ORIGINAL ARTICLE

Effect of *Curcuma zedoaria* Rosc root extracts on behavioral and radiology changes in arthritic rats

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ABSTRACT

The present study was conducted to evaluate the effects of petroleum ether, chloroform, and methanol root extracts of *Curcuma zedoaria* Rosc (Family: Zingiberaceae) on behavioral and radiology aspects of Freund's Complete Adjuvant (FCA)-induced monoarthritis in left ankle joint of rats using open-field test. Traditionally, *Curcuma zedoaria* root has been used as anti-inflammatory and antiarthritic drug. Behavioral aspects include latency time to explore, ambulatory, rearing, grooming, urination, and defecation. Animals were divided into ten groups each of six rats, all the animals were subjected to open-field test before the induction of arthritis at 0 day and thereafter 3, 7, 14 21, 28, 35, and 42 days of postinoculation FCA injection. The rat was placed in an open field and observed all behavioral aspects for 5 minutes and radiography analysis was made on day 42. Selected doses were 10 mg/kg.i.p. Indomethacin 200 mg/kg.p.o. marketed herbal drug Rumalaya forte and 200 and 400 mg/kg.p.o. of each extracts, respectively. The results showed significant decrease in ambulation and rearing; however, increase in latency time to explore and grooming, urination, and defecation in control group, but in contrast, drug-treated groups showed significant recovery in all behavioral aspects except methanol groups. On the basis of radiography examination, control and methanol groups showed highest swelling compared with normal group; however, all drug-treated groups showed significant reduced swelling. Treatments with petroleum ether and chloroform extracts recovery were observed in behavioral and radiological aspects in arthritic rats.

Key words: Behavioral aspects, *Curcuma zedoaria* rosc, monoarthritis, open-field test, radiology

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology. The disease is characterized by articular inflammation and by the formation of an inflammatory and invasive tissue, rheumatoid pannus that eventually leads to the destruction of joints.[1] Recently, it has been reported that microorganism including bacteria, viruses, fungi, parasites, bacterial DNA, and bacterial toxin may exacerbate the inflammatory response at the joint and bone. *Mycobacterium tuberculosis* and *Mycobacterium leprae* are the most severe and more common *Mycobacterium* causing joint and bone diseases.[2] Anti-inflammatory drugs have not been used successfully in all cases due to side effects such as gastric lesions caused by nonsteroidal anti-inflammatory drug and steroids are used to suppress the symptoms, while disease-modifying antirheumatic drugs and biological therapy, all of these agents are associated with numerous side effects.[3,4] This limitation has necessitated the search for novel therapeutic products are directed toward traditional system of medicine for the discovery of drugs that are long-acting antiarthritic with minimum side effects.[5] Although there is no ideal animal model for RA at this time, rat adjuvant arthritis shares many features of human RA.[6] The sensitivity of this model to

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evaluate antiarthritic agents[7] and support the behavioral and radiology aspects during adjuvant arthritis is the best available model for RA to evaluate the new antiarthritic drug development. *Curcuma zedoaria* Rosc is commonly known as white turmeric, consist of dried pieces of rhizome,[8] a large perennial herb with underground tuberous root-stock, growing widely in eastern Himalayas and in most deciduous forest of the central region of Karnataka and Kerala, also cultivated throughout India.[9] Traditionally, the plant has been used as an analgesic, anti-inflammatory, antiarthritic, diuretic, antiallergic, antiulcer, and antiasthmatic.[10] Reported pharmacologically evaluation on *Curcuma zedoaria* Rosc are reported for antimicrobial,[11] antifungal activity,[12] antiamoebic activity,[13] analgesic activity, antinociceptive activity,[14,15] antiallergic activity,[16] antiulcer activity,[17] anticancer activity,[18] and hepatoprotective activity.[19] Freund's Complete Adjuvant (FCA)-induced monoarthritis in rat model are widely used to evaluate potential antiarthritic drugs for clinical use. Therefore, morphological similarities to human disease and capacity of the model to predict efficacy in human beings are important criteria in model selection. RA with a proven track record of predictability for efficacy on behavioral and radiology aspects in rat adjuvant arthritis is important criteria to evaluate antiarthritic drugs. On the basis of literature survey, no scientific study was carried out on this plant or its preparation for its behavioral and radiography aspects on FCA-induced arthritis in rats. Hence, the present study was carried out to validate and substantiate its traditional use in the treatment of arthritis.

