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ASSESSMENT OF THE ANTI-INFLAMMATORY AND ANTIOXIDANT ROLES OF RESVERATROL IN ARTHRITIC RATS

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ABSTRACT

Background: Resveratrol, an antioxidant compound, known to be used for the attenuation of the pro-oxidant effects of toxicants.

Objectives: Evaluation of the anti-inflammatory and antioxidant impact of resveratrol in treatment of arthritis in rats.

Materials and Methods: Rats were assigned into five groups: negative control, positive control (arthritis was induced by freund's complete adjuvant), arthritic rats received celecoxib (30mg/kg, p.o), arthritic rats received resveratrol (50mg/kg, p.o.), and arthritic rats received combination of both drugs (10 rats/ each group).

Results: Arthritis significantly elevated cyclooxygenase-2, interleukin-1β, tumor necrosis factor-α, lysosomal enzymes, some biochemical liver parameters, and decreased caspase 3activity in serum and significantly increased myeloperoxidase, malondialdhyde and nitric oxide levels: reduced glutathione contents in paw tissues and albumin level in blood serum. The treatment combination of resveratrol with celecoxib induced an additive anti-inflammatory, biochemical and antioxidant effects.

Conclusion: Resveratrol potentiates the anti-inflammatory and antioxidant effects of celecoxib in adjuvant induced arthritis.

Key words: Resveratrol; Celecoxib; Arthritis; Freund's complete adjuvant.

INTRODUCTION

Resveratrol (trans-3, 5, 4', trihydroxystilbene) one of stilbene family of polyphenols, that was isolated for the first time from the white hellebore's roots (Veratrum grandiflorum O. Loes) in 1940 *(Rege et al., 2014)*. It is widely existed in grapes, fruits, some nutritional products and therapeutical plants. Resveratrol exerts many pharmacological effects (immune modulatory, anti inflammatory, antioxidant as well as anti-tumor activity) *(Bereswill et al., 2010, Tyagi et al., 2011* and *Kavas et al., 2013)*. Resveratrol has been reported to inhibit cyclooxygenase (COX-1 and COX-2) enzymatic activities, which are involved in the pathogenesis cascade of rheumatoid arthritis (RA) *(Ya et al., 2011)*. Resveratrol was shown to inhibit numerous experimental autoimmune diseases *Shindler et al. (2010)* relied on the previous in-vivo

studies, as anti arthritic and anti-inflammatory mechanisms but its' mechanism still inadequate *(Chen et al., 2013* and *Tian et al., 2013)*.

Rheumatoid arthritis is a chronic inflammatory disease of cartilage and bones, leading to joint deformity, disability and bone erosions *(Karmakar et al., 2010)*. The pathological features of RA including excessive hyperplasia and chronic joint inflammation of the synovial tissue *(Bax et al., 2011)*. Additionally, these changes resulted from a consequence formation of pro-inflammatory cytokines, especially tumor necrosis factor-α (TNF-α) and some proteases *(Lan et al., 2016)*. Current RA treatment depends on management of symptoms, mainly pain control, which relies on nonpharmacological and pharmacological combination approaches that are designed to the patient's demands and risk factors. NSAIDs are the most frequently approved drugs for RA treatment *(Gordo et al., 2017)*.

Celecoxib was the first coxib to be introduced into the clinical use and was thusly endorsed worldwide for an assortment of signs including those of osteoarthritis and rheumatoid arthritis *(Fidahic et al., 2017)*. Celecoxib is a specific non-steroidal anti-inflammatory drug (NSAID) targeted for COX -2 enzyme inhibition. Thus, it showed a gastrointestinal tolerability profile better than the other nonselective NSAIDs. Furtherfore, The relative efficiency of celecoxib was more than that of ibuprofen, diclofenac and naproxin in relieving the symptoms concomitant with RA *(Gordo et al., 2017)*. In a study performed by Kusunoki and his *(Co-workers, 2008)*, Celecoxib was proved to inhibit synovial hyperplasia by direct induction of apoptosis in human synovial fibroblasts.

