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EFFECT OF CISPLATIN ON ALBINO RATS PAROTID GLAND AND THE POSSIBLE PROTECTIVE ACTION OF SESAME AND MORINGA OILS

Khaled El-Haddad*

ABSTRACT

Introduction: Cisplatin is a common anticancer chemotherapeutic drug that has several side effects, which necessitated the introduction of palliative materials to minimize these side effects. The natural oils extracted from herbal plants revealed promising effects in this regard.

Aim of the work: To evaluate the potential protective properties of sesame and moringa oils to minimize the effects of cisplatin on the parotid gland of albino rats.

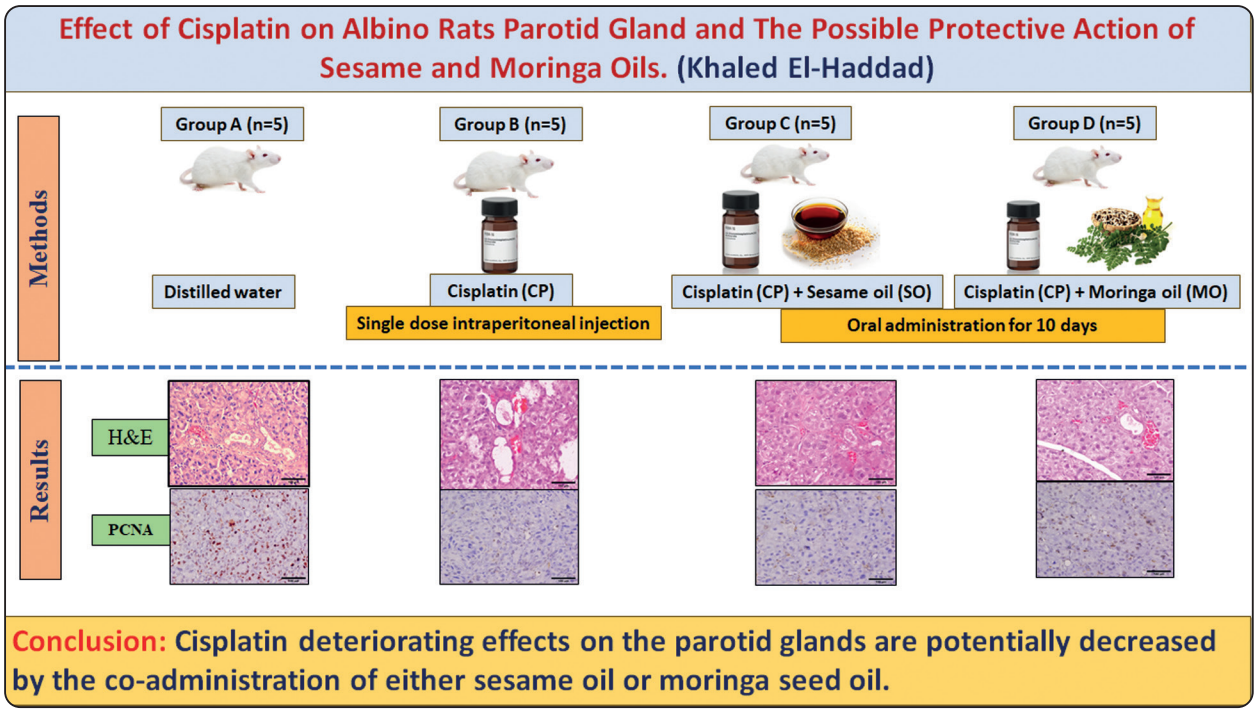
Materials & Methods: Twenty adult male albino rats were equally divided into 4 groups: Group A: control, with no treatment; group B: received a single dose of intraperitoneal injection of cisplatin (5 mg/kg body weight). Group C and D received oral sesame and moringa seed oils, respectively (5mg/kg/day for 10 days), in addition to the same cisplatin dose as group B. The parotid glands were examined via routine histological staining and immunohistochemical staining for Proliferating cell nuclear antigen (PCNA).

Results: Cisplatin group revealed degenerative changes and vacuolations in the acini, distortion in the ducts, congestion in the blood vessels, and decrease in PCNA expression compared to control group. There were enhanced histological features in the sesame and moringa treated rats with non-significant change in PCNA expression compared to cisplatin group.

Conclusion: Cisplatin deteriorating effects on the parotid glands are potentially decreased by the co-administration of either sesame oil or moringa seed oil.

KEYWORDS: Cisplatin, Parotid, Sesame oil, Moringa seed oil.

* Assistant Professor, Department of Oral Biology, Faculty of Dentistry, Ain Shams University, Cairo, Egypt.



