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# Nano selenium-lovastatin mixture modulate inflammatory cascade in arthritic irradiated model

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► ***Original article***

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## ABSTRACT

***Background***: The development of nanotechnology has been a boon to mankind as its significance paved the way for several applications in therapeutics. This study was to evaluate the anti-arthritic capability of nano Selenium-lovastatin mixture (Lov-Se) against inflammatory cascade in arthritic irradiated rats. ***Materials and Methods***: Animal model of Arthritis was organized by subcutaneous injection of Complete Freund's adjuvant; CFA. Rats were exposed to γ-radiation (2Gy every 3 days up to total dose of 8 Gy). Lov-Se (1ml ≈ 20 mg $kg^{-1}$ $day^{-1}$Lov and 0.1 mg $kg^{-1}$ $day^{-1}$Se) was administrated by daily oral injection. The antioxidant parameters (heart glutathione peroxides; GSH-Px, catalase; CAT, superoxide dismutase; SOD, xanthine dehydrogenase; XDH, reduced glutathione; GSH and blood selenium; Se), oxidant markers (heart Xanthine oxidase; XO, Nitric oxide; NO, protein carbonyls and thiobarbituric acid reactive substances; TBARS) and the inflammatory molecules (serum tumor necrosis factor-alpha TNF-α, C-reactive protein; CRP and rheumatoid factor; RF) were determined. ***Results:*** The arthritic and arthritic irradiated rats were displayed augment oxidative stress, inflammatory cascade and impaired antioxidant status compared to control. ***Conclusion:*** The data revealed that Lov-Se administration ameliorate oxidative, antioxidants parameters as well as inflammatory factors. The prolonged administration of Lov-Se mixture in appropriate concentration could exert a considerable systemic anti-inflammatory action through adjustment of red-ox tone and the integration of XDH/XO ratio.

***Keywords:*** *Arthritis, γ-radiation, nano selenium-lovastatin, antioxidant, oxidative stress, inflammation.*

## INTRODUCTION

A number of pathological conditions including rheumatic diseases have been proposed to be induced by oxidative stress; a state where excess production of reactive oxygen species (ROS) exceeds the antioxidant protection. Several paradoxes of redox-related biochemistry are discussed in connection with rheumatic disease and a possible role of oxidative stress is considered in pathogenesis of rheumatoid arthritis (RA) [(1)].

RA is characterized by a persistent inflammation in the synovial membranes of joints, associated with migration of activated phagocytes and other leukocytes into synovial and periarticular tissue. The latter processes could be concerned as early steps of pathogenesis and prognosis of RA. Important signal substances derived from the activated macrophages are the oxygen radicals, such as superoxide anion radical ($O_2^{\bullet -}$) and hydrogen peroxide ($H_2O_2$) and the cytokines, such as tumor necrosis factor-alpha (TNF-α). These mediating substances play key roles in the progression of the rheumatoid inflammation. Furthermore, activated neutrophils produce $O_2^{\bullet -}$, $H_2O_2$ and hypochlorous acid as a bactericide. As a side-effect of such defense and due to a large number of activated phagocytes,

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the tissue experiences damage because of the ROS attack on DNA, lipid and proteins [1].

Individuals working in radiology-related occupations are among persons exposed to long-term low levels of ionizing radiation that have been shown to have immunocompromising effects due to occupation [2]. Ionizing radiation collides with molecules in living cells generating clusters of free radicals known as ROS, including free radicals (H+: hydrogen ion, $H^{\bullet}$: hydrogen radical, $H_2O_2$, $OH^{\bullet}$: hydroxyl radical). These free radicals randomly damage cellular constituents including DNA and react with almost all structural and functional organic molecules, including proteins and lipids. Free radicals are also formed as an indirect consequence of irradiation by phagocytic cells that have become activated during removal of radiation-injured tissues. Studies strongly suggest that oxidative stress from ionizing radiation exposure can trigger a cascade of events, including altered immune function, cellular transformation, and tissue damage.

However, the immune system can resist this oxidative stress by scavenging free radicals and neutralizing them. Superoxide dismutase (SOD) is catalyzes the dismutation of $O_2^{\bullet-}$ into $O_2$ and $H_2O_2$. Together with catalase (CAT) and glutathione peroxides (GSH-Px), these are the major intracellular enzymes that protect cells and its constituents from oxygen toxicity [3].

Statins are widely used to lower the blood cholesterol level in patients of hypercholesterolemia. They competitively inhibit the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methyl glutaryl coenzyme A reductase. Among the statins, lovastatin was the first statin approved as a hypocholesterolemic drug. Lovastatin as an inhibitor of the rate limiting enzyme of the mevalonate pathway, blocks the induction of inducible nitric oxide synthase (iNOS) and proinflammatory cytokines TNF-α, interleukin (IL)-1β and IL-6) in rat astrocytes, microglia and macrophages [4]. Many microorganisms such as *Monascus purpureus* have been reported as lovastatin producing fungi [5]. *Monascus purpureus* rice, popularly called red yeast rice, is described as the fermented product of rice on which red yeast has been grown [6]. The antioxidant effect of statins is related to its ability to reduce free radical formation. It was reported that, lipid peroxidation reduction accompanied with preservation of SOD activity was observed in lovastatin treated rabbits [7]. In addition, lovastatin was effective in lowering hepatic lipid peroxidation in animals fed a high cholesterol diet [8]. The cellular GSH-Px activity was enhanced in the cells treated with lovastatin and increased $H_2O_2$ scavenging by endothelial cells [9].

Selenium (Se) is an essential element for human health. It has been recognized as antioxidant [10]. The antioxidant function of Se can help to ameliorate the damage induced by the ultraviolet-β radiation in humans [11]. This element was found to have a role in immune function [10], where the deficiency in Se is associated with immune dysfunction, impaired resistance to microbial and viral infections, inadequate phagocytosis and antibody production, and increased cancer risk [12]. It was shown that Nano-Se has a similar bioavailability in rat, and much less acute toxicity in mice compared with selenite. The biological activities of Nano-Se may come from the special properties of the nanoparticles [13].