The objective of this study was directed to investigate the potential anti-inflammatory effects of resveratrol with celecoxib in treatment of RA.

MATERIALS AND METHODS

Drugs and Chemicals: Celecoxib was gifted from Kekule Company, India. Resveratrol, and all other chemicals were obtained in analytical and purified grade (Sigma-Aldrich, Chemical Co., St. Louis, USA.).

Experimental animals: Fifty male Wistar albino rats, weighing 180 ± 20 g, were obtained from the animal house of the National Organization for Drug Control & Research, Giza, Egypt. They were housed under normal laboratory environmental conditions; controlled temperature (25± 2?C) and normal light/ dark cycle, in 40x60x25 cm cage (5 rats per cage). Standard pellet diet and water was allowed ad libitum. The investigations complies with the guide for care and use of laboratory animals published by the US National institutes of Health (NIH NO.85-23, revised in 1985). Rats were acclimated for 1 week. Rats were randomly distributed into five equal groups:

Group I: negative control group. **Group II:** arthritis induced rats, served as positive control, received an equivalent volume of 5 % DMSO (dimethyl sulfoxide, solvent of both drugs) based on body weight. **Group III:** arthritic rats received celecoxib (30 mg/kg) *(Kansal et al., 2011)*. **Group IV:** arthritic rats received resveratrol (50 mg/kg) *(Chen et*

al., 2014). **Group V:** arthritic rats received both celecoxib and resveratrol.

Induction of arthritis: Arthritis was induced according to *(Kalaiselvan and Rasool, 2014)* by a single intradermal injection of 0.1 ml of complete freund's adjuvant (heat-killed Mycobacterium tuberculosis (10 mg) in paraffin oil (1 ml)) into the right hind paw. All treatments were administered orally from day 11 to day 23. On the 24th day, at the end of the experimental period, blood was collected allowed to clot at room temperature for 1 h and centrifuged at 3000 ×g for 10 minutes to obtain serum. The paw tissues were immediately dissected out and homogenized in ice-cold 0.01M Tris HCl buffer, pH 7.4 to give a 10% homogenate. Blood serum and tissues homogenates of paws were used for biochemical and inflammatory mediator analysis.

Serum parameters: COX-2, interleukin-1β (IL-1β) and TNF-α, were determined by enzyme-linked immunosorbent assay (ELISA) kits (Invitrogen Corp., USA) according to *(Refaat et al., 2015), (Lin et al., 2017)* and *(Zhao et al., 2017)* and respectively. Caspase 3 was determined using caspase-3 Colorimetric Protease Assay kit (Invitrogen Corp., USA) according to *(Nicholson et al., 1995)*. Lysosomal enzymes activities (Acid phosphatase (ACP), β- N-acetyl glucosaminidase (β-NAG) and β- galactosidase (β-GAL)) were determined spectrophotometrically at 405 nm *(Van Hoof and Hers 1968)*. Total protein, albumin , ALT, AST and ALP were determined colorimetrically according to *(Henry et al., 1974), (Doumas et al., 1971), (Reitman & Frankel, 1957)* and *(Hausamen et al., 1967)* respectively.

Tissue parameters: The subcutaneous tissue of the hind paw and surrounding the tibiotarsal joints of all rats were removed and homogenized *(Barsante et al., 2005)*. It was stored at -80°C for determination of reduced glutathione (GSH), malodialdhyde (MDA), nitric oxide (NO) level and myeloperoxidase activity (MPO) colorimetrically according to *(Beutler et al., 1963), (Uchiyama & Mihara, 1978), (Badami et al., 2003)* and *(Babior, 1978)* respectively.

Statistical analysis: The statistical analysis was performed by Graphpad prism version 5 (Graphpad prism software). Means and standard error of means (S.E.M.) were calculated, and statistical significance was tested by one-way ANOVA. The strength of association between pairs of variables was assessed by LSD comparison. The level of significance was set at $P \leq 0.05$.

