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A comparative study of the effect of Cinnamomum zeylanicum extract and nanocomplex on some immunological and physiological parameters before and after MTX treatment loading

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***Abstract*---**The current study aimed to know the protective effect of the aqueous extract of Cinnamon zeylanicum and the free Cinnamon nanocomplex loaded with MTX treatment to reduce the effect of arthritis induced with Complete Freunds (CFA Adjuvant) in male albino rats by studying some changes in immunological and histological parameters. Atomic force microscope (AFM) revealed the appearance of changes in the surface of nanocomposites loaded with treatment. The immunological results indicated that the induction of rheumatoid arthritis (RF) in male white G2 rats led to a significant increase ($P<0.05$) in the level of IL-8 cytokine concentrations 86.31 pg/ml compared with the negative control group at 24.41 pg/ml. There was also a significant decrease ($P<0.05$) in the level of IL-8 concentration in the G7 group dosed with cinnamon nanocomplex loaded with MTX treatment pg/ml (37.45) and the results of histological parameters showed that there was a significant increase in white blood cells in the positive control group G2 (14.00) compared to With the negative control group G1 (5.433), while in the group G7 there was a significant decrease ($p<0.05$) (9.433). The results of the current study showed that giving the aqueous extract of the cinnamon plant contributed to reducing the pathological effects of arthritis, but when the cinnamon extract was converted into a nanocomposite, it increased the effectiveness of the extract by stopping the damage caused by arthritis. The results of the current study showed that the

use of cinnamon is safe and does not cause any harm. Toxicity to the body in the dose used.

***Keywords*---**cinnamomum zeylanicum, nanocomplex, immunological, physiological.

Introduction

Nanosystems have many advantages over microsystems such as circulation in the bloodstream for longer periods without being recognized by macrophages (Elkhoury *et al.* 2021) ease of tissue penetration through capillaries and biological membranes, and ability to be readily absorbed by cells, indicating To highly effective treatment at the target site. (M. Khan et al. 2021) , while maintaining the effect in the desired area over a period of days or even weeks. This is because these nanoparticles have many advantages such as small controllable size, large surface area to mass ratio, and functional structure (Gagliardi *et al.* 2021) . These properties make nanoparticles, a suitable delivery system for antimicrobials. (Chenthamara *et al.* 2019). The most common presentation of rheumatoid arthritis is symmetric inflammatory arthritis, especially of the hands and feet, although any synovial joint can be affected, especially the membrane (synovial). This membrane consists of two or three layers of epithelial cells and contains synovial fluid . where this membrane in the affected joints is thicker with a collection of a number of inflammatory cells (T lymphocytes, macrophages) rheumatoid arthritis is able to cause significant damage to the joints, which can impair movement and seriously disrupt a person's life. Where it was found that the synovial fluid, in case of inflammation, contains neutrophils, these cells destroy the synovial cartilage through enzymes secreted by these cells (Aletaha *et al.* 2010) .

The most cellular kinetics (cytokines), which are found in fluid and articular tissue is tumor necrosis factor-alpha (TNF-α- Tumor necrosis factor) is a protein secreted by cells of the immune system, in the body, where if secreted in an excessive amount leads to the occurrence of rheumatoid arthritis And the interleukins represented by (Interleukin-1,20), where (TNF-α) activates the inflammatory state, by activating T lymphocytes (CD4+), which stimulates the activity of monocytes and macrophages (Macrophage, Monocyte), which are called in Fibroplast like synoviocyte (FLS). Stimulation of these inflammatory mediators leads to the appearance of degrading cells of cartilage and bone tissue in the synovial fluid. In addition, these cells are stimulated by surface expression, (expression of cell surface molecules) by T cells, and then T cells T(CD4+) stimulates B-cell lymphocytes, where they activate and differentiate to produce immune proteins such as Rheumatoid factor –RF (Alzabin and Williams 2011)

Material and Method

Experimental and animal design

Thirty-five male laboratory white rats were used, weighing 180-220 g and aged (10-11 weeks), the infection appeared by injection of 0.1 ml of (CFA) in the sole of

the right foot in the first six weeks and 14 days after injection for each group (Adeneye *et al.* 2014).

- The first group G1: A daily dose of plain water is given, and the negative control group is considered to be the negative control
- The second group G2: (0.1) ml of CFA was injected into the sole of the right foot on the first day of the experiment to induce arthritis, and it was considered a positive control group.
- The third group G3: Induced arthritis and taken orally 14 days after induction of arthritis with free methotrexate.
- Group four G4: Arthritis induced and administered orally 14 days after induction of arthritis with cold aqueous cinnamon extract at a concentration of 350 mg/kg.
- Group five G5: Induced arthritis and administered orally 14 days after induction of arthritis with nanocomposite (cinnamon extract) at a concentration of 350 mg/kg.
- Group six G6: Induced arthritis and administered orally 14 days after induction of arthritis with cold aqueous cinnamon extract dissolved in methotrexate treatment at a concentration of 350 mg/kg.
- Group seven G7: Induced arthritis and administered orally 14 days after induction of arthritis with the nanocomposite loaded with MTX methotrexate treatment at a concentration of 350 mg/kg.

