Results in Chemistry 5 (2023) 100913

Contents lists available at ScienceDirect

Results in Chemistry

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Green chemistry and anti-inflammatory activity of silver nanoparticles using an aqueous curcumin extract

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ARTICLE INFO

Keywords:
Silver nanoparticles, curcumin
Biosynthesis
Adjuvant arthritis
Anti-inflammatory effect

ABSTRACT

Rat models are sensitive to the induction of arthritis with adjuvants. Therefore, they are beneficial for studying this pathogenesis through the induction of adjuvant arthritis by injection of Complete Freund's Adjuvant (CFA). An eco-friendly green chemistry approach was utilized to synthesize silver nanoparticles (AgNPs) using an aqueous extract of curcumin root as a capping and reducing agent. AgNPs formation was evaluated by X-ray diffraction (XRD), scanning electron microscopy (SEM), and UV–vis spectroscopy analyses. The study aims to assess *in vivo* inhibitory effect of AgNPs on complete Freund's adjuvant-induced arthritis in rats. Therefore, male albino rats were divided into four groups: Normal control; arthritic rats untreated; arthritis rats received standard drug (dexamethasone) as a positive control for 14 days; and arthritis rats received 100 mg/kg AgNPs for 14 days. The results showed that the AgNPs exhibit anti-inflammatory effects in rats arthritis model by reducing the edema and levels of interleukin-6 (IL-6) and high-sensitive C-reactive protein (hs-CRP) in the paw tissues compared to the arthritic rats untreated. Overall, these findings evidence that the AgNPs have a potential promising anti-inflammatory effect against arthritis disease.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by stubborn inflammation that damages the articular cartilage and subchondral bone to varying degrees [1]. It is considered the most common cause of physical disability, with prevalence rates ranging from 0.3 to 1.5 percent and a female-to-male ratio of 3:1 [2,3]. The primary lesion of RA is abnormal synovium enlargement. Many proinflammatory mediators, chemokines, and metalloproteinases are released from fibroblast-like synoviocytes. These mediators are responsible for the deterioration of the extracellular matrix and cartilage [4]. Therefore, inhibition of these mediators is the primary goal of RA treatment. Conventional treatments such as NSAIDs and immunosuppressive therapies have long been used in RA treatment. However, prolonged use of these drugs may cause undesirable side effects, for example, peptic ulcer [5]. Therefore, new drugs with fewer side effects are urgently needed [3].

Recently, several studies have shown that medicinal plants can be considerably improved RA symptoms with fewer side effects [6]. Curcuma longa or turmeric is a plant grown in Asia and tropical nations. It is commonly used as a spice as well as being known for its medicinal effects [1]. Curcumin, also called diferuloylmethane, is the primary natural polyphenol extracted from the rhizome of the turmeric plant. It is credited with a wide range of biological properties, including antioxidants, anti-inflammatory, and wound healing [7]. In addition, Wright and co-workers demonstrated that curcumin has anti-tumor activity [8]. Another study showed the potential effect of curcumin on RA. Wang and his colleagues found that curcumin reduces inflammation by inhibiting NF-κB and promoting macrophage apoptosis [9]. Moreover, curcumin has significantly been shown to reduce paw swelling in rats by diminishing levels of MMP-1, MMP-3, TNF-α, and IL-1β, supporting evidence that curcumin has an anti-arthritic effect [10].

Despite the beneficial effects of curcumin, a study has shown that curcumin has low solubility and bioavailability [11]. Several methods can be used to overcome this obstacle, for instance, preparation based on emulsions of liposomes and nanoparticles [12]. Recently, nanoparticles designed using curcumin have entered a wide field of therapeutics. A recent study has shown that nanoparticle formulation increases curcumin's pharmacological and biological effects [6]. Hettiarachchi and co-workers have proved that nano-curcumin is more potent than traditional

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https://doi.org/10.1016/j.rechem.2023.100913
Received 27 March 2023; Accepted 30 March 2023
Available online 1 April 2023

curcumin, which contributes to the physical properties of nano formula such as surface charge and particle size [13].

