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Original Article

Therapeutic Evaluation of Camel Milk-Derived Lactoferrin for *in vivo* Anti-Arthritic Efficacy

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ABSTRACT

Background: Arthritis is a prevalent chronic inflammatory condition that significantly impacts individual's quality of life. Lactoferrin (Lf), a multifunctional glycoprotein found in CM, has shown promising anti-inflammatory and immunomodulatory properties. However, there is limited research on the anti-arthritic activity of Camel Milk (CM)-derived Lf. This study aims to evaluate the effectiveness of Lf isolated from CM in alleviating arthritis symptoms, providing valuable insights into its therapeutic potential for arthritis management. **Objectives:** The primary objective of this research is to assess the anti-arthritic activity of Lf isolated from CM. **Materials and Methods:** The anti-arthritic activity of Lf, administered was evaluated using two *in vivo* models. MSU induced arthritis model contained six groups containing six Wistar albino rats each. Negative control (Phosphate buffer saline), Positive control (monosodium urate crystals), Standard (indomethacin) and Test (CM, 5 mL/kg and 10 mL/kg, p.o and Lf 100 mg/kg, p.o). Collagen type-II induced arthritis model also contained six groups containing six Wistar albino rats each. Negative control (Phosphate buffer saline), Positive control (collagen type-II), Standard (ibuprofen) and Test (CM, 5 mL/kg and 10 mL/kg, p.o and Lf 100 mg/kg, p.o). **Results:** The data obtained from the a fore mentioned models demonstrated that Lf (100 mg/kg), in conjunction with CM administered at doses of 5 mL/kg and 10 mL/kg, exhibited anti-arthritic activity, resulting in a noticeable reduction in inflammation. **Conclusion:** This research study provides evidence supporting the effectiveness of Lf in alleviating arthritis symptoms by significantly reducing inflammation in the animal models tested.

Keywords: Lactoferrin, Camel milk, Monosodium urate crystals, Collagen type-II, Arthritis, Inflammation.

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INTRODUCTION

Arthritis is a debilitating condition characterized by chronic inflammation and joint damage, affecting millions of individuals worldwide. The quest for effective and safe treatment options for arthritis continues to be a major area of research. In recent years, natural compounds derived from various sources have gained attention for their potential therapeutic properties in managing arthritis and its associated symptoms.[1] Lactoferrin (Lf), a glycoprotein abundantly found in milk, has emerged as a promising bioactive molecule with diverse biological functions. It exhibits immunomodulatory, anti-inflammatory and antimicrobial activities, making it an attractive candidate for investigating its potential in arthritis management of particular interest is Lf derived from Camel Milk (CM), which possesses unique composition and bioactive components that may contribute to enhanced therapeutic properties.[2,3] By investigating the anti-arthritic properties of Lf isolated from CM, this study seeks to contribute to the understanding of its therapeutic potential in arthritis management. The findings may shed light on the underlying mechanisms of action and support the development of novel, nature-based therapeutic interventions for arthritis. Ultimately, the goal is to explore Lf derived from CM as a viable natural remedy for arthritis, providing an alternative or complementary approach to conventional treatment strategies. Overall, this research holds promise in uncovering the potential of Lf derived from CM as a valuable therapeutic agent in the management of arthritis, offering new avenues for improved patient care and enhanced quality of life.[4] Lf, a multifunctional glycoprotein found in milk, has gained significant attention for its potential therapeutic applications due to its diverse biological activities.[5-7] Studies have suggested that Lf derived from CM may possess enhanced bioactivity and stability, making it an intriguing option for therapeutic applications. Although limited, the existing literature on the evaluation of anti-arthritic activity of

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Lf isolated from CM shows promising results. These studies have utilized various experimental models, including monosodium urate crystal-induced arthritis and collagen-induced arthritis, to investigate the effects of CM-derived Lf on reducing inflammation and ameliorating arthritis symptoms.[8]

MATERIALS AND METHODS

Materials

CM samples were obtained from Sarika Milk Bhandar, India, from healthy *Camelus dromedarius* in August 2022. The milk was collected aseptically into sterile containers and transported to the laboratory in an ice box to maintain its freshness. Upon arrival, the milk was divided into smaller containers and frozen at -80°C until further processing. Lf for the study was sourced from Sun-Deep Scientific Equipment and Chemicals.