Preparation of the cold aqueous extract of *Cinnamomum zeylanicum*:

It was followed (Parekh and Chanda 2007) in preparing it by taking 20 gm of the vegetable powder in a 500 ml glass beaker, adding 200 ml of distilled water, and placing it in a vibrating incubator for 24 hours at a temperature of 37 °C. The mixture was filtered by a medical gauze consisting of several layers. Then it was placed in glass tubes. The tubes were centrifuged at a speed of 5000 rpm for 10 minutes, then the filtrate was filtered with 0.22 µm perforated filter papers. Powder. The powder was placed in a sealed and opaque tube and kept in the freezer at a temperature of 18°C until use. The process was repeated several times to obtain a sufficient amount of extract.

Preparation of *Cinnamomum zeylanicum* bark extract

The method of (Gauthami *et al.* 2015) was followed by (Sathishkumar *et al.* 2009) Where 2.5 gm of Ceylon cinnamon powder was taken and 100 ml of distilled water was added to it and boiled for 5 minutes in a 500 ml beaker and after filtering by using filter paper No. 1 . The extract was kept at 4 °C.

Prepare the cinnamon nanoparticles

I followed the method (Sathishkumar *et al.* 2009) as follows: One (1 ml) of Ceylon cinnamon bark extract was added to 50 ml of 1 mM silver nitrate (AgNO3) solution and kept at room temperature for 8 hours to produce silver nanoparticles. The solution initially appeared yellowish in color and when silver nitrate was reduced Ag+ changed the dilute form to a dark color. the color change of the solution was measured each time for 1 hour. The color intensity

changed after silver was reduced to nanoparticles from Cinnamon zeylanicum. The reaction and color change with time was recorded.

Diagnostics of nanoparticles:

Examination of the free nanocomposite loaded with MTX treatment by FT-IR (Fourier transforminfrared spectroscopy) and atomic force microscopy (AFM)

X-ray evaluation

Mice were anesthetized by injecting Ketamine Injection, xylazine Injection at a concentration of 0.5 ml each. Radiographs were taken with an X-ray machine (Siemens Mobilett Pluse X-ray, ALWISAM RADIOLOGY CLINC, KARBALA). The focal distance of the film was 60 cm at 55 kV and 3 mA. The severity of joint deformity was clearly scored according to the extent of osteoarthritis, joint spaces, soft tissue inflammation, subchondral erosion, and articular sclerosis (A *et al*. 2015) X-ray images were analyzed and recorded in detail by two certified radiologists who were blinded on treatment groups.

Measuring the effect of arthritis on foot thickness:

Arthritis was evaluated and observed in animals induced with CFA and compared with normal animals. Several readings of the right ankle joint were recorded per day, (0,4,10,15,20) and swelling and redness of the foot were observed when injected with CFA. The percentage increase in foot thickness was calculated using the following equation: (Mahdi *et al*. 2018) .Arthritis assessment % = [foot thickness per day (0) – foot thickness per day (20) / foot thickness per day (20)] x 100

Results and Discussion

Atomic force microscopy images of *Cinnamomum zeylanicum* extract and cinnamon nanoparticle free.

Figure (1) shows the outer surface of the cinnamon extract molecules, where the surface roughness modulus of the cinnamon extract was 6,120nm. When cinnamon extract was converted to the cinnamon nanocomposite, Figure (2), the roughness modulus of this compound became 9,330nm, where the difference before and after the conversion of cinnamon to the nanocomposite was nm. 3,21 This is evidence that the roughness of the outer surface has increased after the transformation of cinnamon into a nanocomposite. As for the square root rate of Ceylon cinnamon extract, it was equal to 7,977 nm, while the complex of cinnamon nanoparticles was 12.74 nm. And the difference in the square root rate is 4,763 nm, and this indicates an increase in crystallinity in addition to the crystal homogeneity of the nanocomposite after the transformation from what is extracted. The surface area of the free cinnamon was 12.05%, while the average surface area ratio was 10.72%, which is conclusive evidence of the formation of nanoparticles from *Cinnamomum zeylanicum* extract.

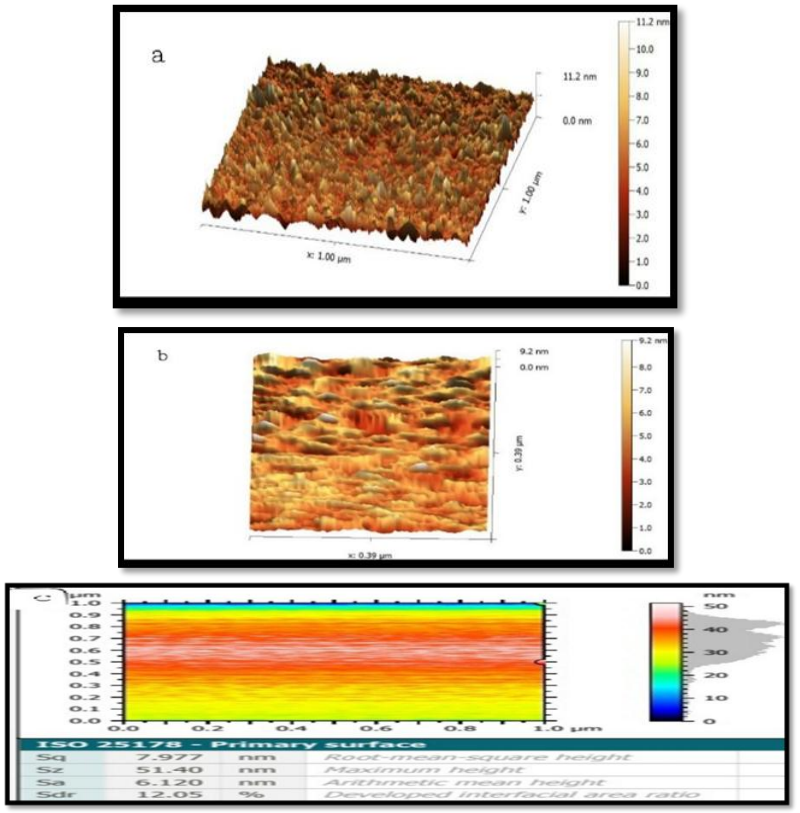

Figure 1. Atomic force microscopy images of free silane cinnamon extract (a) three-dimensional image. (b) two-dimensional image (c) two-dimensional image showing details of the molecules

