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RESEARCH PAPER

Curcumin oil and Grapeseed oil can antagonize the Effect of All-Trans-Retinoic Acid (ATRA) on Rat's Kidney

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A B S T R A C T:

Tretinoin chemically is all-trans retinoic acid associated with retinol groups. It is yellow to light orange crystalline powder that urges the cytodifferentiation and diminish proliferation of acute promyelocytic leukemia (APL) cells in culture and in vivo. The accurate mechanism operation of tretinoin is uncharted. Researchers have shown that tretinoin has potentially teratogenic and toxic side influences in mice, rats, hamster rabbits and patients. The most frequent adverse events in kidney were renal insufficiency, dysuria, acute renal failure, micturition recurrence and renal tubular necrosis and also it causes enlargement of prostate .

There were no adequate and well-controlled studies in animal models. So, monitoring of kidney functions with its texture had to be done. In recent years herbal extract treatment showed capability of ameliorative role for the disturbance of organs functions with toxic and injuries in different tissues especially kidney tissue.

Current research was conducted in 28 days and 49 rats were included and they were divided into seven groups each group containing 7 rats: the first was negative control group gavageed with olive oil at dose (2ml/kg/bw) , while the second and third were positive control groups administrated at dose (15&30 mg/kg/bw) respectively with ATRA ,indeed the others treated groups combinations between the two ATRA concentrations with curcumin oil at dose (50 mg /kg/bw) were included the fourth and fifth groups respectively, and the last two groups administrated grape oil at dose (50 mg /kg/bw) were included the sixth and seventh group respectively .

From this study, we discovered that treating the rats by extracted grapeseed oil with ATRA recovered the damaged kidney architecture near to normal as well as improved their renal functions.

KEY WORDS: All-trans Retinoic acid, curcumin oil, grape seed, antioxidant, nephrotoxicity
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INTRODUCTION

Retinoic acid is one of the pro-vitamin A, relevant composites that extend their impact throughout activation of receptors (Elsayed et al., 2014). Retinoic acid has various effects on physiological means, like; cell growth, differentiation, apoptosis, and inflammation (Zhou et al., 2013).

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The anti-proliferative effects of retinoid are attributable to modulation of gene receptors transcription (Wagner et al., 2000). ATRA is assimilated in the small intestine and esterified as retinyl esters to be transported by blood stream and then it's chiefly conveyed to the liver as a storing house, principally in the hepatic stellate cell. As well as hydrolysis of retinyl esters results in retinol which, then joins to retinol-binding protein (RBP), (Dai et al., 2017). The mechanical effect of this acid on the kidney is not known but retinoid had an indication of kidney dysfunction and is also a risk agent for the progression of

chronic kidney infection (Cravide & Remuzzi, 2013).

Various plant seeds had shown to exhibit medical properties such as antidiabetic, anti-allergic, anti-inflammatory, antibacterial, antioxidant activity (Aggarwal, et al., 2016, Hassan et al., 2017).
Curcumin is one of the medical herbs which are well known for thousands of years and have many useful features. The vital element existing in Curcuma longa of the family Zingiberaceae has a complex of pharmacological impressions inclusive potent anti-inflammatory activity (Nasri et al., 2014, Aggarwal, et al., 2016). Curcumin oil extract (CEO) is gathered from C.Longa which manifest powerful anti-inflammatory and anti-arthritic exploits (Maheshwari et al .,2006).In addition, the oil is utilized for a broad spectrum of dysfunctions, including biliary malady, anorexia, coryza, cough, wound, hepatic dysfunctions, rheumatic diseases, sprains and swellings created by damage and sinusitis (Sukandar et al., 2010). Besides that, curcumin oil improves renal distractions and tissue normalization nearly to the normal state (Nonose et al 2014).
Grapeseed oil (GSO) is an extract of the grape seeds which has been used recently for cosmetics and treating various disorders and wound curing (Shivananda et al., 2011). In addition to cooking, GSO has a variety of health advantages and is admitted as a good and powerful antioxidant mixture for its content of polyphenol, flavonoids, saturated fatty acids and vitamin E (El-Ashmawy et al., 2007, Freitas et al 2008). Many studies refer to the effect of GSO in anti-inflammatory, anti-carcinogenic, platelet aggregation inhibiting and metal chelating properties (Nagib, 2014).

The study was conducted to examine the effect of two natural products curcumin and grapeseed oils against the nephrotoxic effect of all Trans retinoic acid in rats.

1. MATERIALS AND METHODS

1.1. MATERIALS

1.2. Plant Material Collection:

A- Olive oil extract, Curcumin seed oil extract (CEO) and Grapeseed oil extract (GSO) were purchased from local markets in Erbil city, Iraq.
B-Tretinoin Capsules are all-trans retinoic acid (ATRA) supplied as (10mg), two-tone (longitudinally) with reddish-brown opaque and yellow gelatin crust, imprinted with TR" with black paint on the yellow side., American Health packaging. Par Pharmaceuticals (10mg/30UD) NDC68084-075-21packaded from NDC, Columbus, OH 10370-268.

