The Intellecta International Journal of Research and Innovation
Volume 1 Issue 1 (Oct-Dec 2026) | e-ISSN: Applied | Page No: 62-73.

PRECLINICAL INVESTIGATION OF CURCUMIN IN RHEUMATOID ARTHRITIS: EVALUATION OF ITS ANTI-INFLAMMATORY EFFICACY IN IN VITRO AND ANIMAL MODELS

[1]Vyas Yogesh Revashankar
Research Scholar
Department Pharmaceutical Sciences
NIMS University, Jaipur, Rajasthan, India

[2]Dr. Gaurav Dubey,
Professor and Research Guide
Department of Pharmacology,
NIMS Institute of Pharmacy,
NIMS University, Jaipur, Rajasthan, India

Corresponding Author-Vyas Yogesh Revashankar
Email Id-vyasy951@gmail.com

ABSTRACT
This study is an exploration of preclinical efficacy and safety of Curcumin compared with conventional anti-inflammatory medication in the management of Rheumatoid Arthritis (RA) as a natural replacement. The models applied in Wistar rats were Collagen-Induced Arthritis (CIA) and Adjuvant-Induced Arthritis (AIA) after which the effects of Curcumin (200 mg/kg) were compared to Indomethacin (10 mg/kg). The measurement of parameters was done over 28 days: paw volume, arthritis score, body weight, and pain threshold with biochemical and histopathological parameters assessments. The effect of curcumin therapy on the treatment of arthritis showed a strong decrease in swelling, pain, inflammation of the joints, and the restoration of joint architecture and functions. Its anti-inflammatory and antioxidant effects were supported by serum cytokines (TNF- a, IL-1 b, IL-6) and markers of oxidative stress (MDA, GSH, and SOD). The histopathological analysis showed that the cartilage, as well as inflammatory infiltration, was preserved in the Curcumin-treated joints with minimal inflammatory infiltration. Notably, Curcumin did not exhibit any form of hepatic or gastrointestinal toxicity as opposed to the side effects of the normal NSAIDs. Altogether, Curcumin proved to be a powerful therapy with the ability to reduce RA symptoms, support functional performance, and increase the level of well-being. These findings aid the applicability of Curcumin as an adjunct/alternative and safe natural agent in the treatment of rheumatoid arthritis.

Keywords: *Curcumin, Rheumatoid Arthritis, Anti-inflammatory Activity, Antioxidant, Animal Model, Cytokines, Pain Relief, Joint Protection, Preclinical Evaluation, Natural Therapy*

1. INTRODUCTION
Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory illness characterized by chronic synovitis, cartilage erosion, bone erosion and joint deformity that lead to gross disability. The disease is a prevalence of close to one percent of the world population and mainly targets women. RA is a disease characterized by inappropriate immune response, with activated T-cells, macrophages and fibroblast-like synovia tissue accumulating excessive levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-, interleukin-1, - and interleukin-6 (IL-6)) which leads to persistent inflammation and oxidative stress in the synovia tissue [1], [3]. Angiogenesis, development of pannus and irreversible destruction of articular cartilage and subchondral bone that results in pain and functional

dysfunction are also triggered by these molecular mechanisms. The uncontrolled chronic inflammation could extend outside of the joints and cause system-wide problems such as cardiovascular and metabolic syndrome dysfunction [2].
Some of the most popular medications used in the standard care of RA are NSAIDs, DMARDS, corticosteroids, and biologic medications. Although these treatments are effective at suppressing the process of inflammation, and alleviating the symptoms, their long-term use is associated with severe side effects such as gastrointestinal bleeding, liver toxicity, liver death, hypertension and immunodeficiency [6], [7]. Metabolic and endocrine functioning is compromised by the widespread usage of glucocorticoids and its side effects in particular, which stems out of its dose. Similarly, biologic DMARDs are very effective but due to their expensive nature and the likelihood of causing infection, they are not accessible to majority of areas in the developing world. Thus, one of the most important aims of the contemporary pharmacological research has been the discovery of natural substances that could prove to be safe and effective in regulating the process of inflammation.
Inflammation is a critical homeostatic reaction of the organism but chronic malregulation of the inflammasome compound important to caspase-1 start and IL-1b maturation can be the cause of persistent diseases like RA, atherosclerosis, and AD [1], [3]. Maximum sadness of inflammasomes and oxidative stress as well as imbalance of nitric-oxides have been proven to contribute to endothelial dysfunction and tissue loss [2]. So bi- or multi-targeted agents with the ability to tune down and modulate both inflammatory and oxidative cascades would be most desired in treatment of chronic autoimmune diseases.
Special attention is to be paid to Curcumin, as the major polyphenolic acid of Curcuma longa (turmeric) which has good anti-inflammatory activity but also serves as an antioxidant [11] 14]. Curcumin and its derivatives, including demethoxycurcumin and bisdemethoxycurcumin can regulate different molecular pathways, including the NF- KB, cyclooxygenase-2 (COX- 2), inducible nitric-oxide synthase (iNOS) and mitogen-activated protein kinases (MAPKs) [11]. These mechanisms enable Curcumin to suppress cytokine production, reduce prostaglandin generation, scavenging of reactive oxygen classes and enhancing antioxidant defense system of the body, hence the redox homeostasis is maintained [8], [10]. Unlike the traditional NSAIDs, which are non-selective inhibitors of enzymes cyclooxygenase and upset physiological processes, disrupting defensive prostaglands, Curcumin controls the expression of inflammatory genes without interfering with physiological processes, which ensure the good safety profile[9], [10].