Medicinal plant-based nanomaterials via a green chemistry approach have lately been used as a new potential approach to manage several diseases [14–16]. AgNPs have gained considerable interest due to their distinct chemical, biological, and physical features [17,18]. In contrast to traditional methods, which seem pricey and risky, the green chemistry strategy seems simple, fast, sustainable, and environmentally friendly [19,20]. Recently, AgNPs have been used in a variety of medical applications, including anti-angiogenic, anticancer, antibacterial, antifungal, and antiviral [21].

AgNPs have recently been utilized as anti-inflammatory agents. However, the anti-inflammatory responses of AgNPs remain limited [21,22]. As a result, it is critical for developing AgNPs with high therapeutic efficacy with fewer side effects to mitigate the risk of inflammation. The goal of this study is to create AgNPs in an innovative method utilizing curcumin extract via a green chemistry approach. We also looked into the *invivo* antiarthritic effects of synthesized AgNPs as new anti-inflammation agents.

2. Experimental details

2.1. Materials

2.1.1. Chemicals

Dexamethasone, Complete Freund's Adjuvant, and silver nitrate ($AgNO_3$) were supplied from Sigma Aldrich (USA). Turmeric rhizomes in dry form were bought from nearby stores in Iraq and classified in Iraqi Center for Classification of Medicinal Plants. The rhizomes (50 gm) were coarsely mashed in an electric blender and stored until use.

2.1.2. Experimental animals

Iraqi center for cancer and medical genetics research (ICCMGR) provided 25 mature male Wistar-albino rats, weighing 150–200 g and aged between 8 and 12 weeks. Individual cages made of stainless steel held the rats. The rats lived inside an air-conditioned house with a 12-hour diurnal cycle between 21 and 23 °C. Rats spent ten days acclimating before the trial. The animals were given a balanced diet and unlimited access to tap water. The Anbar University Research Ethical Committee gave its permission to the experimental procedure (approval number: 70-27-06-2022). The use and care of laboratory animals were conducted in accordance with international standards.

2.2. Methods

2.2.1. Green chemistry strategy for AgNP synthesis

A unique automated system was created to synthesize AgNPs [23]. The transfer between phases, action of pumps and heaters, and calculation of the required quantities are done automatically by inserting data through the software unit, as illustrated in Fig. 1. As a reducing agent, 1 g of curcumin powder was added to the system's beaker 1. Then, with the aid of a magnetic stirrer, 100 ml of deionized water was added, and heater one was turned on. After turning on the system and reaching 70 °C, heater one was activated and ran for one hour while stirring at 200 rpm. The filtered aqueous extract is then automatically collected in flask 1 while the vacuum filtration begins. In the next step, 20 ml of the