INTRODUCTION

Cisplatin "cis-diamminedichloroplatinum II" is the first platinum-based anti-cancer medication. It is approved by the Food and Drug Administration (FDA) [1]. Cisplatin possesses several anti-cancer mechanisms. DNA damage and the formation of reactive oxygen species (ROS) are essential factors in these mechanisms [2]. Furthermore, cisplatin induces cancer cells' apoptosis via intrinsic and extrinsic processes, including caspase-dependent cellular protein degradation [3]. Despite cisplatin being globally approved, many side effects have been reported, including nausea, vomiting, diarrhea, ageusia, xerostomia, decreased sweating, and dehydration [4]. More severe adverse effects were reported, such as neurotoxicity, gastrointestinal toxicity, ototoxicity, cardiotoxicity, and nephrotoxicity [5].

Oral manifestations of the cancer therapy adverse effects are very common. One of the most widely investigated is oral mucositis [6]. However, xerostomia resulting from chemotherapy has been reported to aggravate the oral mucositis and hinder the healing process. This was suggested to be due to loss of salivary cleansing action and antimicrobial effects [7]. The structural defects in salivary glands induced by chemotherapy were reported by many authors. There are parenchymal defects indicated by atrophied acini and cytoplasmic vacuoles in their secretory cells in the submandibular glands [8-10]. Likewise, parotid glands have been reported to demonstrate damaging effects following chemotherapy, particularly in combined chemo-radiotherapy, where there is a higher possibility of parotid gland destruction [11,12].

The reported side effects of cisplatin necessitated the introduction of palliative treatment modalities. Many natural products have been documented to possess advantageous effects in counteracting the adverse effects of cisplatin particularly those of antioxidant properties [8,10,13].

One of the antioxidant herbal plants is sesame (Sesamum indicum Linn), which belongs to the Pedaliaceae plant family. The health promotion uses of sesame are numerous, including anti-inflammatory effects in addition to antioxidant, and

anticancer properties. It decreases hypertension and cholesterol levels and protects the liver, kidney, and cardiovascular system [14]. Sesame oil (SO) is extracted during the first processing of sesame seeds. It is an aromatic oil containing high amount of unsaturated fatty acids and other bioactive agents including natural vitamin E and phenols [15]. **Oboulbiga et al.** summarized the benefits of SO and reported that it could regulate diabetes, cardiovascular diseases, and malignant tumors. It is capable of reducing blood pressure, cholesterol levels, and inflammation and could prevent oxidative stress and nerve degeneration [16].

Another plant that has antioxidant capability is Moringa oleifera, also called the "tree of life" or "miracle tree," and belongs to the Moringaceae family. It has several medical and non-medical uses [17]. The seed oil of the moringa plant contains various fatty acids, calcium, and tocopherols. Moringa seed oil (MO) has antioxidant, liver protection, and anticancer effects in addition to its uses in the cosmetic field [18]. MO possesses anti-inflammatory criteria due to its high content of linoleic fatty acid, which may protect the skin from inflammatory injuries [19]. MO can also be used as a potential antibacterial agent due to the presence of benzyl isothiocyanate [20].

Due to the promising antioxidant and other protective properties of both MO and SO, the aim of the current work was to compare their effects in modulating the effects of cisplatin on the structure of the parotid gland in albino rats.

MATERIALS AND METHODS

Materials:

1- Cisplatin (CAS Number 15663-27-1), obtained from Sigma Aldrich (St. Louis, MO).

2- *Sesame oil:* Was obtained by cold pressing in National Research Institute, Egypt. The seeds were cold-pressed in a Komet single-screw oil presser. The oil was purified by sedimentation[25].

3- Moringa oil: Extracted from the Moringa Olifera seeds using the cold pressing process. The seeds were dried, and their shell was removed, exposing the kernels, which were dried for one week. The kernels were pressed in the cold presser, and the oil was dropped and purified from residues by sedimentation and then filtered to be ready for use [26].

Animals: Twenty adult male albino rats weighing 200-250 grams, on average, were used in the current study and housed in the medical animal research center of the faculty of Medicine, Ain Shams University, in controlled temperature and ventilation. The study design and processes were approved by the Committee of Research Ethics, Faculty of Dentistry, Ain Shams University (approval number: FDASU-Rec PC 072328).

The sample size estimation was verified using G*Power version 3.1.9.7 and was guided by the results of previous research [21]. A power analysis was calculated to have acceptable power to apply a two-sided statistical test to reject the null hypothesis that there is no difference between groups. The assumed alpha level was of (0.05), and a beta level was of (0.15), i.e., power = 85% and an effect size of (0.9). The predicted sample size was (20), i.e., 5 samples per group. To detect differences between groups regarding the positive reactions to PCNA stain.

