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Anti-inflammatory and antioxidant effects of turmeric extracts in rat adjuvant arthritis

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ABSTRACT

The aim of the study was to evaluate the antioxidant, immunomodulatory and anti-arthritic effects of turmeric extracts (Standard and CurQfen) on rat adjuvant arthritis. The impact of the treatment was investigated on pro- and antioxidant status, serum interleukins IL-17 and IL-1β, blood indices, joint swelling, and histological changes in the joints, liver and body weight. Both turmeric extracts improved blood indices, decreased the level of pro-inflammatory cytokines, and enhanced antioxidant level. Both extracts diminished swelling and normalized histological structure in soft periarticular tissues, synovial membrane and hyaline cartilage. No negative effect on the liver was observed. CurQfen was more effective than Standard extract. The strong antioxidative, anti-inflammatory and immunomodulatory effects of the turmeric extracts suggest their usefulness in the treatment of autoimmune arthritis as monotherapy or in combination with traditional anti-arthritic drugs.

Key words: turmeric extracts; antioxidant activity; adjuvant arthritis; rats

Introduction

Rheumatoid arthritis (RA) is a common and severe autoimmune disease with no effective treatment so far. Rat adjuvant arthritis (AA) is one of the RA experimental models characterized by autoimmune joint damage with synovial hyperplasia, increased angiogenesis, inflammatory cell infiltration and cartilage erosions. Therefore, AA is often used in the preclinical search for new anti-rheumatic drugs (ROY and GHOSH, 2013).

Natural herbal compounds in appropriate doses are non-harmful and non-toxic, therefore they are becoming increasingly important in conventional

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medicine, including treatment of chronic diseases (PIROTTA, 2010). Some plants alleviate the side effects of traditional chemical treatment, enhance the beneficial effect of drugs, or prevent recurrence of the disease. It has been shown that the turmeric plant has anti-inflammatory properties and can be used for treatment of arthritis (TATY ANNA et al., 2011; KERTIA et al., 2012; GUPTA et al., 2013). Turmeric (*Curcuma longa*) is rich in vitamins C, B1, B2, and B3, and micro and macro elements. It has strong antioxidant properties and eliminates free radicals produced by metabolic processes, inflammation and oxidative stress implicated in the pathogenesis of arthritis. Clinical and basic studies stress the detrimental role of reactive oxygen species (ROS) in chronic inflammation (FILIPPIN et al., 2008; MIRSHAFIEY and MOHSENZADEGAN, 2008). A pro-oxidant/antioxidant imbalance occurs in RA and AA due to the increase in damaging cellular reactions and crippled antioxidant defense systems (MINUZ et al., 2006).

The impaired antioxidant system affects the balance of pro-inflammatory/anti-inflammatory cytokines, and plays an essential role in the pathogenesis of RA (MATEEN et al., 2016). Pro-inflammatory cytokines, such as TNF-α and IL-1β, are considered to be the main pathogenic cytokines in RA (WAN et al., 2017; WU et al., 2018). They mediate the production of other cytokines, chemokines and degrading enzymes, reinforcing the progression of the disease (KAN et al., 2014; RAJAGOPAL et al., 2017). IL-17 is a pro-inflammatory cytokine similar to IL-1β and TNF-α, and also plays an important role in the pathogenesis of RA (CHABAUD et al., 2000; MIOSSEC, 2003).

The aim of this study was to investigate the effect of two different turmeric extracts on oxidative stress, inflammatory and immune response in rat adjuvant arthritis.

Materials and methods

Materials. Freund's Complete adjuvant (FCA) was purchased from Sigma Aldrich (Calbiochem, USA) and used to induce AA. Trichloroacetate, orthophosphoric, thiobarbituric, nitrogen, ascorbic acid, iron sulphate, ammonium molybdate, hydrogen peroxide, 10% neutral buffered formalin, hematoxylin and eosin, picrofuchsin and toluidine blue were obtained from Sigma-Aldrich Chemie and Fluka Chemie GmbH (Germany); Ketamidor 10% from Richer Pharma AG (Wels, Austria) and Sedaxylan from Eurovet Animal Health B.V. (Netherlands); tetrachloroauric acid and tannic acid from Carl Roth GmbH & Co (Germany); sodium citrate from Penta (Czech Republic). A commercial ELISA Abcam® kit for IL-17 test and a Thermo Scientific Rat IL-1β ELISA Kit for detection of IL-1β were used.