The anti-inflammatory and antioxidant properties of Nano selenium and lovastatin hypothesize the possibility of using a combination of the two substances to combat chronic inflammation in adjuvant arthritic rats. In the present work, the Lov-Se effects on the changes induced by RA and/or radiation exposure on TNF-α, C-reactive protein (CRP) and rheumatoid factor (RF) were observed. Also, its action on markers of the oxidative stress [thiobarbituric acid reactive substances; TBARS, protein carbonyl and nitric oxide (NO)] as well as antioxidant parameters [glutathione; GSH, Xanthine Oxidoreductase (XOR), SOD, CAT, GSH-Px and Se] were examined.

## MATERIALS AND METHODS

### *Experimental animals*

Female albino rats (120-150g) obtained from the Egyptian Holding Company for Biological Products and vaccines were used as



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experimental animals. Animals were kept under standard conditions of temperature and humidity along the experimental period. The rats were fed on standard pellets of concentrated diet containing all the necessary nutritive elements. Liberal water intakes were available. Animal procedures were performed in accordance with the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals.

***Induction of arthritis with an adjuvant***

Rats were injected subcutaneously with a single dose of 0.8 ml of Complete Freund's adjuvant (CFA) (product of BD, USA) containing 400 µg dry *mycobacterium butyricum* into the dorsal root of the tail under ether anesthesia [14]. The day of adjuvant injection is referred to as day zero.

***Radiation Facility***

Whole body γ-irradiation of rats was performed with a Canadian gamma cell-40, (137Cs) at the NCRRT, Cairo, Egypt at a dose rate of 0.46Gy $min^{-1}$.

***Preparation of Nano Selenium-lovastatin mixture (Lov-Se)***

A mixture consisted of (obtained by chemical reaction) and lovastatin (derived from fungal fermentation on rice; Monascus purpureus have been reported as lovastatin producing fungi) were prepared, verified and characterized according to the method of [15], at National Center for Radiation Research and Technology laboratories, Cairo, Egypt.

***Experimental Set Up***

The efficacy of Lov-Se Mixture was evaluated at three time intervals 1st, 15th and 29th day post the experimental time zero. The development of arthritis require about 2 weeks after adjuvant injection [14]. The experimental animals were divided into 6 groups: *Group 7:* Normal control (n=18), rats were daily received 1ml distilled water via oral tube. *Group8:* Lov-Se (n=12), rats were received oral administrations of the lab prepared agents (1ml) (≈20 mg $kg^{-1}$ $day^{-1}$Lov and 0.1mg $kg^{-1}$ $day^{-1}$Se nanoparticle) starting from the time zero of the experiment. *Group 9:* Arthritic (n=18), rats of this group were inoculated by adjuvant inducer CFA and received 1 ml distilled water daily starting from the zero time of the experiment. *Group 0:* Arthritic Irradiated (n=18), rats of this group were inoculated by adjuvant inducer, exposed to γ-radiation (2Gy every 3 days up to total dose of 8 Gy) and received 1ml distilled water orally starting at zero time of the experiment. *Group1:* Arthritic Lov-Se (n=18), all rats of this group were inoculated by adjuvant inducer at time zero of the experiment. Twelve rats were received successive doses of Lov-Se starting at time zero whereas, the rest of animals received the mixture doses starting from day 15th of the experiment (after proliferation of arthritis by the adjuvant) and continued until 28th day. *Group 2:* Arthritic Irradiation Lov-Se (n=18), all rats of this group were inoculated by adjuvant inducer at time zero of the experiment and exposed to γ-radiation. As in the previous group, 12 rats were received successive doses of Lov-Se starting at time zero and the rest of animals received the mixture doses starting from day 15th of the experiment and continued to 28th day. Six rats from each group were sacrificed on the 1st, 15th and 29th day post the experiment time zero except group 2 which include 12 rats, 6 were sacrificed at the 1st day to be compared with the rats of the other groups that sacrificed on the 1st day. The other 6 rats were sacrificed at the 15th day to be compared with the rats of the other groups that sacrificed on the 15th and 29th day post the time zero. After an overnight fast, rats were anesthetized with ether and then sacrificed. Blood samples from each rat were collected by retro-orbital puncture using blood capillary tubes. Blood sample was divided into 2 parts; first part was collected on diNa-EDTA and the other part was left to coagulate to obtain serum. Heart was directly separated after sacrificing, washed in ice-cold saline then the heart samples were homogenized in doubly distilled water (10% W/V) using homogenizer then the cell debris was removed by centrifugation at 3000 rpm for 10min. The homogenates supernatant, blood and serum were subjected to the following biochemical analysis.

