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The effect of *Moringa oleifera* leaves extract and low level laser therapy on rheumatoid arthritis healing: Research on laboratory rats

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ABSTRACT

Background. Rheumatoid arthritis (RA) is the most common form of autoimmune disease. Both laser therapy and Moringa leaf extracts are effective in promoting various mechanisms, such as cartilage repair, DNA synthesis, and analgesic and anti-inflammatory effects, at both the cellular and systemic levels.

Objective. This study aimed to investigate the effects of low-level laser therapy and *Moringa oleifera* leaf extract on lipid profile changes and RA healing in male *Wistar albino* rats.

Subjects and methods. RA was induced in 40 laboratory rats, which were divided equally into four groups. The first group was left untreated as the positive control. The second group was treated with low-level laser therapy (LLLT). The third group was treated with *M. oleifera* leaf extract, and the fourth group was treated with both LLLT and *M. oleifera* leaf extract. Blood was drawn from the animals before and during the treatment period to monitor changes in the lipid profile.

Results. The results showed a change in the levels of blood lipids (cholesterol, triglycerides (TG), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and high-density lipoproteins (HDL)) after the disease was confirmed, with a return to normal levels in the treatment groups at varying proportions.

Conclusions. The results demonstrate the potential for using LLLT and Moringa leaf extracts to treat arthritis and resist high oxidative stress, particularly in the early stages of infection. Arthritis can be controlled and its progression limited through the use of laser therapy and *Moringa oleifera* leaf extract, both of which have shown therapeutic effectiveness and the ability to return disease-associated changes to normal levels. The average Rf post-induction was approximately 258.43 ± 27.09 on the 14th day, showing significant differences compared to the control group. WBC and ESR levels increased in all groups following the initial signs of the disease and returned to normal in the treatment groups, with notable differences between these groups.

Keywords: blood, lipid profile, low-level laser therapy, *M. oleifera*, rheumatoid arthritis (RA)

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory, and autoimmune disorder of unknown cause. It mostly affects synovial joints, which can result in joint degeneration and long-term impairment. It usually begins as subtle symmetrical arthritis and progresses in an unpredictable and varied way; however, disability and pain can be reduced with early diagnosis and rapid, suitable treatment [1].

Preclinical and early-stage RA patients are widely accepted to share a lipid profile that exhibits moderate atherosclerotic features due to metabolic syndrome and systemic low-grade inflammation [2]. In relation to the lower HDL-C level, it manifests as normal or slightly elevated triglyceride (TG), low-density

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lipoprotein (LDL), and total cholesterol (TC) levels. In contrast, patients with chronic progressive RA frequently or permanently experience elevated inflammation levels. The term "lipid paradox" describes how the recurrence and remission processes might result in lipolysis and lower lipid (mostly TC and LDL) levels [3]. A consistent observation is that the HDL levels of RA patients fall across a range of illness stages [4]. Despite the fact that numerous medications are recommended to treat arthritis, it is well recognized that these drugs can have a number of adverse effects, such as immunodeficiency, humoral changes, and gastrointestinal issues. Thus, the search for drugs with fewer adverse effects that can be administered over an extended period of time is critical [5].

When polar extracts of *Moringa oleifera* leaves were added, oxidative stress was effectively regulated, motor and sensory function recovery was induced, and nerve formation was facilitated [6]. The antioxidant potential and phenolic content of many dietary supplements made from *M. oleifera* have been investigated in a recent study. Regardless of how these supplements were presented, the study discovered a significant association, showing that a higher phenolic content in these supplements was associated with increased antioxidant activity [7]. Alkaloids, tannins, phenolic compounds, saponins, and steroids are also abundant. These substances may have immune-stimulating, antibacterial, antioxidant, and anticarcinogenic properties [8]. Studies have shown that leaves have more antioxidant activity than other plant components [9].

Low-intensity lasers are believed to lessen pain and accelerate healing by reducing inflammation. An increase in cell division can lead to healing. Because treating arthritis is difficult, low-level laser therapy (LLLT) has been the subject of several investigations in recent years [10].

LLLT primarily stimulates the activation of the respiratory chain of mitochondria and the initiation of cellular communication to enhance the proliferation of numerous cells, particularly in response to red and near-infrared light [11].