1.3. Animals model

The experiments were conducted at the animal house of the University of Sallahaddin, college of Education, Department of Biology, Erbil, Iraq. Adult Sprague Dawley strain albino rats at 9-10 months' age and 250-350 body weighing were obtained from an upbringing colonist kept on a usual rodent chow and water ad libitum and a 12 h artificial light/dark cycle, were kept in well–ventilated cage at room temperature under controlled condition of ambient temperature 250C. The animals were given standard rat pellets and tap water ad libitum.
The experiments were conducted over 49 rats, divided into seven groups and each group contained 7 rats for 28 days: control group: The rats were given olive oil (2ml/kg/bw) with standard chow and tap water ad libitum, ATRA given at dosage of (15&30 mg/kg/bw) in second and third groups respectively, CEO treated dosage (50 mg /kg/bw) + ATRA at dosage of (15&30 mg/kg/bw) in fourth and fifth groups respectively, GSO treated at dosage (50 mg /kg/bw) + ATRA at a dosage of (15&30 mg/kg/bw) in sixth and seventh groups respectively ,The rats in all groups were receiving materials orally by gavage.
The experiments were completed within 28 days. At the end, animals were sacrificed and dissected and their kidneys were taken for histological examinations.

1.4. Blood sampling

Blood samples were taken from peripheral veins by 5 ml syringe. Put into gel and clot-activator tubes for serum separation. Their sera were separated by 3000 round per minute centrifugation for 20 min. They were frozen at −80°C for chemical assays of renal function tests (blood urea, serum creatinine and uric acid) for all study groups (Cheng et al., 2005).

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1.5. Histopathological examinations

Kidney tissues were preserved in neutral buffered formalin 10% solution and were processed to obtain Formalin Fixed Paraffin Embedded (FFBE) blocks. Changes were assessed in histopathological sections at 5-micron cuts stained with hematoxylins and eosin (H&E) stains (Murice-Lambert et al., 1989).

1.6. Statistical analysis

The data was coded and entered using the statistical analysis, Graph Pad Prism 8 was used to analyze the data wich was done by Shapiro-wilk test and Kolmogorov-Smirnov test.

2. RESULTS

The persistence project was programmed for and conducted over 49 rats, divided into seven groups each group contained 7 rats for 28 days: the first group was negative control group gavageed with olive oil at dose (2ml/kg/bw) , while the second and third were positive control groups administrated at dose of (15&30 mg/kg/bw) respectively with ATRA, and for the fourth and fifth treated groups; combinations between the two ATRA concentrations with curcumin oil at dose of (50 mg /kg/bw) were used consequently, also the last two groups administrated grape oil at dose of (50 mg /kg/bw) which included the sixth and seventh group consequently.

The outline treatise of kidney function values were revealed considerable effects. Blood urea values in combinations groups include ATRA2+CEO, and ATRA2+GSO affected significantly *$p<0.05$ and **$P<0.01$ in comparison with the ATRA1 and ATRA2 respectively, while other treated groups had no significant effects showed in Figure 1. In additions, the values of serum creatinine were significantly influences *$p<0.05$ and **$P<0.01$ among treated groups ATRA1 and ATRA2 with ATRA2+COE and ATRA2 + GSO respectively, as it is manifest in Figure 2. The last examinations involved serum uric acid values were showed an effect *$p<0.05$ between ATRA2 with all treated groups as obvious in Figure 3.

The rats' renal tissue sections were investigated for changes in all study groups. ATRA2 (high dose) showed more histologic alteration Figures 6 and 7, than ATRA1 (low dose) Figure 5, including the inflammatory cells infiltration, necrosis of renal tubules, blood vessels wall thickenings, blood vessel congestion, interstitial hyperplasia, haemorrhage, hydropic degeneration, fibroblast hyperplasia, glomerular congestions and glomerular necrosis. In ATRA1 and ATRA2 with curcumin oil Figures 8, 9 and 10 respectively, no frank changes appear in the renal sections in comparison with the spun clique of grape oil especially ATRA1 +GSO Figure 11 and 12 which is upkeep the section more than ATRA2+GSO Figure 13 and 14 for recovered nephrotoxicity nearly to the normal state Figure 1.

3. DISCUSSION

Tretinoin persuaded toxicities in lab animals and human was recognized when retinoid is given repeatedly. So, collectively known as hypervitaminosis was now standard therapy for acute myelocytic leukaemia (Tallman et al., 2000, Saadedin et al, 2004). All-Trans retinoic acid (ATRA) cased nephritic disorder, dysuria, sever renal failure, micturition frequency and renal tubular necrosis. Also, documented enlarged prostate (Thomas et al., 2000). The outcomes of the research obviously indicated the impact of ATRA1 and ATRA2 on rats' kidney functional test values which interpret the difference among the study groups' data. Furthermore, the disturbance of kidney's physiological test improved as seen in the significant reduction of renal function test values blood urea, serum creatinine and uric acid which elevated significantly *$p<0.05$ and **$P<0.01$ in comparison with the treated groups CEO and GSO in the present data by dependent two different doses of ATRA .