MATERIALS AND METHODS

Plant Material

Roots of *Curcuma zedoaria* Rosc (*CZ*) were collected in the month of February, 2009 from Cochin, Kerala, India. Roots were identified by Dr. A. K. S. Rawat, Scientist-E, National Botanical Research Institute, Lucknow, India (Specification no [NBRI-SOP-202]). A voucher specimen of the root itself is deposited in the department for future reference.

Preparation of Extracts

The root of *CZ* were washed in tap water, cut into small pieces, and then shade dried. The dried pieces were then pulverized with an electric blender, and a yellow powder obtained (25-45 mesh size). The powdered material was subjected to successive extractions using petroleum ether (40-60), chloroform, and methanol for 72 hours.[20,21] These obtained extracts were evaporated under vacuum by flash evaporator to give residues.

Chemicals

FCA was purchased from Sigma Aldrich.[22] Indomethacin obtained from GMH Pharmaceutical Karnal, Haryana, India. Antiarthritic herbal drug Rumalaya forte tablets were obtained from Himalayan drug store local market Belgaum, India. All other chemicals used were analytical grade and were obtained from Qualigen Fine Chemicals, Mumbai (India).

Animals

Female Wistar rats (150-170 g) were used for the present study, which were obtained from K. L. E. University's College of Pharmacy, Belgaum, India. Food and water were supplied (*ad libitum*) and kept under controlled temperature 27 ± 2° C with a 12-hour light-dark cycle. The experimental procedures were conducted in accordance to the direction of Institutional Animal Ethics committee, (CPCSEA), Government of India, resolution No. 31/7/2010-13). Due to painful condition imposed on animals, the numbers of subjects used were restricted to the minimum six per group that allowed reliable statistical analysis of the results.

Acute Toxicity Studies

The acute oral toxicity studies were carried out according to the guidelines set by Organization for Economic Co-operation and Development (OECD) 425. Female Wistar rats (160-200) were used for this study. The roots of each extracts of *Curcuma zedoaria* Rosc, at different doses (175, 550, 1 500, 2 000, and 5 000 mg/kg), were administered orally to normal rats. During the first four hours after the drug administration, the animals were observed for gross behavioral changes such as hyperactivity, grooming, convulsions, sedation, hypothermia, body weight, and mortality up to 14 days.[23]

Preparation of Test Solutions and Selection of Animal Groups

All extract were dissolved in normal saline in normal saline and trichurated with 2% tween 60 making a suspension. The dose calculation was based on w/w and calculated for each extract. Animals were divided into ten groups each of six animals. Group-I: treated with 5 ml/kg.p.o. normal saline + mineral oil kept as normal. Group-II: treated with 5 ml/kg.p.o. normal saline + FCA served as control. Group-III: treated with 10 mg/kg.i.p. indomethacin + FCA served as standard-I. Group-IV: treated with 200 mg/kg.p.o Rumalaya forte + FCA served as standard-II. Group-V: treated with 200 mg/kg.p.o petroleum ether extract + FCA served as PEE-1. Group-VI: treated with 400 mg/kg petroleum ether extract + FCA served as PEE-II. Group-VII: treated with 200 mg/kg.p.o chloroform extract + FCA served as CH-I. Group-VIII: treated with 400 mg/kg.p.o chloroform extract + FCA served as CH-II. Group-IX: treated with 200 mg/kg.p.o methanol extract + FCA served as ME-I. Group-X: treated with 400 mg/kg.p.o. methanol extract + FCA served as ME-II. Mineral oil was injected in normal group and FCA injected in control and drug treated groups through intra-articular injection in left ankle joint of rats on 0 day.

