

# ATORVASTATIN AMELIORATES CISPLATIN INDUCED OXIDATIVE STRESS IN EHRlich ASCITES SOLID TUMOR-BEARING MICE: A PROSPECTIVE CASE CONTROL STUDY

By

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## ABSTRACT

**Background:** A relationship was observed between cholesterol and the development of many cancer types. However, the efficacy of the addition of hypolipidimic medications to cancer treatment regimen is unclear.

**Objective:** To study the possible effects of atorvastatin on Ehrlich solid tumor bearing mice treated with cisplatin and to explore atorvastatin effects on inflammation and oxidative stress. **Materials and methods:** Sixty female Swiss albino mice were divided into five equal groups: Negative control, positive control, cisplatin treated, atorvastatin-treated and combination of cisplatin-and atorvastatin-treated group. Tumor volume, total antioxidant capacity, catalase, malondialdehyde, C-reactive protein and angiogenin were determined. **Results:** Markers of oxidative stress were the worst in cisplatin-treated group and the best in combination-treated group as there was significant increase in serum catalase and a relative increase in serum total antioxidant capacity (TAC) than cisplatin treated group. Moreover, serum malondialdehyde (MDA) showed relative decrease in combination-treated group than cisplatin-treated group.

**Conclusion:** The use of atorvastatin/cisplatin combination therapy increased antioxidant enzymes and decreased cisplatin induced oxidative stress pointing at the antioxidant effect of atorvastatin as a possible mechanism for its anticancer activity.

**Keywords:** Breast cancer, Ehrlich Ascites Carcinoma, Cisplatin, Atorvastatin, Oxidative Stress, Angiogenin.

## INTRODUCTION

Breast cancer is a malignant tumor occurs in breast cells. Incidence of breast cancer is increasing worldwide, despite the huge improvement in breast cancer prognosis and survival (Torre et al., 2017). In Egypt, the incidence of breast cancer between women reached almost 18.9% of all diagnosed cancer cases (Ashraf et al., 2013).

Solid Ehrlich ascites carcinoma is an undifferentiated carcinoma, that has the high transplantable capacity, quick multiplication, no-relapse, short life expectancy, 100% malignancy and does not have tumor specific transplantation antigen. It resembles human tumors and is regularly utilized as a model of solid tumor experiments (Ozaslan et al., 2011).

Cisplatin is one of the early successes of chemotherapy for solid tumors. It is often used as a part in combination-treatment with other anticancer agents (Apps *et al.*, 2015). It has a toxic profile including nephrotoxicity, gastrointestinal toxicity, neurotoxicity, ototoxicity and oxidative stress (Salman *et al.*, 2014).

Many studies have discussed the actions of statins, besides their usage in cardiovascular and coronary heart diseases as cholesterol-lowering agents. They have found that statins exhibit a vast range of pleiotropic effects that may significantly contribute to the treatment of other diseases, such as inflammatory and pathologic conditions and even tumors. A potent inhibition of the endogenous mevalonate pathway is the commonly known pharmacological activity of statins, which leads directly to decrease in the biosynthesis of cholesterol and numerous isoprenoids such as geranylgeranyl pyrophosphate (GGPP1) and farnesyl pyrophosphate (FPP) (Oesterle *et al.*, 2017).

Statins bind to mammalian HMG-CoA reductase at nanomolar concentrations, leading to an effective displacement of the natural substrate HMGCoA (Kabel *et al.*, 2013).

The aim of this study was to study the possible effects of atorvastatin on Ehrlich solid tumor bearing mice-treated with cisplatin, and to explore atorvastatin effects on inflammation and oxidative stress.

## MATERIALS AND METHODS

### Animals:

In the present study, we used adult female Swiss albino mice were obtained

from the animal house of the National Cancer Institute (NCI), weighing 18 to 20 g. Mice were fed standard pellet chow (El-Nasr Chemical Company, Cairo, Egypt) and were allowed free access to water. For acclimation, animals were housed in normal temperature and normal dark/light cycle for one week before the experiment.