Studies in human have demonstrated a complex behavior of ATRA, concluded that its elimination was dependent and capacity-limited (Camacho, 2003). Recently, recorded that an ATRA inducible side effects are increased to nearly 10-fold above normal after 3 hours of ATRA administration in rats (Lampen, et al., 2001, Ozpolat et al., 2003). As well as retinoid performs a critical role in various physiological and disordered processes such as proliferation, differentiation, apoptosis and visibility (Gudas, 2012). The influence of various nephritic disorders is ATRA dose-dependent which boost the danger of prolonged

renal disease and secondary kidney complications (Xu et al., 2004). Indeed, researchers recorded similar outcomes of renal histopathological identifications which improved the present results of renal sections, including that higher dose of ATRA (30%), caused additional infarctions in renal textures; like glomerular congestion ,glomerular necrosis, macrophage cell, necrosis in interstitial space, vascular wall thickening and inflammatory cells infiltrations, as well as interstitial hyperplasia , cells infiltrations , haemorrhage and necrosis in renal tubules.

Meanwhile, some histological changes which were induced by low dose of ATRA (15%), caused blood vessels congestion, degeneration of convoluted tubules and inflammatory cells infiltrations.

In fact, retinoid receptors in the improvement of diverse renal destructions were not quite realized (Kavukcu et al., 2001). The researcher recorded that retinoid receptors induced nephrotoxicity and injury , also it developed many complications in its function (Miller et al., 2010, Zhou et al., 2012).

In recent years, the sizable emphasis has been focused on the greatness of the naturally accessible botanicals that can be employed in individuals with everyday diet because of their components' anti-oxidant and anti-inflammatory properties (Ugur et al., 2015).

Curcumin was the main turmeric component and in addition to its anti-inflammatory and anti-oxidant effects, it has chemo preventive properties (Ugur et al., 2015, Ramazan, et al., 2016). It also has different biological and pharmacological effects like anti-ischemic, anti-bacterial, anti-fungal and anti-carcinogenic effects. These effects are due to different methoxy substance in the chemical composition of this compound (Chiagoziem et al., 2014, Kumar et al., 2017).

Curcumin extracts oil is a curcumin formulation exhibit bioavailability (Antony et al., 2008). (Chiagoziem et al., 2014, Aggarwal et al., 2016), investigated that the CEO has no noxious consequences and it was used safely in the treated animals. Also, no significant influence was induced in the first 48 hours compared to the control group. As no considerable differences were seen in the CEO used animals, it was resolved that CEO doesn't have any mutagenic potential.

(Kizhakkedath, 2013, Parasuraman, 2011) Researchers also agreed with the present findings, as the sections of tow isolated compartment rats with high dose of ATRA and low dose of ATRA which were treated with CEO respectively showed blood vessels congestion, vaculation of convoluted tubules and necrosis. As well as, showed glomerular congestion, hydropic degeneration of convoluted tubules, fibroblast hyperplasia, reduced bowman spaces and inflammatory cells infiltrations. From these findings we conclude that more time was needed for curcumin to recover low dose of ATRA and high dose of ATRA tissue damage.

Present results indicated that's no real recovering change occurs in renal rats' sections affected by ATRA. That might be related to the short duration which is 28 days, for evaluated protective and therapeutics role to exert its actions and against ATRA toxicity. Further evaluations need to be done on the CEO in order to explore and impact their practical applications, which can be used in different doses and durations on varying animals' models.

Grapeseed oil has been investigated to possess many characteristics, including antioxidant, anti-inflammatory, anti-carcinogenic, platelet aggregations inhibiting and metal chelating properties (Al-Attar et al., 2015, Alawi, et al., 2018). So GSO has a high level of anti-oxidant vitamin E, which makes the oil very stable and cures lesions (Shi, and Pohorly , 2003, Stojiljkovic et al.,2008, Mohsen et al., 2019).

Nephrotoxicity is a dilemma property by functional alterations which are generated by difficulties of protein formations, glutathione deficiency, lipid peroxidation and mitochondrial impairment. Besides, oxidative destruction is speculated to be one of the principal mechanisms initiated in approximately all chronic renal diagnostic methods (Gutin et al., 2008, Shinagawa et al., 2015, Erisir et al .,2018 , Rasheed et al .,2018).

Further, the rat groups treated with GSO showed significant improvements in renal function test values of blood urea, creatinine and uric acid.

Moreover, treatment of rats with GSO for 28 days after intoxication with ATRA at both doses, serum kidney biochemical alteration were returned significantly $*p<0.05$ and $**P<0.01$ to normal levels with the improvement of renal tissue changes (Xia et al., 2010).

Finally, treated rats with GSO + high dose of ATRA showed slight changes in the renal tissues

when compared with GSO + low dose of ATRA which is against the nephrotoxicity and the tissues appeared nearly within normal. The protective effects of GSO are referred to its powerful antioxidant mixture for its content of polyphenol, flavonoids, saturated fatty acids and vitamin E which contains free radical scavenging properties (Garavaglia et al., 2016,Yousefaetal,2018). On top of that, vitamin E has a great role in anti-inflammatory, anti-carcinogenic, platelet aggregation inhibiting and metal chelating properties (Nagib, 2014) .