As an autoimmune disease, RA is associated with immune cell dysfunction at various developmental stages. The pathophysiology of RA inflammation involves numerous cell types, including T cells, B cells, dendritic cells (DCs), neutrophils, macrophages, and fibroblast-like synoviocytes. Lipid metabolites can affect RA progression by regulating the activity and function of these cells. Lipid abnormalities help accelerate atherosclerosis and increase the risk of cardiovascular disease (CVD), which is the main cause of increased mortality in RA patients.

The aim of this study was to evaluate the effects of *M. oleifera* leaf extract and LLLT on changes in the lipid profile of rats used as models of arthritis.

MATERIALS AND METHODS

Animals model

Forty male adult *Wistar albino* rats, aged 4–9 months and weighing 350–450 g, were used in this study. The animals were fed regular pellets ad libitum and housed in conventional cages with unlimited access to tap water. This model was chosen because it has many desirable characteristics that suit the needs of this study. Each cage was housed in a climate-controlled space with a temperature between 20 and 24°C. Ten days before the trial, the animals were allowed to acclimatize.

In the current study, we explained the Rheumatoid Factor, WBCs, and ESR values during and after treatment to assess arthritis as an arthritic index to denote the improvement of arthritis in the rat models.

Induced arthritis in animals

On the first and third days of the experiment, 0.1 ml of a 2% concentration of formaldehyde (HCHO) was injected into the plantar area of the left hind paw of the rat to induce experimental arthritis [12]. Ten days after the procedure, the foot exhibited alterations such as redness, swelling, and lameness. On the fourteenth day, the total thickness of the feet increased significantly ($P < 0.05$), reaching 5.88 ± 0.68 mm compared to 4.07 ± 0.31 mm on the first day. Animals were randomly divided into four groups (10 rats per group) as follows:

Group 1 (G I) (Control): Arthritic rats (without treatment) were administered a standard diet.

Group 2 (G II): Treatment with LLLT.

Group 3 (G III): Treatment with *M. oleifera* leaf extract.

Group 4 (G IV): Treatment with both LLLT and *M. oleifera* leaf extract.

Procedure for extraction

After the *Moringa oleifera* leaves were ground into a powder, they were weighed (15 g) and dissolved in 100 mL of 70% distilled water. The mixture was stirred using a magnetic stirring device for an entire day at a comfortable temperature of 25°C. Two layers of cotton gauze were used to filter out the extracted solution. The filtrate was then dried at 40°C. Next, 1 g of the dried powder was dissolved in 5 mL of distilled water to create an extraction solution of 200 mg/mL. The dosing of the treated groups began on the fourteenth, nineteenth, twenty-fourth, and twenty-ninth days of treatment (with an average animal weight of 300 g, based on the concentration). The dosage was 1.5 mL for each animal.

Diode laser

GaAlAs (gallium aluminum arsenide) was used as the active medium in the semiconductor crystal laser system. Diode lasers with a wavelength of 915 nm, maximum output power of 100 mW, density of 32 J/cm², and pulse frequency of 10 kHz were utilized. Radiation started on the fourteenth, nineteenth, twenty-fourth, and twenty-ninth days of treatment with 1.20 minutes of radiation per session. Radiation was applied 1 cm apart from the edematous skin of the paws.

Blood sampling

A combination of ketamine hydrochloride (10 mg/kg) and xylazine (3 mg/kg) was used to draw blood under general anesthesia at regular intervals from the heart after disinfection with 70% alcohol. Five milliliters of blood were drawn on the first, fourteenth, twentieth, twenty-fifth, and thirtieth days following the operation. Of this, 1.5 mL was used in the Westergren method for measuring ESR, 1 mL was used to obtain plasma for determining rheumatoid factor (RF), and 2.5 mL was separated by centrifugation at 2500 rpm for 15 minutes to obtain serum, which was used to measure WBC count and lipid profile during the treatment period. TC, TG, HDL, and LDL levels were analyzed using commercial analytical kits from BIOLABO SA (02160 Miazy, France).

Statistical analysis

Statistically significant differences between groups were computed using the Minitab program. Differences were considered statistically significant at $P \leq 0.05$.