Animals. Twenty-one, sexually mature, male Wistar rats (10 weeks of age, body weight 180-220 g) were used for the experiment. The animals were housed in plastic cages and maintained under standard conditions, in the vivarium of The Department of Biomodels, State Research Institute Center for Innovative Medicine (Vilnius, Lithuania). They had free access to a standard pellet diet (JCS; Litagra Company Group, Lithuania) and drinking water. The use of animals in this study was in accordance with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. The experiment on rats was performed with the prior approval of the Lithuanian Laboratory Animal Use Ethics Committee, under the State Food and Veterinary Service (No. 0177).

Adjuvant arthritis, its evaluation and treatment. AA was induced by injecting 0.1 mL of FCA into the left hind paw. The appearance of arthritis was evaluated clinically and histologically post-mortem. Body weight and joint swelling changes were recorded 3 times a week. Two parameters were monitored to evaluate the pathological process in joints: joint swelling measured plethysmometrically (PVP1001; Kent Scientific Incorporation, USA) and the appearance of polyarthritis in other limbs (not injected with FCA). The effects of two dry turmeric extracts received from the pharmaceutical company Aksada: Standard (95% of curcuminoids) and CurQfen (Curcumin/Fenugreek Complex, containing 35% curcuminoids) were assessed continuously from the day AA was induced.

The rats were divided into 3 groups (7 animals in each): Group I was prophylactically treated with Standard extract (30 mg/kg), Group II - with CurQfen extract (30 mg/kg), and Group III was the control without turmeric treatment. The extracts were suspended in 1% starch gel and injected through the probe into the stomach 5 times a week in a volume of 1 mL. Each animal in the control AA group received 1 mL of starch gel as the vehicle. The duration of the experiment was 17 days.

At the end of experiment the animals were euthanized by decapitation under ketamidor-sedaxylan anesthesia. The overall status of the animals, organ weight and macroscopic changes were evaluated. Blood, liver and injected paws were collected for further investigation. Leukocyte count was determined using a Picoscale automatic blood counter (MEDICOR, Typ PS4, Hungary), and erythrocyte sedimentation rate (ESR) was estimated by the standard method. Blood samples were centrifuged at 800 x g for 10 min to obtain serum samples which were stored frozen at -20 °C until testing.

Pro-/antioxidant activity of blood serum. The concentration of malondialdehyde (MDA), catalase (CAT) activity and the total antioxidant activity (AOA) in the blood serum was investigated by the methods of GAVRILOV et al. (1987), KOROLIUK et al. (1988) and GALAKTIONOVA et al. (1998), respectively. All methods used are described in detail in our previously published study (AKRAMAS et al., 2015).

Histology. The samples from the injected paws and liver were fixed in 10% neutral formalin solution. After decalcification and paraffin embedding, sections of 5 micrometer thickness were stained with hematoxylin-eosin, picrofuchsin and toluidine blue for histopathological examination under a light microscope. Double blind histological assessment of changes in the tissues was performed using a 4-point score (0-3), where 0 indicated the absence of changes, 1 - minimal changes, 2 - moderate changes, 3 - severe changes.

Level of IL-17 and IL-1β in blood serum. The level of IL-17 was measured by enzyme-linked immunosorbent assay (ELISA), using a kit specific for rats (ab119536-IL-17 Rat ELISA Kit) according to the procedure recommended by the manufacturer's instructions (ELISA Abcam®, UK). IL-1β levels in the blood serum were measured using a Thermo Scientific Rat IL-1β ELISA Kit. Each sample was assayed in duplicate.

Statistics. Statistical analysis was done by one-way analysis of variance ANOVA using PRISM Software (GraphPad Software, San Diego, CA, USA) followed by the Student's t test. The non-parametric Mann-Whitney U test was used to evaluate histological changes. All data were expressed as the mean ± SEM, and considered to be statistically significant at $P<0.05$. The results of the tested groups were compared with the results of the control AA group.