RESULTS

The activity of COX-2 was measured in addition to other pro-inflammatory and apoptotic mediators such as IL-1β, TNF-α and caspase 3 activities to explore the prospective mechanism of resveratrol alone and in combination with celecoxib on synovial hyperplasia. In comparison with control group, a high level of COX-2, IL-1β and TNF-α levels were found in the RA positive control group along with a decrease in caspase3 activity. The resveratrol and celecoxib-treated groups exhibited a significantly decreased COX-2 IL-1β and TNF-α levels with a marked

increase in caspase 3 activity. The combination between celecoxib and resveratrol significantly decreased both COX-2, IL-1β and TNF-α levels as compared from RA positive control with synergistic marked increase in caspase 3 activity (fig. 1).

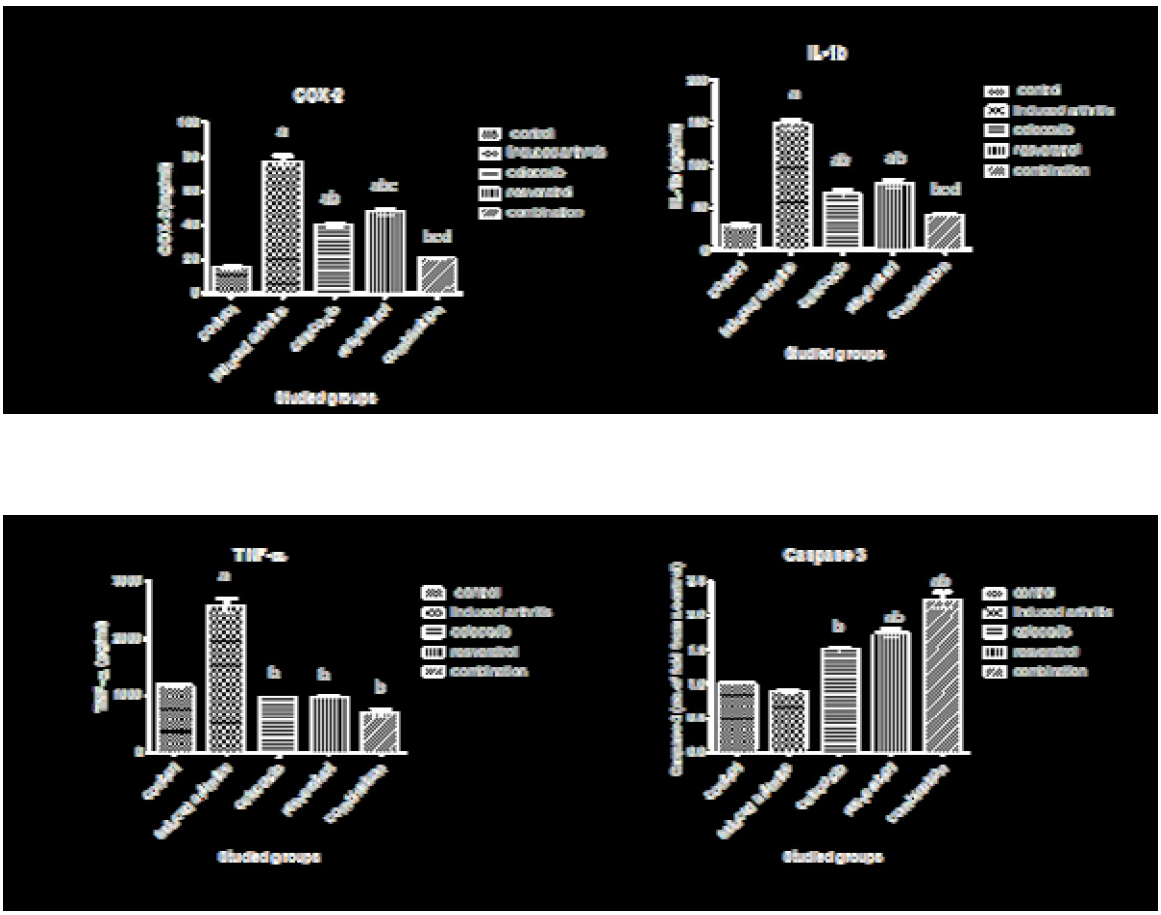

Figure (1): Effects of resveratrol and celecoxib alone or in combination on COX-2 activity, IL-1β, TNF-α and caspase3 activities in rat serum. (Mean ± S.E.M.) (n=10) a: significant difference from normal control group. **b:** significant difference from positive control group. **c:** significant difference from celecoxib group. **d:** significant difference from resveratrol group.