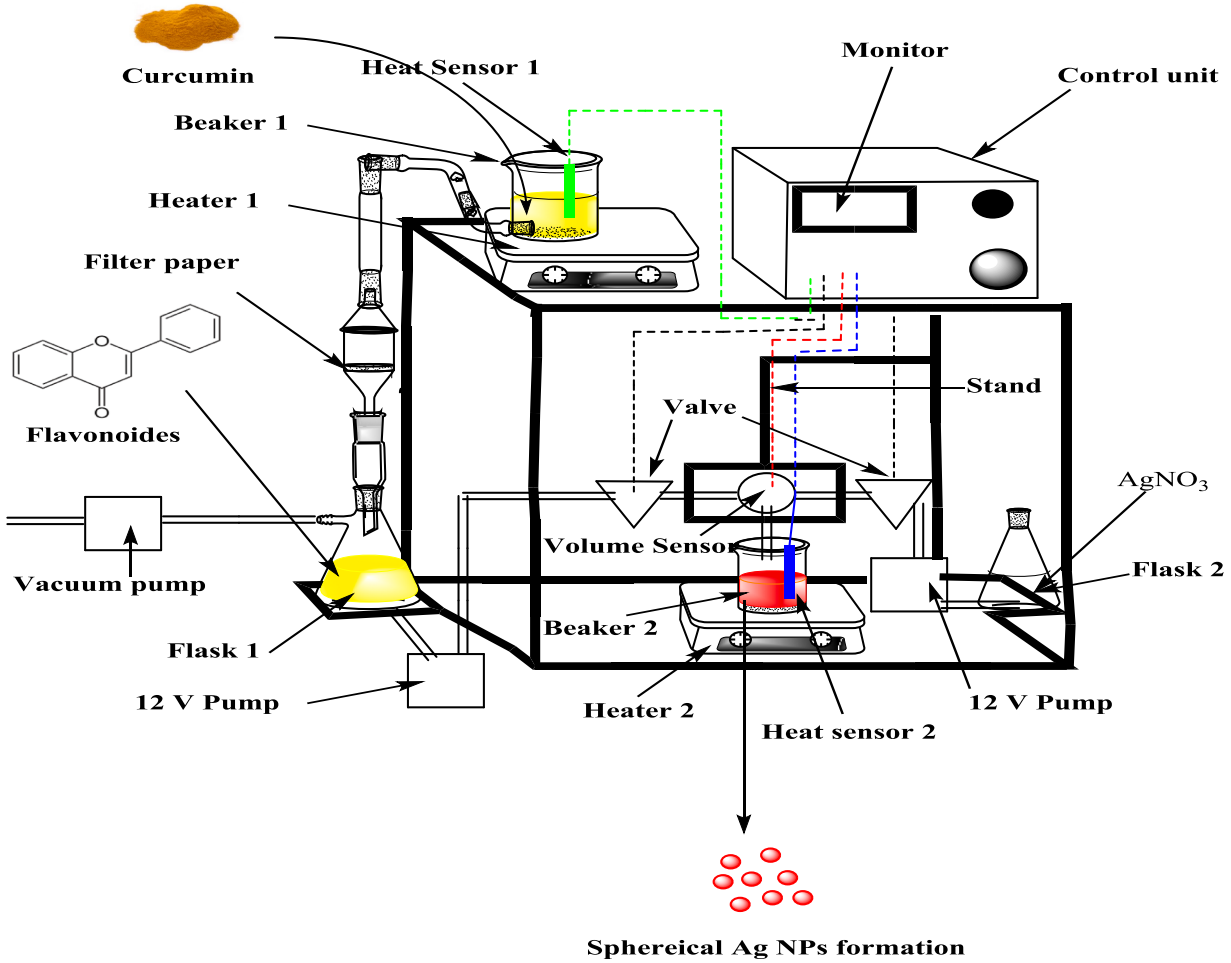

Fig. 1. Schematic of an innovative automated system for preparing of AgNPs.

extract was pumped from flask one to beaker two, which was placed in heater two. Then, $AgNO_3$ solution (20 ml, 0.1 M) was transferred from flask two to beaker one. When the temperature has reached 70 °C in the third stage, heater two begins to run for 20 min. Finally, Centrifugation at 12000 rpm for 15 minutes separated AgNPs from the solution, which was then washed four times with deionized water. The green chemical approach was effective in obtaining AgNPs.

2.2.2. AgNPs characterization

A T80 UV/VIS spectrophotometer was utilized to measure the optical absorption spectra of the AgNPs in the wavelength region of 200–600 nm. To identify AgNPs morphology and size, scanning electron microscopy (SEM) was employed (Carl Zeiss, Germany). X-ray diffraction (XRD) was also employed to characterize the structure and crystalline size of AgNPs using an automated diffraction meter (Shimadzu 6000 XRD) [24].

2.2.3. Complete Freund's Adjuvant-induced arthritis model

Complete Freund's adjuvant (0.1 ml) was injected into the left hind footpad of Wistar rats, arthritis was generated. Over two days, the animals were monitored for arthritic signs. To determine the pharmacological activity, AgNPs in comparison to dexamethasone were examined.