Results

Clinical and hematological data. No macroscopic changes in the internal organs were found at the end of the experiment. The weight of the kidney and spleen was significantly lower by 12.4% ($P<0.05$) and 23.7% ($P<0.01$) respectively in the group of animals treated with CurQfen, indicating the positive effect of this extract (Table 1). Treatment with Standard turmeric extract only markedly decreased the spleen weight by 18.4% ($P<0.01$).

Both turmeric extracts significantly reduced joint swelling (Fig. 1), but CurQfen was more effective. At the end of the experiment, joint swelling was reduced by 53.6% ($P<0.0001$) in the CurQfen group, and by 41.3% ($P<0.001$) in the Standard extract group, so the CurQfen was more effective by 12.3%.

The analysis of blood parameters at the end of the experiment (Fig. 2) showed a statistically significant decrease in ESR in both treated groups ($P<0.0001$).

Leukocytosis was significantly reduced: the Standard extract decreased the leukocyte count by 42.1% ($P<0.001$) and CurQfen - by 48.6% ($P<0.001$).

Table 1. Body and organ weight in rats with AA, treated with turmeric extracts

Groups	Body weight (g)	Relative weight of organs (g/kg^{-1})			
		Liver	Kidneys	Spleen	Thymus
I AA + C. longa	233.28 ± 10.65	3.27 ± 0.09	0.80 ± 0.02	0.31 ± 0.01*	0.22 ± 0.02
II AA + CurQfen	238.71 ± 14.11	3.16 ± 0.09	0.78 ± 0.02*	0.29 ± 0.02*	0.27 ± 0.01
III AA control	223.12 ± 11.71	3.42 ± 0.15	0.89 ± 0.04	0.38 ± 0.02	0.24 ± 0.02

Adjuvant arthritis (AA) was induced by injection 0.1 mL of Freund's complete adjuvant (FCA) into the left hind paw. The test groups with AA were treated from the day AA was induced: Group I - Standard turmeric extract (*Curcuma longa*; 30 mg/kg), Group II - dry CurQfen (30 mg/kg), Group III - AA control without treatment. The preparations were suspended in 1% starch gel and injected through the probe into the stomach in a volume of 1 mL, five times a week. The control AA group received the same volume of starch gel. * The differences are significant in comparison with the control AA group.

Table 2. Histological liver changes in arthritic rats treated with turmeric extracts

Index		Groups		
		I AA + *C. longa*	II AA + CurQfen	III AA control
Alteration of parenchyma		0.57 ± 0.07	0.57 ± 0.07	0.64 ± 0.09
V. centralis hypervolemia		0.28 ± 0.10*	0.14 ± 0.09*	0.57 ± 0.07
Inflammatory infiltration in hepatic stroma	Lymphocytes	0.57 ± 0.07	0.21 ± 0.10*	0.71 ± 0.10
	Macrophages	0	0	0.07 ± 0.07
	General	0.57 ± 0.07	0.21 ± 0.10*	0.71 ± 0.10
	Penetration into the lobule	0.28 ± 0.15	0*	0.43 ± 0.17
Fibrosis		0.21 ± 0.10*	0.21 ± 0.15*	0.71 ± 0.10

C. longa (a standard turmeric extract - 95% of curcuminoids) - 30 mg/kg; dry CurQfen - 30 mg/kg. * The differences are significant in comparison with the control AA group.