RESULTS

Rheumatoid factor

The average rheumatoid factor (RF) value in the animals on day 0, before the experiment, was approximately 190.81 ± 83.5. After the induction of the disease and the appearance of symptoms, before dividing the animals into the experimental groups, the average RF value increased to 258.43 ± 27.09 on the 14th day after induction. The animals were then divided into four groups. On day 30 of the experiment, the RF value in the treatment groups showed significant differences compared to the control group, as shown in Table 1.

TABLE 1. Rf value at thirtieth day of experiment

Group	RF(IU/ml)
G I (n=10)	340.24±67.94[b]
G II(n=10)	210.69±43.06[a]
G III(n=10)	203.57±95.82[a]
G IV(n=10)	183.08±37.26[a]

Similar letters indicate no significant difference
Different letters indicate a significant difference

White blood cells count (WBCs) and erythrocyte sedimentation rate (ESR)

WBC and ESR levels increased in every group following the first sign of the disease and returned to normal in the treatment groups, with notable differences between these groups and the control group. The differences in WBC count between the groups during the trial period were as follows: between G I and G II ($P \leq 0.021$), between G I and G III ($P \leq 0.019$), and between G I and G IV ($P \leq 0.040$). The differences in ESR between the groups during the trial period were as follows: between G I and G II ($P \leq 0.049$), between G I and G III ($P \leq 0.051$), and between G I and G IV ($P \leq 0.0372$), as shown in Tables 2 and 3, respectively.

TABLE 2. WBCs account in experimental groups

days	G I	G II	G III	GIV
0	14.26±2.33	13.8±0.76	12.64±2.07	14.08±0.35
14	17.3c±4.61	16.08±2.79	16.44±7.81	17.02±5.24
20	18.94±7.09	14.26±1.24	14.66±0.167	15.38±5.10
25	19.54±4.13	13.88±6.52	13.76±3.91	14.22±2.44
30	20.246±11.54	13.64±5.93	12.8±7.34	13.94±3.73

TABLE 3. ESR levels in experimental groups

days	G I	G II	G III	GIV
0	1.5±33.2	1.1±3.02	1.2±0.65	1.2±0.03
14	5.9±1.08	4.9±0.82	5±2.87	5.2±2.13
20	8.4±2.20	3.8±1.07	3.7±1.49	3.4±1.32
25	9.7±3.54	2±0.09	2.2±0.34	1.2±0.033
30	10.9±0.82	1.3±2.8	1.3±2.06	0.4±11.1

Lipid profile results

The results showed a noticeable increase in the levels of cholesterol, LDL, TG, and VLDL in the blood of animals with arthritis, compared with the control group. In contrast, the blood of animals in the treatment groups showed a decrease in lipid values, with levels returning to almost normal after the experimental period. As shown in Figures 1, 2, 3, and 4, there was a noticeable decrease in HDL levels in the blood of control group animals, with a significant difference observed in the treatment group animals, as shown in Figure 5.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease that primarily affects the synovium of peripheral joints, leading to joint degeneration and early disability. Additionally, the high prevalence and mortality rate of cardiovascular diseases (CVD) are linked to RA. The relationship between RA and lipid metabolism has gained attention in recent years. Clinical testing frequently reveals alterations in plasma lipid levels in RA pa-