The adjuvant-induced arthritic group had significantly elevated all the liver enzymes (ALP, AST and ALT) and total protein and globulin and significantly decreased albumin level in rat serum as compared to negative control. Arthritic rats treated with celecoxib and resveratrol alone exhibited significant reduction in serum liver enzymes (except ALT activity for celecoxib) and ameliorated the biochemical parameters as compared to arthritic rats. Furthermore, combination of regimens caused more reduction in serum levels and in total protein and globulin and significant increase in albumin level than each drug alone nearly approaching to the normal levels (Table 1).

Table (1): Effect of treatments with resveratrol, celecoxib and their combination on the liver enzymes and different biochemical parameters in adjuvant-induced arthritis rats (Mean ±S.E.M.)

Groups / Parameters	Negative control	Positive control	Celecoxib	Resveratrol	Combination
ALP (U/ml)	**143.7±4.15**	**263.4±12.9** [a]	**169.3±6.2** [b]	**180.6±7.2** [ab]	**168.8±9.9** [ab]
AST (U/ml)	**52.4±2.2**	**80.2±4.5** [a]	**57.5±3.6** [b]	**58.3±5.5** [b]	**48.5±3.1** [b]
ALT (U/ml)	**6.9±0.8**	**11.3±1.1** [a]	**8.1±0.8**	**8.2±0.8**	**8.5±0.7**
Total protein (g/dl)	**7.5±0.3**	**13.5±0.3** [a]	**9.5±0.3** [b]	**9.1±0.5** [b]	**8.6±0.4** [b]
Albumin (g/dl)	**4.3±0.12**	**3.18±0.2** [a]	**3.9±0.1** [b]	**4.5±0.1** [bc]	**4.69±0.1** [bc]
Globulin (g/dl)	**3.3±0.2**	**10.2±0.2** [a]	**5.3±0.2** [ab]	**4.4±0.3** [ab]	**3.5±0.3** [bcd]

a: significant difference from normal control group**. b:** significant difference from positive control group. **c:** significant difference from celecoxib group. **d:** significant difference from resveratrol group.

Both resveratrol and celecoxib significantly decreased the activities of both β-NAG and β-GAL. Interestingly, combination of both substances had lowered the three lysosomal activities close to the level of the negative control (table 2).

Table (2): Effect of treatments with resveratrol, celecoxib and their combination on some serum lysosomal enzymes in serum rats (Mean±S.E.M)

Groups / Parameters	Negative control	Positive control	Celecoxib	Resveratrol	Combination
ACP (nmol/ml/hr)	**1915±60.6**	**2447±182.4** [a]	**2044±72.2**	**1818±75.4** [b]	**1882±98.4** [b]
β-NAG (nmol/ml/hr)	**653.3±24.1**	**1066±17** [a]	**761.4±47.1** [b]	**734.9±57.2** [b]	**586±35.1** [bc]
β-GAL (nmol/ml/hr)	**523.3±48.9**	**990.4±42.7** [a]	**763.2±57.9** [ab]	**729.1±37.1** [ab]	**443.3±55.4** [bcd]

a: significant difference from normal control group. **b:** significant difference from positive control group. **c:** significant difference from celecoxib group. **d:** significant difference from resveratrol group.

The established role of reactive oxygen species in inflammatory conditions is well-defined. The drugs that have antioxidant activity with anti-inflammatory/analgesic activity may provide a viable route to safer anti- inflammatory/analgesic agents. A substantial elevation in MDA, NO levels and MPO activity together with a significant decrement in

the GSH level were determined in arthritic rats as compared to non-arthritic rats. Combination of both drugs revealed a significant amelioration in the oxidative status by lowering the MDA, NO levels and MPO activity along with elevating the GSH content in arthritic rats (fig. 2).