The rats were divided into 4 groups (five rats each):

1. **Group A (Control group):** Received no treatment.
2. **Group B (Cisplatin)**: Received a single dose of cisplatin (5 mg/kg body weight) via intra-peritoneal injection [22].
3. **Group C (Sesame oil + cisplatin):** Received cisplatin, same as in group B, with co-administration of sesame oil oral dose, 5mg/ kg body weight, daily for 10 days [23].

4. **Group D (Moringa oil + cisplatin):** Received cisplatin, same as in group B, with co-administration of moringa oil oral dose , 5mg/kg body weight, daily for 10 days [24].

Samples preparation: At the specified dates, rats were sacrificed and the parotid glands were dissected. The fixed specimens were dehydrated in ascending alcohol concentrations, then immersed in xylene, and embedded in paraffin blocks for sectioning by the microtome. The samples were stained with hematoxylin and eosin (H&E) for the histological assessment of the glandular tissues. The Proliferating Cell Nuclear Antigen (PCNA) immunohistochemical marker was used to evaluate the proliferation in the examined samples.

Immuno-histomorphometric analysis: The immuno-stained samples were examined under the light microscope (Olympus, Japan) connected to a digital camera. Five fields from each examined slide were captured with x400 magnification and the number of the PCNA positive cells was counted using the (Image J) software of the computerized image analyzer program "ImageJ" (version 1.53e Wayne Rasband & contributors National Institute of Health, USA).

Statistical analysis: The data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were non-parametric, hence, were presented as median with inter-quartile range (IQR). Data were tested for normality by Kolmogorov-Smirnov and Shapiro-Wilk Test. For multiple-group comparisons, Kruskall Wallis test was used. While Mann Whitney U test was used for two-group comparisons. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant if it is <0.05.

RESULTS

1- Histological results (H&E):

Examination of the group A (control group) samples revealed normal histological features of the parotid gland, showing densely packed serous acini with spherical open-faced nuclei containing prominent nucleoli and homogeneously stained cytoplasm with minimal vacuoles. There were various-sized ducts, small intra-lobular ducts, and larger interlobular ducts with distinct epithelial lining. The connective tissue septa between lobules showed well-defined intact blood vessels (Fig.1).

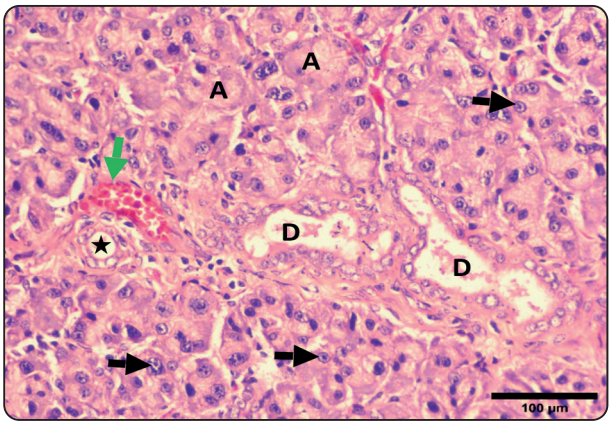


Fig. (1) Photomicrograph of the control group showing serous acini with homogeneously stained cytoplasm with minimal vacuoles (A) and spherical nuclei (black arrows) and the associated intra-lobular duct (Star). The connective tissue showed interlobular ducts (D) and intact blood vessel (green arrow) (H&E. x400).

Group B (Cisplatin) specimens displayed apparent signs of degenerative changes. The serous acini lost their outline and integrity with many vacuoles observed in the cytoplasm. The nuclei of serous acini had homogenous basophilic staining (Fig. 2A). Occasionally, the degeneration in acini was evident as wide empty areas in the gland structure. Some blood vessels showed congested red blood corpuscles (RBCs) with loss of endothelial continuity (Fig. 2B). Moreover, the duct system revealed distorted and atrophied epithelial lining with characteristic scalloped pattern and occasional stagnated secretion (Fig. 3).