Induction of Monoarthritis

For the induction of monoarthritis in female Wistar rats, all the rats were anesthetized with 40 mg/kg *thiopentone* sodium intraperitoneally. Mineral oil was injected in left ankle joint of normal group of animals. FCA were injected into left ankle joint of control and drug-treated group, the tarsal area of hind paw was grasped and the fossa distal and medial to the "lateral malleolus" of the fibula was palpated. A 26 G needle was introduced into the capsule of the tibiotarsal joint percutaneously by directing it cephalad, mesiad, and superiorly from the midpoint of the "inframalleolar fossa," until a distinct loss of resistance was felt approximately 4 mm and complete adjuvant or vehicle was injected. With a true intracapsular injection, a firm resistance to injection was characteristically felt after the injection of 0.1 ml of FCA.[24]

Behavioral Observation (open-field test)

For behavioral observations, all the animals were subjected to open-field test before the induction of arthritis and thereafter 3, 14, 21, 28, 35, and 42 days of postinoculation of FCA injection. Rat was placed in an open field in the sound-attenuated room. The floor was white polyvinyl with a black grid dividing open field into 84 squares (10 × 10). Illumination was provided by a bulb (60 W) placed above the center of the field, while the rest of the room was darkened.[25,26] The rat was initially placed in the corner or in center of the field and observed for 5 minutes for all behavioral tests. After each animal observations test, the open field was cleaned with wet sponge and tissue paper[27] and all observations were made between 18.00 and 20.00 hours.

Based on the previous scientific data on behavioral observations of normal rats, the following behaviors were quantified: (I) Latency time to explore: means that time taken "to start explore (second)" from insertion time; (II) Ambulatory behavior: means that the rat "crossed grid line" (horizontal locomotor activity); (III) Rearing, means that the "look for" sometime in air for this it elevates its head and forepaws, almost standing up, (vertical locomotor activity); (IV) Grooming behavior: means licking parts of the rat body or sometimes rubbing the ears, nose, and head or the snout with forepaws, and preening; (V) Urinations: (number of urine passes) considered as anxiety behavior of rat; (VI) Defecation: (number of boluses pass) also considered as anxiety behavior of rat during open-field observation.[28]

Radiography Examination

At the end of the experiments, all rats were anesthetized with 40 mg/kg sodium thiopental intraperitoneal injection. Once anesthetized, the animals were constantly kept on X-ray plate, the projections of the left ankle joint were taken at day 42. The following parameters were evaluated blind using the tarsometatarsal region: erosion, a destruction of bony structure resulting in irregular bone surface; periosteal reaction, a fine ossified line, paralleling normal bone producing bone thickening; increase in soft tissue which was manifested as an increase in width of the soft tissue; and calcification. The parameters were using score which follows: 0, no sign; 1, mild; 2, moderate; and 3, severe.[29]

Statistical Analysis

All values are presented as mean ± SEM. Differences between means were assessed by one-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test; $P < 0.05$ was considered significant.

RESULTS

No toxic effects were observed after treatment with root extracts of *Curcuma zedoaria* at higher dose of 5000 mg/kg body weight. Hence, there were no lethal effects in any of the groups. Two different doses (200 and 400 mg/kg) were chosen from each extracts for further experimentation.

Latency time to explore significant ($P < 0.001$) increase in normal group during 7 to 14 days, but recovery was observed near to initial value, was achieved during 21 to 42 days. However, control group and methanol group showed significant ($P < 0.001$) increase in latency time during 3 to 42 days compared with 0 day. But in Standard-I, Standard-II, and *CZ* extracts, administered groups were also showed significant ($P < 0.001$) increases in latency time during 3 to 7 days but significant ($P < 0.001$) decrease during 14 days to last day of the study compared with 0 day [Figure 1].