Methods

Separation of Whey and Casein Fractions from CM for Lf Isolation

Cream was separated from milk by centrifugation at 5,000 rotations per min (rpm) for 30 min at 4°C using a high-speed centrifuge. Residual cream residues were eliminated using Whatsman Qualitative Filter Paper. The defatted milk was diluted with water and its initial pH was determined using a pH meter. Gradual addition of 1 N hydrochloric acid under stirring was performed until the pH reached 4.6 to precipitate casein.[9,10] The resulting casein pellet was separated from the liquid phase by centrifugation at 12,000 rpm for 30 min at 4°C. The whey supernatant, representing the liquid fraction after casein removal, was collected for Lf extraction after chilling it to 4°C. These steps of centrifugation, filtration, acidification and subsequent centrifugation were crucial for obtaining specific milk components and preparing them for further analysis.[11,12]

Isolation of Lf from CM Whey

The isolation of Lf from the whey sample involved the following steps: adjusting the whey supernatant pH to 6.8 by adding 2 N sodium hydroxide (NaOH), adding a 45% $(NH_4)_2SO_4$ solution, stirring at 420 rpm for an hr at room temperature, centrifuging at 10,000 rpm for 30 min at 4°C to remove the protein precipitate, adjusting the supernatant pH to 4.0 by adding 1N Hydrochloric acid (HCl) with agitation and then raising the pH to 8.3 by adding 2N NaOH.[13-15] The caseins in the CM sample were precipitated by lowering the pH to 4.0, while Lf was precipitated by raising the pH to 8.3. Magnetic stirring was performed while adding an 80% $(NH_4)_2SO_4$ solution and the mixture was left to sit at 4°C with agitation. The isolated Lf was obtained by centrifuging the sample, dialyzing it against sodium phosphate buffer and water and freezing it for further research. The characterization of Lf was performed using Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) to analyze its protein composition and purity. Different samples, including skimmed milk, supernatant and the Lf pellet, were loaded onto the gel for analysis.[16]

Characterization of Lf

The SDS-PAGE analysis revealed that the SM sample contained multiple proteins, including Lf, Camel Serum Albumin (CSA), Immunoglobulin (Ig), beta Casein (-CN), kappa casein (-casein), TNF-Related Apoptosis-Inducing Ligand (TRAIL)

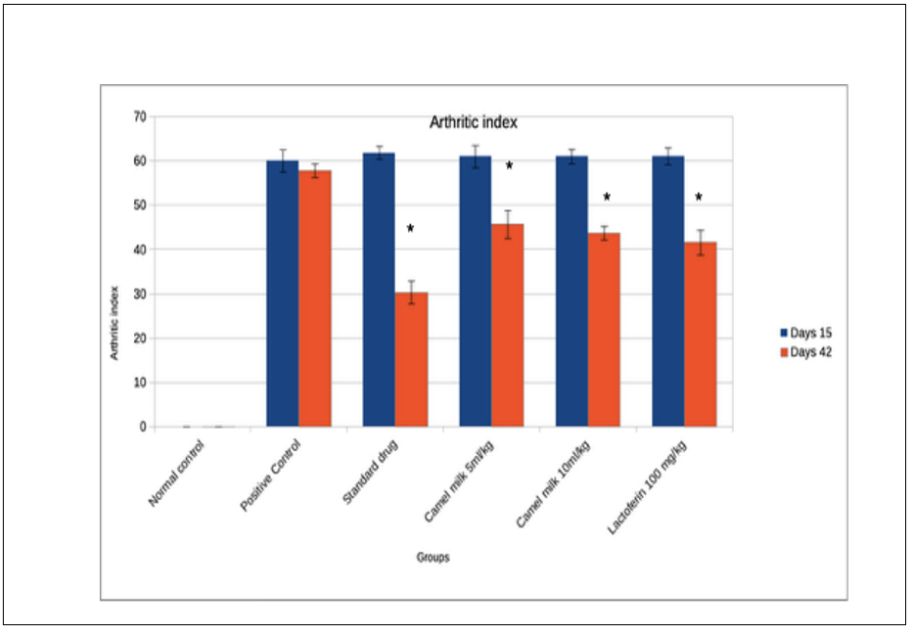


Figure 1: Assessment of arthritic index in CIA rats. Effect of various CM and Lf dosages on the arthritic index. The data are shown as Mean SD. * - notably different from the corresponding induced group ($p<0.05$).