Table 3. Histological changes in AA joints after treatment with turmeric extracts

Tissue	Index		Groups		
			I AA + C. longa	II AA + CurQfen	III AA control
Soft periarticular tissues	Leukocytes		0.83 ± 0.36	0.70 ± 0.12*	1.71 ± 0.39
	Edema		0.83 ± 0.10*	1.20 ± 0.25*	2.29 ± 0.10
	Angiomatosis		0.92 ± 0.15*	1.60 ± 0.19	2.00 ± 0.15
	Fibrosis		1.25 ± 0.21*	1.00 ± 0.22*	0
	γ-metachromasia		0.58 ± 0.20*	0.20 ± 0.12*	1.36 ± 0.18
Synovium	Proliferation		1.67 ± 0.17*	1.20 ± 0.12*	2.21 ± 0.15
	Edema		0.67 ± 0.10*	0.70 ± 0.12*	1.29 ± 0.18
	Inflammatory infiltration	Lymphocytes	1.33 ± 0.17	0.60 ± 0.29*	1.79 ± 0.15
		Leukocytes	0.50 ± 0.22*	0.10 ± 0.10*	1.43 ± 0.33
		General	1.50 ± 0.13*	0.60 ± 0.24*	2.00 ± 0.15
	Fibrosis		0.75 ± 0.21*	0.60 ± 0.37	0
Cartilage	Erosion		0.33 ± 0.17*	0.10 ± 0.10*	1.36 ± 0.28
	Pannus		0.50 ± 0.22*	0.20 ± 0.20*	1.43 ± 0.27
	Thinning of cartilage		0.17 ± 0.17*	0*	0.71 ± 0.18

Each parameter was scored on a 0 to 3 point scale, where 0 means the absence of changes, 1 - minimal changes, 2 - moderate changes, 3 - severe changes. * The differences are significant in comparison with the control AA group.

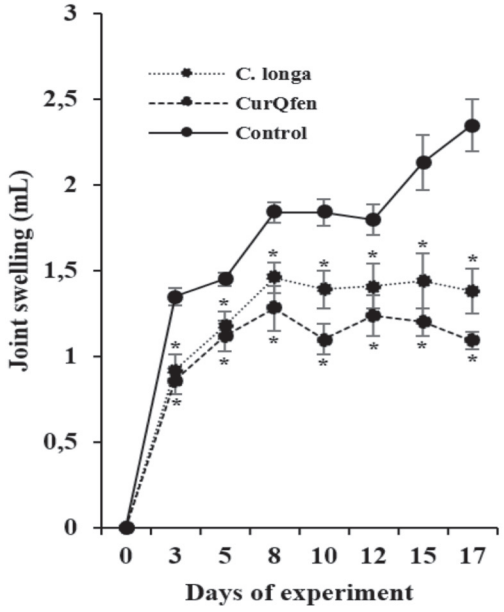

Fig. 1. Swelling of joints in rats with adjuvant arthritis (AA) treated with turmeric extracts. Standard turmeric extract from *Curcuma longa* (95% of curcuminoids; 30 mg/kg), and dry CurQfen extract (30 mg/kg).
* The differences are significant in comparison with the control AA group.

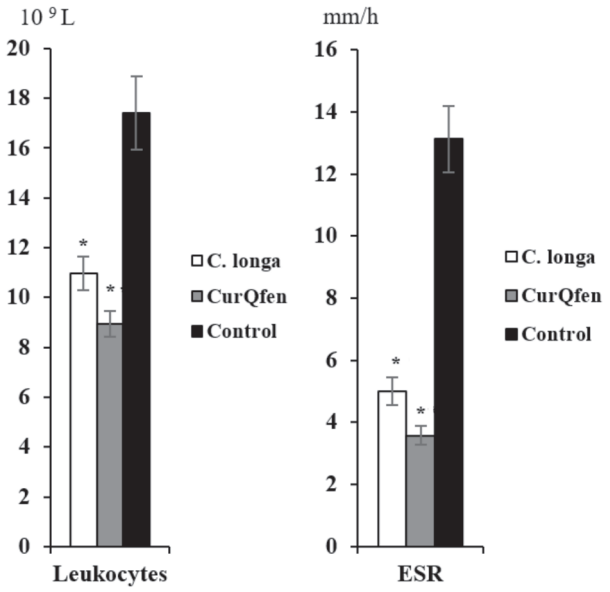

Fig. 2. Blood indices (leukocyte count and erythrocyte sedimentation rate) in rats with adjuvant arthritis (AA) treated with turmeric extracts. Standard turmeric extract from *Curcuma longa* (95% of curcuminoids; 30 mg/kg), and dry CurQfen extract (30 mg/kg). * The differences are significant in comparison with the control AA group.