2.2.4. Experimental study

Four categories of 5 rats were formed at random. Other than the healthy control group, rats in the other groups received a 0.1 ml injection of CFA into the left hind footpad to induce arthritis. Rats were classified as follows: Group I: Healthy control rats; Group II: Arthritis-untreated control rats; Group III: Arthritis rats treated with dexamethasone (intraperitoneal) at a daily dosage of 100 μg/kg from the third to the fourteenth day as a standard drug [25]; Group IV: Arthritis rats were given 100 mg/kg of AgNPs orally every day from the third to the fourteenth day [22].

2.2.5. Hind paw volume evaluation

A Vernier caliper (Mitutoyo, Japan) was used to measure the diameter of rat paw edema before CFA injection (Day 0) and after administration of dexamethasone and AgNPs post induction of inflammation by CFA as shown in Fig. 2. Rat paw volume was calculated by measuring the difference between the paw volume in the treated group at the end of days 7 and 14 and the paw volume in the control group as previously described [26].

2.2.6. Plasma IL-6 and hs-CRP analysis

After two weeks, blood samples from rats' tail veins were obtained and immediately centrifuged at 4000 rpm for 5 min in tubes containing Ethylenediaminetetraacetic acid (EDTA). The plasma was then taken and kept at −20 °C to be measured for IL-6 and hs-CRP levels. Following the manufacturer's instructions, ELISA method was employed to measure IL-6 and hs-CRP concentrations using commercially available kits (Elabscience Biotechnology, USA). IL-6 and hs-CRP analyses were determined utilizing a Biotek ELx 800 microplate reader (U.S.A).

2.3. Statistical analysis

The trials were done three times. The findings are presented as mean ± SD. The GraphPad Prism 5.01 was employed to calculate the data. The statistical significance was evaluated by one-way ANOVA followed by Tukey post-test, p-values of 0.05 were deemed significant.

3. Results and discussion

3.1. AgNPs characterization

3.1.1. UV–Visible spectrometric assessment of AgNPs

Using UV–visible spectroscopy, the production of AgNPs is initially confirmed by monitoring the surface plasmon resonance band [27]. As part of a green chemistry approach, curcumin served as a preliminary to convert Ag^{+} to Ag^{o} and create a stable AgNPs formation. In this investigation, a distinct SPR absorption peak formed at a wavelength of 470 nm, which is related to AgNPs formation. According to a past study, AgNPs produced with Prunus africana extract as a reductant had a broad absorption peak between 417 and 475 nm [28].

