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# Comparative Effects Of Leflunomide And Physical Exercise On Body Weight, Synovial Joints, Articular Diameters, Paw Volume And Arthritic Score Index Following Complete Freund Adjuvant Induced Rheumatoid Arthritis In Wistar Rats (Rattus Nervogicus)

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***Abstract:***
*Rheumatoid Arthritis Is A Systemic Connective Disease That Affects The Normal Morphological Structures Of Synovial Joints In The Body. It Is An Autoimmune Disease That Completely Destroys The Articular Ends Of Bones, Their Articular Cartilages, And Synovium, Leading To Joint Immobility And Eventual Disability. The Use Of Leflunomide (DMARD) Or Physical Exercises, Either As Monotherapy Or In Combination, In The Management Of Rheumatoid Arthritis Has Remained A Subject Of Controversy. There Is No Scientific Data That Shows The Ameliorating Effect Of Either In The Restoration Of Normal Joint Structures, And It Is Also Unclear Which Doses Would Be Most Effective When Used As A Monotherapeutic Approach Or In Combination.Although There Is No Known Cure For Rheumatoid Arthritis, The Use Of Leflunomide Or Physical Exercise As Treatment Options Has Been Documented In The Literature To Reduce Disease Progression. In This Study, A Controlled-Experimental Study Design Was Adopted, Using Male Wistar Rats As The Experimental Model In The SAFARI Animal House Of JKUAT. A Sample Size Of 55 Adult Wistar Rats Obtained From A Pure Breed Colony Was Used. These Rats Were Randomly Assigned To Two Broad Study Groups: 10 Rats In The Control Group (5 Positive And 5 Negative Control) And 45 Rats In The Experimental Group.The 45 Rats In The Experimental Group Were Further Subdivided Into 9 Experimental Study Groups As Follows: 15 Rats For Physical Exercise, 15 Rats For Leflunomide Therapy, And 15 Rats For Combined Therapy With Both Leflunomide And Physical Exercise. To Determine The Effects Of Varied Doses In The Three Study Categories In Restoring The Degenerated Joint Structures, The 15 Rats In Each Of The Above Three Study Groups Were Further Subdivided Into Three Rats Each According To Doses Of Low, Medium, And High. For Example, In The Leflunomide Group: 5 Rats Received The Low Dose Of 5mg/Kg/Bwt, 5 Rats Received The Medium Dose Of 7.5mg/Kg/Bwt, And 5 Rats Received The High Dose Of 10mg/Kg/Bwt. Similarly, In The Physical Exercise Group, 5 Rats Were Assigned To The Low-Intensity Exercise Group (0-30 Minutes), 5 Rats To The Medium-Intensity Exercise Group (30-60 Minutes), And 5 Rats To The High-Intensity Exercise Group (60-90 Minutes). The Combined Therapy Group Received Both Leflunomide And Physical Exercise At The Corresponding Doses And Exercise Intensities As Described Above. Physical Exercise Was Administered By Exposing The Rats To Swimming In A Timed Warm Water Pool.All Rats Received Standard Rodent Pellets And Water Ad Libitum Throughout The Entire Experimental Period. The Rats In The Positive Control And Experimental Groups Received Complete Freund Adjuvant (CFA) To Induce Rheumatoid Arthritis 3 Weeks Before The Beginning Of The Experiment. The Experimental Group Received Varied Doses Of Leflunomide Therapy According To Their Study Groups: 15 Mg/Kg/Bwt For The High Dose Group, 10 Mg/Kg/Bwt For The Medium Dose Group, And 5 Mg/Kg/Bwt For The Low Dose Group. The Rats In The Physical Exercise Experimental Group Were Also Divided Into Low, Medium, And High Intensity Exercise Groups Based On The Duration Of Exercise Per Day. The Combined Therapy Group Received Both Leflunomide And Physical Exercise Corresponding To The Doses And Exercise Intensity Described Above.Animal Weights Were Recorded Daily, And Articular Diameters Were Measured At Three Time Points: Before Induction, After Induction, And After Treatment. All Animals Were Humanely Sacrificed At The End Of The 9th Week. The Data Were Entered Into An Excel Sheet And Analyzed Using SPSS Version25.Comparative Inferential Statistics Were Tested Using One-Way And Two-Way Analysis Of Variance (ANOVA) For The Means Within And Between Groups. A P-Value Of Less Than 0.05 Was Considered Significant. Friedman Tests Were Used To Assess The Day Of Onset And Arthritis Severity Scores Between The Groups, And The Wilcoxon Test Was Used To Determine*

