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Eicosapentaenoic Acid Silica Nanoemulsion Protects Against *in vivo* Drug-Induced Nephrotoxicity

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Abstract

Nephrotoxicity is the hallmark of anti-neoplastic drug metabolism. It causes oxidative stress and is associated with considerable morbidity and mortality. Eicosapentaenoic acid (EPA), an omega-3 fatty acid with anti-inflammatory and antioxidant properties, may reduce organ toxicity associated with chemotherapy. We hypothesized that EPA, particularly when loaded into a silica nanoemulsion to enhance stability and bioavailability, would protect against cisplatin-induced nephrotoxicity. Forty rats were divided randomly into five groups: Group I (control group): healthy rats received a vehicle. Group II (EPA): healthy rats received EPA. Group III (cisplatin group): healthy rats received cisplatin. Group IV (treated group I): healthy rats received cisplatin before receiving EPA. Group V (treated group II): healthy rats received cisplatin and EPA silica nanoemulsion. After the experimental period, serum was separated to determine urea and creatinine. In addition, blood urea nitrogen (BUN) was calculated. Also, kidney homogenate was used to detect the reduced glutathione (GSH), malondialdehyde (MDA), and total antioxidant capacity (TAC) using a colorimetric method. While high-performance liquid chromatography (HPLC) was used to find out the amounts of erythrocyte membrane fatty acids and urine 8-hydroxy-2-deoxyguanosine (8-OHdG), additionally, histopathological investigations were carried out to confirm our hypothesis. Our data showed that there was a significant increase in creatinine, BUN, MDA, 8-OHdG, arachidonic acid (AA), and linoleic acid (LA) concomitant with a significant reduction in GSH, TAC, and alpha-linolenic acid (ALA) in cisplatin group when compared to the control group. Additionally, our findings displayed a significant decrease in creatinine, BUN, MDA, 8-OHdG, AA, and LA associated with a significant increase in GSH, TAC, and ALA in all treated groups when compared with the cisplatin group. However, an improbable progress was detected between the treated group I, and the treated group II. These biochemical outcomes were supported by the histopathological results. The study revealed that EPA silica nanoemulsion could play a beneficial role in the management of nephrotoxicity caused by chemotherapy drugs while treating various types of cancers.

Keywords: Nephrotoxicity; Cisplatin; Eicosapentaenoic acid; Silica nanoemulsion; Experimental animals.

1. Introduction

Renal physiology regulates blood pressure, erythropoiesis, the generation of certain enzymes and hormones, the water and acid-base balance, and electrolyte composition, all of which are crucial for preserving homeostasis. The removal of potentially hazardous materials from the body, such as medications, infectious agents, and toxicants, is its primary duty. Additionally, as part of preserving general homeostasis, which is controlled by the central nervous system (CNS), the kidneys have the capacity to coordinate inter-organ signaling [1].

Cisplatin, also known as cis-diamminedichloroplatinum or CDDP, is a platinum-based chemotherapy medication that is frequently used to treat a variety of tumors. Nevertheless, there is an inherent danger of kidney damage when using CDDP in chemotherapy. Numerous processes are responsible for renal damage, such as the activation of caspase-9 and the stimulation of cytochrome c release from proximal tubular epithelial cells. Moreover, CDDP causes tubular cells to produce tumor necrosis factor-alpha (TNF-α), which sets off an inflammatory cascade that ultimately causes damage or death to tubular cells. Furthermore, tubular epithelial cells' toxicity is closely correlated with endothelial dysfunction and vasoconstriction caused by CDDP, which results in decreased renal blood flow [2].

The main adverse effect that limits the dosage of many chemotherapy drugs, such as cisplatin and doxorubicin therapy, is nephrotoxicity. These are first-line anti-cancer medications that lead to nephrotoxicity, which is an early sign of oxidative stress. Cisplatin-induced nephrotoxicity (CIN) is a cancer-related comorbidity that affects up to 28–36% of cancer patients and causes pathological alterations in the kidneys, especially in individuals with solid tumors in the nasopharynx, ovary, and lungs. High lipid peroxidation of the cellular membranes results in decreased glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and elevation of oxidative stress biomarkers, malondialdehyde (MDA), and TNF-α, which causes renal tubule dysfunction when cisplatin toxicity is high [1].

With its ability to alter plasma properties such as fluidity, permeability, and the equilibrium between ceramide and sphingomyelin, eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, has been shown to affect the composition

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of cellular membranes [3]. This effect has been linked to apoptosis [4]. Furthermore, it has minimal to no cytotoxic effect on normal cells while inhibiting the proliferation of tumor cells [5]. Because of its well-known anti-inflammatory properties, EPA may be particularly crucial in controlling oxidative stress and inflammatory reactions, two important aspects of the pathogenesis of diabetes. The distinct anti-inflammatory characteristics of EPA have demonstrated potential in modifying indicators associated with insulin resistance and dyslipidemia [6].