4. CONCLUSION

Grapeseed oil succeeded in reducing the nephrotoxicity induced by all-trans retinoic acid in rats.

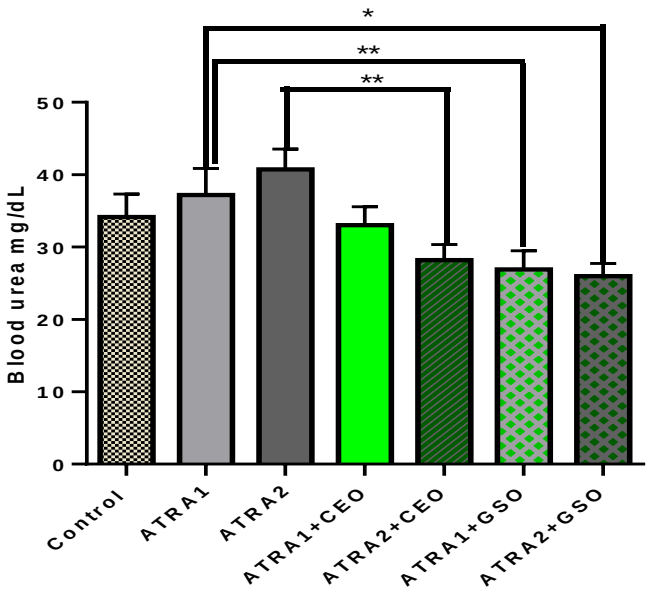

Figure1. Blood urea in the treated groups, n=7(values are Mean ± SE) mg/dl.

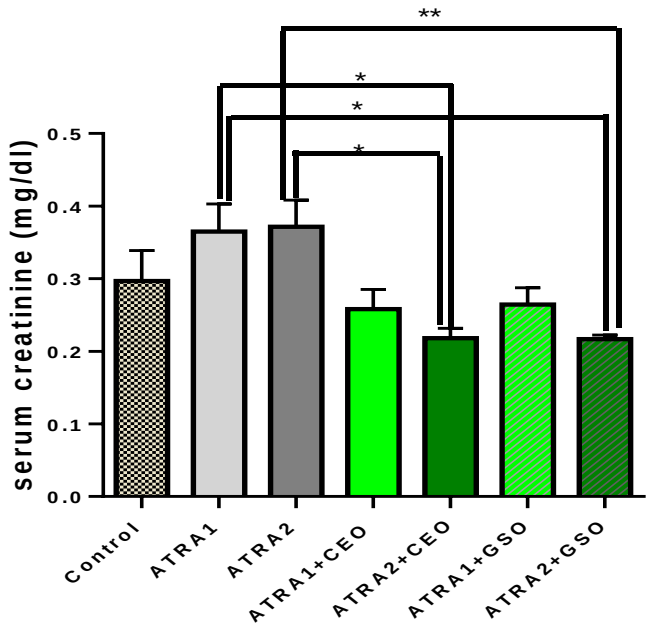

Figure 2. Serum creatinine in the treated groups, n=7 (values are Mean ± SE) mg/dl.

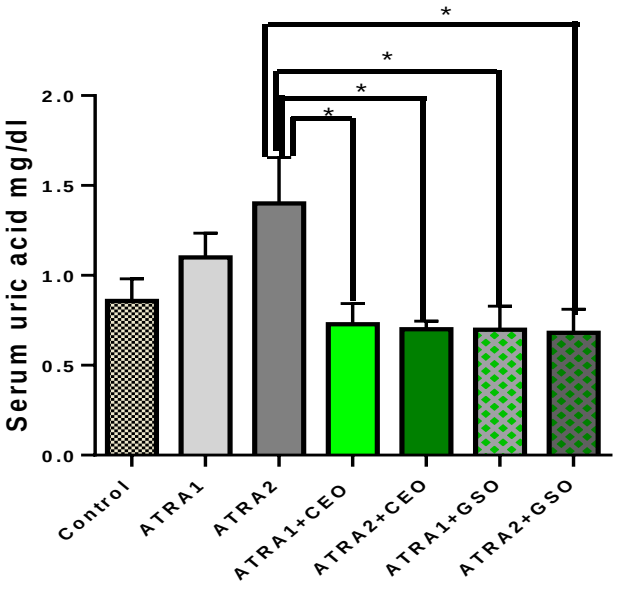

Figure 3. Serum uric acid in the treated groups, n=7 (values are Mean ± SE) mg/dl.