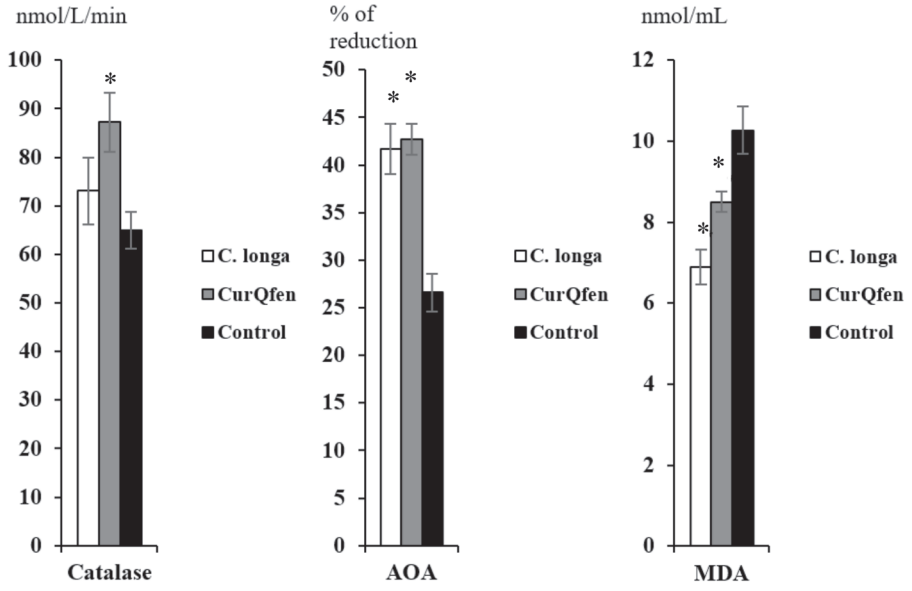

Fig. 3. Pro-/antioxidant activity (catalase, antioxidant activity - AOA, malondyaldehyde - MDA) in rats with adjuvant arthritis (AA) treated with turmeric extracts. Standard turmeric extract from *Curcuma longa* (95% of curcuminoids; 30 mg/kg), and dry CurQfen extract (30 mg/kg). * The differences are significant in comparison with the control AA group.

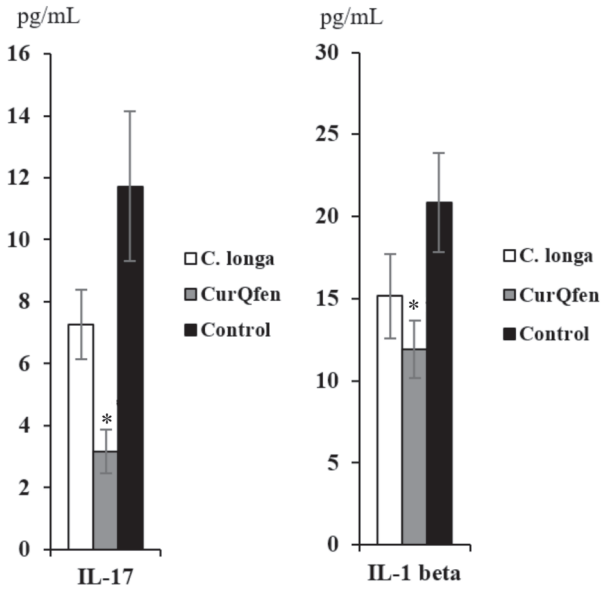

Fig. 4. Interleukin (IL-17 and IL-1β) levels in rats with adjuvant arthritis treated with turmeric extracts. Standard turmeric extract from *Curcuma longa* (95% of curcuminoids; 30 mg/kg), and dry CurQfen extract (30 mg/kg). * The differences are significant in comparison with the control AA group.

The effect of turmeric extracts on lipid peroxidation and antioxidant activity. The AA-induced serum lipid peroxidation defined by MDA (Fig. 3), decreased significantly by 32.9% (P<0.001) after treatment with the Standard extract, while the use of CurQfen lowered the MDA level by 17.2% (P<0.02). CAT activity in Group I and Group II increased by 12.6% and 34.5% (P<0.01), and the total antioxidant activity (AOA) - by 56.7% (P<0.001) and 60.4% (P<0.001) respectively, compared to the control AA group.