Ambulatory decrease in normal group at 3 day but significant ($P < 0.01$) increase during 7 to 14 days and maintained again near to normal value at day 42 were observed. Control group showed significant ($P < 0.001$) decrease ambulatory during 3 days to last day of experiment compared with 0 week. However, All drug-treated groups had decreased ambulatory during 3 to 7 days, whereas,

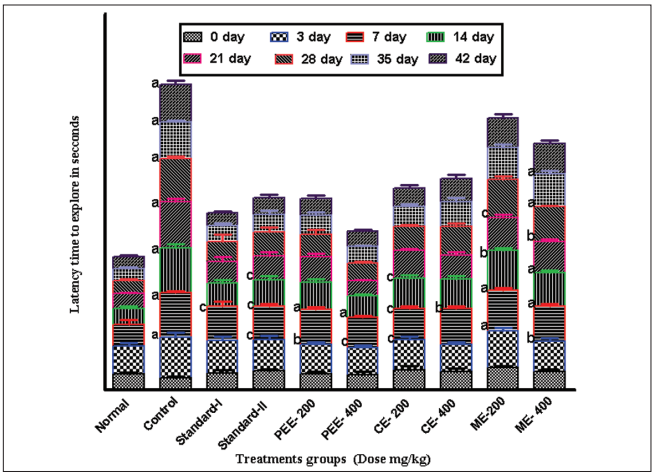

Figure 1: Each value is expressed as mean ± SEM. The levels of significance in latency behavioral changes were analyzed by Dennett's multiple range comparisons tests, all groups compared with 0 day. P value less than 0.05 was considered as significant. $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$

increased ambulatory during 14 to 28 days and achieved near to normal value during 35 to 42 days, except methanol groups compared with 0 day [Figure 2].

Rearing decreased in all groups at 3 and 7 days. In normal group, rearing were increased during 14 to 42 days but in control group, rearing significantly ($P < 0.001$) decreased throughout the study. In all drug-treated groups, progressive recovery was observed during 14 to 28 days and a return to near initial values was achieved during 35 to 42 days, except in methanol groups, rearing was identical in methanol and control group compared with 0 day [Figure 3].

Grooming was increased during 3 to 14 days in normal group, but decreases during 14 to 28 days; furthermore, decrease in level of initial values during 35 to 42 days compared with 0 day was observed. In control group, grooming was increased during 3 to 28 days and reached near to normal value at day 42 compared with 0 day. In all drug-treated groups increased grooming during 3 to 21 days, but decreases during 28 to 42 days compared with 0 day [Figure 4].

Urination in all groups of animals were decreased at day 3, but there were increase in the frequency of urine at 7 days of observation compared with 0 day. However, control group showed highly significant increase in frequency of urinations in 7 days, but decrease in frequencies of urine during 14 days to last day of study compared with 0 day. Standard-I and petroleum ether 200 mg/kg groups showed significant ($P < 0.001$) decrease in frequency of urinations during 7 to 42 days compared with 0 day. Standard-II and chloroform 200 mg/kg groups showed ($P < 0.001$) significant decrease in urine frequency during 14 to 42 days. Petroleum 400 and methanol 200 mg/kg groups showed significant ($P < 0.001$) decrease in frequency during 21 to 42 days; however, methanol 400 mg/kg did not show significant result throughout study compared with 0 day [Figure 5].

Defecation results are shown in Figure 6; mostly all groups showed decrease defecations during 3 to 42 days compared with 0 day; however, decreased significant ($P < 0.001$) frequency of defecations were observed during 3 to 42 days in normal group compared with 0 day. Standard-II, petroleum ether and chloroform 400 mg/kg groups showed decreased significant ($P < 0.05$) defecation in frequency during 7 to 42 days; however, standard-I showed significant ($P < 0.01$) reduction during 21 to 42 day compared with 0 days. Chloroform 200 mg/kg and methanol group showed decrease in the significant ($P < 0.01$) frequency of defecation during 28 to 42 days compared with 0 days.

Radiographic examination of left ankle joint of rats at 42 day revealed the severe soft tissues swelling; however, there were no signs of narrowing of the joint spaces and the subsequent destruction of the bones and cartilages in the ankle joint compared with normal group [Figures 7A and B]. In all drug-treated groups, the soft tissue swellings were reduced, except methanol groups which showed near to control group [Figures 7C-J].