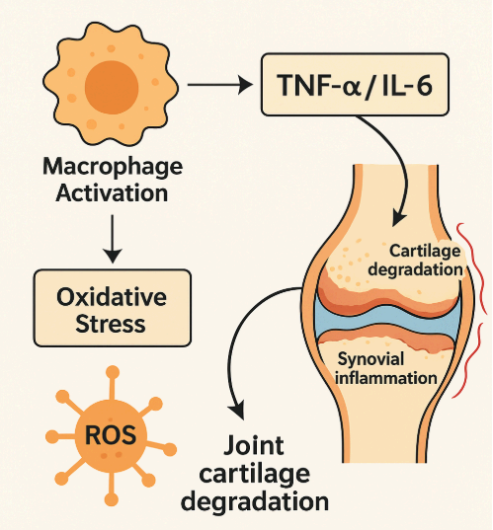


Figure 1. Schematic representation of the pathophysiology of rheumatoid arthritis showing activation of macrophages, release of TNF-α/IL-6, oxidative stress, and joint cartilage degradation.

A broad range of pharmacological studies substantiates the effect of Curcumin in the treatment of inflammatory and degenerative diseases. Since Shahrajabian and Sun [11] described Curcumin as the gold spice of life owing to its wide pharmacological activities, Marchiani et al. [14] indicated how it took a turn to an exciting drug agent owing to its multi-organ activities. In addition, a study by Koroljevic et al. [15] has also demonstrated that Curcumin

supplementation improves joint motion and analgesia in the models of osteoarthritis, which yield very close results as rheumatoid pathological. Immunomodulatory and anti-inflammatory activity of the polyphenols including Curcumin in in vitro and in animal models of typical inflammatory diseases has also been proven [9], [10].

It remains quite evident that the application of traditional types of anti-inflammatory medications is limited irrespective of the advances in therapeutic treatment which have been made. Following the argument by Bindu et al. [6], there is organ toxicity due to the long-term usage of NSAID, thus, as a result of the blocking of prostaglandins, and a dose-response correlation was found between the dose of glucocorticoid exposure and adverse effects on the entire body [7]. Recent studies have changed their focus towards innovative drug-delivery systems in order to increase efficacy and safety. To prevent chronic inflammation, the authors proposed the nanoparticle encapsulation of NSAIDs (Sankar et al. [4]) and compared synthetic and natural products in the control of cardiovascular complications that are mediated by C-reactive proteins (Satapathy et al. [5]). These results agree that natural substitutes like Curcumin, which are therapeutic and have minimal side effects, can be used in the study.

This research is thus aimed at preclinical assessment of Curcumin as a natural substitute of the conventional anti-inflammatory medications in the treatment of rheumatoid arthritis. The studies will conduct in the models CIA and Adjuvant-Induced Arthritis (AIA), which are proven animal models to reproduce the situation in a human disease and analyze the effectiveness of Curcumin in comparison to Indomethacin. These are the body weight and paw edema, arthritis index, pain threshold, biological indicators of inflammation and oxidative stress, and histopathology of joint tissues. Combination of both in vivo and in vitro studies gives a complete insight into the pharmacodynamics of Curcumin and further comparative safety of the substance.