The effect of turmeric extracts on serum IL-17 and IL-1β levels. Changes in cytokine IL-17 and IL-1β levels in blood serum after treatment with the two turmeric extracts are shown in Fig. 4. Turmeric extracts diminished serum levels of IL-17 by 38.1% (Standard, P>0.05) and 72.9% (CurQfen, P<0.01). Only CurQfen had a significant impact compared to the control AA group.

Although serum levels of IL-1β in Groups I and II were lower than in the control AA group, a significant reduction in this cytokine was only detected in the group treated with CurQfen (42.8%, P<0.05). The treatment with Standard extract reduced the amount of IL-1β insignificantly (27.3%).

Histological changes in the liver. Changes in the liver after treatment of AA with the two turmeric extracts are presented in Table 2. Both extracts significantly reduced lobular *vena centralis* hypervolemia compared to the control AA group (Standard, P<0.05; CurQfen, P<0.01).

The lymphocytic infiltration of the hepatic stroma (P<0.01) and the general inflammatory response (P<0.01) were significantly lower after the treatment with CurQfen. No penetration of inflammatory cells into the hepatic stroma (P<0.05) was observed after the treatment. Both turmeric extracts (Standard - P<0.01; CurQfen - P<0.02) strongly inhibited fibrotic processes in the liver compared to the control AA group.

Histological findings in the joints. Histological changes in the joint tissues are presented in Table 3 and Fig. 5. CurQfen extract significantly reduced inflammatory infiltration with leukocytes in the soft periarticular tissues by 59% (P<0.01), as compared to the control AA group. This effect was not detected when using the Standard turmeric extract.

Both tested extracts significantly suppressed soft tissue edema: the Standard extract diminished it by 63.8% (P<0.0001) and the CurQfen extract - by 47.6% (P<0.002). A significant reduction in blood vessel proliferation was observed after using Standard turmeric extract (P<0.001). Meanwhile, fibrosis was stimulated after treatment with both extracts (P<0.001) compared with the control AA group, in which no signs of fibrosis were detected. Although both extracts inhibited γ-metachromasia, CurQfen showed a more pronounced effect (85.3% decrease compared to the controls, P<0.001) while Standard extract showed a smaller decrease (57.4%, P<0.001). Synovial proliferation was significantly inhibited by both extracts (Standard - 24.4%, P<0.05; CurQfen - 45.7%, P<0.001).

Statistically significant differences between the treated and the control AA groups were found in assessing synovial edema, with similar levels of inhibition (by 48% in Group I, P<0.02 and by 45.7% in Group II, P<0.02). Both extracts significantly reduced synovial inflammatory leukocytic infiltration (Standard extract - by 65%, P<0.05; CurQfen - by 93%, P<0.01). CurQfen also significantly decreased lymphocytic infiltration of the synovial membrane by 66% (P<0.01), while