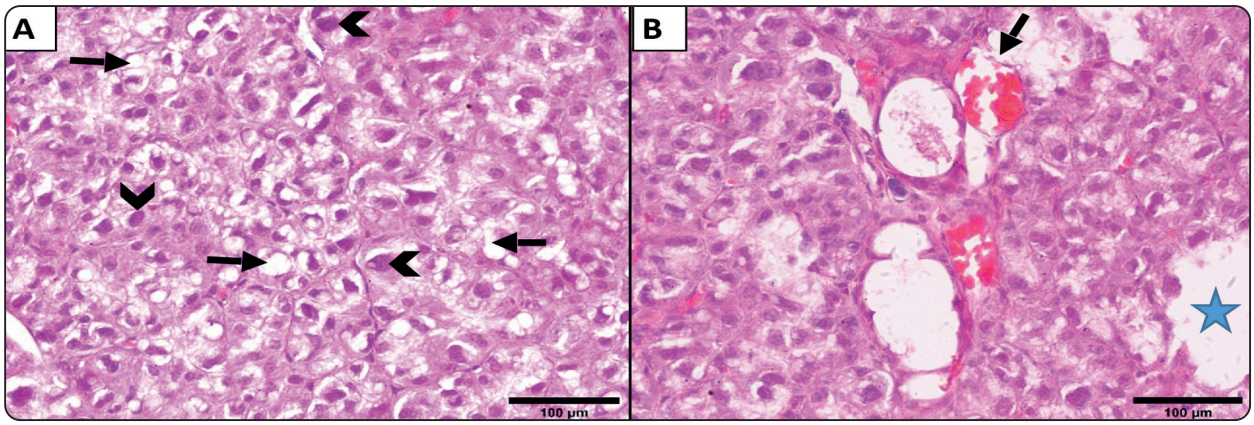


Fig. (2) Photomicrograph of the group B (cisplatin) showing (A): Serous acini lost their integrity and had cytoplasmic vacuoles (arrows). The nuclei had homogenous basophilic staining (arrow heads). (B): Wide empty area (star) and congested blood vessel with loss of endothelial continuity (arrow) (H&E. x400).

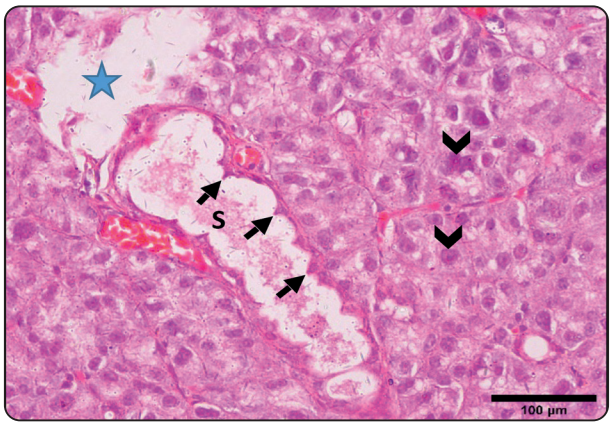


Fig. (3) Photomicrograph of the group B (cisplatin) showing nuclei with homogenous staining (arrow heads), wide empty areas (star) and distorted epithelial lining of the duct with scalloped pattern (arrows) and stagnated secretion (S) (H&E. x400).

Group C (sesame oil + cisplatin) showed enhanced histological features compared with group B. The acinar outline was preserved and the cellular boundaries were clear in some regions. The cytoplasm was comparable to that of the control group. Some acini showed perinuclear hallow (Fig. 4). However, some samples showed cytoplasmic vacuoles but apparently less than those found in group B. The nuclei of serous cells displayed several sizes and morphologies, some showed homogenous color and others preserved the open-faced appearance with the prominent nucleoli. The salivary ducts had almost intact epithelial lining (Fig. 5).

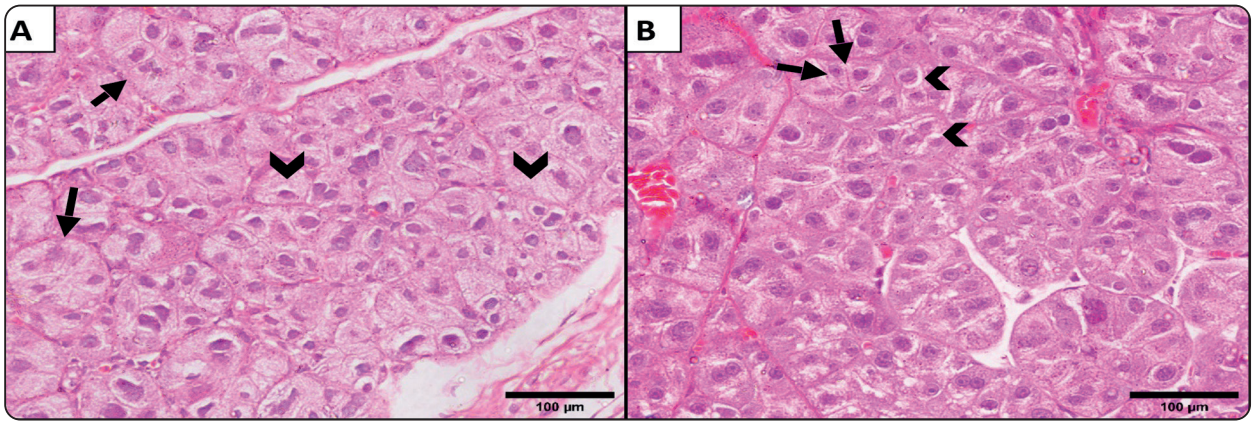


Fig. (4) Photomicrograph of the group C (sesame + cisplatin) showing (A): clear acinar outline (arrows) and well-stained cytoplasm (arrow heads). (B): Clear cellular boundaries (arrow) and perinuclear hallows (arrow heads) (H&E. x400).