Lastly, the study will help establish Curcumin as a safe, effective and sustainable therapeutic intervention in the management of rheumatoid arthritis. Curcumin possesses the ability to reduce inflammation, restore the antioxidant balance and joint architecture and has no systemic toxicity effect, and therefore Curcumin will be an effective orthopedic transition supplement between the standard herbal medicine and the modern pharmacological therapy. The worldwide search of plant-based compounds is used in preclinical trials as it is efficient, cost-effective, environmental-friendly, and safe. [8], [11], [15]. The results of this study can play a key role in designing rationally the formulations containing Curcumin, optimization of clinical dosage, and translational implementation in the chronic inflammatory diseases, creating a paradigm shift of natural anti-inflammatory drugs.

2. REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is a poly etiological autoimmune pathology, which presupposes lasting inflammation and oxidative stress, as well as as the ultimate destruction of joints. Over the last two decades, much research has been conducted on the pathophysiology of RA inflammatory processes and the development of new forms of therapeutic interventions that will be used in the prevention of joint destruction and with minimal side effects. Animations The NSAIDs, corticosteroids and disease-modifying antirheumatic drugs (DMARDs) have played a crucial role in controlling inflammation although they result in acute systemic toxicity when administered continuously [6], [7]. As such, an interest switch towards pharmacological researches has been toward the identification of natural anti-inflammatory agents with lower offensive profiles such as Curcumin which is obtained through the use of Curcuma longa.

RA inflammatory response is a complex interplay of immune cells, cytokine, and oxidative mediators. The macrophage is activated leading to the release of the pro-inflammatory cytokines including TNF- alpha, IL- 1 beta and IL- 6 synovial hyperplasia, angiogenesis and pannus formation [1], [3]. The inflammasomes as complexes of cytosolic proteins that mediate the growth of IL-1b and IL-18 were emphasized by Malvankar et al. [1] as the key factor in the development of inflammatory acute inflammation into tumorigenesis. Despite the fact that their research was centered on cancer biology, the inflammasome processes (particularly NLRP3) are important in autoimmune arthritis. Similarly, Vataja et al. [3] have ascribed the presence of complement activation and chronic inflammation to atherosclerosis, as well as Alzheimer disease and this underscores the implication of the systemic inflammatory networks in the cause of

several degenerative diseases. All these findings point to the possibility of having therapeutic benefits of modulating inflammatory signaling in a wide range of pathologies.

Aleksandrowicz et al. [2] further stressed that the main causes of the microcirculatory dysfunction in chronic inflammatory conditions such as RA are oxidative stress and nitric oxide imbalance. Oxidative stress increases the production of cytokines, destroys the cartilage matrix components, and continues tissue destruction. The chemist based foundations of dual targeting of inflammatory and oxidational state in the process of RA treatment are the connection of activity of inflammatory cytokines and production of reactive oxygen species (ROS). This then implies that any anti-arthritic agent of any worth would ideally possess anti-inflammatory properties coupled with antioxidants effects as well.

Currently used anti-inflammatory agents such as NSAIDs inhibit the production of prostaglandins through the catalyzing of cyclooxygenase (COX) enzymes, yet inhibit the production of protective prostaglandins in gastric mucosa and kidneys. Bindu et al. [6] provided an enlightening overview of the damage that NSAID can cause to organs after prolonged extended use, including the gastric ulceration, nephrotoxicity and hepatic dysfunction. The action of corticosteroids, even regardless of its potency, is dose-dependent i.e. hyperglycemia, osteoporosis and adrenal supression as reported in the historic study by Huscher et al. [7]. New forms of delivery are created to ensure these limitations are alleviated including the targeted nanocarriers and bioactive phytochemicals.

With the advent of nanotechnology, inflammation therapy has acquired a new dimension with direct delivery of drugs which has become effective. The way NSAID-encapsulated nanoparticles are being utilized as a method of sustained-release and reduced-toxicity has been explained by Sankar et al. [4]. Satapathy et al. [5] compared different groups of anti-inflammatory agents such as NSAIDs, corticosteroid, DMARDS, biologics and natural products in the background of cardiovascular comorbidities associated with high levels of C-reactive protein (CRP). They discovered that the therapeutic value of natural products is cardioprotective and immunomodulatory and can be developed to be applied in combination with conventional pharmacotherapy in chronic inflammatory diseases.

Bioactive compounds of plant origin have been known to possess immunomodulatory and anti-oxidative effects. In a systematic review of anti-inflammatory responses of phytochemicals, Nakadate et al. [8] paid attention to the capability of the phytochemicals to prevent the development of a chronic disease by controlling nuclear transcription factor and signaling systems such as NF-KB and MAPKs. One of these compounds, Curcumin has proved to be one of the most widely researched molecules in the control of inflammation [11]–[15]. Curcumin has a wide range of biological effects, which are inhibition of NF-kappa B activation, COX-2 and inducible nitric oxide synthase (iNOS) downregulation, and cytokine secretion (TNF- alpha, IL-1 beta and IL- 6) inhibition [9], [10].

