Oral administration of curcumin (Curcuma longa) can attenuate the neutrophil inflammatory response in zymosan-induced arthritis in rats[1]

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ABSTRACT

PURPOSE: To evaluate the effect of curcumin in the acute phase of zymosan-induced arthritis.

METHODS: Twenty-eight male rats were subjected to intra-articular infiltration of zymosan of both knees and, in four the infiltration was made with saline. The animals were divided into five groups second received every six hours by gavage: corn oil by (positive and negative control); curcumin (100 mg/kg); prednisone 1 mg/kg/day; prednisone 8 mg/kg. All animals were sacrificed after six, 12, 24 and 48 hours of the infiltration. The knees were removed for evaluation of neutrophil infiltration. The number of neutrophils was counted by computer-assisted analysis of the images. The neutrophil infiltrate was stratified into four grades: 0 = normal; + = mild; ++/+++ = moderate; > ++++ = severe. The results were compared using the Mann-Whitney test and the variance by Kruskal-Wallis test adopting a significance level of 5% ($p<0.05$).

RESULTS: Curcumin reduces inflammatory activity in the first six hours after zymosan-induced arthritis when compared to saline ($p<0.01$). This was also observed in animals subjected to administration of prednisone (1 mg/kg) and those treated with prednisone (8 mg/kg). Curcumin was more effective than lower doses of prednisone in the first six hours after induction of the arthritis. After 12, 24 and 48 hours, curcumin does not have the same anti-inflammatory effects when compared to prednisone. After 48 hours, prednisone is more effective than curcumin in reducing the inflammatory infiltrate regardless of the dose of prednisone used.

CONCLUSION: Oral administration of curcumin reduces inflammation in the first six hours after experimentally zymosan-induced arthritis.

Key words: Arthritis, Experimental. Zymosan. Curcumin. Prednisone. Neutrophil Infiltration. Numerical Analysis, Computer-Assisted. Rats.

Introduction

Arthritis is a degenerative joint disease with a high prevalence and is a major cause of disability worldwide[1]. The continuous inflammatory process leads to progressive destruction of the cartilage, bone changes and chronic inflammation of the synovial membranes. The intense and continuous pain in the involved joints limits movements and results in the patient becoming depressed and isolated from his/her social life[2,3]. In addition to interfering with the quality of life, arthritis has a substantial impact on treatment and medical care costs[4].

Arthritis can affect any joint. However, in descending order, the knees are the most commonly affected joints, followed by the hips, hands, spine, wrists and ankles[3]. It is estimated that 35% of individuals over 30 years of age already show clinical and radiological signs of arthritis in the knees and that 85% of patients over 70 years of age have radiographic changes in their knee joints that allow the diagnosis of disease[1,3]. Although the etiology of arthritis is still uncertain, some risk factors have been related to its pathogenesis, including age, endocrine and metabolic disorders, ethnic, genetic and mechanical trauma[1].

Symptoms in patients with arthritis are related to joint wear, synovitis of repetition, degeneration of ligaments, joint capsule changes, osteoporosis, presence of joint effusion, and most likely the formation of crystal deposits (apatite) in the synovial membrane. Pain is the primary and dominant symptom in patients with arthritis of any kind. It features variable intensity according to the phase of the disease and may be cyclic or constant, and it is worse with joint movement and improves with rest. In mild forms, the pain appears only after application of pressure on the involved joint, and it improves with rest and analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs). With the progression of the frame, pain becomes more intense, with patients requiring higher doses of anti-inflammatory medications and having shorter pain-free intervals. In severe forms, pain arises even at rest, which makes any attempt of motion impossible; therefore, the patient needs to use stronger analgesics, including opioids and glucocorticoids (GC). Patients are frequently also treated with GC by mouth or by joint infiltration as well as with immunosuppressive drugs and more recently monoclonal anti-TNF-α. With the progressive degeneration of articular cartilage, inflammation by continuous stiffness is of variable length, resulting in limitation of motion and crepitus of the joint during flexion and extension.

Studies in experimental models of arthritis have shown that neutrophils are the first cells to migrate into the joint[5]. The activated neutrophils promote phagocytosis of immune complexes formed in the early stages, releasing reactive oxygen species (ROS) and thus leading to an oxidative stress on the articular cartilage and eicosanoids that increase the production of proinflammatory cytokines[5]. The inflammatory response causes an increase in blood flow and local transudation of histamine and serotonin, thereby increasing the neutrophil infiltration, with consequent overproduction of ROS. Studies have shown that in the pathogenesis of arthritis, damage to the cartilage is related to oxidative stress caused by the excessive formation of ROS, as well as by blocking or reducing the signaling pathways of antioxidant systems[6,7].