Since EPA, frequently found in fish oil, is unsaturated, its effectiveness is irreversibly altered during processing. Therefore, developing an EPA nanocarrier is essential to enhancing EPA's pharmacological and bioavailability characteristics and expanding its application in biomedical fields [7]

Nanotechnology has been improving the lives of individuals recently and is still expanding into new areas. Because of their unique physicochemical characteristics, which include quick, efficient, specifically designed solutions, increased **stability,** biodegradability, biocompatibility, and affordability, nanoparticles can be used in a variety of industrial, imaging, engineering, and medicinal sectors [8, 9]

The application of nanotechnology to human health is one of the most significant and beneficial areas of study. In this instance, it is crucial to use the technique and its byproducts in a range of health areas, such as diagnostics (such as imaging and diagnostic systems in biochemistry and clinical histopathological laboratories), therapeutics (drug, surgery, and radiation), and prevention (such as nutritious food, clean drinking water, improved soil quality, and its fertilizer, nutrients, supplements, and vaccines) [9]. Therefore, the purpose of our research was to evaluate the effects of eicosapentaenoic acid (EPA) on the management of nephrotoxicity caused by cisplatin in an animal model, whether EPA was taken alone or with silica nanoemulsion.

2. Materials and Methods

Chemicals:

Cisplatin (1mg/mL) was purchased from a local pharmacy. High-performance liquid chromatography (HPLC) standards for 8-hydroxy-2-deoxyguanosine (8-OHdG), and fattyacids (EPA, arachidonic acid (AA), oleic acid (OA), alpha-linolenic acid (ALA), andlinoleic acid (LA)) were purchased from Sigma Chemical Company, St. Louis, MO, USA.

Animals:

A total of forty male albino rats, weighing 140 ±10 g, were purchased from the animal house of the National Research Centre in Giza, Egypt. They were kept in individual suspended stainless steel cages at a temperature of 22 ± 2 °C, with a 12-hour light/12-hour dark cycle. Prior to the experiment, the rats were given seven to ten days to acclimate; they were also given free access to food and water. The National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 86-23, amended 1985) was followed in animal procedures **[10].**

Methods

Preparation of Eicosapentaenoic acid (EPA) nanoemulsion:

The EPA-loaded silica nanoemulsion was prepared according to our previous work **Hussein et al [7].** The average particle size was determined using dynamic light scattering (DLS), resulting in particles with a mean diameter of 90 nm and a polydispersity index (PDI) of 0.074, indicating uniform particle distribution.

Induction of nephrotoxicity:

Cisplatin was injected in animals (intraperitoneal) for one time at a dose of 10 mg/kg body weight, as modified from the method described previously **[8].**

Experimental design:

Forty rats were divided randomly into 5 groups (8 rats for each group) as follows:

- Group I (control group): healthy rats received a vehicle.
- Group II (EPA): healthy rats received EPA in a dose of 500 mg/kg b.wt. /day orally for 6 weeks, according to **Sarbolouki et al [11].**
- Group III (cisplatin group): healthy rats receivedcisplatin before receiving a vehicle.
- Group IV (treated groupI): healthy rats received cisplatin and then received EPA in a dose of 500 mg/kg b.wt. Per day orally for 6 weeks, according to **Sarbolouki et al [11].**
- Group V (treated groupII): healthy rats received cisplatin and then received EPA silica nanoemulsion in a dose of 500 mg/kg b.wt. /day orally for 6 weeks.

Sample collections:

- To collect urine, rats were put in metabolic cages for 24 hours. The urine samples were centrifuged and kept at -20 °C until used to estimate 8-hydroxy-2-deoxyguanosine (8- OHdG).

- Blood samples were collected from the orbital venous plexus, let to clot at 37°C, and centrifuged to separate sera.

- Kidney was removed quickly from each animal to prepare for biochemical and pathological studies.

Preparation of kidney tissue homogenate:

Kidney tissue weighing one gram was divided into small pieces and homogenized using phosphate buffer (pH 7.4). The homogenate was then centrifuged at 5000 rpm for 10 min at 4 °C using a cooling centrifuge (Laborzentrifugen, 2K15, Sigma,

Germany); the clear supernatant was then removed and utilized to measure the total antioxidant capacity (TAC), malondialdehyde (MDA), and glutathione (GSH) **[12, 13].**

Biochemical analysis

Kidney functions:

Blood urea was estimated calorimetrically, as described previously **[14],** while serum creatinine was determined by the kinetic method, as reported by **Laresn et al [15].** Blood urea nitrogen (BUN) was calculated according to the following formula:

$$BUN\ (mg/dL) = urea\ (mmol/L) \times 2.8$$ **[16].**

Determination of oxidants/antioxidants parameters in kidney tissue homogenate:

Kidney GSH, MDA, and TAC were determined according to **Watanabe et al [17], Mihara and Uchiyama [18],** and **Bartosz [19]** respectively.

Determination of urinary 8- OHdG by HPLC:

HPLC system was used to measure the concentration of 8-OHdG **[20, 21].** Shortly, serial dilutions of the 8-OHdG standard were prepared and injected onto HPLC to draw a standard curve with varying concentrations after the standard was dissolved in ultrapure water.

Processing of samples:

One ml urine sample was utilized to extract 8-OHdG using a Strata C18-E (55 um, 70A) column. After being dried with a nitrogen gas stream, the eluents were reconstituted in five milliliters of ultrapure water. Each sample was injected the HPLC in a volume of 20 µL.