*Significances. Pearson Tests Were Used To Perform Cross-Correlation Analyses, And Linear Regression Analyses Were Performed With Arthritis Scores Index As Independent Variables. P-Values Less Than 0.05 Were Considered Statistically Different, And Pearson's Correlation Coefficient Was Used For Comparisons Of Strength And Direction Of Association Among Different Parameters. The Data Were Presented Using Bar Charts, Graphs, Tables, And Graphs Trends. Significant Differences (P < 0.05) Were Observed For The Diseased Group Rats Compared To The Negative Control And Treatment Group Rats. In Conclusion, Leflunomide And Physical Exercise May Have A Synergistic Joint Protection Effect, And Therefore, Both Can Be Recommended To Be Used Concurrently In Treatment Of Rheumatoid Arthritis.*

***Key Words:*** *Comparative, Rheumatoid Arthritis, Leflunomide And Physical Exercise*

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## I. Introduction

Rheumatoid arthritis is a chronic autoimmune inflammatory disease that affects the body's own articular joint tissues in all synovial joints. It is characterized by synovitis, which leads to painful swelling, destruction of enthuses, and joint deformity over time (Bullock et al., 2019). Globally, rheumatoid arthritis affects up to 30% of the population, which is approximately 2.5 billion people (Cross et al., 2014). If left untreated for extended periods, rheumatoid arthritis can cause bone erosion and subsequent joint deformity, resulting in loss of mobility and overall disability (Guo et al., 2018).

The choice between using leflunomide, a commonly used anti-rheumatic drug (cDMARD), and physical exercises as treatment options for rheumatoid arthritis has been a topic of controversy. Some studies advocate for using leflunomide alone, with or without physical exercises, while others prefer a combined therapeutic approach using leflunomide in combination with physical exercises (Guo et al., 2018). This controversy poses challenges for clinicians in making the best treatment choices and negatively impacts treatment outcomes for patients (Fraenkel et al., 2021). To resolve this controversy, this study aims to investigate the histostereological and histomorphological ameliorative effects of these two treatment approaches, either as monotherapy or in combination, to generate data that can guide clinicians in choosing the most effective approach for achieving optimal treatment outcomes (Guo et al., 2018).

In rheumatoid arthritis, the synovial membrane, responsible for producing synovial fluid, swells and thickens, leading to excessive synovial fluid production and hyperplasia (Guo et al., 2018). This further contributes to swelling, inflammation, and joint pain and stiffness. Immunohistological staining of the joint synovium reveals an increased number of synoviocytes and infiltration of immune and inflammatory cells, including macrophages, B- and T-lymphocytes, plasma cells, and dendritic cells (Guo et al., 2018). Elevated levels of cytokines are also observed. Cytokines play a central role in perpetuating synovial inflammation, and the persistent chronic inflammatory response, along with ongoing joint destruction, may be a result of sustained recruitment, impaired apoptosis, and inappropriate retention of immune and inflammatory cells (Maru, 2020).