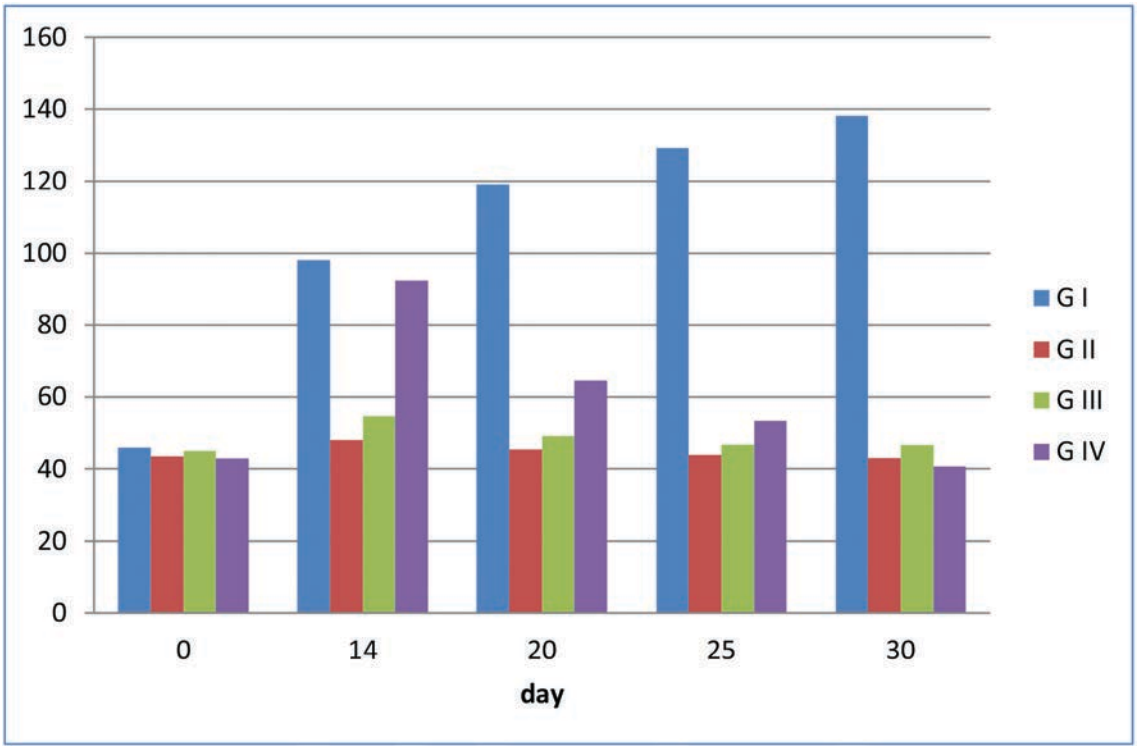

FIGURE 1. The differentiation of cholesterol levels among the groups during the trial period (between G I and G II at P ≤ 0.020, between G I and G III at P ≤ 0.025 and between G I and G IV at P ≤ 0.047)

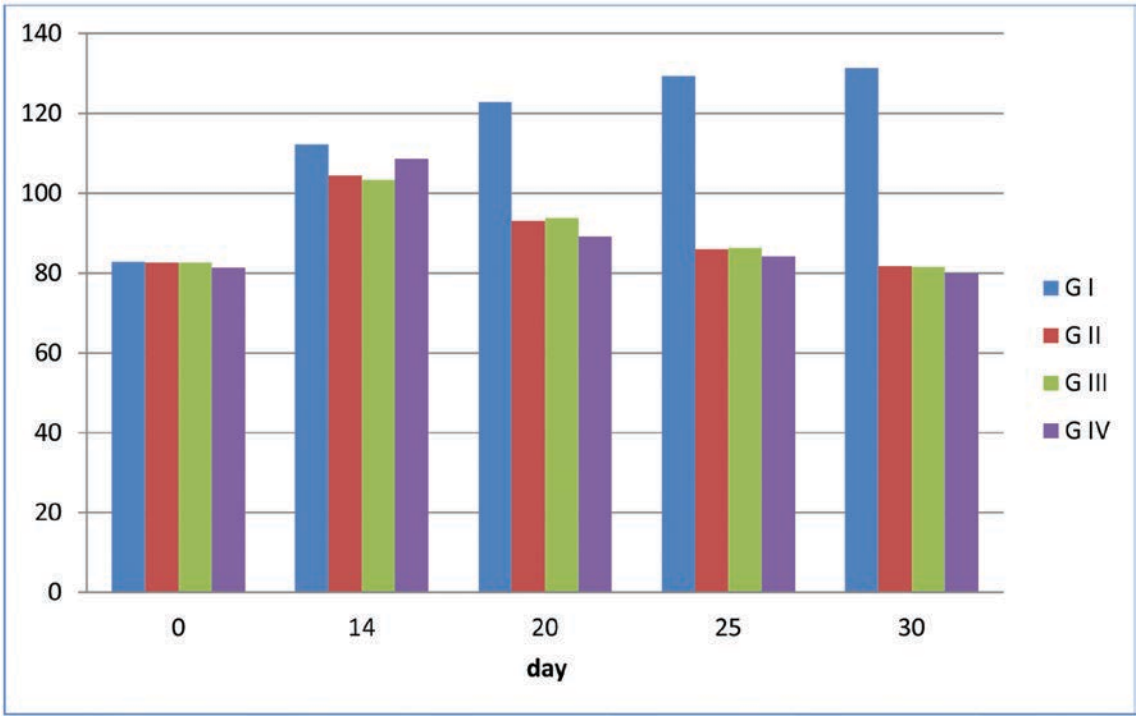

FIGURE 2. The differentiation of Tg Levels among the groups during the trial period (between G I and G II at P ≤ 0.045, between G I and G III at P ≤ 0.044 and between G I and G IV at P ≤ 0.039)