HPLC condition:

HPLC system (Agilent technologies 1100 series) was equipped with a quaternary pump (Quat Pump, G131A model). A 25/10/965 v/v combination of acetonitrile, methanol, and phosphate buffer served as the mobile phase. 8.8 g of potassium dihydrogen phosphate (KH2PO4) was dissolved in 1000 ml of ultrapure water, and the pH was adjusted to 3.5 to prepare the phosphate buffer. The mobile phase was filter twice using Whatman membrane filter (pore size 0.45µ, diameter 47 mm) .After that, the buffer was eluted in a reverse phase column; an electrochemical detector was set at cell potential of 600 mV and a flow rate of 1 ml/min after .The urine 8-OHdG concentration was derived from the standard curve and divided by the urinary creatinine, which was obtained using Larsen's kinetic technique **[15].**

Determination of erythrocyte membrane fatty acids by HPLC

High performance liquid chromatography (HPLC) was used to determine the erythrocyte membrane fatty acid fractions, including EPA, arachidonic acid (AA), linoleic acid (LA), alpha linolenic acid (ALA), and oleic acid (OA). The cell membrane was homogenized using a 2:1 volume ratio of 2% acetic acid and diethyl ether. The solution was filtered, centrifuged at 500 x g, and the organic phase was evaporated until it was completely dry. The extract was mixed with 200 microliters of acetonitrilebefore injected onto HPLC.

HPLC condition:

C18 column (260 X 4.6, particle size 5 µm) was used for separation: acetonitrile/water (70/30) v/v was used as a mobile phase; it was supplied by isocratic elution at a flow rate of 1 ml/min, with the UV detector set to 200 nm. Several standards dilutions' peak areas were identified. Using Agilent Chem Station software for LC and LC/MC systems (Agilent Technologies), the standard curve created by graphing peak areas against the corresponding concentrations was used to compute the sample concentrations **[22].**

Histological investigations:

Following a 48-hour fixation in 10% formalin, the renal tissue specimens underwent washing, alcohol dehydration in increasing concentrations, xylene clearing, and paraffin block embedding. For a histological analysis, five-micron thick wax slices were produced, mounted on sanitized slides, and stained with hematoxylin and eosin **[23].**

Statistical analysis

One-way ANOVA was conducted to assess between-group differences, followed by the Least Significant Difference (LSD) post hoc test for pairwise comparisons. A significance level of $p<0.05p < 0.05p<0.05$ was used to determine statistical significance, with 95% confidence intervals reported for all mean differences to provide insight into the precision of the observed effects.

3. Results and Discussion

Cisplatin is a commonly used chemotherapeutic drug employed to treat many kinds of cancer. Nephrotoxicity, however, is one of its main negative impacts. Acute kidney injury (AKI), defined as an abrupt deterioration in renal functioning, can be driven by the long-term effects of cisplatin. Furthermore, AKI is frequently reversible and usually develops soon after cisplatin administration. Severe or repeated episodes of AKI, however, can cause permanent kidney damage, reduced renal function, and raise the chance of developing chronic kidney disease, which is typified by a gradual loss of kidney function over time. Both kidney function and the glomerular filtration rate (GFR) may be compromised. Finding ways to minimize its negative effects was therefore crucial and required **[24, 25].** Hence, the goal of this study was to help finding a solution using EPA to reduce the side effects of the chemotherapy, as well as to increase its benefit by using nanotechnology to raise the stability of EPA by loading it onto silica nanoemulsion. This study investigated the protective effects of eicosapentaenoic acid (EPA) and EPA-loaded silica nanoemulsions in a cisplatin-induced nephrotoxicity model. Results show that EPA, especially in its nanoemulsion

form, significantly reduces biomarkers of kidney injury, oxidative stress, and inflammation. These outcomes likely arise from EPA's anti-inflammatory, antioxidant, and membrane-stabilizing properties, as well as its modulation of fatty acid composition within renal tissues **[24, 25].**

Creatinine is a waste product generated from the breakdown of creatine phosphate in the muscles; it is eliminated in the urine after being filtered by the kidneys. Nephrotoxicity can cause harm or dysfunction to the kidneys, which can impair their capacity to filter and excrete creatinine efficiently. Consequently, there may be an increase in blood creatinine levels, which suggests impaired kidney function **[26].** The amount of nitrogen in the blood that results from protein breakdown is measured by blood urea nitrogen (BUN). The kidneys filter urea, a byproduct of protein metabolism, which is expelled in urine. Increased blood urea levels result from the kidneys' inability to effectively filter and remove urea during nephrotoxicity **[27].**

Table 1: Blood ureanitrogen (BUN) and serum creatinine levels in different studied groups.

Parameters / Groups	Creatinine (mg/dl)	BUN (mmol/L)
Control	0.66± 0.04	4.67± 0.21
EPA	0.57± 0.05	4.12± 0.17
Cisplatin	2.34± 0.11	7.43± 0.22[a]
Treated group I	1.10± 0.05[a, b]	5.91± 0.34[a, b]
Treated group II	0.82± 0.05[b, c]	5.12± 0.25[b, c]

A *p*-value <0.05 was interpreted as a demonstrating statistical significance. (a) Significant difference as compared to control group. (b) Significant difference as compared tocisplatin group, (c) Significance difference as compared totreated group I.