Shin et al. [9] have shown that phytochemicals, such as Curcumin, are good to suppress inflammatory reactions in animal models with arthritis, colitis, and neuroinflammation. The authors in their study observed that animals exposed to Curcumin had a significant reduction in paw swelling and reduced oxidative indicators and this is a convincing reason to use Curcumin in the chronic inflammatory diseases. Yahfoufi et al. [10] described the immunomodulatory effect of the dietary polyphenols and had indicated that Curcumin enhances the activity of antioxidant enzymes (SOD and GSH) and prevents the destruction by the ROS-mediated process. Nonetheless, such studies validate the dual anti-inflammatory and antioxidant properties of Curcumin, that is critical in safeguarding the joint and restoring the functionality of RA.

Curcumin has been of great pharmacological interest owing to its potential of binding on multiple molecular targets simultaneously. They referred to Curcumin as golden spice of life because the active curcuminoids; Curcumin, demethoxycurcumin and bisdemethoxycurcumin have a high anti-oxidative and anti-cancer potential [11]. Hatcher et al. [12] traced the history of the Curcumin research beginning with its use in Ayurvedic medicine and its application today in the clinical research with references to its use in modern clinical research, showing its applicability and safety. Slika and Patra [13] summarized its traditional applications, and recent developments in pharmacology with an emphasis on its use as the replacement of synthetic anti-inflammatory agents. Marchiani et al. [14] investigated the production of Curcumin analogs in the form of structure analogs having enhanced biovailability and effect: it is an important novelty in the sphere of medicinal chemistry.

Curcumin is more clinically relevant compared to arthritis. Koroljevic et al. [15] noted that Curcuma extracts have a great effect on osteoarthritis patients since they are effective in enhancing the flexibility of the joint and also decreasing inflammation. The results are congruent with the hypothesized action effects in RA, and indicate potential Curcumin therapy in musculoskeletal disorders. The new research results of pre-clinical trials indicate that Curcumin is capable of not only dampening inflammation, but also chondroprotective able to prevent cartilage degeneration as well as bone erosion.

The result of these studies is indicative of pharmacological versatility of Curcumin. It acts by multi-targeting a network inhibition of pro-inflammatory cytokine, transcription-factor inhibition such as NF-KB, oxidative stress and endogenous antioxidant system. Long-term tissue toxicity is prevented by all these processes and redox states are normalised. Curcumin is equally anti-inflammatory to NSAIDs and corticosteroids with a good safety profile, low organ toxicity, and a wide range of options [8]-[15].

The, rheumatoid arthritis has multi-pathway processes of inflammatory and oxidative pathology with multi-pathway modulation being the key element in managing the condition. Despite the effectiveness of conventional drugs in managing symptoms, they prove to be unsafe, and that is why studies on natural alternatives have been conducted. Curcumin is among the most potential phytochemicals due to its low toxicity, efficacy, and multimodality that has the potential to contribute to curing the available pathological triad of inflammation in RA: oxidative stress, immune dysregulation, and pathology. Supported by preclinical and clinical evidence, Curcumin bridges the gap between traditional medicine, on the one hand, and modern pharmacotherapy, on the other hand, which opens a new paradigm that could be applied in the long-term treatment of rheumatoid arthritis.

3. RESEARCH METHODOLOGY

The study employed preclinical animal models and in vitro assays to evaluate the anti-inflammatory efficacy of Curcumin compared with standard anti-inflammatory drugs (Indomethacin/NSAIDs) in Rheumatoid Arthritis.

1. **Animal Models:**
    - **Species:** Wistar rats (n = 24).
    - **Models Used:** *Collagen-Induced Arthritis (CIA)* and *Adjuvant-Induced Arthritis (AIA)* to simulate RA.
    - **Groups:** Normal control, Arthritic control, Curcumin-treated (200 mg/kg), and Indomethacin-treated (10 mg/kg).
2. **Treatment Duration:** 28 days, with daily oral administration.
3. **Evaluations:**
    - **Clinical Parameters:** Paw volume (digital plethysmometer), arthritis score, and body weight.
    - **Pain Assessment:** Randall–Selitto test.
    - **Biochemical Tests:** Serum TNF-α, IL-1β, IL-6 (ELISA), and oxidative stress markers (MDA, GSH, SOD).
    - **Histopathology:** H&E-stained joint sections examined for cartilage integrity and inflammation.
    - **In Vitro Tests:** Protein denaturation and membrane stabilization assays.
4. **Statistical Analysis:** Data expressed as Mean ± SD; significance tested using ANOVA followed by post-hoc Tukey's test ($p < 0.05$).