To relieve limiting painful symptoms, most patients use anti-inflammatory and analgesic medications in a continuous manner. For ease of acquisition and the concomitant analgesic, anti-inflammatory hormonal and non-steroidal drugs are commonly consumed. Chronic use of these substances, often without medical supervision, at a high dosage for long periods results in serious adverse effects on the digestive, renal, cardiac and hematologic systems. Finding natural substances with potential antioxidant effects that also have anti-inflammatory and analgesic effects and low rates of side effects is an old aspiration. New substances are constantly being tested, showing activity against arthritis both *in vitro* and *in vivo*.

A natural substance that has shown amazing effects for the treatment of osteoarthritis is curcumin, the active ingredient extracted from the root of *Curcuma longa* (Indian curry), which was already used by Ayurvedic medicine[8]. Among the many potential uses of the curcumin, its intense antioxidant activity stands out[9,10]. When considering that there is a significant formation of ROS by the synovium in patients with arthritis, it is possible that curcumin will be useful in treating this disease[11]. It is possible that the antioxidant effects of curcumin can minimize oxidative damage to the articular cartilage and improve the symptoms of the disease. However, to the best of our knowledge, the anti-inflammatory effects of curcumin have not been tested in experimental models of zymosan-induced arthritis[12-14]. Thus, the aim of this study was to determine whether oral administration of curcumin enhances the acute inflammatory response in experimental arthritis.

Methods

This study was approved in accordance with Federal Law No. 11.794 (10/08/2008) and the Ethics Committee in Animal Research of Sao Francisco University receiving the certificate No. 003.06.11 (09/ 22/2011).

Forty male SPF Wistar rats (300-350g) were obtained from the central vivarium of the Sao Francisco University School of Medicine. The rats were maintained under 12-hour light/dark cycles and fed a standard rodent chow diet. The animals were deprived of food, but not water, for 12 hours prior to the surgical procedure.

Arthritis induction

The experiment was started at 6 o'clock in the morning. The animals were initially weighed, and the induction of arthritis was always performed under general anesthesia by intraperitoneal administration of 0.1 ml/100 g of a 1:1 (v/v) solution of ketamine (50 mg/ml) and xylazine (20 mg/ml). The induction of the arthritis was performed on 24 animals of the experimental group and four of the positive control group by infiltration of 0.05 mL zymosan (1 mg/50 μL) in both knee joints using disposable insulin syringes. Four animals of the negative control group received the same intra-articular volume of saline.

Experimental groups

The animals were divided into the following five groups: A) Positive control: after the induction of arthritis, the animals received gastric gavage with corn oil every six hours for 48 hours (n=4); B) Negative control: the rats received intra-articular infiltration with saline in both knees and gastric gavage with corn oil every six hours for 48 hours (n=4); C) Curcumin: after the induction of arthritis, the animals received gastric gavage every six hours for 48 hours with curcumin (Sigma-Aldrich Ltd., USA) at dose 100 mg/kg (n=8); D) after the induction of arthritis, the rats received gastric gavage every six hours for 48 hours with prednisone at dose of 1 mg/kg/day (n=8); E) after the induction of the arthritis, the animals received gastric gavage every six hours for 48 hours with prednisone at dose of 8 mg/kg/day (n=8). The animals in all experimental groups were sacrificed after six, 12, 24 and 48 hours.

After sacrifice, tissue samples containing the cartilage and synovial of both knees were removed. Fragments prepared for histological analysis were immersed in 10% neutral buffered formalin (Sigma, St. Louis, MO, USA) for 24 h, dehydrated in increasing ethanol concentrations, and embedded in paraffin. Thereafter, 5-μm sections of tissue were cut using a rotary microtome (Leica Biosystems, Nussloch, Germany), mounted on glass slides, cleared, hydrated and stained with hematoxylin-eosin (HE) for histological evaluation. Slide analysis was performed by a pathologist experienced in arthritis who was unaware of the source material and the objectives of the study using an optical microscope (Eclipse DS-50, Nikon Inc., Osaka, Japan). Photomicrographs were taken with a digital video-capture camera (DS-Fi-50; Nikon Inc., Osaka, Japan) coupled to the microscope body. The number of neutrophils per field was measured by computer-assisted image analysis system (NIS-Elements; Nikon Inc., Osaka, Japan), evaluating the image of three random fields in each histological slide. The final value adopted for each slide was represented by the median of the values found in the evaluation of the three selected fields.