The data in **Table 1** showed that there was a significant increase ($P < 0.05$) in creatinine and BUN levels in the cisplatin group when compared to the control group. Also, our data showed a significant decrease ($P < 0.05$) in creatinine and BUN in all treated groups when compared with the cisplatin group. Moreover, a remarkable variation was detected between treated group I and treated group II. It was observed that the treated group II which received EPA silica nanoemulsion showed improvement in the results than the treated group I which received only EPA.

Nephrotoxicity due to cisplatin is strongly associated with inflammation, which drives kidney injury through up regulated pro-inflammatory pathways. In this study, groups treated with EPA, particularly in nanoemulsion form, showed marked reductions in creatinine and blood urea nitrogen (BUN) levels, signifying improved kidney function. These effects are likely due to EPA's ability to inhibit inflammation by modulating eicosanoid synthesis pathways. As an omega-3 fatty acid, EPA competes with arachidonic acid (AA) which is omega -6 fatty acid in the cell membranes, reducing the production of pro-inflammatory eicosanoids like leukotrienes and prostaglandins while promoting anti-inflammatory mediators **[28, 29].** This mechanism helps counteract the inflammatory responses associated with nephrotoxicity, supporting renal function preservation in EPA-treated groups.

The data in **(Table 2)** showed no statistically significant difference between the EPA group and control group indicating its safety.In addition, a significant increase ($P<0.05$) in MDA, 8-OHdG, while a significant decrease ($P<0.05$) in glutathione (GSH), and total antioxidant capacity (TAC) in cisplatin group when compared to the control group. However, a significant improvement ($P<0.05$) in these parameters (MDA, 8-OHdG, GSH and TAC) in the treated groups when compared with the cisplatin group was observed. On the other hand, a noteworthy variation was noted between treated groups I and II; it was noted that the results of treated group II, which got EPA in the form of silica nanoemulsion, were better than those of treated group I, which received EPA.

Cisplatin-induced nephrotoxicity is linked to an increase in reactive oxygen species (ROS), which leads to oxidative stress and cellular damage in renal tissues. In our study, EPA-treated groups exhibited significantly lower levels of malondialdehyde (MDA) and 8-OHdG, which are markers of lipid peroxidation and oxidative DNA damage, respectively. EPA's antioxidant properties, including its role in scavenging ROS, help maintain cellular redox balance by reducing oxidative damage to kidney cells **[26, 30].** These effects were more pronounced in the EPA nanoemulsion group, which likely benefited from the enhanced bioavailability and cellular uptake provided by the nanoemulsion formulation.

Table 2: Kidney Oxidants/ antioxidantsparameters andurinary 8-OHdG**in different studied groups.**

Parameters / Groups	MDA (nmol/g tissue)	GSH (mg/g tissue)	TAC (mM/g tissue)	8-OHdG (g/mg creatinine)
Control	24.22±1.1	120.4± 4.2	21.24 ± 0.91	4.1± 0.21
EPA	23.04±0.91	119.5± 3.8	20.67± 0.88	3.9± 0.17
Cisplatin	72.01±1.9[a]	56.34± 2.1[a]	8.12 ± 0.67[a]	12.32± 0.22[a]
Treated groupI	47.25±1.4[a, b]	84.27± 2.4[a, b]	12.71 ± 0.93[a, b]	8.11± 0.21[a, b]
Treated groupII	31.05±1.4[a, b, c]	116.20± 3.1[a, b, c]	17.8 ± 1.4[a, b, c]	4.6± 0.14[b, c]

A *p*-value <0.05 was interpreted as a demonstrating statistical significance. (a) Significant difference as compared to control group. (b) Significant difference as compared to cisplatin group, (c) Significant difference as compared to treated I group.