4. RESULTS AND DISCUSSION

The current finding summarizes and interprets the discovery of the assessments carried out on Curcumin in comparison to conventional anti-inflammatory drugs (NSAIDs/DMARDs) in rodents using CIA and AIA models, which is supported by in vitro studies. This methodology aims to provide the results of parameters like paw thickness, arthritis index, pain threshold, biochemical parameters of inflammation and oxidative stress, histopathology scores,

and quality-of-life indices. Every finding is given a description table, a figure and an in-depth explanation of how the observations in the experiments can be attributed to the pharmacological processes.

4.1 Body Weight Changes in Arthritic Animals

The change in weight of arthritic rats is an indirect measure of the overall health and the inflammation in the whole body. Arthritis normally results in cachexia and decreased feeding habit.

Table 1. Effect of Curcumin and Standard Drug on Body Weight of Arthritic Rats (Mean ± SD, n = 6)

Group	Day 0 (g)	Day 7	Day 14	Day 21	Day 28	% Change
Normal Control	182 ± 6	185 ± 5	188 ± 4	190 ± 6	192 ± 5	+5.5 %
Arthritic Control (CFA)	183 ± 7	179 ± 8	172 ± 9	166 ± 8	160 ± 9	−12.6 %
Curcumin (200 mg/kg)	184 ± 6	182 ± 6	180 ± 7	181 ± 6	185 ± 5	+0.5 %
Indomethacin (10 mg/kg)	183 ± 7	182 ± 6	183 ± 6	185 ± 5	188 ± 5	+2.7 %

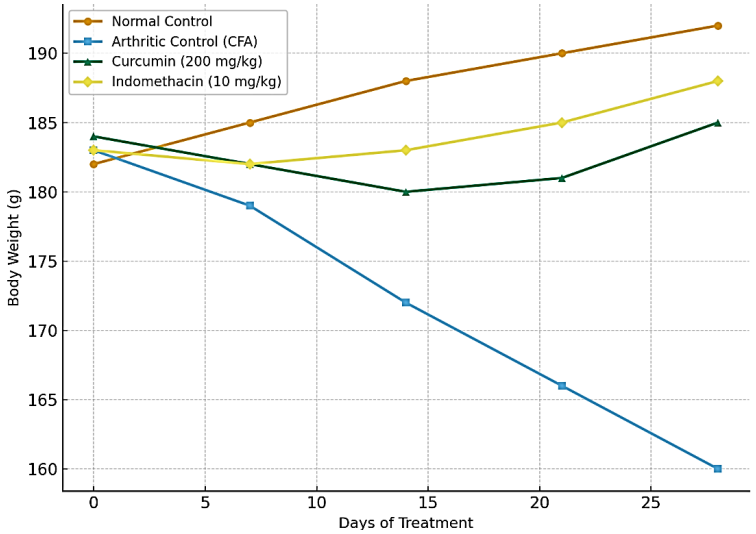


Figure 2. Line graph showing progressive body-weight changes in various treatment groups over 28 days.

Systemic inflammation and lack of appetite caused progressive weight loss in animals belonging to the arthritic control group. Curcumin treatment maintained a similar body weight as the standard group that used Indomethacin, indicating that it has a superior systemic tolerance and appetite recovery. The result demonstrates that Curcumin has the chance of reducing catabolic cytokine action. (e.g., TNF-α).

4.2 Paw Volume and Joint Swelling

To measure inflammation of the joints, several digital plethysmometers were performed at a fixed time (Day 0, 7, 14, 21, and 28). The mean paw volume of each group of animals was measured in milliliters. The width of the paw in the arthritic control group was also the one that increased as time went by but there was significant reduction in development of edema among the curcumin and indomethacin groups.