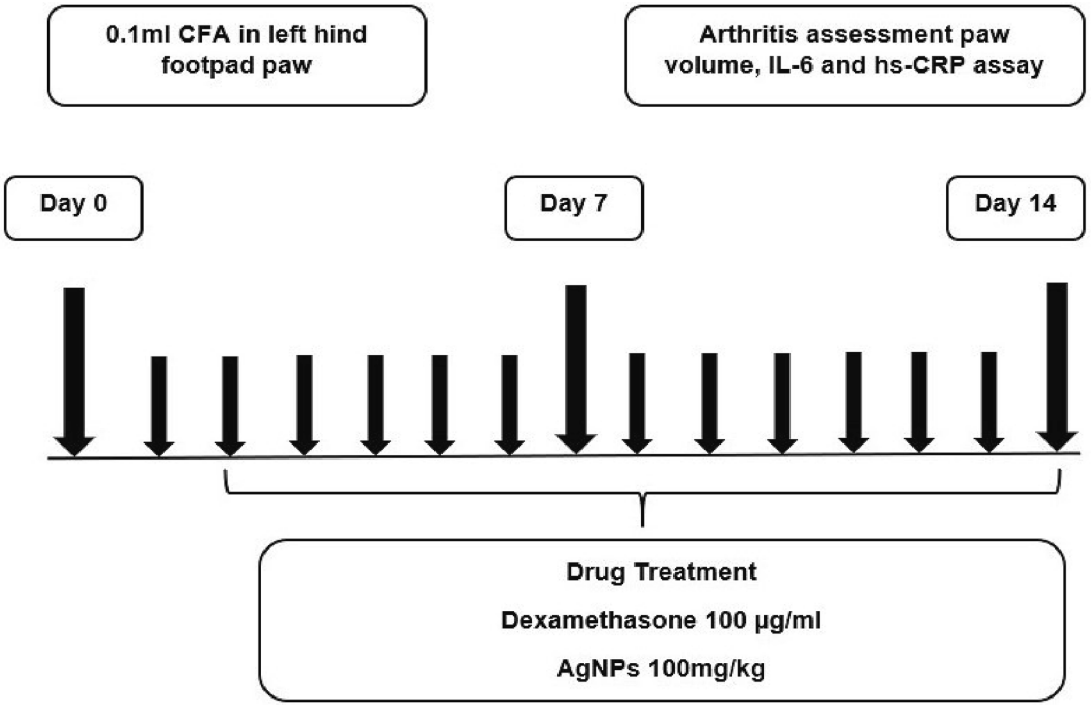

Fig. 2. Schematic representation of CFA-induced RA in rats.

3.1.2. SEM assessment of AgNPs

SEM assessment is typically utilized for estimating the morphological properties as well as the size of the produced nanomaterials [29,30]. SEM images revealed the production of AgNPs from curcumin extract in spherical shape and size of 30.99–68.20 nm as shown in Fig. 3. These size differences could be attributed to the biomolecules from the curcumin extract, which served as the capping surface of AgNPs. The majority of the nanoparticles were clustered which may be due to the interaction of concentrated AgNPs with the biomolecules utilized in biosynthesis, confirming the results obtained by previous studies [28,31].

3.1.3. XRD assessment of AgNPs

Several studies reported that generated crystalline AgNPs through green synthesis using plant extracts showed XRD diffraction peaks corresponding to the AgNPs at the 111, 200, 220, and 311 planes [16,32]. Fig. 4 depicts the X-ray diffraction pattern of curcumin-produced AgNPs. Using this method, pure AgNPs' crystal structure was determined. The standard reference for the XRD pattern is the Joint Committee on Powder Diffraction Standards (JCPDS) data file card No. 00-004-0783. The typical diffraction peaks for AgNPs are found at (2θ) 38.20°, 44.51°, 64.62°, and 76.90°, corresponding to 111, 200, 220, and 311 planes of the face-centered cubic (fcc) for the AgNPs, respectively. The diffraction peak was located at 38.2°, suggesting that AgNPs preferentially grow in the 111-crystal plane during preparation [33]. Additional peaks were also observed due to root extract containing chemical molecules for reducing silver ions and stabilizing nanoparticles [32,34].

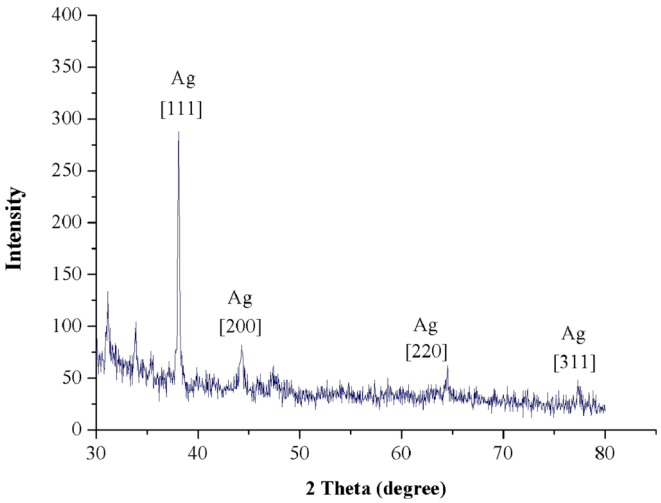

Fig. 4. XRD spectrum of green synthesized AgNPs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. In vivo studies

3.2.1. Effect of AgNPs and dexamethasone on CFA-induced paw edema in rats

Inflammation is a primary immune response of tissues against foreign particles, resulting in immune system activation and increased production of pro-inflammatory cytokines [35,36]. AgNPs have recently played a major role in the fighting of inflammation, however, their anti-inflammatory responses are still limited [22,37]. Continuing the previous studies, AgNPs synthesized from curcumin extract were evaluated as an anti-inflammatory agent using a model of CFA-induced edema in the hindfoot pad. A Vernier caliper was used to measure the paw volume before CFA injections and after dexamethasone and AgNPs treatment. Evaluation of arthritis on the first day after receiving a CFA injection, there was a little swelling and redness. Nevertheless, on the two days, there was noticeable arthritic symptom such as edema, redness, deformity, and ankylosis.