***Biochemical assay***

The levels of serum TNF-α (pg/ml) were measured by enzyme- linked immunosorbent



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assay (ELISA) kit (ASSAYPRO, USA), following the manufacturer's instructions [16]. Also, serum CRP levels (mg/l) were measured by ELISA kit (Monobind Inc. Lake Forest, USA) [17]. Serum RF levels were measured by ELISA kit (ORGENTEC Diagnostika GmbH, Germany) [18]. The XOR system including xanthine dehydrogenase, XDH and xanthine oxidase, XO activities (U/mg protein) were assayed by measurement of uric acid formation in the presence or absence of NADP at 37 $^0$C, as described by [19] Lipid peroxidation product, malondialdehyde (MDA), was measured (n mole/g wet tissue) by thiobarbituric acid assay, which is based on MDA reaction with thiobarbituric acid forming TBARS, a pink colored complex exhibiting a maximum absorption at 532 nm [20]. The protein carbonyl content (m mole/mg protein) was estimated by the method of [21]. The photometric carbonyl assay is based on the reaction of 2, 4-dinitrophenylhydrazine with carbonyl groups to produce 2, 4-dinitrophenyl-hydrazone. NO was measured (nmole/g wet tissue) as stable end product, nitrite, according to the method of [22] The assay is based on the reduction of nitrate by vanadium trichloride combined with the detection by acidic Griess reaction. The diazotization of sulfanilic acid with nitrite at acidic pH and subsequent coupling with N-(10 naphthyl)-ethylene diamine produced an intensely colored product that is measured at 540nm. SOD activity was assayed via the method of [23], based on the inhibition of $O_2^{\bullet -}$ generated by phenazine methosulfate that converts nitroblue tetrazolium (NBT) to NBT-diformazan, which absorbs light at 560nm. SOD activity was defined as the amount of enzyme required to give 50% inhibition of NBT reduction and expressed as units/ mg protein. CAT activity was determined following the procedure described by [24] where the disappearance of peroxide is followed spectrophotometrically at 240nm. One unit of the enzyme is expressed as m moles of $H_2O_2$ utilized per minute per g protein. GSH-Px activity (U/mg protein) was assayed according to the method of [25]. The activity of GSH-Px expressed as GSH consumed per min per mg protein. The GSH content was determined photometrically at 412 nm using 5, 5-dithiobis-2 -nitrobenzoic acid [26]. Blood Se content was detected by atomic absorption estimation which involves the measurement of the light absorbed by selenium atom at ground state [27]. The concentration of Se was calculated by using standard curve specific for the element [28]. The protein content was determined according to the Folin–Lowry method [29].

### *Statistical analysis*

The SPSS/PC computer program was used for statistical analysis of the results. Data were analyzed using one-way analysis of variance (ANOVA) followed by post hoc test for multiple comparisons. The data were expressed as mean ± SE. Differences were considered significant at ($P \leq 0.05$).

## RESULTS

In rats treated with Lov-Se, no significant changes ($P \geq 0.05$) was observed in serum TNF-α, CRP and RF and levels when compared with control rats along experimental intervals. In the arthritic rats, the TNF-α were significantly increased ($P \leq 0.05$) at 15 and 29 day while CRP increased at 1, 15 and 29 day and RF at 15 and 29 days. In arthritic irradiated rats, significant increase was observed in TNF-α at 1, 15 and 29 day, in CRP at 15 and 29 day whereas RF at 15 day. In arthritic Lov-Se rats, TNF-α was displayed significantly increase at 29 day whereas CRP and RF exhibit no significant changes. In arthritic irradiated Lov-Se rats, significant increase in TNF-α was at 29 day while no significant changes were in serum CRP and RF. Lov-Se induced significant improvements in inflammatory markers of arthritic Lov-Se and arthritic irradiated Lov-Se rats when compared to arthritic and arthritic irradiated rats (table 1).

In rats treated with Lov-Se, no significant changes in heart XO and XDH activities and NO contents were observed when compared with control rats (table 2). Significant decrease in heart XDH activity in arthritic and arthritic irradiated rats at 1, 15 and 29 day compared to control. The heart NO concentration was

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significantly decreased in arthritic and arthritic irradiated rats at 15 and 29. Significant increase was observed in heart XO activity of arthritic and arthritic irradiated rats at 1, 15 and 29 day. In arthritic Lov-Se rats, significant decreases in heart XDH at 1, 15 and 29 day of experimental intervals as compared to control. Significant increases in heart XO were noticed at 1, 15 and 29 day. No significant changes were observed in heart NO concentration along all experimental intervals. In arthritic irradiated Lov-Se rats, significant decreases in heart XDH activity were recorded at 1, 15 and 29 day. Significant decreases in heart NO and significant increases in heart XO were recorded at 15 and 29 days (table 2). The arthritic Lov-Se and arthritic irradiated Lov-Se rats showed significant improvement in heart XOR system and NO contents as compared to arthritic and arthritic irradiated rats (table 2).

**Table 1.** The change in serum CRP (µg/ml), RF (U/ml) and α-TNF (pg/ml) levels of different animal groups.

| | Day | Control | Lov-Se | Arthritis | Arthritis Irradiated | Arthritis Lov-Se | Arthritis Irradiated Lov-Se |
|---|---|---|---|---|---|---|---|
| α-TNF LSD =24.10 | 1 | 101.83±5.30$^{a,c}$ | 106.92±7.89$^{a,c,g}$ (4.99) | 108.00±9.28$^{a,b,c,d}$ (6.06) | 131.44±11.02$^{b,d,f}$ (29.08) | 101.00±7.38$^{a,c}$ (0.80) | 117.18±7.97$^{a,b,d,f}$ (15.07) |
| | 15 | 99.00±5.47$^{a,c}$ | 107.99±7.36$^{a,b,c,d}$ (9.08) | 132.00±8.68$^{d,f}$ (33.33) | 125.99±8.69$^{b,d,f,g}$ (27.26) | 100.22±7.65$^{a,c}$ (1.23) | 102.10±6.65$^{a,c,g}$ (3.13) |
| | 29 | 104.00±5.26$^{a,c,g}$ | 107.99±7.36$^{a,b,c}$ (3.84) | 131.15± 9.00$^{b,d,f}$ (26.10) | 165.45±14.01$^{e}$ (59.09) | 139.15±9.19$^{f}$ (33.79) | 138.50±10.18$^{f}$ (33.17) |
| CRP LSD =10.49 | 1 | 44.34±2.35$^{a,e,f}$ | 41.52±2.53$^{a,e}$ (6.36) | 56.02±4.24$^{b,c}$ (26.34) | 48.87±3.63$^{a,b,c,e}$ (10.22) | 51.76±3.56$^{a,b,c}$ (16.73) | 43.62±3.81$^{a,e,f}$ (1.62) |
| | 15 | 44.80±2.32$^{a,e,f}$ | 46.95±3.31$^{a,b,e,f}$ (4.80) | 58.28±5.45$^{c}$ (30.09) | 57.47±3.96$^{c}$ (28.28) | 42.89±3.37$^{a,e,f}$ (4.26) | 42.23±3.48$^{a,e,f}$ (5.74) |
| | 29 | 45.63±2.65$^{a,b,e,f}$ | 46.95±3.31$^{a,b,e,f}$ (2.89) | 57.68±3.77$^{c}$ (26.41) | 78.58±5.88$^{d}$ (72.21) | 41.17±3.19$^{e}$ (9.77) | 52.04±3.86$^{c,f}$ (14.05) |
| RF LSD=12.71 | 1 | 52.64±2.88$^{a,b}$ | 53.43±3.75$^{a,b}$ (1.50) | 62.79±4.64$^{b,c,g}$ (19.28) | 64.82±5.28$^{b,c,e}$ (23.14) | 58.73±4.95$^{a,b,d}$ (11.57) | 60.26±4.87$^{a,b,c}$ (14.48) |
| | 15 | 51.37±2.65$^{a,g}$ | 49.47±3.23$^{a}$ (3.70) | 72.38±5.09$^{c,e}$ (40.90) | 68.49±5.55$^{c,d,e}$ (33.33) | 56.40±4.98$^{a,b,d}$ (9.79) | 55.81±4.22$^{a,b,f}$ (8.64) |
| | 29 | 54.00±3.03$^{a,b,f}$ | 49.47±3.23$^{a}$ (8.39) | 75.67±4.79$^{e}$ (40.13) | 66.50±4.89$^{c,d,e,f}$ (23.15) | 58.35±5.27$^{a,b,d}$ (8.06) | 60.53±5.13$^{a,b,c}$ (12.09) |