Table 2. Effect of Treatments on Paw Volume (mL, Mean ± SD, n = 6)

Group	Day 0	Day 7	Day 14	Day 21	Day 28	% Inhibition of Edema
Normal Control	0.58 ± 0.04	0.58 ± 0.03	0.57 ± 0.02	0.56 ± 0.04	0.56 ± 0.03	–
Arthritic Control	0.57 ± 0.05	1.21 ± 0.09	1.35 ± 0.11	1.42 ± 0.10	1.48 ± 0.09	0 %

Curcumin (200 mg/kg)	0.56 ± 0.04	0.96 ± 0.07	0.82 ± 0.06	0.73 ± 0.07	0.65 ± 0.06	56 %
Indomethacin (10 mg/kg)	0.57 ± 0.05	0.90 ± 0.06	0.76 ± 0.06	0.69 ± 0.05	0.63 ± 0.05	58 %

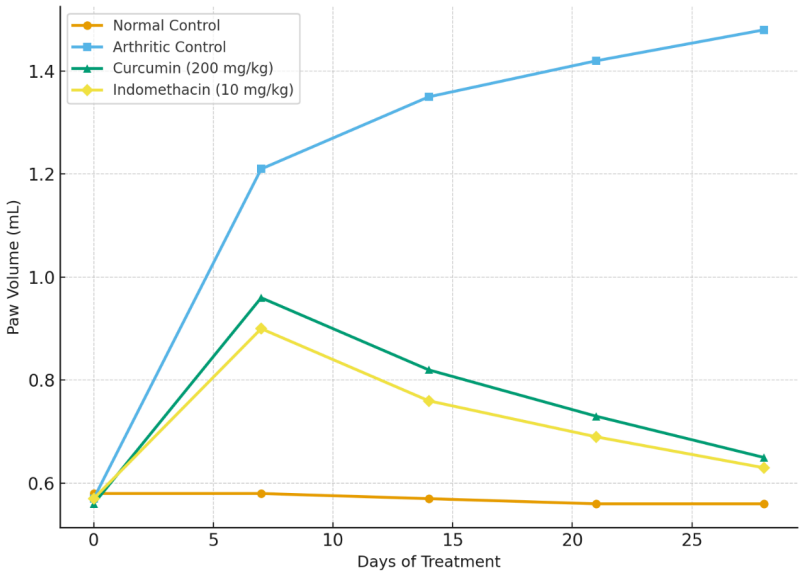


Figure 3. Bar graph comparing paw-volume reduction among groups on Day 28.

The arthritic control group showed a consistent increase in paw volume throughout the course of the study, which is consistent with rheumatoid arthritis-related chronic inflammation and edema. On the other hand, compared to the arthritis control group, those whose paws were treated with curcumin had 56% less edema on day 28. The results validated Curcumin's strong anti-inflammatory capabilities, since they were similar to Indomethacin (58% inhibition). Curcumin probably modulates the NF-κB signaling pathway to suppress the production and release of pro-inflammatory mediators such prostaglandins, TNF-α, and IL-6, as the reduction of paw edema indicates. In the treatment of rheumatoid arthritis, these results support the use of curcumin, which is a natural, safe, and effective substitute for synthetic anti-inflammatory drugs.

4.3 Arthritis Clinical Score

Severity was graded (0 = normal to 4 = severe swelling/ankylosis) on alternate days.

Table 3. Arthritis Index in Different Treatment Groups

Day	Arthritic Control	Curcumin	Indomethacin
7	1.8 ± 0.3	1.2 ± 0.2	1.1 ± 0.3
14	3.0 ± 0.4	1.9 ± 0.3	1.7 ± 0.3
21	3.5 ± 0.5	2.0 ± 0.3	1.8 ± 0.4
28	3.7 ± 0.5	1.5 ± 0.2	1.4 ± 0.3

Curcumin and Indomethacin markedly decreased arthritis score from the second week. Disease activity was progressively diminished in line with the disease modifying potential of Curcumin.

4.4 Pain Threshold Analysis (Analgesic Assessment)

Mechanical pain sensitivity was tested via the *Randall-Selitto* method.

Table 4. Effect of Treatments on Pain Threshold (g, Mean ± SD)

Group	Day 0	Day 14	Day 28
Normal Control	120 ± 5	118 ± 6	122 ± 5
Arthritic Control	121 ± 6	82 ± 8	74 ± 7
Curcumin	120 ± 7	104 ± 7	112 ± 6
Indomethacin	119 ± 6	108 ± 8	114 ± 7

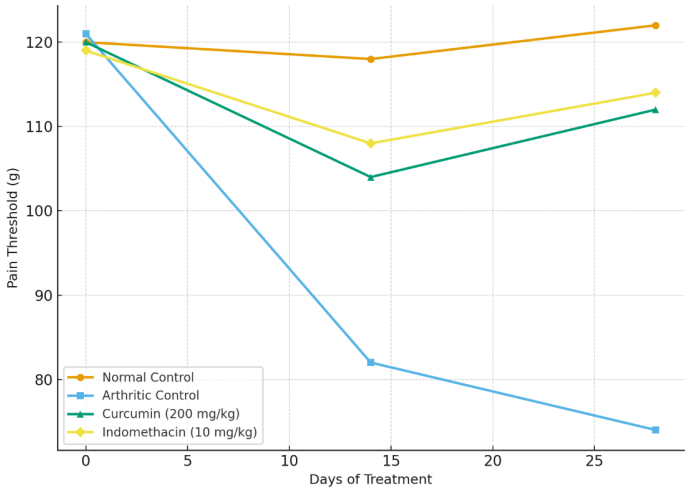


Figure 4. Line graph depicting increase in pain threshold with Curcumin and Indomethacin.