The intensity of the inflammatory infiltrate was graded in crosses (from - to 6+) according to the number of neutrophils founded in each histological fields. The final value adopted for each animal was the average found after analysis of three distinct histological fields and represents the inflammatory grade. According to the points obtained in the inflammatory grade, graduation was stratified as absent (0), mild (1 and 2), moderate (3 and 4) and severe (5 and 6), to what is called the degree of inflammation (Table 1).

TABLE 1 - Grading scale of degree of the inflammation.

Degree of inflammation	Score	Histological characteristics
Absent	0	normal
Mild	1-2	Mild intensity
Moderate	3-4	Moderate intensity
Severe	5-6	Severe intensity

The statistical analysis of the obtained results was performed using a significance level of 5% ($p<0.05$). The data obtained from the analyzed colon segment in each experimental group were expressed as the mean values and the respective standard error using SPSS statistical software version 13.0 (SPSS Inc., Chicago, USA) for Windows. Significant results are marked with a simple asterisk when $p<0.05$ and with a double asterisk when $p<0.01$. The Mann-Whitney test was used to compare inflammation scores between the control and experimental animal groups. The Kruskal-Wallis test was used to analyze the variance in the degree of inflammation between the different groups.

Results

Figure 1A shows the synovial membrane and articular cartilage removed from a normal animal's knee in the negative control group (not subjected to infiltration with zymosan). Figure 1B shows the articular cartilage and the synovia of a knee removed from an animal in the control positive group after six hours of gastric gavage with corn oil.

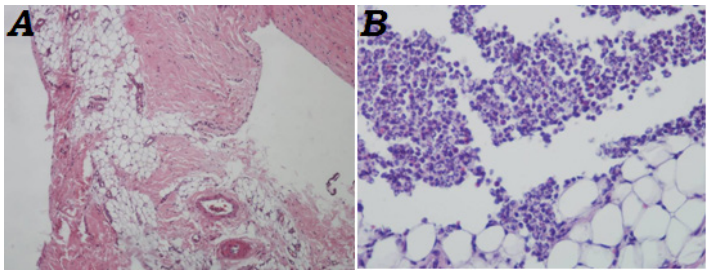

FIGURE 1 - A: Synovial membrane and articular cartilage from animal's knee after six hours of negative control group showing without neutrophil infiltration (HE x100). **B:** Synovial membrane and articular cartilage from animal's knee after six hours of positive control group showing severe neutrophil infiltrate (HE x100).

Figure 2A shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with curcumin (100 mg/kg) after six hours of articular-induced arthritis with zymosan. Figure 2B shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with curcumin (100 mg/kg) after 48 hours of articular-induced arthritis with zymosan.

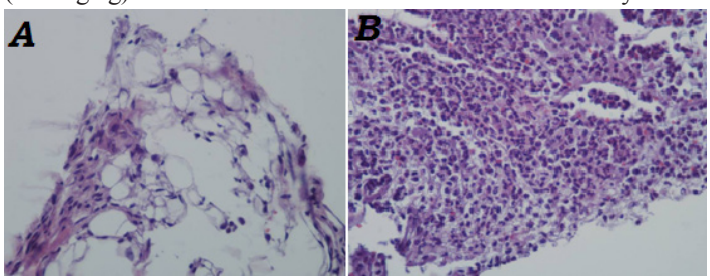

FIGURE 2 - A: Synovial membrane and articular cartilage from animal's knee after six hours of curcumin (100 mg/kg) oral gavage showing mild neutrophil infiltration (HE x100). **B:** Synovial membrane and articular cartilage from animal's knee after 48 hours of curcumin (100 mg/kg) oral gavage showing severe neutrophil infiltration (HE x100).

Figures 3A shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with prednisone (1 mg/kg) after six hours of induction of arthritis with zymosan. Figures 3B shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with prednisone (1 mg/kg) after 48 hours of articular-induced arthritis with zymosan.