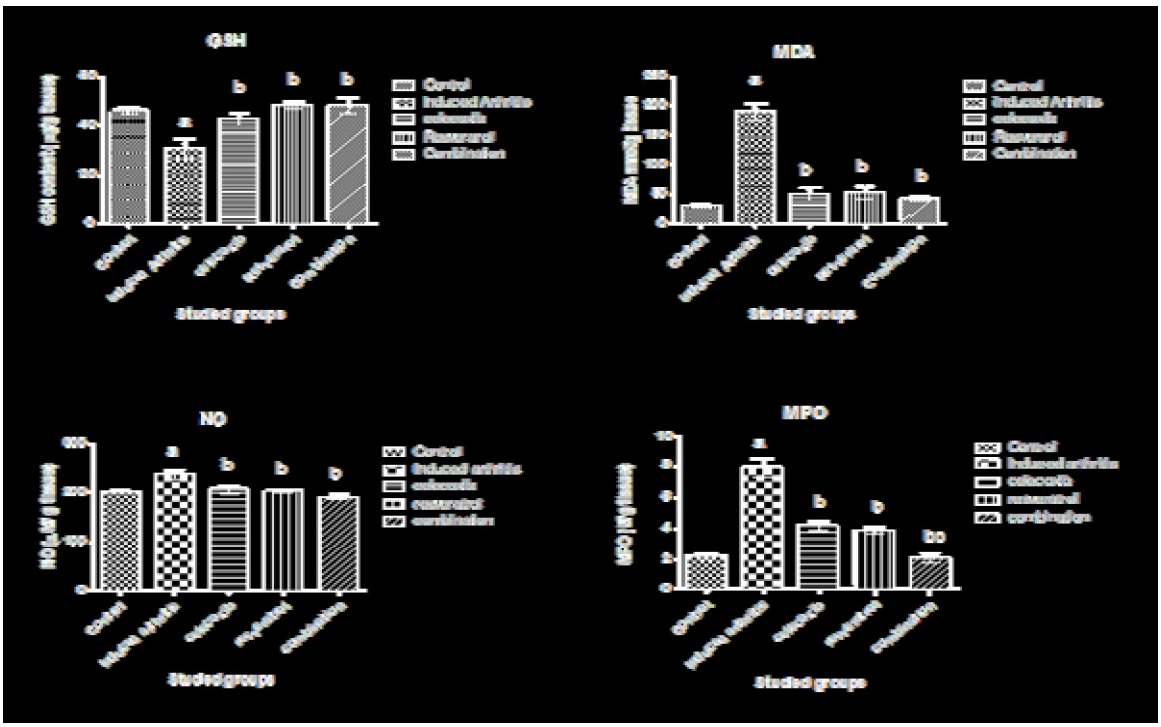

Figure (2): Effects of resveratrol and celecoxib alone or in combination on GSH, MDA, NO and MPO activities in paw tissue in rats. (Mean ± S.E.M.) (n=10) a: significant difference from normal control group. **b:** significant difference from positive control group. **c:** significant difference from celecoxib group. **d:** significant difference from resveratrol group.

DISCUSSION

The present study evaluated the protective effect of combined therapy of resveratrol and celecoxib, as a COX-2 inhibitor, in the treatment of adjuvant induced arthritis. As rheumatoid arthritis (RA) is an auto-immune, systemic disease destroying mainly the joint leading to its deformity and disability. Adjuvant induced arthritis is a well stablished model to study the pathogenesis of RA and to test a new potential anti-arthritic drugs. Additionally, human RA is closely resemble adjuvant induced arthritis in the immunological, pathological and biochemical features *(Liu et al., 2018)*.