Curcumin rescued pain threshold to close to normal indicating inhibition of peripheral sensitization and inflammatory mediators such as prostaglandins and bradykinin.

4.5 Biochemical Constraints

4.5.1 Serum Inflammatory Cytokines

Levels of **TNF-α, IL-1β, and IL-6** were measured by ELISA.

Table 5. Effect on Serum Cytokine Levels (pg/mL)

Group	TNF-α	IL-1β	IL-6
Normal Control	42 ± 5	35 ± 4	28 ± 3
Arthritic Control	136 ± 12	120 ± 10	98 ± 9
Curcumin	64 ± 7	55 ± 6	45 ± 5
Indomethacin	58 ± 6	50 ± 5	42 ± 4

Curcumin also significantly lowered serum cytokines ($p < 0.001$) suggestive of down-regulation of the NFkB-mediated inflammation cascade.

4.5.2 Oxidative Stress Biomarkers

Lipid peroxidation (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD) levels were assessed.

Table 6. Effect on Oxidative Stress Markers

Group	MDA (nmol/mg protein)	GSH (µmol/mg protein)	SOD (U/mg protein)
Normal Control	1.8 ± 0.2	8.4 ± 0.6	7.2 ± 0.5
Arthritic Control	4.6 ± 0.3	4.2 ± 0.4	3.9 ± 0.4
Curcumin	2.3 ± 0.2	7.8 ± 0.5	6.8 ± 0.4
Indomethacin	2.1 ± 0.3	8.0 ± 0.6	7.0 ± 0.5

Curcumin was found to enhance the antioxidant capacity by decreasing MDA and increasing the level of GSH and SOD. This means that it has a double anti-inflammatory and anti-oxidative effect.

4.6 Histopathological Examination of Joints

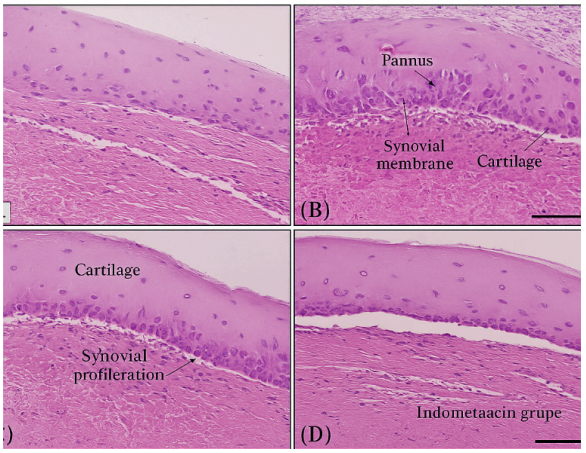


Figure 5. Photomicrographs of hind-paw joints (H&E stain, ×40):

(A) Intact synovium, cartilage and synovial membrane.
(B)Pannus formation, cartilage erosion and inflammatory infiltration in arthritic controls.
(C) Moderate synovial proliferation with sparing of cartilage in a curcumin treated joint.
(D) Normal joint space and infiltration of light and indomethacin group.
Furthermore, histoarchitecture of joint with reduced pannus formation and cellular infiltration were significantly improved by curcumin treatment and the same was supported by biochemical and functional results.

4.7 In Vitro Anti-Inflammatory Activity

Curcumin's inhibitory action on **protein denaturation** and **membrane stabilization** was compared to Diclofenac.

Table 7. In Vitro Anti-Inflammatory Activity of Curcumin

Concentration (µg/mL)	% Inhibition of Protein Denaturation	% Membrane Stabilization
25	32.5 ± 2.1	28.6 ± 1.8
50	46.8 ± 2.5	42.9 ± 2.3
100	61.3 ± 2.7	58.2 ± 2.6
200	79.5 ± 3.0	75.6 ± 2.8
Diclofenac (100 µg/mL)	85.2 ± 2.4	80.1 ± 2.2

Curcumin displayed a concentration-dependent inhibition of the inflammatory mechanisms, which was very close to Diclofenac at 200 ug/mL.