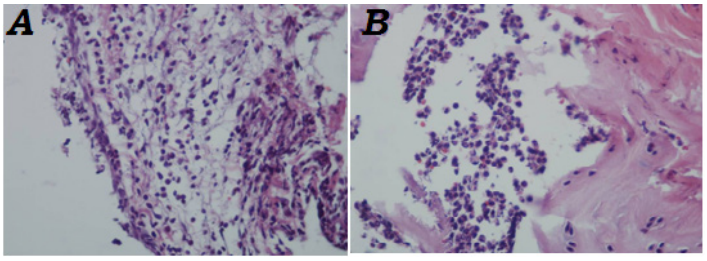

FIGURE 3 - A: Synovial membrane and articular cartilage from animal's knee after six hours of prednisone (1 mg/kg) oral gavage showing moderate neutrophil infiltration (HE x100). **B:** Synovial membrane and articular cartilage from animal's knee after 48 hours of prednisone (1 mg/kg) oral gavage showing moderate neutrophil infiltration (HE x100).

Figure 4A shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with prednisone (8 mg/kg) after six hours of induction of arthritis with zymosan. Figure 4B shows the articular cartilage and synovial membrane removed from an animal in the experimental group subjected to gastric gavage with prednisone (8 mg/kg) after 48 hours of articular-induced arthritis with zymosan.

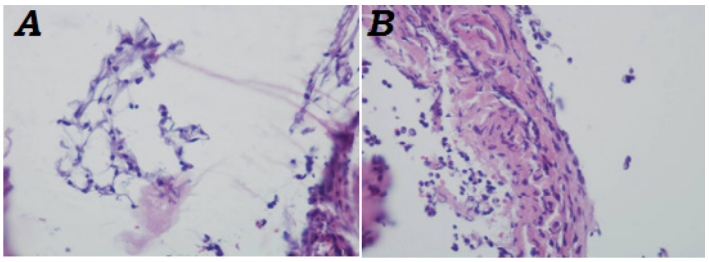

FIGURE 4 - A: Synovial membrane and articular cartilage from animal's knee after six hours of prednisone (8 mg/kg) oral gavage showing mild neutrophil infiltration (HE x100). **B:** Synovial membrane and articular cartilage from animal's knee after 48 hours of curcumin (100 mg/kg) oral gavage showing moderate neutrophil infiltration (HE x100).

Table 2 shows the mean values with their respective standard errors and the inflammatory scores at six, 12, 24 and 48 hours after gavage with corn oil, curcumin (100 mg/kg), and the different concentrations of prednisone (1 mg/kg, 8 mg/kg).

TABLE 2 - Degree of inflammation score after intervention with corn oil, curcumin, prednisone (1 mg/kg) and prednisone (8 mg/kg) in the knee arthritis induced by zymosan.

	Mean ± Standard Error			
Hours	**Corn oil**	**Curcumin**	**Prednisone (1 mg/kg)**	**Prednisone (8 mg/kg)**
6	5.75±0.25	2.33±0.42** †	4.33±0.42*	2.16±0.16††
12	5.75±0.25	5.75±0.25	4.00±1.20	4.75±0.47
24	5.75±0.25	5.75±0.25	5.50±0.28	5.50±0.28
48	5.75±0.25	5.75±0.25	3.50±1.40	3.50±1.40

mg/kg, milligrams/kilograms. * = $p<0.05$ (control × prednisone 1 mg/kg); ** = $p<0.01$ (control × curcumin and control × prednisone 8 mg/kg), † = $p<0.05$ (curcumin × prednisone 1 mg / kg); †† = $p<0.01$ (prednisone 1 mg / kg × prednisone 8 mg/kg). Mann-Whitney test.

Table 3 shows the variations in the inflammatory scores in animals of the positive control and experimental groups subjected to gastric gavage with corn oil, curcumin (100 mg/kg), and different concentrations of prednisone (1 mg/kg, 8 mg/kg) at different time points during the experiment.

TABLE 3 - Degree of inflammation score after intervention with corn oil, curcumin, and different concentrations of prednisone (1 mg/kg, 8 mg/kg) in knee arthritis induced by zymosan.

	Hours			
Hours	**6**	**12**	**24**	**48**
Corn oil	5.75±0.25	5.75±0.25	5.75±0.25	5.75±0.25
Curcumin	2.33±0.42**	5.25±0.25	5.75±0.25	5.75±0.25
Prednisone (1 mg/kg/day)	4.33±0.42	4.00±1.20	5.50±0.28	3.50±1.40*
Prednisone (8 mg/kg/day)	2.16±0.16**	4.75±0.47	5.50±0.28	3.50±1.40

mg/kg, milligrams/kilograms. Kruskal-Wallis test. * = $p<0.05$ (48 hours × 6, 12 and 24 hours); ** = $p<0.01$ (6 hours × 12, 24 and 48 hours).