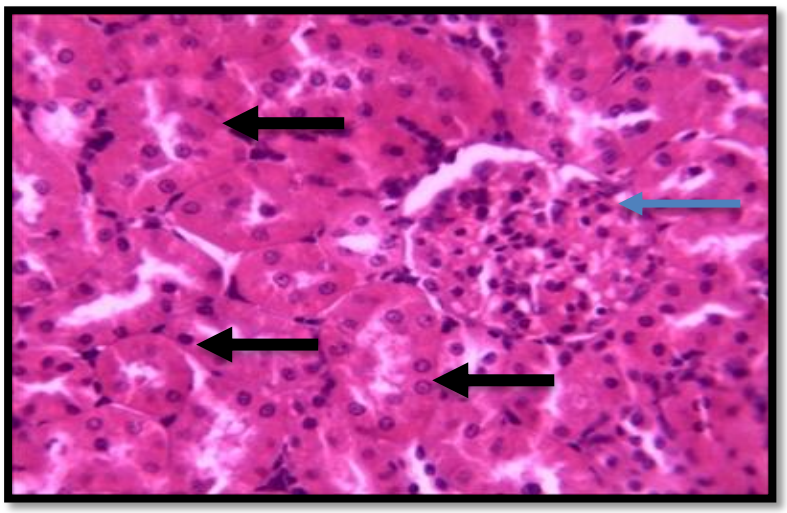

Figure 4. Kidney tissue section of normal rat treated with olive oil (2%) showed normal looking glomeruli (blue arrow) and tubules (black arrows) H&E 400 xs.

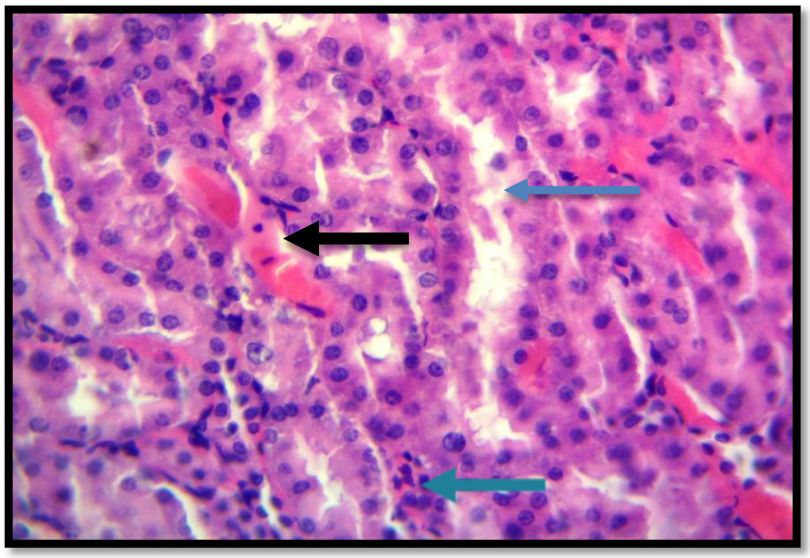

Figure5. Kidney tissue section administrated rats with ATRA (15%), showed blood vessels congestion (black arrow), degeneration of convoluted tubules (gray arrow), and inflammatory cells infiltrations (blue arrow), H&E 400x.

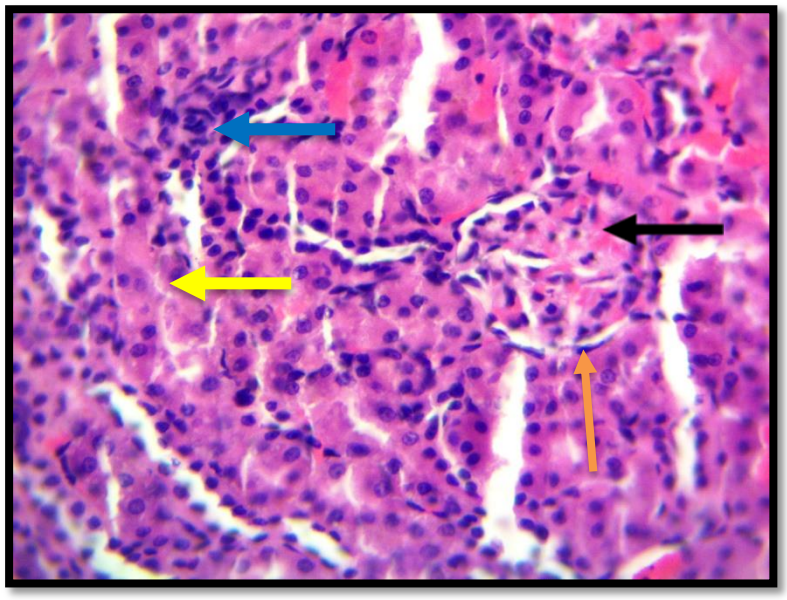

Figure 6.Kidney tissue section administrated rats with ATRA (30%), showed glomerular congestion (black arrow), hydropic degeneration of convoluted tubules (yellow arrow), fibroblast hyperplasia (orang arrow), and inflammatory cells infiltrations (blue arrow), H&E 400x.