The hind left paw of the arthritis control rats significantly differed from the hind foot paw of the normal rats. It developed edema in the footpad paw after 48 h. The CFA-injected footpad's edema value gradually increased and peaked at 14 days ($p < 0.001$) compared to the healthy control rats. Dexamethasone (100 μg/kg) as a positive control and AgNPs (100 mg/kg) significantly inhibited the development of paw swelling. Our results in Fig. 5 revealed that the injection of

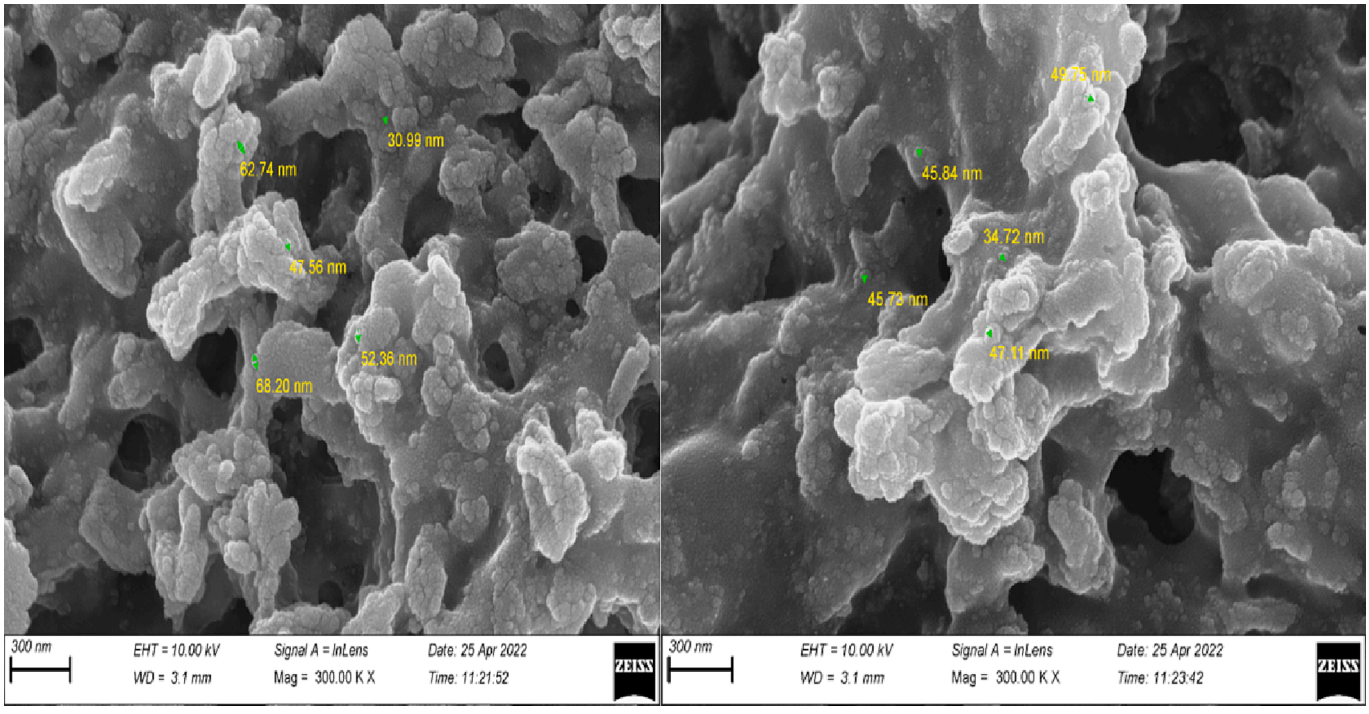

Fig. 3. SEM images of AgNPs.