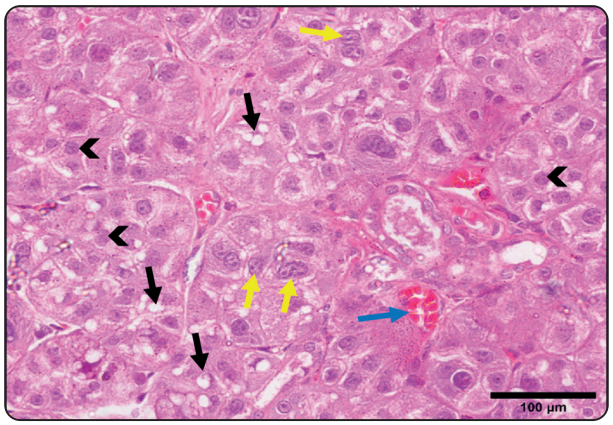


Fig. (5) Photomicrograph of the group C (sesame + cisplatin) showing cytoplasmic vacuoles (black arrows), serous cells' nuclei with homogenous color (arrow heads) and others with open-faced appearance with the prominent nucleoli (yellow arrows). The salivary ducts had almost intact epithelial lining (D) and the blood vessels with mild congestion (blue arrow) (H&E. x400).

Samples of group D (moringa oil + cisplatin) displayed similar histological features as in group C regarding the acinar outlines and the less apparently observed cellular vacuolation along with intact ducts (Fig. 6A). The open-faced nuclei with prominent nucleoli were evident. The ducts retained their lining in some regions associated with relatively congested blood vessels (Fig. 6B). Occasionally, the excretory duct had distorted outline and the neighboring blood vessel was dilated and enclosed congested RBCs (Fig. 7).

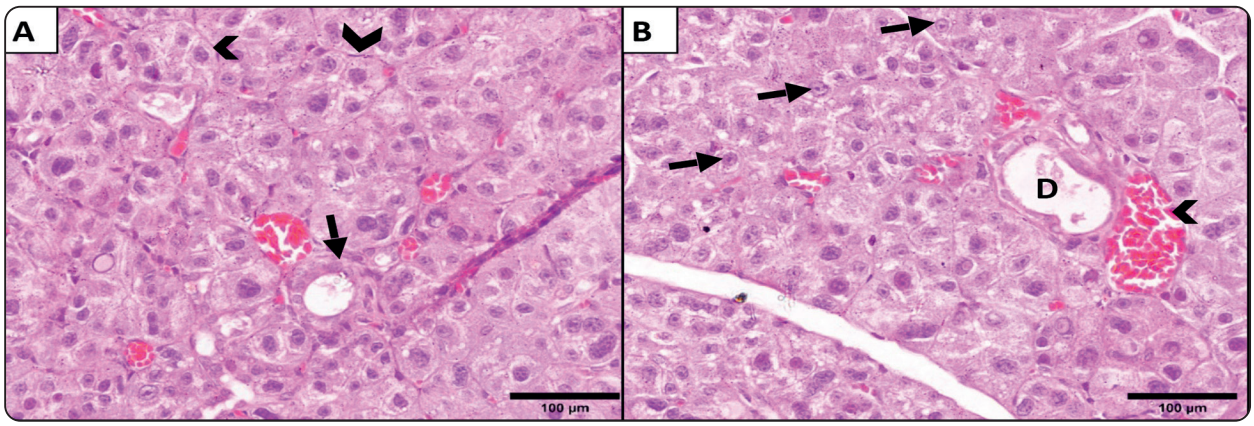


Fig. (6) Photomicrograph of the group D (moringa + cisplatin) showing (A): clear acinar outlines (arrow heads) and intact intralobular duct (arrow) (B): Open-faced nuclei with prominent nucleoli (arrows). The duct retained their lining (D) and associated with relatively congested blood vessels (arrow head) (H&E. x400).