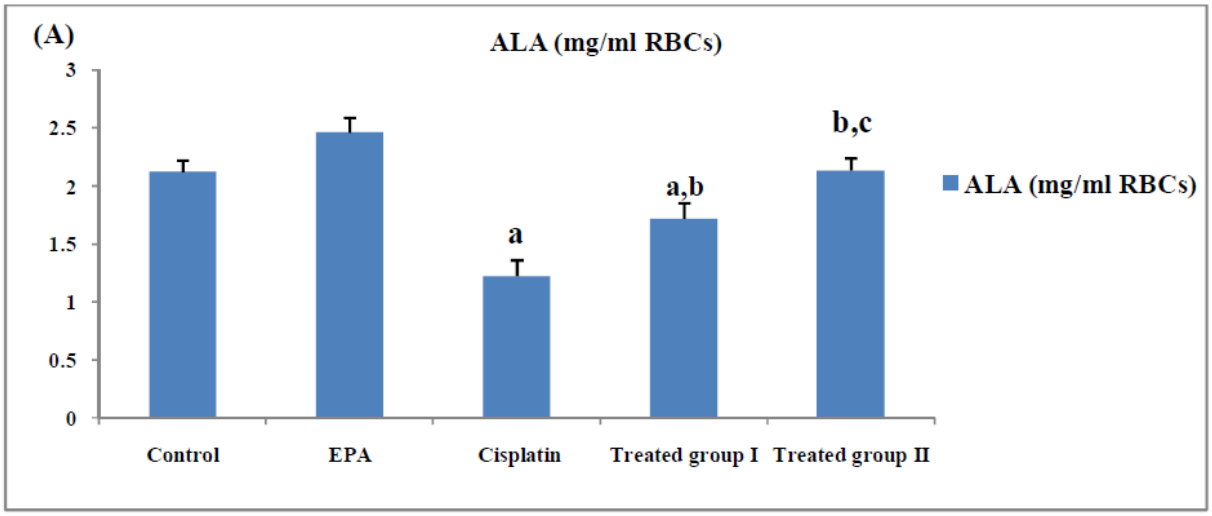
Our results showed that eicosapentaenoic acid (EPA) exerts significant antioxidant effects by enhancing glutathione (GSH) levels and promoting total antioxidant capacity (TAC). EPA plays a crucial role in reducing oxidative stress and inflammation, which indirectly supports increased GSH levels. It has been demonstrated to activate nuclear factor erythroid 2-related factor 2 (Nrf2), leading to elevated expression of antioxidant genes, including those involved in GSH synthesis **[31].** Furthermore, the anti-inflammatory properties of EPA contribute to a decreased demand for GSH, facilitating its accumulation **[32].** In terms of total antioxidant capacity, EPA enhances mitochondrial function and increases substrate availability through β-oxidation of fatty acids, which promotes overall antioxidant activity **[33].** Additionally, EPA has been found to up regulate the activity of enzymes involved in antioxidant defense through AMP-activated protein kinase (AMPK) activation **[34].** Collectively, these mechanisms illustrate the potential of EPA in promoting cellular health by bolstering antioxidant defenses and enhancing metabolic efficiency **(Table 2)**.

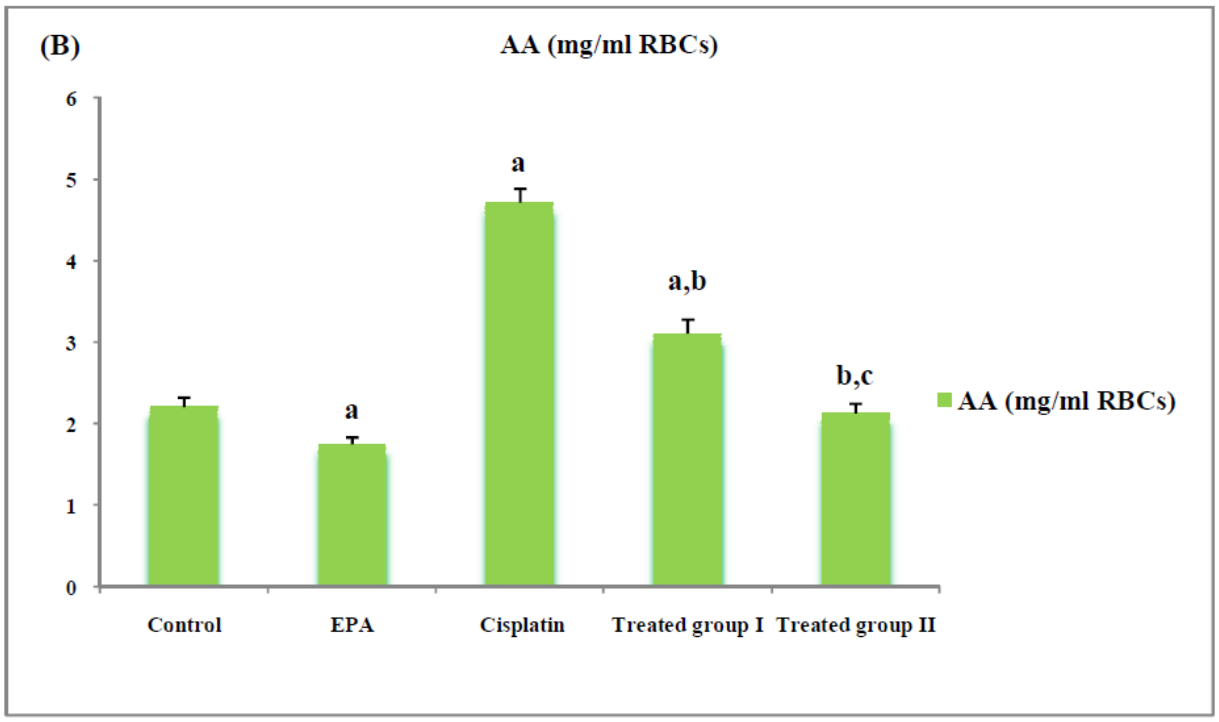
Figure (1) shows that when comparing the cisplatin group to the control group, there was a significant increase ($P < 0.05$) in AA and LA and a significant decrease ($P < 0.05$) in ALA, but no discernable change in OA. Furthermore, in comparison to the cisplatin group, our data demonstrated a substantial rise ($P < 0.05$) in ALA, no change in OA with all treatment groups, and a significant decrease ($P < 0.05$) in AA and LA. Besides, no statistically significant difference was observed between the EPA group and the control group; on the other hand, a noteworthy variation was noted between treated groups I and II. Results were noted to be better in treated group II (EPA silica nanoemulsion) than in treated group I(EPA in its oil form).