tients. Furthermore, the systemic inflammatory condition and pharmacological treatments in arthritis patients can significantly interfere with the body's metabolic state. The advent of lipid metabolomics has steadily identified small-molecule lipid alterations and potential metabolic mechanisms, allowing for a more thorough understanding of the systemic changes in lipid metabolism following treatment or the metabolic processes in RA patients [13].

The etiology of arthritis, in addition to the presence of autoantibodies, is multifaceted and not fully understood. Inflammation of the joints and cartilage degradation are primary physiological features of RA. These processes are caused by immune cells invading the synovial joint lining and the cytokine

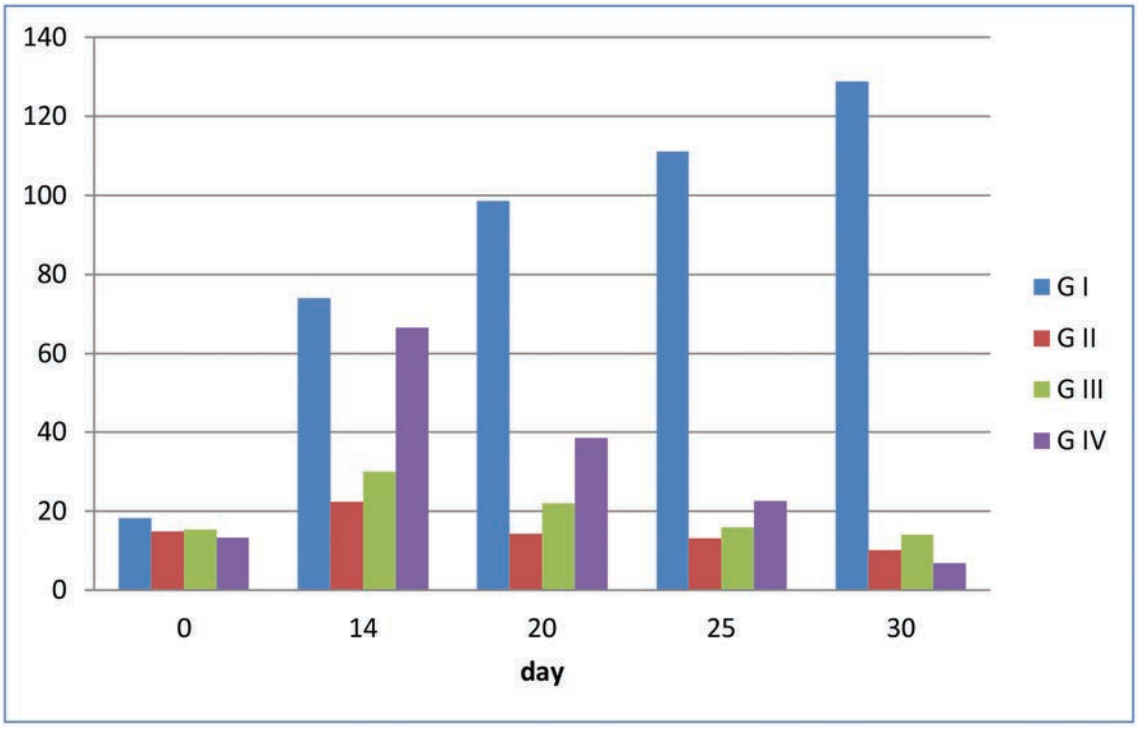

FIGURE 3. The differentiation of LDL Levels among the groups during the trial period (between G I and G II at P ≤ 0.021, between G I and G III at P ≤ 0.026 and between G I and G IV at P ≤ 0.042)