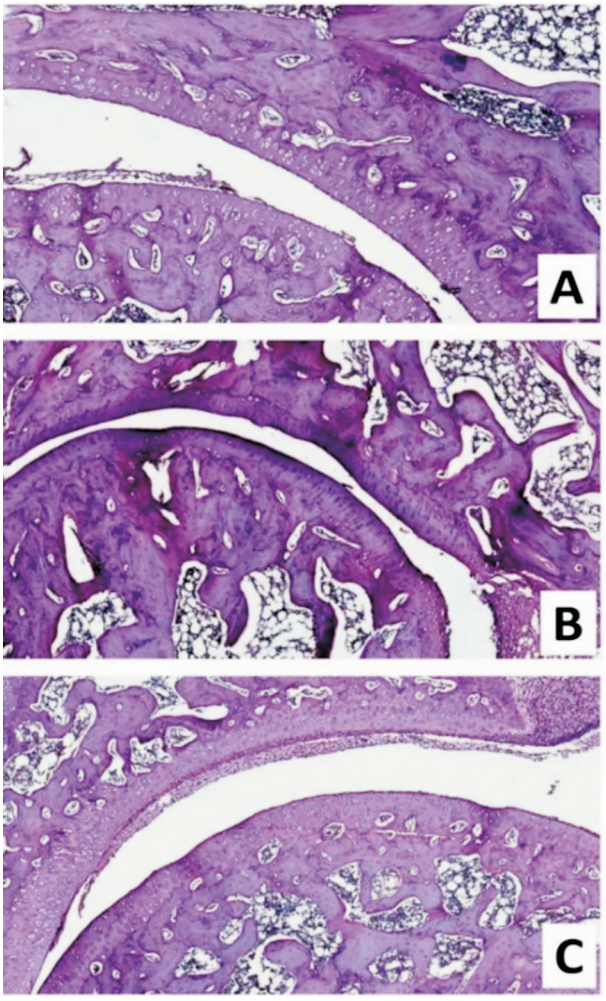

Fig. 5. Histological image of joint cartilage in rats with adjuvant arthritis after treatment with turmeric extracts. A - Standard turmeric extract from *Curcuma longa* (95% of curcuminoids; 30 mg/kg): prevailing smooth surface of hyaline cartilage, small remnants of pannus. B - dry CurQfen (30 mg/kg): no pannus, smooth articular surface without erosion, consolidation of subchondral bone. C - AA control without treatment: continuous pannus, erosion of hyaline cartilage. H&E, ×100.

the Standard extract induced only a 25.7% lower infiltration (changes were near to significant; t = 2.03) compared with the control AA group. General inflammatory response was diminished by both extracts (Standard extract - by 25%, P<0.05; CurQfen - by 70%, P<0.001).

No fibrotic processes in the synovial membrane were observed in the control AA group, but were significantly enhanced after using the Standard turmeric extract (P<0.01), while treatment with CurQfen only increased fibrosis insignificantly.

The hyaline cartilage erosions were significantly reduced in the Standard and CurQfen groups, by 75.7% (P<0.02) and 92.6% (P<0.002), respectively. Both extracts significantly inhibited pannus formation (Table 3; Fig. 5), but a more pronounced effect was detected from using CurQfen (86% inhibition vs. control; P<0.01) and a smaller effect - with Standard extract (65%, P<0.05). Only one rat in Group I showed cartilage thinning, which significantly differed from the control AA group (P<0.05). No signs of cartilage thinning were detected in the CurQfen group (P<0.002 compared with the control AA group).

Summarizing pathological changes in the joints, we conclude that the CurQfen extract showed a more positive effect on soft periarticular tissues than the Standard extract (inhibition of leukocyte infiltration and γ-metachromasia). CurQfen improved the structure of the synovium by diminishing synovial membrane proliferation, decreasing leukocyte infiltration, and by reducing cartilage erosions and pannus formation.

Discussion

In recent years, many researchers have been looking intensively for biologically active substances in various plants and trying to apply them for treatment of inflammatory processes, including RA (JIANG et al., 2010; GANESAN et al., 2016). Joint inflammation is also not rare in domestic animals. In veterinary practice, turmeric extracts are used in dogs, chickens, cows, mice, and calves (COMBLAIN et al., 2017; DANESHYAR et al., 2012; KARAMALAKOVA et al., 2019, WINKLER et al., 2015). In this study using rats with AA, we investigated the antioxidative, anti-inflammatory and immunomodulatory effects of two dry turmeric extracts produced by the pharmaceutical company Aksada. Since in our previous investigations performed with herbal preparations their effects were compared with the effect of diclofenac (AKRAMAS et al., 2015; AKRAMAS et al., 2017), in this study we only included a control group. Diclofenac showed the same or a slightly greater positive effect than

turmeric extracts. In order to decrease the number of animals used, the healthy control group was not included in this study. In our previous experiments we showed that all investigated indices in the tested groups significantly differed from the group of healthy rats (AKRAMAS et al., 2017). Both extracts were used in weight-calculated doses corresponding to human doses. CurQfen extract is better absorbed and reaches many times greater concentrations in plasma compared to Standard extract (KRISHNAKUMAR et al., 2015; KUMAR et al., 2016). Therefore, we believe that its effect is superior to the effect of Standard extract. Although both investigated extracts significantly reduced joint swelling, the CurQfen extract was 12.3% more effective than the Standard extract.