Table 1: Grouping of animals for collagen type-II induced arthritis. Animals were separated into 6 groups, each containing 6 animals.

Group-I	Negative control-Animals were treated with sterilized Phosphate buffer saline 50 mg/kg, subplanter.
Group-II	Positive control-Animals were treated with Lyophilized type II collagen, 25 mg/kg, i.d.
Group-III	Standard-Animals were treated with standard drug ibuprofen, 40 mg/kg, p.o.
Group-IV	Animals were treated with camel milk as a tested drug, 5 mL/kg, p.o.
Group-V	Animals were treated with camel milk as a test drug, 10 mL/kg, p.o.
Group-VI	Animals were treated with test drug Lactoferrin isolated from camel milk, 100mg/kg, p.o.

Table 2: Grouping of animals for Monosodium Urate crystals (MSU) induced arthritis. Animals were separated into 6 groups, each containing 6 animals.

Group-I	Negative control-Animals were treated with sterilized Phosphate buffer saline, 50 mg/kg, subplanter.
Group-II	Positive control-Animals were treated with MSU, 25 mg/kg, subplanter.
Group-III	MSU induced rat were treated with indomethacin, 5 mg/kg, i.d.
Group-IV	MSU induced rats were treated with CM as a test drug, 5 mL/kg, p.o.
Group-V	MSU induced rats were treated with CM drug as a test drug, 10 mL/kg, p.o.
Group-VI	Animals were treated with test drug Lf isolated from CM, 100 mg/kg, p.o.

and Alpha-Lactalbumin (-LA). The Supernatant (S) obtained after centrifugation exhibited a protein profile that included CSA, Ig, s1-CN, s2-CN, CN, casein, TRAIL and LA, but Lf was not present. In contrast, the Lf pellet specifically contained Lf, along with serum albumin, the predominant protein in whey. The identity of Lf was confirmed by comparing it to bovine Lf loaded and Bovine Serum Albumin (BSA) served as a reference protein. A molecular weight marker was also included for accurate molecular weight determination.[17] This SDS-PAGE analysis provided insights into the protein composition and purity of the isolated Lf from CM. The presence of Lf in the specific pellet fraction confirmed successful isolation. These findings contribute to the characterization of CM-derived Lf, supporting its potential application in further research and as a potential therapeutic agent in various biomedical applications.[17]

Animals Study

Male animals that are pathogen free Wistar albino rats (100-150 g b. wt, 6-8 weeks old) were utilized for the duration of the investigation. These rats were acquired from the institute's main animal house facility. Before beginning the trial, the animals were given 10-12 weeks to acclimatize in polypropylene cages. Pellet meal (Provimi Animal Nutrition India Pvt. Ltd, Bangalore, India) and running water were provided free-of-charge to the rats. The rats were provided with humane care and housed in accordance with the standards set out by the Committee for the Control and Supervision of Experiments on Animals (CCSEA), which included a light/dark cycle of 14:10 hr an ambient temperature of 22°C and a humidity range of 40 to 45%.[18]

According to Campo *et al.* (2003), Collagen type-II (CII) produced arthritis in rats. To recap, CII was emulsified with an identical amount of Complete Freund's Adjuvant (CFA) after being dissolved in 0.1 M CH_3COOH (2 mg/mL) at 4°C overnight. Subcutaneous injections of 200g of CII were given to each rat near the tail base.[19] On day 14, rats were given a booster dose of the same antigen formulation. On day 25, joint inflammation was evaluated by a blinded independent observer who was unaware of the treatment strategy. Four limbs were scored macroscopically one point for each swollen or red toe, one point for each digit or knuckle in the middle of the foot and five points for an enlarged ankle was used track the progression of arthritis. By summing together, the values for all four paws, an arthritic index was arrived. Each rat was judged to have been induced with RA if it received a score of 60 or above (Table 1).[20]

MSU crystals Induced Arthritis

Synthesis of MSU crystals

About 4.0 g uric acid was dissolved and heated in 800 mL of distilled water. The pH was adjusted to 8.9 using Sodium Hydroxide (NaOH) at 60°C. Then overnight, the mixture was chilled in a frigid environment at 4°C. The synthesized MSU crystal was washed and dried. Crystals in the shape of needles were retrieved and suspended in sterile saline. Before administration, MSU crystals were checked for bacterial endo-toxin free contamination using agar plate method (Table 2).

