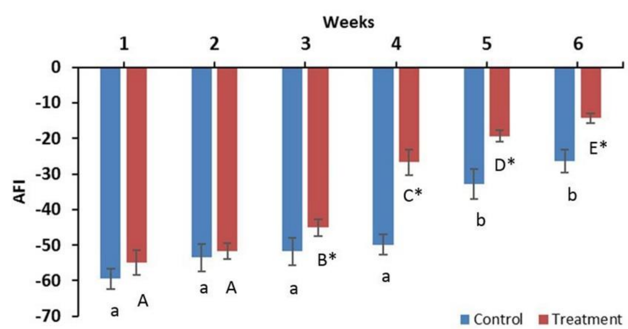

Figure 2. Mean values and the standard deviation of AFI during six weeks after surgery. Asterisks (*) indicate significant differences between control and treatment groups ($p<0.05$); Uppercase letters indicate significant differences in different time points is treatment group ($p<0.05$); and lowercase letters indicate significant differences in different time points is control group ($p<0.05$).

Macroscopic evaluation

Considerable peritendinous adhesions were observed around the repair site which required sharp dissection to break in control group. However, in treatment group, little

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dissection was applied to detach the tendon from the surrounding tissues. Statistically, adhesion score was significantly lower in curcumin treated group ($p<0.05$, Figure 3).

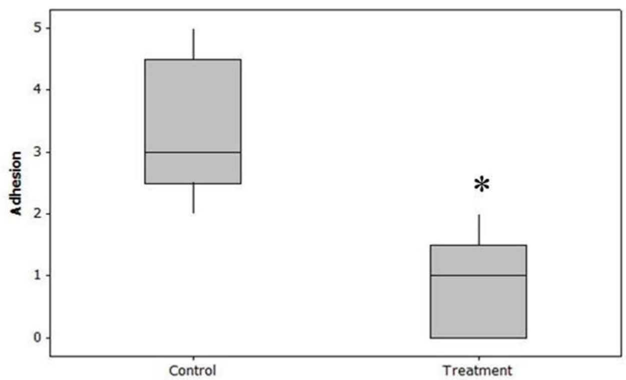

Figure 3. Box plot of adhesion formation score of tendon repairs six week after surgery. Asterisk (*) indicates significant decrease adhesion formation in curcumin treated tendons compared to controls ($p<0.05$).

Histopathological evaluation

Histopathology revealed significant decrease in number of ovoid-shaped tenoblasts, inflammatory cells and new vessels in treatment group ($p<0.05$). Fibroblasts with elongated and hyperchromatic nuclei were observed among parallel collagen fibers in H & E stain (Figure 4). The distance between adjacent collagen bundles were significantly lower in curcumin treated tendons compared to the controls ($p<0.05$), indicating higher density (Figure 5). The results of histopathological evaluations are summarized in Table 1.

Table 1. Histopathological evaluation of experimental rat model of Achilles tendon injury.

Groups	Number of fibroblasts	Number of inflammatory cells	Number of neovessels	Distance between collagen bundles (µm)
Control	12.83 ± 3.87	14.00 ± 5.15	7.40 ± 2.07	156.40 ± 6.69
Treatment	4.50 ± 1.87*	2.40 ± 1.95*	3.40 ± 1.51*	133.80 ± 5.12*

Asterisk (*) indicates significant differences between groups ($p<0.05$).

Mechanical evaluation

The mode of failure was rupture at the repair site of samples under tensile test. The test revealed increased mechanical properties of repairs in terms of ultimate load, yield load, ultimate Stress, and energy absorption in treatment group ($p<0.05$). However, no significant differences were noted in strain and stiffness between two groups ($p>0.05$). The results of mechanical evaluations are presented in Table 2.