Leflunomide acts as a selective inhibitor of pyrimidine synthesis through its active metabolite A77 1726, which reversibly inhibits dihydroorotate dehydrogenase (DHODH) at low doses. This metabolite is a rate-limiting step in the synthesis of pyrimidines (Breedveld & Dayer, 2000; Smolen et al., 2000). By inhibiting DHODH, A77 1726 prevents lymphocytes from accumulating sufficient pyrimidines for DNA synthesis. At higher doses, A77 1726 inhibits tyrosine kinases involved in early T cell and B cell signaling during the G0/G1 phase of the cell cycle (Breedveld & Dayer, 2000). Leflunomide prevents the expansion of activated and autoimmune lymphocytes by interfering with cell cycle progression due to inadequate production of rUMP and utilizing mechanisms involving p53.

Exercise therapy has emerged as a paradigm for the treatment of rheumatoid arthritis due to its cost-effectiveness and absence of side effects. Exercise has been shown to inhibit bone destruction and the formation of bone spurs (Pitcher, 2018). It improves cardiovascular circulation, reducing the risk of

cardiovascular and metabolic complications. Biochemical studies using experimental rat models subjected to treadmill running have demonstrated that physical exercises inhibit the production of connexin 43 and TNF, which are key factors in rheumatoid arthritis (Allen et al., 2018). Exercise therapy has also been found to suppress pro-inflammatory cytokines, contributing to the inhibition of joint destruction through molecular mechanisms (Maddison et al., 2005).

The natural course of rheumatoid arthritis is divided into an induction phase following immunological sensitization, a pre-arthritis phase characterized by autoantibody production, and an established phase in which arthritis occurs and progresses. Pharmacotherapy has shown effectiveness in the established phase, where cytokine production is high. However, the effectiveness phase of exercise therapy is not well defined. This research aims to answer these questions.

Currently, rheumatoid arthritis affects approximately 2.5 billion people worldwide, with about 700 million people in sub-Saharan Africa, of which 80% are women and 20% are men (Reginster, 2002). Despite the absence of a known cure, the management of rheumatoid arthritis progression to end-stage disease using cDMARDs like leflunomide, and exercise therapy has been a subject of controversy. Some authors advocate for the use of leflunomide alone as the monotherapy of choice for restoring joint structures, while others prefer combined therapy with physical exercise (Symmons et al., 2006).

## II. Materials and Methods

**Study Design:** Static control experimental laboratory posttest study design was used

**Study Location**: The animal experiment was carried out at JKUAT safari animal house. The rats were raised in an environment at 27±2˚C with 55±5% humidity and a 12 h light/dark cycle. All rats had free access to food and water *ad libitum* .

**Study Duration:** November 2020 to July 2022.

**Sample size:** 55 Adults wistar rats

**Sample size calculation:** The sample population was drawn after the resources equation where a total of 55 wistar rats were included in the experiment,

**Rat grouping:** Out of 55 wistar rats 10 rats was assigned to control group and 45 rats was assign to experimental group. Through simple random sampling, 5 rats were assigned to negative control group and 5 rats to diseased control group, to determine the effects the effects of both leflunomide and physical exercise of 45 rats were assigned to two major group of leflunomide treatment group and physical exercise treatment group. Leflunomide group was further assigned to low, medium and high dose groups (5mg,7.5mg and 10mg/bwt per day), while physical exercise group were further assigned into low, medium and high intensity swimming group (low, medium and high intensity swimming group).

**Drugs administration and physical exercise**

According to the previous methods, the experiment involved inducing inflammation in rat groups, except for the negative control group. The inflammation was induced by subcutaneously injecting 0.1 ml of complete Freund's adjuvant at the base of the tail. The intragastric administration of leflunomide and physical exercise treatments started on the 10th day and continued until the 72nd day of the experiment.

In the leflunomide group, rats were administered leflunomide via intragastric administration once a day at 9 am. The dosage used was 10 mg/kg body weight, 7.5 mg/kg body weight, and 5 mg/kg body weight, respectively.

For the physical exercise (swimming) group, the exercise sessions were conducted once daily starting from 9 am. The swimming was performed at a temperature of 30 degrees Celsius and at different intensities. The low-intensity swimming group swam for 30 minutes, the medium-intensity group swam for 60 minutes, and the high-intensity group swam for 90 minutes.