All the experiments were performed in accordance with institutional guidelines for ethical care of animals. The study protocol was approved by research ethics committee, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

This study included 60 animals divided equally into the following groups:

- Group (1): Normal mice received vehicle only and served as a negative control group.
- Group (2): Ehrlich solid tumor bearing mice that received vehicle and served as a positive group.
- Group (3): Ehrlich solid tumor (EAC) bearing mice that received a single intraperitoneal dose of cisplatin (7.5mg/kg) on the 12<sup>th</sup> day of EAC cells inoculation.
- Group (4): Ehrlich solid tumor bearing mice that received an intraperitoneal dose of atorvastatin (20 mg/kg) on alternate days for 3 weeks after EAC cells inoculation.
- Group (5): Ehrlich solid tumor bearing mice that received a combination of cisplatin (a single intraperitoneal dose (7.5mg/kg) on the 12<sup>th</sup> day of EAC cells inoculation) and atorvastatin (20 mg/kg) on alternate days for 3 weeks after EAC cells inoculation.

All mice on all groups (except negative control group) were exposed to the following:

**Cell line:** A line of Ehrlich Ascites Carcinoma (EAC) cells was used. The parent line was supplied through the courtesy of Dr. C. Benckhuysen, Netherlands Cancer Institute, Amsterdam, Netherlands. It was used for in vivo experiments, where solid tumors were induced in mice by subcutaneous inoculation of 0.1 ml of EAC cells containing  $5 \times 10^5$  viable tumor cells into the right thigh of the hind limb of mice. A palpable solid tumor mass (about 100 mm<sup>3</sup>) developed within 12 days (Osman et al., 1993). On day 22 after S.C. inoculation of EAC cells, blood was withdrawn from retro-orbital artery into vacuum tubes, and then serum was separated and stored at -20°C for determination of serological markers. Animals were sacrificed; tumor tissues were removed, washed with normal saline and fixed in 10% formalin for histopathological examinations. Tumor dimensions were measured using Vernier caliper, then tumor volume was calculated by the modified ellipsoidal formula (Jia et al., 2005) {Tumor Volume = length  $\times$  width<sup>2</sup>  $\times$  0.52}.

Autopsy samples were taken from mice tumor tissues in different groups and fixed in 10% formal saline for twenty four hours. Washing was done using sterilized water, then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in

paraffin at 56 degree in hot air oven for twenty four hours. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by slide microtome. The obtained tissue sections were collected on glass slides, deparaffinized, and stained by hematoxylin and eosin stains for examination through the light electric microscope (Banchroft et al., 2012).

**Serum laboratory investigations included** malondialdehyde, total antioxidant capacity and catalase measured by spectrophotometric techniques (Ohkawa et al., 1979; Fossati et al., 1980 and Koracevic, 2001). C - reactive protein and angiogenin were measured by ELISA (Patterson & Higginbotham, 1965 and Hu & Riordan, 1993). All were done according to the manufacturer's instructions.

Cisplatin was obtained as Cisplatin® (Mylan, USA). It was administered by intraperitoneal injection in a dose of 7.5 mg/kg body weight. Atorvastatin was obtained as LIPITOR®, (Pfizer, Egypt). It was dissolved in 10% ethanol solution at a concentration of 2mg/ml and administered by intraperitoneal injection in a dose of 20 mg/kg body weight (Abd-El- Rahman and Abd-El-Motelb, 2011).

**Statistical methods:** IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016) was used for data analysis. Data were expressed as Mean  $\pm$  SE for quantitative parametric measures. Comparison between the groups for parametric data was done using Analysis of Variance (ANOVA) followed by Post-hoc. The

probability of error at 0.05 was considered significant.

## RESULTS

**Effect of Atorvastatin on tumor volume:** Intraperitoneal administration of

atorvastatin to mice resulted in significant decrease in tumor volume compared to positive control group. The tumor volume relatively decreased in combination group that received cisplatin/ atorvastatin when compared with cisplatin group (Table 1).

**Table (1):** Mean  $\pm$  SE of tumor volume (mm<sup>3</sup>) in all studied groups.

Groups Tumor volume(mm <sup>3</sup> )	Positive control group (No=12)	Cisplatin-treated group (No=12)	Atorvastatin- treated group (No=12)	Combination- treated group (No=12)
<b>Range</b>	0.04- 0.09	0.003- 0.04	0.01- 0.04	0.005- 0.03
<b>Mean <math>\pm</math> SE</b>	0.07 $\pm$ 0.005	0.02 $\pm$ 0.003 <sup>b</sup>	0.02 $\pm$ 0.003 <sup>b</sup>	0.01 $\pm$ 0.002 <sup>bd</sup>

<sup>b</sup> Significant from +ve control group.