DISCUSSION

The present study was to investigate the effect of root extracts of *Curcuma zedoaria* Rosc on behavioral and radiology changes in monoarthritis rats. Behavioral approach to the arthritic rats which has been proposed as an animal model for chronic pain and radiography approach were made at day 42 for conformed status of disease.[29] Behavioral observations were made over the 42 days

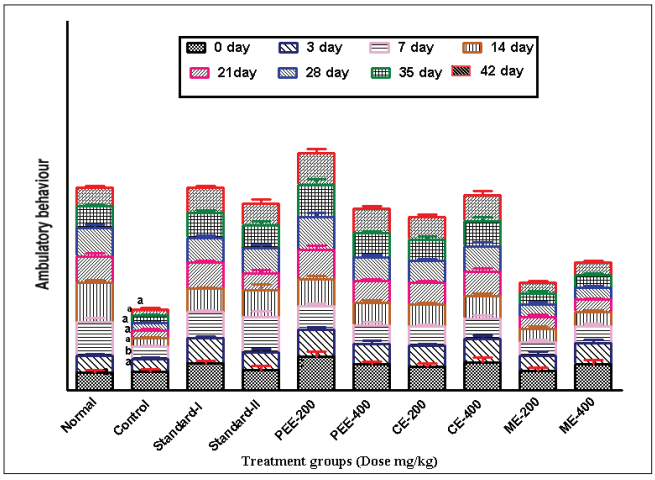

Figure 2: Quantification of ambulatory behavior is expressed as (horizontal locomotors). Values are represented as mean ± SEM and analyzed by one way ANOVA, Dennett's multiple comparisons range test. All groups compared with 0 day. *P* value less than 0.05 was considered as significant. $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$

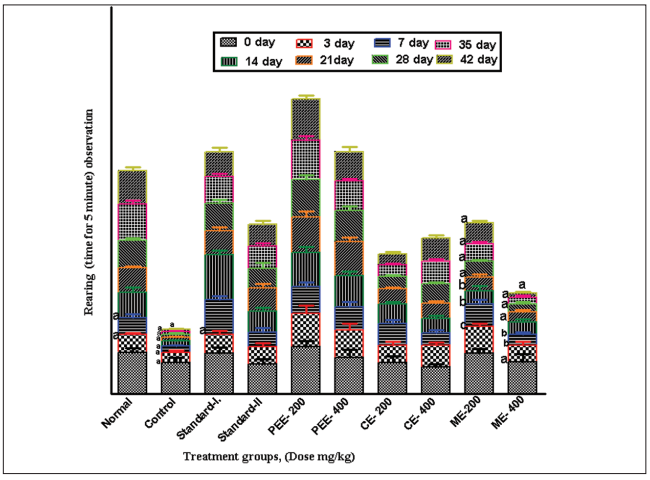

Figure 3: Rearing behavior elements are quantified by vertical locomotors. Each value expressed as mean ± SEM and analyzed by one way ANOVA, Dunnett's multiplies comparison test. All groups compared with 0 day. *P* value less than 0.05 was considered as significant $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$

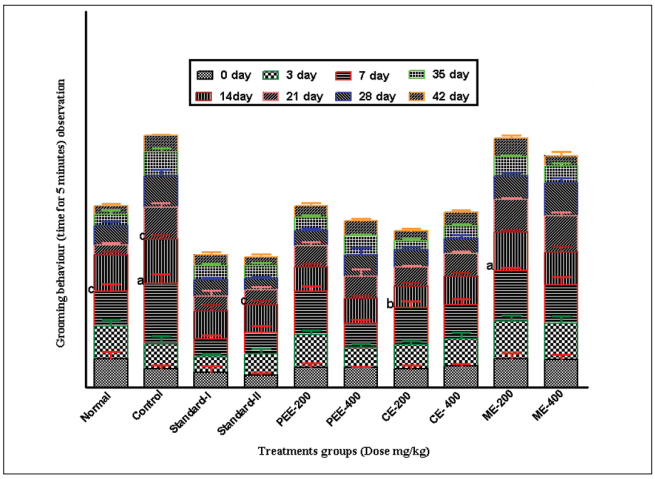

Figure 4: Values are represented as mean ± SEM analyzed by Dennett's multiple comparisons range test. All groups compared with 0 day, *P* value less than 0.05 was considered as significant $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$