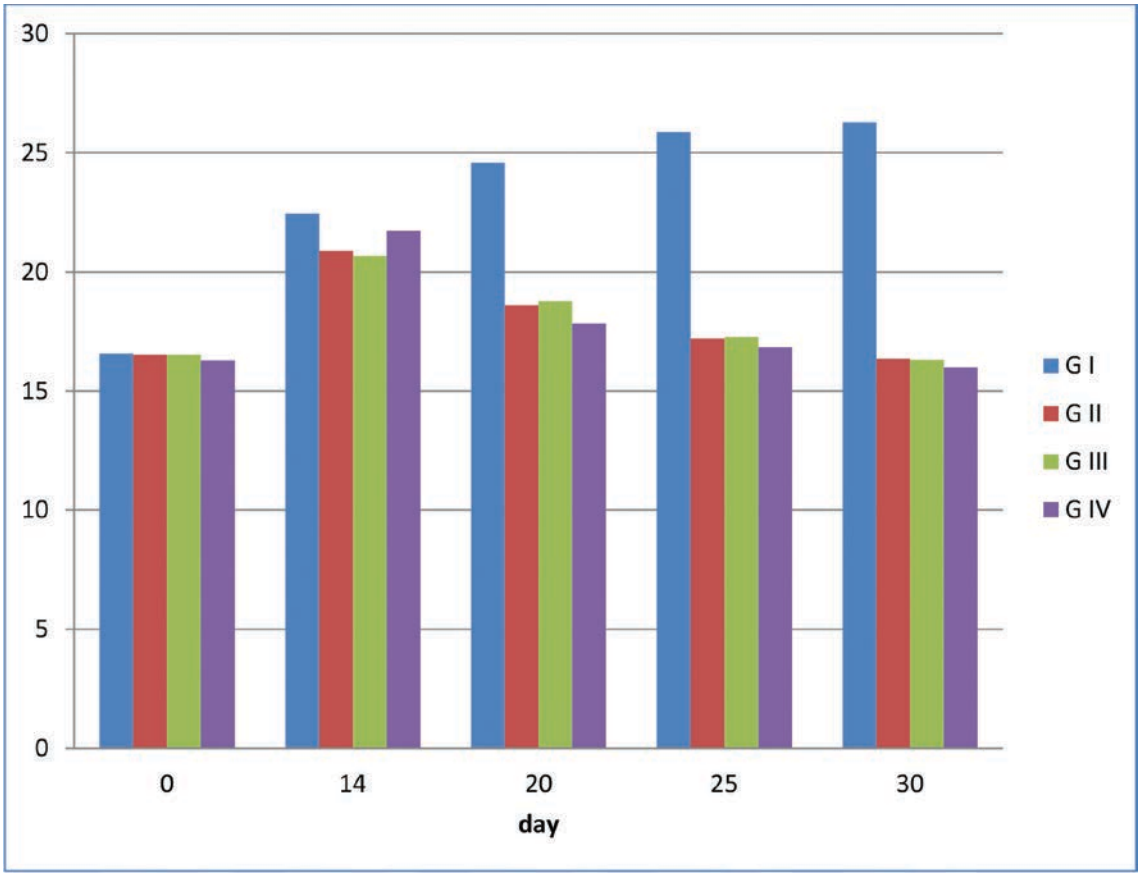

FIGURE 4. The differentiation of VLDL levels among the groups during the trial period (between G I and G II at P ≤ 0.045 , between G I and G III at P ≤ 0.044 and between G I and G IV at P ≤ 0.042)