It is known that pro-inflammatory cytokines, such as IL-1β, IL-17, TNF-α, and IL-6, play a detrimental role in the inflammatory processes. TNF-α and IL-6, mainly produced by M1 macrophages, are considered to be major pro-inflammatory cytokines in the RA, and both are responsible for joint damage (MATEEN et al., 2016). IL-1β plays a significant role in the pathogenesis of arthritis (KUNCHA et al., 2013; WU et al., 2018; ABOREHAB et al., 2017). IL-17 enhances production of IL-1β, TNF-α and IL-6 in RA patients (SHI et al., 2015). Its concentration significantly increases in rats with AA, compared with healthy animals, as demonstrated in our previous study (AKRAMAS et al., 2017). In the present study both extracts improved the blood indices and reduced the amount of IL-17 and IL-1β, however only CurQfen significantly inhibited these interleukins, as compared with the control AA group.

No adverse animal behavior or clinical signs were observed in the rats treated with turmeric extracts. Histological examination showed less damage in the hepatic parenchyma and stroma in turmeric treated AA groups than in the control group.

A significantly higher leukocyte count and ESR were found in the control rats with AA than in the turmeric treated groups. Turmeric extracts improved blood parameters, reduced the level of pro-inflammatory cytokines, and showed a non-toxic effect.

Our study shows that CAT activity and AOA are lower in animals with AA. Reduced activity of antioxidant enzymes correlates with increased lipid peroxidation, measured by the amount of MDA. The MDA is a good index of lipid peroxidation products (HUANG et al., 2012). Our data showed that MDA levels were significantly lower in the turmeric treated groups. These results corresponded to other authors' findings, which showed that turmeric extracts could reduce inflammation, enhance antioxidant activity and eliminate the direct damaging effect of free radicals (TATY ANNA et al., 2011; NONOSE et al., 2014).

In summary, our data show that turmeric extracts significantly improve the clinical, biochemical, immunological and histological indices of the pathological process in rat AA. Turmeric extracts display anti-inflammatory effects, suppress oxidative stress and inhibit the pathological process in arthritic joints.

We conclude that these extracts, particularly CurQfen, can be useful in the treatment of human and animal rheumatic diseases, in addition to traditional drug therapy.

Since they enhance anti-inflammatory, antioxidative and immunosuppressive activity in experimental arthritis, they can serve as preventive or therapeutic agents for treatment of autoimmune diseases, whether as mono-therapy or in combination with other drugs, to alleviate the side effects of medication.

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SAŽETAK

Cilj ovoga istraživanja bio je procijeniti antioksidacijske, imunomodulacijske i antiartritične učinke ekstrakta kurkume (standardni i CurQfen) na štakore s adjuvantnim artritisom. Istražen je utjecaj ekstrakta kurkume na prooksidacijski i antioksidacijski status, serumske interleukine IL-17 i IL-1β, krvne pokazatelje, otekline zglobova i histološke promjene u zglobovima i jetri te na tjelesnu masu. Oba su ekstrakta kurkume dovela do poboljšanja krvnih pokazatelja, smanjila su razine proupalnih citokina i poboljšala antioksidacijski status. Također su oba ekstrakta kurkume smanjila otekline i normalizirala histološku strukturu u mekim periartikularnim tkivima, sinovijskoj membrani i zglobnoj hrskavici. Nije zapažen negativan učinak na jetru. CurQfen je bio učinkovitiji od standardnog ekstrakta. Jaki antioksidacijski, protuupalni i imunomodulacijski učinci ekstrakta kurkume pokazuju da on može biti koristan u liječenju autoimunosnog artritisa kao monoterapija ili u kombinaciji s tradicionalnim lijekovima za liječenje artritisa.

Ključne riječi: ekstrakti kurkume; antioksidacijska aktivnost; adjuvantni artritis; štakori