After 7 days, rats were evaluated for ankle size, body weight, arthritis severity, paw swelling, joint swelling, inflammatory cell media to release and histologic analysis. The whole experiment lasted 42 days. A single dosage of MSU crystal was injected 1 hr before the start of the medication treatment and then the pharmaceuticals were given once daily for 3 days. Using a Vernier scale, the paw thickness of inflamed rats was measured at regular intervals for 3 days before to sacrifice.[21] 24 hr after the last dosage of medication was given, the animals were sacrifice via cervical dislocation. After letting the blood sit for 30 min, it was centrifuged for 15 min at 3000 rpm and 30°C to separate the serum. After surgically removing the ankle joint, ice-cold

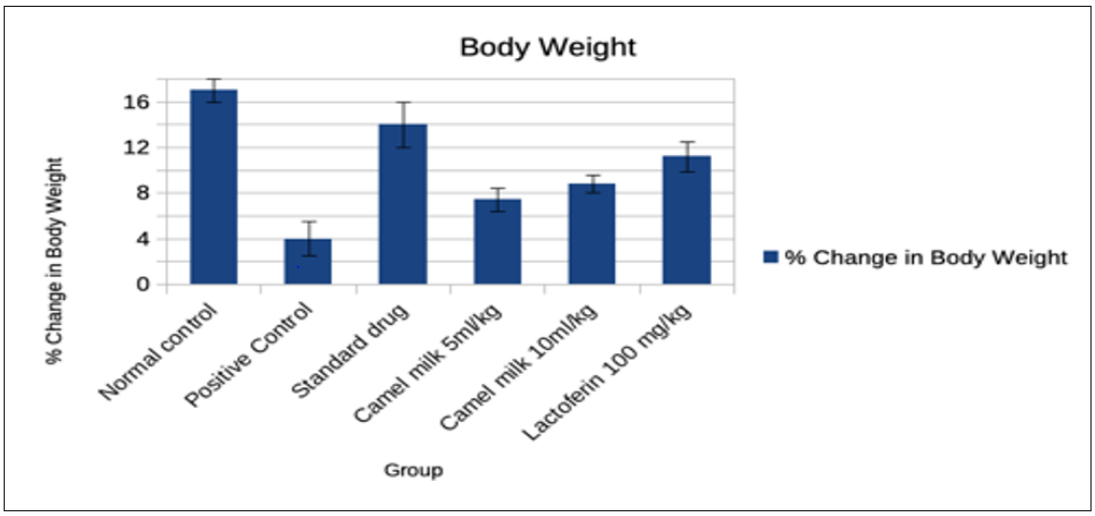


Figure 2: Influence of CM and Lf on percent change in body weights in CIA rats on day 42.