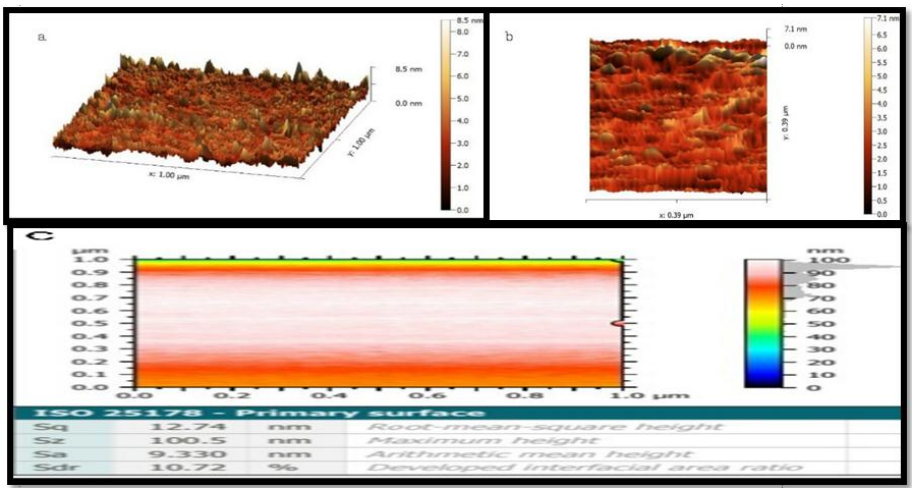

Figure 2. Atomic force microscopy images of cinnamon nanocomposite (a) three-dimensional image (b), two-dimensional image (c) two-dimensional image showing the details of the molecules

Atomic force microscopy images of cinnamon nanocomposite before and after loading MTX treatment

The results, as shown in Figure (2), (3) related to the atomic force microscope (AFM), showed that the free Cinnamon nanocomposite, as explained previously, has a roughness modulus of 9,330 nm. When suppository with MTX treatment, it became 6.502 nm, and the difference was in the roughness modulus before and after The loading is 2,282 nm, and this is clear evidence that the size of the particle that was loaded on the surface of the nanocomposite has an important role in the surface roughness and its crystal system in addition to the surface homogeneity. As for the root square rate of the cinnamon nanocomposite loaded with MTX treatment, it was 8,317nm to be the difference before and after loading. 4,423 nm, this indicates that the greater the difference, the evidence of the increase in the crystal structure produced after loading than before loading. As for the height rate of the Cinnamon nanocomposite loaded with MTX treatment, it was, 37,77 nm, while the average surface area is 7.610 nm.

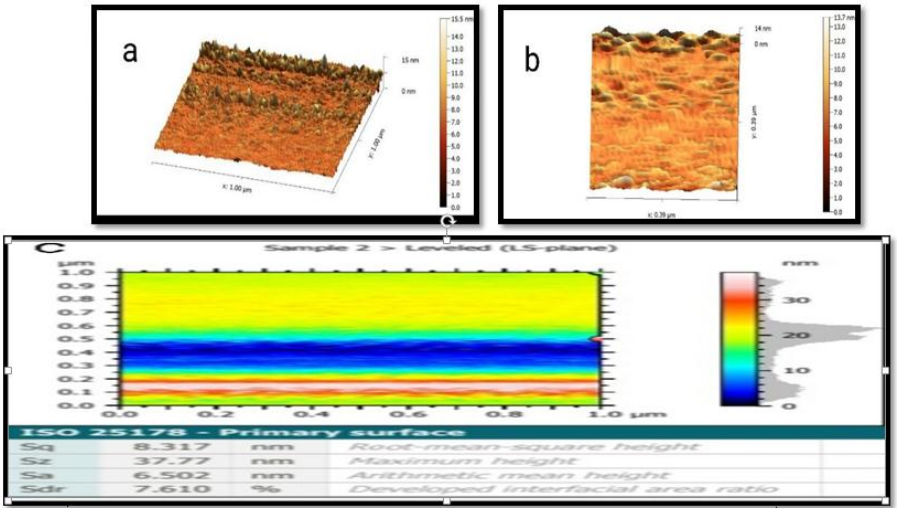

Figure 3. Atomic force microscopy images of cinnamon nanocomposite loaded with MTX treatment. (a) Three-dimensional image (b), two-dimensional image (c) two-dimensional image showing the details of the molecules

FTIR infrared spectrum of Cinnamon nano-solution before and after loading of MTX treatment