Each value represents the mean± S.E. (n=6). %: Percentage of changes from control group.
Values with unlike superscript letters are significantly different (P≤0.05). The values that have the same superscript letters are not significantly different (p> 0.05).
LSD: Least Significant Difference

**Table 2**. The change in heart XDH (U/ mg protein) and XO (U/ mg protein) activities and NO levels (m mole/g wt tissues) in different animal groups.

| | Day | Control | Lov-Se | Arthritis | Arthritis Irradiated | Arthritis Lov-Se | Arthritis Irradiated Lov-Se |
|---|---|---|---|---|---|---|---|
| XDH LSD =0.17 | 1 | 1.23±0.062$^{a}$ | 1.19±0.083$^{a}$ (3.25) | 0.73±0.045$^{b}$ (-40.65) | 0.69±0.056$^{b,d}$ (-43.90) | 0.91±0.083$^{c,f}$ (-26.02) | 0.93±0.070$^{c}$ (-24.39) |
| | 15 | 1.11±0.062$^{a}$ | 1.13±0.089$^{a}$ (1.80) | 0.54±0.038$^{d,e}$ (-51.35) | 0.58±0.041$^{b,d,e}$ (-47.75) | 0.64±0.047$^{b,d,g}$ (-42.34) | 0.74±0.065$^{b,f}$ (-33.33) |
| | 29 | 1.15±0.063$^{a}$ | 1.13±0.089$^{a}$ (1.74) | 0.46±0.043$^{e}$ (-60.00) | 0.51±0.048$^{e,g}$ (55.65) | 0.72±0.047$^{b}$ (-37.39) | 0.70±0.055$^{b,d}$ (-39.13) |
| XO LSD =0.259 | 1 | 0.77±0.039$^{a,b}$ | 0.71±0.061$^{a}$ (7.79) | 1.22±0.084$^{c,e}$ (58.44) | 1.23±0.111$^{c,e}$ (59.74) | 1.03±0.075$^{c,i}$ (33.77) | 0.99±0.082$^{b,c,f}$ (28.57) |
| | 15 | 0.74±0.042$^{a,f}$ | 0.66±0.057$^{a}$ (10.81) | 1.37±0.130$^{e,g}$ (63.00) | 1.52±0.123$^{g}$ (105.41) | 1.21±0.101$^{c,e}$ (63.51) | 1.08±0.101$^{c,h}$ (45.95) |
| | 29 | 0.79±0.041$^{a,b,i}$ | 0.66±0.057$^{a}$ (16.45) | 1.34±0.119$^{e,g,h}$ (69.62) | 1.43±0.115$^{e,g}$ (81.01) | 1.09±0.098$^{c,h}$ (37.97) | 1.05±0.095$^{c}$ (32.91) |
| NOLSD =1.91 | 1 | 10.07± 0.54$^{a}$ | 10.51± 0.72$^{a}$ (4.37) | 9.47±0.79$^{a,c}$ (5.96) | 8.80±0.77$^{a,c,f}$ (12.61) | 10.12±0.75$^{a}$ (00.50) | 9.29±0.63$^{a,c}$ (7.75) |
| | 15 | 10.24± 0.56$^{a}$ | 9.85± 0.72$^{a,d,e}$ (3.81) | 8.11±0.72$^{c,d,f}$ (-20.80) | 7.87±0.66$^{b,c,f}$ (-23.14) | 9.67±0.65$^{a,c}$ (5.57) | 9.75±0.77$^{a,c}$ (4.79) |
| | 29 | 10.00±0.53$^{a,d}$ | 9.85± 0.72$^{a,d,e}$ (1.50) | 7.97±0.68$^{b,c,e,f}$ (-20.30) | 7.38±0.61$^{f}$ (-26.20) | 8.85±0.69$^{a,c,f}$ (11.50) | 8.69±0.62$^{a,c,f}$ (13.10) |

Each value represents the mean± S.E. (n=6). %: Percentage of changes from control group.
Values with unlike superscript letters are significantly different (P≤0.05). The values that have the same superscript letters are not significantly different (p> 0.05).
LSD: Least Significant Difference



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In rats treated with Lov-Se, no significant changes in heart concentration of TBARS and protein carbonyl when compared with control rats. Heart TBARS contents showed significant increases in arthritic and arthritic irradiated rats at 1, 15 and 29 days. The protein carbonyl contents showed significant increase in arthritic rats at 15 and 29 and arthritic irradiated rats at 1, 15 and 29 day (table 3). Administrations of Lov-Se, significantly increased heart TBARS contents in arthritic Lov-Se rats at the 15 and 29 day and in arthritic irradiated Lov-Se rats at 1, 15 and 29 than controls. The protein carbonyl contents showed significant increases in arthritic Lov-Se rats at the 15 and 29 day and in arthritic irradiated Lov-Se rats at 15 and 29 days (table 3). Lov-Se induced significant improvement in heart TBARS and protein carbonyl of arthritic Lov-Se and arthritic irradiated Lov-Se rats when compared to arthritic and arthritic irradiated rats (table 3).