EPA plays a significant role in modulating the balance of omega-3 and omega-6 fatty acids in cell membranes, which is critical for regulating inflammation and enhancing cellular resilience. EPA competes with arachidonic acid (AA) for incorporation into cell membranes; since AA is a precursor for pro-inflammatory eicosanoids, a reduction in AA levels due to EPA treatment leads to a shift towards the production of less inflammatory mediators **[35].** This increase in omega-3 fatty acids, particularly in relation to omega-6 fatty acids, limits the availability of AA and thereby diminishes the overall inflammatory response in tissues, including the kidneys **[36].**

Furthermore, the alteration in fatty acid composition influences membrane fluidity and the activity of membrane-associated proteins, which contributes to improved cellular resilience against stressors **[37].** Enhanced resilience can support kidney function and overall renal health. Additionally, EPA-derived eicosanoids activate different signaling pathways compared to those derived from AA, with certain EPA-derived mediators, such as E-series resolvins, promoting the resolution of inflammation. This highlights the potential of EPA not only to reduce pro-inflammatory signaling but also to actively resolve inflammation, thereby fostering healing and mitigating chronic inflammatory states **[32].**

These findings suggest that EPA's modulation of fatty acid composition and inflammatory pathways plays a vital role in supporting renal health and highlights the therapeutic potential of omega-3 fatty acids in managing inflammation-related disorders.

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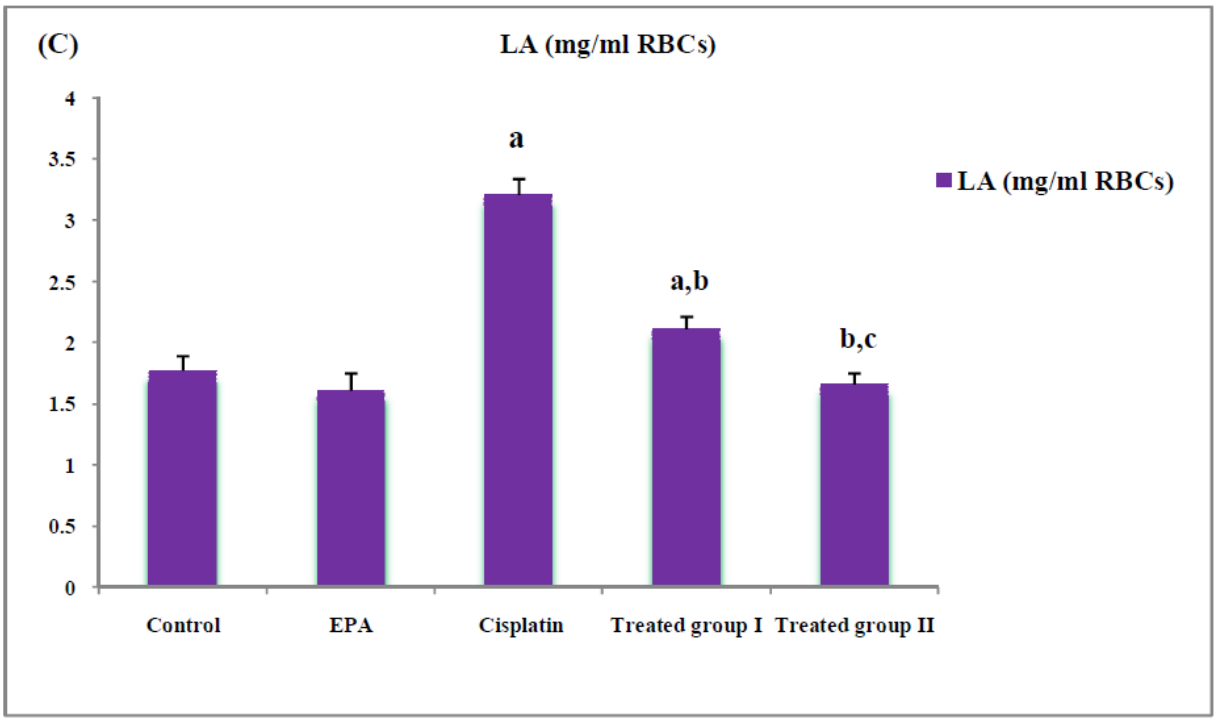
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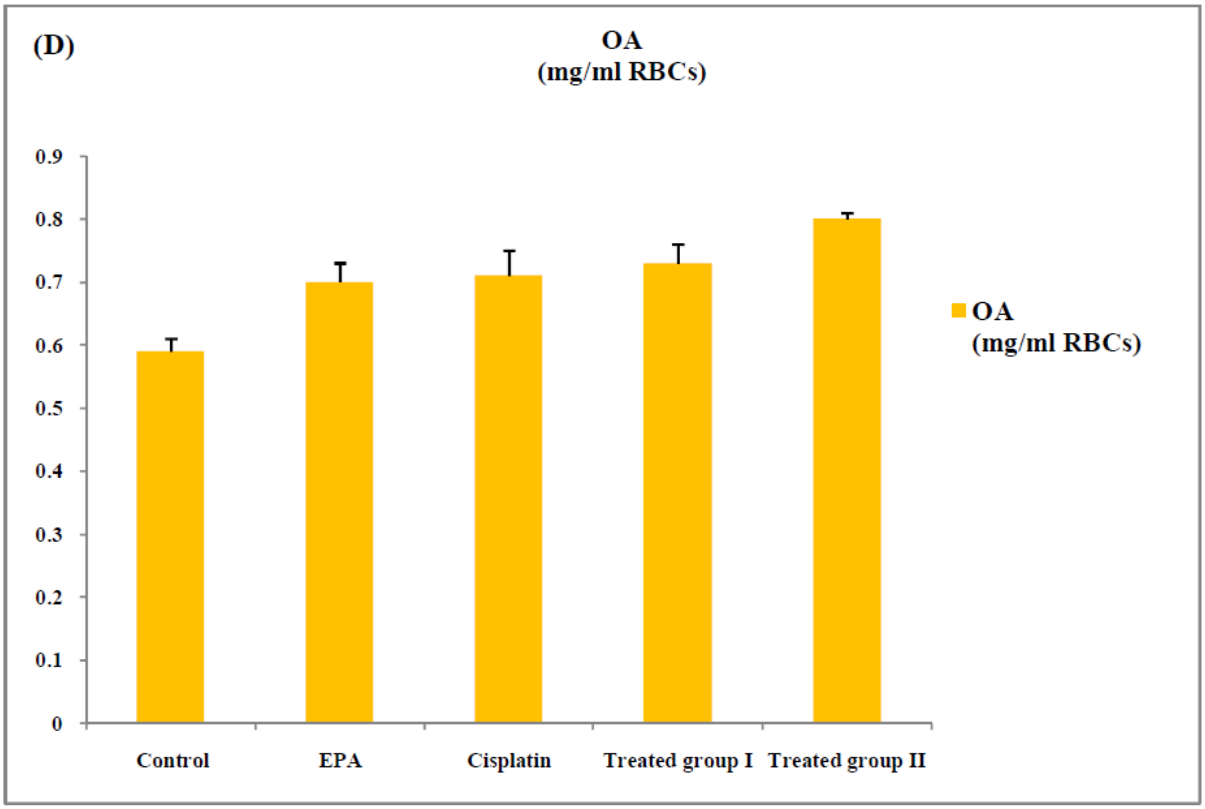