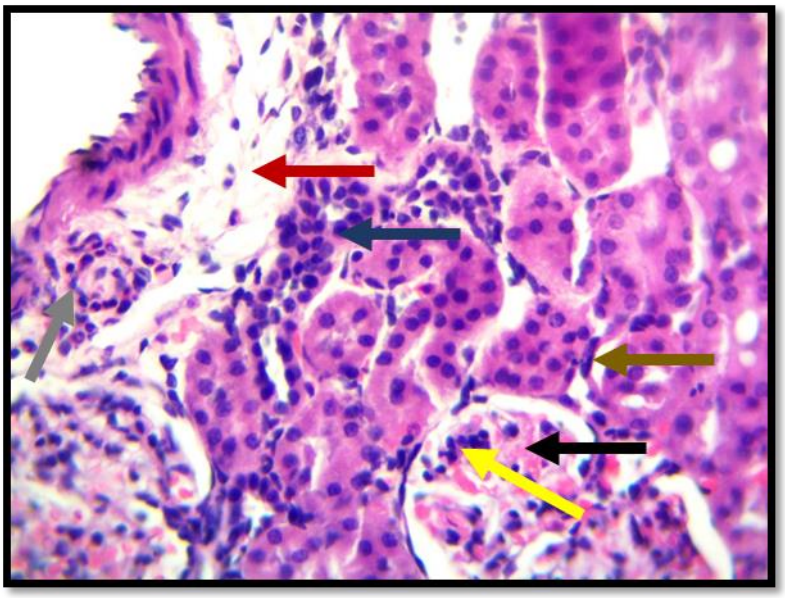

Figure 7. Kidney tissue section administrated rats with ATRA (30%), showed glomerular congestion (black arrow), and necrosis (yellow arrow), macrophage cell (brawn arrow), necrosis in interstitial space (red arrow), vascular wall thickening (gray arrow), and inflammatory cells infiltrations (blue arrow), H&E 400x.

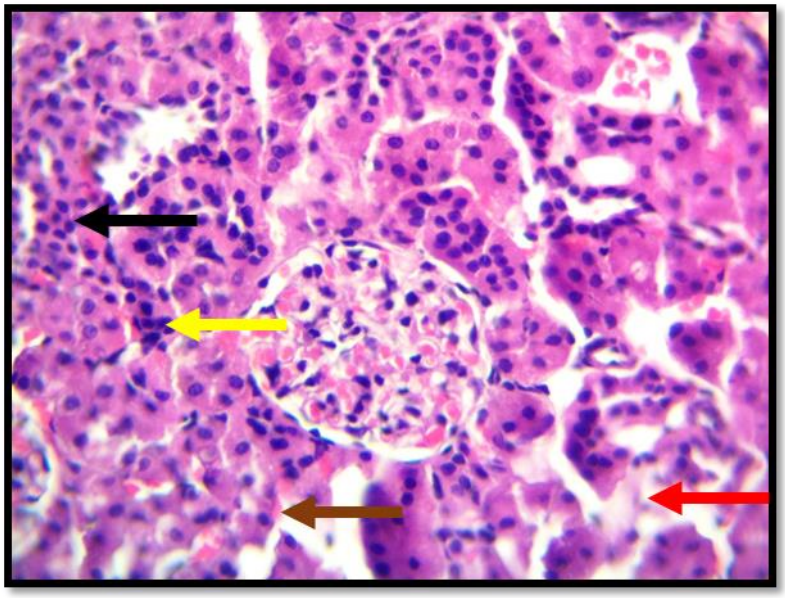

Figure 8.Kidney tissue section administrated rats with ATRA (15%) + CEO (50%), showed interstitial hyperplasia (black arrow), inflammatory cells infiltrations (yellow arrow), haemorrhage (brawn arrow), and necrosis in renal tubules (red arrow), H&E 400x.

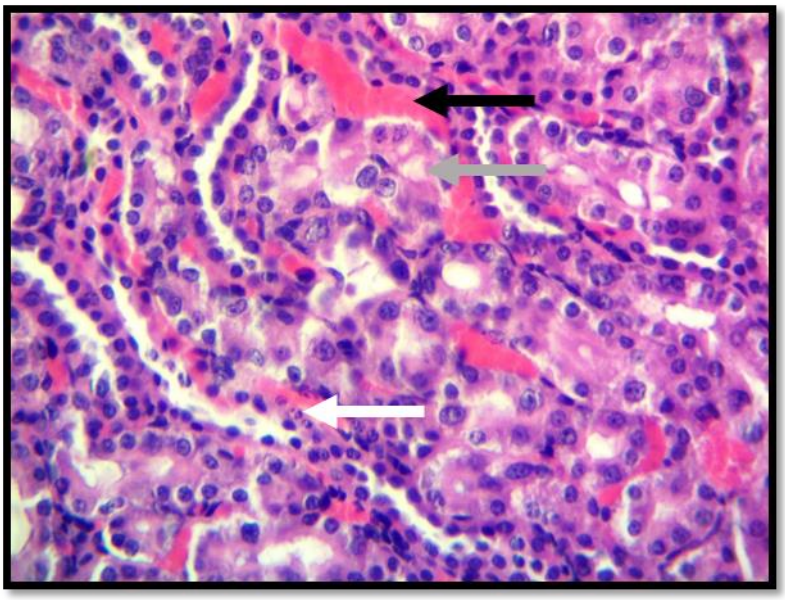

Figure 9. Kidney tissue section treated rats with ATRA (30%) + CEO (50%), showed blood vessels congestion (black arrow), vaculation of convoluted tubules (grey arrow), and necrosis (white arrow), H&E 400x.