Discussion

The main objective of the treatment of different forms of arthritis is to reduce inflammation within the joints[15]. There are several drugs that meet that goal, and among them, substances that interrupt the inflammatory cascade deserve a prominent place. For decades, the use of substances with anti-inflammatory action has been the main treatment option. The anti-inflammatory medications can be divided into the following two major groups: steroids and non-steroids substances.

Different types of GC mainly represent the steroids class. GC are hormones produced and secreted by the cortical region of the adrenal glands and are involved in various physiological functions and adaptation to stress[15]. Cortisol or hydrocortisone is the main circulating GC produced by humans, and its synthesis is regulated by the pituitary hormone adrenocorticotropic hormone (ACTH), which is released in response to stimulation by a neuropeptide called corticotrophin-releasing factor produced in the hypothalamus. Cortisol and its synthetic analogues are well absorbed from the gastrointestinal tract, and its intra-articular use is often performed by rheumatologists and orthopedists when other systemic actions of these drugs are unwanted. Continued use of GC is associated with various side effects, mainly represented by the development of peptic ulcers associated with gastrointestinal bleeding, congestive heart failure, cardiac edema in the lower limbs, osteoporosis, immune suppression and Cushing's syndrome.

Anti-inflammatory non-steroidal (AINS) medications are substances that block cyclooxygenase, thereby preventing the synthesis of eicosanoids by the metabolic pathway of the arachidonic acid cascade[15]. Despite being universally effective and used in the form of mild and moderate arthritis, the use of AINS is limited due to the high incidence of side effects such as digestive disorders (acute gastric mucosal lesions, gastrointestinal bleeding and peptic ulcer), severe anaphylactic reactions, kidney failure, abnormal platelet aggregation, bleeding diathesis and myocardial infarction.

With the aim of finding natural substances that exhibit anti-inflammatory activity in the treatment of arthritis and that exhibit minimal side effects, the efficacies of a number of natural substances are being increasingly tested in experimental models of arthritis[16,17]. Among these substances, curcumin, derived from the root of the plant *Curcuma longa*, which is rich in diferuloylmethane, has been one of the most promising natural active ingredients[17-19]. Its use for the treatment of various inflammatory diseases, including arthritis, has already been described for thousands of years by Ayurvedic medicine and traditional Chinese medicine[11]. The active ingredient was identified more than two centuries ago[20]. Curcumin has a potent immunomodulatory effect on the inflammatory response and may regulate the activation of T lymphocytes, B-lymphocytes, macrophages, neutrophils and dendritic cells. Recent studies have demonstrated that curcumin can also decrease the tissue expression of various pro-inflammatory cytokines, including TNF-α. IL-1, IL-2, IL-6, IL-12, and inactivating transcription factor NF-kB and, at low doses, stimulate antibody production[21-23]. These effects appear to confirm the potential of curcumin for the treatment of arthritis in human and experimental models of induced-arthritis[24-26].

Several experimental animal models have investigated the anti-inflammatory effects of curcumin. Initial studies evaluating its effect on carrageenan-induced edema in the fat pads of rats' paws confirmed that doses between 50 and 200 mg/kg were able to reduce tissue swelling. Experimental models in mice showed that 50% curcumin reduces local edema at a dose of 48 mg/kg, and a similar effect is observed with similar doses of cortisone and phenylbutazone. In addition, doses of 20-80 mg/kg reduced edema and inflammatory infiltrate in rats. The administration of curcumin also inhibits formaldehyde-induced arthritis in rats at a dose of 40 mg/kg, and this dose has negligible levels on peptic ulcer formation compared to phenylbutazone, and without any acute toxicity at doses of up to 2 g/kg[27]. A double-blind, randomized controlled trial compared the administration of curcumin with phenylbutazone. After administration of 1.200 mg/day of curcumin, the authors found improvement in joint swelling, morning stiffness and increased length of ambulation in patients with severe rheumatoid arthritis[28]. However, few studies have evaluated the effects of curcumin on acute inflammatory changes of articular cartilage in experimental arthritis[25,29-32]. Despite curcumin being used for centuries in Indian medicine as an anti-inflammatory substance, evaluation of its therapeutic effects in

experimental arthritis has been limited[33]. No studies have evaluated the effects of curcumin in an experimental arthritis model induced by zymosan or compared the effects of substance with prednisone, which makes this a pioneer study.