<sup>d</sup> significant from atorvastatin-treated group.

**Effect of Atorvastatin on oxidative stress:** Positive control group showed significant decrease in serum catalase and serum TAC with significant increase in serum MDA compared to the negative control group. Markers of oxidative stress were the worst in cisplatin-treated group. MDA showed highly significant increase in cisplatin group than all other groups even positive control group. Serum catalase and serum TAC were the lowest in cisplatin-treated group when compared with other treated groups.

Intraperitoneal administration of atorvastatin to mice resulted in significant increase in serum catalase and serum TAC

with relative decrease in serum MDA compared to positive control group.

Regarding combination-treated group, there was a significant increase in serum catalase than cisplatin-treated group and a relative increase in serum TAC than cisplatin- treated group. Moreover, serum MDA showed relative decrease in combination-treated group than cisplatin-treated group (Table 2).

**Table (2):** Mean ± SE of oxidative stress markers in all studied groups.

Groups Oxidative Stress Markers	Negative control group (No=12)	Positive control group (No=12)	Cisplatin-treated group (No=12)	Atorvastatin-treated group (No=12)	Combination-treated group (No=12)
<b>Serum MDA (mg/dL)</b>					
<b>Range</b>	10.0- 16.8	14.5- 21.1	24.2- 28.2	15.3- 19.7	19.7- 27.1
<b>Mean ± SE</b>	13.7±0.6	18.3±0.6 <sup>a</sup>	25.9±0.4 <sup>ab</sup>	17.5±0.4 <sup>c</sup>	22.9±0.8 <sup>abd</sup>
<b>Serum TAC (mg/dL)</b>					
<b>Range</b>	3.4- 4.9	0.9- 2.6	2.1- 3.2	2.2- 3.5	3.0- 3.3
<b>Mean ± SE</b>	4.1±0.1	2.1±0.2 <sup>a</sup>	2.5±0.1 <sup>a</sup>	3.2±0.06 <sup>ab</sup>	3.2±0.03 <sup>ab</sup>
<b>Serum Catalase (mg/dL)</b>					
<b>Range</b>	506.6- 631.6	241.3- 282.0	286.6- 395.7	445.4- 530.3	342.1- 654.6
<b>Mean ± SE</b>	557.6±10.9	261.5±3.9 <sup>a</sup>	338.3±10.2 <sup>a</sup>	479.7±8.5 <sup>bc</sup>	461.7±32.9 <sup>bc</sup>

<sup>a</sup> Significant from negative control group .

<sup>b</sup> Significant from positive control group .

<sup>c</sup> Significant from cisplatin-treated group .

<sup>d</sup> significant from atorvastatin-treated group .

**Effect of Atorvastatin on serum CRP:** All treated groups showed significant decrease in serum CRP compared to positive control group. When comparing

the three treated groups together, combination-treated group showed the lowest value (Table 3).

**Table (3):** Mean ± SE of serum CRP (mg/dL) in all studied groups.

Groups Serum CRP (mg/dL)	Negative control group (No=12)	Positive control group (No=12)	Cisplatin-treated group (No=12)	Atorvastatin-treated group (No=12)	Combination-treated group (No=12)
<b>Range</b>	3.000- 8.000	7.500- 13.00	5.900- 9.00	6.000- 9.500	5.500- 9.00
<b>Mean ± SE</b>	6.275±0.4859	10.52±0.6084 <sup>a</sup>	7.583±0.3183 <sup>b</sup>	7.767±0.3016 <sup>b</sup>	7.000±0.2319 <sup>bd</sup>

<sup>a</sup> Significant from negative control group.

<sup>b</sup> Significant from positive control group .

<sup>d</sup> significant from atorvastatin-treated group .

**Effect of atorvastatin on serum angiogenin:** All treated groups showed significant decrease in serum angiogenin compared to positive control group. When

comparing the three treated groups together, combination-treated group showed the lowest value (Table 4).