Fig. 1: Fatty acids parameters in different studied groups. A *p*-value <0.05 was interpreted as a demonstrating statistical significance **(a)** Significant difference as compared to control group. **(b)** Significant difference as compared to cisplatin group, **(c)**Significant difference as compared to treated I group. **ALA,** alpha linolenic acid; **AA,** arachidonic acid; **LA,** linoleic acid; **OA,** Oleic acid.

Histopathological results

The results of the biochemical investigations were validated by the renal histology examination performed with hematoxylin and eosin (H&E) staining **(Figure 2)**.

Cisplatin-induced toxicity can destabilize cellular membranes, leading to increased vulnerability of renal cells to structural damage and apoptosis. Histopathological analysis in this study showed reduced tubular degeneration and inflammation in EPA-treated groups, with the nanoemulsion group exhibiting the most significant improvements. EPA is known to enhance cell membrane stability and fluidity, integrating into cell membranes and thus protecting cells from damage **[4].** By stabilizing membrane integrity, EPA likely reduces cell leakage and apoptosis, preserving kidney function even in the presence of nephrotoxic agents like cisplatin.

Across all metrics, the EPA-loaded silica nanoemulsion outperformed free EPA. The enhanced bioavailability and cellular uptake provided by the nanoemulsion likely contributed to more consistent renal protection. Dynamic Light Scattering (DLS) measurements indicated a particle size increase upon EPA encapsulation, supporting improved pharmacokinetic properties that may enable prolonged EPA retention within renal tissues. Additionally, the porous structure of the nanoemulsion facilitates sustained EPA release, ensuring continuous protection against cisplatin-induced oxidative stress and inflammation **[7, 28].**