The results (Fig. 4) showed the presence of a sharp peak superimposed between 3897.99-3747.04 cm-¹, which is due to the extension of the O-H hydroxyl groups contained in the alcohol synthesis, while the peak at a frequency of 2.63435 cm-¹ is due to the expansion of the N-H amine group. At frequencies (2356,51,2327,97,2072,33) cm-¹ resulting from the vibration of the C=O=C bond and it has a strong extension, while the vibrations between (1842.74-1732,54) cm-¹ It corresponds to the vibrations of the C=O bonds of (vinyl/phenyl ester). The band represented at frequency 1652.73 cm-¹ expresses the C-H bond of aromatic compounds, 1635.50 cm-¹. It goes back to the C=C bond extension of the alkene. As for the frequencies between (1558,50 – 1505.71 (cm-¹) goes back to

the extension of the N-O bond. As for the bands between (1495.07 – 1393,57) they are caused by the vibration of the C-H bond. The peak at frequency 667.64 cm $^{-1}$ is caused by the C-I bond. The presence of rings aromatic and alkene bonds, respectively.

These bands indicate extended vibrational bands responsible for compounds such as flavonoids and terpenoids and thus can be considered responsible for the effective coverage and stabilization of the obtained AgNPs. That the presence of organic functional groups, such as alkanes, aromatic compounds and amine bonds played a major role in the production and stability of AgNPs. (Huang et al. 2007) . (Banerjee et al. 2014) The appearance of the transverse band at the top 3850.92 cm-^{1} is evidence of the stretching of the hydroxyl group O-H bond as in Figure (5), while we notice the disappearance of the frequencies located within (3867.28-3741.49) cm-1 that were present in compound Cinnamon nano, and this confirms the treatment of the treatment on the compound Cinnamon nanoparticles, the band 273435.27 cm-1 is due to the vibrations of the N-H bond of the amine groups, while the frequency between (2359.84-2330.36 cm-^{1} is attributed to the presence of an O=C=O bond, The band is 1634.74 cm-1 due to the presence of the C=C bond and the N-O bond, which is found at the frequency of 1505.10 cm-1. As for the bands (1471.29 – 1455.86) cm-1, respectively, they belong to the C-H bond, band 1386. 05 cm-1 has been shifted to 1384.12 cm-1 The band 1089.39 cm-1 has been shifted to the new position 1112.87 cm-1, while the band 667.49 cm-1, which belongs to the C=C bond, remains at almost the same frequencies on the surface of the cinnamon complex nanoparticles, which clearly confirms the loading of MTX treatment on the surface of the Cinnamon nanocomposite .(Sadoon and Ghareeb 2020)

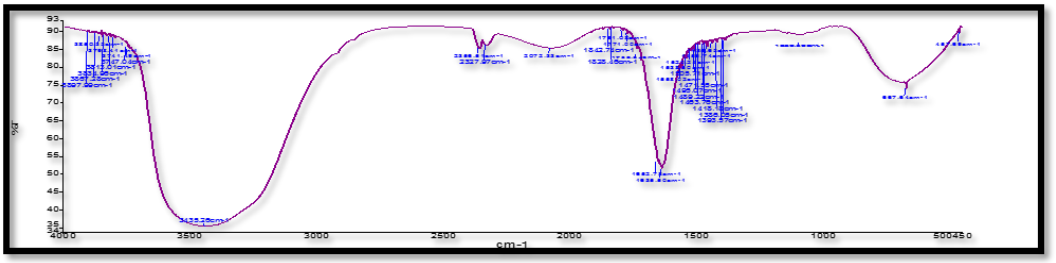

Figure 4. Shows the FT-IR spectrum of the free Cinnamon nanocomposite

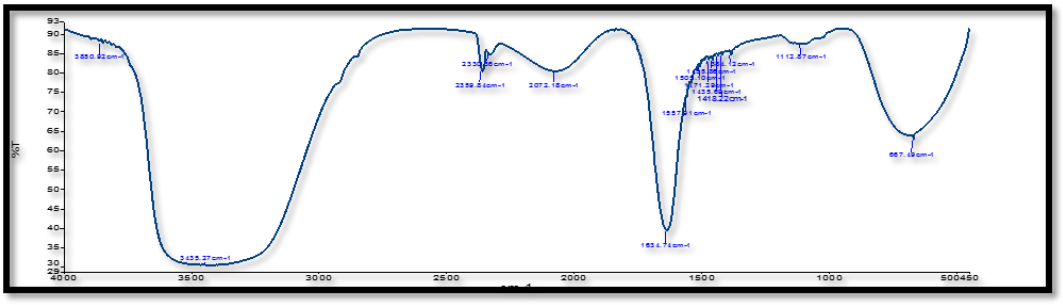

Figure 5. Shows the FT-IR spectrum of cinnamon nanocomposite loaded with MTX treatment

The effect of treatment on immune variables
Effect of treatment with free MTX, free cinnamon extract, free cinnamon nanocomposite and cinnamon extract with MTX treatment and cinnamon nanocomposite loaded with MTX treatment on IL-8 concentration.