Some studies have evaluated the effects of curcumin alone or combination with other medications with anti-inflammatory effects. Taty Anna *et al*.[19], evaluated increasing doses of curcumin (30, 60 and 110 mg/mL/kg) associated with GC (betamethasone at a dose of 0.5 mg/mL/kg) applied orally daily for four weeks in an experimental model of collagen-induced arthritis. They showed that there was significant improvement in inflammatory score, radiographic score and erythrocyte sedimentation rate in animals treated with the higher doses. However, the main criticism is that the study cannot evaluate if the effect is due to curcumin alone or, more likely, the synergism between the two substances. Ramadan *et al*.[22], compared the anti-inflammatory and antioxidant roots of curcumin and ginger, both at a dose of 200 mg/kg, in an experimental model of adjuvant-induced arthritis. They found that both rhizomes were able to reduce the incidence and severity of arthritis by increasing and decreasing proinflammatory and anti-inflammatory cytokines, respectively, and activating the antioxidant defense systems. When compared to curcumin extract of ginger and indomethacin, they found that curcumin showed an anti-arthritic effect that was superior that of other substances, particularly when administered from the day of the induction of arthritis. They concluded that the results proved that the anti-inflammatory and antioxidant effects of curcumin are stronger than those of ginger and indomethacin. Its low cost and lack of adverse effects make the substance potentially effective in treating arthritis[22]. Phase 1 studies have shown that even high doses of curcumin (12 g/day), although safe, present with low availability in serum[16]. Because the extract of *Curcuma longa* is not water soluble, we chose to dissolve it in corn oil. Other authors have chosen to dissolve the plant extract in olive oil[19]. Therefore, it is possible that the vehicle used has also interfered with the absorption. A previous study demonstrated that the use of pure oral powder of a commercialized extract containing 94% of the three main curcuminoids is more potent in preventing arthritis than essential oil substances[31]. It is possible that the administration of curcumin parenteral could provide higher availability; however, this type of administration diminishes the advantage of using the substance over other drug options for the treatment of arthritis. The use of nanoparticles or curcumin involved in phospholipid complexes, or the synthesis of analogous substances, appears to have solved the problems of low bioavailability because they favor the absorption and metabolism delay[31].

In this this study when were counted the number of neutrophils per field in the control (positive and negative) and the experimental groups (curcumin, prednisone 1 mg/kg and 8 mg/kg) six hours after the induction of arthritis by zymosan was found lower number of neutrophils per field in negative control group than the positive control group ($p<0.01$). When comparing animals subjected to gastric gavage with curcumin and prednisone (1 mg/kg) with the positive controls, we found a significant reduction in the numbers of neutrophils per field ($p<0.01$). After 12 hours of the intervention with curcumin and the two doses of prednisone, we could not find a reduction in the number of neutrophils compared with the positive control group, but a significantly higher number was observed when compared with the negative control. After 48 hours of intervention, we confirmed that animals subjected to gastric gavage with 1 mg/kg of prednisone had a lower number of neutrophils counted per field than the positive control group ($p<0.01$). After 48 hours, the intervention of both substances did not reduce the number of neutrophils when compared with the positive control group. In other words, the results of this study shown that curcumin has early anti-inflammatory activity. It's reduces the inflammation in the joint within the first six hours after the induction of arthritis, showing similar therapeutic efficacy even at doses comparable to steroids immunosuppressive doses and exceeding the anti-inflammatory effects observed with GC. However, after 12 and 24 hours, the anti-inflammatory effects of curcumin become similar to those of prednisone at both doses and do not alter the degree of inflammation. These findings may be related to low plasma and tissue levels of curcumin due to the low absorption by the digestive tract, and rapid systemic metabolism and elimination[18]. It is possible that the use of drugs by the parenteral route, dissolved in lipid vehicles capable of intravenous administration, can enhance the activity of the substance during that period.

The results of this study suggest that curcumin may be a useful drug for treating the acute phase of arthritis; however, additional studies have to be performed to improve the effectiveness of the substance. Research comparing increasing concentrations of the drug through different routes of administration, and especially improving their bioavailability, are still required to enable the use of curcumin.

Conclusion

Oral administration of curcumin may be a useful strategy for treating the initial phase of zymosan-induced arthritis.

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