The negative control group received saline injections daily, while the positive control group did not receive any treatment.

On the 72nd day of the experiment, all the rats were humanely sacrificed. It is mentioned that all the animal experimental protocols were conducted according to the ethical guidelines of animal ethics and the guidelines of Jomo Kenyatta University of Agriculture and Technology

**Body weight and paw volume measurements**

The daily body weight of the rats was measured from 0th day till the end of the experimental period. There after the percentage weights increment was calculated by doing difference between initial and final weight over the initial weight of the animals and multiplied by 100%.

$$\text{Percentage of body weight} = \frac{\text{Body weight on day 0} - \text{Body on day 72}}{\text{Body weight on day 0}} \times 100\%$$

The paw volume of rats both the fore and hind paws was measured on initial day (0th day) before CFA injection and subsequently after induction on 15th day and 72th day using plethysometer (Figure1.1). The hind paw volume was calculated by subtracting final paw volume from the initial volume.

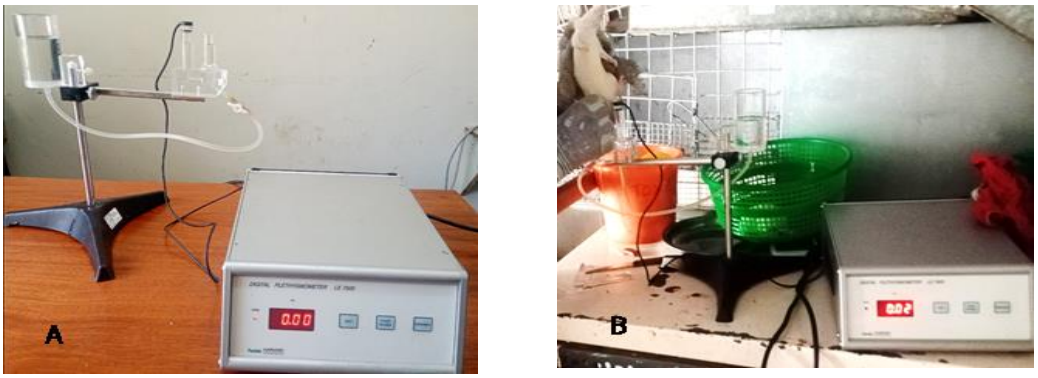


**Figure 1.1:** photo*gram showing: **A** calibrations of plethysometer, **B**; showing how to measure of hind limbs* volumes of the wistar rat

**Articular diameter**

In this study, the gross morphometry of the joints was assessed, and the inflammatory edema was quantified. The measurement of articular diameter was conducted using a digital caliper. The measurements were taken before the induction of inflammation, after induction, and after the treatment, following the protocol described by Fernando et al. (2020).

Severe and acute inflammation of the joints was observed within 30 minutes of injection with complete Freund's adjuvant. The inflammation reached its peak within 3 to 4 days and often persisted for 20 to 25 days. However, it's important to note that the injected site was not included in the arthritis severity scoring protocol since swelling always occurs at the injected site, even when arthritis is absent in other limbs.

The circumference of the fore and hind paws, as well as the shoulder, elbow, hip, knee, and ankle joints, were evaluated. The measurements were taken using a digital caliper, with the nearest measurement recorded to 0.01 mm. These measurements were performed to assess the changes in joint size and swelling throughout the experimental period

**Arthritic score**

n this study, the severity of arthritis in the paws of the animals was evaluated periodically every three days. The evaluation was performed using an arthritic score protocol, which involved assigning a grade ranging from 0 to 4 to each animal based on the observed symptoms.

The grading system used in the arthritic score protocol is as follows:

Grade 0: Indicates the absence of swelling in the paws.

Grade 1: Denotes mild swelling or erythema in one of the fingers in the paw.

Grade 2: Shows swelling in one or more paws.

Grade 3: Displays swelling of the wrist or ankle.

Grade 4: Specifies severe arthritic swelling in the fingers and wrist.