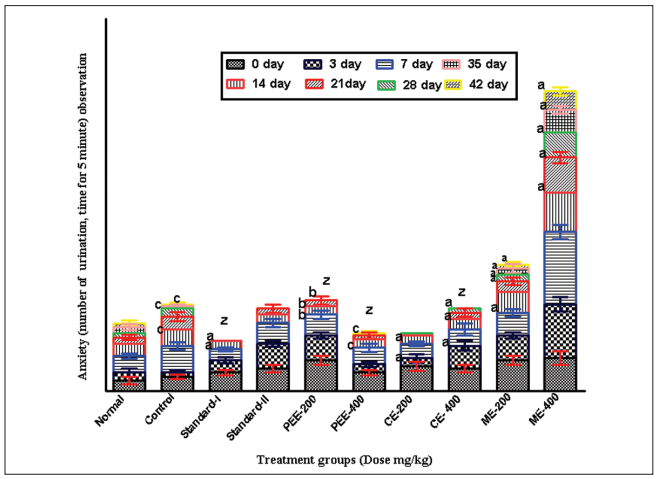

Figure 5: Anxiety behavior of arthritic rats were quantification in number of boluses. Values are represented as mean ± SEM. All groups compared with 0 day, *P* value less than 0.05 was considered as significant. $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$. Z indicates 0 value significant decrease urination during observation not showed in diagram

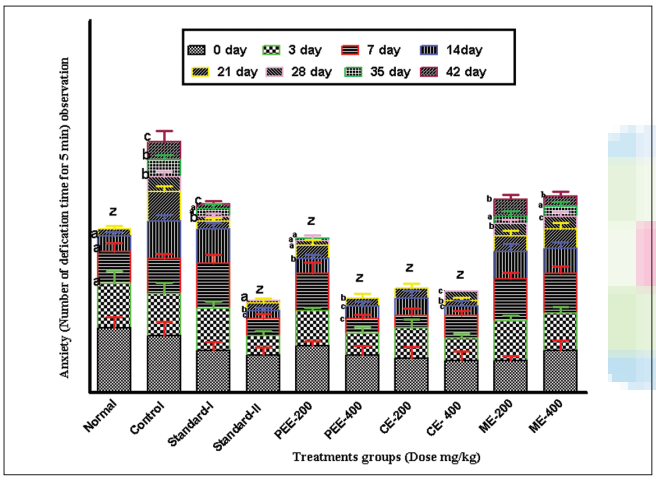

Figure 6: Values are expressed as mean ± SEM. All groups compared with 0 day, *P* value less than 0.05 was considered as significant $^{c}P < 0.05$, $^{b}P < 0.01$, $^{a}P < 0.001$". Z indicates 0 value significant decrease urination during observation not showed in diagram. Each groups compared with 0 day

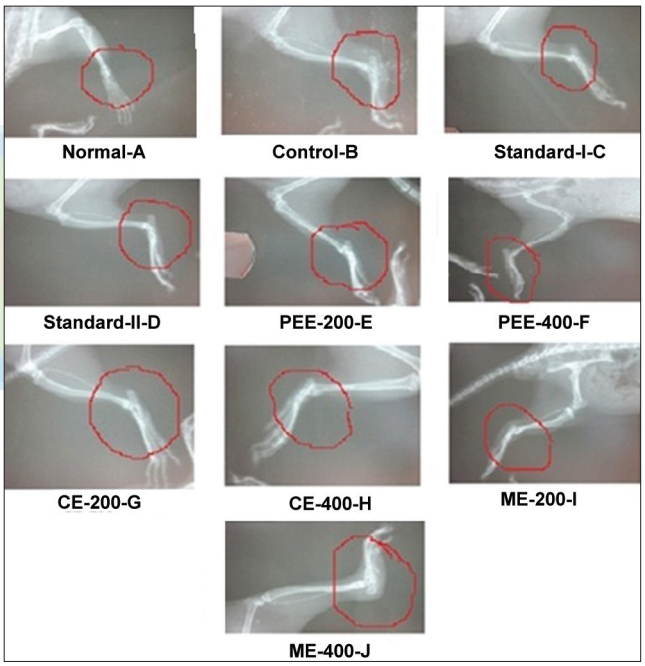

Figure 7: (A-J) Radiograph showed effect of *Curcuma zedoaria* root extracts on FCA-induced monoarthritis in left ankle joint of rats on 42 day. Control joint compared with normal joint and drug-treated joint compared with control joint