The results of the current study show a table (1) that when inducing rheumatoid arthritis by CFA, it causes a significant ($p<0.05$) increase in the average concentration of IL-8 in the serum of white male rats. The results of the current study agree with (Qian, Kuang, and Wang 2017) where This study demonstrated that CFA is an excellent model for the study of experimental immunopathology for rheumatoid arthritis as it shares many features with this distinct clinical condition, such as infiltration of T cells and B cells, joint synovial hypertrophy, destruction of articular cartilage or joint fusion. Its concentration level reached (86.31,118.62) Pg/ml in the positive control group (G2) for the full and half-term of treatment, respectively, compared with the negative control group G1, as its concentration level reached (24.41,24.92) Pg/ml for the full and half-term of treatment, respectively. , This is consistent with the findings of the study (Pabón-Porras *et al.* 2019) (Hajishengallis and Chavakis 2021) (Hamzeh-Cognasse et *al.* 2015) (Navegantes et al. 2017), which attributed the reason to the high numbers of platelets It is clear that the infiltration of monocytes in the joints of the arthritic-induced mice caused the secretion of IL-8.

The results of the current study in Table (1) indicate that animals induced with RA and treated with MTX (G3) treatment will have significant significant decrease in IL-8 concentrations ($p<0.05$) for the treatment rate with a concentration of (60.90, 53.66) pg/ml. Compared with the positive control group (G2) for the average of two treatment periods as well, which is consistent with the study (Liu *et al.* 2021) (Quan *et al.* 2008) (Leyva-López *et al.* 2016) , which indicated that the use of methotrexate treatments has a significant role in inhibiting Production of IL-8 through its effect on cyclooxygenase enzymes (COX-1, COX-2) and as a result inhibiting the production of IL-8, which is mainly synthesized by macrophages during COX-1 activity, which causes the aggregation of these cells and the production of quantities of this compound as well as It lowers IL-8 production by acting synergistically with other treatments such as Infliximab (IFX) by reducing the production of antibody towards IFX (ATI) antibodies.

The results of Table (1) indicate a significant decrease ($p<0.05$) in the level of IL-8 concentration in the members of the G4 group treated with cinnamon extract, as its concentration level reached (78.54,81.98) pg/ml compared with the positive control group G2 within the full period. (six weeks) and half term (three weeks) Inflammation is mediated by a cascade of free radicals and inflammatory cytokines. Macrophage is a source of inflammatory cytokines, which are important cells for phagocytosis and molecular immunity and this is in agreement with the study(Hao *et al.* 2019) , which showed that CS-LO (C. subavenium Leaf Oil) did not only inhibit iNOS (nitric oxide synthase) and COX- expression 2 (cyclooxygenase) and the subsequent production of (nitric oxide (NO) and (PGE2) prostaglandin E2 but also decreased the expression of IL-1β, IL-6 and TNF-α in vitro and in vivo. The main C. subavenium leaf is a potential anti-inflammatory agent, and a study (Anderson *et al.* 2013) showed that polyphenols not only improve insulin function, but also antioxidants and anti-inflammatory

compounds to counteract the negative effects of insulin resistance and obesityobesity

The results of Table (1) showed a significant decrease ($p<0.05$) in the concentration of IL-8 in a group that was dosed with the compound C.Z.Nano free G5 (C.Z.Nano), as its concentration level reached (73.88,67.10) pg/ml during the whole period (six weeks) and half (three weeks) respectively compared to the positive control group and the results of the current study were matched with (Pahan and Pahan 2020) , where this study showed that cinnamon, whether in the form of powder or extract, is able to modify various autoimmune pathways as well as protect animals from Various autoimmune disorders Several studies have also confirmed that it reduces glucose and increases insulin in the blood of rats (Verspohl, Bauer, and Neddermann 2005) and lowers blood pressure (Anderson *et al.* 2013) , and cinnamon powder reduces glucose and triglyceride levels. And LDL cholesterol in people with type 2 diabetes (A. Khan *et al.* 2003) , (Mandal *et al.* 2021) and delayed gastric emptying without affecting satiety (Hlebowicz *et al.* 2009) and cinnamon extract displays its polyphenols. Both insulin-dependent effects in insulin-sensitive cells such as adipocytes and insulin-independent effects in non-insulin-sensitive cells such as macrophages. Therefore, the benefit of cinnamon is likely due to its multiple effects, including insulin-boosting and anti-inflammatory effects.While the results of Table (1) showed a significant decrease ($p<0.05$) in the concentration of IL-8 in the group that was dosed with cinnamon extract with MTX (G6) (60.25,52.63)pg/ml for the full period (six weeks) and the half period (three weeks). Respectively compared with the positive control group, and when comparing the full and half-term of this group with a group that was given MTX free G3 treatment, there is no significant difference between them.

The results of the current study agree with (Balekar *et al.* 2014) . This study showed that the efficiency of the device can be enhanced. Immune system by using a stimulant. Plant-based natural medicines are believed to enhance the body's natural resistance against infections and its immune activities. An increasing interest in herbal medicine research is the search for promising and cost-effective immunosuppressive compounds from natural products. Consumption of dietary polyphenols leads to beneficial effects on human health as in the case of prevention and/or attenuation of cardiovascular, inflammatory, neurodegenerative, and neoplastic diseases. Once ingested, dietary polyphenols are able to interact and influence the function of many biological systems in the host, even including the gut and immunity. Several studies have reported plant-derived procyanidines to have a cytokine inhibitory effect in vitro (Mao *et al.* 2002) (Terra *et al.* 2009). Similar effects have been attributed to cinnamon bark extract and polyphenols. Polyphenols (Cao, Urban, and Anderson 2008) (Vaclav and Jana 2013).