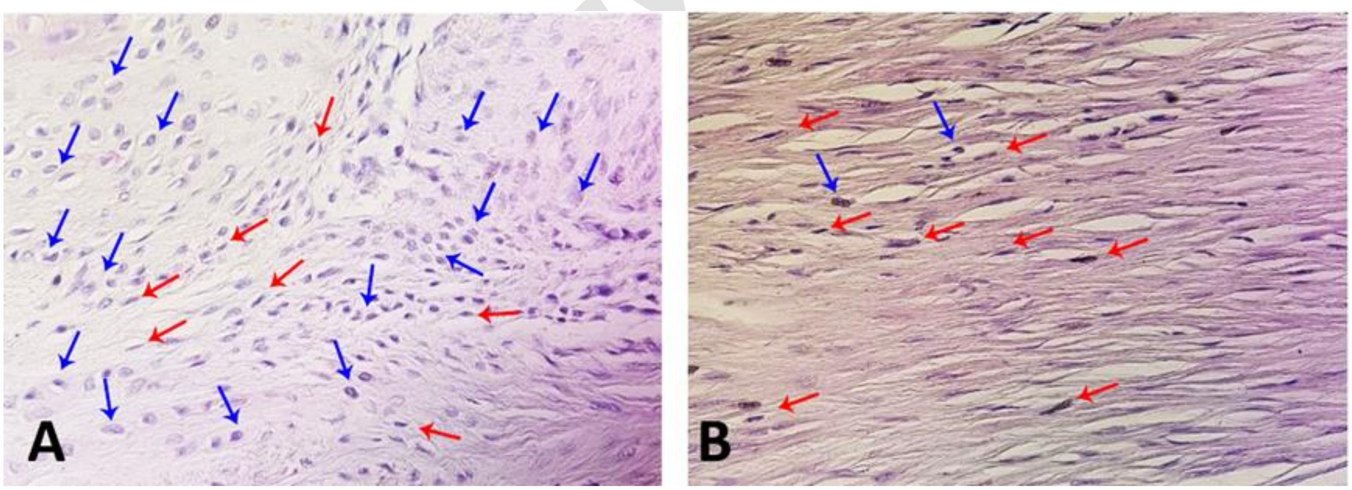

Figure 4. In the control group (A), abundant tenoblasts with large and oval nuclei (blue arrows) were observed among the haphazardly oriented collagen fibers, while in the treatment group (B) fewer tenoblast (red arrows) and mostly mature fibroblast (tenocytes; red arrows) with elongated and hyperchromatic nuclei, were observed in line with collagen fibers. Parallel orientation of the cells indicate improved remodeling of collagen fibers (Hematoxylin and eosin, 400×).

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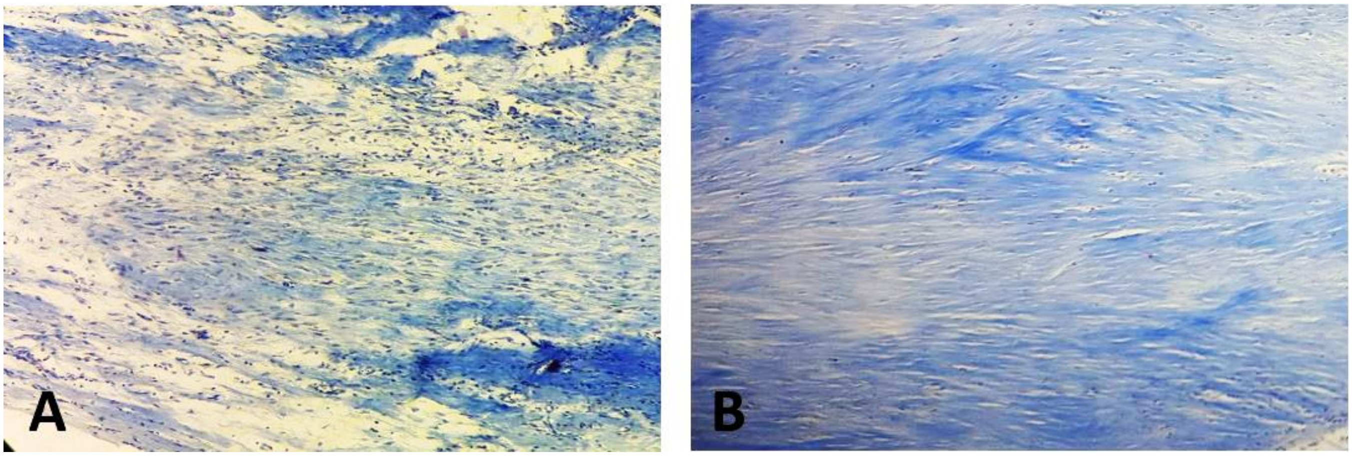

Figure 5. Masson's Trichrome stain showed dense collagen fibers deposition in treatment group (B) compared to control group (A) showing scattered fibers in random orientation (100×).

Table 2. Mechanical properties of experimental rat model of Achilles tendon injury.