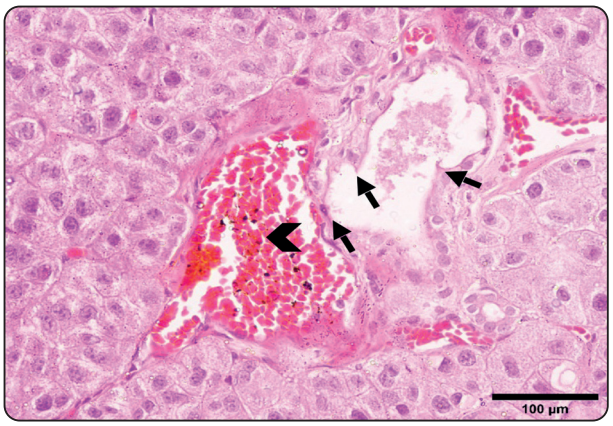


Fig. (7) Photomicrograph of the group D (moringa + cisplatin) showing the excretory duct with distorted outline (arrows) and the neighboring blood vessels is dilated and enclosed congested RBCs (arrow head) (H&E. x400).

2- Immuno-histochemical results (PCNA)

The cellular reaction to PCNA marker was most observed in group A. The immunopositive cells were rarely detected in group B. Similarly, the cells of group C showed rare positive reaction while the samples of group D revealed slight increase in the immunopositive cells in comparison to the groups B and C (Fig. 8).

3- Statistical results

The highest median value of number of PCNA positive cells was in control group (24.2). This was

followed by Cisplatin + Moringa oil (10.2), then Cisplatin group (0.2) while the least value was in Cisplatin + Sesame oil (1.5). Kruskal Wallis test revealed a statistically significant difference between groups (P=0.001). Mann-Whitney test revealed no significant difference between all pairs of compared groups (p>0.05) except the comparison between control group and each of the remaining groups (p<0.05) (Table 1, Fig. 9)