## DISCUSSION

The persistent production of large amounts of ROS may induce changes in signal transduction and gene expression determining a chronic oxidative stress condition. An imbalance in the pro- and anti-inflammatory molecules due to the dysregulation of redox homeostasis (oxidants / anti-oxidants) could play a role in the pathophysiology of chronic inflammatory disorders as autoimmune rheumatic diseases. Therefore, the oxidative stress may trigger inflammatory activity and subsequently induce a flare of the disease [30].

The inflammatory promoters (TNF-α), a potent cytokine that exerts diverse effects by stimulating a variety of cells, were significantly increased in arthritic and arthritic irradiated rats as compared to control. These increases were accompanied by remarkable increases in the marker of underlying systemic inflammation (CRP) as well as the serum RF (table 1).

The recorded increases in TNF-α could be accredited to the primary targeting of mononuclear phagocytes (MPCs) and dendritic cells (DCs) cells by adjuvant components, which can produce TNF-α [31]. TNF-α might increased due to radiation-induced signaling events via ROS generation which cause the activation of NF -kB and its translocation into the nucleus. ROS directly activates NF-kB or firstly activates protein kinase c that in turn activates NF-kB to induce TNF-α [32]. TNF-α promotes inflammation by stimulating fibroblasts to express cell adhesion molecules (CAMs), such as intercellular adhesion molecule 1(ICAM-1). These adhesion molecules interact with their respective ligands on the surface of leukocytes, resulting in increased transport of leukocytes into inflammatory sites and increased secretion of TNF-α [33].

More to the point, the increases in CRP level could be interpreted in the view of its performance as acute phase reactant. An increase in serum CRP have been detected

**Table 3.**The change in TBARS (nmole/g wt tissues) and Protein carbonyl (P mole/mg protein) contents in heart of different animal groups.

| | Day | Control | Lov-Se | Arthritis | Arthritis Irradiated | Arthritis Lov-Se | Arthritis Irradiated Lov-Se |
|---|---|---|---|---|---|---|---|
| TBARS LSD =83,69 | 1 | 172.46±9.19$^{a}$ | 176.28±13.47$^{a}$ (2.22) | 269.41±23.37$^{b,f}$ (56.22) | 346.04±21.05$^{b,d}$ (100.65) | 207.31±13.54$^{a,f}$ (20.21) | 316.80±24.10$^{b,d}$ (83.69) |
| | 15 | 162.52±9.18$^{a}$ | 170.52±10.88$^{a}$ (4.92) | 364.66±33.08$^{d,e,g}$ (124.38) | 564.31±36.42$^{c}$ (247.22) | 345.52±21.12$^{b,e,h}$ (112.60) | 461.38±27.90$^{i}$ (183.89) |
| | 29 | 169.00±8.54$^{a}$ | 170.52±10.88$^{a}$ (0.89) | 435.10±42.12$^{g,i}$ (157.46) | 803.45±65.17$^{j}$ (375.41) | 391.04±34.87$^{d,g,h,i}$ (131.38) | 586.38±43.09$^{c}$ (246.97) |
| Protein carbonyl LSD =8.83 | 1 | 34.42±1.80$^{a,c}$ | 32.00±2.82$^{c}$ (7.03) | 41.29±2.65$^{a,e,f,g,h}$ (2.42) | 44.07±3.61$^{d,e}$ (28.04) | 38.50±2.45$^{a,c,e,f}$ (11.85) | 43.19±3.76$^{a,e,d}$ (25.48) |
| | 15 | 37.74±1.89$^{a,c,e}$ | 34.54±3.34$^{a,c}$ (8.48) | 47.00±3.35$^{b,d,f}$ (24.54) | 52.00±4.16$^{b,d}$ (37.78) | 33.39±3.19$^{c,g}$ (11.53) | 35.33±2.52$^{a,c,e}$ (6.39) |
| | 29 | 35.50±1.96$^{a,c,e}$ | 34.54±3.34$^{a,c}$ (2.70) | 48.80±4.47$^{b,d,h}$ (37.46) | 53.37±3.79$^{b}$ (50.34) | 34.22±2.80$^{c,g}$ (3.61) | 34.28±3.17$^{c,g}$ (3.44) |

Each value represents the mean± S.E. (n=6). %: Percentage of changes from control group.
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during acute stages of a variety of diseases, including various infections, and noninfectious illnesses such as rheumatic diseases, myocardial infarction, and malignancies [34] and also after radiation exposure [35]. Besides, the production of CRP is triggered by various proinflammatory cytokines derived either from monocytes and/or macrophages. The proinflammatory response results in the increased secretion of IL-1β and TNF-α which results in the release of the messenger cytokine, IL-6 which in turn stimulates the secretion of CRP. CRP stimulates monocyte release of inflammatory cytokines such as TNF-α and may also directly act as a proinflammatory stimulus to phagocytic cells [36]. CRP has been suggested to play a direct role in inducing the expression of CAMs such as ICAM-1 and vascular adhesion molecule 1 (VCAM-1) and E-selectin and decreasing endothelial nitric oxide synthase (eNOS) in endothelial cells. CAMs are involved in leukocyte recruitment into endothelium. Among them, the platelet/endothelial cell adhesion molecule-1 (PECAM-1) is one of the endothelial junction proteins playing a distinct role in leukocyte trans-endothelial migration (TEM), which is associated with vascular inflammation and atherogenesis [37].