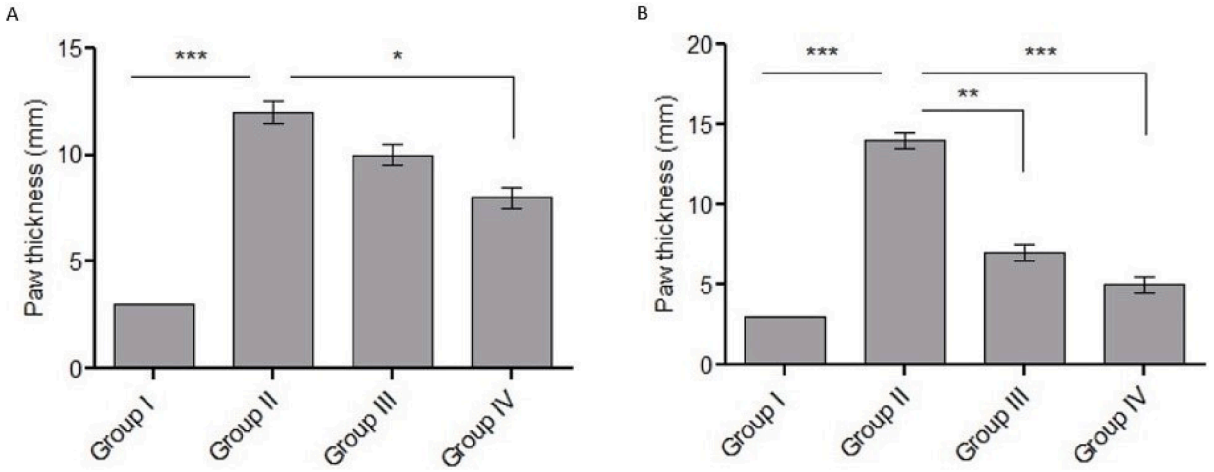

Fig. 5. Paw edema evaluated (mm) after 7 and 14 days of Complete Freund's Adjuvant injection in male Wistar rats treated with dexamethasone and AgNPs. The values are means ± standard deviations. For statistical analysis, a one-way ANOVA was utilized. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to the normal control group and arthritis-untreated group.

dexamethasone in rats considerably decreased the CFA-induced inflammation on the seventh day by 23 % ($p < 0.05$), and the inhibition significantly reduced on the fourteenth day by 64 % ($p < 0.01$) compared to the arthritis-untreated group. Moreover, AgNPs significantly reduced CFA-induced inflammation by 45 % and 82 % ($p < 0.05$ and $p < 0.001$, respectively) after 7 and 14 days. This study suggests that the administration of AgNPs reduced paw edema better than dexamethasone, and presented anti-inflammatory effects stronger than dexamethasone.

Our findings were consistent with other studies that found AgNPs to have anti-inflammatory features. A similar impact was observed in arthritic Wistar rats administered with AgNPs synthesized from Viburnum opulus fruit extract, where AgNPs reduced paw volume increase by impairing inflammatory responses linked with swelling formation [38]. Furthermore, AgNPs obtained from European black elderberry fruit extract exhibited a significant anti-inflammatory effect by reducing the inflammatory edema rate post carrageenan injection in Wister rats, providing evidence for AgNPs' potential role as an anti-arthritic agent [26].