Groups	Ultimate load (N)	Yield load (N)	Ultimate stress (MPa)	Energy absorption (J)	Strain (%)	Stiffness (MPa/mm)
Control	4.15 ± 1.10	3.50 ± 0.90	0.55 ± 0.15	5.66 ± 2.25	21.35 ± 5.15	4.14 ± 0.86
Treatment	9.03 ± 0.12*	8.22 ± 0.15*	2.40 ± 1.05*	20.15 ± 3.30*	13.15 ± 2.36	8.15 ± 3.19

Asterisk (*) indicates significant differences between groups ($p<0.05$).

4. Discussion

It is believed that inflammation can negatively affect the healing process.[16] Although inflammation is essential to begin the repair process by recruiting inflammatory cells to debride the necrotic tissue, previous studies showed that inflammatory cytokines impair wound repair by reducing collagen deposition, vascularization and finally cause decrease in mechanical properties of the repairs.[17,18] Therefore, to increase the quality of the repairs it is crucial to decrease the inflammation in the early stage of wound healing.[16]

NSAIDS and steroids are effective in treating tendinitis to control pain and prevent the occurrence of inflammatory signals that cause tissue degradation.[19-21] However, they are associated with undesired adverse effects such as headache, gastrointestinal ulcers, renal toxicities, vomiting, diarrhea, constipation, drowsiness and fatigue.[22-24] Therefore, there is a serious need for new alternatives with fewer side effects.

In the present study, curcumin, an herbal extract, with powerful anti-inflammatory properties was used in an experimentally induced rat model of Achilles tendon injury.

There are several studies revealing anti-inflammatory properties of curcumin,[25-28] and it has been used as an effective alternative to NSAID therapy for inflammatory responses such as arthritis.[29-30]

Normally, tendon inflammatory phase lasts for two weeks and gradually number of inflammatory cells subside,[31-32] however, in the presence of suture material it usually persists until the suture remains in the tissue.[33] According to Greenberg and Clark, this excessive inflammatory response will interfere with the proliferative phase of healing, therefore, due to the scar formation the tensile strength of the wound repair will decrease.[33] In the present study, although non absorbable suture material was used for tenorrhaphy, significant decrease in inflammatory cells was observed in curcumin-treated group by histopathology. This was in accordance with Kim *et al*. who reported that curcumin decreased inflammation and prevented collagen matrix disruption in rat Achilles tendon.

However, in control group remarkable inflammatory cells infiltration was observed at six weeks post-surgery. This chronic inflammation causes persistent degradation of extracellular matrix including collagen fibers. The main structural component of tendon are the collagen fibers which are responsible for its mechanical strength, therefore, theoretically the repairs are expected to show lower mechanical properties. The mechanical testing in the present study, revealed that curcumin-treated tendons withstand higher tensile loads compared to controls. Significant increase in ultimate and yield loads, stress and energy absorption capacity indicated that curcumin administration resulted in more collagen deposition and remodelling. Although not significant, but improved

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stiffness and strain in treatment group also reflect increased cross link of collagen fibers by curcumin which normally it takes several months to take place.[34,35]

On the other hand, histopathology revealed significant decrease in number of mature fibroblasts and neo-vessels within compact and longitudinally arranged collagen fibers in treatment group. It seems curcumin accelerated tendon repair to a shorter period of time (i.e., six weeks), because these above mentioned characteristics are similar to the histopathological manifestations of tendon remodelling phase which is believed to start after approximately ten weeks.[1]

Similarly, Dai *et al*. reported that curcumin administration resulted in formation of thick, dense and well-aligned collagen bundles in a dermal wound healing model of rats.[36] Reportedly, increase in collagen content, earlier maturation of collagen fibers along with significant increase in tensile strength were observed by curcumin on skin wounds in rats.[12]

In another study, oral administration of curcumin for 14 days also resulted in higher expression of collagen type I and III and increased concentration of hydroxyproline in rat tendon, as reported by Jiang *et al*.[3] They also showed decreased tissue malondialdehyde levels and elevated manganese-dependent superoxide dismutase activity in curcumin treated repairs which reveals scavenging oxygen-derived free radicals. It is believed that antioxidant therapy has beneficial effects on tendon healing.[3]

The infiltration of inflammatory cells into the repair site of tenotomy is considered as the main factor to produce scar tissue and adhesion between neotendon and surrounding tissues.[37]

The adhesion formation inhibits the gliding function of tendon and therefore, limits the range of motion of affected limb.[38] According to gross examination of repairs, lower adhesion formation was noticed in curcumin treated group. The authors concluded that it is not only due to anti adhesive and fibrinolytic activity properties of curcumin,[39-41] but also its analgesic and anti-inflammatory effects[42-43] allowed the rats to recover earlier form the post-operative pain and use their limbs, therefore it diminished the adhesion.