The results of the present study showed that administration of Freund's complete adjuvant in rat had generated a stage of inflammation. These cytokines induce the expression of inducible COX-2 activity, leading to PGE2 production. Therefore, development of arthritis can be suppressed by a COX-2 inhibitor such as celecoxib *(Sun et al., 2015)*. These earlier findings are in the same line with this study that showed a significant increase in plasma levels of COX-2, IL-1β and TNF-α .

COX-2 has an important role in the pathogenesis of many chronic inflammatory diseases due to its capability to yield large amounts of pro-inflammatory prostaglandins at the site of inflammation *(Wei et al., 2018)*. Increasing the activity of COX-2 activity in RA resulted in increasing the production of serum TNF-α, IL-1β and IL-6 *(El-Ghazaly et al., 2010, Moutang, 2013* and *Yang et al., 2017)*. Our results showed that celecoxib and resveratrol has anti-inflammatory properties as they both showed to be involved in destruction of pro-inflammatory and pro-oxidants mediators revealed by their ability to decrease serum COX-2 activity and other inflammatory cytokines and their combination showed a synergistic decrease effect on its activity .

Apoptosis is a process controlling gene activation, expression and control. Apoptotic factors are released from mitochondria when their functions are depressed. The mitochondria's morphologic and functional change activates caspase, followed by the release of cytochrome *(Duan et al., 2016)*. The present data clearly demonstrated that combination of both drugs significantly increased caspase 3 activity. *Refaat and his Co-workers. (2013)* reported that celecoxib induces apoptosis by a mechanism which is still unclear. Indeed, celecoxib inhibit RASFs proliferation and induce apoptosis through COX-2 and PPARγ-independent mechanisms. This proves that caspase cascade has an important role in apoptosis induction by celecoxib.

Lysosomal enzymes also have an essential role in the inflammatory process thought stimulation of inflammatory mediators (thromboxanes, prostaglandins and leukotrienes). These enzymes participate in degradation of structural macromolecules which are found in the connective tissues and cartilage proteoglycans *(Mythilipriya et al., 2008)*. In the present work, combination of celecoxib and resveratrol showed a significant reduction in the activities of the lysosomal enzymes. This reduction indicates a membrane-stabilizing effects of celecoxib and resveratrol. As rupture of these membranes leads to release of glycohydrolases which destroy the cartilage matrix, therefore, drugs that possess anti-inflammatory activity is capable to stabilize the membranes and aid in the treatment of arthritis .

In adjuvant induced arthritis, hepatic lesions occurred which lead to elevation of liver markers enzymes like AST, ALT, ALP and chronic inflammation occurred which was evidenced by the significant increase in serum total proteins and globulin levels with a significant decrease in albumin levels. The present study showed an increase in the activities of these marker enzymes in adjuvant induced arthritis indicates liver damage and bone loss. Furthermore, it was considered that half serum ALP comes from bone, which is a marker for bone metabolism *(Ashkavand et al., 2014* and *Liu et al., 2018)*. Treatment with combination of celecoxib and resveratrol resulted in a decrement in the activities of these enzymes and this effect may be attributed to their membrane stabilizing effects and cytoprotective role *(Coradini et al., 2014)*.