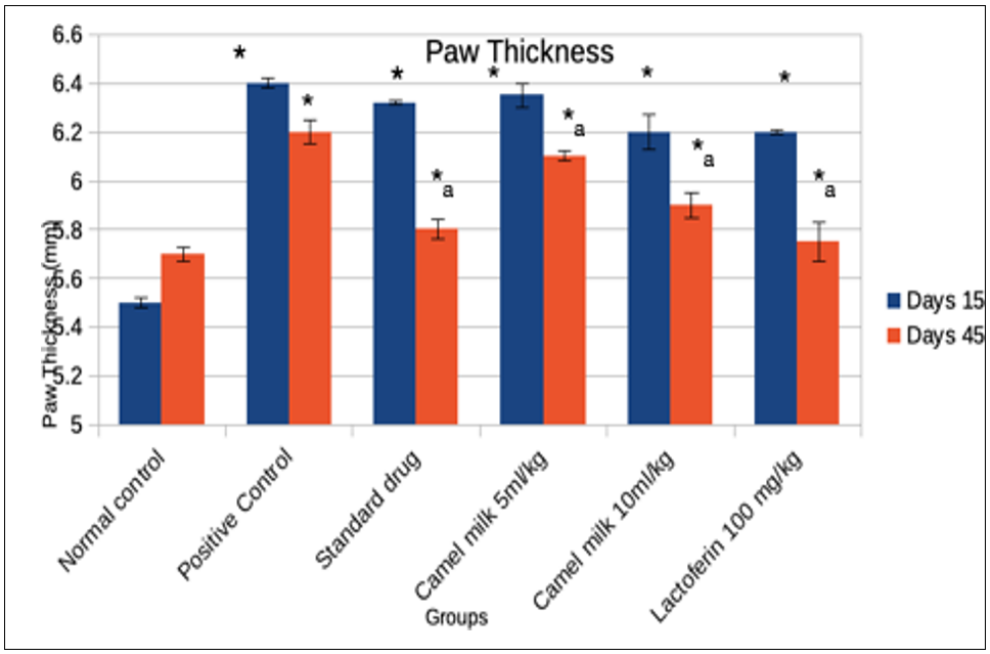


Figure 3: Effect of CM and Lf on foot paw thickness in CIA rats. Significantly different from the respective induced group ($p<0.05$), *- Significantly different from the corresponding control. The treatment was started on 15th day for 30 days.

saline (0.9% NaCl) was used to suffuse the area. An ankle joint homogenate (10%) was produced in a sodium phosphate buffer (0.1 M, pH 7.4) that was refrigerated and the supernatant was separated by centrifugation at 10 k rpm for 30 min at 4°C for biochemical analysis. The collected supernatant was frozen at -80°C for further study.[22]

Assessment of Disease Development

Clinical Assessment of Arthritis

Paw Thickness Measurement

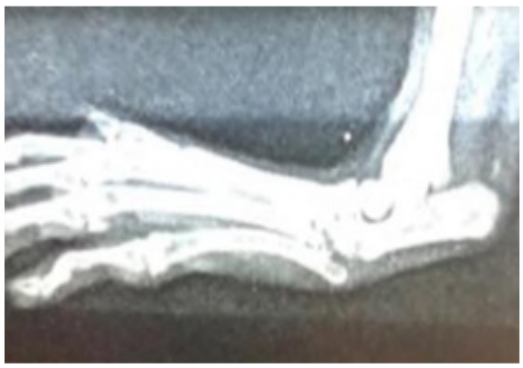
The hind paws of rats were measured for thickness using a Vernier caliper to assess the severity of arthritis on a macroscopic level. Measurements were taken laterally and vertically at the base of the footpad.

Body Weight Recording

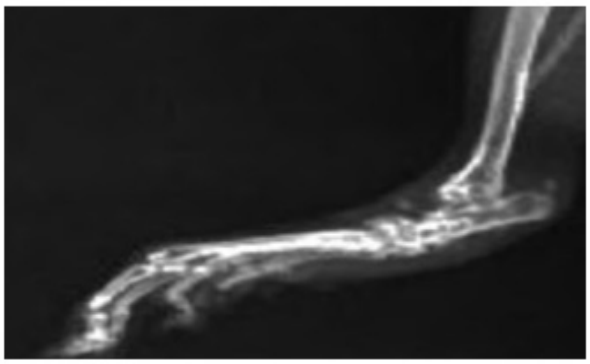
The body weights of rats were recorded twice weekly using an electronic weighing scale.

Arthritis Index Calculation

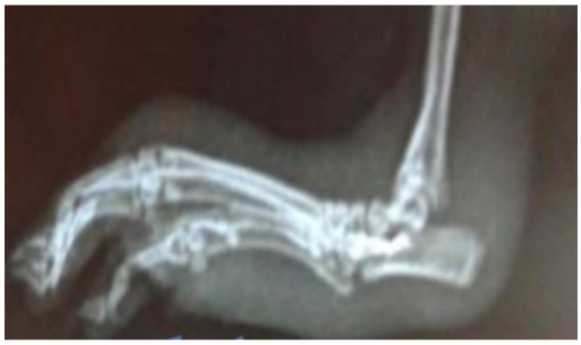
The arthritic index was determined by summing the scores of all four paws. A score of 60 or higher was considered indicative of Rheumatoid Arthritis (RA) development.