It is believed that early mobilization encourages intrinsic mechanism of tendon healing and diminishes the formation of adhesions.[44]

According to Tran *et al*. early mobilization increases the tensile strength of repair site.[45] Although mechanical evaluation of repairs has been referred the gold standard to assess the effectiveness of any treatment modality on tendon healing,[46,47] this method is not applicable for *in vivo* measurements. Therefore, Achilles functional index seems to be more practical and useful approach in this regard. It is known as the most definitive indicator of Achilles tendon function recovery after tenotomy.[48,49] In the present study, AFI was progressively improved in the treatment group week by week while the gait disturbance was almost apparent in control rats until the end of study. Although the functional deficits were gradually resolved in both groups, the first significant difference in treatment group was observed at the third week three versus fifth week for control group.

The result of the present study, taken together, indicate that oral curcumin could ameliorate tendon healing by reducing inflammation, accelerating proliferation and remodelling phases, and attenuating adhesion formation and finally resulting early ambulation of rats after Achilles tenotomy and suture repair. We conclude that short-term oral administration of curcumin could be considered as a beneficial therapeutic agent in the management of tendon injuries.

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Conflict of interest

The authors report no conflict of interest.

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چکیده

اثرات تجویز خوراکی کوتاه مدت کورکومین بر التیام زردپی آشیل رت

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هدف– به دلیل خون‌رسانی ضعیف و پایین بودن میزان متابولیسم زردپی، التیام آن همیشه ازنظر ساختار بافتی و خصوصیات عملکردی ضعیف تراز سطح طبیعی می‌باشد. کورکومین واجد خواص ضدالتهابی، آنتی اکسیدانتی و التیام بخشی می‌باشد. هدف این مطالعه، بررسی تأثیر تجویز کورکومین بر التیام جراحت تجربی زردپی آشیل رت با ارزیابی‌های هیستوپاتولوژی، بیومکانیکی و عملکردی بود.

طرح مطالعه– مطالعه تجربی.

حیوانات– بیست‌وچهار رت نر نژاد اسپراگ داولی.

روش کار– بیست‌وچهار رت نر به‌صورت تصادفی به دو گروه شاهد و درمان تقسیم شدند. پس از آماده‌سازی آسپتیک، برش عرضی کامل در بخش میانی زردپی آشیل راست ایجاد و به دنبال آن با الگوی کسلر تغییریافته بخیه شد. نرمال سالین و کورکومین (۱۰۰ میلی‌گرم بر کیلوگرم) به‌صورت خوراکی به مدت هفت روز به ترتیب در گروه‌های شاهد و درمان تجویز شد. شش هفته بعد نمونه‌برداری انجام شد.

نتایج– چسبندگی کمتری در اطراف زردپی در گروه درمان مشاهده شد. بر اساس هیستوپاتولوژی در گروه درمان افزایش در تراکم و آرایش منظم رشته‌های کلاژن، کاهش تعداد فیبروبلاست‌ها و سلول‌های التهابی و رگ زایی کمتر در مقایسه با گروه شاهد مشاهده شد که نشان‌دهنده بلوغ زودرس بافت جوانه‌ای تحت تأثیر کورکومین می‌باشد. ارزیابی بیومکانیکی افزایش معنی‌دار در میزان حداکثر نیرو، نیرو در نقطه تسلیم و انرژی جذب‌شده در گروه درمان را نشان داد. بعلاوه، بر اساس آنالیز رد پای رت‌ها، بهبود عملکردی زردپی مشاهده شد.

نتیجه‌گیری و کاربرد بالینی– مطالعه حاضر نشان داد که تجویز کوتاه‌مدت کورکومین به‌صورت خوراکی منجر به بهبود ساختار بافتی، خصوصیات بیومکانیکی و عملکردی زردپی آشیل در رت‌ها شد.

واژه‌های کلیدی– زردپی آشیل، بیومکانیکی، کورکومین، شاخص عملکردی، هیستوپاتولوژی.

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