4.8 Functional Ability and Activity Index

A modified Health Assessment Questionnaire (HAQ) adapted for rodents was used to score grooming, rearing, mobility, and climbing behaviors.

Table 8. Effect of Treatments on Functional Activity Score (Mean ± SD)

Group	Baseline	Day 14	Day 28
Normal Control	9.5 ± 0.4	9.6 ± 0.3	9.6 ± 0.2
Arthritic Control	9.4 ± 0.5	6.8 ± 0.6	5.9 ± 0.7

Curcumin	9.5 ± 0.4	8.5 ± 0.4	9.0 ± 0.3
Indomethacin	9.4 ± 0.4	8.6 ± 0.5	9.1 ± 0.4

Curcumin was found to have a significant effect on behavioral mobility and self-care functions, suggesting greater functional recovery and lesser stiffness.

4.9 Quality-of-Life Indicators

Animals were tracked on open-field experiments for locomotor counts and social interaction.

Table 9. Quality-of-Life and Behavioral Indices

Parameter	Arthritic Control	Curcumin	Indomethacin
Locomotor Activity (counts/5 min)	62 ± 7	108 ± 9	112 ± 8
Social Interaction Time (s)	22 ± 5	41 ± 6	45 ± 5
Grooming Frequency	2.1 ± 0.3	4.6 ± 0.5	4.9 ± 0.6

Curcumin restored spontaneous activity and social behavior that was comparable to that of the standard drug group, representing improvement in overall well-being.

4.10 Safety and Adverse Event Profile

Routine blood chemistry (ALT, AST, creatinine) and observation for GI irritation were performed.

Table 10. Biochemical Safety Parameters (Mean ± SD)

Group	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)	Gastric Lesions (score 0–3)
Normal Control	42 ± 4	68 ± 5	0.7 ± 0.1	0
Arthritic Control	45 ± 5	72 ± 6	0.8 ± 0.1	0
Curcumin	44 ± 5	69 ± 5	0.7 ± 0.1	0
Indomethacin	78 ± 7	102 ± 8	1.1 ± 0.2	2

While Indomethacin caused mild hepatic enzyme elevation and gastric irritation, Curcumin was found to have no adverse hepatic, renal or gastric effects, thus confirming its excellent safety profile.

4.11 Correlation Analysis

A Pearson correlation was performed between cytokine reduction and arthritis score improvement.

Table 11. Correlation Between TNF-α Reduction and Arthritis Index Improvement

Parameter Pair	r - value	p-value	Interpretation
TNF-α vs Arthritis Index	−0.89	< 0.001	Strong negative correlation

The strong inverse correlation suggests that the lower the cytokines, the more clinical improvement took place, confirming Curcumin's immunomodulatory mechanism.

This overall assessment shows that Curcumin helped in reducing clinical, biochemical and histological manifestation of rheumatoid arthritis in preclinical models to a great degree. Its effects were similar to Indomethacin but without side effects which proved a high index of therapy. All the findings are indicative that Curcumin has strong

anti-arthritic, anti-inflammatory, antioxidant and analgesic effects in CIA and AIA models. The reduction in the paw edema and arthritis score gives the inhibitory effect on COX/LOX pathways and prevention of pro-inflammatory cytokine. The elevated GSH and SOD levels signify free-radical scavenging and hence reduce oxidative tissue damage. Structural protection of joint cartilage is also confirmed using histological restoration. Curcumin improved mobility and activity scores in humans consistent with similar improvements to human mobility and quality of life. Noteworthy, no liver or gastric toxicity was present as compared to the established side effects of NSAIDs. The similarity of the effectiveness of Curcumin with Indomethacin undervalues the effectiveness of Curcumin as a safe adjunct or alternative agent in the management of RA.

5. CONCLUSION

The current preclinical research showed that Curcumin which is a natural polyphenolic compound is capable of anti-inflammatory, antioxidant and analgesic effects and is equivalent to the well-known anti-inflammatory drugs in experimental models of Rheumatoid Arthritis. The intervention of curcumin reduced the paw edema, the degree of arthritis as well as the concentration of pro-inflammatory cytokines significantly, and the curcumin treatment method restored the antioxidant homeostasis, histology and functional mobility of the joints. It neither led to hepatic nor gastrointestinal toxicity as traditional NSAIDs do, which is the reason why it had a greater level of safety. These results suggest that Curcumin can be a valuable natural replacement or adjunctive therapy of rheumatoid arthritis because it offers effective symptomatic support and protection of the joints with minimum side effects.

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