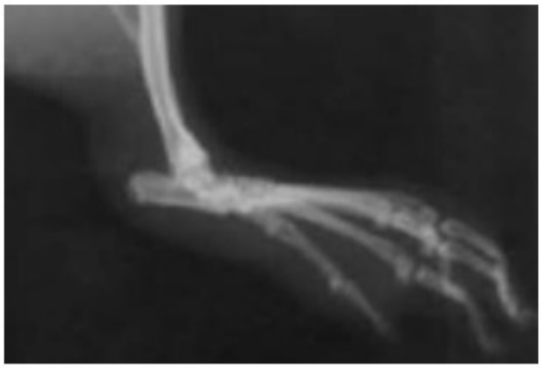
4a. Negative Control.



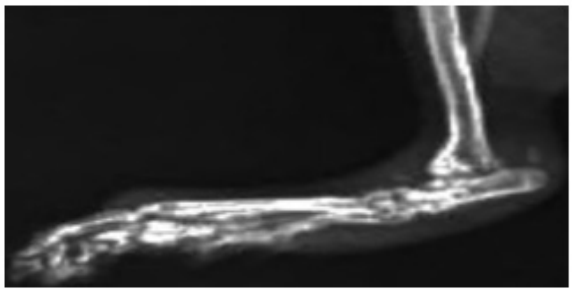
4c. Standard drug.



4b. Positive Control (Disease induced).



4d. CM 5 mL/kg drug.



4e. CM 10 mL/kg.

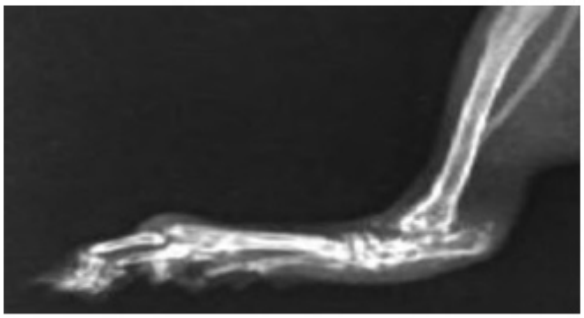


Figure 4f: Lf 100 mg/kg.

Figure 4: Representative radiographic hind paw images (X-rays) of CIA rats.

RESULTS

Radiographic Assessment of Joints

Radiographs of normal and arthritic rat hind paws were analyzed on the final day of the experiment (Day 42) using an X-ray equipment. Radiologic scoring was performed based on established criteria, including mild alterations such as joint erosion and disfigurement, severe changes such as bone erosion and osteophyte growth and no radiologic changes.[23]

Effect of Lf on Clinical Parameters in CIA

The therapeutic potential of Lf in a CIA model was investigated. Arthritis symptoms, including swollen paws, erythema in ankle joints and involvement of metatarsal and interphalangeal joints, were observed in disease control animals. Administration of Lf resulted in a significant reduction in arthritic score compared to the disease control group. Paw volume and thickness were also reduced by Lf treatment, with a dosage-dependent effect. Lf's effects were compared to the gold standard treatment (Figure 1).[24]

Effect of Lf on Arthritic Index

Arthritic symptoms appeared in rats following immunization with CII and the arthritic index was used to evaluate the effectiveness of CM and Lf in treating arthritis. The arthritic index was highest in CIA rats but decreased in rats treated with CM, Lf and a conventional medication. The reduction in the arthritic index indicated the effectiveness of these treatments in halting the progression of arthritis (Figure 1).[25]

Effect of Lf on Body Weight

Changes in body weight were measured to assess the inflammatory response in the CIA model. Rats treated with CM and Lf showed a trend towards improved body weight gain compared to the disease control group. The standard drug group displayed significantly better results, indicating the potential of Lf to ameliorate weight loss and reduce inflammation associated with arthritis (Figure 2).[26]

Foot Paw Thickness Assay

Foot pad swelling is an indicator of arthritis severity in the CIA model. Lf and CM administration significantly reduced foot paw edema in a dose-dependent manner. The highest inhibition was observed in the Lf treated group (Figure 3).[27]