The highest arthritic score fixed for rats induced with complete Freund's adjuvant (CFA) in this study is score 8. This score represents the most severe arthritic condition observed in the animals.

Figure 3.1 in the study likely illustrates the distribution of the arthritic scores among the experimental groups, providing a visual representation of the severity of arthritis over time


**Figure 3.1**: *Photogram showing A: the hind limb swelling B: erythema of the skin of the positive control rats*

## III. RESULTS

**Effect of leflunomide and physical exercise on body weight, articular diameter, and hind paw volume and arthritic index score.**

**Body weight**

The body weight of rats induced with CFA was significantly decreased compared to the negative control group and the treatment groups that received leflunomide and physical exercise (as shown in the figure). There was a statistically significant difference observed in the positive induced group when compared to the control group and the treatment groups that received leflunomide at high, medium, and low doses, as well as physical exercise at high, medium and low levels.

**Table 1: Showing means body weight before induction, after induction and means percentage body weight changes in group rats**

| Group | Means Body Weight before induction | Means Body weight after treatment |
|---|---|---|
| **Control** | **214.40±25.44** | **229.40±37.37** |
| **Diseased group** | **206.20±4.20** | **235.80±8.06** |
| **PEL** | **220.60±21.29** | **219.80±17.55** |
| **PEM** | **220.60±18.83** | **248.40±10.84** |
| **PEH** | **234.8±15.20** | **266.00±16.26** |
| **LEFL** | **224.20±12..23** | **227.60±16.03** |
| **LEFM** | **210.20±10.82** | **220.60±10.03** |
| **LEFH** | **204.8±2.60** | **218.00±12.70** |
| **LEFHPEL** | **227.60±31.08** | **234.00±32.72** |
| **LEFHPEM** | **214.40±20.25** | **232.00±24.73** |
| **LEFHPEH** | **230.60±18.93** | **253.40±17.23** |
| **P-VALUE** | **.392** | **.402** |

**Key**: **PEL**-physical exercise low intensity, **PEM**- physical exercise medium intensity **PEH**- physical exercise high intensity, **LEF L**-Leflunomide low dose, LEF **M** Leflunomide medium dose, **LEF H** Leflunomide high dose,**LEFH PEL**_Leflunomide high dose plus physical exercise low intensity , **LEFH PEM**-Leflunomide high dose plus physical exercise low intensity **LEFH PEH**-Leflunomide high dose plus physical exercise low intensity

**Paw volume**

Fore and hind paw volume of the induced group rats was markedly increased compared to negative control group and treatment group of leflunomide and physical exercise. Leflunomide treated and physical treated arthritic rats showed decrease in paw volume compared with CFA induced rats. Paw volume of all the animals in each group increase initially but decrease after treatment with leflunomide and physical exercise.

**Table 2: Showing the means paw volume**

| | Elbow joint | Wrist joint | Knee joint | Ankle joint |
|---|---|---|---|---|
| **Control** | 0.3260±.4930 | .3700 ±.0432 | .4760±.093 | .3080±.0542 |
| **Diseased control** | 0.5320±.0909 | .4520±.0571 | .5600±.042 | .5270±.0613 |
| **PEL** | 0.3820±.0769 | .3080±.0834 | .3500±.036 | .3360±.0974 |
| **PEM** | 0.4540±.0415 | .4480±.0729 | .4700±.070 | .3380±.9872 |
| **PEH** | 0.4220±.0914 | 3480±.1164 | .3625±.0960 | .3400±.9621 |
| **LEF L** | 0.4100±.0935 | .3360±.0798 | .3100±.089 | .3460±.8762 |
| **LEFM** | 0.4320±0.3347 | .3140±.0512 | .2980±.033 | .3480±.7510 |
| **LEFH** | 0.4600±.0374 | .3460±.0083 | .3380±.020 | .3480±.6413 |
| **LEHPEL** | 0.4700±.5780 | .3400±.0158 | .3400±.053 | .3140±.1236 |
| **LEHPEM** | 0.4960±.4561 | .3380±.0414 | .3820±.040 | .5240±.7616 |
| **LEFHPEH** | 0.4660±.0832 | .3460±.0114 | .3852±.025 | .5232±.234 |
| **F value** | 3.431 | 1.761 | 8.894 | 1.73 |
| **P value** | 0.002 | 0.097 | 0.001 | 0.001 |