The results of Table (1) showed a significant decrease ($p<0.05$) in the concentration of IL-8 in the G7 group that was dosed with cinnamon nanocompound loaded with MTX (45.33,37.45) pg/ml in both the full and half periods, respectively, compared to the control group. On the comparison of the period (three weeks) (45.33) pg/ml for this group with the group G3)) for the whole period (six weeks) (53.66) pg/ml, we note that there is a more significant decrease ($p<0.05$) in the G7 group than in the G3 group. And there was no significant

difference ($p<0.05$) from the negative control group, and this study agreed with (W. Chen et al. 2022) (Gharagozloo *et al.* 2013) , Which showed that traditional medicines or natural products are a feasible way to achieve a breakthrough in the treatment of rheumatoid arthritis. This indicates a shorter recovery time During the reduction of the treatment time and the dose given to 50%.

The results of the current study are in agreement with the findings of (Bashi, Alsajjad, and AlAwad 2018) (Rau and Herborn 2004) (Persson 2012), (Weinstock *et al.* 2021) , which indicated that the loading of MTX treatment on the nanocomposite Theranostic gold (Au))-shell NPs or Polysialic acid (PSA)-trimethyl chitosan (TMC) NPs (Xerogel) stimulate the formation of antibodies towards specific receptors of CD46 macrophages, And loading the MTX treatment is much more effective than the free treatment in inhibiting IL-8 production and eliminating the progression of arthritis significantly in experimental animals.It also agreed with the study (Pahan and Pahan 2020), (Roth-Walter *et al.* 2014) (Stevens and Allred 2022) , which confirmed that most studies and research in vitro and in vivo on cinnamaldehyde as an essential therapeutic agent in cinnamon oil, New drugs based on complex mixtures of natural compounds may offer therapeutic potential for treating diabetes. The immunosuppressive effect of cinnamaldehyde induced inhibition of proliferation and induction of apoptosis in immune cells.

Table 1

Shows the IL-8 cytokine concentrations pg/ml before and after treatment with free MTX, free cinnamon extract, free cinnamon nanocomposite, cinnamon extract with MTX treatment, and cinnamon nanocomposite loaded with MTX treatment

Transaction groups		Mean±Standard Error IL-8 pg/ml	LSD/Total
Negative control (G1)	**Treatment (three weeks)**	**24.92±1.30**	**13.379**
	Treatment (six weeks)	**24.41±0.64**	
	Total	**24.67±0.93**	
Positive control (G2)	**Treatment (three weeks)**	**118.62±12.39**	
	Treatment (six weeks)	**86.31±0.70**	
	Total	**102.47±12.58**	
MTX (G3)	**Treatment (three weeks)**	**60.90±1.80**	
	Treatment (six weeks)	**53.66±0.84**	
	Total	**57.28±2.53**	
C.Z. (G4)	**Treatment (three weeks)**	**81.98±0.55**	
	Treatment (six weeks)	**78.54±1.00**	
	Total	**80.26±1.27**	
C.Z.Nano. (G5)	**Treatment (three weeks)**	**73.88±2.18**	
	Treatment (six weeks)	**67.10±1.46**	
	Total	**70.49±2.65**	
C.Z. MTX+ (G6	**Treatment (three weeks)**	**60.25±2.96**	
	Treatment (six weeks)	**52.63±1.51**	
	Total	**56.44±3.13**	
C.Z.Nano +MTX (G7)	**Treatment (three weeks)**	**45.33±0.38**	
	Treatment (six weeks)	**37.45±3.09**	
	Total	**41.39±3.10**	

Effect of treatment with MTX treatment, cinnamon extract, free cinnamon compound, cinnamon extract with MTX treatment and cinnamon nano compound loaded with MTX treatment on blood picture parameters.

In Table (2), the results of the MCV (mean corpuscular volume) analysis of the average corpuscular volume of the positive control group G2 showed that there was a significant increase ($p<0.05$) where it was μm^3 (58.533) compared to the negative control group G1, which amounted to μm^3 (43.650) as for the groups. Oral treatments do not show significant differences between these groups and the G2-positive control groups represented by MTX (G3) μm^3 51.050, Cinnamon extract (G4) 52.900 µm, and Cinnamon Free Nanogen (G5) μm^3 55,533, cinnamon extract supplemented with MTX treatment (G3). G6) μm^3 56.500, as for the cinnamon nano compound loaded with MTX treatment (G7) μm^3 49.416, there was no significant difference for this group (G7) compared to the negative control group G1. As for the results of the analysis of (Hemoglobin) HGB, the percentage of hemoglobin in red blood cells in Table (2) The positive control group was G2, in which rheumatoid arthritis was induced by injecting CFA at concentrations (0.1) ml into the right ankle, which had a significant increase ($p<0.05$) of 17.916 gm/dl compared to the positive control group. Gm/dl10.916 either in the aggregates (G3, G4, G5, G6, G7). Gm/dl (13.383, 13.600, 14.566, 11.600, 12.483), respectively. We note the absence of significant differences with the negative control group. As for the analysis of (Mean corpuscular hemoglobin) MCH, the average globular hemoglobin, the results of Table (2) showed that there are significant differences ($p< 0.05$) between the positive control group G2, where the result of the analysis was Pg/cell (35.466) compared to the negative control group. , and treatment with cinnamon extract (G4) and cinnamon nanocomplex (G5), cinnamon extract with MTX treatment (G6) and cinnamon nanocomplex loaded with MTX (G7) Pg/cell treatment (22.333,24.383,24.850,26.366,25.916) compared with the Negative control group G1