The results obtained reveals to normal concentration of RF except at the day 15$^{th}$ where a noticeable increase was recorded in serum of arthritic and arthritic irradiated rats (table 1). These increases in serum RF recorded at 15 days could be due to the inflammatory disorders associated with adjuvant injection and radiation exposure which are manifested by high serum TNF-α and CRP levels (Table 1). Serum RF is the immunological expression of an individual's immune system reaction to the presence of an immunoglobulin molecule that is recognized as "non-self." This response to the "non-self" immunoglobulin results in the presence of immune complexes. Higher the levels of serum RF, higher are the development of inflammation [38] RF production is possibly an indicator of some important pathways of RA [39]. The adjuvant induction of arthritis in rats is associated with an increase in the serum levels of RF and CRP [40].

The acute phase responses developed after radiation exposure and adjuvant injection manifested by increases in inflammatory molecules (TNF-α, CRP and RF) might partially responsible for Se depletion recorded in serum (table 4). The circulating Se concentrations were significantly lower in patients with acute injury or trauma of tissues, suggesting changes in the body distribution of Se during the acute phase response [34].

However, the results obtained pointed out the tone adjustment of the inflammatory markers due to Lov-Se administration (table 1). This could be attributed to the Mixture nanoselenium constituent that compensate to Se loss. This assignment put forward the possible role of nanoselenium in regulation of inflammatory reaction by suppression of inflammatory gene expression. Se inhibited the activation of transcription factors, NF-κB, induced by many pro-inflammatory stimuli such as lipopolysaccharide and TNF-α, the product of inflammatory gene expression [12]. The amelioration of CRP concentration due the administration of Se could be interpreted as indirect cascade of inhibited transcription factor NF-kB and the subsequent down regulation of TNF-α [34]. Further, the synchronized existence of Lovastatin in the Mixture might participate to the ameliorative status observed among the inflammatory indicators. Lovastatin has identified as an extracellular inhibitor of lymphocyte - function - associated antigen 1 (LFA-1). LFA-1 is constitutively expressed in an inactive state on the surface of leukocytes. In response to several stimuli, LFA-1 binds to ICAM -1 and provides a potent co-stimulatory signal for activated T cells. Lovastatin was shown to decrease LFA-1-mediated leukocyte adhesion to ICAM-1 and T-cell co-stimulation. It bind to a hitherto unknown site in the LFA-1 I (inserted) domain. This site is distant from the ICAM-1-binding site and termed the 'lovastatin site' (L-site), which indicates that lovastatin, inhibits LFA-1 via an allosteric mechanism. Subsequently, the leukocyte as a producer of TNF-α was prevented from reaching the site of inflammation [41]. In addition, The CRP inducted CAMs expression and endothelial cells mediated



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adhesion might partially reversed by lovastatin [37].

The overproduction of ROS especially $O_2^{\bullet -}$ might be due to alteration induced in heart XOR in damaged tissue. XOR is a complex consisting of two inters convert-able enzymes XDH and XO. Significant changes in XOR activity of the heart comparing to control were observed in arthritic and arthritic irradiated rats (table 2). This could be related to the recorded increase of the TNF-α in arthritic and arthritic irradiated rats as evident in the present experiment (table 1). The inflammatory reaction results in the expression of various cytokines in addition to XOR alteration is stimulated by TNF-α, that initiate the conversion from the XDH to the XO form [42]. The exposure of rat to fractionated γ-radiation induced a significant increase in XO activity paralleled with significant decrease in XDH activity [35]. The high XO activity leads to overproduction of $O_2^{\bullet -}$, where XO depends on oxygen while XDH depends on $NAD^+$ as electron acceptors during their action [43].

The administration of Lov-Se amendment the XOR system changes induced in heart of arthritic and arthritic irradiated rats (table 2). Each of the Mixture constituent was claimed for its antioxidant and free radical scavenging activities. So, Lov-Se could neutralize free radicals released in the heart tissue and substantially preserve the XDH form plentiful in XOR complex and arrest one of the main biological ROS generators. The protective effect of Se resulted from antioxidant activity including stabilization in the intracellular defense systems and reduction in the lipid peroxidation products by scavenging the free radicals and ROS [44]. Lovastatin might inhibit free radical generation from leukocytes and other tissues by inhibiting the isoprenoid reaction during the activation of NADPH oxidase [9]. The administration of mixture Lov-Se reduced the radiation-induced

**Table 4.** The change in blood Se (µg/ml) and, SOD (U/mg protein), CAT (U/g protein) and GSH-Px (U/mg protein) activities and GSH (mgGSH/g wt tissues) content of heart in different animal groups.