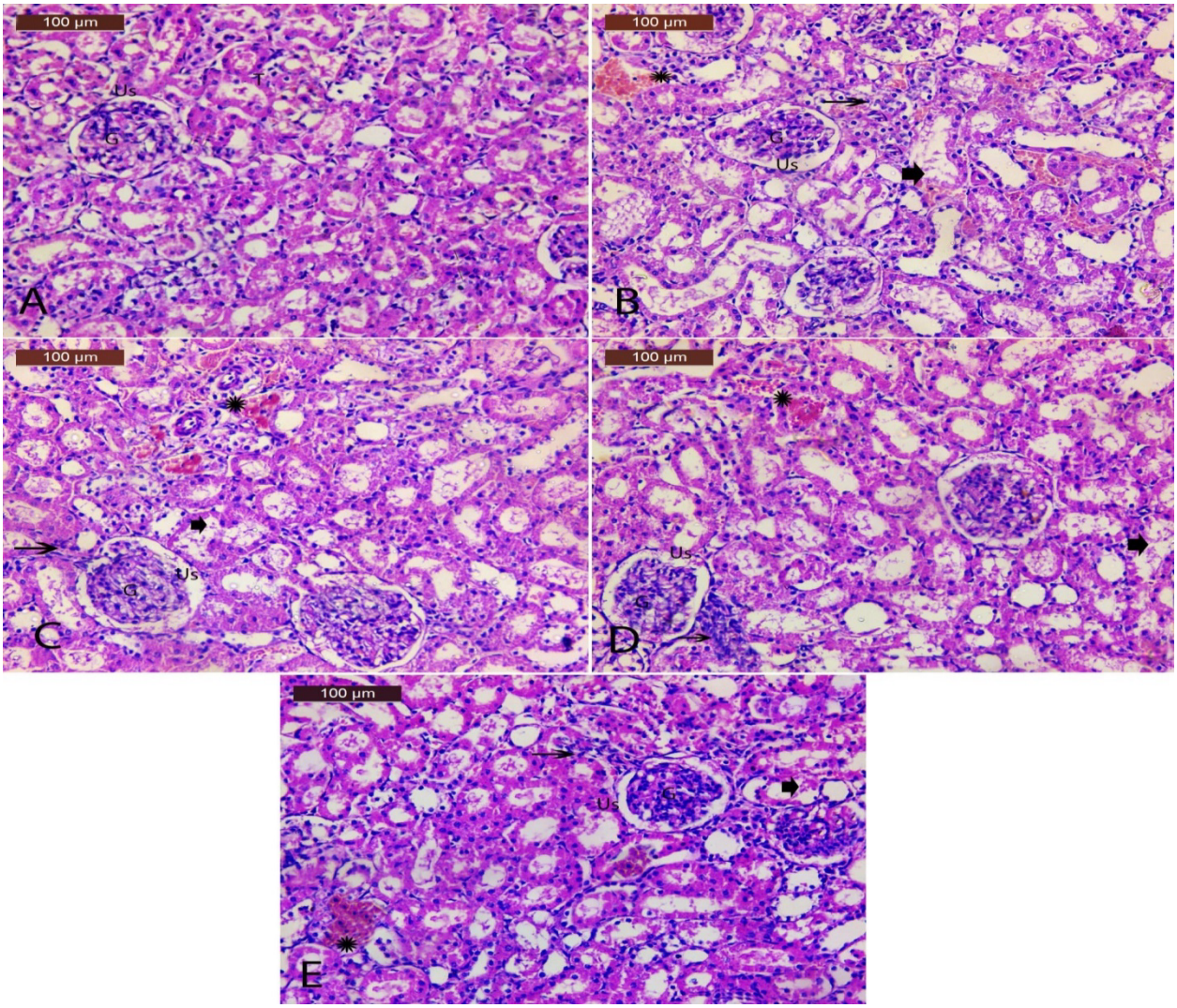

Fig. 2. A photomicrograph of renal section from kidney stained with H & E. [A] Control group exhibiting normal histological structure with normal appearance of renal corpuscle containing the glomerulus tuft (G) and surrounding urinary space (Us), intact renal tubules with vascular nucleus (T). **[B]** Cisplatin group showing atrophied glomerulus tufts (G), dilated urinary space (Us), hemorrhage in interstitial tissues (star), severe renal tubule degeneration (arrowhead) with pyknotic nuclei (P), and inflammatory cells aggregation in interstitial tissues (arrow). **[C]** Cisplatin and treatment group I showed a moderate reduction in the size of glomerulus tuft (G), mild dilated urinary space (Us), and mild hemorrhage in interstitial tissues (star), renal tubules appeared normal and others revealed degenerative cells, mild inflammatory cells (arrowhead) with pyknotic nuclei (P). **[D]** Cisplatin and treatment group II showed a moderate reduction in the size of glomerulus tuft (G), mild dilated urinary space (Us), and mild hemorrhage in interstitial tissues (star), renal tubules appeared normal and others revealed focally mild degenerative renal tubules, mild inflammatory cells (arrowhead) with pyknotic nuclei (P). **[E]** EPA group displays a glomerulus tuft (G) with virtually normal histological structure, surrounded by the urine space (Us) and with the majority of the renal tubules intact but few renal tubules showed degenerative renal tubules (arrowhead), mild inflammatory cells (arrow) with pyknotic nuclei (P).

4. Conclusions

This research demonstrated that eicosapentaenoic acid (EPA) silica nanoemulsion may be useful in managing chemotherapy-induced nephrotoxicity in the treatment of a variety of cancers. These improvements were mediated through the anti-inflammatory and anti-oxidative capacities of EPA. In particular, the new formulation (EPAwhen loaded into a silica nanoemulsion) became capable to enhance the stability as well as the bioavailabilityof EPA and could protect against cisplatin-induced nephrotoxicity in rat models.

Conflicts of interest

The authors declare that there are no conflicts of interest related to this research paper.

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