The results of Table (2) showed that MCHC (Mean corpuscular hemoglobin concentration) analysis of the average concentration of red blood cells for the positive control G2 reached gm/dl (40.583), meaning that there is a significant increase ($p<0.05$) compared to the negative control group G1 gm/dl. 31.900) and no significant differences ($p<0.05$) with the groups (G3, G4, G5, G6, G7), where the results of the analysis were gm/dl (33.266, 33.133, 37.616, 39.083, 37.466) compared to the negative control group G1 .The results of Table (3) show that the group of animals with G2 arthritis had a significant ($p<0.05$) increase in the level of LYM concentration (lymphocytes) that reached $\times 10^3/\mu m^3$ (6.666) compared to the negative control group (G1) $\times 10^3/\mu m^3$ (1.683). While the treatment group reached the treatment. (6.466) $\times 10^3$ $/\mu m^3$ (G3) MTX There was a significant difference ($p<0.05$) with the negative control group, the group (G4) that was treated with cinnamon extract had a concentration of LYM $\times 10^3$ $/\mu m^3$ (5.216), G5 amounted to $\times 10^3/$ μm^3 (9.033), while there was a clear significant decrease ($p<0.05$) in both groups G6 and G7, reaching $\times 10^3/\mu m^3$ (3,683,4.666), respectively compared to the negative control group G1.

The results of the analysis in Table (3) showed that the concentration of WBC white blood cells in the group of animals in which G2 rheumatoid arthritis was induced by injecting CFA substance at concentrations of (0.1) ml in the right

ankle, that there was a significant significant increase ($p<0.05$) that reached $\times 10^3$ /µm³ (14.000) compared to the negative control group. × 10^3 /µm³ (5.433) treatment with MTX (G3), cinnamon extract (G4), treatment with cinnamon nanocompound (G5), and cinnamon nano extract with MTX (G6) treatment, and treatment with cinnamon nanocompound loaded with MTX (G7) showed significant decrease ($p<0.05$) was $\times 10^3$/µm³.(11.116, 8.850, 8.216, 9.433,10.683), respectively when compared to the untreated group with arthritis
As for the analysis of (Granulocytes) GRA, as its results show in Table (3), it was found that there was a significant increase ($p<0.05$) in the value of GRA in the positive control group G2, which was 10^3/µm³ (7.683) compared to the negative control group G1. $\times 10^3$ /µm³(2.966), while there were no significant differences ($p<0.05$) with the other groups (G3, G4, G5, G6, G7) compared to the negative control group G1, and when compared with the positive control group, there was a significant decrease ($p<0.05$) . Was 10^3 /µm³ (1.683,2.833,3.650,1.866,3.700)

As for the results of the RBC analysis (RED BLOOD CELL) shown in Table (3), it was shown that there was a significant ($p<0.05$) increase in the positive control group G2 that reached $\times 10^3$/µm³ (11.186) compared with the negative control group G1$\times 10^6$/µm³. 4.913) As for the groups that were treated with MTX treatment (G3), cinnamon extract (G4), cinnamon nano compound (G5) and cinnamon extract added to it with MTX treatment (G6), we notice a slight significant difference ($p<0.05$) for these groups with the control group. The negative amount was $\times 10^6$/ µm³ (6.831, 8.008, 6.355, 7.016), respectively, and when comparing these groups with the positive control group, a significant decrease ($p<0.05$) was observed. As for the group that was dosed with cinnamon nano compound loaded with MTX (G7) treatment, it was There was a clear significant decrease ($p<0.05$) reaching $\times 10^6$/µm³ (5.646) compared with the positive control group G2.

The results of the current study showed that there is a significant increase in red blood cells RBC and (, (MCH, MCHC, MCV), and the reason for the increase is due to the consequent increase in oxygen exchange. This study agrees with what was stated (Ekeanyanwu and Njoku 2014) , where the reason The increase leads to the overproduction of hematopoietic regulatory elements such as colony-stimulating factors, erythropoietin and thrombopoietin by the stroma cells and macrophages in the bone marrow. Bone marrow, which leads to the production of more red blood cells that carry more oxygen to the body's organs, and one of the reasons for the increase in this hormone, or the secretion of some tumors to it, or the injury of the body with a lack of oxygen. The results of this study contradict those obtained (Nigatu *et al.* 2017) (Al-Naseem *et al.* 2021) (Islam, Islam, and Sultana 2020) (Corrado *et al.* 2017) . These studies confirmed a decrease in the total number of red blood cells in patients with In rheumatoid arthritis, approximately 17% of RA patients were found to have low hemoglobin levels and met WHO criteria (Hajar 2015) Cell migration is important in innate and adaptive immune responses and leukocyte recruitment to sites of acute or chronic inflammation (Lin *et al.* 2015) Inadequate leukocyte assembly reduces inflammatory responses and initiates pathological processes of inflammation (Poulet *et al.* 2010) Leukocytes sharply increase as the body's first line of defense (Kebede *et al.* 2016) Concentration of white blood cells and lymphocytes possibly triggering a mechanism Immune defense (Nafiu *et al.* 2020) Increasing the

number of white blood cells by stimulation during the rise of inflammatory cytokines (G. Chen et *al.* 2020) and when using MTX treatment, we notice a decrease in the values of (RBC, MCV, MCHC, MCH) and this corresponds to With a study (Elbeialy 2022) (De Rotte *et al.* 2018) approximately 60% of the drugs used are of natural origin at present(Albert *et al.* 2021) , RA patients who are likely to be unresponsive to MTX therapy, may treat (Additionally) with other biologics or medicines(De Rotte *et al.* 2018) plants can be used to treat a myriad of diseases (Saganuwan 2017) . A natural flavonoid, widely present in many plants (X. Chen et *al.* 2021) possessing strong antioxidant activity (Ekeanyanwu and Njoku 2014) and osteoarthritis healing effects (Choudhary et *al.* 2014) offering potential benefits for human health (Ekeanyanwu and Njoku 2014) .