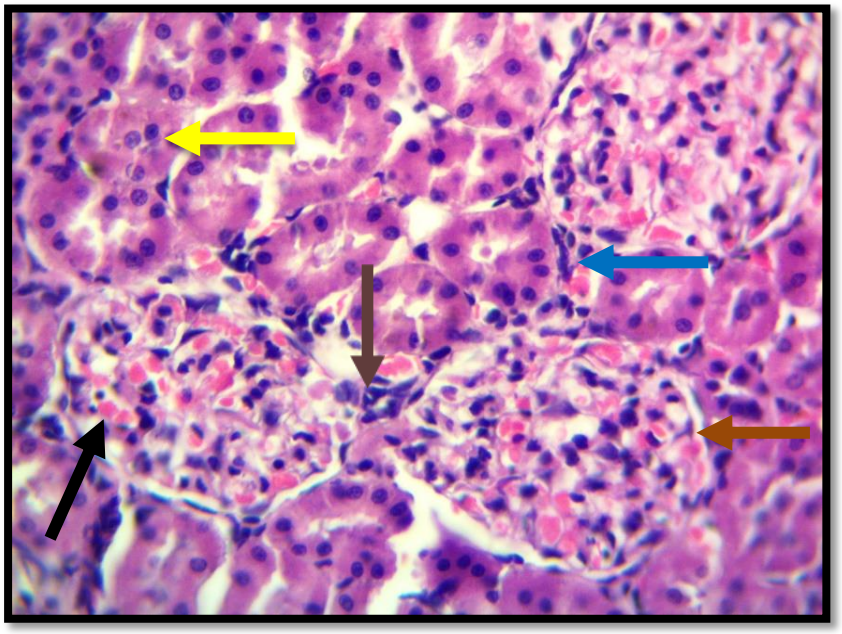

Figure 10. Kidney treated rats with ATRA (30 %) + CEO (50%), showed glomerular congestion (black arrow), hydropic degeneration of convoluted tubules (yellow arrow), fibroblast hyperplasia (brawn arrow), reduced bowman spaces (green arrow), and inflammatory cells infiltrations (blue arrow), H&E 400x.

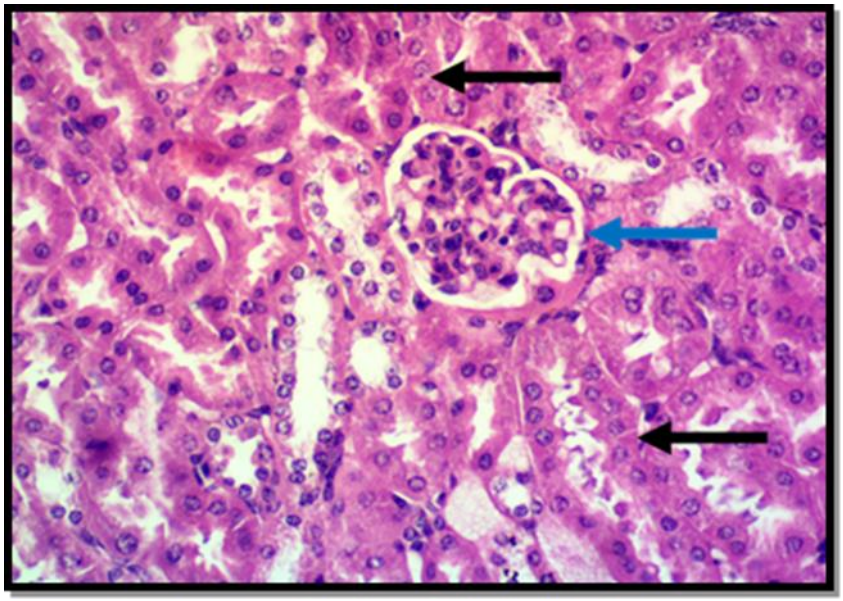

Figure 11. Kidney tissue section administrated rats with ATRA (30%) + GOE (50%), showed nearly appearance in comparison to the normal tissue, convoluted tubules (black arrow), glomerular (blue arrow), H&E 400x.