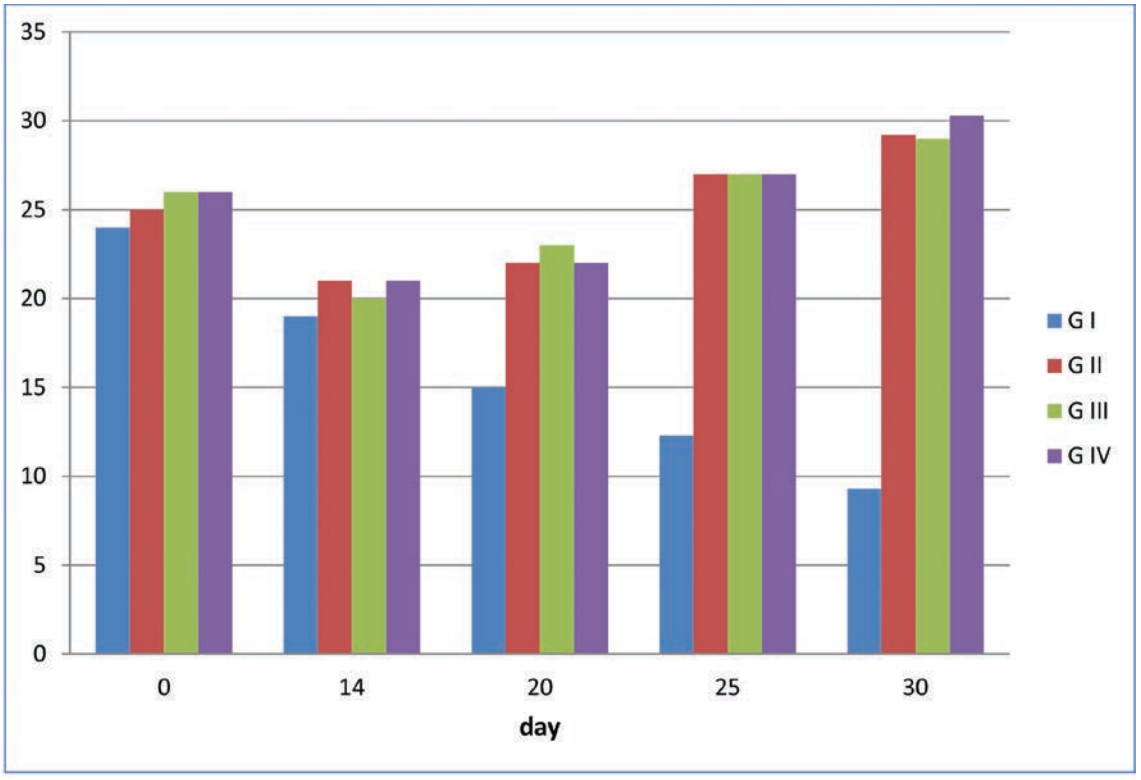

FIGURE 5. The differentiation of HDL levels among the groups during the trial period (between G I and G II at P ≤ 0.025, between G I and G III at P ≤ 0.024 and between G I and G IV at P ≤ 0.023)

network that follows [14]. One important aspect of RA pathophysiology is thought to be compromised adaptive immune responses. The synovial membrane surface and fluid are exposed to numerous pro-inflammatory cytokines released by activated T helper cells [15]. Recently, activated macrophages have been shown to release additional anti-inflammatory cytokines, which feed into a self-amplifying inflammatory mediator loop, causing B cells to proliferate and differentiate. This results in the production of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) [14].

In addition to promoting oxidative stress, elevated levels of pro-inflammatory cytokines contribute to dyslipidemia in individuals with RA [16]. Between 55% and 65% of patients with RA have dyslipidemia, which can be identified in the early phases of the disease or even before the formal diagnosis of RA, when autoimmunity (RF, ACPA) and inflammation are typically elevated. An unfavorable lipoprotein profile—characterized by reduced HDL and variations in LDL and total cholesterol (TC) levels—is associated with both active and untreated RA [17]. Several studies have reported inconsistent outcomes concerning LDL and TC levels, likely due to variations in study design, sample sizes, population, treatment effects, and confounders. As the TC/HDL ratio increases with decreasing HDL, this ratio becomes a significant predictive indicator for cardiovascular diseases and has been linked to disease activity and an atherogenic index [18]. Additionally, a change in the structure of HDL has been found to account for its reduced atheroprotective effect, thereby explaining the increased risk of cardiovascular diseases in RA patients [19].

Fadaei and Davies suggested that HDL, as part of the innate immune system, shows a correlation between inflammation and HDL activity. In individuals with metabolic syndrome and chronic low-grade inflammation, there is a significant functional impairment of HDL levels. Similarly, in patients with RA—particularly during the active phase—HDL levels exhibit notable deviations. These changes are summarized as a decrease in HDL2 particles (which are anti-atherosclerotic subfractions) and a shift in HDL activity from anti-inflammatory to pro-inflammatory. Changes in key proteins and lipids are likely involved in the process by which pro-inflammatory HDL is formed [20][21].

Increased LDL levels are considered a strong indicator of cardiovascular diseases (CVD); lowering LDL-C levels through medications results in a significant reduction in CVD risk [22]. According to Rhoads and Major, there were more small, dense LDL particles in the RA group compared to the positive control group, but fewer small HDL particles. This is because small, compact LDL particles are more prone to oxidation and can enter endothelial cells more easily than larger particles. Atherosclerosis is caused by the excessive buildup of cholesterol in tissues, transported by LDL from the liver. LDL enters the artery when endothelial cells are damaged, and

small, dense LDL is converted into oxidized LDL, which is then engulfed by macrophages to form foam cells via innate and adaptive immunity [23].