**Key**: **PEL**-physical exercise low intensity, **PEM**- physical exercise medium intensity **PEH**- physical exercise high intensity, **LEF L**-Leflunomide low dose ,**LEF M** Leflunomide medium dose, **LEF H** Leflunomide high dose,**LEFH PEL**_Leflunomide high dose plus physical exercise low intensity , **LEFH PEM**-Leflunomide

high dose plus physical exercise low intensity **LEFH PEH**-Leflunomide high dose plus physical exercise low intensity

**Articular diameter**

There was statistical significant different (P 0.05) of articular diameter of positive control rats compared with the negative control group and treatment groups in both anterior- posterior and lateral measurements. While there was no significant different on control and treatment group of leflunomide and physical exercise

**Table 4.1: Showing the gross means articular diameters of the control,diseased and treatment groups .**

| | Elbow joints | Wrist joints | Knee joints | Ankle joints |
|---|---|---|---|---|
| **Control** | 3.7080±.5502 | 4.7080±.3483 | 5.1400±.554 | 5.900±.1871 |
| **Positive control** | 4.8060±..2797 | 5.3160±.3283 | 6.2600±336 | 6.606±.2510 |
| **PEL** | 4.9280±.61740 | 4.4720±.24905 | 5.840±.3286 | 6.540±.6189 |
| **PEM** | 5.2590±.43182 | 5.794±.40439 | 5.80±.3082 | 7.040±.3209 |
| **PEH** | 5.180±..48350 | 5.6800±.3721 | 5.940±.5179 | 6.960±.5079 |
| **LEF L** | 4.980±.17277 | 5.6060±.5395 | 5.900±.4415 | 6.480±.5404 |
| **LEFM** | 5.350±.16857 | 5.6060±.260 | 5.580±.2490 | 6.060±.5505 |
| **LEFH** | 5.384±..20372 | 5.8380±.203 | 5.6600±.2302 | 6.700±.3808 |
| **LEHPEL** | 5.7560±.2884 | 5.9300±.35199 | 5.5400±.2302 | 6.500±.2387 |
| **LEHPEM** | 6.320±.44842 | 6.4240±.3466 | 5.6260±.2405 | 7.180±.4712 |
| **LEFHPEH** | 4.494±..1412 | 7.0180±.1883 | 5.7420±.2717 | 7.120±.4868 |
| **F Value** | 15.696 | 21.613 | 3.147 | 4.479 |
| **P value** | .000 | 0.000 | .0004 | .000 |

Key: **PEL**-physical exercise low intensity, **PEM**- physical exercise medium intensity **PEH-** physical exercise high intensity, **LEF L**-Leflunomide low dose, **LEF M** Leflunomide medium dose, **LEF H** Leflunomide high dose,**LEFH PEL**_Leflunomide high dose plus physical exercise low intensity , **LEFH PEM**-Leflunomide high dose plus physical exercise low intensity **LEFH PEH**-Leflunomide high dose plus physical exercise low intensity

**Arthritic score**

Arthritic rats showed marked rise in arthritic score index of diseased control group compared with that of non-treated and treatment group as showed by figure 4 below. Leflunomide treated rats portrayed clear decreased in arthritic score with that of control group rats. Physical exercise treated rats also displayed reduction in arthritic score when compared with CFA induced rats. CFA induced rats resulted in increase in arthritic score index compared with negative control and treatment group both leflunomide and physical exercise. CFA induced rats administered with leflunomide and physical exercise displayed decline in arthritic score in comparison to diseased control animals. There was an overall significant difference P= 0.000 (P<0.001) $\chi 2$= 371.529