Effect of CM and Lf on Radiographic Analysis

Radiographic analysis was conducted to evaluate the joint damage and protective effects of CM and Lf in a CIA model. Disease control animals exhibited features such as soft tissue enlargement, edema, joint erosion and bone loss and osteophyte formation. However, treatment with CM and Lf improved these arthritic changes compared to the disease control group. Radiographic scores, indicating bone erosion and joint deterioration, were significantly reduced by CM and Lf. These findings suggest that CM-derived Lf has beneficial effects in the CIA model, as evidenced by improvements in clinical parameters, arthritic index, body weight, paw thickness and radiographic analysis. The results indicate the potential of Lf as a therapeutic intervention for arthritis, exhibiting dose-dependent effects and comparable efficacy to CM and standard medications. These findings support further exploration of Lf as a potential treatment for arthritis, demonstrating its ability to reduce inflammation and protect against joint damage (Figure 4).

DISCUSSION

An ongoing inflammation-related disorder is rheumatoid arthritis. that leads to joint damage and inflammation. Inflammation significantly influences the onset and severity of RA, involving immune cells, proinflammatory cytokines and transcription factors. The proinflammatory cytokines such as TNF-α and IL-6 are involved in chronic joint inflammation and destruction in RA. In contrast, the anti-inflammatory cytokine IL-10 is found in low concentrations in RA patients. Transcription factors like Nuclear Factor kappa B (NF-kB) are activated by proinflammatory cytokines and regulate the manifestation of inflammatory agents.

The data and findings indicate the potential therapeutic effects of CM and camel Lf in RA. Animal models of RA, including CIA and monosodium urate-induced arthritis, demonstrate the anti-inflammatory and anti-arthritic properties of CM and Lf. Treatment with CM extracts reduces the severity of arthritis, comparable to the anti-inflammatory medication indomethacin and ibuprofen. CM and Lf also improve body weight gain, indicating reduced inflammation, since higher body weight can contribute to inflammation and may exacerbate symptoms in individuals with RA. Furthermore, they decrease paw thickness, reflecting reduced joint swelling. Thicker paws indicate increased inflammation and swelling associated with arthritis. CM's antioxidant properties, attributed to vitamin C, vitamin E, zinc, selenium and Lf, help neutralize free radicals and reduce oxidative stress commonly observed in RA. These effects highlight the potential of CM and Lf in managing RA. However, further research, including clinical trials, is necessary to determine their efficacy and safety in humans. Nonetheless, CM and Lf offer promising alternatives for future RA treatments due to their anti-inflammatory, antioxidant and anti-arthritic properties.

CONCLUSION

Camel Milk (CM) and camel Lf showed promise as potential therapeutic options for RA. They possess unique anti-inflammatory and antioxidant properties due to the presence of antioxidants such as vitamin C, vitamin E, zinc, selenium and Lf. Animal studies using models of RA have demonstrated that CM and Lf can reduce the severity of arthritis, improve body weight gain and decrease joint swelling. These findings suggest that they have anti-inflammatory and anti-arthritic effects. As current RA treatments can have harmful consequences with long-term use, exploring alternative options like CM and Lf is important. However, further research is required to fully understand their mechanisms of action, optimal dosages and long-term effects in the treatment of RA.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Camel Milk (CM) has been demonstrated to be effective in treating a board range of illness.

The common chronic inflammatory disease known as arthritis has a major negative influence on a person's quality of life.

The multifunctional glycoprotein lactoferrin, which is present in camel milk, has demonstrated positive immunomodulatory and anti-inflammatory effects. The anti-arthritic properties of lactoferrin produced from camel milk have, however, received little attention.

This study seeks to assess the efficacy of camel milk lactoferrin isolated in reducing arthritic symptoms, offering useful insights into its medicinal potential for significantly treating arthritis.

ABBREVIATIONS

CM: Camel Milk; **Lf:** Lactoferrin; **RA:** Rheumatoid Arthritis; **CII:** Collagen type-II; **rpm:** Rotation per min; **BSA:** Bovine serum albumin; **Ig:** Immunoglobin; **i.d:** Intra dermal; **CIA:** Collagen induced arthritis; **CSA:** Camel serum albumin; **CCSEA:** Committee for the Control and Supervision of Experiments on Animals; **HCl:** Hydrochloric acid; **CFA:** Complete Freund's adjuvant.

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