| | Day | Control | Lov-Se | Arthritis | Arthritis Irradiated | Arthritis Lov-Se | Arthritis Irradiated Lov-Se |
|---|---|---|---|---|---|---|---|
| **SOD LSD =331.79** | **1** | 1824.3±103.3$^{a,b,c}$ | 2058.7±193.1$^{c}$ (12.85) | 1548.1±93.4$^{b,f,g}$ (15.14) | 1841.1±153.9$^{a,b,c}$ (0.92) | 1604.6±141.5$^{a,b,g}$ (12.04) | 1927.1±144.5$^{a,c}$ (5.64) |
| | **15** | 1790.6±101.3$^{a,c,f}$ | 1612.5±147.8$^{a,b,h}$ (9.95) | 1051.4±91.5$^{d,e}$ (-41.28) | 1275.8±93.7$^{d,g}$ (-28.75) | 1619.8±121.5$^{a,b,h}$ (9.54) | 1453.4±106.7$^{g,h}$ (-18.83) |
| | **29** | 1817.0±95.3$^{a,b,c}$ | 1612.5±147.8$^{a,b,h}$ (11.25) | 855.6±73.8$^{e}$ (-52.91) | 848.99±66.91$^{e}$ (-53.28) | 1450.3±97.0$^{g,h}$ (-20.18) | 1471.5±105.6$^{f,g,h}$ (-19.01) |
| **CAT LSD =0.449** | **1** | 2.59±0.143$^{a,g,h}$ | 2.60±0.271$^{a,g,h}$ (0.39) | 1.97±0.151$^{b,e}$ (-35.52) | 1.78±0.126$^{c,e}$ (-31.27) | 2.46±0.200$^{a,f,g,h}$ (5.02) | 2.25±0.209$^{b,g}$ (13.13) |
| | **15** | 2.48±0.139$^{a,f,g,h}$ | 2.67±0.176$^{g,h}$ (7.66) | 1.35±0.113$^{c,d}$ (-45.56) | 1.41±0.122$^{c,d}$ (-43.15) | 2.14±0.176$^{b,f,e}$ (13.71) | 2.18±0.164$^{a,b,e}$ (12.10) |
| | **29** | 2.70±0.144$^{h}$ | 2.67±0.176g,h (1.11) | 1.31±0.107$^{d}$ (-51.48) | 1.28±0.114d (-52.59) | 1.97±0.131$^{b,e}$ (-27.04) | 1.87±0.133$^{b,e}$ (-30.74) |
| **GSH-Px LSD =0.019** | **1** | 0.112±0.0057$^{a,b,f}$ | 0.105±0.0065$^{a,b,f,g}$ (6.25) | 0.110±0.0076$^{a,b,f}$ (1.79) | 0.100±0.0093$^{a,f,g}$ (-10.71) | 0.120±0.0084$^{b}$ (7.14) | 0.119±0.0085$^{b}$ (8.18) |
| | **15** | 0.106±0.0055$^{a,b,f,g}$ | 0.110±0.0068$^{a,b,f}$ (3.77) | 0.061±0.0054$^{c,e}$ (-42.45) | 0.055±0.0045$^{e}$ (-48.11) | 0.094±0.0067$^{f,h}$ (11.32) | 0.091±0.0072$^{d,g,h}$ (14.15) |
| | **29** | 0.110±0.0056$^{a,b,f}$ | 0.110±0.0068$^{a,b,f}$ (0.00) | 0.058±0.0053$^{c,e}$ (-47.27) | 0.062±0.0047$^{c,e}$ (-43.64) | 0.080±0.0055$^{d,h}$ (-27.27) | 0.075±0.0057$^{c,d}$ (-31.82) |
| **GSH LSD =3.15** | **1** | 19.77±1.00$^{a}$ | 19.53±1.39$^{a}$ (1.21) | 18.56±1.37$^{a,f}$ (6.12) | 18.44±1.20$^{a,f}$ (6.73) | 19.14±1.32$^{a}$ (3.19) | 18.90±1.25$^{a}$ (4.40) |
| | **15** | 20.00±1.06$^{a}$ | 19.89±1.39$^{a}$ (0.55) | 11.48±0.93$^{b,c,e}$ (-42.60) | 10.39±0.89$^{b,d,e}$ (-48.05) | 15.49±1.33$^{f,g}$ (-22.55) | 13.71±0.95$^{c,g}$ (-31.45) |
| | **29** | 20.30±1.05$^{a}$ | 19.89±1.39$^{a}$ (2.02) | 9.55±0.86$^{b,e}$ (-52.96) | 8.54±0.60$^{b}$ (-57.93) | 13.19±1.03$^{c,d,g}$ (-35.02) | 12.54±0.83$^{c,e,g}$ (-38.23) |
| **Se LSD =0.064** | **1** | 0.398±0.022$^{a,f}$ | 0.400±0.029$^{a,h}$ (0.50) | 0.384±0.029$^{a,b,g}$ (3.52) | 0.250±0.016$^{c,e}$ (35.68) | 0.395±0.028$^{a,f}$ (0.75) | 0.286±0.021$^{d,e}$ (-28.14) |
| | **15** | 0.430±0.023$^{a}$ | 0.386±0.031$^{a,b}$ (10.23) | 0.215±0.018$^{c}$ (-50.00) | 0.255±0.017$^{c,e}$ (-35.68) | 0.340±0.022$^{b,d,f,h}$ (-20.93) | 0.334±0.024$^{b,f,d,g}$ (-22.32) |
| | **29** | 0.409±0.022$^{a}$ | 0.386±0.031$^{a,b}$ (5.75) | 0.217±0.016$^{c}$ (-46.94) | 0.256±0.016$^{c,e}$ (-37.41) | 0.320±0.024$^{d,g}$ (-21.76) | 0.314±0.021$^{e,d}$ (-23.23) |

Each value represents the mean± S.E. (n=6). %: Percentage of changes from control group.
Values with unlike superscript letters are significantly different (P≤0.05). The values that have the same superscript letters are not significantly different (p> 0.05).
LSD: Least Significant Difference



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heart injury via amending the antioxidant molecules and decreasing lipid and protein oxidation [15].

A major systemic event that occurs in the rat following the induction of inflammation is a marked alteration in the cellular defense mechanism [45]. The experimental results displayed an excessive degree of oxidative stress in adjuvant arthritis and arthritis irradiated model evident by increased lipid peroxidation index (TBARS), protein oxidation product protein carbonyl in coincidence with impaired antioxidant components (SOD, CAT, GSH-Px activities and GSH level) and NO content (tables 2, 3 and 4). These results stipulate the imbalance between ROS production and antioxidant defense and identify 'oxidative stress' which through a series of events deregulates the cellular function leading to various pathological conditions.

In adjuvant arthritis, the polymorphonuclear leukocytes are activated, and ROS are generated in excessive amounts. These are reactive ephemeral molecules known to play an important role in the progression of various diseases. During chronic inflammation, protective mechanisms increase to the levels which cause damage to the tissue. Increased concentrations of ROS cause enormous lipid peroxidation production, leading to toxic damage to tissues [46]. Also, Lipid peroxidation could result from a cascade of events induced by ionizing radiation in biological systems. Free radicals generated by radiation attack the fatty acid component of membrane lipids and produce lipid peroxidation products, which cause interphase cell death [47].