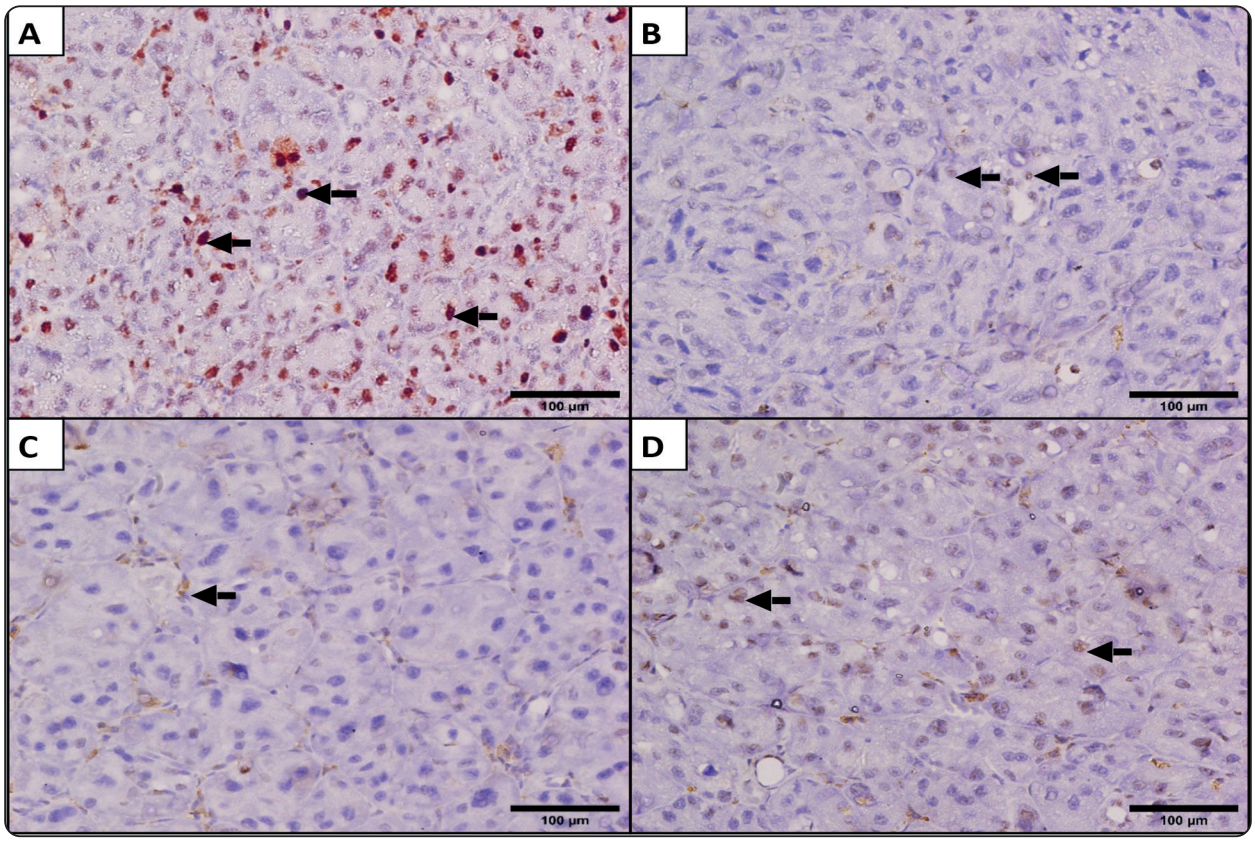


Fig. (8): Photomicrograph of the tested groups showing (A): numerous immune-positive cells in group A (arrows). (B): group B and (C): group C, both showed rare immunopositive cells (arrows). (D): group D with slight increase in the immunopositive cells (arrows) (PCNA. x400).

TABLE (1) Median and IQR of number of PCNA positive cells in the field for each group and Kruskal Wallis test for non-parametric quantitative data between the four groups followed by Mann Whitney test between each two group.

Average number of PCNA positive cells	**I: Control group**	**II: Cisplatin group**	**III: Cisplatin + Sesame oil**	**IV: Cisplatin + Moringa oil**	**p-value**
Median	24.2	0.2	1.5	10.2	0.001*
(IQR)	(18.4-38.6)	(0-3.6)	(0-4.65)	(2.55-15.45)	
Mean±SD	27.64±12.04	1.48±2.02	2.05±2.53	9.40±7.08	
Range	15.6-47	0-4.4	0-5.2	0-17.2	
P value (between each two groups)					
I: Control		0.001*	0.001*	0.002*	
II: Cisplatin			0.910	0.133	
III: Cisplatin + Sesame oil				0.182	

IQR: interquartile range *: Significant level at P value < 0.05

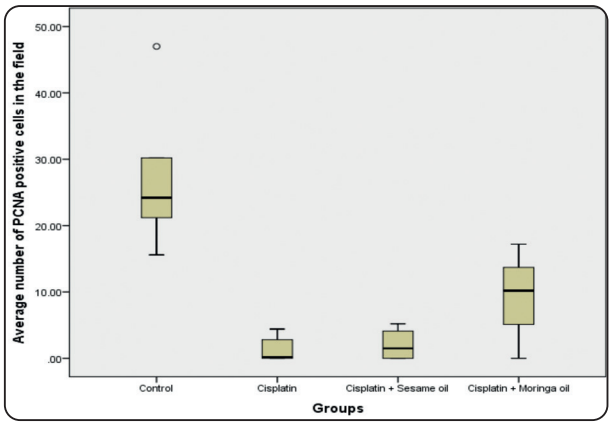


Fig. (9): Box plot between groups according to number of PCNA positive cells.

DISCUSSION

The current study concerned with the assessment of the effects of cisplatin on the parotid gland structure and to compare between the possible protective effects of two natural products, sesame oil and moringa oil. Cisplatin was selected to represent the chemotherapy as it is used as first-choice of chemotherapy for management of various malignancies, such as leukemia, head and neck cancers, and sarcomas [27]. In the current study, intraperitoneal injection of cisplatin was selected because this route of administration has been found to be efficient in reversing the neoplastic transformation [28].

Cisplatin has many mechanisms of action, oxidative stress is one of the important mechanisms [2], thus the use of antioxidants such as sesame oil and moringa oil could be promising in this regard. The oral administration of the oils in the current study was an appropriate technique due to its easy application and it is mimic to the ordinary rout of administration of these natural products in human.

Two investigation methodologies were used in the current study, routine histological examination for descriptive analysis of the structural changes in the parotid gland tissues. PCNA immunohistochemical marker was used to evaluate the proliferative potential of the cells as it is reported that cisplatin causes damage of DNA [2,29].

Examination of parotid glands samples of group B (cisplatin treated) revealed the presence of cytoplasmic vacuoles and degenerative changes in the gland. These degenerative changes associated with cisplatin agreed with **El-Messiry et al.** [8] who found vacuolated cytoplasm, and atrophied salivary acini in the submandibular glands of rats subjected to cisplatin. Additionally, the cellular vacuolation was reported by **Kitashima,** [9] who examined ultrastructural deviations of rat submandibular glands as a result of cisplatin intraperitoneal injection and found that the acinar cells contained vacuolation one day after cisplatin administration. Regarding the parotid glands, it was reported that the radiotherapy tends to cause more destruction in parotid glands when combined with chemotherapy [11].