**Table (4):** Mean  $\pm$  SE of serum angiogenin (mg/dL) of studied groups.

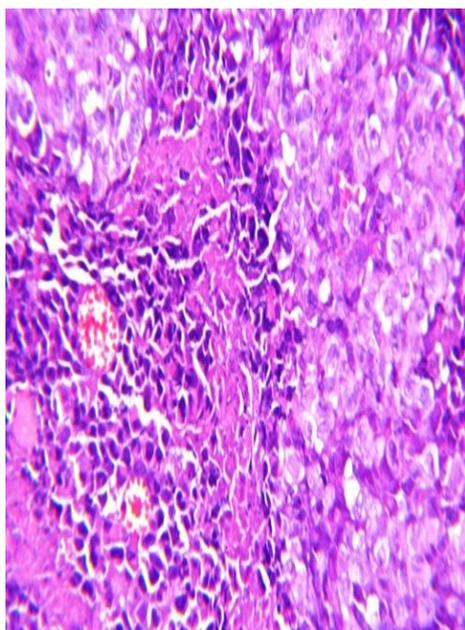
Groups Serum angiogenin (mg/dL)	Negative control group (No=12)	Positive control group (No=12)	Cisplatin- treated group (No=12)	Atorvastatin- treated group (No=12)	Combination- treated group (No=12)
<b>Range</b>	75.00- 200.0	300.0- 625.0	140.0- 215.0	175.0- 225.0	150.0- 220.0
<b>Mean <math>\pm</math> SE</b>	117.1 $\pm$ 12.89	387.5 $\pm$ 33.5 <sup>a</sup>	177.5 $\pm$ 7.918 <sup>b</sup>	200.0 $\pm$ 4.807 <sup>b</sup>	176.3 $\pm$ 6.829 <sup>b</sup>

<sup>a</sup> Significant from negative control group .

<sup>b</sup> Significant from positive control group .

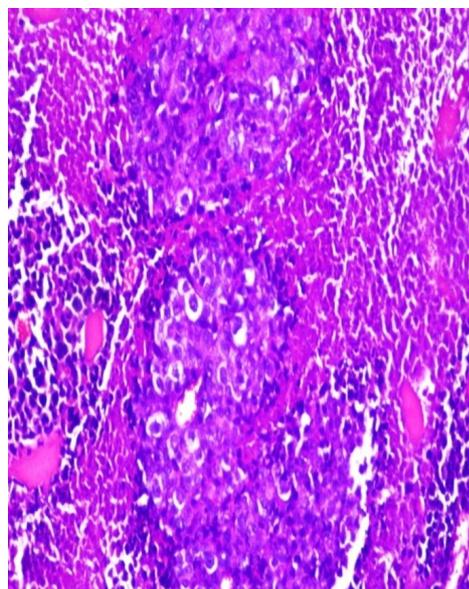
### Histopathological findings

Ehrlich tumor cells appeared intact and had criteria of anaplasia as hyperchromatic nuclei with few mitosis as well as polarity and pleomorphism in both subcutaneous tissue and between the muscle bundles (Fig.1- IPx 200).



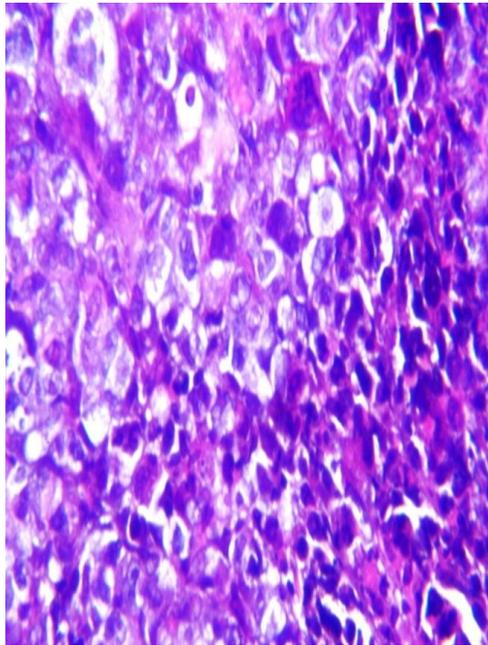
**Figure (1): Positive control group**

Most of the tumor cells showed apoptosis and necrosis (Fig.2- IPx100).