Moringa oleifera chemicals have been shown to combat inflammation through several mechanisms [24]: (a) Pro-inflammatory enzyme inhibition: Moringa contains quercetin and kaempferol, which block the function of pro-inflammatory enzymes like lipoxygenase (LOX) and cyclooxygenase (COX), which play key roles in synthesizing inflammatory mediators such as leukotrienes and prostaglandins; (b) Cytokine production modulation: Isothiocyanates, a class of compounds found in Moringa, modulate inflammatory signaling pathways, including the NF-kappa B pathway. These compounds also inhibit the synthesis of pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), while boosting the synthesis of cytokines that reduce inflammation [25]; (c) Antioxidant activity: The flavonoids and polyphenols in Moringa help reduce inflammation and oxidative stress, potentially modifying cytokine synthesis and blocking pro-inflammatory enzyme functions [26].

Moringa leaves are rich in saponins, which bind to bile acids and block cholesterol absorption, thereby reducing enterohepatic circulation. Additionally, they promote the excretion of cholesterol in feces, lowering serum cholesterol levels. In hyperlipidemic rats, Moringa leaf extract has been shown to reduce serum lipid levels [27]. The reduction in RF levels may be attributed to the active ingredients in Moringa, including steroids, alkaloids, tannins, phenolics, and saponins [28].

Flavonoids and antioxidants in Moringa extracts likely contribute to the plant's anti-inflammatory effects. These compounds are abundant in both the leaves and seeds of the Moringaceae family and are responsible for preventing osteoporosis by increasing bone mineral density. Furthermore, the administration of Moringa leaves or seeds affects the production of TNF-α and IL-6—two cytokines crucial in preventing RA development in rats [29][30].

Zhao et al. reported that mitochondria absorb laser photonic energy, converting it into chemical kinetic power, which results in increased ATP synthesis. ATP, the cell's energy source, is essential for processes such as protein, RNA, and DNA synthesis, which are critical for cell growth [31].

Wickenheisser et al. stated that laser light must be absorbed and alter the internal state of cells to initiate various processes, including the synthesis of ATP, RNA, DNA, and proteins. These processes are essential for enzyme synthesis, modulation of prostaglandin synthesis, reduction in lipid peroxidation rates, immune system stimulation (both specific and non-specific), antioxidant effects, improved blood circulation, microcirculation activation, collagen synthesis enhancement, tissue regeneration, and anti-inflammatory and anti-allergic effects [32].

Limitations

This study had several limitations. First, long-term changes in lipid profiles were not examined. This study focused on the early changes in lipid profiles following the induction of arthritis, and future studies should recheck lipid profiles for a longer duration to assess the effect of laser therapy and Moringa extract. Second, due to the short duration of this study, we did not investigate the long-term effects of laser therapy and plant extracts on lipid profiles. Additionally, we did not conduct long-term follow-ups on the animals after RA onset to explore the relative roles of inflammation and cholesterol in the development of cardiovascular diseases.

CONCLUSION

Laser radiation and *Moringa oleifera* leaf extract have shown therapeutic effectiveness in controlling arthritis and limiting the disease's progression. Both treatments demonstrated the potential to reverse changes associated with the disease, restoring levels to those seen prior to infection. Specifically, the average rheumatoid factor (RF) value following disease induction was 258.43 ± 27.09 on day 14, which significantly differed from the control group. White blood cell (WBC) counts and erythrocyte sedimentation rate (ESR) levels increased following the onset of the disease but returned to normal in the therapy groups, with notable differences between these groups and the control group. Furthermore, the control group exhibited a continued increase in cholesterol, LDL, triglycerides (TG), and very-low-density lipoprotein (VLDL) levels, alongside a noticeable decrease in HDL. In contrast, the treatment groups showed improvements in these lipid profile parameters.

Ethics clearance:
The study received approval from Al-Muthanna University's local ethics the committee.

Data availability:
Data are available upon reasonable request.

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This research did not receive any specific fund.

Conflicts of interest: None

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