The cytotoxic effect of cisplatin could be explained by sequential events starts with the cisplatin entry to the cells, where it is hydrolyzed, forming water-cisplatin complexes [30] which are able to damage DNA [31] which in turn leads to series of processes ending in high expression of pro-apoptotic protein called (Bcl-associated X) that increases mitochondrial membrane permeability and activation of caspase 3 [32]. Accordingly, this DNA damage caused by cisplatin could explain the observed nuclear changes in the current study. The PCNA positive reaction in the present study was rare in the cisplatin treated rats, which indicates the proliferation impairment due to this DNA damage caused by cisplatin.

The blood vessels of cisplatin treated rats in the present study showed congested RBCs. This was in accordance to **Luke et al**. [33] who reported marked RBCs congestion in the kidneys of the rats received single doses of 5 mg/kg of cisplatin. Also, the congestion of the blood vessels was reported by **Salah & Alfathi,** [34] who studied the effect of cisplatin on the pregnant mouse brain and lung and reported inflammatory cells and pulmonary blood vessel congestion in the mice injected intraperitonealy by cisplatin 3.5 mg/kg.

The ductal epithelium was degenerated in the present study in the cisplatin group. Similar effects were reported in previous study conducted on epithelial cells of the renal tubules of the rats received intraperitoneal injection of cisplatin. The authors reported epithelial cell death and increased caspase-3 levels [35]. The epithelial cell death could be due to the same mechanisms of cisplatin cytotoxicity.

The rats of group C, received sesame oil with cisplatin showed histological features indicating the protective effect of sesame against the cisplatin effects. This modulatory effect of sesame was in accordance with **El-Messiry et al.** [8] who studied the possible protective effects of sesame oil on the submandibular gland of cisplatin treated rats. The authors reported that the histological features of sesame treated rats were almost similar to control group with densely packed serous acini and normal salivary ducts. However, there were some occasional vacuoles and few ductal distortions which agreed also with the results of the current study.

The histological examination in the current study denoted occasional superior protective effects regarding the blood vessels' congestion and the integrity of the ductal epithelium of the sesame oil treated rats. This agreed with **Sankar et al.** [36] who proved that sesame oil delivers greater defense against lipid peroxidation in relation to other natural oils.

Interestingly, the PCNA immunopositive reaction in the sesame oil group was slightly more than cisplatin group with statistically non-significant difference which agreed with **Amirhasan et al.** [37] who reported that sesame oil causes decrease in PCNA reaction in the experimentally induced cancer lesions. This is a great advantage in using sesame oil as it indicates that the oil is antioxidant which protect the normal cells from the cisplatin effects, without affecting the anti-cancer potential of cisplatin caused by the action on proliferation mechanisms.

The second natural oil in the current study was moringa seed oil which revealed enhanced histological morphology comparable to the sesame oil with non-significant difference in the PCNA expression and occasional congested blood vessels and distorted ductal epithelial linings. However, the overall histological and immunohistochemical assay of both oils were comparable. The positive effects of moringa in the present study coincides with **Zouboulis et al**. [38] who reported that moringa seed oil has numerous preferred properties including anti-inflammatory effects and the induction of cell proliferation.

The results of the present work agreed with studies reporting that moringa plant is also known as the "tree of life" or "miracle tree," which has medical and non-medical uses [15]. The constituents isolated from the seeds and leaves of moringa are reported to manage in about eighty diseases [39]. Additionally, **Fu et al.** [40] reported that moringa seed oil has antioxidant and anticancer effects [40].

The findings of the present work revealed the protection of parotid gland by moringa oil. This was in accordance to **Moawad et al.** [24] who demonstrated that moringa extract has protected the parotid gland against the cisplatin damaging potential. The decreased vacuolation in the salivary acini in our results was in agreement with the outcomes of **Al Shammari and El-Mehiry**, [41] study on the effects of moringa against the cisplatin deteriorating effects in the rats' kidneys, where the authors found that the antioxidant effect of moringa is of significant importance in reduction of the cisplatin-induced destruction. The occasional congestion in the blood vessels could be a pro-inflammatory action of moringa which was reported by **Letawe et al**. [42] who stated that moringa might exhibit pro-inflammatory actions under certain conditions.

The current study has shed light on the protective potential of sesame oil and moringa seed oil against the effects of cisplatin on parotid glands. The findings of the present work could be continued to introduce the optimum dosage and treatment administration times of these oils in addition to the possibility to combine between them to obtain a synergistic effect which needs further investigation.

CONCLUSIONS

From the results of the present study and within its limitations, it could be concluded that both sesame oil and moringa seed oil has potential protective effects against the undesirable effects of cisplatin on the parotid gland without altering the anti-cancer effects of cisplatin on the nuclear proliferation levels.

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CONFLICT OF INTEREST

No conflict of interest.

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