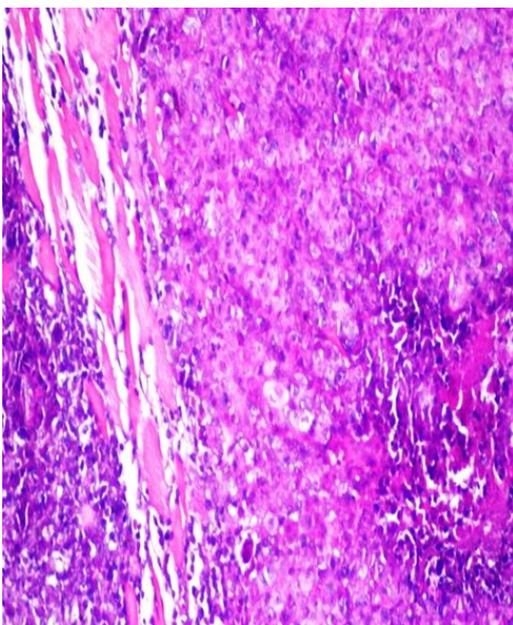
**Figure (2): Cisplatin-treated group.**

There was necrosis in few number of the tumor cells all over the area of tumor at the subcutaneous tissue as well as between the hyalinized muscle bundles (Fig.3- IPx 200).



**Fig. (3): Atorvastatin-treated group.**

The tumor cells showed apoptosis and necrosis in most of them (Fig.4- IPx100).



**Fig. (4): Combination-treated group.**

## DISCUSSION

Breast cancer is the most frequently diagnosed cancer among women and the most cancer related deaths around the world (Siegel et al., 2016).

Transplantable models of cancer have the advantage of low cost, easy reproducibility and accessibility (Gaballah et al., 2017). Ehrlich ascites carcinoma resembles human tumors. So, they are frequently used in tumor studies. It is the most sensitive to chemotherapy due to the fact that it is undifferentiated and has a rapid growth rate (Ozaslan et al., 2011).

The present study was performed to estimate the effect of atorvastatin on Ehrlich solid tumor bearing mice as a combination treatment with cisplatin or as the sole treatment regimen, trying to find logic explanations and mechanisms of its action on tumor tissues also trying to explore whether the addition of atorvastatin to cisplatin in the treatment regimen of breast cancer is of value.

Statins, among the most commonly recommended drugs around the world, are cholesterol-lowering agents act by inhibition of the endogenous mevalonate pathway leading to reduction in the biosynthesis of cholesterol and isoprenoids (Oesterle et al., 2017). Moreover, statins may act as direct inhibitors to P-glycoprotein expression (Goard et al., 2010), that was proved to be responsible for resistance of tumors to chemotherapeutic agents (Xu et al., 2010).

In the present work, tumor volume decreased significantly in atorvastatin-treated group and combination-treated group than positive control group. Upon histopathological examination tumor cells showed apoptosis and necrosis in most cells of combination group compared with cisplatin-treated group. These results agreed with Huang et al. (2010) who reported that atorvastatin induced apoptosis and slows tumor growth in

mice. **Pisanti et al. (2014)** reported that there may be synergistic anticancer effects of statins with chemotherapeutic drugs due to induction of apoptosis such as cisplatin with cetuximab showing antiproliferative effects in K-Ras mutant cells. Also, **Hindler et al. (2006)** stated that there might be synergistic interactions between statins and chemotherapeutic agents such as cisplatin, methotrexate and doxorubicin.

In the current study, MDA levels significantly increased in cisplatin-treated group than positive control group reflecting cisplatin oxidative stress side effect. In combination-treated group, there was a relative reduction in MDA levels when compared with cisplatin-treated group. Moreover, serum catalase increased significantly in atorvastatin and combination-treated groups when compared with cisplatin-treated group.

In agreement with our results, **Boorla et al. (2014)** showed that treatment of experimental animals with cisplatin and atorvastatin significantly decreased the level of MDA compared to that received cisplatin alone.

Interestingly, there was a reduction in CRP and angiogenin levels in atorvastatin-treated group almost similar to that occurred in cisplatin-treated group. Also, synergistic reductions in their levels were observed upon using combination of cisplatin and atorvastatin compared to cisplatin only although these reductions were not significant that may be attributed to small sample size or the doses of drugs used in our experiment.

Our results were in harmony with **Ghaisas et al. (2010)** who found that atorvastatin can improve the antioxidant

status and had anti-inflammatory effects which may contribute to its antitumor effect.