Induction of oxidative stress has an essential role in arthritis pathogenesis

(Bozbaş et al., 2018). COX-2 over expression is associated with oxidative stress through the production of free radicals and formation of lipid peroxides *(Grotto et al., 2009)*. Moreover, NO overproduction, in cartilage tissue, may directly modifies proteins by oxidation and in advance contributes in pathological disorders. Additionally, NO may react with superoxide to produce peroxynitrate, which is a potent destructive pro-oxidant agent in cartilage, which is able to mediate chondrocytes apoptosis *(Lomri, 2008)*. Our results also showed that the MDA content in rat paw was remarkably increased in adjuvant induced arthritis group comparable to the control group, suggesting that the pro-inflammatory mediators release might participate in lipid peroxidation. Furthermore, a significant elevated serum levels of oxidative stress marker enzymes, MDA and NO in RA patients were documented *(Qui?onez-Flores et al., 2016)*. It was reported that over production in ROS especially H2O2 which is produced by MPO and other sources, affects the inflammatory process by altering the function of many proteins and activating many enzymes and receptors *(Rossato et al., 2014)*. Our results showed that combination of celecoxib and resveratrol had significantly ameliorated the oxidative status by reducing MDA and NO level, MPO activity and increasing GSH content. These finding was in the same line with other reports who reported the anti-inflammatory and anti- oxidant effects of celecoxib and resveratrol *(Udenigwe et al., 2008, Refaat et al., 2013, Ashkavand et al., 2014, Hamzaa & El-Shenawyb, 2017* and *Melekh et al., 2017)*. *Chavez et al. (2010)* reported that celecoxib supported the recovery of livers with necrotic and cholestatic damage through its antioxidant activities that were manifested by restoration of redox equilibrium and inhibition of lipid peroxidation. Interestingly, our combination therapy showed a synergism between celecoxib and resveratrol in arthritis treatment through their anti-inflammatory, anti-apoptotic and antioxidant mechanisms.

CONCLUSION

Our study demonstrated the potential synergistic therapeutic benefits of resveratrol in combination with celecoxib in arthritis treatment through its antiinflammatory, antioxidant and proapoptotic effects.

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تقييم الدور المضاد للإلتهاب و المضاد للأكسدة للريسفيراترول في الجرذان المصابة بإلتهاب المفاصل

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خلفيـــة البحـــث : ريســفيراترول هــو مركــب مضــاد للأكســدة ، ويســتخدم للتخفيــف مــن الآثار السلبية لأكسدة المواد السامة.

الهـــدف مـــن البحـــث: تقيـــيم التـــأثير المضـــاد للإلتهـــاب و المضـــاد للأكســـدة للريسفيراترول في علاج إلتهاب المفاصل الروماتويدي في الجرذان.

مـــواد و طـــرق البحـــث: تـــم تقســـييم الجـــرذان إلـــي خمســـة مجموعـــات: مجموعـــة ضـــابطة،مجموعة إيجابيـــة (تـــم إســـتخدام مســـاعد فرونـــد الكامـــل للحـــث علـــى إلتهـــاب المفاصـــل الروماتويـــدي)، ومجموعـــة السيليكوكســـيب مصـــابة بإلتهـــاب المفاصـــل (٣٠ مجم/كـــم، عـــن طريـــق الفـــم) ، ومجموعـــة الريســـفيراترول مصـــابة بإلتهـــاب المفاصـــل (٥٠ مجم/ كم، عن طريق الفم)، والمجموعة التي تضم العقارين .

النتـــائج: أظهرإلتهـــاب المفاصـــل الروماتويـــدي ارتفاعـــا ملحوظـــا فـــي نشـــاط إنزيمـــات سيكلوأوكســـيجيناز-اثنـــين، الانترليـــوكين ١-ب، ومعامـــل خفـــض الـــورم-ألفـــا ،الكاســـباس ٣ ، وبعـــض إنزيمـــات الليـــزوزوم ، إلـــي جانـــب إرتفـــاع فـــي مســـتوي بعـــض المعـــاملات الكبديـــة الحيويـــة فـــي مصـــل الـــدم ،كمـــا أظهـــرت النتـــائج إرتفاعـــا ملحوظـــا فـــي مســـتويات المايلوبوكســـيداز ، ومســـتويات مالونديالهيـــد وأكســـيد النتريـــك ؛ مـــع إنخفـــاض ملحـــوظ فـــي مســـتوي الجلوتـــاثيون فـــي أنســـجة القـــدم والألبيـــومين فـــي مصـــل الـــدم. و قـــد أدي مـــزج الريســـفيراترول إلـــي السيليكوكســـيب إلـــي زيـــادة التـــأثير المضـــاد للإلتهـــاب والمضـــاد للأكسدة عن كل دواء علي حدة.

الإســـتنتاج: : يقـــوي الريســـفيراترول التـــأثيرات المضـــادة للإلتهابـــات والأكســـدة مـــع السيليكوكسيب في علاج إلتهاب المفاصل الروماتويدي.