The action of ROS on proteins results in the formation of carbonyl groups with a relatively longer half-life with respect to lipid peroxidation products. The carbonyl group content, in heart tissues was evaluated as the most general respected indicator for both protein oxidation and free radical reaction intensity. The significantly high carbonyl recorded in the present study (table 3) provide evidence for both the inefficiency of protective systems in preventing covalent modification of proteins and the impairment of antioxidant system [48]. The oxidation of protein can modulate biochemical properties such as enzyme activities, the DNA binding of transcription factors and susceptibility to proteolytic degradation [49].

Above and beyond, NO is a multifunctional molecule that is implicated in a wide variety of physiological and pathological processes. The concentrations of NO, under nonpathological conditions, are in the nanomolar and under conditions of oxidant injury in the micromolar range. The tissue content of NO react rapidly with $O_2^{\bullet -}$ to form peroxynitrite ($ONOO^-$), which is itself cytotoxic and readily decomposes into the highly reactive and toxic $^{\bullet}OH$ and nitrogen dioxide ($NO_2$). This might compromise the decreases in NO concentration in heart tissue of arthritic and arthritic irradiated rats (table 2) where a lot of $O_2^{\bullet -}$ are produced. The $ONOO^-$ is much more reactive than NO or $O_2^{\bullet -}$ which causes different chemical reactions in biological system including nitration of tyrosine residues of proteins, triggering of lipid peroxidation, inactivation of aconitases, inhibition of the mitochondrial electron transport, and oxidation of biological thiol compounds [50]. The concurrent decreases of heart GSH observed in the present study (table 4) might pledge the influence of biological thiol compound due to the formation of $ONOO^-$. Further, the decreases in NO could attribute to the decrease in NO synthase expression by CRP [51].

The disturbances in heart antioxidant system manifested by decreases in SOD and CAT activities in addition to decreases in GSH-Px activity as well as GSH concentration could be attributed to the free radical antioxidant response (table 4). SOD catalyzes the dismutation of $O_2^{\bullet -}$, a first product of molecular oxygen reduction, into $H_2O_2$. $O_2^{\bullet -}$ is an important source of hydroperoxides and other reactive free radicals and decreased SOD activity sustained the damages induced by $O_2^{\bullet -}$ and other related radicals. Decreased SOD activity indicates a degradation process in which SOD is degraded by ROS during the detoxifying processes [48]. In addition, low CAT activities might induce the accumulation of $H_2O_2$ which is a potent membrane destructive agent.



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CAT catalyses the decomposition of $H_2O_2$ to $H_2O$ and $O_2$ and protect cell from oxidative damage by $H_2O_2$ and $^{\bullet}OH$ [45]. The GSH-Px enzyme uses GSH as a substratum in reactions that catalyze reduction of $H_2O_2$, of fatty acids, and organic hydroperoxides into water and hydroxylated fatty acids. Also, lower levels of GSH result in lower activity of GSH-Px, which, in turn, may increase vulnerability to oxidative stress. In addition to reduction of available GSH, the reduction of GSH-Px activity may also be caused by the process of enzyme inactivation. The enzyme itself may be inactive under conditions of intense oxidative stress, which contributes to low GSH-Px activity [52].

Lov-Se administration to arthritic and arthritic irradiated rats lowered significantly the lipid peroxidation and protein oxidation in terms of TBARS and carbonyl content, respectively, with concomitant amelioration in the activities of the antioxidant enzymes as well as GSH and NO contents (tables 2, 3 and 4). The modulatory action of the Mixture might be attributed to the synergistic effect of its constituents. Evidence demonstrated that, the antioxidant effect of lovastatin result from the lovastatin's activating effect on GSH-Px and its stimulatory effect on scavenging $H_2O_2$ by endothelial cells [9]. Lovastatin inhibits the synthesis of $O_2^{\bullet -}$ and protects intracellular SOD. It is also known to inhibit ROS permeation into the cellular membrane and consequently, decrease damages occur. Lovastatin reduces the stress by removing $O_2^{\bullet -}$ and this in turn reduces the requirement of CAT activity [53]. Furthermore, Se is an essential element, plays an important antioxidant role, binding active site of GSH-Px and thioredoxin reductase. The protective effect of Se resulted from antioxidant activity including stabilization in the intracellular defense systems and reduction in the lipid peroxidation products by scavenging the free radicals and ROS [44]. Dietary Se supplementation increases the oxidative stability of tissue by increasing the activity of GSH-Px and also Se interferes with the oxidative disorder by balancing the redox state and controlling the activation of kinases and transcription factors [54]. Nano-Se possesses equal efficacy in increasing the activity of GSH-Px, thioredoxin reductase and Glutathione S -transferase, but has much lower toxicity, suggesting that Nano-Se can serve as a potential chemopreventive agent with significantly reduced risk of Se toxicity [55].

The amelioration in heart NO content might be due to the antioxidant and free radical scavenging activities of the Mixture component which deteriorate the opportunity of NO, superoxide reaction. Lovastatin could adjust NO concentration by increasing eNOS expression [56]. NO serves as antioxidant effectors by suppressing XO activity in actual cellular systems [57].

Accordingly, it could be suggested that oral administration of Lov-Se mixture posses a considerable anti-inflammatory and antioxidants properties, thereby counteracting normal tissue damage provoked by radiation and CFA. The protective effect of Lov-Se mixture may relate with its adjustment of red-ox tone and the integration of XDH/XO ratio and inhibition of transcription factors (NF-κB) activation. Lov-Se mixture could recommend as a promising anti inflammatory and antioxidant combination during the treatment of rheumatoid arthritis.

***Conflicts of interest:*** *none to declare.*

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