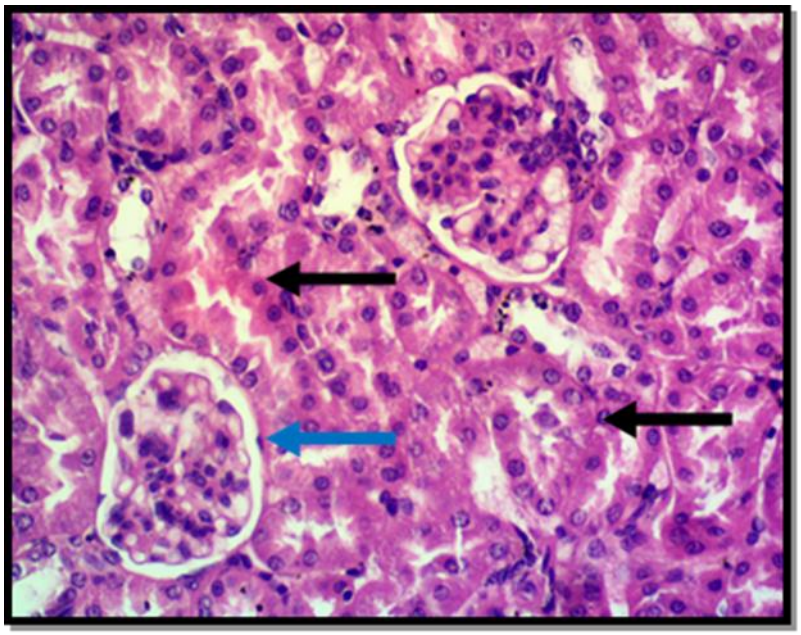

Figure 12. Kidney tissue section administrated rats with ATRA (30%) + GOE (50%), showed nearly appearance in comparison within normal tissue, convoluted tubules (black arrow), glomerulus (blue arrow), H&E 400x.

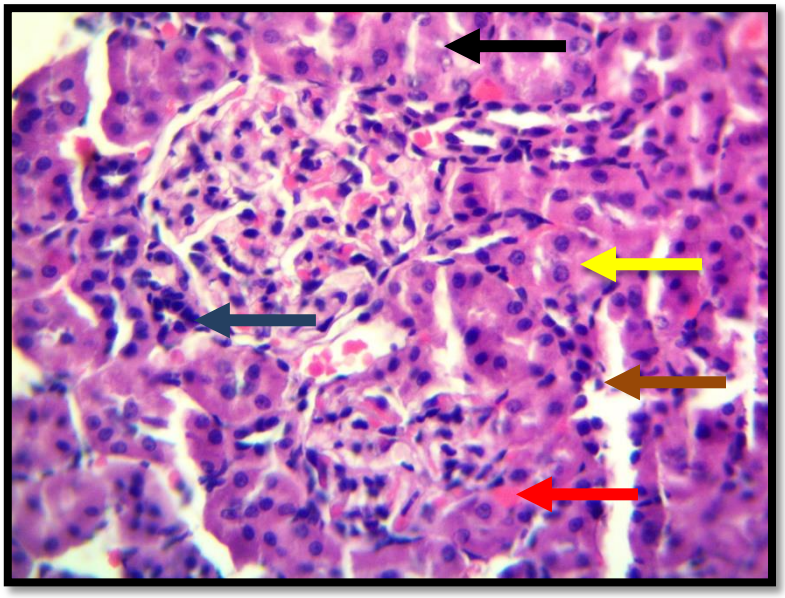

Figure 13. Kidney tissue section administrated rats with ATRA (15%) + GOE (50%), showed vaculation (black arrow), hydropic degeneration of convoluted tubules (yellow arrow), necrosis (green arrow), hemorrhage (red arrow), and inflammatory cells infiltrations (blue arrow), H&E 400x.

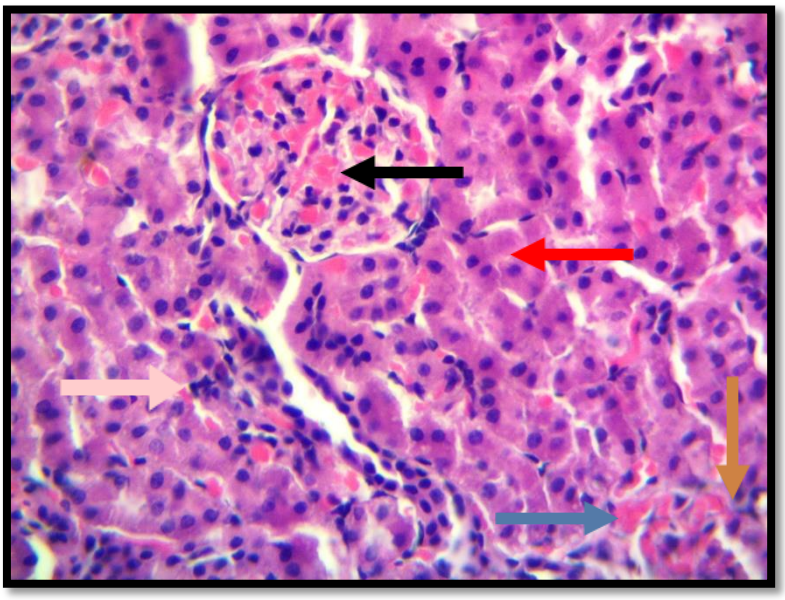

Figure 14. Kidney tissue section administrated rats with ATRA (15%) + GOE (50), showed glomerulus congestion (black arrow), hydropic degeneration of convoluted tubules (red arrow), interstitial hyperplasia (green arrow) hemorrhage (blue arrow) and inflammatory cells infiltrations (pink arrow) H&E 400x.

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