**Table 4: Showing the chi-square result of arthritic score index**

| Test Statisticsa | |
|---|---|
| N | 55 |
| Chi-Square | 371.529 |
| df | 19 |
| Asymp. Sig. | .000 |
| a. Friedman Test | |

## IV. Discussion

**Rats weight and paw volume**

The current study observed a marked reduction in body weight in rats induced with complete Freund's adjuvant (CFA), which is consistent with findings from previous studies by Li et al. (2018) and Gao et al. (2010). This decrease in body weight can be attributed to several factors. Firstly, the rats may experience difficulty in assessing feeds and water due to joint pain caused by joint inflammation. Additionally, there may be underlying pathophysiological changes in the body associated with disease progression, as mentioned by Maru (2020).

Rats with induced arthritis often exhibit characteristic symptoms similar to those seen in humans with rheumatoid arthritis, including morning stiffness, polyarticular pain, and swelling. The stiffness and difficulty in moving the paws observed in the rats resemble the human experience of joint stiffness and difficulty in forming a normal gait pattern. Arthralgia, accompanied by swelling and limited mobility, is commonly observed in joints

such as the proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints, as well as the knees, feet, hands, elbows, and cervical spine (Ten Brinck et al., 2018).

In the treatment groups receiving leflunomide at varying dosages, a significant increase in weight was observed. Similar observations have been reported by Abbas et al. (2022). This weight gain can be attributed to the ameliorative effects of leflunomide on the joints, leading to improved physiological well-being and subsequently better feeding and physical activity in the rats.

The present study also noted a marked increase in paw volume in rats induced with CFA compared to the control group and the treatment groups receiving leflunomide and physical exercise. This observation aligns with the findings of Cui et al. (2019) and can be attributed to the inflammatory process causing swelling and the formation of nodules on the joints and the overlying skin.

Arthritic rats exhibited a significant increase in the arthritic index score compared to the control group. However, rats treated with leflunomide and physical exercise demonstrated a clear decrease in the arthritic score. Various dosages of leflunomide and physical exercise were associated with a reduction in the arthritic score compared to rats induced with CFA.

Physical exercise (PE) has been widely recommended for preserving the health of the general population and patients with rheumatoid arthritis. PE induces several intracellular signaling pathways that promote cellular endurance and adaptation in the musculoskeletal system. It also influences the regulation of innate immunity and inflammation, as mentioned by Alzarea et al. (2022) and Aide et al. (2023).

Overall, the study provides evidence that both leflunomide and physical exercise have potential benefits in alleviating the symptoms and severity of rheumatoid arthritis in the experimental rat model

## V. Conclusion

The findings from the current study suggest that the combination of leflunomide and physical exercise demonstrated protective and ameliorative effects against rheumatoid arthritis in rats. These effects were observed through various measures such as increased body weight, reduced swelling in the paws, and decreased arthritic score. Both leflunomide and physical exercise showed promising anti-arthritic activity when administered individually, supporting their potential as effective treatment options.

The combination of leflunomide and physical exercise offers a comprehensive approach to managing rheumatoid arthritis due to their complementary properties. Leflunomide acts as a medication that targets the underlying inflammatory processes in the body, while physical exercise provides benefits such as improved joint mobility, strength, and overall physical well-being.

Based on these observations, the concurrent use of leflunomide and physical exercise appears to be a promising approach for arthritis treatment. However, it is important to note that further research and clinical studies are necessary to confirm these findings and determine the optimal dosage, duration, and safety considerations for using this combination therapy in human patients.

Patients with rheumatoid arthritis should consult with their healthcare providers to discuss the potential benefits and risks of incorporating leflunomide and physical exercise into their treatment plan. Individualized approaches and considerations should be taken into account to ensure the best outcomes for each patient.

**Conflicts of interest**

I declare that there is no conflicts of interest and no
Ethical conflicts among the authors or the experimental methodology.

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