The results of the current study are in agreement with a study (Pandey *et al.* 2021) that suggested the development of a MTX delivery system by nanoparticle-loaded loaded methotrexate for the treatment of rheumatoid arthritis. It is a promising delivery system to avoid drug-induced hepatotoxicity in rheumatoid arthritis. Nanoparticles deliver drugs to inflamed tissues in rheumatoid arthritis (RA) more effectively and this is in agreement with what was indicated by the study (Mani et *al.* 2016) conducted on black pepper plant, where this study proved that silver nanoparticles stabilized with Piper nigrum extract (S- AgNPs) and had strong anti-arthritic activity.

Our result is consistent with other studies (Leonavičiene et *al.* 2012) (Rao *et al.* 2018) where gold nanoparticles have been used in the treatment of osteoarthritis. These studies demonstrated that drug delivery to inflamed tissues in rheumatoid arthritis (RA) is more effective. . And fewer side effects. Reduced degenerative changes with mild articular changes. Relatively lower influx of inflammatory cells and a non-toxic effect of AuNPs on vital organs. Treatment of mice with gold nanoparticles showed a decrease in histological changes and had an antioxidant effect by increasing the level of the antioxidant enzyme catalase. Continuous intra-articular use of AuNPs not only reduced inflammation, joint swelling, and the development of arthritis, but also reduced histological changes in articular tissues without toxic effects on internal organs.There have been several attempts to develop novel MTX therapy delivery systems that enhance the therapeutic effect on arthritis to overcome the shortcomings. In this study the MTX-loaded Cinnamon nanocomposite was used to treat rheumatoid arthritis. Nano-sized carriers (green nanotechnology) are promising methods that can selectively deliver therapeutic agents to sites of inflammation in a controlled or sustainable and safe manner.

Table 2
Effect of treatment with MTX, free cinnamon extract, free cinnamon nanocomposite, cinnamon extract with MTX and cinnamon nanocomposite loaded with MTX on blood picture in male albino rats with arthritis rheumatoid

Groups	N	MCV Mean ± Std Error $(\mu m)^3$	HGB Mean ± Std. Error gm/dl	MCH Mean ± Std. Error Pg/cell	MCHC Mean ± Std. Error gm/dl
G1 Control Negative	6	43.650 ± 0.872	10.916 ± 0.496	27.066 ± 0.168	31.900 ± 0.290
G2 Control Positive	6	58.533 ± 0.868	17.916 ± 0.619	35.466 ± 0.098	40.583 ± 0.506
G3 MTX	6	51.050 ± 0.488	12.483 ± 0.411	25.916 ± 0.313	37.466 ± 0.172
G4 C.Z.	6	39.083 ± 0.468	11.600 ± 0.293	26.366 ± 0.348	39.083 ± 0.468
G5 C.Z.nano		55.533 ± 0.755	14.566 ± 0.227	24.850 ± 0.363	37.616 ± 0.253
G6 C.Z.+ MTX	6	56.500 ± 1.200	13.600 ± 0.260	24.383 ± 0.254	33.133 ± 0.421
G7 C.Z.nano+ MTX		49.416 ± 0.522	13.383 ± 0.249	22.333 ± 0.168	33.266 ± 0.447
LSD		3.846	1.656	1.344	1.732

Table 3
Effect of treatment with MTX, free cinnamon extract, free cinnamon nanocomposite, cinnamon extract with MTX and cinnamon nanocomposite loaded with MTX on blood cell count $^{3}\times10^{3}/\mu m$ in male albino rats with rheumatoid arthritis

Groups	N	LYM Mean ± Std. Error ($\times10^{3}$ /μm^{3})	WBC Mean ± Std. Error ($\times10^{3}$ /μm^{3})	GRA Mean ± Std. Error ($\times 10^{3}$/ μm^{3})	RBC Mean ± Std. Error ($\times10^{6}$/ μm^{3})
G1 Control Negative	6	1.683 ± 0.210	5.433± 0.033	2.966± 0.212	4.913 ± 0.060
G2 Control Positive	6	6.666 ± 0.432	14.00 ± 0.363.	7.683 ± 0.316	11.186 ± 0.252
G3 MTX	6	6.466 ± 0.420	11.116 ± 0.168	3.700± 0.115	7.016 ± 0.211
G4 C.Z.	6	5.216 ± 0.377	8.850 ± 0.099	1.866 ± 0.154	6.355 ± 0.215
G5 C.Z.nano		9.033 ± 0.391	8.216 ± 0.231	3.650 ± 0.125	8.008 ± 0.212
G6 C.Z.+ MTX	6	4.666 ± 0.423	10.683 ± 0.355	2.833± 0.176	6.831 ± 0.206
G7 C.Z.nano+MTX	6	3.683 ± 0.319	9.433± 0.033	1.683 ± 0.119	5.646 ± 0.285
LSD		1.647	0.708	0.841	0.859

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