3.2.2. The impact of AgNPs on plasma IL-6 and hs-CRP concentration in arthritic rats induced by CFA

IL-6 and CRP plasma concentrations appear to be positively linked with inflammation; IL-6 levels in CFA appear as the plasmatic marker in paw edema and arthritis [39]. These plasma markers have been evaluated as indicators of the inflammatory state during RA in rats. On day 14, as shown in Fig. 6, the concentration of IL-6 in the CFA group was significantly higher compared to the healthy rats' group ($p > 0.01$), however, IL-6 levels reverted to normal values after treatment with dexamethasone and AgNPs. As expected, dexamethasone treatment lowered the plasma IL-6 concentration of the CFA-induced arthritis group ($p > 0.01$) compared to the arthritis-untreated group. Interestingly, AgNPs treatment was also effective in reducing the plasma IL-6 concentration of the CFA-induced arthritis group ($p > 0.01$) compared to the arthritis-untreated group. Plasma hs-CRP concentration was assessed as an indicator of inflammatory status in the RA, which corresponded to the elevated plasma IL-6 concentration found in CFA-induced arthritis [40]. CFA rats had higher hs-CRP levels than healthy control rats ($p > 0.05$). However, hs-CRP concentration returned to normal values post-treatment with dexamethasone and AgNPs on day 14 as shown in Fig. 6. The findings showed a significant impact of therapies on plasma hs-CRP levels. On day 14, hs-CRP levels significantly declined using dexamethasone and AgNPs compared with the arthritis-untreated group ($p > 0.05$).

Our results suggest that the AgNPs treatment could reduce inflammation during RA progression by inhibiting pro-inflammatory cytokines such as IL-6 and CRP. A recent study showed that the AgNPs synthesized from Viburnum opulus fruit extract reduced plasmatic IL-6 concentration in arthritic Wistar rats [38]. Moreover, AgNPs derived from European black elderberry fruit extract demonstrated a promising anti-inflammatory effect by lowering cytokine levels in rat paw tissues [26]. A porcine contact inflammatory skin model revealed that nanosilver treatment significantly enhances apoptosis in inflammatory cells while decreasing pro-inflammatory interleukins levels [41].

4. Conclusion

Aqueous extracts of curcumin root extract have been successfully utilized for the green synthesis of AgNPs. The shape of crystalline nanoparticles was stated by UV–visible, SEM, and XRD analysis. SEM analysis showed that AgNPs are spherical and range in size from 30.99 to 68.20 nm. By investigating their anti-inflammatory properties in rats with CFA-induced arthritis. AgNPs provide a chance to develop new anti-inflammatory drugs. AgNPs were successful in lowering inflammation and preventing arthritis progression. In addition to improving clinical symptoms of RA, AgNPs also improved plasma IL-6 and hs-CRP concentrations. Overall, the results clearly suggested a possible alternative therapeutic strategy for controlling arthritis.

CRediT authorship contribution statement

Atheer A. Khashan: Writing – original draft, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. **Yousaf Dawood:** Writing – original draft, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. **Yousif H. Khalaf:** Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

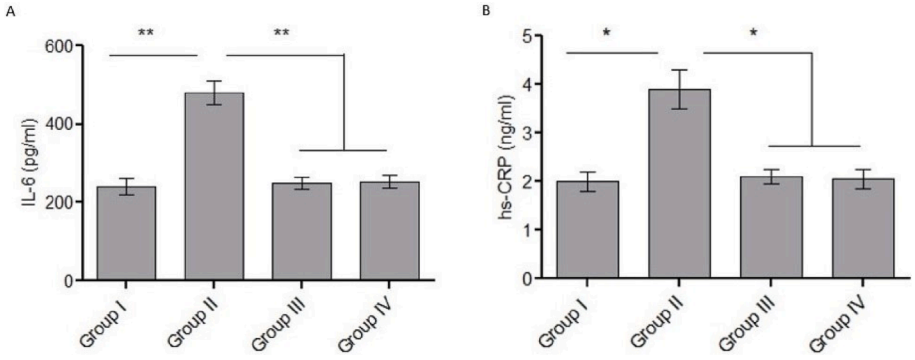

Fig. 6. IL-6 (A) and hs-CRP (B) levels before and after 14 days of CFA injection in male Wistar rats treated with dexamethasone and AgNPs. The values are means ± standard deviations. For statistical analysis, a one-way ANOVA was utilized. *p < 0.05, **p < 0.01 compared to the normal control group and arthritis-untreated group.

Data availability

Data will be made available on request.

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