postinoculation period; latency time to explore, ambulatory, rearing, grooming,[25,27] urination, and defecation. The latency time to explore in FCA-induced arthritic rats has shown gradual delay in exploration ability. Treatment with indomethacin and rumalaya forte has shown an appreciable and significant decrease in latency time to explore in open field during 14 to 42 days. Extract-treated groups improved the condition by decreasing latency time to explore in open field during 14 days to throughout the study. However, latency time to explore was identical in methanol groups and control group. Control group showed gradual decrease in ambulatory and rearing behavior during 3 to 42 days of the study. However, all drug-treated groups showed decline in ambulatory and rearing at 3 days and improvement in mobility and spontaneous condition during 7 to 28 days, but complete reversal of arthritis antiambulatory behavior during 35 to 42 days. Grooming [Figure 4] was affected by arthritis during 3 to 14 days in normal group but in control group, it was affected during 3 to 28 days and recovery at day 42. In all drug-treated groups, grooming was affected by arthritis during 3 to 21 days, but strongly improved during 28 to 42 days.

The angiogenic and anxiolytic effects of drug treatment on FCA-induced arthritic rats were studied by considering

the frequency of urination and defecation in five minutes of exploratory. The fear due to arthritis induces anxiety in the animals when placed in an open field. The ultimate manifestation of anxiety in the animals is exhibited by decrease in the motor activity. Anxiolytic agents are expected to increase the motor activity, which were measured by frequency of urine and defecation during observation.[26]

Urine frequencies were reduced in 3 days but elevated the frequency of urinations in 7 days observation period at 28 days. In control group, higher frequency of urine was recorded during observation period; however, drug-treated animal showed reduced urine frequency during 14 to 42 days, except methanol 400 mg/kg group [Figure 5].

Defecations frequency was higher in control group during observation period, but there was significant decrease in defecation frequency in standard-1 petroleum ether during 14 to 42 days; however, standard-II, chloroform and methanol drug-treated group showed decreased frequency of defecation during 21 to 42 days of study. In present study, the radiographic examination revealed the severe soft tissue swelling, but not the subsequent destruction of the bones, cartilages, and narrowing of the joint spaces in the ankle joint of control and methanol groups at day 42; however, standard-I, standard-II, petroleum ether and chloroform extract showed significant reduction in soft tissue swelling; among these extracts, petroleum ether 200 mg/kg showed high reduction in soft tissue swelling of arthritic joint near to indomethacin-treated group [Figure 6].

Based on present studies, we validate the traditional and folk claims of the use of root *Curcuma zedoaria* Rosc in the treatment of RA. Petroleum ether and chloroform extracts at both dose showed on behavior doses showed on behavior studies confirms its ability to overcome stress, anxiety, and abnormality in mobility and protective effect on arthritic rats joint at day 42. It is considered that investigation for these medicinal properties might give scientific authentication to traditional clam use of root *Curcuma zedoaria* Rosc in the therapy of RA.

CONCLUSION

It has also been suggested that FCA-induced RA has a widespread effect on physiological homeostasis due to the severe discomfort in animals. In present studies, the control group showed gradual decrease in ambulatory and rearing behavior and gradual increase in latency time to explore, grooming, urinations, and defecations were observed. However, in drug-treated groups recovery were observed in ambulatory and rearing behavior whereas decrease in latency time to explore grooming, urinations, and defecations. Whereas, methanol groups have failed in all accepts. Radiograph showed increase swelling in control and methanol joints but reduction in drug-treated groups. These observations support the efficacy of extracts treatment in behavior modulation induced by arthritis by decreasing irritation, anxiety, increased intention to walk, and reduction swelling of rats joint. This shows the possible applicability of petroleum ether and chloroform root extracts of *Curcuma zedoaria* used in symptomatic treatment of arthritis.

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