CRP and angiogenin results support the idea that atorvastatin has anticancerous effect by itself, because CRP has been always used as a sensitive diagnostic/prognostic marker both for tumor progression and responsiveness to chemotherapy in solid tumors (**El-Mesery et al., 2009**). Also, angiogenin has been detected in almost all types of solid tumors, playing a major role in tumor angiogenesis and its expression was found to be up-regulated in many types of cancers (**Li and Hu, 2012**).

**Gazzerro et al. (2012)** discussed the pleiotropic effects of statins, suggesting a potential use of these compounds beyond their lipid-lowering properties in several acute and chronic diseases mediated by both direct (via modulation of the immune-response), and indirect (via inhibition of platelet functions) mechanisms.

Also, **Yang et al. (2012)** stated that statins may act as chemoprotective agents against various types of cancers. Statins are potent inhibitors of HMG-CoA reductase, an enzyme responsible for the conversion of HMG-CoA to mevalonate. This action reduces synthesis of non-sterol products which are essential for the isoprenylation of intracellular second messenger mitogenic signaling proteins like Ras (**Wali et al., 2009**). Another mechanism for atorvastatin possible effect on tumor suppression was explained by **Goard et al. (2010)** who stated that statins may act as direct inhibitors to P-glycoprotein expression. P-glycoprotein expression was proved to be responsible

for resistance of tumors to chemotherapeutic agents (Xu et al., 2010).

### CONCLUSION

The addition of atorvastatin to cisplatin anticancer treatment regimen ameliorates cisplatin induced oxidative stress, and had some sort of synergistic anticancer effect against Ehrlich solid tumors in mice.

### ACKNOWLEDGMENTS

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## دور الأتورفاستاتين في تقليل الأوكسدة الناجمة عن إستخدام السيسبلاتين في الفئران الحاملة لورم إيرليك الصلب : دراسة إستباقية مقارنة للحالات والضوابط

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**خلفية البحث :** لوحظ وجود علاقة بين الكوليسترول وتحسن العديد من أنواع السرطان. ومع ذلك، فإن فعالية إضافة الأدوية المخفضة للدهون في علاج السرطان غير واضحة.

**الهدف من البحث:** وقد أجريت هذه الدراسة لتقييم الدور المحتمل للأتورفاستاتين على الفئران الحاملة لورم إيرليك الصلب والمعالجة بالسيسبلاتين وتأثيرها على الالتهاب والأوكسدة.

**مواد وطرق البحث:** أجريت هذه الدراسة على مجموعة من الفئران عددها ستون فأرا تم تقسيمها إلى خمس مجموعات : مجموعة سليمة استخدمت كمجموعة ضابطة ،مجموعة مصابة دون علاج، مجموعة تعالج بالسيسبلاتين منفردا، مجموعة تعالج بالأتورفاستاتين منفردا، مجموعة تعالج بالأتورفاستاتين والسيسبلاتين معا. ومن ثم تم إزالة أنسجة الورم لفحوصات الأنسجة وتم جمع عينات الدم وفصل المصل لفحوصات المختبر للكثايز وإجمالي القدرة المضادة للأوكسدة والمالونالدهايد والانجيوجينين وبروتين سي التفاعلي.

**النتائج:-** كانت دلالات الأوكسدة هي الأسوأ في المجموعة المعالجة بالسيسبلاتين والأفضل في المجموعة المعالجة بالأتورفاستاتين والسيسبلاتين معاً. كما كان هناك زيادة كبيرة في الكثايز في الدم وزيادة نسبية في إجمالي القدرة المضادة للأوكسدة من المجموعة المعالجة بالسيسبلاتين. وعلاوة على ذلك، أظهر المالونديالدهيد إنخفاضاً نسبياً في مجموعة الجمع بين الأتورفاستاتين والسيسبلاتين عن المجموعة المعالجة بالسيسبلاتين.

**الإستنتاج:** أدى الاستخدام الثنائي لعلاج الأتورفاستاتين / السيسبلاتين إلى زيادة إنزيمات مضادات الأوكسدة وإنخفاض الإجهاد التأكسدي الناجم عن سيسبلاتين مما يعكس التأثير المضاد للأوكسدة من الأتورفاستاتين كألية محتملة لنشاطه المضاد للسرطان .